# Lower Respiratory Tract Infection in Adults - Carriage as a Diagnostic, Home-based Care and Vaccine Development

Thesis submitted in accordance with the requirements of the University of Liverpool for the degree of Doctor in Philosophy (PhD)

by

Dr Andrea M. Collins

MBChB, MRCP, Resp. SCE

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# Declaration

This thesis is the result of my own work and effort. In some instances, work was performed in conjunction with colleagues.

The research in this thesis was carried out at the Liverpool School of Tropical Medicine (LSTM), the Royal Liverpool and Broadgreen University Hospital (RLBUHT) and University Hospital Aintree (UHA).

The material contained in this thesis has not been presented, nor is currently being presented, either wholly or in part, for any other degree or qualification.

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Specific individual contributions are detailed at the end of each chapter.

# Publications and Awards

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1. **Collins AM**, Johnstone CMK, Gritzfeld JF, Banyard A, Hancock CA, Wright AD, Macfarlane L, Ferreira DM, Gordon SB. Pneumococcal Colonisation Rates in Patients Admitted to a UK Hospital with Lower Respiratory Tract Infection – a prospective case-control study. J. Clin. Microbiol. doi:10.1128/JCM.02008-15. **CHAPTER 3**

2. **Collins AM**, Wilks S, Wootton DG, Wright A, Davies L, Hadcroft J, Gordon S. Early Supported Discharge Scheme (ESDS) for Pneumonia & Lower Respiratory Tract Infection (LRTI): are there enough suitable patients? Thorax 2011;66:A32 doi:10.1136/thoraxjnl-2011-201054b.65. **CHAPTER 4**

3. **Collins AM**, Wilks S, Wootton DG, Gordon SB. Supported home-care schemes: the key to increasing outpatient care? European Respiratory Journal. 2012;39(2):508. **CHAPTER 4**

4. **Collins AM**, Hancock C, Gordon SB. Feasibility study for Early Supported Discharge in Adults with Respiratory Infection in the UK. BMC Pulmonary Medicine 2014. DOI: 10.1186/1471-2466-14-25. **CHAPTER 5**

5. **Collins AM**, Wright AD, Mitsi E, Gritzfeld JF, Hancock CA, Pennington SH, Wang D, Morton B, Ferreira DM, Gordon SB. First Human Challenge Testing of a Pneumococcal Vaccine - Double Blind Randomised Controlled Trial. Am J Respir Crit Care Med. 2015 Oct 1;192(7):853-8. doi: 10.1164/rccm.201503-0542OC. **CHAPTER 7**

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1. **Collins AM**, Hancock CA, Khan J, Gordon SB. Home First Pilot: A Study of Early Supported Discharge in Patients with Lower Respiratory Tract Infections. **CHAPTER 6**

2. Trimble A*, Wright AD*, Hancock CA, Wang D, Gordon SB, Ferreira DM, **Collins AM**. Pneumococcal Colonisation is an Asymptomatic Event in Healthy Adults using an Experimental Human Colonisation Model. Plos One – currently under revision.

## Publications arising during the course of the PhD

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3. Mitsi E, Roche AM, Reiné J, Zangari T, Owugha JT, Pennington SH, Gritzfeld JF, Wright AD, **Collins AM**, van Selm S, de Jonge MI, Gordon SB, Weiser JN, Ferreira DM. Agglutination by anti-capsular polysaccharide antibody is associated with protection

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## Awards

- **Early Career Investigator Award Winner from the British Lung Foundation –** British Thoracic Society Conference, London, December 2014

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## Glossary of Terms

A&E - accident and emergency department

AA - admission avoidance

ACTRITE - COPD community nursing team in Liverpool – The Acute Chest Triage Rapid Intervention Team

ADL - activities of daily living

ADR - adverse drug reaction

AKD - acute kidney disease

AMAU - acute medical admissions unit

AMTS - abbreviated mini-mental test score

APR - annual progress report

ARDS - adult acute respiratory distress syndrome

ATS - american thoracic society

AUC - area under the curve

B.D - twice daily (for medications)

BAL - bronchoalveolar lavage

BMI -body mass index

BREATHE-EASY - british lung foundation support group

BTS - british thoracic society

CAP - community acquired pneumonia

CAPITA - community-acquired pneumonia immunization trial in Adults

CAP-Sym - community-acquired pneumonia symptom questionnaire

CAS - central allocation service (IRAS)

CBS - central booking service (IRAS)

CCF - congestive cardiac failure

CCG - clinical commissioning groups

CFU - colony forming units

CI - chief investigator

CI - confidence intervals

CKD - chronic kidney disease

CMT - core medical trainee

COPD - chronic obstructive pulmonary disease

CRB-65 - pneumonia scoring system used in the community similar to CURB-65 but omitting urea

CRF - case report form

CRP - c - reactive protein

CRU - clinical research unit

CSF - cerebrospinal fluid

CSP – co-ordinated system for gaining NHS permissions

CTA - clinical trial authorisation

CTIMP - clinical trials of investigation medicinal products

CURB-65 - pneumonia severity score/mortality index

CXR - chest radiograph/X-ray

DBRCT - double blind randomised controlled trial

DMSC/DMC - data monitoring and safety committee

DoI - declaration of Interest

ECG - electrocardiogram

ED - emergency department

EHPC - experimental human pneumococcal colonisation/ carriage

ELISA - enzyme-linked immunosorbent assay

EMA - european and medicines authority

ERS - european respiratory society

ESDS - early supported discharge

ETOH - ethanol / alcohol

EudraCT - european clinical trials database

EWS - early warning score

EWTD - european working time directive

F1 - foundation year 1 doctor

$FiO_2$ - forced inspired oxygen concentration

GCS - Glasgow coma scale

GPQ - general practitioner questionnaire

GPS - global positioning system

GEE - generalised estimating equation

GL - generalized linear

GP - general practitioner

GRID - governance registration information document

HAH - hospital at home

HAI - hospital acquired Infection

HAP - hospital acquired pneumonia

HES - hospital episode statistics

HF - home first

HIV - human immunodeficiency virus

HOME FIRST - home followed up with infection respiratory support team

HR - heart rate

ICD-10 - international statistical classification of diseases and related health problems 10th revision

ICE - results checking system at RLBUHT

ID - infectious disease

IE - infective exacerbation

IHD - ischaemic heart disease

ICT - immunochromatographic membrane test

ICO - information commissioner

INR - international normalised ratio

ITT - intention-to-treat

IMP - investigational medicinal product

IPD - invasive pneumococcal disease

IRAS - integrated research application system

ISRCTN - international standard randomised controlled trials no.

IV - intravenous

JCVI - joint committee and vaccines and immunisations

JRO - joint research office

LHP - liverpool health partnership

LOHS - length of hospital stay

LOS - length of stay

LRTI - lower respiratory tract infection

LSTM - liverpool school of tropical medicine

LTOT - long term oxygen therapy

MDT - multi-disciplinary team

MHRA - medicines and healthcare products regulatory authority

MI - myocardial infarction

MOP - manual of procedures

MRI - Manchester royal infirmary

MRSA - methicillin-resistant staphylococcus aureus

MTA - materials transfer agreement

NCT - national clinical trials

NHS - national health service

NHSLA - NHS litigation authority

NIHR - national institute of health research

NOK - next of kin

NSTEMI - non-ST elevation myocardial infarction

NVT - non-vaccine type (serotype)

NW - nasal wash

NW LRTI study - nasal wash and lower respiratory tract infection study - Chapter 4

O2 - oxygen

O2 sats - oxygen saturations (%)

OM - otitis media

OPA - outpatient appointment

OPA - opsonophagocytic assay

OR - odds ratio

OT - occupational therapy/ist

PCV - pneumococcal conjugate vaccine

PCV EHPC study - pneumococcal conjugate vaccine and experimental human pneumococcal carriage study

PE - pulmonary embolus

PI - primary investigator

PIL - patient information leaflet

po - oral route (for medications)

PPI - patient and public engagement

PPV - polysaccharide pneumococcal vaccine

PSI - pneumonia severity index

PU - pass urine

qPCR - quantitative polymerase chain reaction

RCT - randomised controlled trial

RD&I - research, development and innovation department

REC - research and ethics committee

RECRI - functional recovery from respiratory tract infection

RGT - research governance team

RLBUHT - royal liverpool and broadgreen hospital trust

RR - respiratory rate

SAE - serious adverse event

SBP - systolic blood pressure

SD - standard deviation

SF-12 - functional and quality of life assessment tool (short form-12) questionnaire

SHC - standard hospital care

sIMPD - simplified IMP dossier

SmPC - summary of product characteristics

SOAR – pneumonia scoring system (systemic blood pressure, oxygen saturations, age and respiratory rate)

SOP - standard operating protocols

SSIF - site specific information form

SUSAR - suspected unexpected serious adverse reactions

T.D.S - three times per day (for medication)

TOPS - the over-volunteering protection system

ToR - terms of reference

tCTU - tropical clinical trials unit

TSC - trial steering committee

TTO - to take out (dispensed medication)

U&Es - urea and electrolytes

UHA - university hospital aintree

UHSM - university hospital south Manchester

UK - united kingdom

UKRN - UK research network

URTI - upper respiratory tract infection

VT - vaccine (sero)type

WCC - white cell count

WHO - world health organisation

WOCBP - women of child-bearing potential.

# Abstract

## Introduction

Lower Respiratory Tract Infection (LRTI) and pneumonia are leading causes of death in the UK and costly health problems to the NHS. The aetiological pathogen is rarely found making targeted therapy difficult, hospital bed pressures are growing year on year and our current vaccinations are sub-optimal.

## Key questions

Current UK priorities include 1) Better diagnostics - without knowing the causal pathogen we cannot treat our patients effectively nor determine what pathogen to develop better vaccines against. Could nasal samples from hospitalised patients with LRTI/pneumonia be useful in aetiological diagnosis? 2) Better therapeutics – acute hospital bed pressures and hospital acquired infections rates are increasing. Could hospitalised patients with LRTI/pneumonia be discharged home sooner by support and treatment in the community from an early supported discharge scheme (ESDS)? 3) Better prevention – current pneumonia vaccines are inadequate. Could a new experimental model in humans using live pneumococcal bacteria help us to select from candidate pneumococcal vaccines?

## Main findings

We found that prior antibiotic treatment meant that nasal sampling in hospitalised patients was not useful. ESDS is safe and reduces the total hospital bed days with high rates of patient and carer/next of kin satisfaction. A large recruitment effort is needed. Using our Experimental Human Pneumococcal Carriage (EHPC) model confirmed that the current pneumococcal vaccine reduces rates of pneumococcal acquisition and carriage density.

**Implications**

A community based study of nasal sampling techniques in patients with LRTI/pneumonia prior to antibiotic therapy may be useful. An ESDS is worthwhile but needs better integration within well-established CCG-funded chronic obstructive pulmonary disease (COPD) schemes to form a 'Respiratory ESDS' and a national multi-site RCT trial. Our robust EHPC model can now be used to test novel candidate vaccines using a smaller sample size and shorter timescales than clinical community studies in order to reduce cost and time to market

# CHAPTER 1: Introduction

## 1.1 Burden of Pneumonia and Lower Respiratory Tract Infection (LRTI)

In the developed world pneumonia and lower respiratory tract infection (LRTI) remain a common cause of GP consultation, hospital admission and death (1). Acute respiratory illness is the most common reason for consulting a GP in the UK. In the adult population, the annual incidence is 5–11/1000 population with 22–42% admitted to hospital and 5–10% requiring intensive care management. CAP and LRTI are major causes of hospital admission worldwide and admission rates continue to rise (2). In the UK, they are important health problems that are very costly to the NHS. In England from 2009-10 there were ≥ 260,000 admissions with pneumonia, influenza and LRTI combined; more admissions than ischaemic heart disease and with 2.3 million bed days annually; more bed days than cerebrovascular disease (3). Mortality rates are high with over 66 000 people dying from pneumonia and influenza in the UK in 1999 (4).

In Europe, pneumonia costs over €10 billion annually with inpatient care accounting for €5.7 billion, outpatient care €0.5 billion and drugs €0.2 billion (5). In the USA, 90% of CAP

expenditure relates to the cost of in-patient care (6). In the UK, direct CAP health care costs in 1992-3 were £441 million annually (7).

Major risk groups include children, the elderly, the immunocompromised (HIV) and those with co-morbidities. This thesis concentrates on the general adult population including those ≥65 yrs olds and with co-morbidities.

In the UK, CAP mostly affects the older population (5) with the median age being 76yrs old and two-thirds over 65yrs old (7). The annual incidence is up to 22.4/1000 in those over 85 years old (8). The elderly may present later to medical services or have delayed diagnosis due to altered clinical and physical signs (9); their clinical disease course may also differ from younger adults. Elderly patients presenting with severe pneumonia, poor pre-morbid functional status and with recent antibiotic exposure have increased risk of multi-resistant organisms (10). It has been reported that 2-year mortality was independently related to severe co-morbidity but not to age (11). The number of elderly admissions in particular is an increasing burden on health resources (12) and in such patients hospital admission may in fact be more detrimental than care in their own residence (13). Over the next decade, the incidence of CAP will increase further as the population ages; as will the associated co-morbidities (14).

Between 25-70% of cases of pneumonia are caused by *Streptococcus pneumoniae* also known as pneumococcus (15) (16); reported rates vary dependent on diagnostic tests and geographical region (17). In the USA, there were approximately 570 000 confirmed pneumococcal pneumonia cases accounting for over 175 000 hospitalisations (18). Mortality rates from pneumococcal pneumonia can exceed 20% (19). The high clinical and econoburden

(5) and increasing incidence of antibiotic resistance make the need for pneumonia prevention even more urgent (20).

## 1.2 Current Priorities in Pneumonia and LRTI

There has been no significant reduction in age standardised mortality rates for pneumonia in the last 25 years (21). Reducing respiratory mortality is a key target of the UK DoH. Since 50% of antibiotics used in the community are for respiratory tract infections (22, 23), the threat of antimicrobial resistance is clear (24). To improve clinical outcomes current priorities in pneumonia and LRTI care in the UK are: 1. Better diagnostics - in order to aid a reduction in antibiotic use or duration of use to reduce the threat of antimicrobial resistance; 2. Reducing morbidity and mortality - early diagnosis and tailored treatment, 'where for care' (reducing hospital length of stay, hospital acquired infection and costs) and care bundles; 3. Pneumonia prevention - through improved pneumococcal vaccinations to protect against pneumonia and LRTI.

This thesis concentrates on:

- Diagnostics - can nasal pneumococcal carriage/ colonisation be used as a means to increase diagnostic precision in patients with LRTI and therefore potentially reduce antibiotic usage? Personalised diagnosis and therapy for the individual.
- Therapeutics - 'where for care'. Can an early supported discharge scheme for patients with LRTI reduce hospital length of stay and costs? Personalised care for the individual.
- Prevention - a new model for testing novel pneumococcal vaccinations. Can an experimental pneumococcal carriage model be used to select from novel candidate

vaccines in order to reduce development costs and time to market? Personalised vaccination for the individual.

### 1.2.1 Diagnostics for Pneumonia and LRTI

#### 1.2.1.1 Definitions - What are Pneumonia and LRTI?

The definitions of both pneumonia and lower respiratory tract infection (LRTI) vary significantly in current literature and clinical practice.

##### 1.2.1.1.1 Pneumonia

Pneumonia is inflammation of lung tissue which is due usually to infection with bacteria, viruses or fungi. Pneumonia presents as an acute illness and can range from a mild illness to a severe life-threatening disease. Although the disease can occur in young and healthy people, it is more common and serious in children, the elderly, the immunocompromised and those with co-morbidities. Pneumonia is pathologically characterised primarily by alveolar inflammation or by alveoli that are filled with fluid.

The classical definition of pneumonia is: symptoms/syndrome of respiratory infection (cough, fever, sweats, sputum, breathlessness, chest pain) with clinical signs / radiological consolidation [either on chest radiograph (CXR) or thoracic computerised tomography (20) (25)]. The definition of CAP may differ depending on whether the setting is primary or secondary care. In primary care, UK GPs do not have the benefit of immediate investigations or radiology, and therefore the diagnosis is often based on clinical features only (7). In community studies the clinical definition of CAP varies widely (7). In the BTS guidelines, (7) CAP in primary care is defined as:

- Symptoms of an acute lower respiratory tract illness (cough and ≥1 other lower respiratory tract symptom)
- New focal chest signs on examination
- At least one systemic feature (either a symptom complex of sweating, fevers, shivers, aches and pains +/- temperature of ≥38°C)
- No other explanation for the illness.

In secondary care CAP is defined in BTS guidelines as (7):

- Symptoms and signs consistent with an acute lower respiratory tract infection (LRTI) associated with new radiographic shadowing for which there is no other explanation (e.g. not pulmonary oedema or infarction)
- The illness is the primary reason for hospital admission.

NICE guidelines use the terms CAP and clinical diagnosis of CAP (26). These are defined as:

- Clinical diagnosis of CAP - Diagnosis based on symptoms and signs of LRTI in a patient who, in the opinion of the GP and in the absence of a CXR, is likely to have CAP. This might be because of the presence of focal chest signs, illness severity or other features. They suggest that this approach in the community has been shown to be both pragmatic and sensible as focal signs correlate strongly with radiological changes.
- CAP - Pneumonia that is acquired outside hospital. When managed in hospital the diagnosis is usually confirmed by CXR. Pneumonia that develops in a nursing home resident is included in this definition.

Hospital-acquired pneumonia (HAP) is defined as pneumonia that develops ≥48 hours or more after hospital admission and that was not incubating at hospital admission.

Only 5-12% of patients in primary care have radiographic pneumonia and 50% of those patients with CXR changes recover without antibiotic therapy (27). In primary care, sputum production, dyspnoea, fever >38$^{o}$C, HR >100bpm, decreased breath sounds, coarse crackles and progression of symptoms after 5 days significantly increased the likelihood of the diagnosis being CAP rather than acute bronchitis (termed LRTI in this thesis) (28). The reported duration of acute bronchitis is around 7 days (29, 30). If a patient does in fact have CAP they are likely deteriorate after several days in the absence of antibiotic treatment. Whilst delaying antibiotic therapy in CAP in primary care may alter recovery speed or duration and potentially increase the risk of bronchiectasis, it does reduce the risk of unnecessary antibiotic prescription for those with simple LRTI. CXR is therefore mostly used in primary care to identify complications (e.g. pleural effusion) or find underlying pathology (e.g. cancer) rather than to diagnose.

#### 1.2.1.1.2 LRTI

LRTI may be used as an 'umbrella term' encompassing infective alveolitis, infective pneumonitis, acute bronchitis, bronchiolitis, tracheitis, tracheobronchitis (all often self-limiting and not requiring antibiotics) and pneumonia. LRTI may be defined as symptoms of respiratory infection with clinical signs (crackles on auscultation) with and without radiological consolidation (31). The 2014 NICE pneumonia guidelines (26) define LRTI as an acute illness (present for 21 days or less), usually with cough as the main symptom, and with at least 1 other lower respiratory tract symptom (such as fever, sputum production, breathlessness, wheeze or chest discomfort or pain) and no alternative explanation (such as

sinusitis or asthma). Pneumonia, acute bronchitis and exacerbation of chronic obstructive airways disease are included in this definition. Upper respiratory tract infection (URTI) is more clearly defined and encompasses the common cold, epiglottitis and laryngitis.

#### 1.2.1.2 Diagnostic Difficulties

There are significant difficulties in diagnosing pneumonia due to varied nomenclature and definitions; particularly when the diagnosis requires a radiological interpretation. This varied nomenclature may hinder research into new diagnostics as well as treatment, management and prognostication. Where the definition requires radiological consolidation, CXR has a high specificity but low sensitivity for CAP, since CXR changes may lag behind the onset of clinical symptoms and can worsen despite an improving clinical picture. In a large case series of hospitalised patients with clinical features of CAP, one third (n=911) had no consolidation on CXR, and no significant mortality difference was noted between groups with or without CXR consolidation (9). Arguably the relevance of the diagnostic term may be less important than assessing severity of the respiratory infection and therefore prognostic risk stratification, treatment options and who will deteriorate and require hospital admission or develop complications.

In this thesis the term 'LRTI' encompasses patients with symptoms of an acute lower respiratory tract infection both with or without pneumonic radiological consolidation and infiltration, as well as those with CAP [BTS definition in secondary care (7)] and HAP (defined as presenting within 14 days of hospital discharge or ≥ 48 hrs after hospital admission).

Since the most common aetiological pathogen causing pneumonia is the pneumococcus, (5, 9) effective prevention and treatment is a top international priority.

### 1.2.1.3 Pneumococcal Pneumonia

*Streptococcus pneumoniae* is an encapsulated Gram positive diplococcus. There are over 90 structurally and serologically distinct pneumococcal strains or serotypes. The serotype is determined by the capsule; this is the outermost layer of the cell and is made of repeating units of simple sugars. The pneumococcus can cause a spectrum of diseases including invasive (organism isolated from a normally sterile site such as CSF [meningitis], blood [bacteraemic pneumonia]) and mucosal [otitis media, sinusitis, pneumonia] disease. Figure 1 demonstrates the inverse relationship between the frequency and severity of pneumococcal disease/carriage (colonisation).

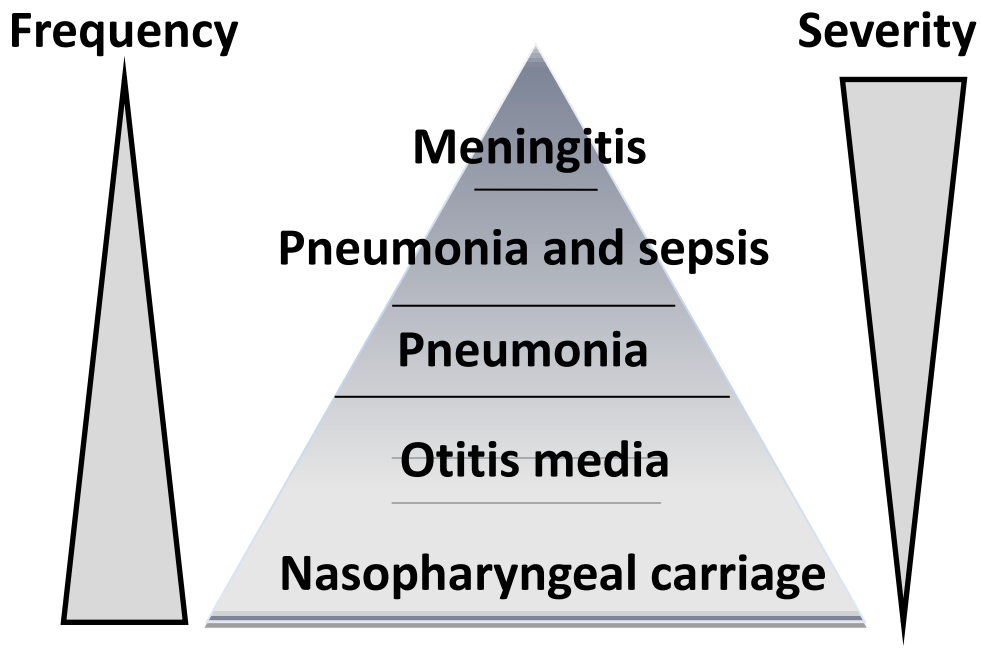


**Figure 1: The Burden of Pneumococcal Disease and Carriage/Colonisation**

(32, 33).

### 1.2.1.4 Microbiological Diagnosis of Pneumococcal Pneumonia

#### 1.2.1.4.1 Overview

Effective management and treatment of pneumococcal pneumonia is hampered by the difficulty in accurately diagnosing (34). Microbiological diagnosis to confirm the pathogen in patients with pneumonia and LRTI remains poor; with no causal micro-organism found in the majority of patients (35, 36). In a US study of >2000 patients with radiographic evidence of pneumonia, a pathogen (viral or bacterial) was detected in only 38%. Indeed, the most common pathogen found was human rhinovirus - 9% and influenza virus - 6% with *Streptococcus pneumoniae* found in only 5%. This is much lower than the commonly quoted '50%' of pneumonia that is thought to be pneumococcal in aetiology (37). In a local pneumonia study in Liverpool only 8 of 155 (5%) patients were pneumococcal positive (by blood culture or sputum) (38). Most epidemiological studies instead report the incidence of bacteraemic or invasive pneumococcal disease (IPD); grossly underestimating the true pneumococcal pneumonia burden in adults (39). For every case of bacteraemic pneumococcal pneumonia, it has been estimated that there are at least 3 additional cases of non-bacteraemic pneumococcal pneumonia (39).

Traditional aetiological tests require a clinical sample (pleural fluid, blood, nasal swab, sputum) to be cultured, a result is usually obtained after 2-3 days. Guidance suggests that clinicians should administer empirical broad-spectrum antibiotics as soon as possible to patients with suspected pneumonia. Unfortunately, this approach affects the yield of these diagnostic tests and leads to complications related to broad-spectrum antibiotic use (40). Antigen detection tests are available for *Streptococcus pneumoniae*. UK guidelines recommend their use for all severe CAP cases. Multiplex quantitative polymerase chain

reaction (qPCR) tests could potentially greatly improve the speed and precision of microbiological diagnosis in pneumonia and LRTI (41).

#### 1.2.1.4.2 Quantitative Polymerase Chain Reaction (qPCR)

Rapid pre-antibiotic aetiological tests could mean more appropriate and targeted antibiotic therapy resulting in decreased antibiotic use and resistance, reduced antibiotic-related complications and a reduction in repeat appointments in primary care and hospital length of stay (26). Unlike classical microbiological culture, real time (rt)-qPCR can deliver results within a few hours (2-6hrs usually), thereby meaning there is potential for this test to have an impact on the critical phase of early clinical care (42).

Rt-qPCR may also have prognostic utility. High pneumococcal load in blood has been associated with septic shock (OR 8.00) and mortality (OR 5.43) in patients with CAP (42, 43) [Figure 2].

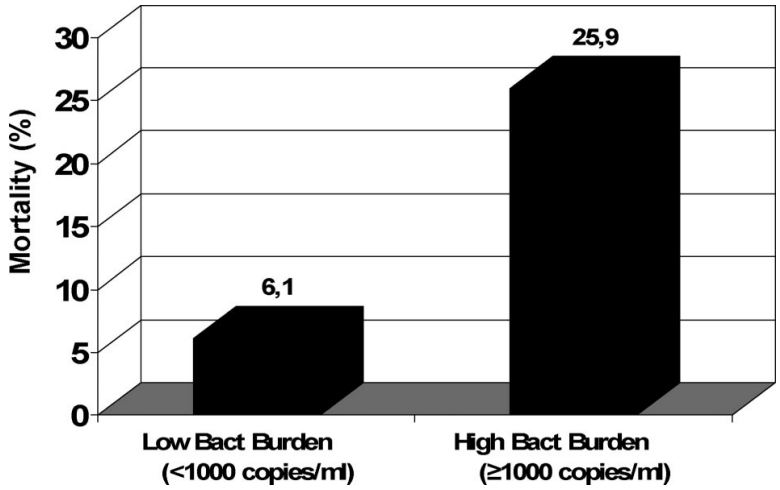


**Figure 2: Pneumococcal Pneumonia Mortality Rate and rt-qPCR Pneumococcal Load**

(42)

CAP severity (as defined by PSI, CURB-65, ICU admission, in-hospital death and admission duration) has been shown to correlate with pneumococcal presence and load/density in serum but not in urine or sputum, using qPCR. In sputum, qPCR shows increased sensitivity compared to classical culture (34). qPCR positive sputum was less common in patients that had received antibiotics prior to hospitalisation (OR 0.52), there was no effect in serum or urine. This study showed no association between bacterial density/load and prior antibiotic therapy whilst another noted lower bacterial density (plasma/pleural fluid) with prior antibiotic therapy (44).

In a South African study of predominantly HIV infected patients with CAP (27% pneumococcal positive on composite diagnostic testing - blood and sputum culture, Gram stain and urine Binax), those with CAP were more frequently nasally colonised than controls (44.9 v 11.7% using classical culture and 62.8 v 19.8% using *lytA* rt-*q*PCR). HIV-infected patients with CAP with positive composite diagnostic tests for pneumococcus had higher density on nasopharyngeal swabs than those without pneumococcus identified on composite testing. The higher the density the more likely the HIV-infected patient with CAP was to be pneumococcal positive on composite testing (45). The authors suggest that adding nasal qPCR bacterial load to pneumonia scoring systems may improve risk stratification to allow a more accurate determination of an individual's clinical outcome (42).

The sensitivity of qPCR is difficult to define since there is no 'gold standard' available. The *LytA* gene is thought to be present in most, if not all pneumococcal serotypes (46). While false positives may still occur however due to non-pneumococcal strains that contain the *LytA* gene (47), *LytA* is more sensitive than *Ply* qPCR (46). It is important to note that if pneumococcus is

found using qPCR it may be difficult to identify if it is indeed a pathogen or simply a coloniser (46, 48), since this technique detects both viable (live) and non-viable (dead) bacteria.

The main challenge in primary care is which of the many patients who currently receive antibiotics do not need them. Antibiotic use in the community for respiratory tract infections is very high. Fifty percent of antibiotics used in the community are for respiratory tract infections and some 70% of patients presenting with acute LRTI symptoms are given antibiotics (22, 23). In most cases antibiotic use is neither warranted nor associated with any known significant benefit (49) (50). There are no adequately powered studies to develop prediction rules for adverse health outcomes in patients in the community with non-pneumonic LRTI which could help to restrict antibiotic treatment to high risk patients only (51). If a clinical diagnosis of CAP is likely, antibiotics should be commenced as soon as possible as this is associated with improved 30-day mortality (52). A 'point-of-care' test (rtPCR) using nasal samples could potentially help make a more accurate diagnosis (of pneumococcal pneumonia) and therefore lead to implementation of a more focused and efficient management strategy allowing more targeted antibiotic therapy (53) both in the community and in hospital practice.

#### 1.2.1.4 Pneumococcal Carriage

##### 1.2.1.4.1 Carriage in Health

Pneumococcal disease is preceded by colonisation of the nasopharynx of uninfected adults and children (54). Nasopharyngeal carriage is thought to be both the source of horizontal spread (transmission) within the community and the source of disease. Children are believed to be the main source of transmission due to their higher frequency (and density) colonisation and higher 'crowding' index (55).

Smoking and crowding are known to effect the nasopharyngeal niche and both increase the rate of carriage (56). The risk of horizontal spread is increased by overcrowding (nursery, prison, hospital) (57-60). Factors including being at the extremes of age, having lower immune status, greater household density, biomass and smoke exposure, lower nutritional status and socio-economic conditions or contact with young children increase carriage rates therefore disease rate (57, 60-66).

Pneumococcal carriage rates vary greatly. Rates ranging from 11-70% (16, 67, 68) are seen in healthy children. Carriage rates are ~10% in the first few months of life to a maximum of ~50% at 3-4 years old declining again to adult rates by the age of 10 years old (69). In adults in developed countries rates range from 1-10% (70, 71). Rates of carriage in those adults without pre-school children in the family are 2-9% and in those with pre-school children are 18% and in the pre-schoolers themselves are 35-54% (70, 71). Carriage episodes occur earlier in low income countries (Figure 3) but in developed countries <50% of children experience their first carriage episode in their first year of life (71).

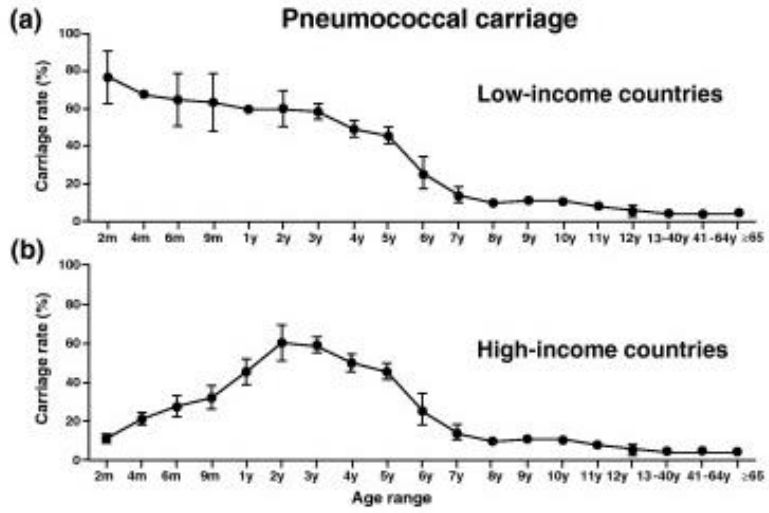


**Figure 3: Population and Carriage Rates in an Israeli Study of Pneumococcal Carriage**

(71)

Carriage rates of 4.6% (n=195) were noted in the elderly (age >65yrs old) in Israel (71) but <1% (n=315) in hospitalised elderly in Australia (72) (10 had respiratory infection at the time of nasal swab).

The duration of carriage varies with age and pneumococcal serotype (73, 74). It has been suggested that the low carriage rates seen in adults may in fact be due to shorter duration of carriage meaning that point estimates are lower, rather than a lack of carriage entirely (75). Studies have shown the younger the infant was at the time of acquisition, the longer a strain is carried for (76, 77).

#### 1.2.1.4.2 Pneumococcal Carriage and Respiratory Infection

Pneumococcal colonisation rates tend to be higher during respiratory tract infection and otitis media. In Chinese children, more frequent pneumococcal colonisation was detected in those with pneumonia than without (78). Vietnamese children with pneumonia had higher density colonisation than those with bronchitis or healthy children (79). An increased nasal pneumococcal PCR load was associated with radiologically confirmed pneumonia, viral co-infection, and presence of pneumococcal capsule in Vietnamese children aged <5yrs old (patients with pneumonia n=274 v with LRTI n=276) (80). This may support the theory of greater adherence during (viral) infections (62) or higher pneumococcal density during infection meaning greater detection. With rising burden of organisms in the nasopharynx at a critical colonisation density, it is believed that the risk of micro-aspiration and therefore pneumonia increases (81, 82).

There is no data on pneumococcal carriage in hospitalised patients with respiratory infection in the UK. It is possible that the UK population could show either the high carriage seen in

South Africa and Vietnam or more likely the low carriage rates seen in Australia. Knowledge of pneumococcal carriage in a population of hospitalised patients with respiratory infection could improve the care of patients with LRTI by increasing understanding about potential new microbiological diagnostic tests (nasal wash, NPS) for these patients and result in more targeted and accurate antibiotic therapy reducing the prescription of unnecessary antibiotics (45). Earlier accurate treatment may reduce the risk of developing more severe disease that could result in hospital admission +/- more prolonged hospital LOS.

#### 1.2.1.4.3 Pneumococcal Carriage and Host Immunity

Children have increased carriage rates and increased disease however it is not clear why the elderly have increased disease but low carriage rates. It is possible that in the elderly a failure to establish occasional pneumococcal carriage (due to defective mucosal T cell function) leads to a loss of the immunising function of carriage and hence increased susceptibility to disease.

It is hypothesised that persistent and recurrent colonisation (and therefore potentially infection) may be due to a poor mucosal immune response, where as a brisk local mucosal immune response may eliminate colonisation (clearance) and protect against re-colonisation and therefore disease (61, 83). Most episodes of carriage result in improved immunity to future infection without the development of disease. Our group has shown for the first time that pneumococcal carriage in adults is an immunising event and induces protective immunity against pneumococcal re-challenge (84-86) (87, 88).

### 1.2.2 Therapeutics

#### 1.2.2.1 Risk Stratification

Arguably assessing disease severity and therefore appropriately risk stratifying (ideally informing prognosis, morbidity and mortality), using optimal treatment strategies and providing best patient care is more important than making a diagnosis. Scoring systems are used to prognosticate by defining mortality risk and consequently the need for hospital admission. Such prognostic models offer an objective complementary assessment of disease severity and are not recommended for exclusive use, hence the caveat of always incorporating clinical judgement (89).

Hospital LOS for CAP has reduced over recent years mainly due to increased use of pneumonia severity scores (e.g. CURB-65, CRB-65 and PSI [Pneumonia Severity Index]) (90). The pneumonia severity scoring systems use initial admission data to predict mortality; they are used to aid clinical decision-making about 'best place of care' for the individual. For community LRTI patients there are no adequately powered studies allowing prediction of adverse health outcomes. Such studies could help to restrict antibiotic treatment to high risk patients only (51). Below the different scoring systems are described in more detail.

**CURB-65:** The patient gains one point for confusion, urea >7mmol/l, respiratory rate ≥30 SBP <90mmHg, DBP ≤60mmHg and age ≥65.

The 30 day mortality rates are CURB-65 0 - 0.6%, 1 - 2.7%, 2 - 6.8%, 3 - 14.0%, 4 or 5 - 27.8%. CURB-65 is used to aid clinical decision making with regards to place of care:

- 0-1: Treat as an outpatient, do not normally require hospitalisation for clinical reasons

- 2: Consider a short stay in hospital or watch closely as an outpatient
- 3-5: Requires hospitalisation and consider need for intensive care unit.

**CRB-65:** In this score, the patient gains one point for confusion (recent), respiratory rate ≥30 SBP <90mmHg, DBP ≤60mmHg and age ≥65. Essentially CRB-65 is the same as CURB-65 but without the urea. It is used to aid clinical decision making with regards to place of care:

- 0: Treat as an outpatient, do not normally require hospitalisation for clinical reasons
- 1-2: Consider hospital referral and assessment
- 3-5: Require urgent hospitalisation.

**SOAR:** This is used for patients in a nursing home with pneumonia to assess best place of care. It modified the CURB-65 by removing confusion and urea and adding in PaO2. One point for Partial arterial oxygen pressure to FIO2 ratio (PaO2/FIO2 ratio) <250, Respiratory rate ≥30, SBP <90mmHg, DBP ≤60mmHg and age≥65. SOAR is used to aid clinical decision making with regards to place of care:

- 0-1: Outpatient management (30-day mortality <8%)
- 2 or more: Inpatient management (30-day mortality 33%)

**PSI (Pneumonia Severity Index)**

The PSI is the most complicated of all the severity scores: It uses the following parameters:

| | |
|---|---|
| **Age** | |
| **Gender** | -10 for female, 0 for male |
| **Nursing home resident** | +10 for yes, 0 for no |
| **Neoplastic disease** | 0 for no, +30 for yes |
| **Liver disease history** | 0 for no, +10 for yes |
| **CHF history** | 0 for no, +10 for yes |
| **Cerebrovascular disease history** | 0 for no, +10 for yes |
| **Renal disease history** | 0 for no, +10 for yes |
| **Altered mental status** | 0 for no, +20 for yes |
| **Respiratory rate > 29** | 0 for no, +20 for yes |
| **Systolic blood pressure < 90 mmHg** | 0 for no, +20 for yes |
| **Temperature < 35C or > 39.9C** | 0 for no, +15 for yes |
| **Pulse > 124** | 0 for no, +10 for yes |
| **pH < 7.35** | 0 for no, +30 for yes |
| **Urea > 29** | 0 for no, +20 for yes |
| **Sodium < 130** | 0 for no, +20 for yes |
| **Glucose > 13.8** | 0 for no, +10 for yes |
| **Haematocrit < 30%** | 0 for no, +10 for yes |
| **Partial pressure of oxygen < 60 mmHg** | 0 for no, +10 for yes |
| **Pleural effusion on x-ray** | 0 for no, +10 for yes |

Step 1:

- If the patient is >50 years of age, assign to risk class II - V and proceed to step 2.
- If the patient is <50 years of age, but has a history of neoplastic disease, congestive heart failure, cerebrovascular disease, renal disease or liver disease, assign to risk class II - V and proceed to step 2.
- If the patient has an altered mental status, pulse ≥ 125/minute, respiratory rate ≥ 30/minute, systolic blood pressure ≤ 90 mm Hg, or temperature < 35° C or ≥ 40° C, assign to risk class II - V and proceed to step 2
- If none of the above apply, assign to risk class I = low risk.

Step 2:

- Assign points based on age, gender, nursing home residence, co-morbid illness, physical examination findings, and laboratory and radiographic findings as listed above.
- Place of care: ≤70 points = low risk therefore outpatient care. 71-90 points = low risk therefore outpatient or admit for observation. 91-130 points = moderate risk therefore inpatient admission. >130 points = high risk therefore inpatient admission.

All the scoring systems have limitations. In community settings CRB-65 may over-predict 30-day mortality, potentially leading to more hospital admissions (91). PSI was developed and validated to identify patients with a low mortality risk who could be safely managed out of hospital but it may potentially underestimate illness severity, especially in young patients without co-morbidities who have abnormal vital signs; whilst overestimating the mortality risk in older patients (as it is heavily age-weighted) with minimal acute disease process but a

high frequency of stable co-morbidities (92). CURB-65 on the other hand may be ideal for identifying patients with a high mortality risk because of acute vital sign derangement who may otherwise be overlooked but can underestimate disease severity in younger patients with subtle vital sign abnormalities and decompensated co-morbid illness. CURB-65 appears to have a higher sensitivity for predicting mortality (93). Another approach in the elderly is SOAR (94) which omits urea and confusion; common in the elderly. PSI and CURB-65 both show a progressive decline in the predictive power for 30-day mortality with increasing patient age (93). Age, in fact, has little impact on mortality after correcting for disease severity variables using PSI, indeed removing age from PSI and CURB-65 does not alter the tools' predictive value; one solution may be much higher age cut-off values. Given that all severity scores have advantages and disadvantages we decided to use CURB-65 for studies in this thesis since it is the most commonly used score in UK hospitals and is easy and simple to use.

The optimum time for a patient to be discharged from hospital is difficult to determine. Pneumonia severity scores are useful to guide the 'best place of care' thereby reducing hospital admissions, but do not assist the clinician is determining 'best time for hospital discharge' – it is instead vital to assess clinical improvement/ stability and response to treatment. BTS guidelines for the discharge of patients with CAP state that patients suitable for discharge should demonstrate clinical stability and '*usually not more than one* of the following – temperature >37.8$^{o}$C, HR >100bpm, RR >24bpm, Systolic BP (SBP) <90mmHg, oxygen ($O_2$) saturations (sats) <90%, inability for oral (po) intake, altered mental state' (95). In 2014, after the projects in this thesis were completed, the 2014 NICE pneumonia guidelines were published recommending that patients with CAP should not 'routinely' be discharged if in the past 24 hours they have had 2 or more of the above findings, temperature > 37.5°C

rather than >37.8 ºC in the BTS recommendations (26). $O_2$ sats ≤90% have good specificity but low sensitivity for adverse outcomes in CAP. $O_2$ sats are more useful in patients with asthma and those aged <50 years old at predicting adverse outcomes but less reliable in nursing home residents and patients with COPD.

### 1.2.2.2 Therapeutics

#### 1.2.2.2.1 Hospital at Home in General

With increasing bed pressures on acute hospital trusts, Hospital at Home (HAH) schemes and innovations that reduce the demand for beds have become increasingly popular (96). Inappropriate hospitals admissions and prolonged hospital stay contribute to the increased risk of hospital-acquired infections (HAI) such as MRSA, *Clostridium difficile* diarrhoea and hospital-acquired pneumonia (HAP).

HAH is defined as a service where active treatment is provided by healthcare professionals in the patient's residence for a condition that otherwise would require acute hospital in-patient care, for a limited time period (97). HAH schemes are commonly divided into admission avoidance [AA] (avoiding hospital admission entirely) and early supported discharge [ESDS], i.e. discharging patients from hospital earlier than standard care thereby reducing hospital LOS. The development of HAH services allows more patients to be managed outside of acute hospitals (98).

The concept of HAH originated with 'Hospitalisation a Domicile' in France in 1961 (99), an idea that many other countries have now adopted. HAH schemes vary in their conformation, disease focus and level of care. In the UK, HAH schemes tend to focus on providing a personal, nurse-led care rather than technical services. HAH schemes exist for COPD, stroke, heart

failure and post-operative patients. However in other countries, such as USA, home intravenous drug administration and blood transfusion is common place (100). Interpreting the function of services in different healthcare systems is not always straightforward. Patient-related outcomes as well as economic outcomes are critical in the efficacy assessment of HAH services.

The concept of HAH is clearly consistent with current strategic NHS policies and the stated objectives and strategies of national research organisations (NIHR/MRC strategy for public health infection research). QIPP (Quality, Innovation, Prevention(s) and Productivity) is a strategy that seeks to improve clinical outcomes and experience for patients and to maximise resource use. QIPP aims to reduce unscheduled hospital admissions by 20%, reduce hospital LOS by 25% and maximise the number of patients controlling their own disease through systematic knowledge transfer and care planning (101). The NHS Outcomes Framework (2011/12) states that it is of paramount importance that we provide safe and effective treatment and care (measured by clinical and patient-reported outcomes) (102). HAH schemes have good fit with the reforms in the current *White Paper* that state we should 'aim to provide the NHS with greater incentives to increase efficiency and quality' and state that 'patient choice will reward the most efficient, high quality services; reducing expenditure on less efficient care' (103).

The success of HAH schemes for acute exacerbations of chronic obstructive pulmonary disease (COPD) in many countries suggests both potential economic and patient and carer benefits (97, 104). It would seem appropriate therefore that such schemes could encompass patients with respiratory infection (with or without underlying chronic respiratory disease). Some patients with bronchiectasis are already discharged from hospital to home intravenous

(IV) antibiotic teams who are often supported by district nurses/community matrons. Patients with acute pneumonia/LRTI could potentially be managed at home safely.

#### 1.2.2.2.2 Hospital at Home for LRTI/ Pneumonia

Pneumonia and LRTI are common and costly health problems to the NHS: They are responsible for more admissions than ischaemic heart disease and more bed days than cerebrovascular disease (3). Despite the fact that ~75% of community acquired pneumonia (CAP) is managed in the community. In Europe and the USA, 57% and 90% of pneumonia/CAP expenditure relates to the cost of in-patient care (5) (6). Reduction of this resource burden is an international priority. Choudhury et al suggested that more patients (18-20%) could be managed at home by family practitioners with application of current guidelines. With the provision of medical support at home many more patients could be managed as outpatients (98, 105, 106).

Strategies to enable increased outpatient care must be safe, acceptable to patients & potentially reduce costs & improve patient outcomes. In a recent meta-analysis, no significant differences in patient satisfaction, mortality or hospital re-admission rates were noted with out-patient care and admission avoidance schemes were considered potentially useful (107).

Earlier discharge and admission avoidance for patients with respiratory infection has become increasingly common but the evidence base in pneumonia and LRTI is very limited (108). A recent meta-analysis suggested that emergency departments should be encouraged to develop strategies to manage more even patients within the community (107).

Despite the widespread adoption of clinical decision tools, a significant proportion of patients admitted with CAP are low-risk (7) but account for a significant proportion of bed days and

costs (106). In community settings, CRB-65 scoring may over-predict the probability of 30-day mortality, potentially leading to more hospital admissions (91). Current guidelines suggest that only patients with CURB-65 >2 generally require hospitalisation, but up to 70% of pneumonia admissions are CURB-65 ≤2 (7).

The median LOS for CAP varies widely from 6 - 12.9 days (98). Physicians tend to over-estimate the likelihood of death from pneumonia (109) and there is large variability in rates and lengths of hospitalisation for patients with pneumonia across nearby geographical regions suggesting that criteria for hospital admission may be not only be uncertain and physician dependent but also dependent on socio-economic status and social support (106, 110, 111). Notably the risk of adverse outcomes (death, readmission rates, delayed return to work/usual activity) does not increase in hospitals with shorter LOS (106).

Despite the fact that most low-risk patients (according to severity score) could be managed as out-patients, factors other than disease severity often prompt or prolong hospital admission such to inability to take oral antibiotics, co-morbid illnesses, low socioeconomic status, homelessness, substance abuse or inability to cope at home alone (105),(112),(106),(90). One study showed that of 253 patients admitted to hospital, over 50% were potentially suitable for out-patient treatment based on 'appropriateness evaluation protocol criteria' for hospital admission. However, factors such as substance abuse and homelessness meant that only 20 patients (8% of all low-risk CAPs) were suitable for unsupervised out-patient treatment; the percentage that would have been suitable with supervision is not known (106). It is probable that with 'HAH style support' available more patients could be managed in the community by supporting them with the factors, other than disease severity, that often prompt or prolong the hospital admission (98). More evidence

regarding early supported discharge schemes (ESDS) to facilitate the discharge of patients with more complex needs is required (107).

Hospital discharge guidance for CAP patients exists (N.B – a patient is usually not discharged if more than one of the following) temperature>37.8$^{o}$C, HR>100 bpm, RR>24 bpm, SBP<90mmHg, saturations <90% on air, inability to intake orally and altered mental state (95, 113). Patients with respiratory infection often have co-morbidities which mean they do not have normal baseline observations i.e. they have increased RR and low saturations (88-92%). Hence using these parameters for discharge may not always be useful and a more pragmatic approach may be needed by the clinician to avoid an extended hospital length of stay (LOS).

The elderly in particular may benefit from HAH, since hospital admission (13) can lead to increased confusion and HAI (96),(114),(115). It has been reported that frail elderly patients with dementia cared for with HAH were less likely to be institutionalised at longer term follow-up. Hospital admission rates for CAP in this group are as high as 25-40%, with an inpatient mortality rate at 10% with even more dying within 1 - 6mths of discharge (116). Expert review suggests the need to investigate which elderly patients with CAP truly benefit from hospitalisation and states that supported home care for patients with CAP 'show enormous potential for improving the care of elderly and disabled patients, and should be further evaluated in terms of efficacy and cost-effectiveness' (117).

Patient satisfaction with HAH is high. An RCT from New Zealand, where both ESD and AA models were used, showed patient satisfaction improved by 40% ($p<0.001$) in those allocated to supported home care (118). A HAH scheme containing a mixed cohort of patients including those with respiratory illness (32% CAP, COPD 28%) reported increased patient satisfaction with HAH (96, 104). Evidence suggests that patient satisfaction is innately related to the

quality of communication and personal care received (119).Findings indicating increased satisfaction for patients allocated to HAH must be balanced against carers satisfaction. Carer satisfaction has been noted to be higher in the HAH group (119).

Evidence suggests that HAH is safe. A non-randomised Spanish study (specifically for CAP patients n=327) showed that whilst the majority (88%) of patients had low risk scores (CURB-65 0-1), patients with higher severity scores could also be safely cared for at home (120). There is no obvious increase in mortality or symptom severity or decline in functional status (118, 121). A meta-analysis on admission avoidance schemes showed that those allocated to HAH had significantly reduced risk of death at 6 months (104). Admission avoidance HAH services reduce hospital admission rates (96) but this may be at the cost of higher re-admission rates (104).

The potential economic benefits to a healthcare system are clear (97). HAH appears to be less expensive than SHC in the specific setting of the individual studies (118, 121) with this service configuration, although evidence for cost effectiveness internationally is clearly limited as is often difficult to compare costs between different healthcare systems and countries. Differences in the way that a service is structured, organised and delivered clearly affect cost (e.g. 24hr care v. once daily visits v. telephone support). A USA study estimated that a ½ day reduction in hospital LOS for CAP patients would generate a potential cost saving of $8500-8900 million annually or $457-846 per episode (based on median LOS 5.3 days and $13000 cost per hospitalisation and a CAP incidence of 1.9%/yr and 20% hospitalisation rate). This suggests that a relatively small decrease in hospital LOS may have a substantial economic impact (6).

### 1.2.3 Prevention

#### 1.2.3.1 Current Pneumococcal Vaccines

The pneumococcal capsule is the current vaccine target because it is the focus of the mature human immune response and it influences pathogen transmission (122), the epidemiology of infection (123) and disease virulence (124). Current pneumococcal vaccines have had great success in decreasing invasive pneumococcal disease (IPD) e.g. bacteraemia and meningitis, but do not confer optimal protection against mucosal disease e.g. non-bacteraemic pneumonia, sinusitis and otitis media, which account for the largest burden of disease. The limitations of the 23 valent polysaccharide vaccine (PPV-23) prompted the development of the conjugate vaccines (PCV).

#### 1.2.3.2 Polysaccharide Pneumococcal Vaccine

The 23-valent polysaccharide pneumococcal vaccination (23vPS/PPV-23 - *Pneumovax* II, Sanofi Pasteur MSD) was first introduced in 1983 (39). The 23 serotypes included in the vaccine account for over 90% of the prevalent disease serotypes in Western countries (125). Its use is currently recommended in most developed countries in those aged ≥65yrs old and in certain high-risk groups in both children aged ≥2yrs old and adults. In the UK, it is recommended as a one-off dose for ≥ 65yrs old. In the Netherlands, it is only recommended in certain high-risk individuals. PPV-23 provides protection against IPD but is less protective against pneumonia in adults (126) and is ineffective in young children. Pneumococcal polysaccharides are unable to bind with class II major histocompatibility complex and are therefore T cell independent antigens. Since long-term protective immune response in children require T cell help and the generation of immunological memory (which is achieved

by conjugating polysaccharide to a protein); the vaccine therefore offers little protection in children (Table 1).

**Table 1: The Properties of the Polysaccharide and Conjugate Vaccines with Regards to Immunity**

| **Property** | **Polysaccharide** | **Conjugate** |
|---|---|---|
| Immunogenicity age <2 yrs | N | Y |
| B-cell dependent immune response | Y | Y |
| T-cell dependent immune response | N | Y |
| Immune memory | N | Y |
| Booster effect | N | Y |
| Long term protection | N | Y |
| Reduction of carriage | N | Y |
| Herd protection | N | Y |
| IPD prevention | Y | Y |
| Pneumonia prevention | N | N |

Evidence for the effectiveness of PPV-23 in the prevention of IPD in adults (including elderly) is mainly limited to non-randomised observational studies, unfortunately the RCT were not adequately powered. There is growing evidence that PPV-23 has no effect on rates of pneumonia in the elderly, with the only adequately powered study having wide confidence intervals (127). Meta-analyses did not answer the question either. Two studies showed that PPV-23 increased the RR of hospitalisation from pneumonia (RR 1.21 and HR 1.14; 95% CI 1.02-1.28 respectively) despite a reduction in the rate of pneumococcal bacteraemia (RR 0.58 and HR 0.56; 95% CI 0.33-0.93 respectively) (128, 129). Another study again showed little evidence of pneumonia protection in high-risk groups or elderly [HR 1.04; 95% CI 0.78-1.38] (130). Influenza vaccination but not pneumococcal vaccination is associated with a reduced risk of all-cause mortality in COPD (131). A recent meta-analysis concluded that there was no evidence to support routine use of PPV-23 to prevent all-cause pneumonia or mortality (132). There is also concern that repeated doses of PPV-23 (boosters) may lead to hypo responsiveness due to apoptosis of memory B cells (133); and that in the elderly the antibodies induced may be less effective due to reduced opsonophagocytic activity [OPA] (134).

PPV-23 coverage in Europe amongst elderly adults remains low. It has a broad spectrum of coverage (80-90% of serotypes responsible for IPD in Europe) and prevents 50-80% of IPD cases requiring hospitalisation, and therefore is very cost effective, regardless of its impact or lack of on pneumonia (135).

#### 1.2.3.3 Pneumococcal Conjugate Vaccine

PCV vaccines couple purified capsular *S. pneumoniae* polysaccharides with a nontoxic carrier protein. PCVs with increasing serotype coverage continue to be produced including PCV-7

(Prevnar, Wyeth – containing serotypes 4, 6B, 9V, 14, 18C, 19F and 23F), 10 (Synflorix, GSK - 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F, and 23F), 13 (Prevenar 13, Pfizer 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F), 15 (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F and 33F conjugated to CRM197). The span of protection afforded against disease-causing serotypes depends on geographical region i.e. for PCV-7 >85% in the USA, 60-70% in Europe and 55% in Asia (136) and for PCV-13 is approximately 80% in high income countries (137).

PCV-13 is currently licensed for use in the UK in the childhood immunisation strategy for children aged 6 weeks to 6 years to protect against IPD, pneumonia and acute otitis media. Since 2011, the European Medicine Agency (EMA) and Food and Drug Administration (FDA) extended the licence to adults aged > 50yrs old as a single dose for the prevention of pneumonia and IPD caused by PCV-13 serotypes (138, 139). The UK Joint Committee on Vaccines and Immunisations (JCVI) does not currently recommend its routine use in high risk groups. There is accumulating evidence of indirect population protection against PCV-13 serotypes across the UK population due to the use of PCV-13 in the routine childhood immunisation programme. The JCVI concluded that the direct benefit from administering PCV-13 in clinical risk groups would lead to a declining benefit in the UK over the coming years and that the effectiveness and cost effectiveness were uncertain. Furthermore, given the evidence of accumulating indirect protection against PCV-13 serotypes across the UK population and the current absence of data on the effectiveness of PCV-13 in older adults, JCVI also advised against the introduction of a routine immunisation programme to offer PCV-13 to older adults in the UK. The JCVI concluded that some clinical risk groups with a particularly high risk of IPD and high rates of mortality may benefit from immunisation with PCV-13 in the short-term (while PCV-13 serotypes continue to circulate) e.g. bone marrow

transplant patients, those with acute and chronic leukaemia, multiple myeloma, or genetic disorders severely affecting the immune system (140). Further JCVI and CDC guidance was expected after the results of a large placebo-controlled PCV-13 study (CAPITA) were available. Pneumococcal conjugate vaccine (PCV) show good serotype-specific immunity against IPD in children (83-94%) and has herd protection effects in adults (by reducing carriage) (141). The success of PCVs can largely be attributed to herd protection. The reduction in carriage of vaccine serotypes in children has resulted in a reduction in the number of circulating vaccine serotypes (and hence population exposure) (142). The reduction in disease has been seen in young infants too young to have been vaccinated (143), in unvaccinated children and in older children and adults too old to have received the vaccine (144). The herd protection effect in African countries has been variable, this may be due to the vaccination schedule and a children catch-up campaign is likely to be needed to generate good herd effect (personal communication Dr Neil French, University of Liverpool).

PCV induces T-cell, as well as B cell, responses and therefore affords a protective immune response in children and the elderly as well as HIV infected patients (145-147). Induced antibody responses in the elderly to PCV-7, were noted to be similar or greater for all vaccine serotypes than those induced by PPV-23, and similar to those in young children. In children <5yrs old PCV-7 is highly effective at reducing vaccine-type (VT) IPD, VT acute otitis media (AOM) episodes and total pneumococcal pneumonia hospitalisations (148-152) (Figure 4).

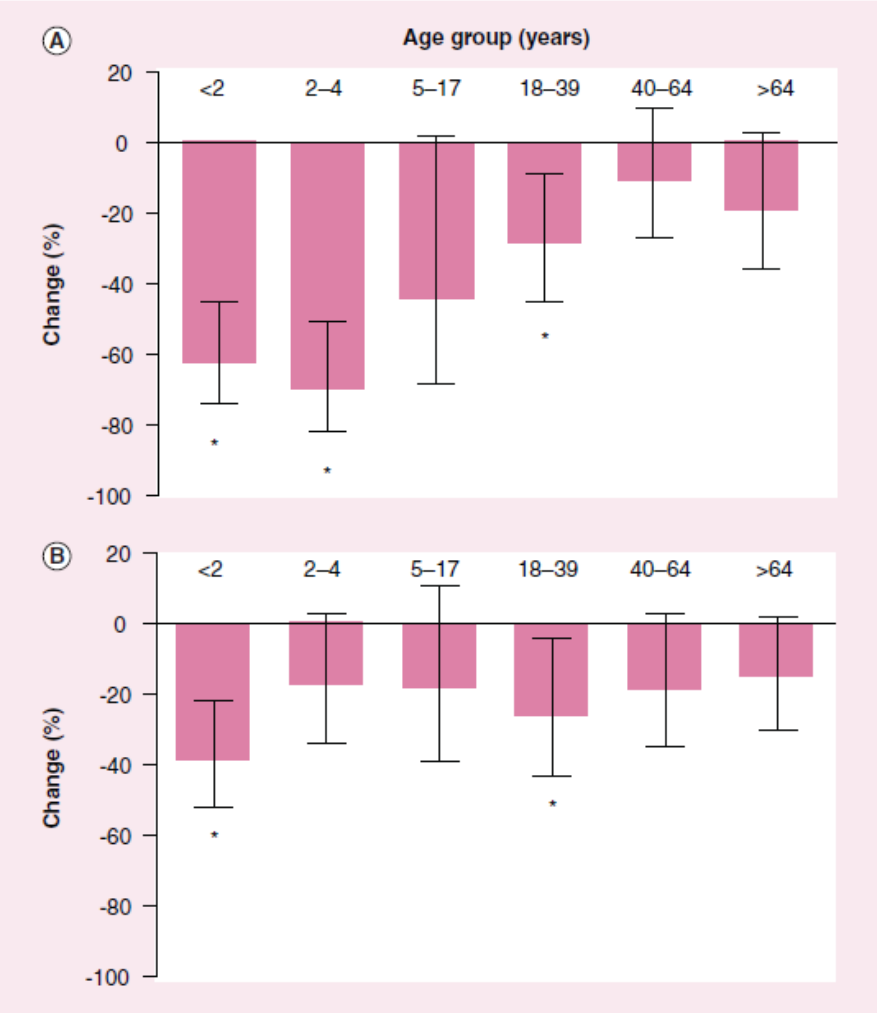


**Figure 4: Change in Hospitalisation Rates in USA for Pneumococcal Pneumonia (A) and All Causes (A) According to Age Group Post PCV-7 Introduction**

(151)

(*statistically significant reduction)

Prior to the introduction of the pneumococcal conjugate vaccine (PCV), the incidence of IPD in children < 2 years old was 44.4/100,000/yr in Europe, 167/100,000/yr in USA and 797/100,000/yr in Mozambique (16). In the post PCV era the incidence in USA has dropped to 23.6/100000/yr in children <5yrs old (153).

Protein-conjugated pneumococcal polysaccharide (PCV) vaccines represent a landmark achievement showing good serotype-specific immunity against IPD (83-94%) in children and an important herd protection effect in adults, but they are not a final solution (141).

PCV is less effective against mucosal disease (AOM, sinusitis and pneumonia) than IPD (154); this may in part be due to differences in mucosal and systemic defence. Defence against systemic infection is dependent on capsule-specific immunoglobulin, complement and phagocytes whilst in mucosal disease (murine models) cellular responses [especially Th17 (155)] are critical (156). Figure 4 shows reduced rates of hospitalisation for all cause pneumonia in the <2's and 18 - 39yr old age groups and reduction for pneumococcal pneumonia in 2 - 4yr old age group. No change was noted in the elderly group (151). Notably estimates of vaccine efficacy against pneumococcal pneumonia are hindered by the diagnostic difficulty of pneumonia. PCVs impact on pneumonia has been shown in children in Gambia and adults ≥65yrs old in the USA with a 33-36% (post PCV-13) (157) and 54% reduction respectively (158). The latter is attributed to herd protection. Studies assessing vaccine effect cannot be compared unless vaccine schedule, valency, epidemiological area, definition of pneumonia and coding are all controlled.

PCV is difficult to manufacture, is expensive, has limited serotype coverage, is associated with serotype replacement and has an unclear effect on pneumonia, so clearly alternative vaccination strategies are needed. PCV is clearly not the full solution. PCV is known to induce anti-capsular antibodies but it is not known whether Th17 responses are also induced. In the

UK due to serotype replacement IPD incidence in children is now similar to that before the introduction of PCV (152). PCV-7 and -9 have shown reduction in VT carriage of up to 14% (159-162). The rate of this replacement also varies geographically. In patients with HIV the rate of IPD caused by pneumococcal serotypes that are not covered by the PCV vaccine (termed non-vaccine types or NVTs) has risen dramatically, a 44% increase from 1999 to 2003 (163). Continuing surveillance is required to determine whether PCVs continue to reduce the rates of disease in the long term.

Epidemiological data have also suggested a reduction in nasopharyngeal carriage by vaccine types after PCV in both children and adults (164, 165), both by direct protection of vaccinated individuals and by the reduction in exposure of unvaccinated individuals to vaccine types through herd protection. The current PCV has greatly decreased the incidence of IPD, through herd protection more than through a direct effect on immunized individuals.

It has been noted that the immunogenicity of PCV is severely restricted if a previous dose of PPV-23 has been received (166). This has been a barrier to design of a large-scale PCV efficacy study in the elderly population (167).

There are at least three major challenges facing the current use and future development of PCVs. Firstly, serotype replacement and resultant replacement disease. Could the solution be to develop vaccines that interfere with invasion and not colonisation? Secondly, optimisation of protection for vulnerable groups. Perhaps a vaccine tailored to that specific group? And thirdly, an issue on a global scale, how to make efficient vaccines available to all in need? This is being addressed by a GAVI Alliance funded project - Pneumococcal vaccines Accelerated Development and Introduction Plan (PneumoADIP) – which aims to accelerate the introduction of pneumococcal vaccinations into low-income countries through partnership

networks between countries, donors, academia, international organizations and industry; in order to prevent 5.4 million deaths in children by 2030.

#### 1.2.3.4 The CAPITA Study

CAPITA (Community Acquired Pneumonia Immunisation Trial in Adults) was a Phase 4 randomised placebo-controlled clinical trial of PCV-13 efficacy in the prevention of vaccine-type (VT) pneumococcal community acquired pneumonia (CAP) and IPD (167-169). The study which began in began in September 2008 took 5 years to complete. This study was conducted in the Netherlands since the elderly population (≥ 65 yrs) there do not routinely receive *Pneumovax* or *PCV,* and are therefore a pneumococcal vaccine naive population.

The primary outcome measure was to compare the number of first episodes of VT pneumococcal CAP in each arm. The secondary outcomes were to compare: 1) the number of first episodes of VT IPD and 2) the number of first episodes of non-bacteraemic/non-invasive VT pneumococcal CAP in each study arm. The study also evaluated carriage rates in a subset of 2000 subjects – data awaited.

Exclusion criteria included: 1) care residents; 2) vaccine hypersensitivity; 3) immunocompromise and 4) receipt of any licensed or experimental pneumococcal vaccine. Almost 85,000 subjects were recruited with a 1:1 random allocation to PCV-13 or placebo-vaccine.

The primary outcome required a clinical definition of CAP, independent interpretation of CXR consistent with pneumonia and determination of pneumococcus serotype (all 3 criteria had to be met for a definition of VT or non-VT pneumococcal pneumonia). Blood culture and positive urinary antigen were used to identify *S. pneumoniae* as the definite causative agent

for CAP. IPD was defined as the presence of pneumococcus in a normally sterile site (including CSF, blood, pleural fluid).

Less than 0.2% of subjects recruited were diagnosed with VT CAP. VT CAP occurred in only 49 subjects in the PCV13 group and 90 persons in the placebo group (vaccine efficacy, 45.6%; 95% CI, 21.8 to 62.5). This was 46% reduction in rates of VT CAP. VT IPD occurred in 7 subjects in the PCV13 and 28 in the placebo group (vaccine efficacy, 75.0%; 95% CI, 41.4 to 90.8). CAP occurred in 747 subjects in the PCV13 and 787 in placebo group (vaccine efficacy, 5.1%; 95% CI, −5.1 to 14.2). This study disappointingly but perhaps not unsurprisingly showed that PCV13 was effective in preventing VT CAP and VT IPD but did not prevent CAP from any cause. The vaccine was not shown to have significant efficacy on mortality. A post-hoc analysis showed that PCV-13 efficacy against VT CAP and VT IPD declined from 65% in 65 year old subjects to 40% in 75 year olds (170).

### 1.2.3.5 Novel Pneumococcal Vaccines and Vaccine Testing Platforms

Pneumococcal disease remains a major global health threat for which new affordable vaccines that confer broad protection against pneumococcal disease are urgently needed, particularly those that protect vulnerable children and adults against pneumonia. This urgency is further increased by a global increase in antibiotic resistance among pneumococci and in the number of susceptible people. New vaccines such as a protein vaccine could potentially overcome the problems faced by PCVs. An Experimental Human Pneumococcal Carriage (EHPC) model could provide a vaccine testing platform to help select from the multiple novel pneumococcal vaccines in development using prevention of carriage as a surrogate of vaccine induced immunity, rather than disease, as an endpoint.

In order to prevent pneumococcal disease should we aim for vaccination to eradicate pneumococcal nasopharyngeal colonisation, or to prevent of bacterial invasion whilst leaving colonisation relatively unaffected? One approach may be to reduce the carriage density rather than carriage rate; this may reduce the rate of horizontal spread and the risk of disease. One major concern about the eradication of pneumococcal carriage is that nasopharyngeal niche may then be prime for other pathogens such as S. *aureus* (171) and N. *meningitidis* instead.

New vaccine development is hindered by the fact that placebo-controlled trials are no longer ethical in children and large sample size and study duration are needed when the primary outcome measure is disease; this increases development costs thereby later negating their use in the poorer countries most in need of such a vaccine. New vaccination routes, such as intranasal are also being examined. This less invasive route may be preferable and particularly useful in children. Since mucosal responses are mostly considered intact in HIV infected subjects, protection may also be afforded in this important immunocompromised group.

New strategies focus mainly on protein antigens. Protein vaccines offer the advantage of serotype independence (and therefore no concerns regarding serotype replacement), reduced cost, protection for all ages and potentially improved protection against mucosal disease.

An ideal protein antigen should be found on the cell surface and be highly expressed and conserved between serotypes. It is likely that multiple proteins are required to have a protective effect (172, 173). Live vaccinations may offer both mucosal and systemic immunity, whilst a whole cell vaccine (inactivated/attenuated) would have low manufacture costs and would offer serotype-independent protection. In mice the killed whole cell vaccine has shown protection against nasopharyngeal carriage and sepsis (174). Pneumococcal protein-based vaccines, live attenuated vaccines and whole cell vaccines are currently in development (Table 2).

**Table 2: Novel Pneumococcal Vaccinations at the Clinical Trial Stage (156)**

| Strategy | Antigens | Advantages | Limitations | Institute | Phase |
|---|---|---|---|---|---|
| Common pneumococcal protein-based vaccines | PspA (pneumococcal surface protein A) | Human antibodies to PspA protect mice from sepsis | Antigen variability; cross-reactive antibodies to human myoglobulin | Sanofi–Pasteur | Phase I complete |
| | PspA & PsaA (pneumococcal surface protein A and the metal-binding proteins pneumococcal surface antigen A) | Protective antibodies against carriage and IPD | Uncertain about exposure of PsaA on pneumococcal surface | Sanofi–Pasteur/ CDC | Phase I complete |
| | PiuA & PiaA (pneumococcal iron uptake A and pneumococcal iron acquisition A) | Antigenically cross-reactive | Immunity to single antigen is not as protective as combination | N/A | Phase I complete |
| | BVH3/11V fusion protein [or PhpA and PhtB] (pneumococcal histidine triad B) | Conserved antigen; surface exposed; interact with human complement. In mice confers protection against sepsis and pneumonia | N/A | ID BioMedical (acquired by GSK) | Phase II complete |
| | Based on PsaA, PcsB & StkP (the metal-binding proteins pneumococcal surface antigen A, protein required for cell wall separation and serine/ threonine protein kinase) | Three conserved antigens, in mice confer protection to carriage, sepsis and pneumonia | N/A | InterCell AG/Novartis/ PATH | Phase I complete |
| | PhtD (pneumococcal histidine triad D) | Protective against sepsis; interaction with human complement | Higher animal survival rates after lethal intranasal challenge | GSK/ Biologicals SA | Phase II complete |
| | PlyD1 (pneumolysin D1) | Present virtually in all strains | Non-toxic pneumolysoids are best active as protein adjuvant rather than protective antigens | Netherlands Vaccine Institute/ Sanofi–Pasteur | Phase I |
| Live attenuated vaccines | Live recombinant attenuated *Salmonella* Typhi expressing PspA | Vaccine is well characterized in mice, induces mucosal response and protection against carriage and sepsis; oral single-dose administration | Expresses PspA that induces reactive antibodies to human myoglobulin | Arizona State University/ Biodesign Institute | Phase I complete |

| Strategy | Antigens | Advantages | Limitations | Institute | Phase |
|---|---|---|---|---|---|
| Whole cell vaccines | Unencapsulated killed (inactivated) whole cell (Rx1 LytA$^{-/-}$, a rough derivative of serotype 2, D39) | Administered as a nasal vaccine and is protective against carriage and sepsis | Mechanism of protection described Th17 in mice, is not elucidate in humans | Children's Hospital Boston/ Butantan Institute/ PATH | Phase II complete |

However, there is a bottleneck in pneumonia vaccine development as clinical trials with tens of thousands of participants are required to compare the new vaccine with the current gold standard vaccine using an outcome of disease reduction. (175). If a new vaccine could protect against colonisation, it could be possible to reduce transmission and achieve herd protection. At least initially studies using a reduction in carriage as an endpoint rather than disease could provide proof of concept for a new vaccine and be a stepping stone to pursuing large and expensive clinical trials with disease endpoints. A model that assesses a reduction or elimination in pneumococcal carriage can therefore be used as a vaccine testing platform. Such a design may be an efficient and cost-effective method to select between vaccine candidates and lend support to Phase 3 trial choice (175).

#### 1.2.3.6 Experimental Human Pneumococcal Carriage/Colonisation (EHPC) Studies

Human challenge models have been used to study disease pathogenesis, investigate new antimicrobials and vaccine efficacy. McCool et al published the first EHPC study in 2002 (176). They inoculated healthy adults with serotypes 23F and 6B and examined the antibody response to carriage. Pre-existing high levels of pneumococcal surface protein A (PspA) [a potential protein vaccine candidate] antibody correlated with protection against experimental carriage.

The EHPC technique is valuable as a vaccine testing platform but is complex and involves a measure of clinical risk from introducing a live pathogen into a human volunteer. The EHPC model can also be used to investigate the immunological correlates of protection. Different serotypes can be used either alone or combined, and different cohorts of subjects inoculated; healthy volunteers; those with respiratory disease; immunocompromised or the elderly.

#### 1.2.3.6.1 The Usefulness of the EHPC Model in Novel Vaccine Testing

Animal models play a key role in screening candidate vaccines, evaluating vaccine formulations, and providing initial safety and efficacy data. However, since the human is the only natural host of the pneumococcus, no animal data can predict vaccine efficacy in humans. The EHPC vaccine testing model could be used to determine the protective effect against carriage of novel vaccines in a small population compared to a placebo group and/or PCV group.

Prior to the study in chapter 7, we developed a safe and reproducible EHPC model. In this model, carefully screened healthy adult participants are inoculated with doses of pneumococci – with a 50% colonisation rate at a density typical of natural colonisation and duration of 1 - 3 weeks (177, 178).

#### 1.2.3.6.2 The Ethics of the EHPC Model

Safety is a major factor in the development of the EHPC model and is achieved through intensive subject screening and monitoring. The current EHPC model in use in England has been validated in over 150 healthy adult subjects in Liverpool. Stringent screening using strict inclusion and exclusion criteria occurs (178). Further information is contained within Chapter 7.

## 1.3 Summary and Study Plans

To summarise**,** Lower Respiratory Tract Infection (LRTI) and pneumonia are a leading cause of death in the UK and a costly health problem to the NHS. The various definitions of LRTI and pneumonia make both comparing current studies and designing future studies challenging. Pneumococcus is thought to be the main cause of LRTI/pneumonia and this thesis therefore focusses on this pathogen predominately.

Current UK priorities include:

1) **Better diagnostics** - Pneumococcal carriage or colonisation is very common in children, common in adults but rare in the elderly. It can be detected by nasal sampling techniques (swabs or washes) using classical microbiological culture or *q*PCR. Given that the aetiological pathogen is rarely found, better diagnostics are important and in an era of increasing antibiotic resistance, targeted antibiotic theory is vital. Nasal sampling has been shown to be useful in patients with pneumonia in South Africa. Could nasal samples from hospitalised patients with LRTI/pneumonia be useful in aetiological diagnosis? CHAPTER 3.

2) **Better therapeutics** - Acute hospital bed pressures and hospital acquired infections rates are increasing. Investigating the possible causes for the increased length of hospital stay (LOHS) in these patients and assessing what an early supported discharge scheme (ESDS) would need to consist of and its potential effect on LOHS is key. CHAPTER 4, 5 AND 6.

3) **Better prevention** - Current pneumonia vaccines are inadequate. New vaccine development is hindered by the fact that placebo-controlled trials are no longer ethical in children and large sample size and study duration are needed when the primary outcome measure is disease; this increases development costs thereby later negating their use in the

poorer countries most in need of such a vaccine. An Experimental Human Pneumococcal Carriage (EHPC) model using live pneumococcal bacteria could provide a vaccine testing platform to help select from the multiple pneumococcal vaccines in development using prevention of carriage as a surrogate of vaccine-induced immunity, rather than disease, as an endpoint. CHAPTER 7.

The next chapter focuses on the complexities of modern clinical research studies and discusses and describes the details of the necessary regulatory processes, our personal experience of the challenges posed and how they were overcome.

# CHAPTER 2: Methods

## 2.1 Overview

Modern clinical studies in NHS premises are subject to well-regulated processes that can be complex; these are summarised in Figure 5. The flowchart describes the process for the studies in this thesis from design to recruitment, highlighting the various approvals required. Particular points relevant to the studies in this thesis are described in further detail under the following headings:

- Research Development and Innovation department (RD&I)
- Ethics (Integrated Research Application System [IRAS] and Research Ethics Committee [REC])
- Medicines and Healthcare Products Regulatory Authority (MHRA)
- Other approvals
- Sponsorship
- Patient and Public Involvement (PPI)
- Recruitment and advertising

This chapter describes the broad methods relevant to all/most of the studies in this thesis. Specific methods relevant to a chapter are considered separately in each chapter to aid ease of reading of this thesis.

| | | |
|---|---|---|
| ALL | Research Development and Innovation department (RD&I) - Study number and title | |
| | Develop study design and initial version of protocol +/- patient and public involvement (PPI) | |
| | Review at local RD&I meeting (with 2 peer reviews required) – provisional intent to sponsor letter granted | |
| | Complete Governance Registration Information Document (GRID) and Declaration of Interest (DoI) form | |
| | Develop all documentation for ethics: including patient information leaflet (PIL), consent form, protocol, GP letter, hospital advert. Set up Data Safety and Monitoring Committee (DMSC) if required. Engage with finance and pharmacy | |
| PCV EHPC | JRO (Joint Research Office) application (CTIMP only) | |
| ALL | Arrange a date for Research Ethics Committee (REC) | HOME FIRST Pilot specific REC |
| | Complete Integrated Research Application System (IRAS) form – complete REC, R&D and Local Comprehensive Research Network (LCRN)/portfolio sections and submit | |
| PCV EHPC only | Medicines and Healthcare Products Regulatory Authority (MHRA) and Clinical Trials Application (CTA) in parallel or series with IRAS and EudraCT no. (CTIMP only) | |
| ALL | ISRCTN (International Standard Randomised Controlled Trials No.) or Clinical Trials.gov registered | |
| | Attend REC | |
| | Address all REC amendments and submit | |
| | REC approval | |
| | Trust agree to sponsor | |

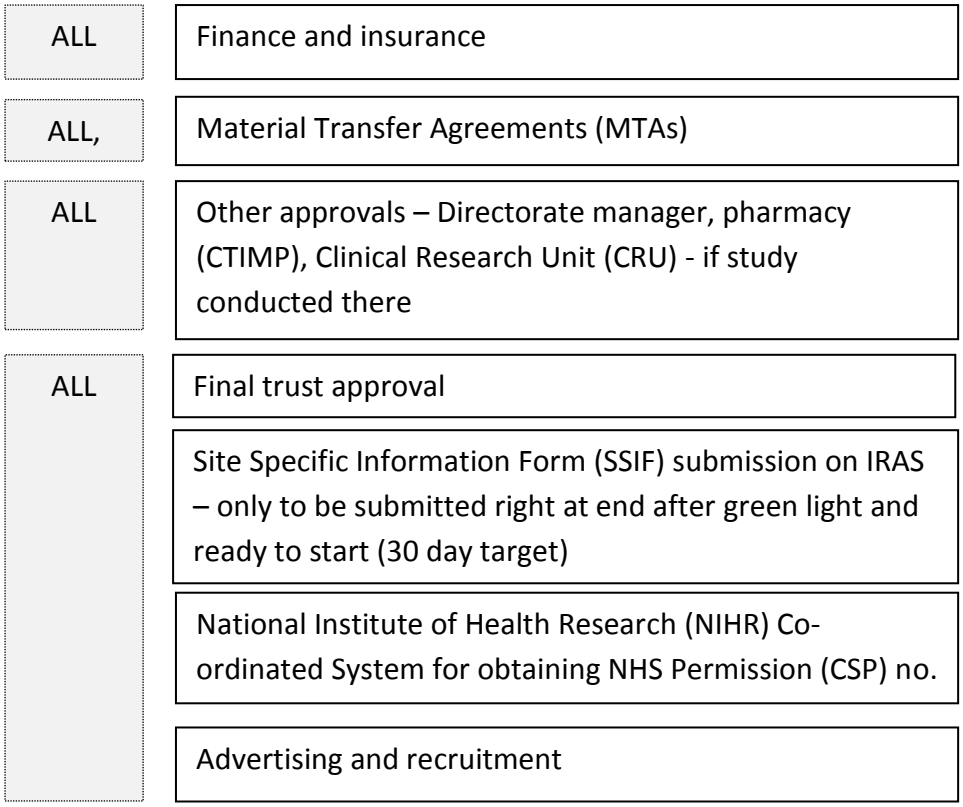


**Figure 5: Complex Process Study Flowchart**

ALL - includes all research studies, since chapter 4 contains audit work only this did not require the same rigorous approval process as the research studies in chapter 3, 5, 6 and 7.

## 2.2 Research Development and Innovation Department (RD&I)

The Royal Liverpool and Broadgreen University Hospitals NHS Trust (RLBUHT) has a legal obligation as a research host site to ensure that it is aware of and records all research undertaken on its premises or by its staff [as per Research Governance Policy (RPOL001)].

In our research, each study protocol was sent to RD&I by a member of the study team along with a Governance Registration Information Document (GRID) [this form outlines what type of study (i.e. CTIMP, non-CTIMP), PI details, which departments within the trust will be used, type of study participants, finance details and LCRN involvement] and a Declaration of Interest (DoI) form. Two peer reviews were arranged via RD&I (one internal and one external to our study group). At the monthly RD&I study meeting [or Joint Research Office (JRO) meeting for all Clinical Trials of Investigation Medicinal Products (CTIMPs) studies], each study was discussed and if there were no concerns or protocol amendments required a provisional intention of sponsor letter was granted. We then completed and submitted an Integrated Research Application System (IRAS) form for each study.

We developed a strong relationship with RD&I offices at RLBUHT and LSTM. Certain RD&I staff members were very knowledgeable about processes and this speeded up the time from study registration to the start of recruitment significantly in the studies in Chapters 3, 5. 6 and 7. We found communication in person or by telephone particularly helpful rather than email.

## 2.3 Ethics: Integrated Research Application System (IRAS) and Research and Ethics Committee (REC)

In all 4 research studies (Chapters 3/5/6 and 7) in this thesis, full NHS Research and Ethics Committee (REC) approval was required since human volunteers (healthy adults or clinical

patients) were to be recruited. The IRAS form and other documents including (at a minimum) – a patient information leaflet (PIL), protocol, any questionnaires, provisional intention to sponsor letter, advert(s), GP letter and a checklist were uploaded. A REC date was obtained by telephoning the Central Booking Service (CBS) which has replaced the Central Allocation System (CAS). During the call the study team member confirmed they were ready to submit (that same day or within 3 working days), provide the IRAS project ID and contact details of the CI and sponsor and answered a series of questions about the study.

Ethical approval for the studies was granted as follows (Table 3).

**Table 3: Ethics Committee (and other necessary) Study Approvals for Research Studies within this Thesis**

| Study | REC | REC approval number | Other approvals/ registrations/ funding | Sponsor |
|---|---|---|---|---|
| **Nasal Wash and Lower Respiratory Tract Infection**<br><br>**Chapter 3** | Liverpool (East) | 12/NW/0713 | NCT 01861184<br><br>Pump priming, NIHR and BRC in microbial disease | RLBUHT<br>LSTM |
| **HOME FIRST Feasibility**<br><br>**Chapter 5** | Liverpool (Central) | 11/NW/0670 | ISRCTN 25542492<br><br>Pump priming, NIHR and BRC in microbial disease | RLBUHT<br>LSTM<br>UHA |
| **HOME FIRST Pilot**<br><br>**Chapter 6** | Manchester (South) | 12/NW/0731 | NCT 02454114<br><br>LHP | RLBUHT<br>LSTM |
| **Pneumococcal Conjugate Vaccine and Experimental Human Pneumococcal Carriage**<br><br>**Chapter 7** | Liverpool (East) | 12/NW/0873 | ISRCTN 45340436<br>EudraCT 2012-005141-20<br><br>BMG GCE II | RLBUHT<br>LSTM |

[REC (Research Ethics Committee , NCT (National Clinical Trials), ISRCTN (International Standard Randomised Controlled Trials No.), EudraCT (European Clinical Trials Database), RLBUHT (Royal Liverpool and Broadgreen University Hospital), UHA (University Hospital Aintree), LSTM (Liverpool School of Tropical Medicine), NIHR (National Institute and Health Research), BRC (Biomedical Research Centre), LHP (Liverpool Health Partners), BMG GCE II (Bill and Melinda Gates Grand Challenge II Programme)].

In the HOME FIRST pilot study we recruited patients who lacked mental capacity, we therefore required approval by a 'flagged REC' (a REC able to approve studies involving adults unable to consent for themselves).

The Mental Capacity Act (MCA) 2005 (179) establishes a framework for the protection of the rights of people who lack capacity to make a decision for themselves and includes safeguards for the conduct of research involving these people. The MCA is designed to ensure that the interests and safety of people who lack capacity are protected when they participate in research and to ensure that their current and previously expressed wishes and feelings are respected. In order for research to be lawful all researchers carrying out studies to which the requirements of the MCA apply, must act in accordance with the act. Medical research involving adults who lack mental capacity to consent, such as HOMEFIRST pilot, can lead to innovations in healthcare that can substantially improve their health and quality of life. Adults lacking capacity should be given the opportunity to participate in research, as excluding them would be discriminatory and would reduce their ability to participate as much as possible in society and would prevent researchers making progress in the understanding of many disorders that can affect the brain, and in the care and treatment of those who have such disorders (180).

In all research, including those involving adults who lack mental capacity, we should comply with accepted principles of good practice, including the Declaration of Helsinki (181) and relevant European and UK legislation. Under UK legislation relating to research involving adults who lack the capacity to consent, REC approval is a legal requirement.

In the HOMEFIRST pilot study since we included patients who lacked mental capacity, their participation needed to be agreed by someone who was independent of the study and who could assess the potential participant's interests in accordance with current guidance. This person was a relative, a carer or an independent representative. The flagged REC pre-meeting process of completing the IRAS form is understandably more complex than a form for a study that only includes participants with capacity. The REC meeting itself was relatively straightforward however since the REC felt that it was important that patients with a lack of capacity were included in our study.

In line with guidance, where possible, we discussed or communicated with the potential participant themselves in a way appropriate to their understanding. If a person who lacked capacity to consent did not seem in agreement with any intervention or part of the study, even if agreement has been given by another person, that person was excluded. If this happened we were expected to inform the individual's independent representative that they will not be taking part despite the representative's agreement, and tell them the reasons for our decision. This did not occur during in the HOMEFIRST pilot.

The key principles we considered with regards to the participation of adults who lack capacity in our research (180) were:

• The interests of the individual must always outweigh those of science and society

• Our research must relate to a condition that affects the individual or the treatment of this condition

• Equally effective research with adults who have the capacity to consent must not be possible

• The potential benefits of the project should outweigh the risks: the level of acceptable risk depends partially on the possible benefit to that individual

• To seek, where possible, the views of those close to the participant

• Only to include a participant where there were no indications that he/she objected to their participation.

In order to decide whether an individual lacked the mental capacity to consent to HOME FIRST pilot study participation (180) we assumed capacity to be present unless it is shown to be absent.

Capacity was absent if, at the time of decision making if:

• The patient in question had impaired functioning of their mind or brain

• This impairment made the person unable to decide whether to participate

The patient was deemed unable to decide whether to take part in research if they could not:

• Understand the information relevant to the decision (information was given in a way that is appropriate to the particular patient)

• Retain that information for long enough to make the decision (this may be for a relatively short time, but still long enough to enable decision making to occur)

• Use or weigh up that information as part of the process of making the decision (they needed to understand the consequences of each option and of not making the decision)

• Communicate their decision through speech.

With regards to consulting carers (or others) the MCA stipulates that before any decision is taken to involve a particular person in REC-approved research, researchers must identify a 'consultee' who is willing to be consulted about the person's participation (180). With regards to the HOME FIRST pilot, we took reasonable steps to identify and consult a 'personal consultee'. This is someone who cares for or is interested in the potential participant's welfare

other than in a professional or paid capacity. If a personal consultee was not available we consulted an independent mental capacity advocate (IMCA). It is good practice to involve any paid carers who are close to the participant in the decision-making process – even if the decision has to be taken by an independent nominee (180).

We gave the consultee the following information in the form of a consultee patient information leaflet (PIL) - why they were being approached, their role as a consultee, an explanation that their role was completely voluntary and details of the study (as would be given to a potential participant with capacity). The consultee then provided 'advice' on whether the potential participant should take part in the study and what, in their opinion, the participant's views and feelings would have been on taking part in the project had they retained capacity. The advice they provide should be recorded on a Consultee Declaration Form – this is rather like a consent form for a patient with capacity but importantly the consultee is giving their advice only and not their consent. If the consultee advised that the person in question would not have wanted to take part in the project, that person was not recruited. Similarly, the participant was withdrawn from the project if at any time the consultee believed that the participant would not have wished to continue. A consultee declaration form was signed by the consultee. Retrospective consent was required for any patients in whom a consultee declaration was initially used but who had re-gained capacity and were able to give their consent.

## 2.4 Medicines and Healthcare Products Regulatory Authority (MHRA)

All CTIMP studies require MHRA approval called Clinical Trial Authorisation (CTA). Either the study sponsor or someone authorised by them must apply. They must obtain a European

Clinical Trials Database (EudraCT) number. The REC submission and approval can occur before, in parallel or after the MHRA submission. Ours occurred before, this may have slowed down the process by 1-2mths overall, but leads to less document changes depending on the amount of alterations made by the REC. We downloaded and completed a CTA application form on the EudraCT website (the IRAS website is an alternative). The study in Chapter 7 (PCV EHPC) was a Phase IV CTIMP study and therefore required MHRA approval. A covering letter, a CTA form, a study protocol, a simplified IMP dossier (sIMPD), a Summary of Product Characteristics (SmPC), a Manufacturer's Authorisation (MA) and a content of the labelling of the IMP were sent with our MHRA application.

The initial assessment of a submission is completed within 30 days. The outcome of a submission can be 1) acceptance of the request for a CTA 2) acceptance of the request for a CTA subject to conditions or 3) grounds for non-acceptance of the request for a CTA – you are informed as to why and will usually have to amend your application and resubmit. We received an outcome 1.

### 2.4.1 Specific Issues Related to a CTIMP study

#### 2.4.1.1 Women of Child-Bearing Potential (WOCBP)

For all CTIMP studies issues related to recruiting women of child-bearing potential (WOCBP) contraception and lactation must be addressed. In chapter 7, since the effects of the Prevenar-13 and Avaxim on the unborn child are not known, women who were pregnant or breast-feeding were not allowed to participate. We confirmed that sexually active women were using an effective form of birth control approved by the study team for 1 month prior to and after the final vaccination. Contraception methods could include – hormonal contraceptives (oral, injection, trans-dermal patch, implants, cervical ring), barrier methods (diaphragm with spermicide or a condom), an intra-uterine device, male sterilisation (for monogamous individuals only) and true abstinence. Women had to have a negative pregnancy test at enrolment and on the day of vaccination and confirmed that they did not intend to become pregnant during the study. During this study, any woman who believed they may be pregnant was urged to notify the study doctor immediately. Recruiting women of child-bearing age is therefore perhaps more challenging in any CTIMP study in terms of work load for the team and documentation. We also had to confirm their contraception with their GP, this was sometimes challenging as not all women get their contraception from their GP.

#### 2.4.1.2 Over-volunteering

In CTIMP studies in order to prevent of 'over-volunteering', The Over-volunteering Protection System (TOPS) database should be used. For the study in chapter 7, we therefore entered the participant's National Insurance (if a UK citizen) or passport number and country of origin (if not a UK citizen) and the date of the last dose of study medicine. We called other research

units to check the participant's details as needed. Participant details may be kept for up to 3 years on this database. A General Practitioner Questionnaire (GPQ) was completed for all participants, this is compulsory in all CTIMP studies. Only 1 patient was picked up by this system as a potential over-volunteer. We continue to use this system to date and find it especially useful to track patients that have previously been used in a pneumococcal carriage study that cannot therefore (usually) be re-inoculated.

## 2.5 Other Approvals

Given the numerous approvals necessary in RLBUHT especially for CTIMP studies, we developed a checklist and used this to ensure all approvals occurred in a timely fashion to improve efficiency when setting up our studies (Table 4). This improved our efficiency and was pasted to the clinical research unit to be used by other research teams in the future.

**Table 4: Study Approvals Checklist**

| **Checklist** | **Tick** |
|---|---|
| Research Development and Innovation (RD&I) number | |
| Study title | |
| Review at local RD&I meeting (with 2 peer reviews required) | |
| JRO (Joint Research Office) application - CTIMP only | |
| GRID Form (Governance Registration Information Document) to RD&I | |
| Declaration of Interest (DoI) form to RD&I | |
| Directorate Manager approval | |
| Intent to Sponsor approval letter (provisional) | |
| Clinical Research Unit (CRU) application | |
| Local Comprehensive Research Network (LCRN) portfolio submission | |
| Research and Ethics Committee (REC) submission [IRAS – REC, R&D and portfolio] | |
| RD&I submission | |
| REC meeting date | |
| REC post-meeting amendments submitted | |

| | |
|---|---|
| REC approval | |
| EudraCT no. | |
| Medicine and Health Products Regulatory Authority (MHRA) Application and Clinical Trials Authorisation (CTA) Application - CTIMP only | |
| Finance | |
| Contracts (commercial) | |
| Material Transfer Agreements (MTAs) | |
| Pharmacy application | |
| Pharmacy green light | |
| Insurance (co – clinical trials) | |
| CRU approval | |
| Site Specific Information Form (SSIF) submission on IRAS – right at end post green light after ready to start (30 day target) | |
| RD&I final approval | |
| ISRCTN (International Standard Randomised Controlled Trials No.) or Clinical Trials.gov registered | |
| NIHR Co-ordinated System for obtaining NHS Permission (CSP) No. | |

| | |
|---|---|
| 30 Day target achieved (date of PI signature on IRAS form) | |

[CTIMP (Clinical Trials of investigational Medicinal Products), EudraCT (European Clinical Trials Database), IRAS (Integrated Research Application System), NIHR (National Institute of Health Research), PI (Primary Investigator)].

## 2.6 Sponsorship

### 2.6.1 Overview

The Trust must ensure that research conducted by its staff or on its premises safeguard's participants and staff and produces accurate and appropriate data which is published. The Trust must recognise the role that research governance has to play as the key driver in the management, design, conduct and delivery of world class clinical research.

All research undertaken in the NHS requires a sponsor according to the Research Governance Framework Edition 2 2005. For the purposes of drug research, sponsorship is defined by the Medicines for Human Use (Clinical Trials) Act regulation 3(1) as the institution who takes responsibility for the initiation, management and financing (or the arranging of financing) of that trial. For the purposes of research being submitted to REC this definition applies to all research.

The Sponsor ensures that the research safeguards the rights, safety, dignity and wellbeing of participants. The sponsor can be any organisation that is a legal entity that funds, initiates, hosts or employs staff involved in research.

Co-sponsorship (in the case of all 4 studies within this thesis between LSTM and RLBUHT +/- UHA) involved formal division of the sponsor responsibilities between the parties. In the case of a CTIMP like the study in Chapter 7 (PCV EHPC) this was by sponsorship agreement. Sponsorship may be withdrawn at the discretion of the Research Governance Committee Chair. A Trial Master File (site file) is a legal requirement for CTIMP studies and was kept in the locked respiratory research office. The sponsors monitored study conduct in proportion to the study risk. Therefore, monitoring for PCV EHPC and HOMEFIRST was relatively tight.

### 2.6.2 Trial Steering Committees (TSCs) and Data Management (and Safety) Committees (DM[S]Cs)

All interventional studies should have a TSC. If a study is blinded in the case of the PCV EHPC study there is also a legal requirement for a DMC. All DMC's should conform to the Damocles Charter 2005. A DMC or DMSC is a group of people that reviews accumulating data during a clinical trial and advises the sponsor on the future management of the trial. They mainly review safety and efficacy data but may also review quality and compliance data.

Not all trials will require a DMC since there is no statutory requirement under the Medicines for Human Use (Clinical Trials) Regulations 2004 for the sponsor to appoint a DMC, and where a DMC is appointed it has no statutory role.

The REC receives interim data about clinical trials in progress reports, annual safety reports or reports of serious adverse events (SAEs), including any suspected unexpected serious adverse reactions (SUSARs) occurring in CTIMPs at UK sites. The REC is not responsible for assessing these data however and relies on assurances from the sponsor that it has adequate monitoring arrangements in place for monitoring the safety and ethical conduct of a clinical trial.

DMC members are usually themselves experienced trialists. A DMC usually consists of at least 3 members consisting of clinicians and at least one statistician. The specific role and function of the DMC is described in a Charter. The Charter describes the DMC's membership, roles, meeting frequency, how decisions are reached and the reporting structure (Table 5). The DAMOCLES group provide a template charter which we then adjusted for the HOMEFIRST pilot (chapter 6) and PCV EHPC (chapter 7) studies (182). The sponsor(s) were responsible for ensuring that a Charter was in place for the DMC. The REC was aware of the proposed role and function of the DMC at the time of the ethical review but did not require a copy of the

Charter. The sponsors maintained oversight of both the HOMEFIRST pilot and PCV EHPC studies by reviewing the open minutes of TSC's and DMC's at the Research Governance Committee meetings.

In the study in chapter 7, the DMSC received weekly updates on all recruitment (by email) and met formally biannually and also in the event of any **s**erious unexpected serious adverse reactions (SUSARs). The DMSC received a weekly safety report from the research team (Table 6). When the DMSC formally met they reviewed the SmPCs (on medicines.org.uk) for both Avaxim and Prevenar-13 vaccinations for updates, any SAEs from the study so far, and updated the protocol as necessary.

**Table 5: Headings from the DAMOCLES Template DMC Charter**

| |
|---|
| **1. INTRODUCTION** |
| • Name of trial (and Sponsor's trial no.)<br>• Objectives of trial<br>• Outline of scope of Charter |
| **2. ROLES AND RESPONSIBILITIES** |
| • A broad statement of the aims of the committee<br>• Terms of reference (ToR)<br>• Specific roles of the DMC |
| **3. BEFORE OR EARLY IN THE TRIAL** |
| • Whether the DMC will have input into the study protocol<br>• Whether the DMC will meet before the start of the trial<br>• Any specific regulatory issues<br>• Any other issues specific to the treatment under study |
| **4. COMPOSITION** |

| |
|---|
| • Membership and size of the DMC including a chair<br><br>• The Chairs responsibilities and role<br><br>• The responsibilities of the trial statistician<br><br>• The responsibilities of the DMC statistician |
| **5. RELATIONSHIPS** |
| • Clarification of whether the DMC is advisory (make recommendations) or executive (make decisions)<br><br>• Payments to DMC members<br><br>• The need for DMC members to disclose information about any competing interests |
| **6. ORGANISATION OF MEETINGS** |
| • Expected frequency of DMC meetings<br><br>• Whether meetings will be face-to-face or by teleconference<br><br>• How DMC meetings will be organised, especially regarding open and closed sessions, including who will be present in each session |
| **7. TRIAL DOCUMENTATION AND PROCEDURES TO ENSURE CONFIDENTIALITY AND PROPER COMMUNICATION** |

| |
|---|
| • Intended content of material to be available in open sessions<br><br>• Intended content of material to be available in closed sessions<br><br>• Whether or not the DMC will be blinded or unblinded to the treatment allocation<br><br>• To whom the DMC will communicate the decisions/ recommendations that they reach and in what form |
| **8. DECISION MAKING** |
| • How decisions or recommendations will be reached within the DMC<br><br>• When the DMC is quorate for decision-making<br><br>• What happens to members who do not attend meetings |
| **10. AFTER THE TRIAL** |
| • Whether the DMC will have the opportunity to approve publications particularly in respect to reporting of any DMC recommendation regarding termination of a trial. |

(Adapted from Data Monitoring Committees in Clinical Trials/ Guidance for Research Ethics Committees – National Patient Safety Agency and National Research Ethics Service. May 2010)

**Table 6: Data Collated on Weekly DMSC Safety Report for the PCV EHPC Study**

| |
|---|
| **Patient ID** |
| **Gender** |
| **Age** |
| **Natural Carrier** |
| **Date of Vaccination** |
| **Vaccination Number** |
| **Vaccine Received** |
| **Adverse Reaction to Vaccine** |
| **Post Vaccine Carriage Status** |
| **Date of Inoculation** |
| **Bacterial Inoculation Dose (CFU/ul)** |
| **Carriage Status at Day 2, 7, 14 and 21** |
| **Post Inoculation Adverse Reaction Symptoms** |
| **Bronchoscopy** |
| **Additional Comments** |

[CFU/ul (colony forming units), carriage/carrier = colonised/colonisation status].

### 2.6.2.1 Adverse Events and Reporting

The following definitions were used throughout this thesis:

- **Adverse drug reaction (ADR):** any untoward and unintended response in a subject to an investigational medicinal product (IMP) which was related to any dose administered to that subject.
- **Unexpected adverse reaction:** an adverse reaction the nature and severity of which was not consistent with the information about the IMP in the SmPC.
- **Serious adverse event (SAE) or serious unexpected serious adverse reaction (SUSAR):** an adverse event, adverse reaction or unexpected adverse reaction, respectively, that: (a) resulted in death (b) was life-threatening (c) required hospitalisation or prolongation of existing hospitalisation (d) resulted in persistent or significant disability or incapacity (e) consisted of a congenital anomaly or birth defect.

In the study in chapter 7, any SAEs were recorded and reported to the DMSC and sponsor (within 24hrs). It is important to note that hypersensitivity reactions to Prevenar-13 including facial oedema, dyspnoea and bronchospasm are rare SAEs. A reaction may result in brief hospitalisation (<48 hours), since only one vaccination occurred in this study, the participant was still able to remain in the study if this occurred. In the event of any SUSAR the trial was to be stopped temporarily for investigation and any further work then referred back to the REC and MHRA for further consideration, through the sponsor (within 7 days) [Figure 6].

Data on adverse events were collected and categorised as follows: headache, sore throat, nasal congestion/ running/ sneezing, myalgia, lethargy, earache/ muffling/ popping, pyrexia,

neck stiffness, hospital admission and other (including shivering, wheezy, cough, abdominal cramps, photophobia, sinus pain and generally unwell).

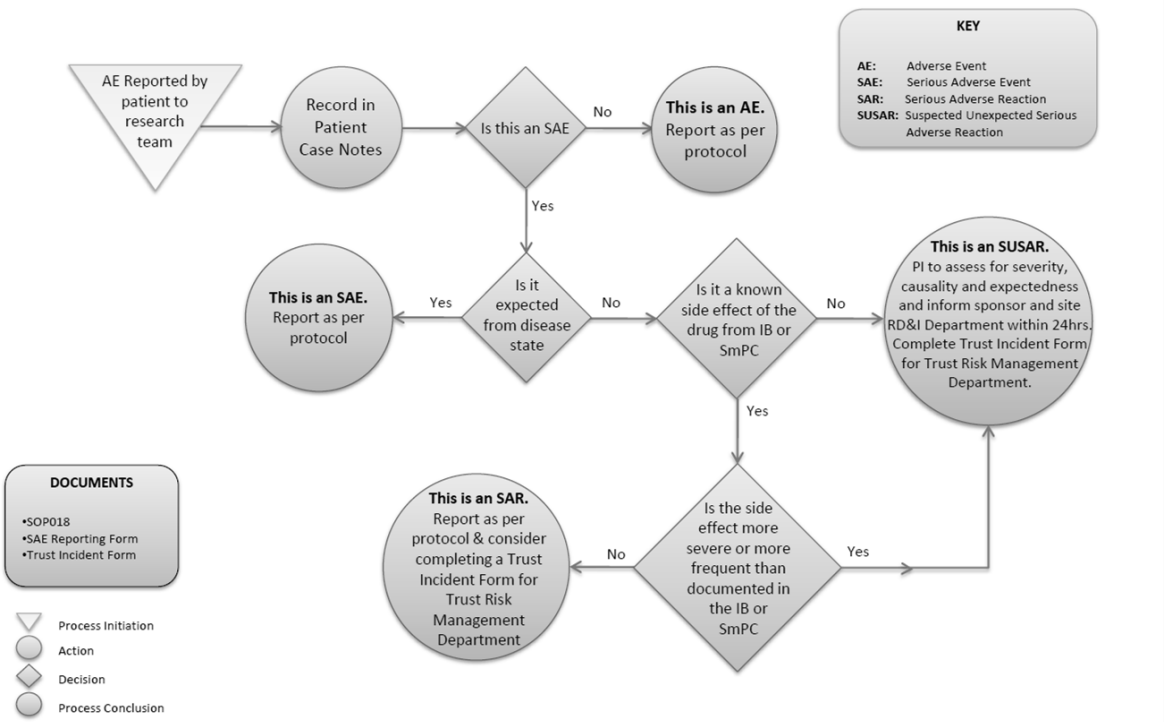


**Figure 6: Trust Adverse Event (AE) and Serious Adverse Event (SAE) Flowchart**

*Adapted from RLBUHT RD&I adverse and serious adverse event flowchart.*

### 2.6.3 Roles and Responsibilities

The RLBUHT Research Governance Committee maintained responsibility for oversight of sponsored research studies and ensured all research undertaken with RLBUHT as sponsor/co-sponsor complied with the Research Governance Framework. Our CI completed the REC, ensured the Trial Master File (site file) was maintained, archived appropriately to have study oversight, ensured the studies were run to relevant legal and national standard requirements and undertook any duties delegated by the sponsor via contract or sponsorship approval letter.

The RD&I staff facilitated the Research Governance Committee, ensured all our research had a confirmed sponsor and undertook oversight activities on behalf of the Research Governance Committee.

## 2.7 Patient and Public Involvement (PPI)

PPI was only used in the HOME FIRST studies (chapters 5 and 6) as these were clinical and very patient relevant. A broad semi-quantitative analysis of the acceptability of HOME FIRST to patients was vital. PPI was very important; we recruited active members of the public to our group. LRTI is an acute disease, and is therefore different to chronic disease PPI groups. We decided upon a 'rolling' cohort of patients for our PPI group. Patients who had participated in other pneumonia studies within the Liverpool area were approached and asked if they would like to be involved in the design of this study. The group was demographically and ethnically representative of the population that presents with LRTI. The British Lung Foundation's 'Breathe-easy' patient support groups were also consulted. The feasibility study was developed with input from nurses and doctors involved with 'COPD early

facilitated discharge schemes'; as well as respiratory physicians from various hospitals, in the UK and New Zealand.

## 2.8 Recruitment and Advertising

Participant recruitment is a major challenge in many research studies involving human subjects and strategies must be carefully considered prior to the start of the study. Recruitment often both takes longer and is more difficult than expected. If a study is unable to fully recruit, this reduction in the sample size leads to reductions in the statistical power of the study. Recruitment involves a number of activities, including identifying eligible participants, adequately explaining the study to the potential participants and retaining participants until study completion. Full details of how participant recruitment will be achieved in a study must be completed on the IRAS form. The protocol and IRAS form must describe exactly how many participants will be identified, approached and recruited.

A REC form must state precisely where the advertising will occur – e.g. a particular University, GP practices or dental surgeries. We learned to be through in our descriptions of where advertising could occur. During studies prior to those in this thesis had learned that we would need to go back to the REC to alter our advertising plan i.e. also advertise in Liverpool John Moore's University campus as well as the University of Liverpool campus. A recruitment strategy that included the University fresher's fair and sports fair proved particularly helpful for the study in Chapter 7, but the strategy of data collection at these events was also vital to maximise the recruitment.

## 2.9 Overview

A clear understanding of the complex processes described in this chapter was fundamental to the smooth and efficient running of the studies themselves ensuring timely and effective recruitment in safe and ethical studies. The processes are frequently over complicated due to ever changing regulations, the acronyms are vast and as a team that was new to many of the processes involved in setting up a CTIMP study, advice and help was difficult to obtain within an NHS institution, unlike within pharmaceutical companies were departments exist for this very purpose. This chapter was partially written as an aide memoire for future trainees at the start of this process to better inform them after our experiences, and explaining how we overcame the challenges.

In the following five chapters each of the studies will be discussed in turn working through from potential new diagnostics (Chapter 3 Pneumococcal Carriage as a Diagnostic in Adults - Lower Respiratory Tract Infection and Nasal Wash Study) , to improving therapeutics through early supported discharge schemes including scoping exercises and audits (Chapter 4 Pneumonia audits), HOME FIRST feasibility (Chapter 5) and pilot (Chapter 6) and finally better prevention through developing a new model to test vaccines (Chapter 7 - the Pneumococcal Conjugate vaccine and Experimental Human Pneumococcal Carriage Study).

# CHAPTER 3: Pneumococcal Carriage as a Diagnostic in Adults – Lower Respiratory Tract Infection and Nasal Wash (LRTI NW) Study.

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## 3.1 INTRODUCTION

Recent studies have shown that detection and quantification of nasal pneumococcus (*Streptococcus pneumoniae*) by quantitative real time *lytA* Polymerase Chain Reaction *(q*PCR) could be used to identify pneumococci as the aetiological pathogen in adults with pneumonia (45) and could be useful as a disease severity marker (183). In that study from South Africa patients with community acquired pneumonia (CAP) were more frequently colonised than controls using classical culture (44.9 v. 11.7%) and *q*PCR (62.8 v. 19.8%) and, in addition, patients with pneumococcal CAP were also noted to have higher colonisation density than asymptomatic controls (45).

The association of pneumonia and pneumococcal colonisation has been previously noted in children in whom those with radiological pneumonia were more frequently colonised with pneumococci than those without (78) and had a higher density of colonisation than those with bronchitis or without disease (79). In contrast, in the elderly very low colonisation rates have been shown; 0.3% in pneumococcal vaccine naive hospitalised Australians (by classical culture) (72) (of which 10 had respiratory infection) and 2.3% in a Portuguese community

cohort (184). Numerous studies have examined natural pneumococcal carriage and it is well known that rates vary by age and geographic area (71). In developed countries, pneumococcal colonisation rates in healthy adults are between 1 - 18%, and are affected by age, immune status, antibiotic use, household composition and contact with children (70, 71). There are no published data on pneumococcal colonisation in hospitalised patients with respiratory infection in the UK.

We therefore aimed to determine the rate and density of pneumococcal colonisation by a) classical culture and b) *q*PCR in hospitalised adult patients with LRTI when compared with age and gender-matched controls in a developed country setting.

## 3.2 METHODS

### 3.2.1 Screening and Recruitment

For full details see the study protocol in Appendix A. We recruited hospitalised adults with LRTI at the Royal Liverpool and Broadgreen University Hospital from January - July 2013 within 72 hours (hrs) of admission. The syndrome of LRTI was defined as; symptoms of respiratory infection with clinical signs +/- radiological consolidation; therefore meeting the BTS definition of pneumonia as used in community (GP) practice. Clinical signs of LRTI included ≥2 of: cough, breathlessness, pleuritic chest pain, fever, increased or new sputum production. Inclusion and exclusion criteria were used (Table 7 and 8).

**Table 7: Inclusion and Exclusion Criteria for LRTI Patients**

| **Inclusion criteria** | **Exclusion criteria** |
|---|---|
| Community-acquired pneumonia (CAP) [radiological consolidation] or LRTI [no radiological consolidation] | Infective exacerbation of COPD (IECOPD) or bronchiectasis [without radiological consolidation] |
| Able to give fully informed consent (mental capacity assessed using trust guidelines) | Aspiration pneumonia |
| Age>18yrs old | Oxygen saturations <86% on air |
| Fluent English speaker | Tuberculosis suspected |
| | Neutropenia |

**Table 8: Inclusion and Exclusion Criteria for Control Patients**

| **Inclusion criteria** | **Exclusion criteria** |
|---|---|
| Able to give fully informed consent (mental capacity assessed using trust guidelines) | Signs/symptoms of respiratory infection |
| Age>18yrs old | Oxygen saturations <86% on air |
| +/- 10 years of recruited LRTI patient | Neutropenia |
| Fluent English speaker | |

Patients with an infective exacerbation of chronic obstructive pulmonary disease (IECOPD) were excluded as these exacerbations are known to commonly be due to viruses (up to 60%) (185, 186), *Haemophilus influenza*e (up to 33%) (187) and *Moraxella catarralis* (around 10%) (188) rather than pneumococcus. Patients who had been a hospital inpatient for ≥72 hrs or had recently been discharged from hospital ≤14 days before were excluded since it is likely their nasal flora would have altered due to hospital exposures. Patients with oxygen saturations <86% on air were excluded since it was felt unsafe to remove their oxygen in order to perform a nasal wash (NW).

A carefully selected control group of hospitalised patients with no signs of respiratory infection were recruited within 7 days (where possible or as soon after as possible) of the LRTI patient. The control group were matched for age (within 10 years of the LRTI patient) and gender. Exclusion criteria were: oxygen saturations <86% on air, neutropenia, ≥ 7 days after admission and recent hospital discharge ≤14 days.

A list of potential participants was generated on a daily basis (Monday to Thursday) in combination the hospital capacity team, ward based case managers and medical co-ordinators in accident and emergency (A&E), acute medical admissions unit (AMAU) and respiratory wards. To recruit for control participants we targeted surgical wards. Patient eligibility was confirmed by review of the medical records. If consent was given baseline clinical data of age, gender, history of presenting complaint, past medical history, vaccination history, antibiotic prescription, and contact with children (defined as at least alternate day contact with children aged ≤ 10yrs) on recruited patients was recorded. NW and urine samples were collected within 12 hours of recruitment. The study was approved by Liverpool

East, North-west NHS Research Ethics Committee (12/NW/0713) and registered with ClinicalTrials.gov (NCT01861184).

### 3.2.2 Sampling

NW was collected on the day of recruitment with a maximum of 20 mls of normal saline instilled into the nasopharynx as previously described (178, 189). A minimum of 5 mls of normal saline was recovered and processed in all cases. Nasal wash processing was as per SOP (Appendix A). In a subset of samples that exceeded 7 mls a proportion of the sample (3 – 5 mls) was removed and centrifuged at 836 x g to obtain cellular material after which the supernatant was re-added to the rest of the sample for the high speed spin.

### 3.2.3 DNA Extraction and *q*PCR

For DNA extraction/*q*PCR methods see Appendix B.

A sample was considered positive if both duplicates had a mean cycle threshold (CT) value of <35 (this value was chosen to maximise positive reactions indicative of moderate amounts of the target nucleic acid but to minimise positive reactions due to environmental contamination). Values of >8,000 copies/ml were considered clinically relevant according to Albrich and colleagues (45).

### 3.2.4 Binax

An immunochromatographic membrane test (ICT) (BinaxNOW *Streptococcus pneumoniae*; Binax) was performed on all patient's unconcentrated urine specimens, according to the manufacturer's recommendations.

### 3.2.5 Statistical Analysis Plan

Using published data showing a carriage rate of 10% in developed countries in healthy adults, 11.7% in healthy South African adults (including HIV positive), 1% in hospitalised elderly Australian patients and 45% in South African patients with CAP; to detect a difference between 1 and 11.7% with an 80% power we required n=107 in each group. To detect a difference between controls of 11% and patients of 45% we required n=55 in each group (power 97.8%) or n=40 (power 91.3%). We aimed to recruit 100 patients with LRTI and 100 controls to the study. 90% power means the ability to demonstrate an association between pneumococcal colonisation rates and disease status (i.e. LRTI) if an association exists I.e. this study has a 90% chance of ending up with a p value of less than 5% if there really was an important difference between the variables. By convention, 80% is an acceptable level of power.

## 3.3 RESULTS

### 3.3.1 Screening and Recruitment

We screened 826 patients and recruited 19 LRTI and 19 control (age, gender and season matched) patients. 217 were 'potential' LRTI patients, of which 198 were not eligible (Figure 7). We planned to recruit 100 patients to each arm of the study, but stopped recruiting early on the grounds of futility due to high overall screen failure rate (778/816, 95.4%); data were analysed after this decision. For those patients with LRTI the recruitment rate was 8.8%, and for controls 3.1%. Recruiting age matched controls was difficult, especially for the younger LRTI patients (aged 36 - 46 yrs old). In 9 cases, the time between the recruitment of the LRTI patient and control was >7 days (range 9 - 43).

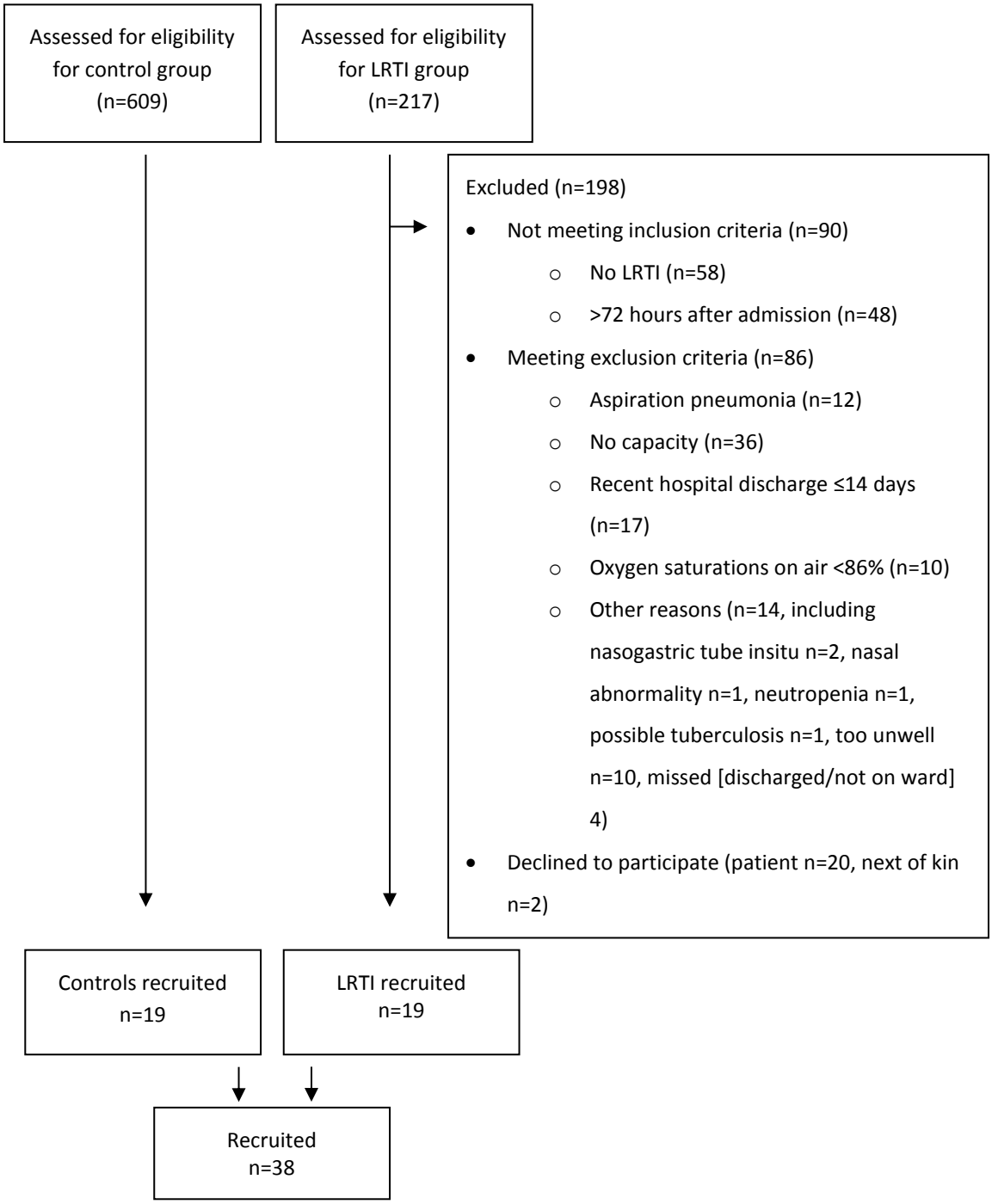


**Figure 7: Screening and Recruitment Flowchart**

Reasons for non-recruitment for lower respiratory tract infection (LRTI) patients are detailed. Total no. screened n = 826. Note multiple reasons for non-recruitment per patient were possible.

58 patients did not have a syndrome of LRTI (acute exacerbation [AE] COPD n=22, AE bronchiectasis n = 5, AE asthma n=3, AE pulmonary fibrosis n= 1 and alternative diagnoses including pulmonary embolus (PE), congestive cardiac failure (CCF), sepsis of unknown cause and adult acute respiratory distress syndrome (ARDS) n = 30), 36 patients did not have capacity to consent (predominately due to dementia or acute delirium), 48 patients were identified >72 hours after admission and 17 after a recent hospital discharge ≤14 days before, 20 patients declined to participate and 2 'next of kin' refused permission for their relative to participate, 10 oxygen saturations <86% on air, 12 aspiration pneumonia, 14 were excluded for other reasons.

### 3.3.2 Sampling: Rate of Colonisation

All recruited patients were successful at providing a nasal sample. One patient was unable to replicate the NW technique (as per protocol) and had a nasopharyngeal swab instead. NW volumes were not significantly different between LRTI patients and controls (Table 9). Pneumococcal colonisation was detected using classical microbiology in 1 LRTI patient and 3 controls (p=0.6). Using *q*PCR 10 LRTI patients and 8 controls were positive (p=0.516) [Table 10]. One of the controls was positive for colonisation by culture but considered negative by *q*PCR as the $C_T$ value was >35.

**Table 9: Baseline Demographics, Antibiotic Status, Nasal Wash Volume Returned and Evidence of Pneumococcal Disease Investigation Results of Patients with Lower Respiratory Tract Infection (LRTI) and Age and Gender Matched Hospitalised Controls.**

| | LRTI (n=19) | Control (n=19) | p value |
|---|---|---|---|
| Gender: Male n (%) | 9 (47.4) | 9 (47.4) | 1.000 * |
| Age Years ± SD | 64.47 ± 15.78 | 64.58 ±14.50 | 0.954 β |
| Smoker/ ex-smoker n (%) | 15 (78.9) | 10 (52.6) | 0.170 α |
| 23 PPV *Pneumovax* n (%) | 7 (36.8) | 8 (42.1) | 0.740 * |
| Contact with children n (%) | 10 (52.6) | 12 (63.2) | 0.511 * |
| Antibiotics at time of recruitment n (%) | 19 (100) | 3 (15.8) | 0.0001 α |
| Nasal wash volume returned (ml) ± SD | 10.14 ± 3.14 | 10.36 ± 4.83 | 0.855 β |
| Evidence of pneumococcal disease:<br><br>Binax urine test positive n (%) | 2 (10.5) | 0 (0) | 0.486 α |
| Evidence of pneumococcal disease:<br><br>Blood or sputum culture positive n % | 0 (0) | N/A | N/A |

*Chi Square, β Mann Whitney U test, α Fisher's Exact, SD standard deviation, PPV polysaccharide vaccine

**Table 10: Pneumococcus Identification (by culture, qPCR) and Density (by qPCR) in Patients with Lower Respiratory Tract Infection (LRTI) and Age and Gender Matched Hospitalised Controls.**

| | LRTI (n=19) | Control (n=19) | p value |
|---|---|---|---|
| Culture positive n (%) | 1 (5) | 3 (15.8) | 0.604 α |
| *q*PCR positive n (%) at detection limit | 10 (52.6) | 8 (42.1) | 0.516 * |
| Density (by *q*PCR) copies/ml geometric mean [95%CI] | 3066 [1225 – 7675] | 2208 [244 – 19972] | 0.408 β |
| Clinically relevant density n (%) [by *q*PCR] >8000 copies/ml | 3 (16) | 4 (21) | 0.999 α |

α Fisher's Exact, *Chi squared, β Mann Whitney U test, *q*PCR quantitative polymerase chain reaction

Note low rates of culture positivity and high rates of qPCR positivity in both LRTI and control groups.

### 3.3.3 Sampling: Density of Colonisation by *q*PCR

For *q*PCR a cut off value of >8000 copies/ml was used to define clinical relevance (45). In our study, 3 LRTI patients and 4 controls had values >8000 copies/ml. Of the 3 LRTI patients, only 1 was culture positive; of the 4 controls, 2 were culture positive (Table 10). Of the 4 patients overall who were culture positive, 3 had >8000 copies/ml, 1 in the LRTI and 2 in the control group.

### 3.3.4 Clinical Data

Antibiotic usage prior to sampling was significantly higher in LRTI patients than controls 19 v. 3 ($p<0.001$). Radiological consolidation was present in 7 out of 19 LRTI patients; only 2 out of 38 urine samples were positive using BinaxNOW. None of the LRTI patients recruited were pneumococcal sputum or blood culture positive. There were no statistical differences between the groups with regards to smoking, contact with children age <10yrs old or 23 PPV *pneumovax* vaccination (Table 9).

## 3.4 DISCUSSION

We found low rates of pneumococcal colonisation by culture in the LRTI group. Antibiotic use prior to hospital admission was high. All LRTI patients had received at least 2 doses (pre-admission/pre-recruitment) prior to NW sampling; this is likely to have resulted in culture negativity. Previous antibiotic therapy has been noted to decrease culture and *q*PCR positivity by up to 50% (45). We also found no significant differences between the LRTI and colonisation groups in either colonisation rates using qPCR or colonisation density.

In our study classical pneumococcal pneumonia was rare. Accurately diagnosing pneumonia is challenging; inter-doctor variability in reporting of radiologically confirmed pneumonia is common (190). The Royal Liverpool hospital has ~1,400 admissions per year that are coded as “pneumonia”; approximately 20% of these cases are not in fact community acquired or the patients have no radiological features of pneumonia. Having ‘pneumonia diagnosed radiologically’ as an inclusion criterion in a study may in fact make the results less applicable to everyday hospital medicine. LRTI may be a more useful term for this clinical syndrome, particularly in instances where the guidelines suggest clinical rather than radiological diagnosis (7). A large number of our patients were referred with potential LRTI but alternative diagnoses such as PE, CCF, non-infective exacerbation of pulmonary fibrosis, sepsis of unknown cause, and aspiration pneumonia were common. This diagnostic imprecision has important implications for the use of NW sampling as a diagnostic technique since it would lead to many inappropriate samples being collected. Liverpool is in northwest England and has the second highest LRTI rate (age standardised episodes/1,000 person years) and the third highest CAP rate nationally (191). It is therefore an ideal area for recruitment for respiratory infection studies, although community antibiotic prescription rates are high.

The main strength of this study is the large number of screened patients; the LRTI patients were well phenotyped, and the controls were matched in age, gender, and time of recruitment and had similar smoking habits, 23PPV (*Pneumovax*) vaccination rates, and child contact. Our cohort did not have CAP by the strict definition of radiological consolidation; rather a broad study group of LRTI patients was chosen due to its clinical relevance in United Kingdom hospital practice and admissions, making these results very generalisable.

Nationally, the antibiotic prescribing rate by GPs for LRTIs is very high but is lower for clinically diagnosed CAP (due to the usual immediate hospitalisation) (191).

The limitations of the study are that this is a single centre study, which may reduce the generalisability of the results, specifically in areas where community antibiotic prescription rates are lower, that we were unable to fully recruit for the study despite the high numbers of individuals screened, and that the NW sampling technique, rather than nasopharyngeal swab may not have been ideal in this population.

In this elderly population research nurses noted poor performance and lower yields after nasal wash than in the cohort of healthy volunteers in which we more commonly use this technique (data not shown). Nevertheless, patient comfort is higher (192), and the sensitivity for colonisation density is very high (193). We know from our Experimental Human Pneumococcal Colonisation (EHPC) studies that antibiotic usage terminates pneumococcal colonisation; after an interim analysis noted 100% antibiotic usage in the LRTI group prior to recruitment and low rates of colonisation (on culture), the study was stopped on the grounds of futility as continued recruitment in this population was considered unethical. Controls in particular were hard to recruit, patients frequently declined to participate. This may have been because they were feeling too unwell and therefore not keen to be involved in a research study, or because they were less motivated to be involved in research of a condition that they felt did not directly affect or benefit them. Recruitment also occurred whilst I was on maternity leave in early 2013. Screening was carried out by two senior nurses (1 an experienced researcher) and a junior doctor. I believe that the lack of clear daily leadership and therefore search strategy meant that the numbers screened were higher than necessary and the whole process less efficient. This process was not aided by difficult old hospital

computer systems (these have more recently been updated at RLBUHT). It would have helped recruitment if there was a small reimbursement for the controls, the REC had informed us that this should be removed from our initial draft protocol unfortunately.

We found very low colonisation rates in LRTI patients. Previous studies have shown colonisation rates of 44.9% and 62.8% in patients with radiologically confirmed CAP compared to 11.7% and 19.8% in controls by culture and *q*PCR, respectively (45); in comparison, we detected colonisation rates of 5% and 15.8% (>8,000 copies/ml) in patients with LRTI and 15.8% and 21.0% (>8,000 copies/ml) in controls. The differences between the two studies may be due to the fact that our patient cohort was considerably older (64.5 versus 38.4 years old) (45), had low rates of radiologically confirmed pneumonia (36.8%), had high rates of prior antibiotic treatment, had high rates of contact with children, and were presumed to be HIV uninfected (the overall incidence of HIV infection is low in Liverpool: 15 cases per 100,000/yr in 2011 [D. Sloan, unpublished local data]). Previously in Liverpool, we found natural colonisation rates of 10% in healthy non-smoking volunteers by classical culture (25/249, aged 23 years old [SD±5.7]) (unpublished data). The higher rate (15.8%) in this cohort may be related to the high rates of contact with children and smoking history or our patients. There were also no significant differences in the colonisation rates in polysaccharide-vaccinated (23PPV, *Pneumovax*) and unvaccinated patients, consistent with previous literature stating that the vaccine does not protect against colonisation (162, 194).

*q*PCR can deliver results within a few hours (usually 3 to 6 hrs), which might impact the critical phase of early clinical care (42); however, it does not distinguish between viable (live) and nonviable (dead) bacteria or determine whether the bacteria are pathogens or colonisers (46, 48). Specificity can also be an issue with *q*PCR, and there have been concerns that *lyt*A may

not discriminate between *Streptococcus pneumoniae* and *Streptococcus viridans*; however, *lyt*A is currently the most widely used target gene for pneumococci, and we have previously shown that our assay specificity (193) is in line with that reported by others (195).

Within this cohort, all LRTI patients had taken antibiotics prior to sampling, which probably accounts for the higher positivity rate of *q*PCR over culture. Although qPCR techniques detect both viable (live) and non-viable (dead) bacteria, prior antibiotic treatment has been shown to lower plasma and pleural fluid PCR load (28) as well as sputum and blood culture positivity. It is not known how rapidly pneumococci will be undetectable by *q*PCR in the NW samples of those with previous pneumococcal colonisation after antibiotic therapy. It may be that antibiotics reduce the pneumococcal load within the nasopharynx level within days. However, a lower cycle threshold value cannot be used in an attempt to compensate for the effect of the antibiotics, due to cross-reactivity from other pathogens (and therefore false positives) and contamination being a limitation with the *q*PCR technique.

Albrich and colleagues suggested that a density of $10^3$ to $10^4$ may be the critical value at which colonisation leads to infection (45); however, we have found densities as high as or higher than these in our cohort of healthy volunteers after experimental colonisation without infection (177, 193). Colonisation densities were not different in the LRTI and control groups; we also found high mean densities of $\geq 10^3$ in those without infection (n = 4 controls). It is possible, therefore, that if colonisation is dense and in the setting of the correct clinical syndrome, then the pneumococcus is a likely pathogen. Again, an important difference between the two study groups may be HIV infection status. Only 10.5% (2/19) of our LRTI group were BinaxNOW positive compared to 72.7% in patients with non-bacteraemic CAP in another study (45). The BinaxNOW results remain positive for at least 7 days after the

initiation of antibiotic treatment (196); notably, our urine samples were taken up to 72 h after admission but often several days after antibiotics had been started.

In conclusion, we have shown that pneumococcal colonisation (assessed by culture and *q*PCR) cannot be used as a method of diagnosis for pneumococcal blood culture-negative hospitalised adults with LRTI in the United Kingdom, since such patients have already received antibiotic therapy in the community setting and the laboratory test is non-discriminatory. Further, the number of adults tested for potential LRTI on screening would be impracticable in terms of staff resources. Potentially a community-based study recruiting patients prior to antibiotic therapy may, however be a useful future step. In such a study, nasal washes could be performed by GPs or nurses in all patients with symptoms of respiratory infection prior to antibiotic therapy with the aim of eventually guiding treatment.

Chapter 4, describes the beginnings of work relating to an early supported discharge scheme for patients with LRTI.

## 3.5 ACKNOWLEDGMENTS

In this chapter, I would specifically like to acknowledge the work of Sr Carole Hancock, Sr Angela Wright and Dr Laura MacFarlane for screening and recruiting patients whilst I was on maternity leave. Sr Angela Wright for her assistance with statistical analysis. Professor Stephen Gordon and Dr Daniela Ferreira for assisting with protocol writing and ethics submission. To all the laboratory staff - Jenna Gritzfeld, Toni Banyard, Shaun Pennington and Dr Catherine Johnstone for sample processing, including nasal wash processing, DNA extraction, *q*PCR and Binax, and analysis.

# CHAPTER 4: Audits to Assess the Causes of Increased Hospital Length of Stay and the Feasibility of Early Supported Discharge in Adults with Pneumonia.

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## 4.1 INTRODUCTION

Hospitals are working at full capacity and are struggling to meet the demands placed upon them (197). Not only are admissions rising yearly, patients are ever more likely to have multiple co-morbidities (198), and an increasing number and complexity of tests and treatments can be provided. Despite these pressures, acute hospital bed capacity has fallen over the past 25 years (199) thus there is a pressing need to reduce both the number of patients admitted and their length of stay (LOS); this is of particular relevance at the Royal Liverpool and Broadgreen University Hospital Trust (RLBUHT) since the new hospital opening in 2017 will have a 15% fewer beds, with the bed capacity reduced from 750 to 646 in total. Achieving reductions in numbers of patients admitted and LOS will require improvements in the efficiency of existing processes and action to address the significant number of in-patients who could be equally well treated elsewhere (199). In addition to the cost-savings, reducing unnecessary bed days also reduces the risk of potentially serious adverse events (SAEs) such as hospital-acquired infections (HAI).

Hospital at Home (HAH) schemes and other innovations that reduce the demand for beds have become increasingly popular (96). They offer the potential to reduce admission rates, LOS and costs (97). They have been successfully implemented for some diseases (e.g. chronic obstructive pulmonary disease [COPD] and heart failure) (104), however little evidence for HAH schemes exists for patients with lower respiratory tract infections (LRTI) and pneumonia. Influenza and LRTI (including pneumonia in this definition) are the most common infection-related causes of hospital admission in the UK (200) but a patient's prolonged LOS is often unrelated to the severity of the acute illness (90). Physicians also tend to over-estimate the likelihood of death from pneumonia (201) and there is large variability in rates of hospitalisation across nearby geographical regions. The risk of adverse outcomes (death, readmission rates, delayed return to work/usual activity) does not vary between hospitals when comparing LOS (106). Dr Foster data benchmarks LOS outliers by diagnostic group for all hospitals in England (202). In 2010, these data indicated that investigating the prolonged LOS amongst patients with pneumonia at RLBUHT should be a Trust priority, due to our hospital being an outlier in terms of increased LOS.

This chapter describes the scoping exercise and feasibility testing by a retrospective coding audit. In part 1 we investigated the possible causes for the increased LOS in patients at RLBUHT (methods and results are presented sequentially), and in part 2 we investigated the proportion of patients in whom the LOS could have potentially been reduced if they were discharged with a hypothetical early supported discharge scheme [ESDS] (again methods and then results discussed sequentially), in order to assess the feasibility of an ESDS for patients with LRTI.

## 4.2 METHODS AND RESULTS

### 1.2.1 Part 1 - Methods

We set out to define the possible causes of increased length of hospital stay (LOHS) for cases of pneumonia. Factors considered included: severity of illness often defined by CURB-65 (actually a mortality risk not severity score), co-morbidities, low oxygen saturations, lack of social support, excess alcohol consumption, illicit drug use and the development of pulmonary or medical complications. During this retrospective case-note audit data were collected to address the clinical coding accuracy for pneumonia, LOS and clinical course during the hospital stay. We assessed all admissions coded as 'pneumonia' over a 2mth period in 2011 (this included hospital-acquired, community-acquired and aspiration pneumonias) and located their case notes. We considered patients to have been correctly coded as pneumonia if they demonstrated ALL 3 of the following 1) symptoms of pneumonia 2) clinical signs of pneumonia and 3) radiological evidence of consolidation.

### 1.2.2 Part 1 – Results

130 patients were admitted and coded as pneumonia during this 6 week period, their case notes were located and assessed.

**Demographics**

The median LOS 7 days in males versus 6.5 (1-43) days in females was similar (p=0.626). In age groups 51-60 yrs old and 81-90 yrs old almost 50% patients died and for those ≥ 90 yrs old mortality was 100% (Figure 8).

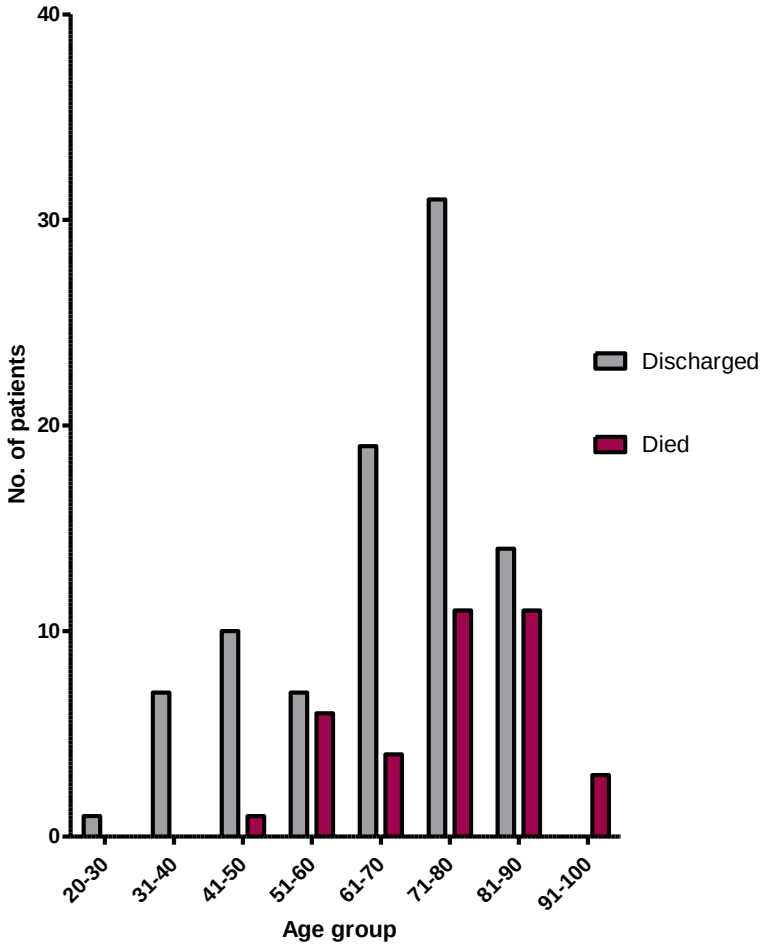


**Figure 8: Patient Age and Outcome - Hospital Discharge or Death for Patients Coded as Pneumonia**

The number of patients grouped by age (in 10 year blocks) discharged from hospital compared with mortality.

**Diagnostic accuracy**

Of the 130 cases reviewed, 47 cases (36%) fulfilled the 3 diagnostic criteria of pneumonia. Median LOS in correctly coded pneumonia cases was 11 days vs 10.5 days for miscoded pneumonia cases (p=0.4).

**Outcome**

Median LOS for patients with vs without associated co-morbidities was 11.4 vs 8.4 days. Median LOS for patients with a complication or another medical condition during their stay (n=26) was 14 vs 7 days for patients who had an uneventful recovery (n=21).

### 1.2.3 Part 2 - Methods

We then performed a further retrospective case-note audit from all admissions coded as ICD-10 'J-code 10-18' (Table 11) over a representative 2-mth period in 2011. We selected every 10$^{th}$ case note for review. Two reviewers reviewed the selected case notes using pre-defined inclusion and exclusion criteria to assess the patients' potential eligibility and suitability to an early supported discharge home care scheme (Table 12 and 13). **Eligibility** is defined in this thesis study as a patient with an appropriate respiratory infection that means they are eligible for a home-based respiratory infection ESDS. J-codes 10-18 were chosen as they include all patients coded by the hospital coding team on hospital discharge as either having a diagnosis of influenza, viral pneumonia, bacterial pneumonia and pneumonia of unknown aetiology. The International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10) 2015 is a medical classification list from the World Health Organisation (WHO). It contains codes for diseases, signs and symptoms, abnormal findings, complaints, social circumstances, and external causes of injury or diseases. J-codes code for diseases of

the respiratory system, whilst G-codes code for diseases of the nervous system and K-codes for the digestive system.

A patient was considered **eligible** if they had a diagnosis of respiratory infection as defined in Table 12. Patients with or without mental capacity were considered **eligible**. A patient was considered **suitable** if they not only had the appropriate diagnosis (i.e. were eligible) but also a number of other criteria (inclusion) were met including 'able to manage activities of daily living with current support' and stable pre-defined observations, whilst other criteria (exclusion) were not met such as, no fixed abode or neutropenia (Table 13). Many of these suitability criteria amount to ensuring the safety of a patient for discharge from hospital.

**Table 11: International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10) 2015. Diseases of the Respiratory System – J10-18**

| |
|---|
| J10 Influenza due to other identified influenza virus |
| J10.0 Influenza with pneumonia, other influenza virus identified |
| J10.1 Influenza with other respiratory manifestations, other influenza virus identified |
| J10.8 Influenza with other manifestations, other influenza virus identified |
| J11 Influenza, virus not identified |
| J11.0 Influenza with pneumonia, virus not identified |
| J11.1 Influenza with other respiratory manifestations, virus not identified |
| J11.8 Influenza with other manifestations, virus not identified |
| J12 Viral pneumonia, not elsewhere classified |
| J12.0 Adenoviral pneumonia |
| J12.1 Respiratory syncytial virus pneumonia |
| J12.2 Parainfluenza virus pneumonia |
| J12.3 Human metapneumovirus pneumonia |
| J12.8 Other viral pneumonia |
| J12.9 Viral pneumonia, unspecified |
| J13 Pneumonia due to *Streptococcus pneumoniae* |
| J14 Pneumonia due to *Haemophilus influenzae* |
| J15 Bacterial pneumonia, not elsewhere classified |
| J15.0 Pneumonia due to *Klebsiella pneumoniae* |
| J15.1 Pneumonia due to *Pseudomonas* |
| J15.2 Pneumonia due to staphylococcus |
| J15.3 Pneumonia due to streptococcus, group B |
| J15.4 Pneumonia due to other streptococci |
| J15.5 Pneumonia due to *Escherichia coli* |
| J15.6 Pneumonia due to other Gram-negative bacteria |
| J15.7 Pneumonia due to *Mycoplasma pneumoniae* |
| J15.8 Other bacterial pneumonia |
| J15.9 Bacterial pneumonia, unspecified |
| J16 Pneumonia due to other infectious organisms, not elsewhere classified |
| J16.0 Chlamydial pneumonia |
| J16.8 Pneumonia due to other specified infectious organisms |
| J17 Pneumonia in diseases classified elsewhere |
| J17.0 Pneumonia in bacterial diseases classified elsewhere |
| J17.1 Pneumonia in viral diseases classified elsewhere |
| J17.2 Pneumonia in mycoses |
| J17.3 Pneumonia in parasitic diseases |
| J17.8 Pneumonia in other diseases classified elsewhere |
| J18 Pneumonia, organism unspecified |
| J18.0 Bronchopneumonia, unspecified |
| J18.1 Lobar pneumonia, unspecified |
| J18.2 Hypostatic pneumonia, unspecified |
| J18.8 Other pneumonia, organism unspecified |

| J18.9 Pneumonia, unspecified |
|---|

**Table 12: Pre-defined Inclusion and Exclusion Criteria to Assess Eligibility to the Early Supported Discharge Scheme (ESDS)**

| **INCLUSION CRITERIA** | **EXCLUSION CRITERIA** |
|---|---|
| **The below criteria were used to assess eligibility for ESDS:** | |
| • Pneumonia - community acquired (CAP) or hospital acquired (HAP)<br>• Acute tracheo-bronchitis & acute bronchitis<br>• Non-pneumonic LRTI<br>• Infective exacerbation of asthma<br>• Infective exacerbation of bronchiectasis<br>• Lung abscess<br>• Pneumonia with concomitant COPD (if this service was not already provided elsewhere) | Acute exacerbations of COPD – infective & non-infective (other services already provided) |

[HAP (hospital acquired pneumonia), CAP (community acquired pneumonia), LRTI (lower respiratory tract infection), COPD (chronic obstructive pulmonary disease)].

**Table 13A: Pre-defined Inclusion and Exclusion Criteria to Assess Suitability to Early Supported Discharge Scheme (ESDS)**

| **INCLUSION CRITERIA** | **EXCLUSION CRITERIA** |
|---|---|
| **The below criteria were used to assess suitability for ESDS:** | |
| Simple pleural effusions only (ideally a diagnostic pleural tap is performed in all cases) | Patients with CURB-65 >3 (MUST be discussed with the study doctor prior to discharge to define treatment ceilings and future plans) |
| Can manage ADLs with current support – immediate OT/ physiotherapist/ social assessment/ care can be arranged prior to discharge (if needed) and continued at home | Patients unable to manage at home even with maximal support from ESDS (this may include some patients IV drug users, with ETOH excess or mental health problems) |
| Has a phone | Serious co-morbidities requiring hospital treatment (e.g: CKD, CCF) or deemed unstable (significant AKD) |
| Age>18yrs old | Neutropenia |
| Improving inflammatory markers (WCC/CRP) | Empyema or complicated parapneumonic effusion |
| Stable or improving U&Es | Sats <92% on air (unless patient has underlying respiratory disease [except asthma] when sats <88% - all these cases MUST be discussed with study doctor) |

| | |
|---|---|
| Patients requiring oral or IV antibiotics | SBP <90mmHg |
| EWS ≤2 (see Table 13B) AND SBP >90 AND mild confusion only. All observations must be stable for 12-24hrs | Suspected MI/NSTEMI OR acute ECG changes (within 5 days of discharge date) |
| | Well enough for discharge without ESDS scheme support |
| | Tuberculosis suspected |
| | No fixed abode |

[ADLs (activities of daily Living), OT (occupational therapist), ESDS (early supported discharge scheme), CKD (chronic kidney disease), CCF (congestive cardiac failure), AKD (acute kidney disease), IV (intravenous), WCC (white cell count), CRP (C-reactive protein), sats (oxygen saturations), U&Es (urea and electrolytes), po (per oral), MI (myocardial infarction), TnI (troponin I), SBP (systolic blood pressure), EWS (early warning score – see Table 13B), NSTEMI (non-ST-elevation myocardial infarction, ECG (electrocardiogram), NOK (next of kin)]. NB: If escalation of care not appropriate & palliative care appropriate if no improvement within 48hrs: then ONLY criteria - stable SBP>90 AND sats>90% air AND phone AND >18yrs old apply

**Table 14B: RLBUHT Early Warning Score Scale**

| Score | 3 | 2 | 1 | 0 | 1 | 2 | 3 |
|---|---|---|---|---|---|---|---|
| Respiratory rate (breaths/min) | >35 | 31-35 | 21-30 | 9-20 | | | <9 |
| SpO2 (%) | <85 | 85-89 | 90-92 | >92 | | | |
| Temperature (C) | | >38.9 | 38-38.9 | 36-37.9 | 35-35.9 | 34-34.9 | <34 |
| Systolic BP (mmHg) | | >199 | | 100-199 | 80-99 | 70-79 | <70 |
| Heart rate (bpm) | >129 | 110-129 | 100-109 | 50-99 | 40-49 | 30-39 | <30 |
| AVPU | | | | Alert | Voice | Pain | Unconscious |

### 1.2.4 Part 2 - Results

54 case notes were randomly selected from 549 admissions. Of the 54 case notes reviewed, 59% (n=31) of patients coded as CAP had a CURB65 <3. The mean age was 70 (18-96) yrs old and mean CURB-65 = 1.93 (range 0-4). Of n=38 CAP patients, CURB-65 scores were as follows: 0-1=32%, 2 = 26%, 3-5 = 34%. 46 patients were **eligible** for ESDS and of these 22 (48%) were suitable. 85% (n=39) of **eligible** patients had co-morbidities, but these did not necessarily make patients **unsuitable** for ESDS. Co-morbidities were common and are described in detail in Table 14. Where discharge was deemed to be delayed reasons are described in Table 15. We calculated the total reduction in LOS with ESDS using our inclusion/exclusion criteria as 2.75 (1-7) days.

**Table 15: Percentage of All Patients Coded as Community-Acquired Pneumonia with the Top Four Associated Co-morbidities**

| CO-MORBIDITY | n (%) |
|---|---|
| Chronic Obstructive Pulmonary Disease (COPD) | 16 (30%) |
| Cancer | 13 (24%) |
| Ischaemic heart disease (IHD) | 10 (19%) |
| Dementia | 8 (15%) |

NB – multiple reasons may apply

**Table 16: Reasons for Delayed Hospital Discharge for Patients Coded as Community-Acquired Pneumonia**

| REASON FOR DELAYED DISCHARGE | n (%) |
|---|---|
| Unstable non-pneumonia acute/ chronic co-morbidities | 9 (17%) |
| Delayed medical review or senior medical review | 6 (11%) |
| Lack of social support | 5 (9%) |
| Awaiting medical investigations<br><br>(Urgent out-patient investigations were deemed suitable) | 2 (4%) |

NB – multiple reasons may apply

## 4.3 DISCUSSION

### Our Findings

Data from the first audit (part 1) showed that although coding at RLBUHT was poor, the specific diagnosis (i.e. LRTI – no radiological consolidation, pneumonia – definite radiological consolidation) had little effect on LOS. The data showed that mortality from pneumonia increases with age and that co-morbidities, complications and co-presenting medical issues were common in these patients and significantly affected LOS. We had hypothesised that women may have a longer LOS as they are more likely to be widowed and therefore living alone with a lack of social support; however, gender had no effect on LOS.

The second audit (part 2) suggested that a proactive ESDS scheme could enable almost 50% of patients to be provided with high-quality safe, effective, efficient patient-centred care, tailored to their needs, in their own home and that this 'hypothetical' intervention was both amenable to and worthy of randomised control trial (RCT) testing. To maximise effectiveness since data from the first audit suggested LOS was the same for both LRTI (no radiological consolidation/ infiltration) and pneumonia (radiological consolidation/ infiltration) we decided that conditions beyond CAP should indeed be included in such a trial. Most patients had co-morbidities but these did not necessarily make patients unsuitable for ESDS. To provide an early discharge we needed to affect the reasons for delayed hospital discharge that we had found in this audit. If a senior experienced clinician was available for daily medical reviews for potentially suitable patients, if there was access to urgent outpatient clinic appointments (the wait at the time of this audit for a respiratory clinic appointment was over 16 weeks) and if we were able to also provide immediate light 'social support' by a team member attending the patient's home up to twice per day (and could assist with some care

needs/bring or arrange food etc) then we may be able to assist with supporting a patient at home to enable an earlier hospital discharge.

We hypothesised that a more heterogeneous group of patients, including those with lower respiratory tract infections (LRTI) and even with hospital-acquired pneumonia (HAP) could also safely benefit from such a scheme. Miscoding is commonplace meaning that these data are in fact from patients with 'LRTI' (with and without radiological consolidation/ infiltration) rather than patients with definite pneumonia (i.e. radiological consolidation/ infiltration). Hospital Episode Statistics (HES) data from England for pneumonia, influenza with respiratory manifestation and acute LRTI (2009-10), showed annual admissions of over 250,000 per year, using this in combination with an ESDS utilising these broader inclusion criteria resulting in a total reduction in median LOS of 2.75 days we calculated a potential saving of 687,500 bed days annually in England. With a conservative estimate of 2400 pneumonia admissions annually & a 10-day mean LOS (=24,000 bed days/yr), an ESDS could result in 6600 bed days/yr saved in the RLBUHT alone.

**Strengths and Weaknesses**

These two audits/ studies are simple and brief with clear aims and objectives. Since the coding was poor what we had initially thought would be pneumonia data were in fact a 'mixed bag' of CAP, HAP and LRTI (with no radiological consolidation/ infiltration). The studies were used as a scoping exercise and feasibility test respectively hence their retrospective nature.

**Similarities and Differences**

ESDS for people with acute exacerbations of COPD exist; care is usually provided by a hospital outreach team which included specialist respiratory nurses and access to usual primary care. A Cochrane review of COPD HAH showed a trend towards lower mortality in the HAH group (P = 0.07); however no firm conclusions could be made with regards to health-related quality of life, and direct costs. The reviewers concluded that selected patients with acute exacerbations of COPD can be safely and successfully treated at home with support from respiratory nurses (203).

Coding difficulties are well known. In the US by assigning sepsis and respiratory failure codes more liberally, hospitals might improve their reported performance for pneumonia. This may bias efforts to compare hospital performance regarding pneumonia outcomes (204).

In the UK between 1997 and 2005 there was a marked increase in hospitalisation rates for patients with a primary diagnosis of pneumonia; the increase was more marked in older adults. As in our data, median LOS, mortality rate and the presence of comorbidities were highest in the older age groups. The median duration of stay in hospital increased with age. The LOS for patients <65 years was 3 days vs 9 days >85 years ($p<0.001$), both notably shorter than our LOS at RLBUHT (8).

**Implications**

These studies imply that an ESDS may indeed be feasible for patients with LRTI and may significantly reduce hospital LOS. Chapter 5 describes how we set-up and ran a feasibility study of an ESDS called HOME FIRST - **Home F**ollowed-up with **I**nfection **R**espiratory **S**upport **T**eam.

## 4.4 ACKNOWLEDGMENTS

In this chapter, I would like to acknowledge my predecessor, Dr Sherouk el-Batrawy for her initiation of the audit process in part 1, Dr Adam Hill, Dr Wei Shen Lim, Dr Mark Woodhead, Prof Stephen Gordon and Dr Dan Wootton who attended a IDRN meeting in Lancashire in 2010 with myself, to discuss and prioritise research ideas related to pneumonia in adults in the UK – the idea of home-based care for patients was initially conceptualised and discussed at this meeting, and Dr John Williams, Dr Lisa Davies and Dr Justine Hadcroft for helping with the ESDS inclusion/exclusion criteria. Dr Sarah Wilks assisted with data collection for part 2 of the audit.

# CHAPTER 5: Home-based Care - HOME FIRST Feasibility Study for Early Supported Discharge in Adults with Respiratory Infection.

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## 5.1 INTRODUCTION

Seventy percent of UK pneumonia admissions are for patients with low-risk pneumonia (CURB-65 score 0-2) (90); guidelines suggest that these patients do not require admission however they account for a significant proportion of bed days and costs (106). Often, factors other than disease severity prompt or prolong hospital admission such as the inability to cope at home alone or to tolerate oral antibiotics, co-morbid illnesses, homelessness and substance abuse (112, 205). Reduction of the resource burden of inpatient care for patients with pneumonia and LRTI is an international priority (5) (6). With the provision of medical support at home (hospital at home – HAH) many more patients with pneumonia and LRTI could be managed as outpatients (98). The evidence base for HAH schemes in pneumonia and LRTI is very limited. A recent expert review suggested that supported home care for patients with CAP 'shows enormous potential for improving the care of elderly and disabled patients, and should be further evaluated in terms of efficacy and cost-effectiveness' (117).

This chapter describes the **Home F**ollowed-up with **I**nfection **R**espiratory **S**upport **T**eam (HOME FIRST) prospective randomised controlled feasibility study. The concept of HOME

FIRST - an early supported discharge scheme (ESDS) for patients with LRTI (including pneumonia in this definition) was developed and we set out to recruit sequential patients admitted to the Royal Liverpool and Broadgreen (RLBUHT) and Aintree University (UHA) Teaching Hospitals with symptoms of LRTI. With this proactive, innovative and creative ESDS we aimed to enable patients with LRTI to be provided with high-quality safe, effective, efficient patient-centred care, tailored to their needs in their own home; therefore, improving the overall experience of the service-user and patient outcomes whilst reducing hospital LOS.

The HOME FIRST strategy was to improve health policy, healthcare delivery and services and to simultaneously reduce hospital length of stay (LOS), an area of major strategic importance to the NHS. A DoH/NHS document stated that 'The NHS will support creative approaches to service provision, which will improve choice, personalisation, efficiency and effectiveness e.g. identify new service solutions to avoid …. hospital admissions and deliver new and innovative services in community settings/homes' (206). There are potential aspirational benefits of such a scheme these may include patient-related benefits such as:

- Reducing risk of HAI (HAP, MRSA and *C. difficile*) (115)
- Able to be cared for in their own home
- Improved sleep (118)
- Faster recovery
- Increased satisfaction (patients and carers) (97, 118)
- Reduced risk of delirium

- Reduced chance of later post hospital discharge institutionalisation.

And health service benefits such as:

- Reduced hospital LOS (economic benefit)
- Reduced risk of HAI (economic benefit)
- Improved self-management of condition (through improved education given by HOME FIRST team as they have more time per patient than clinical staff on the wards).

This was a feasibility study and patients were randomised to either standard hospital care (SHC) or ESDS in order to assess patient's acceptability to the randomisation process.

## 5.2 METHODS

### 5.2.1 Overview

For full details see the study protocol in Appendix A. We carried out a feasibility study of a randomised trial of early supported discharge scheme (ESDS) versus standard hospital care (SHC) for patients admitted to hospital with pneumonia or lower respiratory tract infection (LRTI). We recruited from January – April 2012, aiming to recruit 10 patients to each arm of the study.

Standard hospital care in our city-centre teaching hospital consists of patients being admitted through the emergency department (self-presenting) or directly to the acute medical admissions unit (AMAU) via a GP. All patients that are to remain inpatients then stay on AMAU for at least 12 hours in general prior to ward transfer. On the AMAU, the patient was clerked by a junior doctor, and then reviewed by an acute medical consultant within 12 hours on the post-take ward round prior to transfer to a medical (general, elderly, respiratory or infectious

disease) ward, depending on bed capacity. After this the number and seniority of reviews differs per ward but in general consultant wards rounds occur 2 – 3 times weekly and registrar ward rounds once to twice weekly, the patient was reviewed on a daily basis on week days by a FY1, 2 or CMT trainee when there was no senior doctor ward round. Patients are referred to respiratory medicine for specialist opinion as deemed necessary by their team.

In order to participate, patients were required to meet study eligibility criteria (designed to identify patients suitable for early supported discharge from hospital) and provide written informed consent. With regards to patients with CAP, all CURB-65 scores were considered. We decided to include patients with CAP, HAP, aspiration pneumonia and LRTI. We made this decision as we wanted the scheme to be inclusive of all patients with respiratory infection rather than prescriptive like many of the current COPD schemes that only accept patients without consolidation and with a formal diagnosis of COPD, but without other existing respiratory disease such as chronic asthma or interstitial lung disease.

The main developments / alterations from the pneumonia audits in Chapter 4 were:

1. Patient's still requiring IV antibiotics were excluded from the feasibility study (deemed not yet clinically stable for hospital discharge and therefore not suitable for ESD). This therefore excluded many patients with significant infective exacerbations of bronchiectasis and lung abscesses.

2. Only patients with full mental capacity able to give informed consent were included in the feasibility study.

*3.* Patients in whom further escalation of care was felt to be inappropriate if continued clinical deterioration were to occur were excluded from the feasibility study.

These criteria alterations were made by the study team and the patient and public involvement (PPI) group (see Chapter 2 - Methods) in order to minimise the risk to patients discharged from hospital with HOME FIRST and to enable feasibility testing of the acceptability of randomisation.

### 5.2.2 Safety

#### 5.2.2.1 Patient Safety

An experienced specialist respiratory doctor (a senior respiratory registrar with more than 10 years of clinical experience) and respiratory nurses (band 6) with ward and community experience used strict patient selection criteria (Table 16, 17 and 18) to ensure patient safety. Patients in the HOME FIRST arm received thorough education and personalised verbal and written self-management plan for their specific condition, a digital thermometer and a detailed patient information leaflet (PIL) with 'red-flag' symptoms that should prompt contact with the study team (Appendix C): fever >38$^{o}$C, increasing drowsiness, worsening cough/ sputum or increasingly unwell. The study team provided daily patient monitoring, regular home visit and a 24hr telephone on-call service. A portable observation machine was used by the HOME FIRST team to monitor blood pressure (BP), heart rate (HR), oxygen saturations (sats) and temperature during home visits. Pendant 'lifeline chains' were supplied if necessary. Fast tracked re-admission was arranged if required. A coordinated multi-disciplinary team (MDT) was important to optimise care for patients in the HOME FIRST arm; all patients were discussed at a weekly case-notes meeting. Fast-track readmission was arranged if deemed necessary. We collected data regarding pneumonia recovery (CAP-SYM) and functional health status (SF-12) [see section 5.2.4.5] during the study to allow us to assess any significant lack of return to baseline in order to ensure that early discharge was not

detrimental to a patient's health. CAP-SYM (CAP Symptom questionnaire) is a practical patient-based outcome questionnaire that evaluates symptoms in CAP. It is an 18-item, interviewer-administered questionnaire that measures the severity of 18 symptoms during the past 24 hours using a 6-point Likert scale. It is more responsive than the generic SF-36 as a measure of outcome in CAP (207).

We planned to stop the study if there was any mortality in the HOME FIRST arm whilst patients were at home. In the event of a serious AE (SAE) the REC and sponsor(s) were informed immediately.

#### 5.2.2.2 Staff Safety

Specific important staff safety issues were carefully considered and addressed since staff were attending a patient's own residence. Staff carried personal GPS tracking alarm devices at all times.

#### 5.2.2.3 Sites

The study was conducted at 2 sites, RLBUHT (750 beds in city-centre) and UHA (743 beds in suburban area). They were chosen as they are large tertiary hospitals with high rates of pneumonia and LRTI admission. Liverpool is an area of poor lung health for many reasons including due to tobacco smoking habits, industrial exposures, poverty and malnutrition. The catchment area for the RLBUHT (and UHA) is relatively small (the maximum distance that most patients live from RLBUHT is 6 miles) making home visits relatively practical without long journey times.

### 5.2.4 Screening, Recruitment, Randomisation and Intervention

#### 5.2.4.1 Screening

Patients from AMAU, ED and other wards within RLBUHT and UHA were screened. Potentially eligible patients were identified using a standard protocol. Only patients who would have required *at least one more night of hospitalisation before discharge* were considered. We hypothesised that various reasons for this continued hospitalisation may exist, since there is no specific guidance as to when a patient recovering from LRTI is suitable for discharge and therefore inter-physician variability exists. Where the study doctor considered a patient well enough for discharge without support, the usual medical team were notified. Age, gender and reason(s) for a lack of eligibility/suitability were noted for all screened patients. Patients already on home oxygen ($O_2$) therapy with chronic respiratory disease were included in the study if their saturations were >87% on their usual $FiO_2$. Screened patients were entered into a screening log in order to track their admission.

The study team were in regular communication with bed managers, nursing and medical co-ordinators in A&E, the medical admissions unit and the respiratory wards at RLBUHT and UHA. A list of potential patients was generated on a daily basis in combination with these personnel, and discussed twice per day at pre-defined times (by phone or bleep) to alert the study team to a potential recruit.

#### 5.2.4.2 Inclusion and Exclusion Criteria

All CURB scores were accepted. Tables 16, 17 and 18 describe patient eligibility, inclusion and exclusion criteria in detail.

**Table 17: Eligibility Criteria for the HOME FIRST Feasibility Study**

| | |
|---|---|
| Patients with any of the following conditions: | • Pneumonia – CAP or HAP [radiological consolidation and symptoms/signs of respiratory infection] N.B. if CURB-65 ≥3 MUST have had at least 24hrs of in-patient observation before recruitment.<br><br>• Non-pneumonic lower respiratory tract infection [No radiological consolidation but symptoms/ signs of respiratory infection]<br><br>• Pneumonia with concomitant COPD (if this service is not provided elsewhere) |

[(CAP (community acquired pneumonia), HAP (hospital acquired pneumonia), COPD (chronic obstructive pulmonary disease)].

**Table 18: Inclusion Criteria for the HOME FIRST Feasibility Study – to assess suitability**

| **INCLUSION CRITERIA** | |
|---|---|
| Features on history | • Patient able to give fully informed consent<br>• Has a phone<br>• Age>18yrs old |
| Features on examination (stability indicator) | • ≤2 (EWS – see Table 13B) *AND* SBP>90 *AND* AMTS ≥7. All observations must be stable for 12-24hrs |
| Features of social situation | • Can manage ADLs with current support (immediate OT/physiotherapy/social care can be arranged) |

[EWS (Early warning score), SBP (systolic blood pressure), AMTS (Abbreviated mini-mental test score), WCC (white cell count), CRP (C-reactive protein), U&Es (urea and electrolytes, (ADLs (activities of daily living), OT (occupational therapist)].

The justification for the inclusion criteria were as follows;

- The study was focused on adults with LRTI, therefore it was inappropriate to include patients younger than 18.
- Stable and improving observations indicated a patient was likely to be beginning to recover and therefore with HOME FIRST monitoring, and should therefore be safe to recover at home.
- An early supported discharge scheme (ESDS) should have been of benefit to the patient; therefore it was essential that they were able to manage with activities of daily living (ADLs); otherwise this would have caused more burden to the patient.
- A telephone was required for emergency use and to keep patients updated.
- Fluent English was required in order for the patient to understand the aims of the study, to communicate over the telephone with the study team and if complications arose to be able to take action without a translator.

**Table 19: Exclusion Criteria for the HOME FIRST Feasibility Study – to assess suitability**

| **EXCLUSION CRITERIA** | |
|---|---|
| Features on history | • Well enough for discharge without home care support<br>• No fixed abode |
| Features on examination (instability indicator) | • SBP <90mmHg<br>• Increasing inflammatory markers (WCC/CRP)<br>• Increasing U&Es (If known CKD an increase in baseline of <25% was acceptable, as long as eGFR not <15)<br>• For patients with chronic respiratory illness: sats <88% on air [except asthma]<br>• For patients without chronic respiratory illness: sats <92% on air |
| Features of diagnosis (indicating cause for concern) | • Suspected MI/ raised TnI/ T consistent with NSTEMI within 5 days of discharge<br>• Empyema or complicated parapneumonic effusion<br>• Tuberculosis suspected<br>• Neutropenia<br>• Acute exacerbations of COPD – infective & non-infective (other services are already provided)<br>• Serious co-morbidities requiring hospital treatment (e.g: CKD, CCF) or deemed unstable (significant AKD) |

| | |
|---|---|
| Features of social situation | • Patients unable to manage at home even with maximal support (e.g. IV drug users, alcohol excess or mental health problems) |

[COPD (chronic obstructive pulmonary disease), CKD (chronic kidney disease), CCF (congestive cardiac failure), AKD (acute kidney disease), IV (intravenous), sats (oxygen saturations), MI (myocardial infarction), TnI/T (troponin I/T), SBP (systolic blood pressure), NSTEMI (non-ST-elevation myocardial infarction].

The justification for the exclusion criteria were as follows:

- Acute COPD exacerbations were excluded as these patients were more suited to the ACTRITE (Acute Chest Triage Rapid Intervention Team) discharge team which is an already established service at RLBUHT and UHA.
- Patients observations were required to be within the ranges stated; if not they were excluded as they may have required continued hospital admission or have been at higher risk of deteriorating at home.
- Patients with lower oxygen saturations were carefully considered as their condition may not have improved sufficiently for ESDS – clinical judgement was required for patient safety purposes.
- Serious co-morbidities and other respiratory diseases were considered carefully and patients were excluded if other conditions may have hindered their progress at home and warranted hospital readmission.
- Similarly, to the inclusion criteria, ESDS should aim to benefit the patient, therefore patients were excluded if they did not have a fixed abode or study staff believed they would have struggled even with HOME FIRST support.
- Patients well enough for discharge were discharged as normal as continued support would not necessarily have been of benefit.
- Rather than prescriptive numbers or percentage increase/decrease for CRP/WCC and U&Es, we used a more pragmatic approach of excluding patients only with bloods that were obviously deteriorating. Patients with acute kidney injury could only be considered when their renal function was at or <125% of baseline. If the patient had known CKD an increase in baseline of <25% was acceptable as long as eGFR was not <15.

#### 5.2.4.3 Repeat Reviews

Patients admitted to hospital are generally acutely ill; therefore repeated reviews were often needed in order to track patients' progress to the point where they may have been suitable for recruitment.

- At their screening visit potential patients may not have been well enough for discharge. These patients required repeat review at a defined later date to give time for the condition to settle. Some of these patients ended up being discharged / self-discharge before this first repeat review, whilst others remained unwell for longer requiring continued hospitalisation.
- Some patients were well enough to go home but were awaiting blood or scan results – in some instances these were followed up by HOME FIRST team and did not need to prevent recruitment.

#### 5.2.4.4 Randomisation

If a patient was selected for inclusion and consented to participation, they were then randomly assigned using computer generated random numbers to receive either ESDS or SHC. Allocation was obtained by telephoning an independent co-ordinator (closed envelope system).

#### 5.2.4.5 Recruitment

A clinical examination and mental state (an Abbreviated Mental Test Score [AMTS]) assessment were conducted. A repeat AMTS was then performed if a staff member was concerned about increased confusion in that patient.

Recruited patients provided a clinical history, were examined by the study doctor and completed an SF-12 (Short Form-12) questionnaire (208) (functional and quality of life assessment tool) at day 0 [Appendix D] and two CAP-SYM (Community-Acquired Pneumonia Symptom) questionnaires (207) (symptom score) for day 0 and day 'minus 30' (the patient was asked to recall their symptoms from 30 days prior to study recruitment) [Appendix D].

Baseline clinical data including age, gender, history of presenting complaint, past medical history, a complete social history, drug history and allergies, was recorded by the study doctor. SF-12 and CAP-SYM questionnaires (+/- clinical bloods as needed) were completed on day 0, 2 and 7; for patients who had been discharged, these investigations were performed in their home.

#### 5.2.4.6 Study Intervention – HOME FIRST

The patient was followed by the same study doctor until stable for discharge from the ESDS, after this, care was provided by their general practitioner as usual. Fast-access to discharge medications, a disease-specific patient information leaflet and 'meals-on-wheels' (ready-made food delivery service) were provided as required. Oxygen [$O_2$] (if not already receiving domiciliary $O_2$), intravenous (IV) fluids and IV antibiotics were not provided.

Patients in the ESDS arm were transferred home the same day with appropriate medications, an emergency 24hr contact telephone number, a list of symptoms to prompt healthcare contact (fever> 38$^{o}$C, increasing drowsiness, worsening cough or sputum and/or increasingly unwell) and an observations machine capable of recording temperature, blood pressure (BP), heart rate (HR) and $O_2$ saturations. If discharge was before 3pm the patient was reviewed at home later that evening by the team; if after 3pm the review was the next morning.

For all readmissions a 'treatment failure or complication development' proforma on the CRF was completed. Home visits occurred from 08.00 - 17.00 up to 5-days-per-week. Telephone visits were available 7 days per week with 24hr cover via telephone to the HOME FIRST study team. In the event of an emergency an ambulance was called by either the patient/relative/carer or on-call study member. If the patient needed non-emergency medical attention at home between 17.00 - 08.00 week days or at weekends, a district nurse or out-of-hours GP was contacted by the study team.

#### 5.2.4.6.1 Initial and Subsequent Follow-up with HOMEFIRST

Patients randomised to HOME FIRST care initially received up to twice daily respiratory specialist nurse visits for the first 48 hours. After this time period, the frequency and duration of visits depended on clinical need. Telephone calls were used instead of home visits where the study team felt this suitable. Each visit lasted between 10-30mins.

There was no maximum duration of follow-up. The study nurse established the need for the involvement of other MDT team members. Laboratory tests were performed as clinically indicated at the discretion of the study team. Frequency of venepuncture depended on clinical assessment of need by their regular medical team. If a patient became unwell they called the emergency numbers on the emergency PIL (Appendix C).

Patients discharged from hospital remained the responsibility of the PI during the time that they were supported by HOME FIRST. The patient's GP and hospital consultant (as of discharge day) were informed of any specific interventions and outcomes by dictated discharge summary. Patients recruited to the study that were randomised to SHC remained under the care of their current consultant.

#### 5.2.4.6.2 Discharge from HOME FIRST

In order for discharge from HOMEFIRST, patients had to fulfil all 7 criteria:

(1) Resolution of the reason for prolonged hospitalisation

(2) Temperature<37.5$^{o}$C

(3) SBP>90mmHg

(4) $O_2$ saturations > 86% on oxygen or 90% on air

(5) 50% reduction in highest CRP (unless non-infective reason for high CRP)

(6) Stable non-pneumonic co-morbidities (patient handed over to community team if further follow-up needed)

(7) Able to manage with current care level

#### 5.2.4.6.3 Readmission to Hospital from HOME FIRST

Patients could be readmitted to the hospital as determined by the study team via the bed managers at any time. The PI was notified of all readmissions. Observations in many of our cohort were not expected to be within normal physiological limits due to their many other co-morbidities predominately respiratory and cardiac.

If the team were at all concerned, the study doctor was contacted. They then either arranged for direct readmission via AMAU, arranged to visit the patient, arranged to see the patient in the CRU or gave advice to the patient over the phone. The CRF provided the study team with a guide for recognising patients needing consideration for readmission to hospital, using a simple set of clinical and functional questions. Reasons for readmission were: social concern (by patient or staff), reduced eating & drinking, a fall, increasing CRP/WCC, the inability to

take antibiotics, oxygen saturations drop >2%, RR rise ≥10bpm, Temp ≥38$^{o}$C, persistent symptoms of fever, GCS drop≥2, No PU>12hrs and any other cause of clinical concern.

#### 5.2.4.7 Standard Hospital Care (SHC) Arm

All management and discharge decisions in SHC arm were made by the patient's usual hospital team. Clinical tests were performed at the discretion of the medical team. If any significant or concerning clinical issues were noted during study team's visits, the usual medical team was alerted. Patients recruited to the study who were randomised to SHC remained under the care of their current consultant. SHC comprises of both systematic and as required medical review in our hospitals.

#### 5.2.4.8 Follow-up

Two weeks after recruitment all patients and their next of kin (NOK)/carer received a telephone call from an independent assessor to complete a care satisfaction questionnaire (Appendix D). All patients were asked to attend an outpatient appointment (OPA) at 1 and 6 months post recruitment; a clinical assessment, CAP-SYM, SF-12 and bloods (including serum) +/- chest X-ray were performed.

### 5.2.5 Outcome Measures

Our study question(s) were: (i) Is a study in which patients are randomised to ESDS or SHC acceptable to patients? (ii) Can selected patients with respiratory infection benefit from care at home?

#### 5.2.5.1 Primary

Our primary outcome was patient acceptability to randomisation. We aimed to assess the patient uptake of participation in a study in which participants are randomised to early supported discharge with HOME FIRST or SHC. Uptake/acceptability in this study was defined as - the proportion of patients that are both eligible and suitable (fit all inclusion/exclusion criteria) who are prepared to 'ACCEPT', and give their consent to, be involved in a research study in which they are randomised to either SHC or HOME FIRST compared to the proportion that are eligible and suitable and do not give their consent.

#### 5.2.5.2 Secondary

**A. Safety (mortality and readmission rates)**

We assessed the safety i.e. to ensure there was no delayed recovery (using CAPSYM and SF-12 at 6 weeks), no increase in pneumonia (or non-pneumonia) complications (readmission rates) or increase in mortality in the HOME FIRST arm. HAI/delirium was noted. We aimed for equivalence.

**B. Patient and carer satisfaction**

HOME FIRST should have at least equivalence with SHC. A validated questionnaire was conducted via telephone to both patient and NOK/main carer).

**C. LOS in hospital and total LOS (including hospital and home care)**

**E. Functional status (physical and mental) and quality of life (QOL)**

Validated (CAP-Sym and SF-12) questionnaires were completed to assess recovery. We aimed for equivalence.

**F. Operational and logistical questions -**

e.g. what frequency of home visits is required and for what duration? What is the maximum number of patients that can be safely looked after at home with HOME FIRST at one time?

### 5.2.6 Sample Size and Statistical Methods

To identify >50% decline in consent (at 80% power) required a sample size of 22 patients (to be recruited). We estimated that we would need to screen a minimum of 100 patients in a single winter season.

## 5.3 RESULTS

Patient screening and recruitment are summarised in the consort diagram (Figure 9). Briefly during the 4-month study period 200 patients with symptoms suggestive of respiratory infection were screened. Of these 158 were ineligible (reasons summarised in Table 19), unsuitable or their physician declined. The most common reason for exclusion or non-recruitment was the inability to give informed consent. Broadly these can be categorised into medical reasons (66%), social reasons (19%) and other reasons [‘missed’ or declined] (15%).

Of the 42 eligible patients, 18 declined consent (either patient themselves or NOK or carer), 10 were missed at repeat review and 14 were recruited and randomised to either standard hospital care [SHC] (n=6) or early supported discharge scheme [ESDS] (n=8).

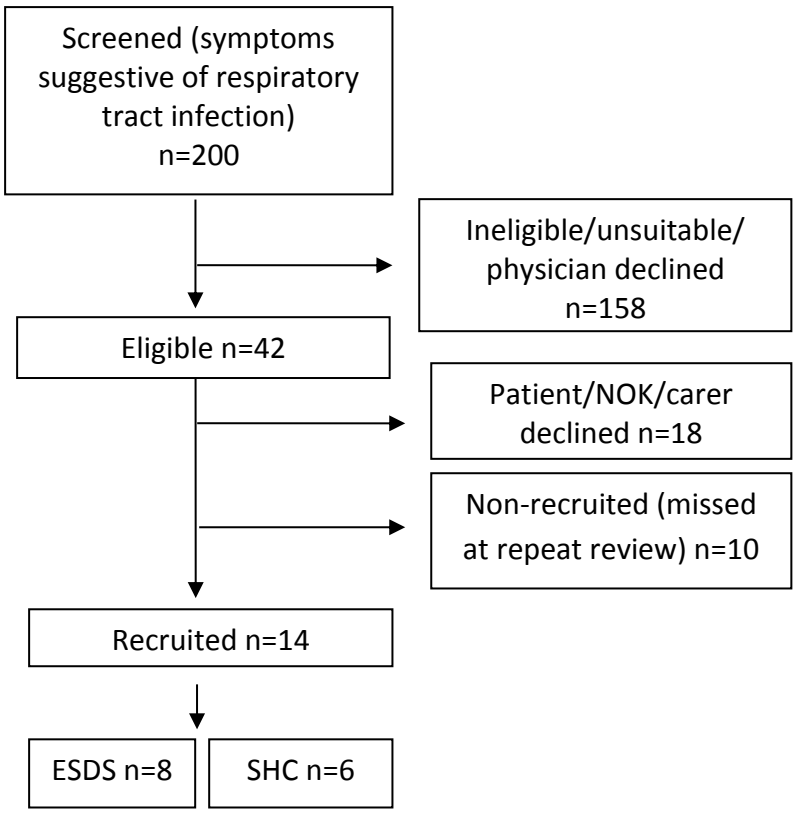


**Figure 9: Screening and Final Recruitment Numbers**

Note no patients withdrew consent or were lost to follow-up. 'Missed' means missed due to logistical reasons e.g. by the time of repeat patient review by the study team the patient was well enough for discharge without ESDS support or the patient was discharged outside of the hours/days of study recruitment.

**Table 20: Reasons for Non-recruitment**

| **Reasons for non-recruitment** | **N** | **%** |
|---|---|---|
| Confusion (Abbreviated Mini-mental Test Score <7) | 37 | 20 |
| Require more complex multi-disciplinary team input (physiotherapy, occupational therapy, social services) | 35 | 19 |
| Infective exacerbation of COPD [other services available] | 20 | 11 |
| Other co-morbidities requiring in patient stay | 18 | 9.5 |
| Clinical deterioration or mental health issues | 17 | 9 |
| Patient declined | 13 | 7 |
| Awaiting investigations to exclude pulmonary emboli | 11 | 6 |
| 'Missed' | 10 | 5 |
| Too well (suitable for discharge without support) | 10 | 5 |
| Carer/next of kin declined | 5 | 2.5 |
| Too hypoxic | 4 | 2 |
| No respiratory infection | 3 | 2 |
| INR issues | 3 | 2 |
| Total | 186 | 100 |

INR – international normalised ratio, COPD – Chronic Obstructive Pulmonary Disease.

The demographics and clinical characteristics of those recruited and those who declined are shown in Table 20. Reasons given by patients for not wishing to consent included extra blood tests [n=1], extra outpatient appointment [n=1], 'feel too unwell for home yet' [n=5] and other ('not keen on research', 'steep stairs', 'daughter on holiday') [n=5]. The mean age of recruited patients was 64.6 (29-90) yrs old; this was lower than in those whose NOK declined consent. Subjects were allocated a CURB-65 score whether or not consolidation was seen on their chest radiograph. New radiological consolidation was defined as definite, possible or none; this was decided by discussion between 2 respiratory clinicians. The median CURB-65 of all recruited patients was 1 (range 0-3), the majority of patients lived with spouse or family (72%) compared to all of those whose NOK declined who lived alone. The average time from admission to recruitment was 8 (1-9) days. Two recruited patients had positive microbiology – one *Haemophilus influenza* in sputum, the other *Streptococcus pneumoniae* in blood cultures.

**Table 21: Demographics and Characteristics of Patients who Declined or were Recruited**

| | Declined | | Recruited | |
|---|---|---|---|---|
| | **Patient (n=13)** | **NOK (n=5)** | **SHC (n=6)** | **ESDS (n=8)** |
| **Age (mean [range])** | 66 [25 – 84] | 79 [68 – 87] | 70 [52 – 90] | 61 [29 – 82] |
| **Gender (M:F)** | 6 : 7 | 3 : 2 | 2 : 4 | 5 : 3 |
| **Smoking status** | Not recorded | | Ex - 3<br>Current - 2<br>Never - 1 | Ex - 3<br>Current - 2<br>Never - 3 |
| **Social history** | Live alone - 4<br>With spouse - 6<br>With family - 3 | Live alone – 5 | Live alone - 3<br>With spouse - 2<br>With family - 1 | Live alone - 1<br>With spouse - 5<br>With family - 2 |
| **CURB-65 (median [range])** | Not recorded | | 2 [1 – 3] | 1 [0 – 2] |
| **Total hospital LOS (mean days [range])** | Not recorded | | 8.33 [1 – 31] | 3.4 [1 – 7] |
| **New radiological consolidation/infiltration** | Not recorded | | Definite - 5<br>Possible - 0<br>None - 1 | Definite - 4<br>Possible - 2<br>None - 2 |

Age, gender, smoking status and social history were recorded from screening data.

**Safety and efficacy of intervention**

Two subjects from SHC, and none from ESDS were readmitted (within 30 days) of discharge. There was 1 death in ESDS arm (known palliative lung cancer) and 1 death in SHC arm (aspiration pneumonia on readmission – possible underlying lung malignancy). The total LOS was 8.33 (1-31) days in SHC and 3.4 (1-7) days in the ESDS arm respectively. One subject from the SHC arm developed a presumed HAI. The maximum number of home visits needed was 4 (generally 1-3). The total LOS in the ESDS was between 2- 6 days. Subject and carer/NOK satisfaction was generally good.

Twelve subjects completed all SF-12 questionnaires [day 0, 2, 7 and 28]. Overall mean increase of 0.4 points (±S.D. 0.2)/subject was seen in SHC, and 1 point/subject in ESDS between day 0 and day 28; therefore, no statistical difference was seen. NB: using the SF-36 (a similar questionnaire with 36 questions) a 20-point change in the scale is believed to represent a clinically meaningful change; using SF-12 at least a 6-point change is deemed necessary for clinical significance).

With regards to symptom improvement, using CAP-SYM questionnaires, % recovery at day 28 (from baseline) could only be calculated in 3 SHC and 6 ESDS patients; with 88% and 90% recovery seen respectively at 28 days; therefore, no statistical difference was seen between the 2 groups.

During the study, we collated a table of the common obstacles to recruitment (Table 21) that mainly refer to staff practice within the hospitals.

**Table 22: Common Obstacles to Recruitment**

| | |
|---|---|
| Medical | • Pneumonia may be a vague diagnosis in hospital practice therefore large numbers of patients with respiratory infection need to be screened to find eligible patients<br>• Lack of capacity to give consent |
| Staff | • Lack of physician 'buy-in' and resistance to change |
| Social | • Hospital stay may be seen as a respite opportunity for some carers |
| Patient belief | • Some patients believe that they must be 100% better before hospital discharge; some were suspicious of a new or research-based service. |

## 5.4 DISCUSSION

In this feasibility study we have shown that using defined criteria for recruitment and a defined interventional package, it is feasible for some patients with LRTI and pneumonia, who would otherwise have been treated in hospital, to be treated at home.

The ESDS package was successfully implemented in 7 patients with no adverse events. Randomisation was acceptable to patients and only deters those who *do not* wish to go home. The main strengths of this study are its novelty. We have been able to recognise common recruitment obstacles and find solutions to aid future project development. It has been noted previously in similar schemes that patient/carer refusal tends to reduce if a scheme becomes an adopted hospital service rather than a research project.

The weaknesses of this study are that it is a small feasibility study in a single city therefore no powered outcome data are available. The criterion of requiring *at least one more night of hospitalisation* is a subjective one. The overall aim of the study is to reduce hospital bed days within a 'real-life' hospital setting in the UK. One more night of hospitalisation may be due to a variety of reasons and cannot simply be defined according to pre-defined signs or symptoms, as appropriate time for discharge for a patient with LRTI is physician-specific and no specific guidelines exist. We considered reasons that a patient would have 'taken up' a bed in hospital for at least one more night if ESDS were not available, these included: the need for further daily INR checks and low molecular weight heparin administration (with no facilities to have this performed immediately daily in the community), physician suggesting a further period of inpatient review for at least 24 hours after having changed from intravenous to oral antibiotics to ensure no pyrexia develops, no ability to get food supplies in at the patient's home until the next day and insufficient ward staff to organise oxygen delivery and

transport the same day, all leading to delayed discharge. All patients recruited received more intensive medical care than standard hospital care due to clinician sampling visits; this may affect the results of satisfaction questionnaires. Questionnaire data may be subject to recall bias. Also day 0 was defined as the day that the patient was deemed fit to be discharged home with support and not the first day of illness or day of admission; therefore this may not have captured the peak impact of the illness on their symptoms.

Using our current model however large numbers of patients needed to be screened (n=200) in order to recruit low numbers (n=14). The main obstacle to eligibility was lack of capacity to give informed consent. The number of eligible patients could be doubled if chronically confused or demented patients were included. Having noticed this as a recruitment obstacle we also considered whether it was indeed appropriate to include such patients in this research. LRTI and pneumonia is very common in elderly patients who may often have dementia/memory loss, of varying severity, and the respiratory infection itself can cause worsening of this condition or even new acute confusion. It is important that such patients are not excluded from future research to which they would potentially benefit from. We also noticed anecdotally virtual visits (via telephone), rather than home visits may be adequate after the first 48hrs after discharge.

Our study, like previous studies of AA and ESDS for CAP and LRTI have shown recruitment may be difficult. In one study, 985 patients needed to be screened to find 214 eligible and 84 recruits, of which 53 had a diagnosis of CAP (209), in another 540 were screened to recruit 25 in each arm of study (118). In patients with COPD exacerbations only 14- 35% of people were both suitable and agreed to be recruited into the HAH trials, which may limit the potential for a hospital at home approach to be used widely in managing COPD exacerbations (210).

Low programme acceptance has been noted due to decline by physician (11%), patient (38%) or next of kin (36%) (211). A study recruiting 55 patients with CAP in New Zealand in 2005 showed improved patient satisfaction by 40% ($p<0.001$) and improved sleep but increased total days of care and no improvement in symptom score or function at 2 & 6 weeks (118). Other studies have shown reduced bed days and hospitalisation (12% reduction) and overall cost reductions of $1489 and $(CAN) 1016 (121, 209).

We interpret our feasibility study data to indicate that to improve recruitment future study directions should include: (1) *Hospital logistics* - working with hospital management to improve hospital systems to reduce time spent screening ineligible patients, increasing recruitment hours up to 12 hours-per-day, 7-days-per-week and improved ESDS 'marketing' (2) *Medical conditions* - the use of consultee declarations and retrospective consent allowing recruitment of suitable patients who lack capacity [Refer to 2.3] (3) *Staff* - improving physician education with regards to pneumonia and LRTI diagnosis and PE risk in order to reduce over-investigation/defensive practice, better study and clinical team integration (knowledge that the study team can reduce the team's workload by facilitating discharge and conducting out-patient appointments) thereby decreasing physician refusal and earlier patient contact with the study team, enabling closer relationships to be formed thereby reducing the likelihood of 'mixed messages'. We estimate that by implementing the various methods described to overcome barriers to recruitment (in particular recruitment of patients without capacity and improving relationships in order to reduce the patient and carer/NOK participatory decline rate Table 19) that we could improve recruitment by >25%.

This is an opportunity to improve health policy, healthcare delivery/services & reduce admission rates and HAI rates; an area of major strategic importance to the NHS. We have

considered what the components of an effective supported home care scheme for CAP would include. A complete service should incorporate fast-access to occupational therapy, physiotherapy and social services as well as to outpatient investigations and clinics.

Future developments to our model may include accepting patients in whom clear decisions have been made that no escalation in care is appropriate if after 48hrs no improvement is seen as terminal care may be more appropriately delivered at home (212) and also encouraging clear management decisions to be made. Accepting patients on IV antibiotics and developing closer links with 'early response teams' in order to facilitate fast and effective discharge of more complex patients may be useful, as the numbers of hospital beds reduce in the UK (97). Constraints during the feasibility study are discussed in detail in Table 22.

Having therefore established that an early supported discharge scheme (ESDS) for patients with lower respiratory tract infection (LRTI) is indeed feasible; Chapter 6 describes the follow on ESDS pilot study.

**Table 23: Constraints During the Feasibility Study**

| Constraint/issue | Reason | Solution likely for the pilot |
|---|---|---|
| 1. Max no. of 2 patients at home any one time due to safety | Due to team size for patient safety | No, funding and therefore staff is limited |
| 2. No weekend/ evening screening/ recruitment/ home visits | Due to team size | No, due to limited staff resource |
| 3. Lack of engagement by CCG and existing community COPD services | Staff shortages and the need for prioritisation of service provision | No, issues likely to remain unresolved |
| 4. No provision for IV abx in community | Safety | Yes, for patients with bronchiectasis by links with the home IV team |
| 5. Did not recruit patients without capacity | Unaware that this would limit recruitment significantly | Yes, ethics to recruit patients without capacity |
| 6. Extensive discussions with regards to ceiling of care needed in some | Many patients judged to have poor QoL, need advanced care planned and decisions to withdraw care if no improvement within a set time period | Partially, difficult as needs significant integration between senior doctors in the usual team and research team |
| 7. Better social care liaison/ integration | Current NHS systems are poorly integrated | No |
| 8. More effective hospital systems to reduce screening times | No current investment in IT systems | No, unlikely to be resolved |
| 9. Patients not well known to junior and nursing staff therefore no active referring of patients | Due to lack of continuity of care due to EWTD and shift patterns | Partial, better integration/ knowledge of the study team |
| 10. Some patients declined consent as they did not wish for NW to be performed | Did not want extra tests | Yes, remove any extra laboratory samples |
| 11. A NOK may decline consent (or tell their relative not to be involved) | May need/ want a temporary break from carer role | No |
| 12. Patients (especially elderly) finding it difficult to come to terms with an alteration in their | Concern as to why it has changed/ don't like change | Yes, earlier integration with the study team |

| | | |
|---|---|---|
| estimated date of discharge (EDD) | | |
| 13. Different physician management – physician decline | No clear guidance | Partially yes, better integration and knowledge of the study and therefore confidence in the safety of the study |
| 14. Randomisation post-recruitment | Only those patients happy to go home consented | No, randomisation pre-consent is difficult and not common practice. |

## 5.5 ACKNOWLEDGEMENTS

In this chapter I would like to acknowledge ward and clinical research staff at UHA and RLBUHT for assisting with screening and recruitment. The study was funded by an LSTM Respiratory Infection Group departmental grant. The concept of studying admission avoidance or early supported discharge for patients with pneumonia was initially discussed at a 'The Pneumonia Consortium' in the Northwest of England in 2011, I would like to give thanks to Dr Adam Hill, Dr Wei Shen Lim and Dr Dan Wootton for their initial input with regards to this concept.

# CHAPTER 6: Home-based Care - Home First Pilot: A Study of Early Supported Discharge in Patients with Lower Respiratory Tract Infections.

## 6.1 INTRODUCTION

Studies in Chapter 5 established that HOME FIRST – an early supported discharge scheme (ESDS) for patients with lower respiratory tract infection (LRTI) - was indeed feasible but protocol alterations were necessary for a pilot study. Despite the large numbers of potentially eligible patients that needed to be screened in order to recruit patients to the feasibility study, satisfaction was generally good, outcomes at least as good as standard hospital care (SHC) and length of hospital stay (LOS) reduced. Earlier discharge clearly reduces hospital LOS, and therefore significantly reduces cost but may also reduce the risk of deconditioning and hospital acquired infections (HAIs) (213). Our new city-centre hospital building, due for completion in 2017, will have 15% fewer beds, therefore it is of primary importance to our trust that we find other ways to care for patients other than continued acute hospital stay.

From feasibility study data, we decided to address various issues within this pilot in order to improve recruitment; the main alteration was to include patients with a lack of capacity. We also decided to include these patients since they may be the most likely to benefit from such

an intervention. We set out to address (1) *Hospital engagement and study-clinical team integration* – improving the 'marketing' strategy in order to improve staff awareness and knowledge particularly targeting AMAU, ED, respiratory, infectious disease, general medical wards and the complex case management/discharge nurses in order to decrease physician refusal. We planned to make staff aware that the study team could facilitate patient discharge and book and conduct outpatient appointments thereby reducing the workload of the usual care hospital team, (2) *Inclusion criteria* – we decided to use consultee declarations and retrospective consent to allow recruitment of suitable patients who lacked capacity [Refer to 2.3], (3) *Early patient-study team contact* – we planned to approach patients and provide them with a study PIL (Appendix C) ideally on AMAU and prior to clinical stability, to enable closer relationships to be formed thereby reducing the likelihood of 'mixed messages' with regards to estimated discharge dates and likely course of disease and hospital stay, in order to reduce patient and NOK refusal.

We were unable to impact on current hospital systems in order to reduce screening time nor were we able to increase staff resource to allow screening and recruitment to 7 days per week, available staff resource only allowed for 4 days per week, home visits 5 day per week and telephone calls 7 days per week.

This chapter describes the HOME FIRST pilot study.

## 6.2 METHODS

### 6.2.1 Overview

For full details see the study protocol (Appendix A). We carried out a randomised interventional clinical pathway pilot study of an early supported discharge scheme (ESDS) –

termed HOME FIRST PILOT, in which we compared ESDS against standard hospital care (SHC) for patients admitted to hospital with LRTI. For improved clarity the main differences between the feasibility and pilot studies are highlighted in bold in Table 23. We developed a manual of procedures (MOP) and made extensive protocol changes from the feasibility study these were: more flowcharts for operational ease, better integration within the hospital, more telephone consultations, a daily clinical review sheet, a maximum duration of visits of 5 working days, 1 recruitment site only, alterations in inclusion and exclusion criteria (predominately including patients without full capacity to consent), a health economic assessment and clearer staff tasks and responsibilities.

### 6.2.2 Manual of Procedures (MOP)

In complex interventional studies an MOP is commonly used; it is a handbook that details the study's conduct and operations as well as facilitating consistency in protocol implementation and data collection across study staff, participants and site(s). It translates the study protocol into a guideline that describes each step of the study and how it is to be executed. Our MOP contained enough detail that the HOME FIRST pilot study could be run by an individual(s) at another site(s) consistently with only the information contained in the MOP and its appendices.

### 6.2.3 Ethical Principles

This is unaltered from the feasibility study (Chapter 5) with the exception of the ethical issues related to participants that lack capacity and consultee declarations which is covered in Chapter 2.

### 6.2.4 Safety and Adverse Event Reporting

This was unaltered from the feasibility study (Chapter 5).

### 6.2.5 Organisation and Governance

#### 6.2.5.1 Timescale

We planned to screen patients for 2 winter seasons; the first from October 2013 - April 2014 and October 2014 – April 2015 (4 days per week).

#### 6.2.5.2 Population

All patients ≥18yrs old admitted to hospital with LRTI were considered for recruitment. There was no upper age limit. For those patients with radiological consolidation/ infiltration suggestive of pneumonia all CURB-65 scores were considered.

#### 6.2.5.3 Study Site

We recruited at one site only; the Royal Liverpool and Broadgreen Hospital Trust [RLBUHT], Liverpool, UK with 750 beds. This hospital is being rebuilt and the new hospital will have ~ 15% fewer beds.

#### 6.2.5.4 Sponsor

The study was also co-sponsored by RLBUHT Research Development and Innovation (RD&I) office and LSTM (R&D Study Number: 4417).

#### 6.2.5.5 Funding

Funding was provided by a £40K grant in 2013 from the Liverpool Health Partnership (LHP). The Bill and Melinda Gates Foundation Grand Challenges II grant and pneumonia pump priming grants were also used.

#### 6.2.5.6 REC

The local NHS Research and Ethics Committee (REC) North-West Liverpool Central (12/NW/0731) approved the study.

### 6.2.6 Screening, Recruitment and Randomisation

This was broadly the same as the feasibility study. Briefly, a list of potential patients was generated on a daily basis (4 days per week). Suitable patients were then approached by the study team who considered the patient's capacity, clinical condition and appropriateness of their current environment for initial study discussion and a PIL was provided. A full clinical examination was performed by the study doctor before recruitment. Consent, consultee declaration and later retrospective consent (as needed) were taken by a fully trained study team member (Refer to 2.3). Baseline clinical data were recorded, these included age, gender, history of presenting complaint, past medical history, a complete social history, drug/vaccination history and allergies. The patient also completed a clinical history, a SF-12 (functional and quality of life assessment tool) and CAP-Sym questionnaires (pneumonia symptom score) (Appendix D). Only patients who were considered to require *at least one more night of hospitalisation* before discharge by the last senior doctor (registrar or consultant) by whom they were seen that day were considered for inclusion.

At screening some patients were eligible but not currently suitable and therefore were reviewed at a later date for reassessment, multiple repeat reviews were often performed. Patients were not recruited at repeat review if they were: 1) completely ineligible according to eligibility criteria, 2) declined consent, 3) 'missed' due to logistical reasons e.g. by the time of the repeat review the patient was believed well enough for discharge without ESDS support or the patient was discharged outside of the study recruitment times, self-discharged or died, 4) the study was currently full to recruitment (a maximum of 2 patients could be cared for by the ESDS at home at one time). The timeline for repeat review was based on the study team's assessment of when a patient may be eligible by anticipating when IV antibiotic treatment would finish, when $O_2$ saturations would improve, when other clinicians / therapists would have assessed the patient, when inpatient investigations would have occurred and also by study team staffing levels.

Where the study doctor considered a patient well enough for discharge without ESDS support, the usual medical team were informed of this specialist respiratory opinion. Age, gender and reason(s) for a lack of eligibility/suitability were recorded for all screened patients.

#### 6.2.6.1 Screening

A potential patient was approached as soon as possible after admission. The first encounter with a patient by the study team was for screening. At this screening visit patients were potentially eligible or ineligible. Patients considered completely ineligible at screening (or at a later repeat review) were not reviewed again.

The main difference from the feasibility study was that the study team considered the patient's capacity and depending on this assessment either provided the patient with a PIL

(Appendix C) or arranged to meet with their consultee (carer/NOK) to discuss the study further. Screened patients were entered into a screening log in order to track their admission.

#### 6.2.6.2 Inclusion and Exclusion Criteria

Patients were required to meet study selection and inclusion/exclusion to determine eligibility and suitability criteria respectively in order to participate (Table 16, 17, 18 and 23). As mentioned patients who were unable to give fully informed written consent due to a lack of capacity were also recruited. A consultee declaration was gained and retrospective consent at a later date if appropriate.

**Table 24: Selection Criteria for the HOME FIRST Pilot Study**

- **EWS ≤2 AND SBP>90 (all observations must be stable for 12-24hrs)**

  *AMTS removed*

- **We have removed 'able to give fully informed consent'**

  *Consultee declaration added*

- **Acute exacerbations of bronchiectasis without consolidation not requiring prolonged IV antibiotic therapy (max B.D[#])**

  *Added*

**Amendments (protocol alterations after January 2014)**

- **$0_2$ sats** ≥ 94% on air **in patients** without **chronic respiratory failure -** included
- **$0_2$ sats ≥ 88% on air or LTOT in patients with chronic respiratory failure – excluding asthma -** included
- **Suspected/proven pulmonary infarct –** excluded

NB - patients with co-existing pulmonary embolus who are prescribed warfarin receive a minimum of 5 days of LMWH (low molecular weight heparin); LMWH is discontinued when INR is therapeutic and stable. LTOT (long term oxygen therapy), EWS (early warning score), SBP (systolic blood pressure), AMTS (abbreviated mini-mental test score), WCC (white cell count), IV (intravenous), B.D (twice daily). [#] NB B.D max antibiotic therapy was the most frequent administration that the HOMEFIRST team were able to provide as we could not get any regular commitment from the home IV team to enable us to provide T.D.S IV antibiotic therapy.

The justification for the changes to the selection criteria were as follows;

- The feasibility study showed that 20% of screened patients were not able to be recruited as they did not have full mental capacity. We believed that these vulnerable patients may in fact be one of the groups that would benefit most from study involvement, therefore patients unable to give consent were included.
- After the SAE in January 2014 we altered the $0_2$ saturations to be in line with the BTS oxygen guidelines.
- Patients with acute exacerbations of bronchiectasis (without consolidation) not requiring IV antibiotics are cared for by ACTRITE (the COPD supported discharge scheme) already.

#### 6.2.6.3 Making Decisions with Physicians in Charge of Patients' Care

This was an important area of development in the pilot study. Doctors involved with usual patient care may not be familiar with the HOME FIRST study so building relationships in order to recruit their (suitable) patients was important. Making joint decisions was important in order to give the best outcome for the patients and to optimise recruitment and follow-up. We believed that facilitating discharges would help form strong relationships with clinicians, pharmacists and ward nursing staff.

#### 6.2.6.4 Repeat Reviews and Consent/ Consultee Declaration

Repeat reviews and the consent procedure were unaltered from the feasibility study. For patients with either transient or permanent lack of capacity, a consultee declaration was obtained. Consent/consultee declaration stickers were put into patients' case notes.

### 6.2.7 Study Intervention – HOME FIRST

If the patient was discharged before 16:00hrs they were reviewed at home later that evening by the team; if after 16:00hrs the review was the next morning before 11:00hrs. The frequency and duration of home visits was determined by communication between the study team, patient and carer/ NOK. Telephone calls were used instead of home visits where appropriate.

### 6.2.8 Aftercare by HOME FIRST

This is mostly unaltered from the feasibility study. At each home visit the daily clinical review sheet in the CRF was completed. Telephone consultations were recorded in the CRF and daily clinical review sheet as per a standard home visit but were recorded as 'telephone consultation' at the bottom of the page.

#### 6.2.8.1 Initial and Subsequent Follow-up with HOMEFIRST

This was unaltered from the feasibility study. Telephone visits were developed further in the pilot.

#### 6.2.8.2 Discharge from Hospital with HOME FIRST

If a patient became unwell they consulted the emergency PIL (Appendix C).

#### 6.2.8.3 Readmission to Hospital from HOME FIRST

The escalation and readmission flowchart was used to determine whether readmission or escalation were warranted (Figure 10).

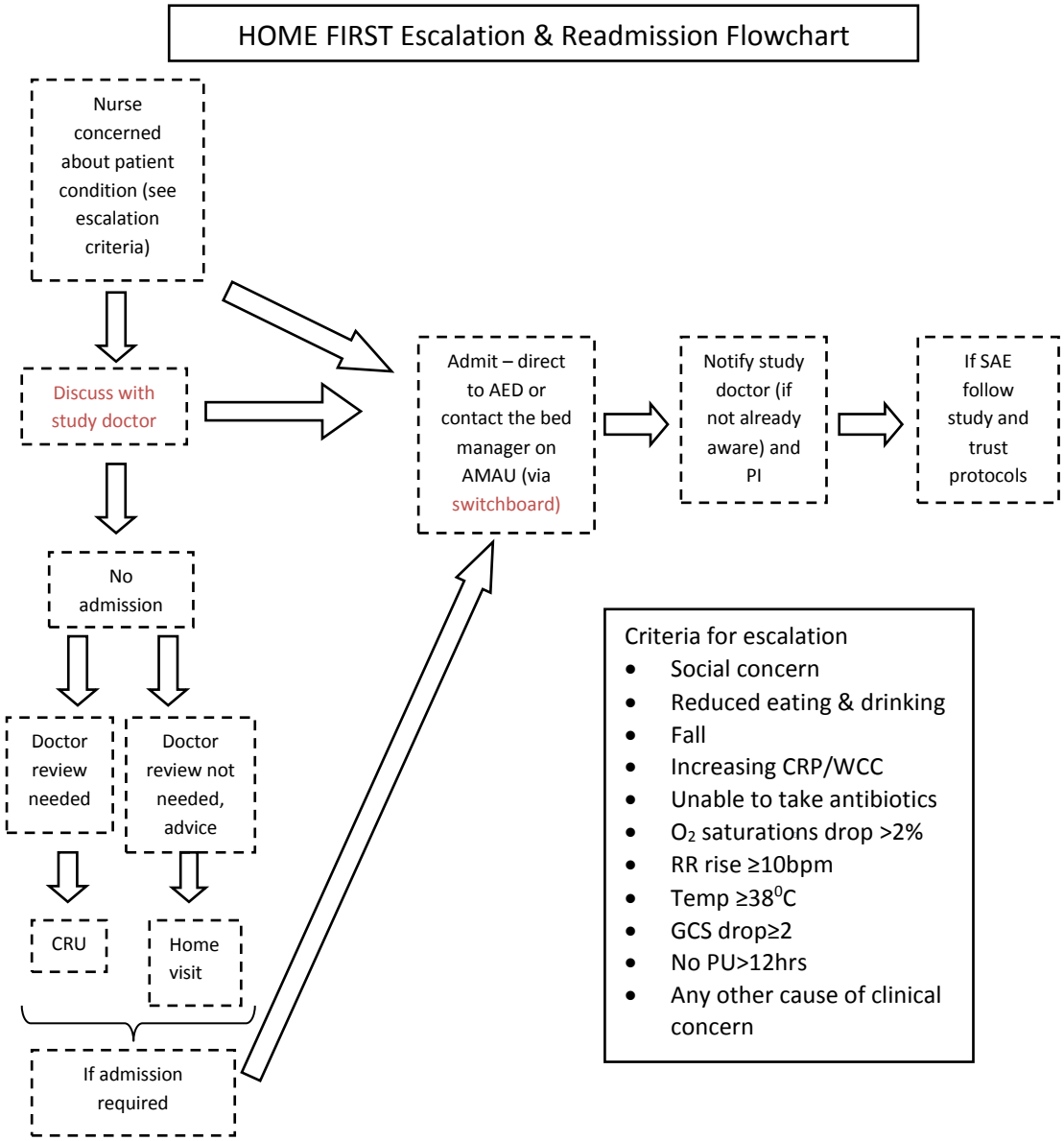


**Figure 10: Escalation and Readmission Flowchart**

[AED (accident and emergency department), AMAU (acute medical admissions unit), CRU (clinical research unit), PI (primary investigator), SAE (serious adverse event), CRP (C-reactive protein), WCC (white cell count), RR (respiratory rate), GCS (Glasgow coma score), PU (pass urine)]

#### 6.2.8.4 Discharge from HOME FIRST

In order for discharge from HOMEFIRST the following 7 criteria must have all been answered YES (Figure 11), although the criteria were unaltered from the feasibility study, a flowchart format was developed. Even if patients fulfilled all these criteria they may still have remained under HOMEFIRST care for up to 5 working days if deemed necessary by the study team. After the maximum duration of 5 working days of home visits if further follow-up was needed the patient was either readmitted to hospital or handed over to the community care team.

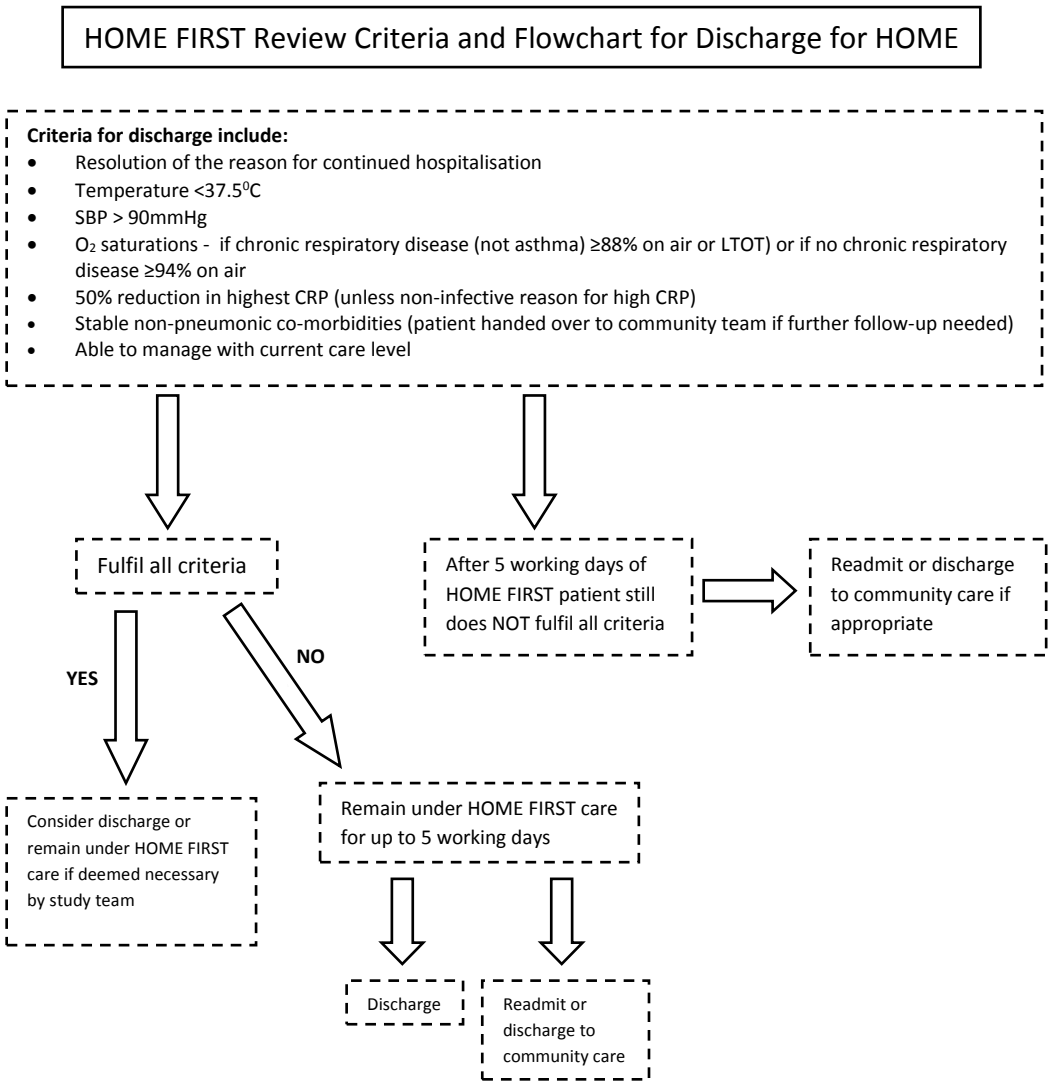


**Figure 11: Discharge Flowchart**

[CRP (C-reactive protein), SBP (systolic blood pressure)]

### 6.2.9 Standard Hospital Care (SHC) Arm

Unaltered from the feasibility study (Chapter 5, 1.2).

### 6.2.10 Follow-up

As in the feasibility study an independent assessor telephoned the patient or carer/ NOK/ consultee in order to complete a validated care satisfaction questionnaire (Appendix D).

All recruited participants were asked to attend an outpatient appointment 6 weeks after recruitment; a clinical assessment (and investigations as needed), RECRI (functional RECovery from Respiratory tract Infection) and CAP-Sym [Community Acquired Pneumonia SYMptom score], SF-12 (Short Form 12 – physical and mental functionality) questionnaires were performed (Appendix D). Further out-patient appointments (outside of the study) were arranged as required.

### 6.2.11 Study Flowchart

A study flowchart was developed (Figure 12).

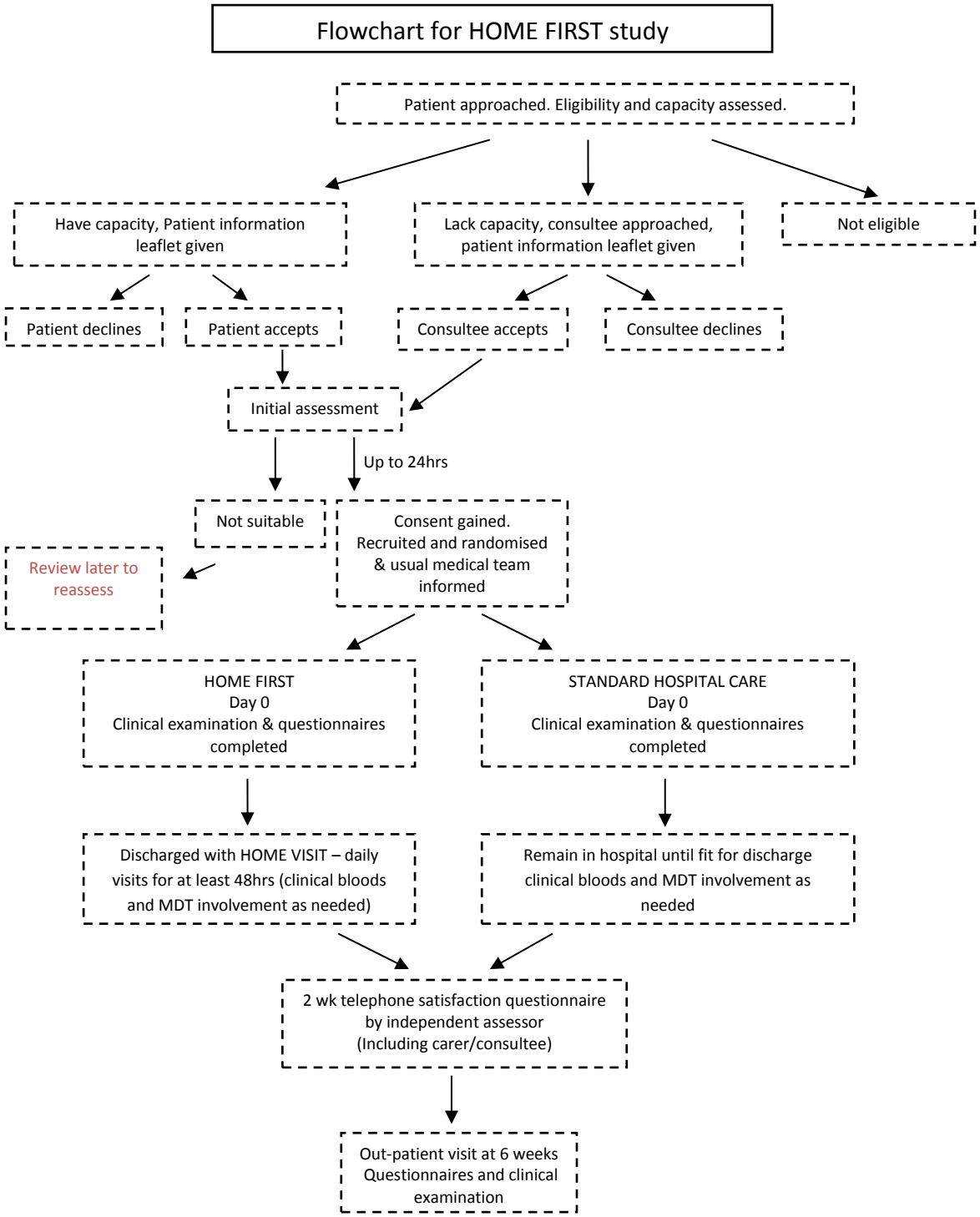


**Figure 12: HOME FIRST PILOT Study Flowchart**

### 6.2.12 Hospital Staff Engagement

We concentrated heavily on this area for the pilot study building on aspects form the feasibility study. Initial engagement involved:

- Adverts in hospital (put up in wards - near to computers where discharges are done and spoke to the nurses and medical teams at the same time)
- Meetings/talks – Ward based, ward rounds, ad hoc visits. Spoke to different people each time. Speciality based, regional speciality meetings, respiratory MDTs, Grand Round, Foundation Doctors' teaching, ward educational sessions on AMAU and respiratory wards.
- Physician involvement – gained physician's 'buy in' to the study idea. Busy clinicians may not always be able to be proactive about referring potentially suitable patients due to service demands.

Continuing engagement involved:

- Repeat meetings were arranged
- Giving positive verbal feedback to staff on their patients that had been part of the study.

### 6.2.13 Sample Size, Statistical Methods, Outcome Measures and Randomisation

Using data on mean hospital LOS from our feasibility study, we estimated that 23 patients per arm were required to allow an 80% power. Any participants withdrawn from the study remained in the data analysis as intention to treat. Statistical analysis was performed using Microsoft Excel 2007, GraphPad Prism 4 and SAS9.4. Unpaired T test and Mann-Whitney U tests were used, p-values >0.05 were considered not significant. For satisfaction scores a linear regression analysis was applied, controlling gender.

Randomisation was as per the feasibility study but the allocation was obtained using a closed envelope system in a locked filing cabinet.

The overall aim was to reduce length of hospital stay (LOHS). Professor Brian Faragher (LSTM research statistician) was involved in statistical discussions.

**Primary Outcome**

Our primary endpoint was 'time to recovery'. At recruitment we recorded participant's best exercise capacity in the last 3 months e.g chair to bed with 1, unlimited exercise tolerance at recruitment. At the 6 week OPA the patient was asked 4 simple questions: (marked on a Likert-type scale in days and weeks):

1. When (if at all) did your sleep return to normal?

2. When (if at all) did your diet/appetite return to normal?

3. When (if at all) did your (pre-defined) exercise capacity return to normal?

4. When (if at all) did your capacity to work or socialise (delete as appropriate) return to normal?

['RECRI' (functional RECovery from Respiratory tract Infection) questionnaire (non-validated)] (Appendix D).

**Secondary Outcome - Clinical**

1. Safety

   The safety of the scheme (i.e. no increase in morbidity (delayed recovery or complications) or mortality in the HOME FIRST arm) was assessed by 6-week mortality and readmission rates, functional status/quality of life (SF-12) and symptom improvement (CAP-SYM)

   We expected HOME FIRST to have at least equivalence with SHC. A SF-12 (physical and mental function) form was completed at day 0 and 6 weeks. A CAP-SYM (disease recovery rate) questionnaire was completed at day 0 (for both day 0 and day minus 30) and 6 weeks.

2. Patient and carer/consultee satisfaction

   We expected HOME FIRST to have at least equivalence with SHC.

3. LOS in hospital and total LOS (including hospital +/- HF home care combined).

**Secondary Outcome - Health Economics**

The research outcome as the number of hospitalisation days saved was applied, comparing the 'costs saved' due to HOME FIRST intervention with its 'intervention costs'. For estimating the 'costs saved' we used number of days of hospitalisation saved due to HOME FIRST and national tariff prices for hospital admissions with pneumonia (NICE, 2014). Category DZ11B was applied (Lobar, atypical or viral pneumonia with complications and comorbidities), there is a non-elective long stay trim point of 20 days, after this any additional days would receive

a tariff of £192/day. The cost of stay in hospital of one episode (20 days on an average) was 2,401 GBP. It implied that each hospitalisation day saved due to intervention meant a cost saved of 2,401/20 or 120 GBP.

On the other hand, to calculate the costs of intervention, we recorded interventional time only. This meant time spent by staff screening patients and attending home visits (visit and travel time). This did not therefore include time spent completing research paperwork and forms for recruited patients or out-patient appointments at 6 weeks (as these are both study specific and would not be an actual cost if this was a full clinical service), nor does it include time spent on study administration, requesting notes, collecting and collating data, time writing discharge medication prescriptions and discharge summaries, liaising with family or arranging transport or meals on wheels. Staff self-reported time data were independently validated; data were collected only during the second winter season of the study therefore the first winter season's time data was extrapolated.

Fuel/mileage and vehicle costs were not added to the calculations - home visits occurred within a 6-mile radius therefore costs were minimal but should be incorporated into future studies.

### 6.2.14 General Research Staff Tasks and Responsibilities

A table was developed to allow clarity of roles and responsibilities (Appendix E).

### 6.2.15 Quality Control and Safety Monitoring

#### 6.2.15.1 Adverse Event Reporting, Patient and Staff Safety and Training

This was unaltered from the feasibility study.

### 6.2.15.2 Trial Monitoring

This area was significantly developed in the pilot study. A Data Monitoring and Safety Committee (DMSC) was formed in January 2014 in the HOME FIRST pilot following an SAE. The DMSC consisted of Dr Rebecca Bancroft, Consultant Physician RLBUHT, Mr Arthur Ricky Kang'ombe, Lecturer/Biostatistician, Liverpool School of Tropical Medicine (LSTM), Dr John Blakey, Clinical Senior Lecturer LSTM and Professor Sasha Shepperd, Professor of Health Services Research, Oxford University. A terms of reference (Appendix E) document was developed. The DMSC provided an independent review of safety data by (1) reviewing emerging safety data throughout the study, these data was presented by spreadsheet weekly with responses copied to all by email. This system proved effective in our other research projects [Chapter 7], (2) reviewing, evaluating and making recommendations to the investigators and sponsor as to whether to modify, suspend, terminate or extend the study and, (3) being notified of any SUSAR without delay. The DMSC also reviewed SAEs/AEs on a regular basis and reviewed and assessed the causality of all AEs with regards to the patient selection criteria. Meetings were held by email circulation. There was one meeting prior to recruitment of 30 patients and one when a decision was made that sufficient patient numbers had been screened. At least weekly handovers occurred to the on-call team.

### 6.2.16 Database Completion

As per the feasibility study but developed further. Collated data for screened patients were initially recorded on paper and then uploaded daily onto an excel spreadsheet. Recruited patient data (SHC and HF) were recorded on an excel spreadsheet and updated with readmission, mortality and HAI data at the 6 week OPA. The main role of the DMSC was safety but they were involved in data management if required.

Time spent screening and attending home visits (including travel time) was recorded in season 2 of the pilot to enable a health economic assessment.

### 6.2.17 Communication

GP letter, study advert and useful contacts list were not significantly altered from the feasibility study.

### 6.2.18 Amendments

During the pilot study a major amendment was submitted to and accepted by REC. The following documents were updated and developed - Clinical daily review form, criteria for discharge, DMSC ToR and charter and blank excel, escalation and readmission flowchart, protocol (the most up to date versions only are contained in this thesis).

## 6.3 RESULTS

We screened 351 hospitalised patients with symptoms suggestive of respiratory infection and a total of 725 screens or reviews were performed between 15th October 2013 and 11th December 2014 (21 weeks of study recruitment – winter season 1 = 15/10/2013 – 1/2/2014 and winter season 2 = 6/10/2014 – 8/12/2014) [Figure 13]. At initial screening of 217 patients were initially ineligible as they required further inpatient treatment (n = 116 required intravenous antibiotics or fluids, n = 43 had low oxygen saturation levels, n=58 various other reasons), repeat review was arranged. 15 patients were recruited at initial screening visit, 10 at first repeat review and 1 at second repeat review. 16 patients were randomised to the HF arm, 10 to the SHC arm. No patients were ever recruited at third or later review. 99 patients were reviewed twice after screening, 35 patients x3 times and 23 ≥ x4 times. The first repeat review ranged from 0 and 14 days after initial screening visit. In total 17 patients declined participation (n=11 patients, n=1 spouse [acting as the consultee], n=5 physician or therapist declined). Of those who declined there was no difference in age noted but those who declined were more likely to live alone without social/family support (Table 25). 26 patients were recruited (26/351) = 7% screening:recruitment rate. No patients withdrew consent or were lost to follow-up after recruitment. No patients required retrospective consent since all patients recruited without capacity had chronic confusion (secondary to dementia) rather than acute delirium.

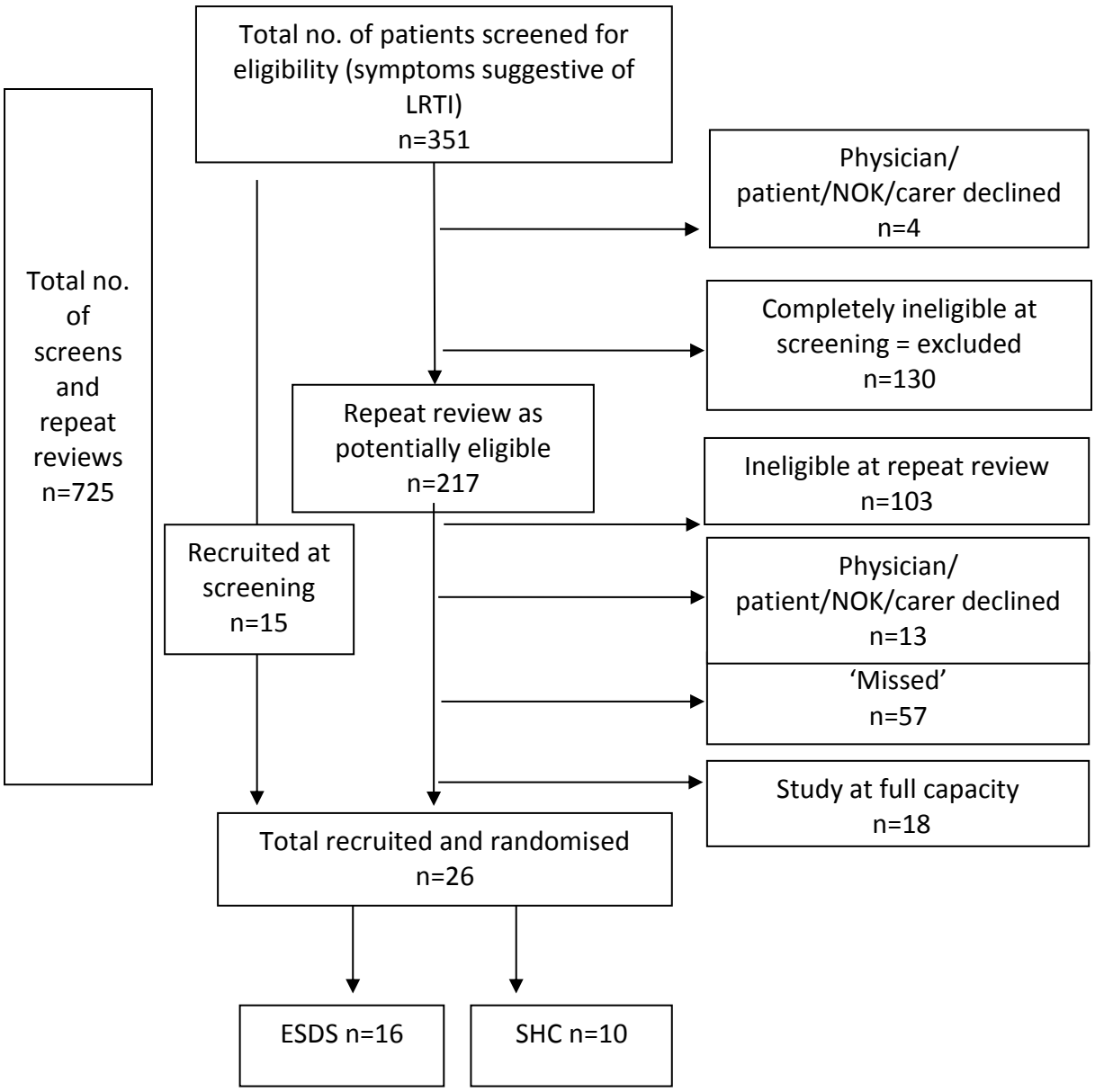


**Figure 13: Consort Flow Diagram**

Initial screening, repeat review and final recruitment numbers are shown.

The most common reason for non-recruitment was the need for continuing inpatient treatment such as IV medications/fluid, $O_2$ or further investigations (43%). The full range of reasons for non-recruitment are shown in Table 24. Broadly these can be categorised into medical reasons (66%), social reasons (14%) and other reasons (20%).

**Table 25: Reasons for Non-recruitment at Initial Screening or Repeat Review(s)**

Multiple reasons may apply for each patient at each visit and at subsequent reviews

| Category | Reasons for non – recruitment at initial screening or repeat review | n | % |
|---|---|---|---|
| **Medical** | Requiring inpatient treatment inc. intravenous / oxygen therapy and / or further investigations including radiology | 307 | 42.3 |
| | Too well (fit for discharge without Home First support) | 39 | 5.4 |
| | Too unwell/ died during repeat reviews | 36 | 5.0 |
| | No lower respiratory tract infection | 35 | 4.8 |
| | Other co-morbidities requiring inpatient stay | 33 | 4.6 |
| **Social** | Require more complex multi-disciplinary team input (physiotherapy, OT, social services) | 79 | 10.9 |
| | Social issues / no fixed abode / non fluent English speaking | 20 | 2.8 |
| | Requiring intermediate care bed | 5 | <1 |
| | Mental health issues | 3 | <1 |
| **Other** | Refused (Patient / clinician / carer / spouse / NOK) | 17 | 2.3 |
| | Missed discharge / patient self -discharged | 55 | 7.6 |
| | Infective exacerbation of COPD (other services available) | 52 | 7.2 |
| | Full to recruitment / study on hold | 18 | 2.5 |

NB: details of the number of refusals in which the patient did or not not have capacity were not recorded.

**Table 26: Demographics and Characteristics of Patients who Declined or were Recruited**

| | Declined | | Recruited | |
|---|---|---|---|---|
| | Patient (n=11) | NOK/ carer/ consultee (n=1) | SHC (n=10) | HF (n=16) |
| Age mean (range) | 68.5 (52-84) | 72 | 74 (62-85) | 66.4 (38-91) |
| Gender M:F | M (5): F (4) | F (1) | M (2): F (8) | M (7): F (9) |
| Smoking history | Not recorded | | Ex - 6<br>Current - 1<br>Never – 2 | Ex - 4<br>Current - 6<br>Never - 6 |
| Social history | Live alone - 6<br>With spouse - 1<br>With family - 1<br>Care home - 1 | With spouse - 1 | Live alone - 3<br>With spouse - 3<br>With family - 2<br>Care home - 2 | Live alone - 3<br>With spouse - 6<br>With family - 5<br>Care home - 2 |
| Capacity n (%) | 11 (100%) | 1 (100%) | 8 (80%) | 15 (94%) |

The mean age of all recruited patients was 69.3 (38-91) yrs old. New radiological consolidation or infective infiltration was defined according to the radiology report (chest radiograph or CT scan). 20 patients had radiological changes consistent with pneumonia, 12 in HF arm and 8 in SHC. On admission the median CURB-65 scores in HF arm were 1 (0-4) and 1 SHC (0-2). The average time from admission to recruitment was 6.6 days (range 1 - 23) days. Of those who had sputum sent for MC&S by their usual hospital care team, 3 patients had sputum positive for *Pseudomonas aeruginosa*, of which 1 was also positive for *Haemophilus influenza.* No patients had positive blood cultures or urinary pneumococcal antigen (Binax, Alere Medical). An outpatient visit was planned at 2 weeks after recruitment for 2 patients in the HF arm to enable a more urgent outpatient review of their medical condition(s).

**Primary outcome**

There was no difference between allocated group and time to recovery (Table 26).

## Table 27: RECRI Data by Time to Recovery per Question

| | | Cumulative number resolved at specified time points in each arm | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Group | Never a problem / already resolved | 1 day | 7 days | 14 days | 21 days | 28 - 42 days | Unresolved | Chronic | No data |
| Q1 | HF (n=16) | 3 (19%) | 5 (31%) | 9 (56%) | 10 (62%) | 10 (62%) | 11 (69%) | 1 (6%) | 2 (13%) | 2 (13%) |
| | SHC (n=10) | 3 (30%) | 3 (30%) | 6 (60%) | 6 (60%) | 6 (60%) | 6 (60%) | 0 (0%) | 2 (20%) | 2 (20%) |
| Q2 | HF (n=16) | 1 (6%) | 2 (13%) | 8 (50%) | 9 (56%) | 9 (56%) | 9 (56%) | 3 (19%) | 2 (13%) | 2 (13%) |
| | SHC (n=10) | 4 (40%) | 7 (70%) | 7 (70%) | 7 (70%) | 8 (80%) | 8 (80%) | 0 (0%) | 0 (0%) | 2 (20%) |
| Q3 | HF (n=16) | 2 (13%) | 2 (13%) | 5 (31%) | 7 (44%) | 8 (50%) | 11 (69%) | 2 (13%) | 1 (6%) | 2 (13%) |
| | SHC (n=10) | 1 (10%) | 1 (10%) | 2 (20%) | 2 (20%) | 3 (30%) | 4 (40%) | 1 (10%) | 3 (30%) | 2 (20%) |
| Q4 | HF (n=16) | 2 (13%) | 3 (19%) | 3 (19%) | 7 (44%) | 8 (50%) | 8 (50%) | 4 (25%) | 2 (13%) | 2 (13%) |
| | SHC (n=10) | 0 (0%) | 0 (0%) | 1 (10%) | 1 (10%) | 1 (10%) | 4 (40%) | 3 (30%) | 1 (10%) | 2 (20%) |

Q1. When (if at all) did your sleep return to normal? Q2. When (if at all) did your diet/appetite return to normal? Q3. When (if at all) did your (pre-defined) exercise capacity return to normal? 4. When (if at all) did your capacity to work or socialise (delete as appropriate) return to normal?

No formal statistical analysis was performed to compare the two study arms here.

**Secondary outcomes**

**Satisfaction**

Patient and carer, next of kin (NOK) or consultee care satisfaction scores (Appendix D) were good in both arms. Patients without capacity or too unwell at 2 weeks were unable to complete this questionnaire. The carer/NOK/consultee satisfaction score in the ESDS group was significantly higher than that in the SHC group (-4.91; 95% CI: -7.12, -2.69; p = 0.0004). There was no statistical significant difference in the patient satisfaction scores (-1.47 CI: -4.49, 1.55; p = 0.3587).

**Functionality**

19 patients completed both SF-12 questionnaires (day 0 and 6 weeks). [3 did not complete the questionnaire as they did not have capacity, 3 died and 1 was withdrawn]. At day 0 HF group mean score was 2.57 versus SHC 2.54 and at 6 weeks 2.62 versus 2.60 respectively. An overall mean increase of 0.06 points/subject was seen in the SHC group, and 0.05 point/subject in the HF group between day 0 and 6 weeks. NB: using the SF-36 (a similar questionnaire with 36 questions) a 20-point change in the scale is believed to represent a clinically meaningful change; using SF-12 at least a 6-point change is deemed necessary for clinical significance.

**Symptom improvement**

19 subjects completed both questionnaires (13 HF, 6 SHC) [3 were not completed due to lack of capacity, 3 died and 1 was withdrawn]. There was no improvement in the mean CAP-SYM scores at 6 weeks in either group from either baseline (day -30) or recruitment (day 0) [Table 27].

**Table 28: CAP-Sym Scores at Baseline, Recruitment and Outpatient Appointment According to Group**

| | HF | SHC |
|---|---|---|
| Baseline [day -30] mean (range) | 1.1 (0.0 – 4.2) | 1.0 (0 – 2.2) |
| Recruitment [day 0] mean (range) | 1.2 (0.2 – 2.9) | 1.2 (0.6 – 2.3) |
| Outpatients [6 weeks] mean (range) | 0.9 (0.0 – 2.4) | 0.9 (0.2 – 2.1) |

Code: 0 = no symptoms, 1 not at all, 2 a little, 3 moderate, 4 quite a bit, 5 extremely.

**Table 29: Data on Inflammatory Makers, Symptom Duration, Pneumococcal Vaccination, Statin Use, Co-Morbidity, CURB-65, Readmission, Mortality and Length of Stay in the Two Study Arms**

| | HF | SHC |
|---|---|---|
| CRP on day of discharge: mean (S.D)* | 74.1 (89.6) | 58.4 (82.0) |
| WCC on day of discharge: mean (S.D)* | 10.7 (4.0) | 11.5 (5.3) |
| Duration of symptoms prior to recruitment (days): mean (S.D)* | 16 (23.9) | 12 (7.6) |
| PPV-23 vaccine received – recollection: n (%)^ | 4 (25) | 5 (50) |
| Current HMG CoA reductase inhibitor use (statin) use: n (%)^ | 4 (25) | 5 (50) |
| Co-morbidities ≥2: n (%)^ | 15 (94) | 9 (90) |
| Mortality at 6 weeks: n (%)^ | 0 (0) | 2 (20) |
| Dementia: n (%)^ | 1 (6) | 2 (20) |
| Readmissions at 6 weeks: n (%)^ | 2 (13) | 1 (10) |
| CURB-65: median (IQR)$^{\beta}$ | 1 (0.5-3) | 1 (1-3) |
| LOS in hospital prior to recruitment - days: median (IQR)$^{\beta}$ | 5.0 (1.5-8) | 5.0 (3-12.8) |
| Total length of HF care – days: median (IQR) | 3 (2-5) | N/A |
| Total length of hospital stay (Hospital +/- HF) - days: median (IQR)$^{\beta}$ | 5.5 (2.3-8.0) [#] | 7.5 (4.0-21.0) |
| Combined LOS (Hospital +/- HF) - days: median (IQR)$^{\beta}$ | 7 (5.3-13.5) | 7.5 (4-21) |
| Satisfaction (mode) - Patient and Carer | Strongly agree | Agree |
| Functionality (SF-12) – mean | 2.57 | 2.54 |

NB: If a CRP was recorded as <5 it was classed as 0 for statistical analysis. Mean CRP and WCC was from the day of discharge or closest measurement to day of discharge. If a participant is readmitted to the hospital from HF they were classed as discharged from HF care.

[#] Participant withdrawn from the HF arm but remained in this analysis as intention to treat. *Unpaired T test. ^Fischer's Exact. $^{\beta}$Mann-whitney U. All p-values >0.05 and therefore not significant.

**Health Economics**

ESDS identified two important inputs that were fundamental to the execution of the intervention in an existing standard NHS system. Staff time was the major cost of intervention. During the study, 725 screenings and reviews enabled 26 patients to be recruited, 16 patients of whom were randomised to ESDS. The costs of doctor and nurse were 1,680 GBP and 1,102 GBP respectively, which resulted in total costs of 2,782 GBP. Distribution of this total amount to 26 enrolled patients corresponded to 107.0 GBP per patient as the cost of intervention. Since 16 patients were recruited to ESDS we found a total cost of 107×16 or 1,712 GBP for patients in the HOME FIRST arm.

We showed that 5 days (length of stay) in hospital can be saved for each patient. Applying the daily hospitalisation tariff of 120 GBP for 5 saved days for each patient, we estimated that HOME FIRST could save a total of 600 GBP per patient and 9,604 GBP for all 16 patients.

If we compare these foregone or saved costs (9,604 GBP) with the costs of intervention or in other words, investment on HOME FIRST (1,195 GBP), we observed that 4.6 GBP can be saved from each GBP invested. If we apply minimum (113 GBP) and maximum (179 GBP) expected values of cost per day for SHC (DoH Tariffs for pneumonia/LRTI 2015-2016), the cost saved from each invested GBP ranges between 4.3 and 7.4 GBP.

If we applied this intervention only at weekends, the salary cost of doctor and nurse increases by 1/3 each therefore invested GBP would result in 3.2 GBP saving (ranges between 3.0 GBP and 5.3 GBP).

**Table 30: Hospital Bed Days and Cost Savings (GBP) due to HOME FIRST**

| **Component** | ***Amount*** |
|---|---|
| ***Intervention costs of 16 patients (GBP)*** | ***1,712*** |
| | |
| ***Cost (GBP) saved by intervention*** | |
| Median number of LOS saved (days) | 5 |
| Cost per day for SHC in general (GBP)[#] | 120 |
| Total saved costs per patient (GBP) | 600 |
| **Total costs saved for 16 patients (GBP)** | **9,604** |
| **Cost saving from each GBP investment** | **4.6** |

#(214)

## 6.4 DISCUSSION

We have shown that using defined ESDS package with defined criteria we can reduce the length of hospital stay (LOHS) in patients with pneumonia and LRTI. We noted a reduction in LOHS (bed days) by 5 days as well as a reduction in the total length of care of 2 days. The scheme is safe; there was no increase in readmission or mortality rates or decrease in recovery rate, functionality or symptom resolution at 6 weeks, and satisfaction was high. The ESDS package was successfully implemented in 15 participants. The scheme in its current form however is difficult to recruit to and large numbers of patients were screened and repeatedly reviewed in order to recruit a small number of patients into the study (26/351 = 7% screening: recruitment). Interestingly the results show that the scheme functioned not necessarily always as an 'early in the admission' discharge scheme that was managing patients with acute LRTI (reflected in the average time from admission to recruitment 6.6 days, despite initial patient screening occurring within 72hrs) but often simply as an 'earlier discharge scheme' suggesting that many patients had in fact recovered from the initial LRTI/CAP but required further convalescence due to multiple co-morbidities and were slower to improve clinically and functionally.

With regards to functionality the lack of any clinically meaningful change between the 2 groups at 6 weeks may suggest either a strong impact of chronic disease/co-morbidities on recovery or a slow return to baseline function (i.e. > 6weeks). The persistently raised CAPSYM scores throughout may be related to chronic disease or to the length of illness prior to eventual hospitalisation and a recovery period of > 6 weeks. The low mean scores throughout reflect the fact that we did not capture the 'peak' of symptoms which is likely to have been on the day of admission rather than the day of recruitment.

Satisfaction scores indicated that both patients and NOK/carers/consultees show a preference for ESDS care; this preference was most notably seen in the carer/NOK/consultee group. Anecdotally patients who were keen to get home and were randomised to ESDS were extremely impressed with the study and very supportive of further work.

As with any complex intervention a number of operational and logistical issues were noted. As a pilot study it is important to note that we were able to reduce clinical staff workload by assisting with patient discharge, this in turn encouraged staff to engage with the research and highlight potential recruits to the study team. A ward discharge always means a new admission often with a new acutely ill patient; this creates a lot of work for ward staff but significantly improves patient flow through the acute hospital. We noted that single patient home visit journeys were costly in terms of staff time; linking these journeys as part of ESDS to other patient home visits as part of an ESDS community 'round' would improve efficiency but would be complicated in terms of co-ordination and logistics. Extensive liaison with the medical team/consultant was often required to allow recruitment. We found that the study needed to be Doctor-led, rather than senior respiratory nurse-led because we often needed to question ('over-rule') a senior clinician's decision to keep a patient in hospital in order to recruit to the study.

We found difficulties in getting hold of NOK/carer/consultee in a timely fashion when a potential suitable patient who did not have capacity to consent was identified; this often delayed or even prevented recruitment (exact numbers were not recorded). Common reasons for this delay were because the consultee was a distant relative, lived a distance away from the hospital, was working or elderly/had reduced mobility or due to incorrect contact details. In terms of consultees declining to complete a consultee declaration form, this only

happened once. This again showed that this early supported discharge scheme was generally well accepted by both patients and consultees/NOKs. In future studies, we would accept patients with all CURB-65 scores since the initial severity score does not affect whether someone is suitable for discharge or not.

**Similarities and differences**

Like previous HAH studies for CAP and LRTI we have shown recruitment may be difficult (215); we recruited 7.4% of screened patients which is comparable to other similar studies at 12% (84/985) (209), 11% (50/540) (118) and 7% in our feasibility study. Like our study a NZ study in patients with CAP showed improved patient satisfaction ($p<0.001$) and no difference in symptom score or function at 6 weeks but they increased total days of care (118). Other studies have, like ours shown reduced bed days and cost reductions (121, 209).

Comparing results from this pilot to our previous feasibility study, the mean age of recruited patients (69.3 versus 64.6 yrs old in feasibility), fewer patients were excluded due to complex MDT issues (physiotherapy, social or OT needs) (10% versus 20%), due to IECOPD (8% versus 11%), and fewer patients/NOK/carer/consultees declined (17% versus 23%).

**Strengths and weaknesses**

One of the main strengths of this novel study is the large effort made to screen patients with potential LRTI. There were no patient withdrawals, one participant in the HF group was 'withdrawn' as they were awaiting discharge to a mental health community bed, but after recruitment this bed was cancelled and discharge was delayed for 7 days whilst he awaited a new bed. Anecdotally hospital discharges were often accelerated by HF screening even if they

were not recruited as the study team often highlighted certain issues and found solutions which enabled the patient to go home earlier.

This was a small pilot study in a single city and therefore no powered outcome data are available. As mentioned in HOME FIRST feasibility study the criterion of requiring *at least one more night of hospitalisation* to be recruited is a subjective one, however the overall aim of the study was to reduce hospital bed days within a 'real-life' UK hospital setting. Continued hospitalisation may be due to a variety of reasons and no specific guidelines on hospital discharge for patients with LRTI existed when this study was performed. The higher prevalence of frailty and comorbidities in the elderly in particular means that improvement in the LRTI itself is often not the factor on which the timing of discharge is dependent (26). NICE guidance from 2014 suggests that the 'benefits of on-site clinical expertise, observations and timely intervention must be balanced against the risk of hospital acquired infection and premature hospital discharge (relapse/readmission) as well as the patients quality of life and social circumstances' (26). For safe hospital discharge: 1) do not routinely discharge patients with CAP if in the past 24 hours they have had ≥2 of the following findings: temperature > 37.5°C, respiratory rate ≥ 24 bpm, heart rate > 100 bpm, SBP ≤ 90 mmHg, $O_2$ saturations < 90% on air, abnormal mental status, inability to eat without assistance (26). With many of our elderly patients with chronic respiratory disease and dementia this would make routine hospital discharge not possible.

We also only collected data for pneumonia symptom severity, functionality and time to recovery at 6 weeks; since it is well known that recovery from pneumonia can take weeks or months, we could expect that no significant improvement in these areas would be noted as early as 6 weeks. With regards to implementing an educational package for Doctors, we found

it hard to access senior Doctors in order to educate and effect change in their practice to adopt a new approach to patient discharge; our only teaching time was at the hospital 'grand round'.

HOME FIRST demonstrated clear savings in treatment costs (costs saved) because of reduced bed days, indicating that it is economically viable. The major intervention components (time costs of doctor and nurse) that had remarkable cost implication for HOME FIRST were captured. Our analysis showed that one invested GBP on HOME FIRST can save 4.6 GBP.

The health tariff used in these calculations of £120/day is at the lower end of other DoH/NICE health tariffs (varying from £113-£179 depending on whether the patient has an LRTI or bronchopneumonia with and without major complications [DZ23A and DZ22C]). The average quoted bed cost/day however is commonly ~ £220 (2015/16 tariff) but is not specific for respiratory infection.

Since we did not record patient specific variables (such as time allocated to each patient) there was no scope to calculating error. Strengths and limitations of our costings and approaches that could improve outcomes (internal and external validation) and totally change our conclusions (robustness) have been considered. Strengths include that time data were collected by each staff member daily. Limitations include that the data were not completed for the entire duration of the study and therefore data have been extrapolated and we also did not record precise data of time spent with each patient. To validate our conclusions, we have calculated the added cost of weekend screening to ensure a cost benefit still exists. The robustness of our data may be completely altered if this were a consultant rather than registrar led scheme. Precise figures have not been calculated. It is well known that HAH schemes that reduce hospital LOS do not often equate to actual savings but in fact improve

patient flow and productivity. A more detailed health economic assessment where all cost components of the intervention have been captured so that a more rigorous analysis calculating not only the average costs, but also the marginal costs and the impact of major cost drivers can be estimated, allowing a sensitivity analysis.

There were various constraints related to the research project and staff resource during study recruitment. For safety, we were unable to recruit any further patients if we had 2 patients actively in the ESDS arm, this meant the time spent screening that week prior to this event was mostly redundant. 57 (26%) of potentially eligible patients were missed at repeat review this was due to self-discharge or discharge on days on non-recruitment due to staffing levels (mostly on Friday/Saturday/Sunday or bank holidays). The main reasons for patients being deemed unsuitable were requiring IV fluids, antibiotics or oxygen therapy. Since many patients' IV antibiotics are three times per day we were unable to recruit these patients. See Chapter 8 for further discussion.

In Chapter 7, we change our focus away from better therapeutics for direct clinical care and towards prevention in the form of pneumonia vaccines. This chapter describes a study involving the inoculation (and carriage) of live pneumococcus in healthy volunteers' noses to assess vaccine efficacy in order to develop a future pneumococcal vaccine testing model.

## 6.5 ACKNOWLEDGEMENTS

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# CHAPTER 7: Vaccine Development - First Human Challenge Testing of a Pneumococcal Vaccine - Double Blind Randomised Controlled Trial (PCV EHPC).

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## 7.1 INTRODUCTION

Pneumococcal disease is a major global health threat for which new vaccines are urgently needed, particularly serotype-independent vaccines that will protect vulnerable children and adults against pneumococcal pneumonia. Pneumococcal disease is the most common cause of preventable death in children and a major cause of death among adults world-wide (216). Major impact on disease prevention requires interruption of colonisation (217). Pneumococcal conjugate vaccine (PCV) has been effective in the prevention of both pneumococcal colonisation (218, 219) and disease (220) in young children, with indirect herd protection in unvaccinated adults due to reduced community colonisation rates. However, the lack of a serotype independent vaccine and the level of protection afforded against mucosal diseases such as pneumonia and otitis media remain problematic in the current pneumococcal vaccination strategy.

There is therefore a clear need for new vaccines with several in development [Table 2] (221). However, there is a bottleneck in non-PCV related vaccine development as clinical trials with tens of thousands of participants are required to compare a new vaccine with the current

gold standard vaccine (PCV) using an outcome of disease reduction. Testing of new vaccines is costly in both time and money. A pathway for licensure of PCV related products now exists based on non-inferiority of immunogenicity bypassing the need for phase III trials (222). This is based on serotype-specific IgG antibody concentration (by ELISA) and functional antibody titres (by OPA).

A reduction in experimental colonisation acquisition rates after vaccination would provide proof-of-concept for both individual protection and an indication of potential reduction in transmission - essential for herd protection. These results would generate confidence for pursuing large and expensive clinical trials with pneumonia, otitis media or invasive pneumococcal disease as end-points (175). Studies of pneumococcal vaccine efficacy against pneumococcal colonisation have been proposed as an effective method to select between vaccine candidates and lend support to Phase 3 trial choice (175).

We have developed experimental human pneumococcal carriage (EHPC) to allow measurement of vaccine protection against induced carriage in healthy adults (177, 178, 193). We first have demonstrated that nasal pneumococcal carriage could be safe and reproducibly achieved in carefully screened healthy adult volunteers. A dose of 80,000CFU/0.1ml/naris of inoculum (serotype 6B pneumococcus) achieved a target carriage rate of 40-60% in reproducibility testing at a density typical of natural colonisation and duration of 1 - 3 weeks (177, 178). We estimated that carriage rates of 50% or greater would allow the EHPC model to have high sensitivity for vaccine efficacy testing with small study numbers.

This chapter describes how we used this model in a double-blind placebo randomised control trial (RCT) to assess whether a current licensed pneumococcal vaccine (13-valent PCV, *Prevenar-13*), has a direct impact on pneumococcal colonisation rates, density and duration and therefore whether the EHPC model can be used as a surrogate for vaccine effectiveness. Pneumococcal conjugate vaccine (PCV) has been effective in the prevention of both pneumococcal colonisation and disease in young children, with indirect herd protection in unvaccinated adults due to reduced community colonisation rates. No previous studies have demonstrated the direct protective effect of PCV on pneumococcal carriage.

In terms of global impact, PCV is currently considered to be an outstanding vaccine success; it sets the standard for future pneumococcal vaccines and is therefore the ideal 'gold standard' for EHPC testing. Here we use this EHPC model to assess whether 13-valent Pneumococcal Conjugate Vaccine (PCV-13, *Prevenar-13*) has a direct impact on experimental pneumococcal colonisation rates, density and duration.

## 7.2 METHODS

### 7.2.1 Ethical Principles

This section considers the main risks and benefits associated with this CTIMP study, namely related to vaccination and bacterial inoculation:

**Vaccination**

All staff were experienced in vaccination administration and fully competent in anaphylaxis management. Full resuscitation equipment and an anaphylaxis trolley was immediately available. The participants remained at the clinic for 20 - 30 mins after vaccination to monitor

for any immediate side effects. Those who received Prevenar-13 (pneumococcal conjugate vaccine [PCV] - 13) received a licensed vaccine outside of the EMA marketing authorisation (licensed for <6yrs old and >50 years old only). Those who received Avaxim (Hepatitis A vaccine) received a licensed vaccine within the marketing authorisation. Both vaccines are generally very safe and well tolerated. Although the benefit to the participant was limited they were however given the opportunity if they wished to, at the end of the study complete the course of vaccinations (if in the Avaxim arm) or have the complete course of vaccinations (if in the PCV arm). Also see vaccination PIL (Appendix C).

**Bacterial Inoculation**

Inoculation of *S. pneumoniae* was performed by highly trained staff according to Liverpool School of Tropical Medicine (LSTM) SOP (Appendix B) with close post-inoculation supervision (24hr on call access to medical professional involved in the study) and follow-up. Specific inclusion and exclusion criteria were set to further protect the participant. Experienced and trained research staff performed venepuncture and NW. Also see inoculation PIL (Appendix B).

### 7.2.3 Trial Design and Participants

For full details see the study protocol in Appendix A. We aimed to recruit 100 non-smoking, healthy participants aged 18-50 years old to this double blind randomised controlled trial performed at the Royal Liverpool and Broadgreen University Teaching Hospital, Liverpool, UK.

Participants were screened as below and then randomised to receive either PCV-13 (*Prevenar-13* containing serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F - Pfizer) or Hepatitis A (*Avaxim* - Sanofi Pasteur MSD) vaccination (control group). Natural

nasopharyngeal pneumococcal colonisation at the time of recruitment/screening was not an exclusion criteria. Serotypes included in the vaccine are termed vaccine types (VTs); those not included are termed non-vaccine types (NVTs). The study was approved by NHS Research and Ethics Committee (REC) [12/NW/0873 Liverpool]. Trial registration: EudraCT: 2012-005141-20 and ISRCTN: 45340436**.**

### 7.2.4 Recruitment and Selection

Advertisements were placed on physical notice boards in public areas, the internet of Universities and Colleges within Liverpool and the surrounding area and RLBUHT and UHA and in the local press inviting healthy volunteers to participate. Students from Liverpool Universities were sent a generic advertisement email inviting them to participate in the research. Public open days and engagement events were also used. Interested persons were asked to contact the research team for further information and an initial appointment was made if they wished to consider participating. The RLBUHT database (*consent4consent*) was also be used to approach those who had previously been involved in research at the RLBUHT.

Prior to attending the CRU potential participants received a patient information leaflet (PIL) [Appendix C]. Potential participants then attended the CRU for an informal chat and if they wished to proceed in the study and were eligible they signed a written consent form.

### 7.2.5 Exclusion Criteria and Details

We excluded participants:

- Who had previously received PPV or PCV or a complete course of hepatitis A vaccination

- With a previous significant adverse reaction to any vaccination
- With close contact to 'at risk' individuals (children, immunosuppressed adults, elderly, chronic ill health) – to minimise risk of pneumococcal transmission
- Who were current smokers or had significant smoking histories (>10 pack years) – to minimise risk of pneumococcal infection
- With asthma (on regular medication) or any other respiratory disease
- Pregnant or breast feeding mothers and women of child-bearing potential who are deemed not to have sufficient, effective birth control in place
- On medication that may affect the immune system in any way – to minimise risk of pneumococcal infection
- Allergic to penicillin/amoxicillin
- Involved in another clinical trial unless observational or non-interventional phase
- Previously involved in an experimental pneumococcal colonisation study
- With a current acute severe febrile illness – to minimise risk of pneumococcal infectio
- With abnormal clinical observations at screening visit (systolic blood pressure <90 or >160 mmHg, pulse rate <40 or >100 beats per minute, oxygen saturations <96% on air)
- With an active medical condition requiring regular hospital appointments – to minimise risk of pneumococcal transmission and infection
- With a pre-inoculation white cell count of <4.0 ($10^9$/L) AND a neutrophil count of <1.5 ($10^9$/L) – to minimise risk of pneumococcal infection

To minimise any effect on inoculation, we excluded participants who had taken any antibiotic therapy <2 weeks prior to inoculation.

### 7.2.6 Randomisation, Blinding, Vaccination and Unblinding

Randomisation was computer-generated and occurred in blocks of ten. An independent statistician from the tropical Clinical Trials Unit (tCTU) at the Liverpool School of Tropical Medicine (LSTM) produced the randomisation schedule and the sealed envelopes containing the study group allocations.

Research (clinical and laboratory) staff and participants were blinded to the vaccination allocation. An unblinded vaccination team was employed to vaccinate study participants. Vaccines were prepared out of sight of the study participants. At the end of the study, the participants were unblinded to the vaccine that they received.

### 7.2.7 Nasopharyngeal Inoculation

Standard operating protocols (SOP) for the preparation of the 6B inoculum stock, the determination of inoculum dose, the inoculation and nasal sampling method, nasal wash (NW) processing, the detection of pneumococcal carriage by culture and measurement of carriage density can be found in Appendix B respectively.

We used our published protocol with full safety cover (178). Briefly a well-characterised penicillin-sensitive 6B serotype pneumococcus (BHN 418, sequence type 138) was grown to mid-log phase in Vegitone broth (Oxoid) and stored in 1ml aliquots containing 20% glycerol at -80°C. Confirmation of serotype was performed using latex agglutination (Statens Serum Institute, Copenhagen) and bacterial purity was confirmed by an independent reference laboratory (Public Health England, Colindale, UK).

The prepared inoculum was taken to the clinical area where the participant was seated in a semi-recumbent position. 100µl of inoculum containing the desired dose (80,000 CFU [colony forming units]/100µl), was instilled into each nostril in a circular motion (178). Following inoculation the participant remained in this position for 10 -15mins. The strain was chosen as its genome is fully sequenced and there are negligible rates of natural colonisation with 6B in Liverpool. The 6B serotype has been used previously by our group and others (176, 177), and we have performed studies (using serotype 23F and 6B) to establish dose, safety and achieve stable colonisation rates (177). See Appendix B SOPs.

### 7.2.8 Nasal Washing and Detection of Pneumococcal Colonisation

Nasal wash (NW) samples were collected pre-vaccine, post-vaccine/pre-inoculation and post-inoculation (day 2, 7, 14, 21). If participants were not colonised at day 2 and 7, they were excluded from NW at day 14. Samples were collected and processed for pneumococcal detection as previously described (178, 192). Briefly, 5ml of 0.9% saline was instilled into each naris, this was repeated twice (10ml total per nares). If less than 10mls was returned, up to 40mls normal saline was used as necessary. All CFU density data were calculated as CFU/ml of NW returned. In less than 3% (n=15) of NW, >20mls of 0.9% saline was required to obtain the required ≥10mls of NW return.

NW samples were transferred immediately to the lab and processed (Appendix B). Participants in whom experimental pneumococci were detected in NW samples at any visit post inoculation were defined as experimentally colonised. All experimentally colonised participants who did not have 2 consecutive culture-negative nasal washes received amoxicillin 500mg T.D.S for 3 days at the end of the study in order to ensure 6B colonisation clearance.

### 7.2.9 Participant Monitoring and Safety

At the pre-vaccination visit a clinical examination, history and pregnancy test (where appropriate) were performed. Participants remained at the clinic for 20-30 minutes after vaccination to monitor for any immediate side effects. Full resuscitation equipment and an anaphylaxis trolley were immediately available. Four weeks after vaccination, participants were inoculated with pneumococcus. Prevenar-13 is a safe vaccine with a very low risk of adverse events (223, 224). It is currently licensed for use in children and in the UK as part of the childhood immunisation programme (effective from 4 September 2006). In adults over 50 years of age vaccinated in US clinical trials the most commonly reported side effects to Prevenar-13 vaccination included: injection site pain/swelling/tenderness, fatigue, headache, muscle pain, limitation of arms movement, decreased appetite, chills and rash. Avaxim was chosen as a suitable control due to its safety profile, preparation (aluminium-containing vaccine), (assumed) lack of effect on nasal colonisation/immunity and health benefit for those involved in the study if the participant were to travel to hepatitis A endemic areas in the future. It is licensed for use in susceptible adults >16 years old. In clinical trials, adverse reactions were usually mild and confined to the first few days after vaccination with spontaneous recovery. Adverse reactions to Avaxim vaccination include (1) Asthenia, mild injection site pain [very common] (2) Headache, nausea, vomiting, decreased appetite, diarrhoea, abdominal pain, myalgia/arthralgia, mild fever [common] (3) Injection site erythema [uncommon] (4) nodule [rare].

Study screening to minimise the risk of pneumococcal infection to participants or contacts included (1) careful study team selection, experienced in human challenge studies (2) careful study design (3) serotype selection (6B) and dosing (4) participant selection and exclusion criteria (5) participant education and rigorous safety procedures including a 24 hour

emergency telephone contact with researchers (including close individual daily monitoring for 7 days post-inoculation via text contact to a specified member of the research team before 1200hrs noon) and access to hospital facilities with prompt treatment if required, a post-inoculation advice sheet (PIL), a digital thermometer and a course of amoxicillin tablets (3 day course of 500mg TDS) in case of emergency. The amoxicillin was only to be taken under three circumstances; in the event that they were unwell and were instructed to take them by the research team, if they were unwell and unable to contact the research team or if they were still colonised with pneumococcus at the end of the study. Home monitoring included a clear flow chart of the necessary intervention should any symptoms develop (Appendix C). If a participant did not make contact by the specified time; a member of the research team contacted them. If no contact was made then a prior defined 'secondary contact' was telephoned.

Data on adverse events were collected and categorised as follows: headache, sore throat, nasal congestion/ running/ sneezing, myalgia, lethargy, earache/ muffling/ popping, pyrexia, neck stiffness, hospital admission and other (including shivering, wheezy, cough, abdominal cramps, photophobia, sinus pain and generally unwell). As per sponsor guidance, any serious adverse events (SAEs) were recorded and reported to the DMSC and sponsor within 24hrs. A Data Monitoring and Safety Committee (DMSC) monitored the study throughout and advised the PI and study team.

### 7.2.10 Endpoints

The primary endpoint was pneumococcal colonisation at any time-point (day 2, 7, 14 or 21). The secondary endpoints were (1) Pneumococcal colonisation at individual time points [day 2, 7, 14 or 21] (2) Pneumococcal density at individual time points and the area under the

density curve, and (3) Pneumococcal colonisation duration, defined as the duration from inoculation to the last confirmed positive NW sample. All endpoints were defined by culture of NW.

### 7.2.11 Statistical Methods, Analysis and Power Calculation

Using data from our dose-ranging and reproducibility studies and data from previous EHPC studies, we estimated that 60% of the control group would be colonised with pneumococci following inoculation and 30% of the PCV group. A 50% reduction of carriage in PCV group was estimated in accordance with modelling studies (225). This allowed a power of 81% when recruiting 50 volunteers to each arm (Table 30).

Analysis was based on the intention-to-treat (ITT) principle. Participants not completing the inoculation limb of the study were removed leading to a modified ITT population. All statistical analyses were performed using SAS 9.2 and Stata 13. Full details are in Appendix A (Statistical Analysis Plan).

### 7.2.12 Study Schedule

A flowchart describing the study schedule in detail with clear timelines is contained in Appendix A.

**Table 31: Power Calculation with Participant Numbers per Study Arm**

| | N | Carriers | Carriers | Carriers | Carriers | **Carriers** | Carriers |
|---|---|---|---|---|---|---|---|
| PCV | 50 | 5 | 5 | 10 | 10 | **15** | 15 |
| Control | 50 | 30 | 25 | 30 | 25 | **30** | 25 |
| Power (%) | | 99 | 99 | 98 | 85 | **81** | 45 |

## 7.3 RESULTS

### 7.3.1 Screening and Recruitment

429 volunteers were screened and 100 participants were recruited between September 2013 and April 2014. Reasons for non-recruitment included close contact with children aged < 5 years old or 'at risk' individuals such as the elderly or those on immunosuppressive medications, asthma (on regular medication), current smoker, >10 pack year smoking history and penicillin/amoxicillin allergy. 99 participants were vaccinated (n=49 PCV, n=50 control – ITT population), 1 participant was removed after recruitment but before randomisation (they had previously received a Hepatitis A vaccination which was not declared on their GPQ) and 3 participants were removed pre-inoculation (n=96 - modified ITT population) [Figure 14]. In less than 3% (n=15) of NW >20mls of normal saline was required to obtain the required ≥10mls of NW return.

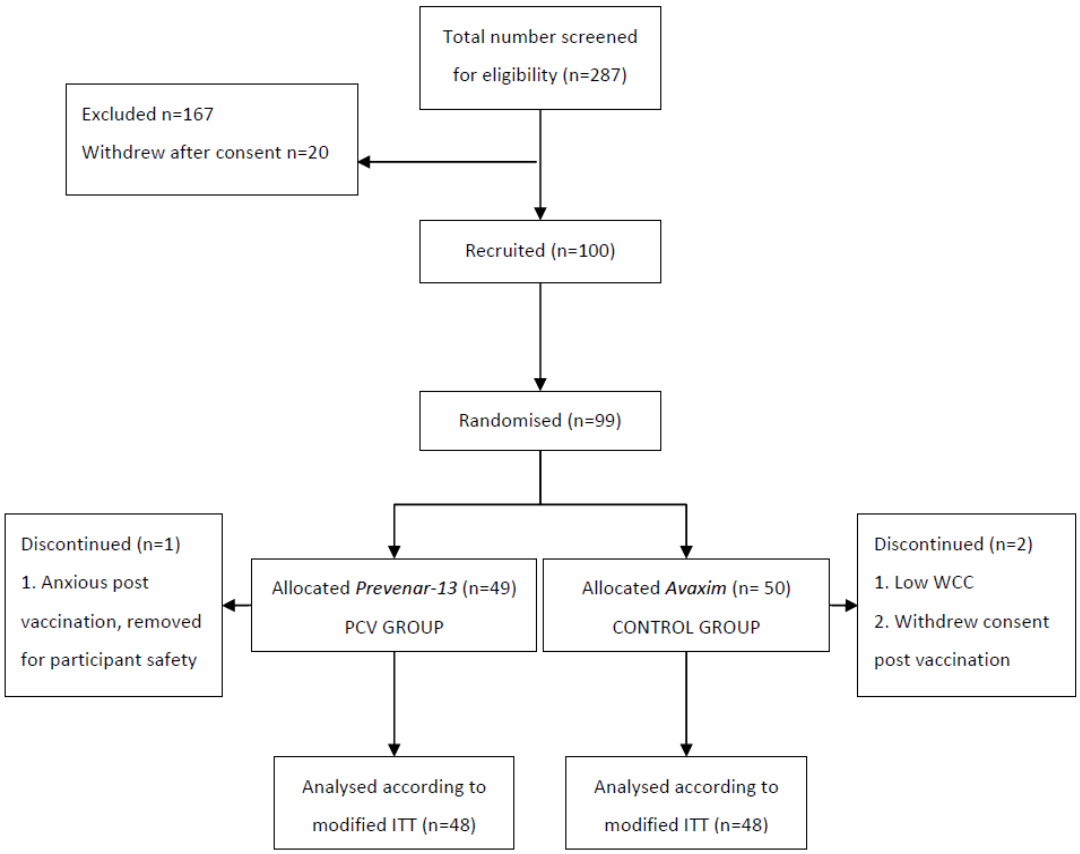


**Figure 14: Consort Flow Diagram**

(Reasons for exclusion: Close contact with 'at risk' individuals (children n = 16, patients n = 41), did not attend appointment n = 18, cannot commit time to the study n = 13, current smokers or >10 pack years n = 11, lived in a Hepatitis A endemic area n = 11, previously involved in an experimental pneumococcal colonisation study n= 9, asthma n=8, allergic to penicillin/amoxicillin n= 7 and other n = 33).

### 7.3.2 Pneumococcal Colonisation Acquisition

Pneumococcal colonisation, with the inoculated 6B serotype, at any time was found in 5/48 (10.4%) participants in the PCV group compared to 23/48 (47.9%) in the control group. The risk ratio of pneumococcal colonisation following PCV compared to control vaccine was 0.22 (CI 0.09 to 0.52, p=0.0007). The corresponding odds ratio was 0.13 (95CI 0.04 to 0.3, p=0.0002). The percentage of colonised participants fell from 8.3% to 4.3% in the PCV group and from 43.8% to 33.3% in the control group between day 2 and day 21, respectively [Table 31]. Amongst the 5 participants colonised in the PCV group, 2 participants were still colonised at day 21. There were no significant differences between the groups with regards to age, gender, time from vaccination to inoculation or dose of inoculum received [Table 32].

**Table 32: 6B Pneumococcal Colonisation Status Assessed According to Vaccination Group at Each and Any Time Point**

| | No. colonised/total no. (%) | | | |
|---|---|---|---|---|
| **Day** | **PCV group (n=48)** | **Control group(n=48)** | **Odds Ratio [95%CI]** | **p value** |
| **Day 2** | 4/48 (8.3) | 21/48 (43.8) | 0.12[0.04-0.38] | 0.0003 |
| **Day 7** | 4/48 (8.3) | 21/48 (43.8) | 0.12[0.04-0.38] | 0.0003 |
| **Day 14** | 1/48 (2.1) | 19/48 (39.6) | 0.05[0.01-0.27]* | 0.0004* |
| **Day 21** | 2/46 (4.3) | 15/45 (33.3) | | |
| **Any day** | 5/48 (10.4) | 23/48 (47.9) | 0.13[0.04-0.37] | 0.0002 |

PCV=Pneumococcal Conjugate Vaccine. *Day 14 and Day 21 were combined to generate a stable estimate. (Note modified ITT analysis [n=96] was used since participants excluded post vaccination but pre-inoculation cannot develop experimental 6B colonisation).

**Table 33: Baseline Demographics of Participants**

| Characteristics | PCV (n=49) | Control (n=50) |
|---|---|---|
| **Age (year)** | 24.1 ± 6.1 | 23.2 ± 6.9 |
| **Male** | 20 (40.8) | 19 (38.0) |
| **Time from vaccination to inoculation (days)** | 35.0 ± 3.9* | 34.1 ± 2.2* |
| **Dose inoculated (CFU/100µl)** | 83203 ± 8026* | 82602 ± 8098* |

Data are number (%) or mean (SD). PCV=Pneumococcal Conjugate Vaccine. *n=48 in each group. (Data as per Intention to Treat analysis – ITT, n=99).

### 7.3.3 Pneumococcal Colonisation Density and Intensity

PCV reduced colonisation density (Figure 15). The density of 6B pneumococci recovered from the nasopharynx of participants in the PCV group was on average three logs lower than the density recovered from the control group, with statistically significant differences seen up to 7 days post inoculation (Table 33 and Figure 16). There was an overall significant reduction in colonisation intensity as measured by the AUC (ratio 0.02, 95%CI 0.00 to 0.51, p=0.017). We did not observe a statistical difference in duration of established colonisation between the groups (p=0.1328).

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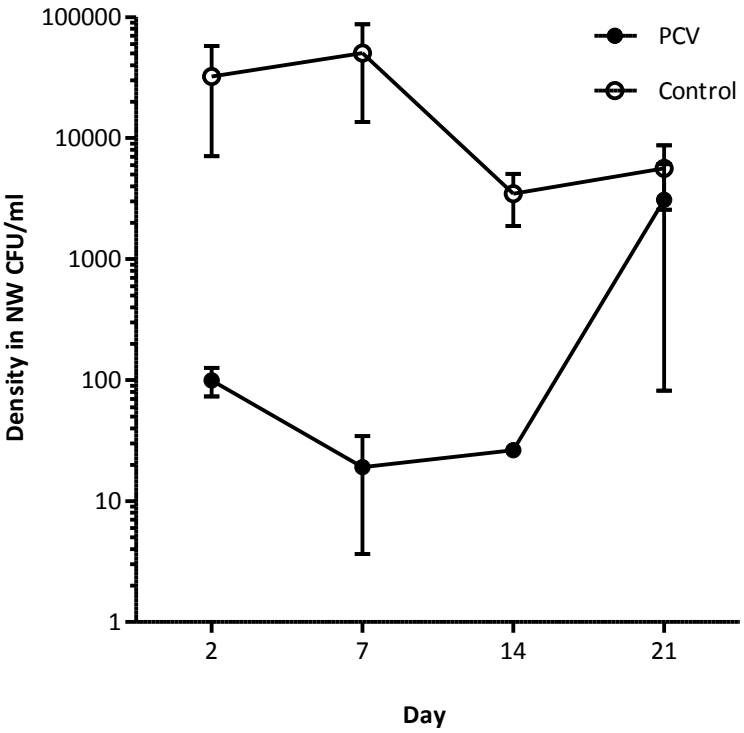


**Figure 15: 6B Pneumococcal Colonisation Intensity (Density [CFU/ml NW] in Relation to Duration of Colonisation [Days]) Post Inoculation at Each Time Point According to Vaccination Group of All Those Colonised**

6B pneumococcal colonisation intensity (density [CFU/ml of NW returned] in relation to duration of colonisation [days]) post inoculation at each time point according to vaccination group. (Values shown are the mean CFU per millilitre ± standard errors of the mean [Full data plotted in Figure 16]).

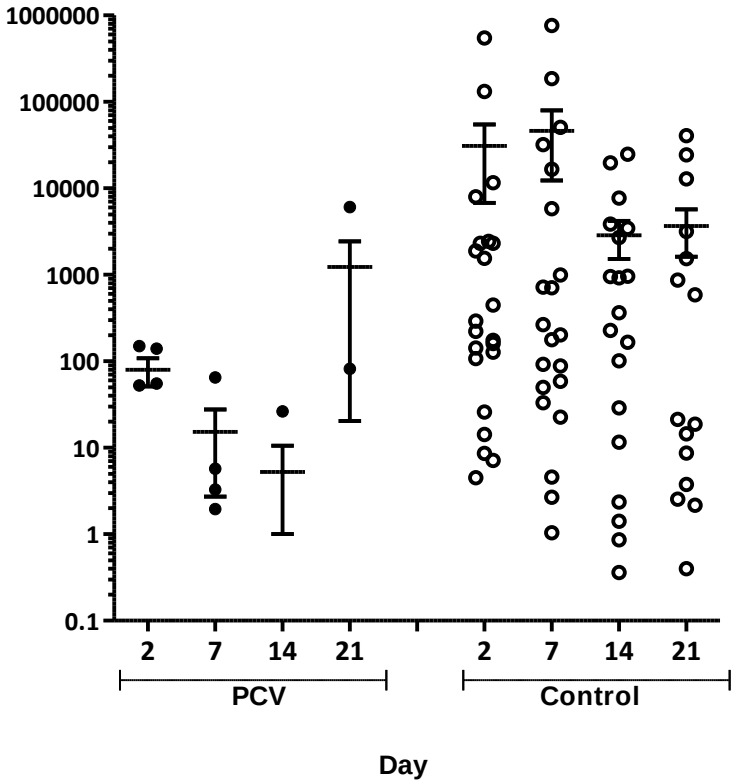


**Figure 16: 6B Pneumococcal Colonisation Density (CFU/ml) Post Inoculation at Each Time Point According to Vaccination Group of All Those Colonised**

Values shown are the mean CFU per millilitre ± standard errors of the mean.

**Table 34: 6B Colonisation Density According to Vaccination Group at Each Time Point**

| | Density (CFU/ml) geometric mean ± SD | | | |
|---|---|---|---|---|
| **Day** | PCV (no. colonised at each time point) | Control (no. colonised at each time point) | Ratio [95% CI] | p value |
| **Day 2** | 99 ± 53 (4) | 33694 ± 120812 (21) | 0.17 [0.04-0.65] | 0.0099 |
| **Day 7** | 19 ± 31 (4) | 50517 ± 169172 (21) | 0.02 [0.00-0.14] | <0.0001 |
| **Day 14** | 26* (1) | 3476 ± 6962 (19) | 1.94 [0.09-43.90]# | 0.6767# |
| **Day 21** | 3085 ± 4247 (2) | 5623 ± 11855 (15) | | |

PCV=Pneumococcal Conjugate Vaccine. *Only 1 observation and SD is unavailable. # Day 14 and Day 21 were combined to generate a stable estimate. Density is only reported in participants who are colonised with 6B. (Note modified ITT analysis [n=96] was used since participants excluded post vaccination but pre-inoculation cannot develop experimental 6B colonisation).

### 7.3.4 Natural Pneumococcal Colonisation

In total 6 participants were naturally colonised, 4 in the PCV and 2 in the control group. In the PCV group, 2 participants were colonised with VT (both serotype 3) and 2 with NVT. In the control group both were NVT (serotype 33 and 8). One participant in the control group was co-colonised with both the inoculated serotype 6B and a naturally acquired serotype 8 (Table 34).

**Table 35: Natural Pneumococcal Colonisation According to Vaccination Group**

| Vaccine group | Experimentally Colonised | Pre-inoculation serotype | Day 2 serotype | Day 7 serotype | Day 14 serotype | Day 21 serotype |
|---|---|---|---|---|---|---|
| **PCV** | No | 23 | 23 | ND | 23 | 23 |
| **PCV** | No | 3 | 3 | 3 | 3 | 3 |
| **PCV** | No | NVT | NVT | NVT | NVT | NVT |
| **PCV** | No | 3 | 3 | 3 | 3 | 3 |
| **Control** | No | 33 | 33 | ND | ND | ND |
| **Control** | Yes | 8 | ND | 6, 8 | 6, 8 | 6 |

NVT - non-vaccine type, serotypes identified by Statens Serum latex kit; ND: not detected

### 7.3.5 Symptoms

#### 7.3.5.1 Post Vaccination

Of those receiving *Prevenar-13*, 12 (24%) had local symptoms [sore arm (n=12), injection site swelling (n=2)]. Of those receiving *Avaxim*, 9 (19%) had local symptoms [sore arm (n=5), injection site pain/redness/swelling (n=4), localised numbness (n=1), neck stiffness (n=1)]. For both vaccines no systemic symptoms were reported and there were no episodes of anaphylaxis.

#### 7.3.5.2 Post Inoculation

14 (48%) colonised and 25 (37%) non-colonised participants reported symptoms. 13 colonised (3 PCV, 10 control) and 23 non-colonised (14 PCV, 9 control) reported minor symptoms at least once up to day 21 post inoculation. Minor symptoms included: headache, sore throat, nasal congestion/ running/ sneezing, myalgia, lethargy, earache/ muffling/ popping, pyrexia, wheeze, mild photophobia, cough, abdominal and sinus pain. One participant (PCV group and 6B colonised) was admitted to hospital overnight 72hrs post-inoculation complaining of pyrexia, lethargy and sore throat. This participant was diagnosed with tonsillitis and a non-toxigenic *Corynebacterium diptheriae* was cultured from throat swabs. Amoxicillin 500mgs TDS was prescribed for 10 days and they made a full and uneventful recovery. The participant was included in the ITT analysis although, as expected, the antibiotic therapy terminated 6B colonisation.

## 7.4 DISCUSSION

In this study we have demonstrated that 6B pneumococcal colonisation acquisition was reduced by 78% in *Prevenar-13* (PCV) vaccinated adults compared to controls. When 6B colonisation did occur post PCV vaccination, this was at a significantly lower density than in control participants. Further, we demonstrated for the first time that EHPC can be used as an innovative approach to test vaccine efficacy in healthy adults using both pneumococcal colonisation acquisition rates and density as important and relevant endpoints.

Human challenge studies in vaccination are not unusual; they have been critical to the development of a wide number of candidate approaches to malaria vaccination (226) and are in development for other infectious diseases (227). We conducted this study as a registered Double Blind Randomised Controlled Trial (DBRCT) to demonstrate proof of principle for EHPC in pneumococcal vaccine testing. The study has a number of strengths in that it is small, quick, safe, economical and precise. The study took 9 months to complete, required only 100 participants, had no SAEs related to pneumococcal inoculation and a budget of ~£500K with the precision of the culture determined colonisation end-point giving the study a definitive answer. Our observations of a reduction in colonisation acquisition rate and density are the same as shown in RCTs conducted in children (164, 228). Using disease as an endpoint, the CAPiTA (Community-Acquired Pneumonia Immunization Trial in Adults) study involved over 85,000 participants from 58 hospitals in the Netherlands over 5 years from 2008, in order to evaluate the efficacy of *Prevenar-13* in adults ≥65 years (167, 169, 229). EHPC studies could be used to select vaccine candidates. Using colonisation as a surrogate endpoint, the cost and time taken from vaccine discovery to product registration and market [often over a 10 year

process with current cost estimates of US$200 - 500 million per vaccine (230)] could be substantially reduced.

The main weakness of the study is that colonisation in healthy adults is not a clinical disease endpoint; nevertheless, it is a critical determinant of transmission not simply a surrogate of protection. Another limitation is that this model is not suitable for use in children. Only a single serotype (6B) was used; our planned future work will also use other serotypes. Prevention of colonisation in children and adults results in herd protection through reduced exposure, therefore this effect is directly relevant to predicting herd protection and hence informing vaccine strategy. The small number of participants with natural colonisation (n=6, 6%) in our study is typical of that expected for UK adults (219), but does not allow conclusions about the effect of PCV-13 vaccination on natural colonisation or its interaction with 6B. We note that whilst it is theoretically possible to have both natural and 6B experimental colonisation, this was only seen in one participant. A short interval between vaccination and pneumococcal challenge was chosen is order to assess the effect on colonisation during the period of optimal immune response to vaccination. Future studies with longer intervals are planned to investigate whether protection wanes with time and will investigate the role of viral co-colonisation. We have previously found no correlation between baseline serum anti-capsular or anti-protein antibody levels and protection from colonisation (177). It may have been useful to include 'zero' points on Figure 16, since this figure may visually underplay the significant difference in colonisation density seen between the PCV and control groups.

Epidemiological data have shown a reduction in nasopharyngeal colonisation after PCV in children and adults (219, 231) both by direct protection of vaccinated individuals and by reduction in exposure of unvaccinated individuals through herd protection. The protective

effectiveness of PCV-13 against VT colonisation in children was ~ 74% (231), we have replicated these findings in adults demonstrating a 78% reduction against VT (6B experimental) colonisation in adults. We have also shown a 10% PCV-13 failure rate. The large effect demonstrated here may either be due to our protocol design (in which we chose to inoculate participants at optimal immunity post PCV-13 vaccination at 4 weeks), or it may be that PCV-13 is particularly effective against type 6B [as has been shown in colonisation studies in children when compared to other VTs, post PCV-7 and -13, such as serotype 19F and 3 (231, 232)]. 6B colonisation rates in children declined from 20% (233) to 0-2% after the introduction of PCV-7 (218, 232, 234, 235) in Europe. Our findings replicate the known impact of PCV on colonisation (impact on density and acquisition but no impact on duration) from both RCT and epidemiological studies (164, 228).

This study provides data to confirm that PCV-13 not only leads to a significant reduction in pneumococcal colonisation acquisition rates, but also reduces the density of colonisation thereby offering further protection by reduced transmission. We suggest that this novel Experimental Human Pneumococcal Colonisation (EHPC) model can be used as a platform for future pneumococcal vaccine testing, using small sample sizes and shorter time scales than community studies in order to reduce time and cost to market. We recommend that colonisation acquisition rate, density and duration are all measured in these studies (177, 178).

## 7.5 ACKNOWLEDGEMENTS

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this project, but were very involved throughout the study. Without the constant hard work of Sr Angie Wright this study would not have been completed so efficiently and smoothly. The DMSC - Professor Robert Read, Chair of Infectious Diseases, University of Sheffield (Chair) – (*Neisseria* human inoculation studies and an expert on mucosal defence against infection); (2) Professor David Lalloo, LSTM – (an experienced clinical trialist with substantial experience of DMSC work) and (3) Dr Brian Faragher, Senior Lecturer in Statistics, LSTM – (experienced in clinical trials and DMSC work). Dr Brian Faragher was also the statistician involved in the initial methodology and Duolao Wang was responsible for writing the full statistical analysis plan and performing the post-study analysis. The analysis in table 32 was performed by myself, I was involved in all statistical planning and post-analysis discussions. Leona Trainor for her assistance with vaccine ordering and pharmaceutical issues, the CRU staff for administering all 'in study' vaccines and the Well-Travelled clinic for any 'post-study' vaccines. To all the laboratory staff - Elena Mitsi, Jenna Gritzfeld, Toni Banyard, Shaun Pennington for preparation of the bacterial inoculum and sample processing, colonisation detection and analysis. Dr Ben Morton, Sr Carole Hancock, David Shaw and Sr Angela Wright for assisting with recruiting and consenting volunteers. Sr Angela Wright for assisting with ethics, MHRA and Trust approvals and for designing the Access database collating the data. Professor Stephen Gordon, Dr Hassan Burhan, Sr Angela Wright, Dr Ben Morton and the infectious Disease doctors for providing on-call and clinical cover as required. Professor Stephen Gordon for coordination of DMSC communications.

# CHAPTER 8: Discussion and Future Studies

## 8.1 General Summary and Discussion of Findings

In this thesis, we have described studies that focus on the diagnostics, therapeutics and prevention of pneumonia and LRTI, key priorities in the UK today.

With regards to diagnostics (Chapter 3) we conclude that neither prevalence nor density of nasal pneumococcal colonisation (assessed by culture or *q*PCR) can be used as a method of microbiological diagnosis in hospitalised adults with LRTI in the UK. Nationally GP antibiotic prescribing for LRTI is very high. Nasal sampling is not a useful diagnostic technique in hospitalised patients, since such patients have usually received at least two doses of antibiotics from their GP prior to nasal wash. We do not recommend nasal sampling in patients admitted to hospital with LRTI in the UK.

With regards to therapeutics and home-based care, we have shown that ESDS (Chapter 4, 5 and 6) is difficult but not impossible to implement and recruit to and that there is demand for such a service. A large recruitment effort is needed. Using defined criteria for recruitment and a defined interventional package treatment of patients with LRTI and pneumonia outside of an acute hospital environment is safe, effective, popular with many patients and their

carers and by reducing length of hospital stay may be cost-saving. In the feasibility study the total hospital length of hospital stay was reduced by 4.9 days in the early supported discharge scheme (ESDS) arm. Patients and carers reported higher satisfaction with care in the ESDS and there were fewer readmissions and hospital-acquired infections. The feasibility study informed the pilot study, therefore we included patients with lack of capacity in the latter in order that the ESDS could benefit more patients. In the pilot study, at 6 weeks there was no increase in readmission or mortality rates or decrease in recovery rate, functionality or symptom resolution in the ESDS group and satisfaction was high. We noted a reduction in LOHS (bed days) by 5 days as well as a reduction in the total length of care of 2 days. Virtual visits (via telephone), rather than home visits seemed adequate after the first 48hrs from discharge.

With regards to prevention and vaccine development (Chapter 7), using our Experimental Human Pneumococcal Carriage (EHPC) model we confirmed that the current pneumococcal vaccine (PCV) reduces rates of pneumococcal acquisition and carriage density in healthy adults. The EHPC model is a safe and efficient method to determine the protective efficacy of new vaccines on pneumococcal colonisation; PCV provides a 'gold standard' against which to test these novel vaccines. Our robust EHPC model can now be used to test novel candidate vaccines using a smaller sample size and shorter timescales than clinical community studies in order to reduce cost and time to market.

Overall, reflecting on the decision made to include LRTI rather than just CAP in order to make the results in these studies more generalisable was useful for the HAH studies (Chapter 5 and 6) but not useful for the LRTI NW study (Chapter 3). The heterogenicity of this group made it potentially more difficult to achieve meaningful microbiological results in terms of

pneumococcal colonisation for the LRTI NW study but recruiting patients with pneumonia alone would have made recruitment even more challenging. When pneumococcus is the pathogenic organism it may more commonly cause pneumonic consolidation (if a timely CXR is performed) rather than a 'simple' LRTI without consolidation like H. *influenza* or respiratory viruses; this means that our chance of finding high pneumococcal density or indeed pneumococcal presence in nasal wash in such patients would have been significantly reduced affecting our results.

## 8.2 The Future

With regards to Chapter 3, since we found that prior antibiotic treatment meant that nasal sampling in these hospitalised patients was not useful; a future community based study of nasal sampling as a diagnostic technique in antibiotic naïve patients with LRTI/pneumonia prior to antibiotic therapy may be useful. Sample size calculations suggest that for an 80% power to detect a difference of 10% in qPCR (52% detection in LRTI patients versus 42% in controls) would require at least 200 patients in each arm. Patients with a clinical diagnosis of CAP (according to NICE definitions) would be included, and we would consider excluding patients with HAP, COPD and bronchiectasis in whom different pathogens are more common. Collaboration with interested local GP surgeries and screening during the winter season would be key.

With regards to chapters 4, 5 and 6, better integration between primary, secondary and social care is key to the success of such a complex interventional model, HOME FIRST. Social support is a key reason for delayed discharges so without the support of physiotherapists, OTs and an instant access care team we will always struggle to discharge such patients, especially with our ever-ageing population with increasingly complex and multiple co-morbidities. A

significant number of patients who have complex social/mental health needs or co-morbidities will however still require inpatient care. The novelty of these studies was a great strength and in developing flowcharts and a manual of procedures for this complex intervention we have paved the way for further future studies. The recruitment was difficult. Another strength was the inclusion of patients without full capacity, this made the REC application process more complicated but we were determined to include such patients as we felt they could benefit significantly from such an intervention.

The potential patient-related (reduced risk of HAI, care in own home, improved sleep, increased recovery rate, improved patient and carer satisfaction, reduced risk of delirium and later post-hospital discharge institutionalisation) and health-service benefits (reduced risk of HAI, improved self-management, reduced hospital LOS and therefore cost) are critical in assessing service impact. Strategies to increase the proportion of low-risk patients with CAP treated in the community have been developed and have been reported as safe, effective and acceptable to patients (107) but there is an urgent need for more evidence regarding ESDS to facilitate the discharge of patients with more complicated needs.

Our pilot study suggests a number of potential improvements to study recruitment procedures would maximise the use of ESDS:

(1) *Hospital logistics* - Recruitment to future pneumonia and LRTI studies will improve if hospitals more proactively engage with research. Since screening is resource intensive; a proactive scheme where ward medical/nursing staff contacted the research team or screening together with the existing hospital community COPD team would be more efficient. Working with hospital management to improve hospital systems to reduce time spent screening ineligible patients may help but the new shift to hospital computer systems rather

than paper notes will help the screening process as this can then be performed remotely daily or twice daily by a trained non-clinical administrator in order to provide lists of potentially suitable patients. Further remote review would also be easier and faster. Increasing recruitment hours up to 12 hours-per-day, 7-days-per-week and more cohesive working between the clinical team, home IV antibiotic team and current community respiratory teams is required for this intervention to work more effectively and efficiently. Improved collaboration with microbiology in order to produce a trust policy for out-patient IV antibiotic therapy for LRTI and pneumonia to enable B.D. IV antibiotic dosing is important. Fast-access to occupational therapy within the hospital, community physiotherapy and social services may also aid recruitment by increasing the number of patients with complex MDT needs recruited. However, all of this would increase cost and therefore affect health economic projections.

(2) *Medical conditions* - Collaboration with palliative care and community elderly care physicians in order to improve advanced care planning (which will also likely improve admission avoidance) will allow patients to be discharged with a 'trial of antibiotic therapy' for a set duration where appropriate with a clear management plan in place in case of further deterioration. Terminal care may be more appropriately delivered at home in such patients (212).

Future developments to the HOME FIRST ESDS model may include accepting patients in whom clear decisions have been made (or encouraging such decisions to be made) that no escalation in care is appropriate if after 48hrs no improvement is seen; terminal care may be more appropriately delivered at home (212). It may also be useful to accept patients on more than

twice per day IV antibiotics and to develop closer links with 'early response teams' in order to facilitate fast and effective discharge of more complex patients.

HAH presents an opportunity to improve health policy, healthcare delivery and services; and to reduce admission rates and HAIs, all areas of major strategic importance internationally. Hospital at Home (HAH) care is a complex clinical model (236) that may work best as part of a portfolio of models for patients with respiratory infection (237). ESDS is likely to more effective in areas with a lack of 'cottage hospital' or intermediate care beds for convalescence. Large numbers are needed to effectively assess safety and effectiveness. We propose that there is a clear need and demand for an ESDS but that better integration within well-established CCG-funded chronic obstructive pulmonary disease (COPD) schemes to form a 'Respiratory ESDS' is required and that a large multi-site RCT with multiple relevant patient-related end-points is required (238). CAPSYM, RECRI, ASF-12 have not been shown to be useful endpoints in either HOME FIRST study. Health-economic analysis, satisfaction, mortality and readmission rates are however useful and important end points.

With regards to Chapter 7, this was a well-run novel carriage study, recruitment at times was still challenging however; we learned a great deal about the ethics process for carriage study work, the best ways to recruit students to such studies and about registering and running CTIMP studies. We have since used this EHPC model to test a novel vaccine in a Phase 2 DBRCT placebo trial. We tested GEN-004 a sub-unit vaccine developed by Genocea Biosciences to determine whether GEN-004 protects against pneumococcal carriage (aiming to become a licenced vaccine against pneumococcal otitis media). We are currently using the EHPC model to investigate whether the nasal live attenuated influenza vaccine (LAIV) has any impact on pneumococcal carriage. The clinical relevance being that increased pneumococcal carriage

rate and density may lead to increased transmission and burden of disease in susceptible individuals. Further pneumococcal vaccine studies are under discussion. We are also planning to inoculate subjects with asthma and the elderly; and also planning a co-infection model with multiple pneumococcal serotypes competing in the same niche.

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# Appendices

## Appendix A

Contains all study protocols (including study flowcharts and statistical analysis plans):

- LRTI and Nasal Wash Study Protocol
- HOME FIRST Feasibility Study Protocol
- HOME FIRST Pilot Study Protocol
- PCV EHPC Study Protocol
- PCV EHPC Study Flowchart
- PCV EHPC Statistical Analysis Plan

# PROTOCOL for LRTI and NASAL WASH Study - a Study of Pneumococcal Carriage in Hospitalised Patients with Lower Respiratory Tract Infections.

## BACKGROUND

### *Pneumococcal carriage*

Pneumococcal disease is preceded by colonisation of the nasopharynx of uninfected adults and children. Pneumococcal carriage rates are known to be around 1-10% in the adult population in developed countries (70, 71) Factors including age, immune status, antibiotic use, household composition and contact with children all affect carriage rates. Lowest rates are seen in those adults without preschool children in the family (2-9%) and highest in those with preschool children (18%). Rates of up to 35-54% are seen in preschool age children (70, 71).

There are no data on pneumococcal carriage in hospitalised patients with respiratory infection in the UK. Pneumococcal carriage in pneumococcal vaccine naive hospitalised elderly (72) in Australia was extremely low, (1 of 315) on nasopharyngeal swab (NPS). Of this cohort only 10 patients had respiratory infection at the time of the nasal swab.

A South African study of predominantly HIV positive patients with community-acquired pneumonia (CAP) identified pneumococcus in 27% of CAP patients using composite diagnostic methods (blood and sputum culture, Gram stain and urine Binax testing). Patients with CAP were more frequently colonised than controls (44.9% v 11.7% using classical culture and 62.8 v 19.8% using *lytA* real time Polymerase Chain Reaction [*rt*PCR]). HIV-infected patients with CAP with positive composite diagnostic tests for pneumococcus had higher density on NPS than those without pneumococcus identified; density was also higher in those with pneumococcal CAP than asymptomatic controls. The higher the density the more likely the HIV-infected patient with CAP was to be pneumococcal positive on composite testing. Quantitative rtPCR could possibly be used as a new method with which to diagnose pneumococcal pneumonia in adults.(45) rtPCR may improve detection and quantification of nasal pneumococcus in patients with LRTI.

In Chinese children, more frequent pneumococcal colonisation was detected in those with pneumonia than without.(78) Vietnamese children with pneumonia had higher density colonisation than those with bronchitis or healthy children.(79)

With rising burden of organisms in the nasopharynx at a critical colonisation density, it is believed that the risk of micro-aspiration and therefore pneumonia increases.(81, 82)

Knowledge of pneumococcal carriage in a population of hospitalised patients with respiratory infection will increase understanding about potential new diagnostics (nasal wash, NPS) for these patients and more targeted antibiotic therapy.(45) Since reduced colonisation is seen as a potential surrogate marker of pneumococcal vaccine efficacy, research in this area, will further knowledge as to whether this can be used as a surrogate in a UK population.

It is possible that the UK population could show either the high carriage seen in South Africa and Vietnam or more likely the low carriage rates seen in Australia. The key question here is - Are carriage rates higher in hospitalised UK patients with lower respiratory tract infection (LRTI) compared to hospitalised age matched patients without LRTI?

### *Improved treatment for lower respiratory tract infection (LRTI)*

Better microbiological diagnostics would lead to more targeted, accurate antibiotic therapy and would reduce the prescription of unnecessary antibiotics. Earlier accurate treatment may reduce the risk of developing more severe disease that results in both hospital admission and a more prolonged hospital stay.

***Improved understanding of the role of pneumococcal carriage and host immunity***

Pneumococcal carriage is an immunising event.(84-86) We have shown for the first time in adults that carriage induces protective immunity against pneumococcal re-challenge.(87, 88) It is possible that in elderly adults a failure to establish occasional pneumococcal carriage (due to defective mucosal T cell function) leads to a loss of the immunising function of carriage and hence increased susceptibility to disease. The key question here is – Do LRTI patients and age matched controls have altered T cell function concurrently?

In mice, carriage correlates with increased T regulatory cell responses in the nasopharynx. Following exposure to low doses of pneumococci there are two scenarios for responses in the nasopharynx (i) an inflammatory response that clears the infection (ii) a T regulatory cell driven response that supports long-term stable carriage. If T reg numbers increase in the nasopharynx carriage occurs (increased levels may contribute to the persistence of that carriage event)(239), if they do not increase pneumococcal clearance occurs. (240)

## STUDY DESIGN OVERVIEW

- **Overall research aim**

  To analyse pneumococcal carriage rates in patients hospitalised with LRTI.

- Primary endpoint

  Rate of pneumococcal carriage in patients hospitalised with LRTI and age matched controls.

- **Secondary endpoints**

  1) Density of pneumococcal carriage in patients hospitalised with LRTI and age matched controls
  2) Alterations of T cell function (Th1, Th17, T regs) in LRTI patients and age matched controls (versus younger adults as part of our existing 'P4' study).

**Study design**

Patients hospitalised with LRTI at the Royal Liverpool and Broadgreen Teaching Hospitals (RLBUHT) between November 2012 and April 2014 will be approached within 72 hours of admission.

Patients recruited into the study will consist of those hospitalised with LRTI and a control group of age matched patients (within +/- 10 years) hospitalised for reasons other than respiratory infection.

**SUBJECTS AND TIMELINES**

Between November 2012 and April 2014 we will aim to recruit 100 patients with LRTI and 100 controls to the study.

**METHOD DETAILS**

- **Recruitment and Selection**

The study team will be in regular communication with bed managers, nursing and medical co-ordinators in A&E, the acute medical admissions unit (AMAU) and the respiratory wards at RLBUHT Monday to Friday. Via regular education and information dissemination events and through daily interaction with the study team, the key staff will be aware of the research study and its aims, objectives and potential participants. A list of potential patients will be generated on a daily basis in combination with these personnel, and discussed twice per day at pre-

defined times (by phone or bleep) to alert the study team of a potential recruit. Controls will be selected in a similar way with regular communication with bed managers, nursing and medical co-ordinators in A&E and AMAU at RLBUHT Monday to Friday.

Relevant parts of a potentially suitable patient's medical notes, blood, microbiology and radiology results will be reviewed by a study team member to assess suitability. If a patient is considered potentially suitable the clinical team will approach the patients and discuss whether they are happy to meet a member of the study team. If the patient agrees, the clinical team member will introduce the study team member to the patient. The study team member will then assess the patient's capacity, clinical condition and appropriateness of their current environment for initial study discussion. The study will be explained to the patient and a patient information sheet provided. A limited clinical examination will be performed by the study doctor before recruitment and consent. Following this, any questions will be answered. Consent may either be obtained at this point, the patient may decline participation all together or after an agreed length of time, to allow patients to discuss with their advocates and for their reflection, consent will be re-visited and further opportunity for questions given (N.B. participating patients must be recruited within 72 hours of presentation to hospital). Only patients able to give fully informed consent will be recruited. Consent will be taken by a fully trained study team member.

Inclusion criteria for LRTI patients

- Non-pneumonic LRTI (no radiological consolidation but the presence of clinical signs) or community acquired pneumonia (radiological consolidation)
- Able to give fully informed consent (mental capacity assessed using trust guidelines)
- Age>18yrs old
- Fluent English speaker

**Exclusion criteria for LRTI patients**

- Infective exacerbation of COPD or bronchiectasis without consolidation
- Oxygen saturations <86% on air
- Tuberculosis suspected
- Neutropenia

Inclusion criteria for controls

- Able to give fully informed consent (mental capacity assessed using trust guidelines)
- Age>18yrs old
- +/- 10 years of recruited LRTI patient
- Fluent English speaker

**Exclusion criteria for controls**

- Signs/symptoms of respiratory infection
- Oxygen saturations <86% on air
- Neutropenia

**Screening, Investigations and Follow-up**

**Screening -** Baseline clinical data which includes age, gender, history of presenting complaint, past medical history, social history, drug and vaccination history and allergies will be recorded. Data will also be collected with regards to contact with babies and children (aged≤10yrs).

**Clinical examination** – will be performed and recorded by the study doctor.

**Investigations and follow-up** – Participants will be seen by the study team at two time points; on recruitment (day 0) and at 6 weeks following hospital discharge in the respiratory infection out-patient clinic. Additional samples will be collected for investigational laboratory work. Blood and nasal wash (or nasal pharyngeal swab [NPS]) samples will collected by a fully trained team member at both time points. A urine sample will be collected at day 0 only. A chest X-ray will be performed if clinically necessary at the respiratory infection out-patient visit.

**SAMPLING AND LABORATORY TECHNIQUES**

**Nasal wash or nasopharyngeal swab** - Nasal wash was chosen by 91% of volunteers as being more comfortable and was more likely to detect pathogens using microbiological culture than NPS.(192) However some patient find the co-ordination needed for this technique too difficult resulting in low volume yield +/- anterior nasal wash only, in such patients a NPS will be taken instead. The nasal wash will be performed using a modified Naclerio method.(189) This is a well validated technique to collect nasal specimens with which we now have 2 years experience. Briefly, 20ml of saline is instilled and held for a few seconds in the naris before being expelled in to a sterile Galli dish. In the event of nasal wash loss (defined as cough/sneeze/swallow) the procedure may then be repeated to obtain an adequate specimen.

**Blood** – Up to 30mls of venous blood will be taken by an appropriately trained team member.

**Urine** – up to 20mls of mid-stream urine will be collected.

**Determination of colonisation** - colonisation will be defined based on the culture (+/-PCR) result of nasal wash/NPS taken at day 0 and 6 weeks. Nasal washes and NPS will be plated on culture media and incubated overnight at 37°C in 5% CO2. Colonies will be confirmed as S. *pneumoniae* using classical techniques including (i) typical draughtsman-like colony morphology (ii) the presence of α-haemolysis (iii) optochin sensitivity (iv) solubility in bile salts and (v) Gram-positive diplococci. Isolates will be typed using a latex agglutination kit (Statens Serum Institute) Density will be determined using a modified version of Miles and Misra dilutions. Isolates will be frozen at -80ºC for storage and reference laboratory confirmation. Results from the cultured nasal wash will also be confirmed using PCR based (LytA) methods of bacterial detection.

**Humoral immunity –** serum will be stored for immunoglobulin assay laboratory work to compliment T cell work as below.

**Cellular immunity (Th1, Th17, Tregs) – central and effector memory T cells –** Flow cytometry will be used to identify T cell populations in peripheral blood and nasal wash samples. Foxp3 will be used to identify T regulatory cells and RORgt as a marker of Th17. In addition, intracellular cytokine staining and ELISA analysis of nasal wash samples will be used to assess patterns of immune responses in patient samples. These assays will be performed to test the hypothesis that LRTI in elderly patients are the result of a failure of tolerance. For this reason we will test for IL-10 and TGFb levels as markers of regulatory responses, and IFNg and TNFa as markers of a more proinflammatory response.(241) If cytokine levels prove difficult to detect in peripheral blood and nasal wash samples we may isolate CD4 T cells from the samples and measure cytokine responses to stimulation with pneumococcal antigens.

## SAFETY NOTES

All samples (nasal wash/NPS, blood, urine) will be taken by experienced members of the study team.

## ANALYSIS PLAN

A research statistician, Dr Brian Faragher from LSTM, has been involved in statistical discussions. Using published data showing a carriage rate of 10% in developed countries in healthy adults, 11.7% in healthy South African adults (including HIV positive), 1% in hospitalised elderly Australian patients and 45% in South African patients with CAP; to detect a difference between 1 and 11.7% with an 80% power we require n=107 in each group. To detect a difference between controls of 11% and patients of 45% we require n=55 in each group (power 97.8%) or n=40 (power 91.3%). Since we will also use carriage density as well as simply culture positive for carriage yes or no; 100 patients in each group will be sufficient. We will need n=30 in each group to investigate T reg, Th1 and Th17 function.

## FUTURE PLAN AND IMPLICATIONS OF THE WORK

Success in this project will result in novel information with regards to the use of pneumococcal carriage in adults as a method of fast microbiological diagnosis in patients with LRTI and also the feasibility of the use of carriage in adults as a surrogate marker of protection from pneumococcal vaccination.

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# PROTOCOL for HOME FIRST: a feasibility study for early supported discharge in patients with lower respiratory tract infections.

**BACKGROUND**

## *The clinical and economic burden of lower respiratory tract infection (LRTI) and pneumonia is high(5)*

The annual incidence of LRTIs in Europe in 2002 was 25.8 million, greater than diabetes and cancer.(2) Pneumonia and LRTI are important health problems that are very costly to the NHS. There were over 260,000 admissions in England with pneumonia, influenza and LRTI combined in 2009, more admissions than ischaemic heart disease; and with 2.3 million bed days annually, more bed days than for stroke/cerebrovascular disease.(3) Community-acquired pneumonia (CAP) is a major cause of hospital admissions worldwide.(5) In Europe, pneumonia costs over €10 billion annually with inpatient care accounting for € 5.7 billion, outpatient care €0.5 billion and drugs €0.2 billion.(5) In the USA, 90% of CAP expenditure relates to the cost of in-patient care.(6) In the UK, direct CAP healthcare costs in 1992-3 were £441 million annually.(95) Seventy percent of UK pneumonia admissions are CURB-65 score 0-2; the median patient age is 76yrs old with two-thirds over 65yrs old.(90) In the UK, CAP is therefore mostly affects the older population,(5) with an annual incidence of up to 22.4 per 1000 in those over 85 years old(8) in whom admission to hospital may in fact be more detrimental than care in their own residence.(13) Over the next decade the incidence of CAP will increase further as the population ages; as will the associated co-morbidities.(14)

## *With support, many LRTI/CAP patients could be managed at home*

Strategies to increase the proportion of low-risk patients with CAP treated in the community have been developed and have been reported as safe, effective and acceptable to patients; with no significant differences in patient satisfaction, mortality or hospital re-admission rates noted.

The Pneumonia Severity Index (PSI), CURB-65 and CRB-65 are pneumonia severity scoring systems that use initial admission data to predict mortality; they are used to aid clinical decision-making about 'best place of care' for the individual. Although hospital length of stay (LOS) for CAP has reduced over recent years mainly due to increased use of these severity scores, in community settings CRB-65 may over-predict 30-day mortality, potentially leading to more hospital admissions.(91) PSI was developed and validated to identify patients with a low mortality risk who could be safely managed out of hospital but it may potentially underestimate illness severity, especially in young patients without co-morbidities who have abnormal vital signs; whilst overestimating the mortality risk in older patients (as it is heavily age-weighted) with minimal acute disease process but a high frequency of stable co-morbidities.(92) CURB-65 on the other hand may be ideal for identifying patients with a high mortality risk because of acute vital sign derangement who may otherwise be overlooked but can underestimate disease severity in older patients with subtle vital sign abnormalities and decompensated co-morbid illness. CURB-65 appears to have a higher sensitivity for predicting mortality(93) whilst PSI overestimates risk in older patients.(13) Another approach in the elderly is SOAR(94) which omits urea and confusion – often common in the elderly. PSI and CURB-65 show a progressive decline in the predictive power for 30-day mortality with increasing patient age.(93) Age in fact has little impact on mortality after correcting for disease severity variables using PSI, indeed removing age from PSI and CURB-65 does not alter the tools' predictive value. One solution to this issue may be much higher age cut-off values.

Pneumonia severity scores are useful to guide the 'best place of care' but clinical improvement/stability and response to treatment are vital to assess the 'best time for hospital discharge'. BTS guidelines for the discharge of patients with CAP state that patients are '*usually not* discharged if *more than one* of the following is present – temp>37.8, HR>100, RR>24, Systolic BP<90, sats<90, inability for oral (po) intake, altered mental state'. (95)

Sats ≤90% have good specificity but low sensitivity for adverse outcomes in CAP. As a parameter it is more useful in patients with asthma and those aged<50 years old at predicting adverse outcomes but less reliable in nursing home residents and patients with COPD; often the most difficult patients to assess out of hospital. Assessment of oxygen sats can therefore be used as an adjunct to decision-making but does not replace CRB-65 use in the community.(242)

Despite the fact that most low-risk patients (according to severity scores) could be managed as out-patients, factors other than disease severity often prompt hospital admission such to inability to take oral antibiotics, co-morbid illnesses, homelessness, substance abuse or inability to cope at home alone.(105),(112),(106),(90) (205) So a significant proportion of patients with CAP are low-risk but account for a significant proportion of bed days and costs; hospital LOS is a significant cost in caring for these patients(213). Low socioeconomic status is known to independently prolong hospital LOS.

Physicians tend to over-estimate the likelihood of death from pneumonia(201) and there is large variability in rates of hospitalisation across nearby geographical regions, suggesting that criteria for hospital admission may be uncertain, physician-dependent and dependent also on socio-economic status and social support.(106, 110, 111) The risk of adverse outcomes (death, readmission rates, delayed return to work/usual activity) does not vary between hospitals when comparing LOS.(106)

A recent expert review suggested the need to further investigate 'which elderly patients with CAP truly benefit from hospitalisation' and stated that supported home care - Hospital at Home (HAH) - showed enormous potential for improving the care of elderly and disabled patients, and should be further evaluated in terms of efficacy and cost-effectiveness.(117) We feel that with careful selection criteria and 24hr help numbers, many patients can be safely discharged and supported at home. Despite the fact that much of the evidence presented is for CAP (a strict definition), we feel that including a more heterogeneous group of patients in our study is important, safe and allows more patients to benefit from our study.

### *Hospital at Home (HAH) schemes are effective in other conditions*

HAH is defined as a service where active treatment is provided by healthcare professionals in the patient's home for a condition that otherwise would require acute hospital in-patient care, for a limited time period.(97) With increasing bed pressures on acute hospital trusts, HAH schemes and other innovations that reduce the demand for beds have become increasingly popular.(96) It has been suggested that 'the widespread development of HAH services may be a cheaper substitute to in-patient care even within health care systems that have well developed primary care services'.(97) HAH schemes may provide a cost effective alternative to acute care.(104) HAH schemes can be admission avoidance (avoiding hospital admission altogether) or early discharge (discharging patients from hospital earlier than standard care and thereby reducing length of stay [LOS]). HAH schemes exist for COPD, stroke, heart failure and post-operative patients. The potential economic benefits to a healthcare system are clear.(97) Patient-related and economic outcomes are both critical in assessing the efficacy of such services. Many HAH schemes specifically for patients with acute exacerbations of chronic obstructive pulmonary disease (COPD) have shown potential economic as well as patient and carer benefits e.g. the Liverpool ACTRITE scheme - invented and pioneered by Dr Lisa Davies (a key collaborator on this study) at University Hospital Aintree in Liverpool in the late 1990's. Therefore Liverpool has significant local expertise in this type of scheme.

Home-care for patients with acute exacerbations of COPD is popular in many countries. Several studies have shown non-inferiority to standard hospital care and potential economic benefit as well as patient and carer benefits.(243-250)

**Reduced mortality** - A recent meta-analysis on 'admission avoidance HAH' schemes showed that those allocated to HAH had a significantly reduced risk of death at 6 months.(104)

**Increased satisfaction** - A HAH scheme containing a mixed cohort of patients including those with respiratory illness (32% CAP, COPD 28%)(96) reported increased patient satisfaction with HAH.(96, 104) Carer satisfaction has been noted to be higher in the HAH group.(119) Evidence suggests that patient satisfaction is innately related to the quality of communication and personal care received.(119)

**Readmissions** - Evidence suggests that admission avoidance HAH services reduce hospital admission rates(96) however some subsequent studies suggest that re-admission rates may increase.(104)

**Functional status** – The CAP severity score may predict functional decline.(13) HAH may not alter quality of life (QOL), function, or cognitive abilities (e.g. mental alertness) more than in-hospital care.(104) HAH may be especially beneficial in older patients (>70 yrs old) who more commonly experience adverse effects such as delirium in hospital.(96),(114),(115) It has been reported that frail elderly patients with dementia cared for with HAH were less likely to be institutionalised at longer term follow-up.

**Health-economics** - HAH services may be less expensive than in-hospital care(104); inter-healthcare cost comparisons can however be difficult. Evidence of cost savings is varied, some schemes are more expensive(97), some showing cost reduction(96, 97) others cost neutral/inconclusive.(104),(97),(118) The cost-effectiveness of COPD HAH schemes has been noted.(251),(245) Differences in the way that a service is structured, organised and delivered will clearly affect cost (e.g. 24hr care v. once daily visits v. telephone support).

## *HAH is in-line with the NIHR/MRC, NHS and government strategy*

The concept of HAH is clearly consistent with current strategic NHS policies and the stated objectives and strategies of national research organisations (NIHR/MRC strategy for public health infection research). QIPP (Quality, Innovation, Prevention(s) and Productivity) is a strategy that seeks to improve clinical outcomes and experience for patients and to maximise resource use. QIPP aims to reduce unscheduled hospital admissions by 20%, reduce hospital LOS by 25% and maximise the number of patients controlling their own disease through systematic knowledge transfer and care planning.(101) The NHS Outcomes Framework (2011/12) states that it is of paramount importance that we provide safe and effective treatment and care (measured by clinical and patient-reported outcomes).(102) This scheme has good fit with the reforms in the current *White Paper* that state we should 'aim to provide the NHS with greater incentives to increase efficiency and quality' and state that 'patient choice will reward the most efficient, high quality services; reducing expenditure on less efficient care'.(103)

Our study is a prime example of worthy research since it is stated that the 'NHS will support creative approaches to service provision, which will improve choice, personalisation, efficiency and effectiveness e.g.: reducing avoidable admissions to acute hospitals through making the best use of social care resource; identify New service solutions to avoid unnecessary attendance to the Emergency Department (ED) and hospital admissions and deliver new and innovative services in community settings/homes.(206) A HAH scheme for patients with LRTI is an example of clinical innovators developing skills and extending roles to enable patients to be managed at home'. As 'champions of clinical quality will use new methodologies to embrace continuous improvement and drive up standards by seeking and using patient, carer and family feedback to improve service provision'.(206) Emergency departments should be encouraged to develop strategies to manage more patients with CAP within the community.(108)

***The HOME FIRST (<u>Home</u> <u>F</u>ollowed-up with <u>I</u>nfection <u>R</u>espiratory <u>S</u>upport <u>T</u>eam) feasibility study is a proactive, innovative and creative scheme which will enable patients with LRTI to be provided with high-quality safe, effective, efficient patient-centred care, tailored to their needs in their own home; therefore improving the overall experience of the service-user, improving patient outcomes and reducing hospital LOS. This is an opportunity to improve health policy, healthcare delivery and services and to simultaneously reduce admission rates, an area of major strategic importance to the NHS.***

## *The experience of HAH for CAP is limited*

Although there is evidence that earlier discharge of CAP patients is safe and effective there is little evidence for early supported discharge schemes.(108) A non-randomised study of a scheme (specifically for CAP patients) from Barcelona showed that the majority of patients have low risk scores (288/327 = 88%) CURB-65 0-1; and only 35 patients CURB-65 2 and 4 patients CURB-65 3-5. This also illustrates that selected patients with higher severity scores can be safely cared for at home.(120) In another study, patient satisfaction improved by 40% ($p<0.001$) in those CAP patients allocated to HAH.(118) A relatively small decrease in hospital LOS may have a substantial economic impact: in the USA, it is estimated that a ½ day reduction in hospital LOS for CAP (due to a change from moxifloxacin to levofloxacin) would generate a potential cost saving of approximately $8500 million annually.(6) A significant cost reduction associated with HAH specifically for CAP patients was noted.

## *There are potential benefits of LRTI/CAP HAH for both patients and the health service*

**Patient-related outcomes**

- Reducing risk of nosocomial infection (hospital-acquired pneumonia, MRSA and C. difficile).(115)
- Able to be cared for in their own home
- Improved sleep
- Faster recovery
- Increased satisfaction (patients and carers)
- Reduced risk of delirium
- Reduced chance of later post hospital discharge institutionalisation.

**Health service benefits**

- Reduced hospital LOS - economic benefit
- Reduced risk of nosocomial infection – economic benefit
- Improved public health awareness of LRTI/CAP and public education
- Improved self-management of condition

## *The hazards of HAH can be anticipated and prevented*

The risks to individuals are limited by the study design:

- **Strict patient selection -** Highly trained respiratory clinical staff (respiratory physicians - consultants and senior SpRs and senior specialist nurses with community experience) will carefully select the correct patients (using strict inclusion/exclusion criteria and using their extensive clinical experience in caring for such patients)
- **Competent and experienced specialist staff**
- **Thorough patient education** – specific patient- individualised self-management plan
- **Rigorous safety procedures for patients** - daily patient monitoring at home, lifeline (pendant alarm) supplied
- **Rigorous safety procedures for staff** – pendant alarms, planned route with set 'call-in' times
- **Regular home visits** - daily reviews will occur to ensure that any clinical deterioration is effectively assessed and managed and patients are re-admitted to hospital if deemed necessary by either the study team or the patient. A coordinated MDT will be key to the HOME FIRST care approach to patient care
- **No delay in recognition of clinical deterioration** – the patient will be given a detailed patient information leaflet with red-flag symptoms, a 24hr emergency telephone contact number. During 08.30 – 19.00 telephone access (with additional home visits as necessary) to a specialist respiratory study nurse and doctor will minimise any risks of delayed recognition of clinical deterioration. The patient's condition is monitored closely at home. Portable observation machines will be used by HOME FIRST to monitor blood pressure (BP), heart rate (HR), oxygen saturations (sats) and temperature during home visits

- **IV antibiotic provision** - patients still requiring IV antibiotics will not be included in our study since we consider that they are not yet stable and therefore unsuitable for HOME FIRST

### *There are immediate operational questions*

- Should HOME FIRST aim to just implement supported earlier discharge or admission avoidance as well?
- What proportion of all hospitalised patients with LRTI/CAP/HAP etc would be suitable for HOME FIRST?
- What proportion of all hospitalised patients with LRTI/CAP/HAP etc consent to the HOME FIRST feasibility study?
- Could the full RCT begin to accept patients who would be palliated after 48hrs if no clinical improvement - what extra MDT services may this require?
- Could the full RCT accept patients directly from the community to avoid hospital admission altogether?
- Are any other staff needed to efficiently run HOME FIRST home care? Is a full-time occupational therapist, social worker or physiotherapy needed?
- What frequency of visits are necessary and for how long?
- What is the maximum numbers of patients that can be safely looked after by HOME FIRST at any one time?

### *There are (i) clinical and (ii) laboratory scientific questions that can be answered in order to guide future treatment algorithms*

- (i) Can a biomarker of recovery be developed that can help to predict whether a patient is likely to be at one end of the recovery spectrum or the other? This may allow us to determine a more tailored strategy for an individual in terms of antibiotic prescription (or not) and duration, and the best 'place of care' e.g. own home with GP support as needed, 'HAH' (supported discharge – early discharge [e.g. HOME FIRST] or admission avoidance), ward bed, HDU or ICU; as well as to develop therapies to aid rehabilitation and improve recovery rate.
- (ii) The correlates of disease, recovery and immunity are poorly understood in CAP. This cohort of patients will be studied as part of a larger project (including patients from our other pneumonia studies) investigating the immunological reasons behind the spectrum of pneumococcal pneumonia disease severity and recovery. The full RCT study will recruit volunteers inoculated with pneumococcus (carriers and non-carriers from the experimental human pneumococcal carriage [EHPC] study), patients with mild and moderate pneumonia (HOME FIRST and PASS cohort) and ICU patients with severe pneumonia. In the future we aim to be able to develop effective future vaccines for pneumococcal pneumonia and to be able to predict the course of an individual's pneumococcal pneumonia early on in the disease process.

## STUDY DESIGN OVERVIEW

- **Principal research outcome and overall aim**

  Our overall aim is to provide a scheme to discharge patients with LRTI safely and effectively back to their own home i.e. proof of concept. Our study question(s): (i) Is a study in which patients are randomised to early supported discharge or standard hospital care acceptable to patients? (ii) Can selected patients with respiratory infection benefit from care at home?

  N.B. HOME FIRST does NOT support patients at home that could have been discharged anyway without support.

  If this study shows the feasibility of HOME FIRST, the second stage is a full multi-centre NIHR funded RCT with 100 patients in each limb. If the RCT shows positive overall effects we will 'roll-out' a fully operational HOME FIRST scheme across the northwest and ultimately nationally +/- internationally.

- **Specific objectives**

A feasibility study, and in the future a full RCT:

- To show equivalence of critical outcomes during an acute illness episode
- Qualitative assessment to show increased patient and carer satisfaction compared to hospital care
- Economic assessment to show financial advantage to care in the community
- Follow-up cohort to ensure re-admission rates are equivalent and to monitor longer term health outcomes (up to 1 year).
- To use our patient and public involvement (PPI) group in order to constantly develop and improve the service.

- Primary endpoint

**This feasibility study will assess the patient uptake to participate in a study in which volunteers are randomised to early supported discharge with HOME FIRST or standard hospital care.**

Uptake/acceptability in this study is defined as - *the proportion of patients that are both eligible and suitable (fit all inclusion/exclusion criteria) who are prepared to 'ACCEPT', and give their consent to, be involved in a research study in which they are randomised to either standard hospital care or HOME FIRST compared to the proportion that are eligible and suitable and do* not *give their consent.* Objectively we are therefore studying the percentage uptake of the HOME FIRST scheme.

- **Secondary endpoints**

**1. Clinical (safety, mortality, satisfaction, readmissions, functional status, quality of life)**

**a. Safety and mortality**

We will assess the safety i.e. ensure there is no increase in mortality in the HOME FIRST limb.

**b. Patient and carer satisfaction**

HOME FIRST should have at least equivalence with standard hospital care.

A validated questionnaire will be conducted over the telephone at 2 weeks by an independent assessor

**c. Re-admission rates, total days of care (HOME FIRST and hospital combined v. Standard care in hospital)/total bed days**

(i) Total number of days of HOME FIRST care and hospital bed days combined v. standard care in hospital (ii) Total in-hospital bed days for both limbs (iii) Readmission rates for both limbs

d. **Functional status (physical and mental) and quality of life (QOL)**

Validated questionnaires will be completed to assess recovery post respiratory infection.

i. A SF-12 (physical and mental function) at day 0, day 2, day 7 and at 1 and 6 mths.
ii. A CAP-SYM (disease recovery rate) will be completed at day 0 (for day minus 30 as well), day 2, day 7 and 1 and 6 mths. [*Day 0 score = A, Day -30 score = B, A - B = C, Day 28 score = D*. The calculation of recovery at one month is *Recovery (%) = 100 (D/C x100*)].

**2. Health service (health-economic, operational)**

**a. Health-economic**

A formal planned health economic analysis (by an NIHR Research Design Service [RDS] recommended health-economist) will measure costs and resource utilisation, using costs that are sensitive to the different resources used during each care episode, to assess the cost-effectiveness of HOME FIRST.

**b. Operational**

This study should answer several operational questions (see operational guidelines section).

**3. Laboratory (microbiology and host response)**

Specific hypotheses and research questions related to the patient group are:

**a. Microbiology**

Hypothesis - We hypothesise that prolonged hospital admission leads to alterations in the naso-pharyngeal and lower respiratory tract flora (colonising microbes), which in turn results in an increased risk of hospital-acquired pneumonia.

Question - Are patients allocated to HOME FIRST at a lower risk of nosocomial pneumonia due to less alteration in naso-pharyngeal and lower respiratory tract flora than those randomised to standard care (i.e. prolonged hospitalisation)?

Method -

**(i) Carriage** – we will perform nasal washings at days 0, 2 and 7 in all patients recruited to the study, in order to assess the relationship between place of care and naso-pharyngeal flora.

**(ii) Lung Human Microbiome Project (LHMP)** – **IN THE FULL RCT ONLY** - we will compare the lower airway microbiome (microbes) in patients in each limb of the HOME FIRST study to assess the relationship between place of care and lower airway flora. The lower airways will be sampled using broncho-alveolar lavage (BAL) and protected specimen brushings (PSB) at bronchoscopy.

Objective - To better understand the alterations in naso-pharyngeal and lower respiratory tract flora that occur with short-term (early discharge – HOME FIRST) and prolonged hospitalisation (standard care).

**b. Biomarker of recovery**

Hypothesis - A biomarker of recovery can identify patients, specifically with confirmed pneumococcal pneumonia (blood/urine PCR positive, blood or sputum-culture positive) and a clearly defined phenotype (mild, moderate, severe disease), at risk of slower recovery:

Question - What differences in anti-inflammatory immunological response to pneumococcal pneumonia are associated with the spectrum of disease recovery?

**(i)** Monitor cfu/ml and copy numbers of pneumococcus in blood by PCR techniques and urine antigen testing in disease and recovery

**(ii)** Blood transcriptomics in disease and recovery

**(iii)** Investigate the acquired humoral and cellular anti-inflammatory phase in serum and nasal wash during recovery.

Objective – in this study, we will test the logistical possibilities of taking and processing these samples, in the full RCT we will develop a biomarker of recovery from pneumococcal CAP.

**Study design**

This is a feasibility study of patients admitted to the Royal Liverpool and Broadgreen (RLBUHT), and Aintree University (UHA) Teaching Hospitals with symptoms of LRTI from November 2011 – March 2012. This is not a full randomised-controlled study but patients will be randomised in order to assess patient's acceptability to the randomisation process within the HOME FIRST scheme. This feasibility study will lead onto a full RCT in the near future, ideally encompassing both early discharge and admission avoidance approaches.

Research to investigate the views of (a) recruited patients (b) the carers of recruited patients to such a scheme will be investigated. A broad semi-quantitative analysis of patient acceptability to HOME FIRST is vital.

PPI is very important; we are currently actively recruiting members of the public to become involved. Since LRTI is an acute disease, so is different to chronic disease PPI groups, this will be a 'rolling' cohort of patients. The PPI group will be demographically and ethnically representative of the population that presents with LRTI. 'Breathe-easy' patient groups are also being consulted.

Our feasibility study has been developed so far with input from nurses and doctors involved with 'COPD early facilitated discharge schemes' and respiratory physicians from various hospitals, including New Zealand.

It is important that the HOME FIRST study recruits from the most representative group of patients so that the results have the widest possible applicability. However this must be balanced against non-maleficence and safety, therefore inclusion and exclusion criteria apply.

**SUBJECTS AND TIMELINES**

From November 2011 we will aim to recruit 10 patients to each limb of the study. Patients randomised to HOME FIRST will be followed up for at least 48hrs after discharge, at least twice per day by our study respiratory nurse(s) for the first 48hrs and at least once in total by the study doctor.

**METHOD DETAILS**

- **Recruitment and Selection**

The study team will be in regular communication with bed managers, nursing and medical co-ordinators in A&E, the medical admissions unit and the respiratory wards at RLBUHT and UHA. Via regular education and information dissemination events and through daily interaction with the study team, the key staff will be aware of the research study and its aims, objectives and potential participants. A list of potential patients will be generated on a daily basis in combination with these personnel, and discussed twice per day at pre-defined times (by phone or bleep) to alert the study team of a potential recruit.

Relevant parts of a potentially suitable patient's medical notes, blood, microbiology and radiology results will be reviewed by a study team member to assess suitability. After this review if the patient is still considered suitable the study team member will then introduce themselves and consider the patient's capacity, clinical stability and appropriateness of their current environment for initial study discussion. The study will be explained to the patient and a patient information sheet will be reviewed. At the end of the process, questions will be answered, consent may either be obtained at that point, the patient may decline participation all together or after an agreed length of time - 'overnight' (giving opportunity for patients to discuss with their advocates and for patient reflection) consent will be re-visited and further opportunity for questions given. Only patients able to give fully informed consent will be able to participate in the feasibility study. Consent will be taken by a fully trained study team member.

Although not all patients screened will be suitable or eligible, all screened patients will have a patient identity code generated and sticker and case report form (CRF) completed and placed in the clinical case notes, this is so

that the usual medical team are aware of the outcome of the assessment and so the study team can record the number of patients screened and reasons for exclusion. A full clinical examination will be performed by the study doctor before recruitment and randomisation.

- Patient Eligibility

Patients with any of the following conditions:

- Pneumonia - community-acquired (CAP) or hospital-acquired (HAP) - pneumonia definition - a series of clinical symptoms with radiological consolidation
  N.B. All pneumonia CURB-65 scores will be considered but patients with CURB-65 ≥3 MUST have had at least 24hrs of in-patient observation before recruitment into the study.
- Acute tracheo-bronchitis & acute bronchitis
- Non-pneumonic lower respiratory tract infection
- Influenza with respiratory manifestations
- Infective exacerbation of bronchiectasis
- Lung abscess
- Pneumonia with concomitant COPD (if this service is not provided elsewhere)

- Patient Suitability

Inclusion criteria must be answered 'YES' and exclusion criteria 'NO' for the patient to be suitable. Certain exclusion criteria relate specifically to either those with or those without chronic respiratory conditions. (# All cases to be discussed with study Dr)

**Inclusion criteria**

- Simple pleural effusions only (#if no diagnostic pleural tap performed please discuss)
- Can manage ADLs with current support (immediate OT/physio/social assessment/care can be arranged prior to discharge (if needed) and continued at home)
- Able to give fully informed consent
- Has a phone
- Age>18yrs old
- EWS ≤2 AND SBP>90 (all observations must be stable for 12-24hrs) AND mild confusion only (defined as an 10-point AMTS ≥7)
- All observations must be stable for 12-24hrs
- Improving inflammatory markers (WCC/CRP)
- Stable or improving U&Es

**Exclusion criteria**

- Acute exacerbations of COPD – infective & non-infective (other services already provided)
- Patients with CURB-65 >3 admitted<24hrs ago
- Patients unable to manage at home even with maximal support from HOME FIRST (this may include some patients IV drug users, with ETOH excess or mental health problems)
- Serious co-morbidities requiring hospital treatment (eg: CKD, CCF) or deemed unstable (significant AKD)
- Suspected MI/raised TnI/T consistent with NSTEMI (Or acute ECG changes) within 5 days of discharge
- Empyema or complicated parapneumonic effusion
- SBP<90mmHg
- Neutropenia
- No fixed abode
- Tuberculosis suspected
- Well enough for discharge without HOME FIRST homecare support
- Sats <92% on air - for patients *without* chronic respiratory illness
  - Sats <88% on air [except asthma sats must be >92%] - for patients *with* chronic respiratory illness. #All such cases MUST be discussed as oxygen assessment may be needed.

- **Screening, Assessment and Follow-up**

**Screening**

- **Clinical examination** – Baseline clinical data which includes age, gender, history of presenting complaint, past medical history, a complete social history, drug history and allergies, will be performed and recorded by the study doctor.

- **Inclusion/exclusion criteria** - We feel that using careful selection criteria and 24hr help telephone number such patients can be safely discharged and supported at home. If a patient is selected for inclusion (based on their eligibility and suitability) and consents to the study; they are then randomised using a computer generated random allocation number, and their allocation is obtained by telephone from an independent randomisation co-ordinator.

**Assessment and follow-up**

a. **Investigations** - Extra samples will be collected for investigational laboratory work (i) Bloods - day 0 (day of recruitment and randomisation), day 2 (48hrs post) and day 7 (in patient's own home if necessary). All venepuncture will be performed by a fully trained member of the study team to minimise patient discomfort. Blood will also be taken at 1 and 6 mth clinic visits (ii) Nasal wash - day 0, 2 and 7. A fully trained member of the study team will perform this in order to minimise patient discomfort (iii) Urine sampling – day 0 and day 7.

b. **Qualitative questionnaires**

i. SF-12 (physical and mental function) [performed 5 times in total] - at recruitment (day 0), day 2, day 7 and at 1 and 6 mth out-patient appointments.
ii. CAP-SYM [performed 6 times in total] - at recruitment day 0 (twice including to complete day minus 30) day 2, day 7 and at 1 and 6 mth out-patient appointments.
iii. Patient (and carer) satisfaction - conducted over the telephone at 2 wks by an independent assessor.

c. **Initial follow-up post discharge**

*Patients randomised to HOME FIRST care* - Initially up to twice daily respiratory specialist nurse visits will occur for 48hrs, after this time period the frequency and duration of visits will depend on clinical need. See daily review diary information sheet. The study nurse will establish the need for the involvement of other MDT team members. Venepuncture will be performed daily AT MOST in the HOME FIRST limb: as for those patients in-hospital frequency of venepuncture depends on clinical assessment of need. The patient will have venepuncture and nasal washes performed at 48hrs and 7 days post-recruitment.
*Patients randomised to standard hospital care* - all management and discharge decisions will be made by the patient's usual hospital team; if any significant or concerning clinical issues are noted during study team's visits, the usual medical team will be alerted. The patient will be seen by a study team member at 48hrs and 7 days for bloods and nasal washes (in patient's own home if already discharged). All patients will be discussed at a weekly case-notes MDT meeting.

d. **Later follow-up**

- All study patients will be followed-up on discharge in the 'Respiratory Infection' out-patient clinic at 1 month to ensure progress (clinical and functional) and again at 6 months to monitor longer-term outcomes. All

patients will also receive a telephone call from an independent person to ask for feedback about their involvement in the study and the care received at 2 wks post randomisation.

- IN THE FULL RCT patients will be offered a bronchoscopy (BAL +/- PSB) - to assess patient 'acceptability' to this technique, in the feasibility study the procedure including risks and benefits, will be discussed with all patients at the 1 mth clinic visit and the patient will be asked whether they would have given their consent to bronchoscopy (at 5-7wks) had it been offered to them.

- **Operational Guidelines**

Patients discharged from hospital will remain the responsibility of the study Dr (chief investigator) during the time that they are supported by HOME FIRST. The patient's GP and hospital consultant (as of discharge day) will be informed of any specific interventions and outcomes using a specific HOME FIRST discharge summary. Patients recruited to the study that are randomised to standard in-hospital care will remain under the care of their current consultant. Patients can be readmitted to the hospital as determined by the study team via bed managers; completion of a treatment failure or complication development proforma on the CRF will occur. New referrals will be accepted between 08.30-16.00 7 days per week. Referrals after 16.00 will be seen the following working day. The team are available for telephone advice from 08.30 - 19.00 7-days-per-week. Home visits will occur from 08.30 - 19.00 7-days-per-week. 24hr cover is available via telephone to the HOME FIRST study team. In the event of an emergency an ambulance will be called. If the patient needs non-emergency medical attention at home between 19.00 - 08.30, a district nurse or out-of-hours GP will be contacted by the study team.

The patient's condition is monitored closely at home. Portable observation machines will be used by HOME FIRST to monitor blood pressure (BP), heart rate (HR), oxygen sats and temperature during home visits. In order to provide consistent, high-quality care; the clinical assessment and evaluation will be carried out using the HOME FIRST CRF. The CRF will remain in the clinical notes, except when patients are visited in their own home when only the CRF will be removed from hospital premises (this contains no patient identifiable information).

In the full RCT we hope to administer home IV antibiotics to patients with pneumonia and other conditions such as bronchiectasis. For safety we feel that patient's still needing IV antibiotics for pneumonia are not yet stable or suitable for supported discharge during the feasibility study.

HOME FIRST will provide coordinated MDT care, provision of 24 hr emergency telephone cover, access to fully trained respiratory study nurse(s) and study doctor(s). The HOME FIRST MDT consists of:

• Study doctors (trained respiratory physicians - consultants and senior SpRs)
• Highly trained respiratory specialist nursing staff
• Close links with a physiotherapist (mobility and respiratory)
• Home help provision (temporary assistance with ADLs by carers) which may include OT or social worker involvement (HOME FIRST has fast access to meals-on-wheels and 'lifeline' devices)
• Close links with palliative care, dietetics, SALT, smoking cessation and community matrons, pharmacy (for rapid dispensing of TTOs).

## ETHICAL ISSUES

The main risks associated with this study are those of deterioration at home (those in the HOME FIRST limb). The main ethical principles under which these risks are considered are those of autonomy and non-maleficence.

- **Autonomy** - The volunteers will be given sufficient information that is written or spoken in a non-jargon way to allow them to understand the objectives behind the research, the risks of any procedures and the possible benefits. They then need to be given time to consider the information before consenting to any

involvement. At no stage should the volunteer feel pressured or persuaded into participating in the research. Once the volunteer has consented to the study, consent can be withdrawn at any time.

- **Beneficence** – improved patient related and health-economic outcomes with HOME FIRST.
- **Non-maleficence** - As researchers we have the responsibility to minimise the risk of harm to the volunteers. This involves the researchers having sufficient knowledge, having reviewed current evidence in the literature about the proposed interventions and making themselves aware of potential risks. Highly trained respiratory clinical staff will be used to ensure that any clinical deterioration is effectively assessed and managed and that patients are re-admitted to hospital if deemed necessary by either the study team or the patient.
- **Justice** - This must be balanced with non-maleficence. The research is open to all individuals with LRTI (not currently provided with a similar early discharge scheme service) but important exclusion criteria are in place, primarily to protect individuals from undue risk.

## SAFETY NOTES

**Patient safety** - All patients will also receive a verbal and written self management plan for their specific condition, a list of symptoms to prompt contact with team and a 24hr contact number. In the CRF a proforma will be completed if any treatment failure or complications requiring hospital re-admission occur. Adverse events will be reported using the correct documentation within the CRF. The study will be stopped if there is any mortality in the HOME FIRST limb whilst patients are at home. Any adverse events will result in a SUSAR form being completed and the ethics committee (REC) and sponsor(s) will be informed immediately.

The risks to individuals are limited by the study design:

- Strict patient selection and inclusion/exclusion criteria
- Fully competent and experienced respiratory staff
- Thorough patient education – specific patient- individualised self-management plan
- Rigorous safety procedures for patients - daily patient monitoring at home (+/- patient operated home telemedicine observations machine)

**Staff safety** – there are specific important safety issues around attending a patient's own home. This is a carefully considered and high priority area. Staff will carry personal alarm devices at all times - if this is activated - a GPS tracking service at a local private security firm will locate the team member and they will immediately attend. They will alert the police as necessary. Team members will have up-to-date conflict resolution training. All team members will print off a daily diary which states all home visits (planned home visit route) detailing times and addresses and contact numbers, if team members do not arrive/telephone at set time points, team members will contact them and if uncontactable the private security firm/police will be called as necessary. Occasionally two team members will attend together if felt necessary. If there are considered to be any threats to the health and safety of the attending member of the study team (either by the patient, the carers, family members, neighbours or the external community) – patients in the HOME FIRST limb will be readmitted to hospital (if necessary) and HOME FIRST attendance will be stopped.

## ANALYSIS PLAN

A research statistician, Dr Brian Faragher from LSTM, has been involved in statistical discussions. The statistical power of this feasibility study is limited by small sample size; therefore statistical significance of clinical outcomes is neither expected nor required. The analysis will be descriptive (summary statistics) only, with no formal between-group comparisons made.

**With regards to the primary outcome of uptake - the percentage of eligible and suitable patients who consented to the study versus those who did not consent will be analysed.**

With regards to secondary endpoints – clinical outcomes such as safety and mortality (7 day, 1 and 6 mths) and rate of readmission will be analysed comparing the HOME FIRST limb with standard hospital care. Validated questionnaires (SF-12, CAP-SYM, and patient and carer satisfaction) will be quantitatively analysed to assess functional status/quality of life/satisfaction. A formal health-economic analysis will measure costs and resource utilisation, using costs that are sensitive to the different resources used during each patient care episode. **In conjunction with the NIHR Research Design Service (RDS) team, analysis methodology has been developed, including the involvement of a health-economist.**

## FUTURE PLAN AND IMPLICATIONS OF THE WORK

Success in this project will result in an application for a NIHR Programme Grant for Applied Research (PGfAR) to fund a full RCT with 100 patients per limb. Dependent on its success the aim is ultimately to 'roll-out' a fully operational HOME FIRST scheme nationally +/- internationally.

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# PROTOCOL for HOME FIRST Pilot: a study of early supported discharge in patients with lower respiratory tract infections.

## BACKGROUND

### *The clinical and economic burden of lower respiratory tract infection (LRTI) is high(5) and with support many more could be managed at home.*

The annual incidence of LRTIs in Europe in 2002 was 25.8 million, which is greater than both diabetes and cancer.(2) Pneumonia and LRTI are important health problems that are very costly to the NHS. In England in 2009 there were more admissions for pneumonia, influenza and LRTI combined than ischaemic heart disease and more bed days than for cerebrovascular disease.(3) Community-acquired pneumonia (CAP) is a major cause of hospital admissions worldwide.(5) In the USA, 90% of CAP expenditure relates to the cost of in-patient care.(6) Seventy percent of UK pneumonia admissions are with mild or moderate pneumonia (CURB-65 score 0-2). Hospital length of stay (LOS) is a significant cost in caring for these patients.(213) In the UK, CAP mostly affects the older population,(5) in whom admission to hospital may in fact be more detrimental than care in their own residence.(13) Over the next decade the incidence of CAP will increase further as the population ages, as will the associated co-morbidities.(14)

Strategies to increase the proportion of low-risk patients with CAP treated in the community have been developed and have been reported as safe, effective and acceptable to patients; with no significant differences in patient satisfaction, mortality or hospital re-admission rates noted.(107)

Despite the fact that most low-risk patients (according to severity scores) could be managed as out-patients, factors other than disease severity often prompt hospital admission such to inability to take oral antibiotics, co-morbid illnesses, homelessness, substance abuse or inability to cope at home alone.(105),(112),(106),(90) (205) Thus a significant proportion of patients with CAP are low-risk but account for a substantial proportion of bed days and costs.

Physicians tend to over-estimate the likelihood of death from pneumonia(201) and there is large variability in rates of hospitalisation across nearby geographical regions, suggesting that criteria for hospital admission may be uncertain, physician-dependent and dependent also on socio-economic status and social support.(106, 110, 111) The risk of adverse outcomes (death, readmission rates, delayed return to work/usual activity) does not vary between hospitals when comparing LOS.(106)

A recent expert review suggested the need to further investigate 'which elderly patients with CAP truly benefit from hospitalisation' and stated that supported home care - Hospital at Home (HAH) - showed enormous potential for improving the care of elderly and disabled patients, and should be further evaluated in terms of efficacy and cost-effectiveness.(117)

Our recent HOME FIRST feasibility study showed that although large numbers of potentially eligible patients needed to be screened in order to recruit patients to the early supported discharge scheme, satisfaction was excellent, outcomes were at least as good and the length of hospital stay was reduced. Notably in this feasibility study, 20% of those screened were not eligible due to an abbreviated mini-mental test score of <7, due to dementia, learning disability or delirium. In fact these patients are one of the key groups most likely to benefit from such an intervention as noted below – this pilot study will therefore include patients unable to give informed consent.

## *Hospital at Home (HAH) schemes are effective in other conditions and potential benefits for those with LRTI is clear*

HAH is defined as a service where active treatment is provided by healthcare professionals in the patient's home for a condition that otherwise would require acute hospital in-patient care, for a limited time period.(97) With increasing bed pressures on acute hospital trusts, HAH schemes and other innovations that reduce the demand for beds have become increasingly popular.(96) HAH schemes may provide a cost effective alternative to acute care.(104) HAH schemes can be admission avoidance (avoiding hospital admission altogether) or early discharge (discharging patients from hospital earlier than standard care and thereby reducing LOS). HAH schemes exist for COPD (243-250), stroke, heart failure and post-operative patients. The potential economic benefits to a healthcare system are clear.(97) HAH schemes have shown **reduced mortality** at 6 months,(104) i**ncreased patient satisfaction**,(96, 104) and **carer satisfaction**,(119) and potentially **reduced readmissions**. HAH may be especially beneficial in older patients (>70 yrs old) who more commonly experience adverse effects such as delirium in hospital.(96),(114),(115) It has been reported that frail elderly patients with dementia cared for with HAH were **less likely to be institutionalised** at longer term follow-up.

**Health-economics** - HAH services may be less expensive than in-hospital care(104); inter-healthcare cost comparisons can however be difficult. Evidence of cost savings is varied, some schemes are more expensive(97), some showing cost reduction(96, 97) others cost neutral/inconclusive.(104),(97),(118) The cost-effectiveness of COPD HAH schemes has been noted.(251),(245) Differences in the way that a service is structured, organised and delivered clearly affect cost.

**Potential benefits for patients with LRTI include:**

**Patient-related outcomes**

- Reducing risk of hospital-acquired infection (hospital-acquired pneumonia, MRSA and C. difficile).(115)
- Able to be cared for in their own home
- Improved sleep
- Faster recovery
- Increased satisfaction (patients and carers)
- Reduced risk of delirium
- Reduced chance of later post hospital discharge institutionalisation.

**Health service benefits**

- Reduced hospital LOS
- Reduced risk of hospital-acquired infection
- Improved public health awareness of LRTI/CAP and public education
- Improved self-management of condition

## *HAH is in-line with the NIHR/MRC, NHS and government strategy*

The concept of HAH is clearly consistent with current strategic NHS policies and the stated objectives and strategies of national research organisations (NIHR/MRC strategy for public health infection research). QIPP (Quality, Innovation, Prevention(s) and Productivity) is a strategy that seeks to improve clinical outcomes and experience for patients and to maximise resource use. QIPP aims to reduce unscheduled hospital admissions by 20%, reduce hospital LOS by 25% and maximise the number of patients controlling their own disease through systematic knowledge transfer and care planning.(101) Emergency departments should be encouraged to develop strategies to manage more patients with CAP within the community.(108)

***The early supported discharge scheme called HOME FIRST (Home Followed-up with Infection Respiratory Support Team) will enable patients with LRTI to be provided with high-quality safe, effective, efficient patient-centred care, tailored to their needs in their own home; therefore aiming to improve the overall experience of the service-user, improve patient outcomes and reduce hospital LOS whilst simultaneously reducing admission rates, an area of major strategic importance to the NHS.***

## *The experience of HAH for pneumonia is limited*

Although there is evidence that earlier discharge of CAP patients is safe and effective there is little evidence for early supported discharge schemes.(108) In an admission avoidance study for patients with CAP, patient satisfaction improved by 40% ($p<0.001$) in those allocated to HAH.(118) Our HOME FIRST feasibility study shows that there is a demand for this service but further research is needed.

## STUDY DESIGN OVERVIEW

- **Overall research aim**

  Our overall aim is to reduce the length of hospital stay. Length of stay is the key indicator of success in this study. We will record the date at which patients in both arms are suitable for discharge by HOME FIRST, however only the HOME FIRST group will be discharged on that day. We will record reasons for the delayed discharge in those randomised to SHC, these will include social, OT and physiotherapy, clinical deterioration, lack of senior review, awaiting investigations that could be performed as an out-patient and 'unclear' to the study team.

- Primary endpoint

Our primary endpoint is time to recovery. This is assessed by our simple 'RECRTI' (functional RECovery from Respiratory Tract Infection) questionnaire (non-validated) which is completed at 6 weeks

Patients (or consultees) will be asked at recruitment to define their/the patient's best exercise capacity in the last 3 months e.g chair to bed with 1, unlimited exercise tolerance etc

At the 6 week out-patient appointment they will be asked 4 simple questions: (marked on a likert-type scale in days and weeks):

1. When (if at all) did your sleep return to normal?
2. When (if at all) did your diet/appetite return to normal?
3. When (if at all) did your (pre-defined) exercise capacity return to normal?
4. When (if at all) did your capacity to work or socialise (delete as appropriate) return to normal?

**Secondary endpoints**

**4. Clinical (safety, mortality, satisfaction, length of stay, readmission, functional status, quality of life)**

**A. Safety and mortality**
We will assess the safety i.e. ensure there is no delayed recovery, no pneumonia (or non-pneumonia) complications or increase in mortality in the HOME FIRST limb.

B. **Patient and carer/consultee satisfaction**
HOME FIRST should have at least equivalence with standard hospital care.
A validated questionnaire will be conducted via telephone at 2 weeks by an independent assessor

**C. Length of hospital stay and total length of stay (including hospital and home care)**

**D. Re-admission rates**
Within 6 weeks of recruitment. Reasons for re-admission will be noted in the case report form.

E. **Functional status (physical and mental) and quality of life (QOL)**
Validated questionnaires will be completed to assess recovery post respiratory infection.

- A SF-12 (physical and mental function) at day 0 and 6 weeks
- A CAP-SYM (disease recovery rate) will be completed at day 0 (for day minus 30 as well) and 6 weeks. [*Day 0 score = A, Day -30 score = B, A - B = C, Day 28 score = D*. The calculation of recovery at one month is *Recovery (%) = 100 (D/C x100*)].

**1. Health-economic**

A formal planned health economic analysis (by Professor Louis Niessen a health-economist at LSTM) will measure costs and resource utilisation (using self-reported staff and independently validated time data collection), using costs that are sensitive to the different resources used during each care episode, to assess the cost-effectiveness of HOME FIRST.

N.B. HOME FIRST does NOT support patients at home that could have been discharged anyway without support.

If this study shows the success of the HOME FIRST pilot, the second stage is a full multi-centre NIHR funded RCT with 100 patients in each limb. If the RCT shows positive overall effects we will 'roll-out' a fully operational HOME FIRST scheme across the northwest and ultimately nationally +/- internationally.

**Study design**

A randomised interventional clinical care pathway study of early supported discharge (termed 'HOME FIRST') versus standard hospital care for patients hospitalised with LRTI.

HOME FIRST will provide coordinated MDT care, provision of 24hr emergency telephone cover, access to fully trained respiratory study nurse(s) and study doctor(s). The HOME FIRST MDT consists of:

• Study doctors (trained respiratory physicians - consultants and senior SpRs)
• Highly trained respiratory specialist nursing staff
• Close links with a physiotherapist (mobility and respiratory)
• Home help provision (temporary assistance with ADLs by carers) which may include occupational therapy or social worker involvement (HOME FIRST has fast access to meals-on-wheels)
• Close links with pharmacy for rapid dispensing of discharge medication.

Patients hospitalised with LRTI at the Royal Liverpool and Broadgreen (RLBUHT) Teaching Hospitals between October 2012 and December 2014 will be approached.

Patients (or the next of kin if the patient is unable to give informed consent) will be offered participation in the study if they fit the strict inclusion/exclusion criteria. They will be then be randomised to receive HOME FIRST or standard hospital care (SHC).

**SUBJECTS AND TIMELINES**

Between October 2012 and December 2014 we will aim to recruit 25 patients to each arm of the study.

**METHOD DETAILS**

- **Recruitment and Selection**

The study team will be in regular communication with bed managers, nursing and medical co-ordinators in A&E, the medical admissions unit and the respiratory wards at RLBUHT. Via regular education and information

dissemination events and through daily interaction with the study team, the key staff will be aware of the research study and its aims, objectives and potential participants. A list of potential patients will be generated on a daily basis in combination with these personnel, and discussed twice per day at pre-defined times (by phone or bleep) to alert the study team of a potential recruit.

Relevant parts of a potentially suitable patient's medical notes, blood, microbiology and radiology results will be reviewed by a study team member to assess suitability. After this review if the patient is still considered suitable the study team member will then introduce themselves and consider the patient's capacity, clinical condition and appropriateness of their current environment for initial study discussion.

If the patient is deemed to have capacity to consent to study participation by the study team then the study will be explained to the patient and the patient information sheet will be reviewed. At the end of the process, questions will be answered, consent may either be obtained at that point, the patient may decline participation all together or after an agreed length of time - 'overnight' (giving opportunity for patients to discuss with their advocates and for patient reflection) consent will be re-visited and further opportunity for questions given.

If the patient is deemed NOT to have capacity to consent to the study then their next of kin will be approached and the relative information leaflet will be discussed and at the end of the process an assent form will be signed if the next of kin is happy for the patient's participation.

If a patient regains capacity during the study they may choose to (a) continue (b) withdraw – allowing data gathered so far to be retained (c) withdraw completely – all data collected up to that point will be destroyed.

Consent, assent and later retrospective consent (as needed) will be taken by a fully trained study team member. A full clinical examination will be performed by the study doctor before recruitment.

- Patient Eligibility

  Patients with any of the following conditions:
  - Pneumonia - community-acquired (CAP) or hospital-acquired (HAP) - pneumonia definition - a series of clinical symptoms with radiological consolidation
    N.B. All pneumonia CURB-65 scores will be considered but patients with CURB-65 ≥3 MUST have had at least 24hrs of in-patient observation before recruitment into part B of the study.
  - Pneumonia with concomitant COPD or bronchiectasis
  - Non-pneumonic lower respiratory tract infection without COPD or bronchiectasis

- Patient Suitability

Appropriate patient selection for the study is paramount. Using strict selection criteria in combination with robust patient safety provisions, including 24-hour telephone support, we suggest that some patients can be safely discharged and supported at home. Inclusion in the scheme is ultimately at the discretion of the experienced study team.

**Inclusion criteria for those without chronic respiratory disease**

- Patients with CAP or HAP with or without concomitant COPD or bronchiectasis
- Patients with lower respiratory tract infection without COPD or bronchiectasis
- Age>18yrs old
- All observations must be stable for 12-24hrs
- EWS ≤2 AND SBP>90 (all observations must be stable for 12-24hrs)

- Has a telephone
- Can manage activities of daily living with current available support (If needed, immediate occupational therapy/physiotherapy/social assessment and care can be arranged prior to discharge and continued at home)
- Improving/stable inflammatory markers
- Improving/stable U&Es
- Fluent English speaker
- Oxygen saturations ≥94% on air(252)

**Inclusion criteria for those with chronic respiratory disease**

- Patients with CAP or HAP with or without concomitant COPD or bronchiectasis
- Patients with lower respiratory tract infection without COPD or bronchiectasis
- Age>18yrs old
- All observations must be stable for 12-24hrs
- SBP>90 (stable for 12-24hrs)
- Has a telephone
- Can manage activities of daily living with current available support (If needed, immediate occupational therapy/physiotherapy/social assessment and care can be arranged prior to discharge and continued at home)
- Improving/stable inflammatory markers
- Improving/stable U&Es
- Oxygen saturations ≥88% on air or oxygen (if long term oxygen therapy [LTOT] is to be provided) (excluding asthma for which oxygen saturations must be ≥94% on air). Oxygen assessment may be needed.(252)
- Fluent English speaker

**Exclusion criteria**

- Acute exacerbations of COPD
- Acute exacerbations of bronchiectasis without consolidation not requiring prolonged requiring intravenous antibiotics
- Patients with CURB-65 >3 admitted <24 hours ago
- Patients unable to manage at home even with maximal support from HOME FIRST (This may include intravenous drug users, patients with history of excess alcohol consumption or mental health problems)
- Empyema or untapped pleural effusion (If no diagnostic pleural tap performed - discuss with study doctor)
- Suspected/proven pulmonary infarct
- Serious co-morbidities requiring hospital treatment (e.g. CKD, CCF) or deemed unstable (significant AKD)
- Suspected MI/raised TnI/T consistent with NSTEMI (Or acute ECG changes) within 5 days of discharge
- SBP<90mmHg
- Neutropenia
- No fixed abode
- Tuberculosis suspected
- Well enough for discharge without HOME FIRST support

- **Screening, Questionnaires and Follow-up**

  1. **Screening**

Baseline clinical data which includes age, gender, history of presenting complaint, past medical history, a complete social history, drug and vaccination history and allergies, will be performed and recorded by the study doctor.

2. **Randomisation**

If a patient is selected for inclusion and consents to participation they are allocated at random to HOME FIRST or SHC. Randomisation is via computer generated random number and patient allocation is obtained by using numbered sealed envelopes.

3. **Questionnaires**

No research investigations will occur except for questionnaires. Clinical bloods and other investigations will be taken/requested as necessary.
SF-12 (physical and mental function) [performed twice in total] - at recruitment (day 0) and 6 weeks

CAP-SYM [performed 3 times in total] - at recruitment day 0 (twice including day minus 30) and 6 weeks

Patient (and carer/consultee) satisfaction - conducted over the telephone at 2 wks by an independent assessor.

4. **Initial follow-up post discharge**

*Patients randomised to HOME FIRST care* will initially receive up to twice daily respiratory specialist nurse visits for the first 48 hours. After this time period, the frequency and duration of visits will depend on clinical need. (See daily review diary information sheet.) The study nurse will establish the need for the involvement of other MDT team members. Laboratory tests will performed as clinically indicated at the discretion of the study team. Venepuncture will be performed by fully trained research staff for clinical purposes as needed in the HOME FIRST limb: as for those patients in the SHC limb frequency of venepuncture depends on clinical assessment of need by their regular medical team.

*Patients randomised to standard hospital care (SHC)* - All management and discharge decisions will be made by the patient's usual hospital team. Clinical tests will be performed at the discretion of the medical team. If any significant or concerning clinical issues are noted during study team's visits, the usual medical team will be alerted.

All patients will be discussed at a weekly case-note MDT meeting.

**5. Later follow-up**

All patients will be followed-up on discharge in the 'Respiratory Infection' out-patient clinic (in the patient's own home if necessary) at 6 weeks, with a repeat chest X-ray if needed.

**Operational Guidelines**

Patients discharged from hospital will remain the responsibility of the Chief Investigator during the time that they are supported by HOME FIRST. The patient's GP and hospital consultant (as of discharge day) will be informed of any specific interventions and outcomes by discharge letter. Patients recruited to the study that are

randomised to SHC will remain under the care of their current consultant. Patients can be readmitted to the hospital as determined by the study team via the bed managers. For all readmissions a 'treatment failure or complication development' proforma on the CRF will be completed. Home visits will occur from 08.00 - 17.00 up to 5-days-per-week. Telephone visits are available 7 days per week. 24hr cover is available via telephone to the HOME FIRST study team, this will be provided by a rotered team of respiratory study research doctors. In the event of an emergency an ambulance will be called. If the patient needs non-emergency medical attention at home between 17.00 - 08.00, a district nurse or out-of-hours GP will be contacted by the study team.

The patient's condition is monitored closely at home. Portable observation machines will be used by HOME FIRST to monitor blood pressure (BP), heart rate (HR), oxygen saturations (sats) and temperature during home visits. In order to provide consistent, high-quality care, the clinical assessment and evaluation will be carried out using the CRF. The CRF, which contains no patient identifiable information, will be removed from hospital premises for home visits.

HOME FIRST will provide coordinated MDT care, provision of 24 hr emergency telephone cover, access to fully trained respiratory study nurse(s) and study doctor(s). The HOME FIRST MDT consists of:

• Study doctors (trained respiratory physicians - consultants and senior SpRs)
• Highly trained respiratory specialist nursing staff
• Close links with a physiotherapist (mobility and respiratory)
• Home help provision (temporary assistance with ADLs by carers) which may include occupational therapy or social worker involvement (HOME FIRST has fast access to meals-on-wheels)
• Close links with pharmacy for rapid dispensing of discharge medication (TTOs).

## SAFETY NOTES

The risks to individuals are limited by the study design:

- **Strict patient selection -** Highly trained respiratory clinical staff (respiratory physicians - consultants and senior SpRs and senior specialist nurses with community experience) will carefully select suitable patients using strict inclusion/exclusion criteria and discretion based on extensive relevant clinical experience.
- **Competent and experienced specialist staff**
- **Thorough patient education** – Specific patient-individualised self-management plan.
- **Regular home visits** - Daily reviews will occur to ensure that any clinical deterioration is effectively assessed and managed and patients are re-admitted to hospital if deemed necessary by either the study team. A coordinated MDT will be key to the HOME FIRST care approach to patient care
- **No delay in recognition of clinical deterioration** – The patient/carer will be given a detailed patient information leaflet with red-flag symptoms, a 24hr emergency telephone contact number. During 08.00 – 17.00 telephone access (with additional home visits as necessary) to a specialist respiratory study nurse and doctor will minimise any risks of delayed recognition of clinical deterioration. The patient's condition is monitored closely at home. Portable observation machines will be used during home visits.
- **Rigorous safety procedures for patients/carers** - All patients/carers will also receive a verbal and written self management plan for their specific condition, a list of symptoms to prompt contact with team and a 24hr contact number (study on-call team). In the CRF a proforma will be completed if any treatment failure or complications requiring hospital re-admission occur. Adverse events will be reported using the correct documentation within the CRF. The study will be stopped if there is any mortality in the HOME FIRST limb whilst patients are at home. Any adverse events will result in a SAE form being completed and the ethics committee (REC) and sponsor(s) will be informed immediately. The risks to individuals are limited by the study design.
- **Rigorous staff safety procedures** – there are specific important safety issues around attending a patient's own home. This is a carefully considered and high priority area. Staff will carry personal alarm devices at all

times. If this is activated, a GPS tracking service at a local private security firm will locate the team member and they will immediately attend. They will alert the police as necessary. Team members will have up-to-date conflict resolution training. All team members will print off a daily diary which states all planned home visits and details times, addresses and contact numbers. If team members do not arrive/telephone at set time points, team members will contact them and if un-contactable the private security firm/police will be called as necessary. Occasionally two team members will attend together if felt necessary. If there are considered to be any threats to the health and safety of the attending member of the study team (either by the patient, the carers, family members, neighbours or the external community), patients in the HOME FIRST limb will be readmitted to hospital (if necessary) and HOME FIRST attendance will be stopped.

- A Data monitoring committee (DMC) has been formed following an SAE in January 2014. The DMC consists Dr Rebecca Bancroft, Consultant Physician RLBUHT, Arthur Ricky Kang'ombe, Lecturer/Biostatistician, Liverpool School of Tropical Medicine and Sasha Shepperd, Professor of Health Services Research, Oxford University. A terms of reference document is available. The DMC will provide the independent review of safety data for this study. To carry out this function, the DMC will (1) Review emerging safety data from the study. Data will be presented to the committee by spreadsheet weekly during the duration of the study. Responses are copied to all by email. This system has proved effective in our other research projects (such as experimental carriage models), (2) review, evaluate and make recommendations to the Investigators and the Trust as to whether to modify, suspend, terminate or extend the study, (3) be notified of any SUSAR without delay. DMC will also review SAEs/AEs on a regular basis and in particular review the causality assessments of all adverse events with regards to the patient selection criteria. Meetings will be held by email circulation. At a minimum there will be one meeting prior to recruitment of 30 patients and one when recruitment is completed or a decision is made that sufficient patient numbers have been screened. Other meetings may take place at the discretion of the members. Other external panel members may also be invited to attend meetings to discuss specific topics.

## ANALYSIS PLAN

A research statistician, Dr Brian Faragher from LSTM, has been involved in statistical discussions.

With regards to the primary outcome of time to recovery, this is a non-inferiority trial. With regards to secondary endpoints, safety and mortality, patient and carer/consultee satisfaction, re-admission rates, functional status (physical and mental) and quality of life (QOL) and costs will be analysed. Clinical outcomes such as safety and mortality and rate of readmission (at 6 weeks) will be analysed comparing the HOME FIRST limb with standard hospital care. Validated questionnaires (SF-12, CAP-SYM, and patient and carer/consultee satisfaction) will be quantitatively analysed to assess functional status/quality of life/satisfaction. A formal health-economic analysis is planned to measure costs and resource utilisation (Professor Louis Niessen), using costs that are sensitive to the different resources used during each patient care episode. **In conjunction with the NIHR Research Design Service (RDS) team, analysis methodology has been developed, including the involvement of a health-economist.**

## FUTURE PLAN AND IMPLICATIONS OF THE WORK

Success in this project will result in an early supported discharge scheme model for patients with LRTI leading to a reduction in hospital LOS, without an increase in re-admission rates or mortality and at least comparable patient satisfaction scores.

Success will result in an application for a NIHR Programme Grant for Applied Research (PGfAR) to fund a full multi-centre RCT with 100 patients per limb. Dependent on its success the aim is ultimately to 'roll-out' a fully operational HOME FIRST scheme nationally.

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**Full title: Pneumococcal Conjugate Vaccine-13 (Prevenar-13) and Experimental Human Pneumococcal Carriage Study (EHPC) Protocol**
**Short title: PCV/EHPC**
**EudraCT no. 2012-005141-20**

**Background**
Pneumococcal disease is a major global health threat for which new vaccines are urgently needed, particularly those that will protect vulnerable children and adults against pneumonia. Testing of new vaccines is costly in both time and money. Experimental Human Pneumococcal Carriage **(**EHPC) is safe and reproducible but has not yet been tested as a means of measuring vaccine protection. We will use current licensed vaccines to measure protection against EHPC.

**Current vaccines**
Pneumococcal polysaccharide vaccination (PPV) provides protection against invasive pneumococcal disease (IPD) but is less protective against pneumonia in adults(126) and is ineffective in young children. Pneumococcal conjugate vaccine (PCV) show good serotype-specific immunity against invasive disease (83-94%) in children and herd immunity effects in adults, by reducing carriage.(141) Prevenar-13 is currently licensed for use in children aged 6 weeks to 6 years. It is also licensed as a single dose vaccination for adults aged>50 yrs old.

**PCV and carriage**

Several studies have described that PCV is immunogenic in children(145) and elderly(146) as well as in HIV-infected subjects.(147) PCV induces systemic B and T cell responses and therefore IPD caused by vaccine types has declined in children following vaccination in the UK.(152) Epidemiological data have also suggested a reduction in nasopharyngeal carriage by vaccine types after PCV in both children and adults,(164, 165) both by direct protection of vaccinated individuals and by the reduction in exposure of unvaccinated individuals to vaccine types through herd protection. Modelling studies of anticapsular immunity have shown that the protection conferred by the serotype-specific immunity elicited during life by natural exposure to pneumococci is estimated as >50%, frequently allowing repeated colonisations with the same serotype.(225) There are no studies, however, demonstrating the direct protective effect of PCV and its serotype-specific induced immunity on pneumococcal carriage.

**Important current questions**
This study will address important current questions with regards to the impact of Prevenar-13 on pneumococcal carriage in adult human subjects. Examination of individuals pre and post Prevenar-13 vaccination, and comparison of the immune response of colonised versus non-colonised subjects and the vaccinated and unvaccinated subjects will provide new information on the innate, cellular and humoral immune responses to PCV vaccination and pneumococcal colonisation. In the future this model will be used in testing the effect of new candidate vaccines.

**Study design overview**
In our previous dose-ranging and reproducibility EHPC studies, we have demonstrated that nasal pneumococcal carriage could be reproducibly achieved in healthy adult volunteers. In this double-blind placebo randomised control trial (RCT) study we will use the EHPC model to carry out **vaccine effect testing**. The dose-response curve predicted a 30-60% endpoint allowing the combined testing for benefit and harm for our future vaccine studies.

Following thorough screening to minimise individual risk of pneumococcal disease and transmission to vulnerable contacts; healthy volunteers will be randomised to receive either Prevenar-13 or hepatitis A (Avaxim) vaccination. 5-12 weeks after vaccination (to which both the volunteer and study team are blinded) the volunteers will be inoculated with 0.1ml serotype 6B pneumococci per nostril at 80,000 cfu/nostril. They will then be followed for up to 3 weeks to determine the presence and duration of pneumococcal carriage, and the nature of the local and systemic immune responses induced.

The **primary endpoint** is PCV-induced protection against pneumococcal carriage. Classical culture methods (and PCR techniques) will be used to detect the presence, density and duration of pneumococcal carriage in nasal wash post inoculation.

The **secondary endpoints** are:
(a) Innate, humoral and cellular responses (detailed below) to pneumococcal colonisation will be assessed by immunological assays performed oncollected samples. In a subgroup of volunteers, bronchoalveolar lavage (BAL) will be collected after vaccination and experimental challenge. These data will allow us to define the host variables that predict colonisation and protection due to PCV

(b) PCV-induced alterations in nasal microbiota when possible

c) The effect of natural pneumococcal colonisation at the time of vaccination on PCV immunogenicity and subsequent post-vaccination colonisation duration and density.

**Aims**
The main study aim is to determine whether PCV is protective against pneumococcal carriage in healthy adult volunteers, in a safe and controlled manner.

The secondary aims are to examine the local and systemic innate, humoral and cellular immune responses to PCV +/- pneumococcal nasal carriage.

**Implications**
The major applications of this study are assessing whether: (a) PCV administered to adults reduces colonisation and therefore may improve herd immunity (b) there is a correlation between immunogenicity of the specific serotype and protection against carriage (c) natural colonisation at time of vaccination is affected by PCV (d) natural colonisation affects the immunogenicity of PCV (e) the EHPC model can be used as a surrogate for vaccine effectiveness (f) synchronous sampling of upper, lower respiratory tract and systemic compartments to determine correlates of PCV-induced protection.

**Subjects and timelines**
We will recruit healthy non-smoking volunteers and randomise them to receive either PCV or hepatitis A vaccine. We will then inoculate them with a well-characterised penicillin-sensitive pneumococcus (6B) and observe the volunteers for the development of pneumococcal carriage. We plan to inoculate up to 100 subjects (sample size calculations and justifications are detailed below). To allow for a drop-out rate of 20% prior to inoculation, up to 120 subjects will be initially recruited.

Outline timetable for volunteers:

- **Week 0** Initial appointment to discuss potential study involvement, consent obtained.
- **Week 1-2** Pre-vaccine samples - nasal wash, urine and blood collection. Clinical examination and history. Pregnancy test.
  Randomised to either Prevenar-13 or Avaxim vaccine arm and first dose of Prevenar-13 or Avaxim administered, pregnancy test prior to vaccination.
  Day 1 post vaccination blood sample
  Day 2 post vaccination blood sample
- **Week 5-15** (10 week variation allows for staggering to inoculate a safe number of participants per week). Post-vaccine samples - nasal wash, urine, throat swab and blood collection
- **Week 6**-**16** Pneumococcal inoculation - 0.1ml serotype 6B pneumococci administered to each nostril at 80,000 cfu/nostril.
  Day 1 post inoculation blood sample
  Day 2 post inoculation nasal wash, throat swab and blood samples

Daily telephone contact with researcher (by telephone) for 7 days following inoculation.

- **Week 7-17** Nasal wash and throat swab (7 days post inoculation)
- **Week 8-18** Nasal wash and throat swab (14 days post inoculation). Only attended by participants that developed carriage at at least one time point post inoculation
- **Week 9-19** Nasal wash, blood and urine (21 days post inoculation, final sample)
- **Week 9-19** UNBLINDING OCCURS AT THIS POINT
- **Week 9-onwards** A subgroup of volunteers may be offered an optional bronchoscopy and BAL [performed post carriage] (consent obtained as per separate consent form attached).
  All experimental carriers who have not had 2 consecutive negative nasal washes will receive amoxicillin 500mg tds for 3 days.
- **Week 9-onwards** Research bronchoscopy and BAL +/- blood sample (if > 2 weeks since study completed). Optional and in a subgroup only. Post-bronchoscopy follow-up occurs within 5 days.
- **Week 9-onwards** Volunteers are offered the full course of vaccine(s) that they did not receive at randomisation (if in Prevenar-13 group) or offered to complete the vaccination course (if in the Avaxim group).

**We will endeavour to take all samples at the above times however to allow maximum flexibility for our volunteers (allowing for illness, bereavements, exams and travel issues) we will allow +/- 7 days for sampling visits as appropriate.**

**Method details**

**1. Recruitment and selection**

Advertisements will be placed on physical notice boards in public areas, the internet of Universities and Colleges within Liverpool and the surrounding area and RLBUHT and University Hospital Aintree and in the local press inviting healthy volunteers to participate. Students from Liverpool Universities will be sent a generic advertisement email inviting them to participate in the research. Public open days and engagement events will be used to advertise the research. Interested persons are asked to contact the research team for further information and an initial appointment will be made should they wish to consider participating. The RLBUHT database (*consent4consent*) may also be used to approach those who have previously been involved in research at the RLBUHT. In order to prevent of 'over-volunteering' we will be using the TOPS database. We will enter into the database the volunteer's National Insurance number (if a UK citizen) or passport number and country of origin (if not a UK citizen) and the date of the last dose of study medicine. We may call other units to check volunteer details. Details may be kept for up to 3 years.

**Inclusion criteria:**

- Adults aged 18-50 yrs - ages chosen to minimise the risk of pneumococcal infection
- Fluent spoken English - to ensure a comprehensive understanding of the research project and their proposed involvement

**Exclusion criteria:**

- Previously received PPV (23-valent pneumococcal polysaccharide vaccine [pneumovax]) or any conjugate vaccine (PCV) - at any age – full vaccine history obtained from General Practitioner as necessary
- Previously received a complete course of hepatitis A vaccination
- Previous significant adverse reaction to any vaccination/immunisation

- Close contact with at risk individuals (children, immunosuppressed adults, elderly, chronic ill health) – to minimise risk of pneumococcal transmission
- Current smoker or significant smoking history (>10 pack yrs) – to minimise risk of pneumococcal infection and optional bronchoscopy
- Current diagnosis of asthma (on regular medication) or respiratory disease – to minimise risk of pneumococcal infection and optional bronchoscopy
- Pregnancy – to minimise risk of pneumococcal infection and no safety data exists for either vaccine in pregnancy
- Breast-feeding mothers - no safety data exists for either vaccine in pregnancy
- Women of child-bearing potential (WOCBP) who are deemed not to have sufficient, effective birth control in place for 1 month prior to vaccination and 1 month after the final vaccination
- On medication that may affect the immune system in any way e.g. steroids, steroid nasal spray
- Allergic to penicillin/amoxicillin
- Involved in another clinical trial unless observational or in follow-up (non-interventional) phase
- Previously been involved in a clinical trial involving experimental human pneumococcal carriage
- Unable to give fully informed consent
- Current acute severe febrile illness.

It is anticipated that 10-15% of screened participants will have natural pneumococcal colonisation at the time of recruitment as demonstrated by the initial nasal wash. These individuals will be permitted to continue in the study and follow an unaltered study protocol.

Vaccination history will be confirmed by the GP. The research team will complete sections of a GP questionnaire, this should be checked and signed by the GP before the patient is commenced in the study.

**2. Screening and preliminary assessment**

**Clinical examination** - the initial clinic visit will include a focused clinical history and targeted clinical examination involving auscultation of the lung fields and heart sounds. Should a previously unrecognised abnormality be identified this will be explained to the individual and appropriate investigations and follow-up will then be arranged by the study doctor. Further participation will be determined at the discretion of the study doctor dependent on the nature of the abnormality detected.

**3. Clinical specimens and collection procedures**

**Nasal wash** - will be performed using a modified Naclerio method.(189) This is a well-used and validated technique to collect nasal cytology specimens with which we now have 2 years experience. Briefly, 5ml of saline is instilled and held for a few seconds in the nares before being expelled in to a sterile Galli pot; this is usually repeated up to 20ml in total. In the event of nasal wash loss (defined as cough/sneeze/swallow) the procedure may then be repeated to obtain an adequate specimen.

**Venous blood** – will be taken by an appropriately trained team member. Up to 40ml of blood will be collected at 3 time points (pre-vaccine, post vaccine and final samples post challenge). An EDTA sample will be taken at both the pre-vaccination and the pre-inoculation/post-vaccination visits.

Extra blood samples - will be taken by an appropriately trained team member. Up to 10mls blood will be taken at pre vaccination (within the 40mls) and day 1 and day 2 post vaccination and day 1 and day 2 post inoculation +/- on the day of the bronchoscopy (if > 2 weeks since study completed) only.

**Urine** – up to 20mls of mid-stream urine is collected at 3 time points (pre-vaccine, post vaccine and final samples post challenge).

**Oropharyngeal swab -** In brief, the individuals tongue will be depressed using a tongue depressor exposing the palatopharyngeal arch. A sample will be obtained by making 5 small circular motions of the right palatopharyngeal in contact with the mucosa whilst avoiding the patients tongue. The oropharyngeal swab will be transferred into growth media, frozen and later analysed for the presence of respiratory pathogens using microbiological culture and molecular techniques. Recent data suggests increased identification of bacteria using oro-pharyngeal swabs in comparison to traditional sampling methods. Therefore we aim to compare results obtained from nasal wash samples using traditional culture and molecular techniques, such as qPCR, with the results from oro-pharyngeal swabs.

**3. Randomisation and blinding**.

Randomisation will be computer-generated and occur in blocks of 10. An independent co-ordinator will produce sealed envelopes containing the study group allocations. The research team will be blinded to the vaccination group as the vaccination will be administered by unblinded staff from the RLBUHT and the Liverpool School of Tropical Medicine (LSTM) Well Travelled Clinic [WTC]) in the RLBUHT clinical research facility (CRF). After the final 21 day post inoculation samples have been taken, un-blinding will occur to allow the study team to offer volunteers the alternative vaccine, these will be administered at the LSTM WTC and arranged by the volunteer directly with the WTC.

**4. The vaccine(s)**

The vaccines will be purchased by the RLBUHT clinical trials pharmaceutical team. The vaccines will be stored at the appropriate temperature as per manufacturer's instructions and stored and administered as per at CRF policy. Prevenar-13 will be purchased from Pfizer Pharmaceuticals and administered in a single dose via intramuscular injection (0.5mL supplied in a prefilled syringe). The hepatitis A vaccine (Avaxim) will be administered as a single dose (0.5mL supplied in a prefilled syringe) by intramuscular injection. The vaccines will be administered by an experienced, trained health care professionals from the RLBUHT or the WTC. As per CRF policy, the participant will be observed for 20-30 minutes following vaccination to ensure that they do not experience a reaction to the vaccine. If any adverse reaction occurs the volunteer will be transferred to the RLBUHT emergency department and the study team informed. Immediate un-blinding will occur in the event of an adverse event requiring medical attention for which knowledge of the vaccine given will effect treatment and ongoing immediate care.

Avaxim has been chosen as a suitable control due to its safety profile, preparation (aluminium-containing vaccine), lack of effect on nasal colonisation/immunity and health benefit for those involved in the study if the volunteer travels to endemic areas in the future. It is licensed for use in susceptible adults >16 years old. Initial protection is achieved with one single dose of vaccine. In order to provide long-term protection, a second dose (booster) should be given preferably between 6 - 12 months after but may be administered up to 36 months after the first dose. The vaccine may also be used to provide the second dose (booster) in subjects who received another inactivated hepatitis A vaccine (monovalent or with purified Vi polysaccharide typhoid) 6 - 36 months previously.

The hepatitis A immunisation course is 2 vaccinations in total. After un-blinding, volunteers in the hepatitis A arm will be offered 1 further hepatitis A vaccination, via the WTC, to complete their course (cost paid for by study) depending on their prior vaccination status. Those in the PCV arm will be offered a full course (2) of hepatitis A vaccinations through the WTC, depending on their prior vaccination status. All these appointments are arranged directly between the volunteer and the WTC after completion of the study.

The RLBUHT clinical trials pharmaceutical team will be responsible for 'over-labelling' both vaccines with a trial specific label which is annex compliant.

**5. Preparation of 6B bacterial stock for inoculation**

**Preparation of bacteria for carriage studies** - mid-log broth culture of pneumococcus (type 6B) will be frozen at -80°C in aliquots of glycerol-enriched media. Frozen aliquots will be thawed and checked for cfu/ml, E-test penicillin susceptibility and purity. These checks will first be carried out in our laboratory and then identification and characterisation will be confirmed in a reference laboratory. On experimental days, aliquots will be thawed, washed twice, and re-suspended at an appropriate density for each inoculation dose.

**Inoculation** - using a P200 micropipette 0.1ml broth containing the desired dose (80,000cfu/nostril) of 6B pneumococcus will be instilled in each nostril. The participant will be seated in a semi-recumbent position. After inoculation, the participant will remain in this position for up to 15mins. Following the inoculation visit the participant will be given a post-inoculation advice sheet (including emergency contact details), thermometer and a course of amoxicillin.

**Determination of colonisation** - colonisation will be defined by the result of nasal washes taken post inoculation. Nasal washes will be plated on culture media and incubated overnight at 37°C in 5% $CO_2$. Colonies will be confirmed as S. *pneumoniae* using classical techniques including (i) typical draughtsman-like colony morphology (ii) the presence of α-haemolysis (iii) optochin sensitivity (iv) solubility in bile salts and (v) Gram-positive diplococci. Typing will be done using a latex agglutination kit to confirm pneumococcal serotypes. Isolates will be frozen at -80ºC for storage and in any case of uncertainty will be confirmed by a reference laboratory. Results from the cultured nasal wash will also be confirmed using moleculat methods of bacterial detection.

**Monitoring of colonisation** - monitoring of colonisation will occur by 48 hour post-inoculation and then weekly nasal washes. Home monitoring will include a clear flow chart of the necessary intervention should any symptoms develop (see patient inoculation information sheet). A three day course of amoxicillin and a digital thermometer are issued. Participants will be required to make text message contact with a specified member of the research team before 1200hrs (noon) every day for 7 days post inoculation. Should they not make contact by the specified time; a member of the research team will contact the volunteer. If no contact is made then a prior defined 'secondary contact' will be telephoned. During the post inoculation period volunteers will have access to a 24/7 on-call telephone service until the end of the study.

**6. Termination of carriage**

All study participants who were experimental carriers, and who have not had 2 consecutive negative nasal washes, will receive amoxicillin 500mg tds for 3 days orally.

**7. Immunological response measurements**

Immunological assays to determine susceptibility to colonisation and immunological response to carriage will be carried out on collected samples.

**Bacterial carriage and microbiota evaluation**

Molecular techniques will be employed to determine the carriage density (primers including *lytA*) of pneumococcus and other nasopharyngeal and lower airway microbiota. Modern techniques include 16S rRNA sequencing, deep sequencing with 454 technology, transcriptomic profiling, and microarray. None of these methods are clinically validated and so we will use conventional techniques to determine the primary endpoint. We will also characterise the dynamics of co-colonisation, particularly of *S. pneumoniae* with staphylococci and *Haemophilus spp*.

**Collaborations**

Samples collected during this study including PBMCs, whole blood, bacterial cell pellets, nasal wash supernatant will be sent to our collaborators (Nationally and Internationally) once Material Transfer Agreements compliant with HTA regulation have been established. These collaborators have expertise that are complementary to our laboratory team and meet the aims of this project.

**End of the study**

Last visit of the last subject (LVLS)

**Provision of additional care after the trial has ended**

No specific provision is necessary in the study

**8. Risks and Benefits**

**Risks**

The main risks associated with this study are those of vaccination, experimental bacterial inoculation and research bronchoscopy. The main ethical principles under which these risks are considered are those of autonomy and non-maleficence.

**Autonomy**

The volunteers will be given sufficient information that is written and spoken in a non-jargon way to allow them to understand the research objectives, the risks of any procedures and the possible benefits. They then need to be given time to consider the information before consenting to any involvement. At no stage should the volunteer feel pressured or persuaded into participating in the research.

We have addressed this by specifying that potential volunteers will be passively recruited after volunteer initiated enquiry, rather than the researcher contacting the individual to prevent any possible influence or coercion on the part of the research team. Volunteers have the right to withdraw their consent and therefore withdraw from the study at any time without giving reason.

**Non-maleficence**

As researchers we have the responsibility to minimise the risk of harm to the volunteers. This involves the researchers having sufficient knowledge, having reviewed current evidence in the literature about the proposed interventions and making themselves aware of potential risks. For bronchoscopy this will be done by following recommended guidelines (BTS 2001). Bronchoscopy will be performed in the correct environment by highly trained and competent staff.

Trained staff will administer the vaccination. Staff are experienced in vaccination administration and fully competent in anaphylaxis management. Full resuscitation equipment and an anaphylaxis trolley are immediately available. The volunteers will remain at the clinic for 20 - 30 mins after vaccination to monitor for any immediate side effects.

Inoculation of *S. pneumoniae* will be as per previous studies and will be performed by highly trained staff with close supervision (24hr on call access to medical professional involved in the research study) and follow-up.

Specific inclusion and exclusion criteria are set to further protect the volunteer. In our previous dose-ranging and reproducibility EHPC studies, we demonstrated that nasal pneumococcal carriage could be reproducibly achieved in healthy adult volunteers.

Those who receive the Prevenar-13 are receiving a licensed vaccine outside of the EMA marketing authorisation (licensed for <6yrs old and >50 years old only). Prevenar-13 when administered to children/babies aged <6yrs

old and adults aged 50-95yrs old was associated with minor adverse reactions/side effects only, as detailed later. It is generally very safe and well tolerated.

Those who receive Avaxim are receiving a licensed vaccine within the marketing authorisation. The safety of this vaccine has been assessed in many clinical trials. It is generally very safe and well tolerated, adverse reactions/side effects are detailed below.

Experienced and trained research staff will perform venepuncture and nasal washes.

**Beneficence**

Although the benefit to the volunteer is limited they are however given the opportunity if they wish, to at the end of the study to complete the course of vaccinations in the arm they were randomly assigned and to have the (course) of vaccination(s) in the other arm of the study. They will also be examined and assessed by a clinical research doctor who may identify unsuspected illness. The patient will also have an opportunity to discuss other illnesses with a trained general medical doctor as they wish.

There is no current data available as to any benefit to those aged 18 – 50 of receiving Prevenar-13.

**Justice**

This must be balanced with non-maleficence. The research is open to all individuals but important exclusion criteria are in place, primarily to protect individuals from undue risk. This study offers the potential for both local (UK) and global impact in the prevention of pneumococcal disease. This value has been underscored by substantial funding from the Gates Foundation as part of the global effort to prevent pneumonia by vaccination.

**Benefits**

Participants will learn about clinical research from their experience and there is a possibility of detecting unsuspected medical problems during clinical examination, which will be further investigated as needed.

Additional health benefits for those involved in the study are that the volunteer has the ability to receive both the Prevenar-13 and Avaxim vaccination as part of the study free of charge. The latter offers 20 years of protection against hep A if they complete the course offered as part of this study.

Remuneration will be offered for travel, time and inconvenience the fees will reflect remuneration and not financial coercion. The payment compensates individuals for time, inconvenience, discomfort and the risk of participation but does not entice individuals to take part in the study for financial gain. The sums offered in this study have been developed over the course of many years for bronchoscopy and over the last 2 years for EHPC.

**9. Safety considerations**

Pneumococcus is responsible for infections including otitis media (OM), sinusitis, pneumonia, bacteraemia and meningitis. The milder forms of infection (OM, sinusitis) are many times more common than the serious invasive forms of disease. While the risk to individuals of developing any infection is very low (10% adults experience colonisation at any time, and the incidence of invasive disease is 20/100,000 patient years), the study is designed to ensure any risk is minimal by appropriate:

- a study team experienced in EHPC
- study design
- careful serotype selection and dosing
- volunteer selection and exclusion criteria
- volunteer education and availability of antibiotics
- rigorous safety procedures including daily monitoring
- 24 hour emergency telephone contact with researchers (including close individual daily monitoring) and access to hospital facilities and prompt treatment if required.

We have experience with inoculating and following over 200 healthy volunteers using several serotypes, and a range of doses. No episodes of pneumococcal infection or SUSARs have occurred in any of our volunteers.

Prevenar-13 is a safe vaccine with a very low risk of adverse events.(223, 224) It is currently licensed for use in children and in the UK as part of the Childhood Immunisation programme (effective from 4 September 2006). In adults over 50 years of age vaccinated in US clinical trials the most commonly reported side effects to Prevenar-13 vaccination included: injection site pain/swelling/tenderness, fatigue, headache, muscle pain, limitation of arms movement, decreased appetite, chills and rash.

Avaxim is a safe vaccine for use in travellers visiting hepatitis A endemic areas. In clinical trials, adverse reactions were usually mild and confined to the first few days after vaccination with spontaneous recovery. The adverse reactions observed with Avaxim include:

- Very common: asthenia, mild injection site pain
- Common reaction: headache, nausea, vomiting, decreased appetite, diarrhoea, abdominal pain, myalgia/arthralgia, mild fever
- Uncommon: injection site erythema
- Rare: injection site nodule

Reactions were less frequently reported after the booster dose than after the first dose. Avaxim was well tolerated in both sero-negative and positive subjects

Trained staff from the LSTM WTC or RLBUHT will administer the vaccination at the clinical research facility (CRF). LSTM WTC, RLBUHT and CRF staff are experienced in vaccination administration and fully competent in anaphylaxis management. Full resuscitation equipment and an anaphylaxis trolley are immediately available. The volunteers will remain at the clinic for 20-30 minutes after vaccination to monitor for any immediate side effects.

The Data Monitoring and Safety Committee (DMSC) is charged with monitoring the study and advising the PI and study team.

It consists of:
(1) Professor Robert C Read, Chair of Infectious Diseases, University of Sheffield (Chair) – supervises *Neisseria* human inoculation studies and is an expert on mucosal defence against infection
(2) Professor David Lalloo, LSTM – an experienced clinical trialist with substantial experience of DMSC work
(3) Dr Brian Faragher, Senior Lecturer in Statistics, LSTM – is experienced in clinical trials and DMSC work.

The DMSC will receive a weekly update on all recruitment (by email) and will meet by formally biannually and in the event of any **s**erious unexpected serious adverse reactions (SUSARs). When the DMSC formally meet they will review the SmPCs (on medicines.org.uk) for both Avaxim and Prevenar-13 for updates and any serious adverse events (SAE's) from the study so far, updating the protocol as necessary.

**Bronchoscopy and BAL**
We have experience of over 1000 of these procedures and have published both an audit of volunteer experience(253) and a visualised version of this technique.(254) A full risk assessment is carried out and a separate hospital consent form is completed. Complication rates are very low (mild symptoms in less than 25% subjects) and no serious adverse events.(255)

**10. Contraception/lactation and women of child-bearing potential (WOCBP)**

The effects of the Prevenar-13 and Avaxim on the unborn child are not known. Women who are pregnant or breast-feeding may not participate. Sexually active women must therefore be using an effective form of birth control approved by the study team for 1 month prior to and after the final vaccination. Contraception methods can include – hormonal contraceptives (oral, injection, trans-dermal patch, implants, cervical ring), barrier

methods (diaphragm with spermicide or a condom), an intra-uterine device, male sterilisation (for monogamous individuals only) and true abstinence. Women must have a negative pregnancy test at enrolment and on the day of vaccination and must confirm that they do not intend to become pregnant during the study. Those who think they may be pregnant are urged to notify the study doctor immediately.

**11. Adverse events**

**Adverse drug reaction (ADR):** any untoward and unintended response in a subject to an investigational medicinal product (IMP) which is related to any dose administered to that subject.

**Unexpected adverse reaction:** an adverse reaction the nature and severity of which is not consistent with the information about the IMP in the summary of product characteristics (SmPC).

**Serious adverse event (SAE) or serious unexpected serious adverse reaction (SUSAR):** an adverse event, adverse reaction or unexpected adverse reaction, respectively, that: (a) results in death (b) is life-threatening (c) requires hospitalisation or prolongation of existing hospitalisation (d) results in persistent or significant disability or incapacity (e) consists of a congenital anomaly or birth defect.

Any SAEs will be recorded and reported to the DMSC and sponsor (within 24hrs). Hypersensitivity reactions including facial oedema, dyspnoea and bronchospasm are rare SAEs to Prevenar-13. The reaction may result in brief hospitalisation (<48 hours) - no further vaccinations are necessary to remain a participant in the study.

In the event of any SUSAR the trial will be stopped temporarily for investigation and any further work referred back to the REC and MHRA for further consideration, through the sponsor (within 7 days).

**12. Analysis plan and sample size**

The primary endpoint of this study is PCV-induced protection against pneumococcal colonisation determined by the presence, density and duration of pneumococcus in nasal wash collected from vaccinated volunteers following experimental pneumococcal inoculation. Using data from our dose-ranging and reproducibility studies and data from previous PCV studies, we estimate that 60% of the control (hepatitis A vaccine) group will be colonised with pneumococci following inoculation and 30% of the PCV group. A 50% reduction of carriage in PCV group was estimated in accordance with modelling studies.(225) This allows a power of 81% when recruiting 50 volunteers to each arm.

| | n | Pneumococcal carriers | Pneumococcal carriers | Pneumococcal carriers | Pneumococcal carriers | Pneumococcal carriers | Pneumococcal carriers |
|---|---|---|---|---|---|---|---|
| PCV | 50 | 5 | 5 | 10 | 10 | 15 | 15 |
| Control | 50 | 30 | 25 | 30 | 25 | 30 | 25 |
| Power (%) | | 99 | 99 | 98 | 85 | 81 | 45 |

Important secondary endpoints including the immune responses, in particular humoral and cellular responses, will also be assessed. Immunological parameters will be compared between pre-vaccination and pre-inoculation values in paired analyses using parametric or non-parametric tests as appropriate. In the case of BAL data, we will only have one sample and therefore we will compare vaccinated colonised (natural and experimental) and non-colonised subjects and by non-paired comparison between groups from our previous experimental carriage studies samples.

Hypotheses regarding bacterial co-colonisation will be tested using molecular techniques. These methods are inherently semi-quantitative and so evaluation will be by comparison of proportions in samples at different time. We will be advised by the statistician Brian Faragher who is also member of our DMSC.

**13. Future plan and implications of the work**

Success in this project will result in:

a) A robust EHPC and vaccine testing protocol that can be used in novel vaccine evaluation

b) New information regarding mucosal responses to Prevenar-13 and bacterial colonisation after vaccination in adults with direct application to mucosal vaccine development

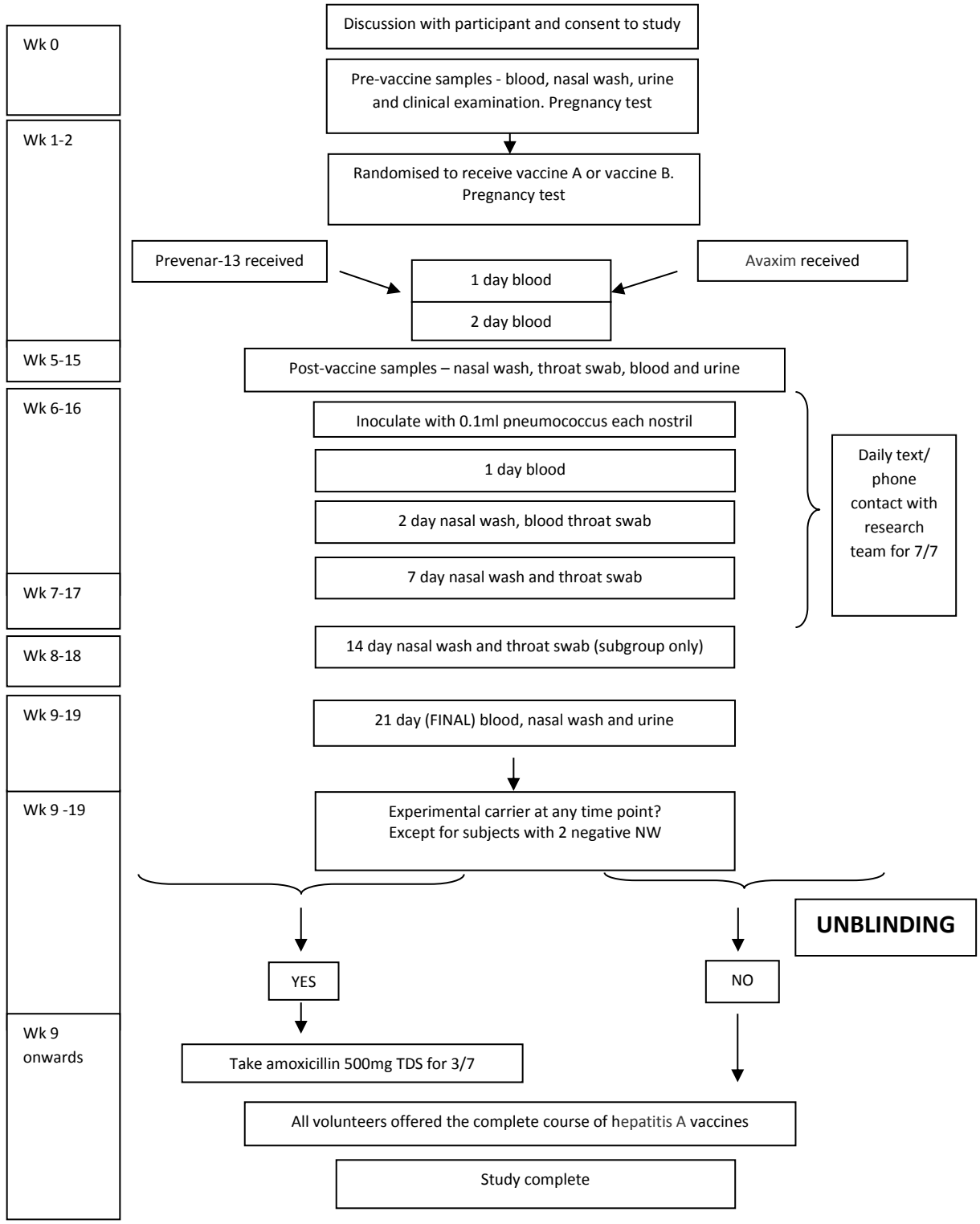
c) A greater understanding of the effect of Prevenar-13 on the nasal microbiota

d) A greater understanding of the effect of natural carriage on the immunogenesis of Prevenar-13.

Future work will be planned to build on both of these anticipated outcomes by engaging with vaccine manufacturing companies and mucosal adjuvant programmes.

**References**

**PCV EHPC Study Schedule Flowchart**



**Pneumococcal Conjugate Vaccine-13 Reduces Experimental Human Pneumococcal Carriage Rates: A Randomised Double-blind Control Trial – STATISTICAL ANALYSIS PLAN**
**Authors:** A M Collins, A D Wright, J F Gritzfeld, E Mitsi, C Hancock, D Shaw, S H Pennington, D Wang, B Morton, D M Ferreira, S B Gordon – to be confirmed.
**EudraCT:** 2012-005141-20
**ISRCTN:** 45340436
**REC ref:** 12/NW/0873

**Introduction**
New vaccines are urgently needed to protect the vulnerable from pneumonia. The 23-valent pneumococcal polysaccharide vaccine (PPV - pneumovax) provides protection against invasive pneumococcal disease (IPD) but is less protective against pneumonia in adults [1] and is ineffective in young children. The pneumococcal conjugate vaccine (PCV) shows good serotype-specific immunity against invasive pneumococcal disease [IPD] (83-94%). (95) The 23-valent pneumococcal polysaccharide vaccine (PPV - pneumovax) provides protection against IPD but is less protective against pneumonia in adults [1]. Several studies have described that PCV is immunogenic in children [3] and elderly [4] as well as in HIV-infected subjects.[5] Epidemiological data have suggested a reduction in nasopharyngeal carriage by vaccine types after PCV in both children and adults,[6, 7] both by direct protection of vaccinated individuals and by the reduction in exposure of unvaccinated individuals to vaccine types (VT) through herd protection. There have been no studies, however, demonstrating the direct protective effect of PCV and its serotype-specific induced immunity on pneumococcal carriage.
We have developed a model of Experimental Human Pneumococcal Carriage (EHPC) in healthy adults and reported that experimental carriage is safe and reproducible. [8] Here we use this model to assess whether 13-valent Pneumococcal Conjugate Vaccine (PCV-13) has a direct impact of pneumococcal carriage.
**Methods**
Ethical approvals were obtained from the National Health Service Research and Ethics Committee (REC 12/NW/0873) and the study was sponsored by the Royal Liverpool and Broadgreen University Hospital Trust and the Liverpool School of Tropical Medicine. The study was approved by MHRA registered with EudraCT: 2012-005141-20 and ISRCTN: 45340436. CONSORT methodology was followed. [9]
**Trial design and participants**
100 non-smoking, healthy volunteers aged between 18-50 years old, were recruited and commenced the study (see CONSORT diagram). Subjects were screened to minimise individual risk of developing pneumococcal disease and transmission to vulnerable contacts; and then randomised 1:1 to receive either 13-valent Pneumococcal Conjugate Vaccine (Prevenar-13) or Hepatitis A (Avaxim) vaccination (control group).
To minimise the risk of transmission, pneumococcal infection and vaccination, we excluded subjects;

(1) That had previously received PPV or PCV or a complete course of hepatitis A vaccination
(2) With a previous significant adverse reaction to any vaccination
(3) With close contact to 'at risk' individuals (children, immunosuppressed adults, elderly, chronic ill health)
(4) Who were current smokers or had significant smoking histories (>10 pack years)

(5) With asthma (on regular medication) or any other respiratory disease
(6) Pregnant or breast feeding mothers and women of child-bearing potential who are deemed not to have sufficient, effective birth control in place
(7) On medication that may affect the immune system in any way
(8) Allergic to penicillin/amoxicillin
(9) Involved in another clinical trial unless observational or non-interventional phase
(10) Previously involved in an experimental pneumococcal carriage study
(11) With a current acute severe febrile illness.

We also excluded all subjects taking any antibiotic therapy <2 weeks prior to inoculation, with abnormal clinical observations at the screening visit (systolic blood pressure <90, >160 mmHg, pulse rate <40, >100 beats per minute, oxygen saturations <96% on air), with an active medical condition requiring regular hospital appointments or with a white cell count pre-inoculation of <4.0 ($10^9$/L) AND a neutrophil count ($10^9$/L).

Screened subjects that were found to have natural pneumococcal colonisation at the time of recruitment as demonstrated by the initial nasal wash continued in the study and followed an unaltered study protocol.

**Randomisation, blinding, vaccination and unblinding**

A double blind randomised study design was performed. Randomisation was computer-generated and occurred in blocks of ten by envelopes. An independent co-ordinator from the tropical Clinical Trials Unit (tCTU) produced sealed envelopes containing the study group allocations. Research (clinical and laboratory) staff and subjects were blinded to vaccination allocation. An unblinded vaccination team was employed to vaccinate study subjects. The vaccines were drawn up out of sight of the study volunteers. At the end of the study (usually day 21 post-inoculation) the subjects were unblinded to the vaccine they received by a research nurse not involved in the conduct of the study.
Hepatitis A vaccine (Avaxim) was chosen as a suitable control predominately due to its safety profile, preparation (aluminium-containing vaccine), lack of effect on nasal colonisation/immunity and health benefit for those involved in the study.

**Subject monitoring and safety**

Pneumococcus is responsible for infections including otitis media, sinusitis, pneumonia, bacteraemia and meningitis. While the risk to individuals of developing any infection is very low, the study was designed to ensure any risk is minimal by appropriate:

- a study team experienced in EHPC
- study design
- careful serotype selection and dosing
- volunteer selection and exclusion criteria
- volunteer education and availability of antibiotics
- rigorous safety procedures including daily monitoring
- 24 hour emergency telephone contact with researchers (including close individual daily monitoring for 7 days post-inoculation via text contact) and access to hospital facilities and prompt treatment if required.

Subjects remained at the clinic for 20-30 minutes after vaccination to monitor for any immediate side effects. Full resuscitation equipment and an anaphylaxis trolley were immediately available. A Data Monitoring and Safety Committee (DMSC) monitored the study throughout.

Data on adverse events was collected. Specific codes were used for: headache (1), sore throat (2), nasal congestion/running (3), myalgia (4), lethargy (5), earache/muffling/popping (6), pyrexia (7), neck stiffness (8), hospital admission (9), other [including shivering, wheezy, cough, abdominal cramps] (10). Serious adverse events (SAE) or serious unexpected serious adverse reactions (SUSAR) were defined as: an adverse event or unexpected adverse reaction that: (a) results in death (b) is life-threatening (c) requires hospitalisation or prolongation of existing hospitalisation (d) results in persistent or significant disability or incapacity. SAEs were recorded and reported to the DMSC and sponsor within 24hrs.

**Sample collection**

Samples were taken pre-vaccine, post-vaccine/pre-inoculation and post-inoculation (day 2, 7, 14, 21). Samples included nasal wash, urine, throat swab, saliva and blood collection. At the pre-vaccination visit a clinical examination, clinical history and a pregnancy test were performed. 5 – 12 weeks post-vaccination the subjects were inoculated with 6B pneumococcus and then followed up for a further 3 weeks for detection of pneumococcal carriage. The day 14 visit was only attended by subjects that were carriage positive (either experimental or natural) at one time point post-inoculation (at day 2 or 7).

**Inoculation**

Bacterial stocks preparation was carried out as previously described [10]. Briefly a clinical isolate of *S. pneumoniae* serotype 6B (sequence type 138) was grown to mid-log phase in Vegitone broth (Oxoid) and stored in 1ml aliquots containing 20% glycerol at -80°C. Confirmation of serotype was performed using latex agglutination (Statens Serum Institute, Copenhagen) and bacterial purity was confirmed by an independent reference laboratory (Health Protection Agency, Colindale, UK).
On each day of inoculation an aliquot was thawed, centrifuged and the bacterial pellet was washed before being re-suspended and diluted in 0.9% sterile saline to reach the desired concentration of

bacteria. For inoculation the stock was then taken to the clinical area of inoculation and using a P200 micropipette 100µl inoculum containing the desired dose (80,000 cfu/100µl/nostril), well-characterised penicillin-sensitive 6B serotype pneumococcus (BHN 418) was instilled in each nostril whilst the subject was then seated in a semi-recumbent position. [11] Serial dilutions of the original inocula were plated onto blood agar for dose confirmation.

After inoculation, the participant remained in this position for up to 15mins. A post-inoculation advice sheet (including emergency contact details), thermometer and a course of amoxicillin was given to all subjects. Monitoring of colonisation occurred by 48 hour post-inoculation and then weekly nasal washes. During the post inoculation period subjects had

access to a 24/7 on-call telephone service and were required to make text contact daily for 7 days with the research team. Secondary point of contact (emergency) telephone details were also taken from all subjects.

**Diagnosis of carriage: colonisation and detection**

Nasal wash (NW) samples were collected pre- and post- inoculation and processed as previously described. [11] [12] Briefly, 5ml of 0.9% saline was instilled into each naris with the subject seated and leaning back supported at 45° to the horizontal. At instillation, the subjects were asked to hold their breath whilst pushing their tongue up and backwards against the roof of the mouth. Saline was held in the nasopharynx for up to 5 seconds and then expelled by gently tipping the head forward and exhaling rapidly through their nose into a sterile foil bowl. Usually this was repeated up to 20ml in total (10ml total per nares), if less than 10mls was returned, up to 40mls normal saline was used as necessary. Notably all CFU density is calculated by taking into account the total volume of saline returned.

NW samples were spun at 3350g for 10 minutes and the supernatant stored at -80°C. The pellet was re-suspended in 100µl of skim milk tryptone glucose glycerol (STGG) medium. 20µl was plated onto Columbia Horse Blood Agar (Oxoid) with gentamicin (Sigma) and the remainder diluted to 1 ml with STGG and plated (50µl) on blood and chocolate agar for determination of co-colonising flora. Remaining STGG samples were stored at -80 °C for confirmation if needed. Plates were inspected after 24 hours incubation at 37 °C, 5% $CO_2$ and alpha haemolytic, draughtsman-like colonies were sub-cultured to determine pneumococcal phenotype. Optochin sensitivity, bile solubility and latex agglutination testing were performed to confirm pneumococcal phenotype. 6B serotype was confirmed using latex agglutination kit (Statens Serum Institute, Copenhagen). Subjects in whom 6B pneumococci were detected in NW samples from any visits post inoculation were defined as experimental carriers. Isolates were frozen at -80°C for storage and reference laboratory confirmation. Results from the cultured NW were also confirmed using PCR based (LytA) methods of bacterial detection and to determine the carriage density.

Saliva samples were collected using salivettes retained for 2 minutes between the gum and buccal mucosa as per the manufacturer's instructions. Oro-pharyngeal swab was obtained by making 5 small circular motions of the palatopharyngeal arch in contact with the mucosa whilst avoiding the patients tongue.

All experimental carriers who did not had 2 consecutive culture-negative nasal washes received amoxicillin 500mg tds for 3 days at the end of the study.

**Sample size and endpoints**

The primary endpoint is PCV-induced protection against pneumococcal colonisation determined by the presence of pneumococcus in NW collected from vaccinated subjects following experimental pneumococcal inoculation at any post treatment time point up to and including day 21, detected using classical microbiological methods.

Secondary endpoints:

- The presence of pneumococcus in NW collected from vaccinated subjects following experimental pneumococcal inoculation at day 2, 7, 14 and 21 detected using classical microbiological methods
- the presence of pneumococcus in NW collected from vaccinated subjects following experimental pneumococcal inoculation at any post treatment time point up to and including day 21 detected using qPCR method
- the presence of pneumococcus in NW collected from vaccinated subjects following experimental pneumococcal inoculation at day 2, 7, 14 and 21 detected using qPCR method
- the density of pneumococcal colonisation in NW collected from vaccinated subjects following experimental pneumococcal inoculation at day 2, 7, 14 and 21
- the duration of pneumococcal colonisation in NW collected from vaccinated subjects following experimental pneumococcal inoculation at the end of study

Using data from our dose-ranging and reproducibility studies and data from previous PCV studies, we estimated that 40 - 60% of the control (hepatitis A vaccine) group will be colonised with pneumococci following inoculation and 30% of the PCV group. A 50% reduction of carriage in PCV group was estimated in accordance with modelling studies. [13] This allowed a power of 81% when recruiting 50 volunteers to each arm.

**Statistical methods and analysis**

Two populations will be considered in the analysis as follows:

**Intent-to-Treat population**

Intent to treat (ITT) will be defined at the moment the randomisation is performed. For the primary outcome analysis in this trial, subjects will be followed with their ITT arm. In analyses referring to a specific number of days, the randomisation day will be considered day 0. A randomised subject who does not have follow-up date due to loss to follow-up will not be included in the ITT population, leading to a modified ITT population.

**Per-protocol population**

Per-protocol (PP) population is based on the treatment group actually assigned to the subject. The PP population will exclude subjects who are known to have received no interventions. Protocol violators include those whose were recruited not vaccinated and also those who were vaccinated but withdrew before inoculation. Natural carriers may also be removed from the population prior to data analysis for the primary outcome.

**Primary endpoint analysis**

Primary outcomes will be summarised by number (%) of events and analysed using a generalized linear model that includes treatment as a single predictor (A=PCV group, B= control group), which will generate risk ratio and odds ratio together with their 95%CIs of having a pneumococcus between PCV and control group. The primary endpoint analysis will be based on ITT population. The main conclusions in the clinical report will be based on the

ITT analysis of the primary outcome. An additional analysis of the primary outcome will also be presented using the PP.

**Secondary outcome analysis**

The binary secondary endpoints will be summarised using number (%) of events at each time point and analysed using a generalised estimating equation (GEE) model, in which treatment (A=PCV group, B= control group), time (day=2, 7, 14 and 21), interaction between treatment and time as fixed effects and subject as random effect. Exchangeable covariance structure will be used. The odds ratio together with their 95%CIs at each time point will be derived.

The continuous secondary endpoints will be summarised using number, mean, standard deviation, median, minimum and maximum at each time point and analysed using a generalised estimating equation (GEE) model, in which treatment (A=PCV group, B= control group), time (day=2, 7, 14 and 21), interaction between treatment and time as fixed effects and subject as random effect. Exchangeable covariance structure will be used. The mean difference together with their 95%CIs at each time point will be derived.

The duration of pneumococcal colonisation in NW collected from vaccinated subjects following experimental pneumococcal inoculation at the end of study will be determined by the presence of pneumococcus in the most recent visit. This data will take only 5 possible values (0, 2, 7, 14 and 21). Empirical studies show that the density and duration of pneumococcal colonisation tended to have a fraction of zero values and did not follow the normal distribution. We will therefore perform a quantile regression analysis on these two outcomes with treatment as only covariate. In case of density analysis, quantile regression analysis will be performed at day 2, 7, 14 and 21 separately. The treatment effect will be derived from the quantile regression model.

Summary descriptive statistics will be used to describe natural carriers (VT and NVT) at different time points (pre-vaccination), post vaccination/pre-inoculation and post inoculation and also density (CFU/ml). Adverse events will also be described by number (%) of patients with at least one adverse events by treatment group for the following adverse events – 1 headache, 2 sore throat, 3 nasal congestion/running, 4 myalgia, 5 lethargy, 6 earache/muffling/popping, 7 pyrexia, 8 neck stiffness, 9 hospital admission, 10 other (including shivering, wheezy, cough, abdominal cramps), according the vaccine group, time (≤2, 2-7, 7-21 days) and carriage status.

**Subgroup analysis**

Subgroup analysis will be performed for primary endpoint by the vaccination status (vaccine type [VT] and non-vaccine type [NVT]). The treatment effect in each of subgroup of the above selected variables will be estimated within the framework of generalised linear model, which will include treatment, vaccination status, and interaction between treatment and vaccination status. Treatment effect within each subgroup of vaccination status will be estimated and presented together with the p-value for the interaction test.

**Baseline data**

Demographics and baseline characteristics will be summarised appropriately by treatment groups. In general for the continuous demographic variables results for each treatment group will be summarised using number of observations, mean, standard deviation, and minimum and maximum values, and for categorical (nominal) variables, the number and percentage of subjects will be used. Baseline data will include, total number of recruits, mean age (+/- SD and range), gender, inoculum dose (CFU/ml), number of natural carriers and VT or NVT) and time from vaccination to inoculation in both groups.

All statistical analyses will be performed using SAS 9.2 and Stata 13.

**References**

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2. Obaro, S.K. and S.A. Madhi, *Bacterial pneumonia vaccines and childhood pneumonia: are we winning, refining, or redefining?* Lancet Infect Dis, 2006. **6**(3): p. 150-61.
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8. Ferreira, D.M., et al., *Controlled human infection and rechallenge with Streptococcus pneumoniae reveals the protective efficacy of carriage in healthy adults.* Am J Respir Crit Care Med, 2013. **187**(8): p. 855-64.
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10. Wright, A.K., et al., *Human nasal challenge with Streptococcus pneumoniae is immunising in the absence of carriage.* PLoS Pathog, 2012. **8**(4): p. e1002622.
11. Gritzfeld, J.F., et al., *Experimental human pneumococcal carriage.* J Vis Exp, 2013(72).
12. Gritzfeld, J.F., et al., *Comparison between nasopharyngeal swab and nasal wash, using culture and PCR, in the detection of potential respiratory pathogens.* BMC Res Notes, 2011. **4**: p. 122.
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# Appendix B

Contains all Standard Operating Procedures (SOPs):

- Nasal Wash Collection Protocol
- Experimental Human *S. pneumoniae* Inoculation Protocol
- Nasal Wash Processing and Pneumococcal Carriage Detection Protocol
- DNA Extraction and qPCR Protocol

# Nasal Wash Collection Protocol

Version 3 (09/01/2015)

## Objective

Nasal Wash Collection/Sampling for EHPC PCV, HF feasibility and LRTI NW protocols.

## Reagents and Materials Required

Saline 20ml
Foil bowl
Gloves
Apron
Tissues
20ml syringe
Centrifuge tube

## Protocol

- Nasal washes (NW) are performed at an initial screening visit, as well as 48 hr, 7, and 14 days post- inoculation
- The volunteer is seated comfortably with their head is tilted back 30° from the vertical
- Ask the volunteer to take a deep breath in and hold their breath whilst pushing their tongue up and backwards against the roof of the mouth
- Whilst in this position, the volunteer is asked to signal that they are ready
- A syringe filled with 20 ml saline is inserted into the anterior nasal space and 5 ml of saline is expelled. The volunteer then leans forward immediately and expels the fluid by exhaling rapidly through their nose into a foil bowl
- Repeat this procedure 3 more times so that each naris has been washed twice and the full 20 ml has been used
- Pool all samples together in a centrifuge tube and send to the laboratory at room temperature for processing.

## References

Naclerio, R.M., *et al.* Mediator release after nasal airway challenge with allergen. *Am. Rev. Respir. Dis.* **128**, 597-602 (1983).

## Risks/Dangers

- *S. pneumoniae* is an opportunistic pathogen, care should be taken to prevent aerosols and subsequent inhalation of bacteria.

# Experimental Human *S. pneumoniae* Inoculation Protocol

Version 1A (22/12/2011)

## Objective

As part of the EHPC protocol, volunteers will be inoculated with 6B pneumococcus.

## Reagents and Materials Required

Blood plates – Oxoid PB0122A

6B stock vial from -80 freezer

Sterile 0.9% NaCl – hospital grade

Microcentrifuge

Microcentrifuge tubes

Pipettes – sterile, EHPC designated, in fume hood

96 well plate – U bottom

All work performed in fume hood

## Protocol

### 30mins prior to inoculation appointment

- Using 6B stock from -80°C freezer, thaw tube and spin in microcentrifuge full speed(13000rpm) for 3mins.
- Take blood plates out of fridge and put in incubator to warm
- Prepare 96-well plate for M&M, adding 180ul saline to each well
- Prepare dilution tubes according to desired dose
- Take 6B tube and remove vegitone broth supernatant
- Add 1ml of saline and resuspend pellet by pipetting up and down
- Centrifuge again at full speed for 3mins
- Remove supernatant and resuspend pellet in 1ml saline
- Prepare dilution tube for inoculation
- Plate out dilutions to determine inoculum dose both PRE and POST inoculation*

### 6B Inoculation

#### 80,000 CFU/100ul dose

- Using 1ml tube ONLY, take 68ul out and add to 1250ul saline, mix vigorously

**Plating changes:**

* Plate dilutions on individual blood plates – tilt plate at slight angle sideways, drop 10ul on left and let it run down length of plate, repeat twice underneath so there are 3 lines of bacteria. Count colonies the next day and divide by 3 as in M&M SOP

*Post plating done IMMEDIATELY upon return to LSTM. Try to limit time between pre and post to 30mins

**Risks/Dangers**

- *S. pneumoniae* is an opportunistic pathogen, care should be taken to prevent aerosols and subsequent inhalation of bacteria.

# Nasal Wash Processing and Pneumococcal Carriage Detection Protocol

Version 2A (09/01/2012)

## Objective

Process NW for PCV EHPC, HF feasibility and NW LRTI protocol and detect presence of pneumococcus.

## Reagents and Materials Required

**Blood plates – Oxoid PB0122A**

**Chocolate plates - Oxoid**

**STGG medium**

O'Brien, K.L. & Nohynek H. Report from a WHO working group: standard method for detecting upper respiratory carriage of *Streptococcus pneumoniae*. *Pediatr Infect Dis J* 2003, 22: e1-11.

Oxoid tryptone-soya broth (CM 129) 3.0ml; glucose 0.5g; Oxoid skim milk powder (CM L31) 2.0g; glycerol 10.0ml; double distilled water 100.00ml. Dispense in 1ml amounts into bijoux's and autoclave at 15lb for no more than 10 min. Store tubes at 4-6°C. Resuspend the pellet at the bottom of the tube before use by vortexing for 10 to 15 s.

**Saline**

For Miles and Misra dilutions – see M&M SOP

**Pipettes**

**96 well plate** – for dilutions

**Eppendorf tubes**

**Cryotubes *** if freezing for extraction

**Centrifuge**

## Protocol

- Centrifuge the samples for 10 min at 3,345 x g
- Remove the supernatant and store as 1 ml aliquots in labelled Eppendorf tubes at -80 °C
- Add 100 µl of STGG medium9 to the pellet and mix thoroughly. Ensure that the total volume in the tube at this point is determined. This dilution will be used in calculating the CFU of a carriage positive NW
- Plate a 20 µl drop of the STGG containing the re-suspended pellet onto a blood agar plate containing gentamicin and streak the entire plate. If the NW is post-inoculation, remove 10 µl from the STGG containing the re-suspended pellet and use for bacterial quantification by M&M method
- Add another 800 µl of STGG to the NW tube and mix thoroughly
- Plate 25 µl onto a blood agar plate and 25 µl onto a chocolate agar plate, streaking the entire plate
- Divide the remaining amount bacteria suspended in STGG medium into 2 cryovials and store at -80 °C
- Incubate the plates at 37 °C overnight in 5% CO2
- Examine the plates the next day for pneumococcus. Pneumococci are identified on plates by colony morphology. Alpha haemolytic colonies with draughtsman morphology are sub-cultured onto blood agar with an optochin disc and incubated overnight. Presumptive pneumococcal colonies that are optochinsensitive are Gram stained to confirm Gram positive diplococci and serotyped using the Statens Serum Institut Pneumotest-Latex kit.

STORAGE

- Add 800ul STGG to the NW tube, pipette up and down
- Divide remaining amount into cryovials (400ul approx into each) for -80°C for later DNA extraction and PCR.
-

## Risks/Dangers

- *S. pneumoniae* is an opportunistic pathogen, care should be taken to prevent aerosols and subsequent inhalation of bacteria.

# DNA Extraction and qPCR Protocol

Version 1 (22/12/2013)

**Objective**

As part of the LRTI NW protocol qPCR was carried out to assess for pneumococcal carriage.

**Reagents and Materials Required**

QIAamp DNA mini kit

Lysozyme Sigma-L-6876

Mutanolysin Sigma-M9901

TE buffer (10mM Tris-HCl, 1 mM EDTA, pH 8.0)

Primers and probe (Carvalho Mda G et al. Evaluation and improvement of real-time PCR assays Targeting LytA, Ply, and PsaA genes for detection of pneumococcal DNA. J Clin Microbiol. 2007 Aug;45(8):2460-6. Epub 2007 May 30.)

10uM working stock – want 200nm final
10uM (V1) = 0.2uM (25ul rxn)
V1 = 0.5ul/rxn

DNA free water (Millipore, H20MB0106)

Plates – Agilent 401334

Strip caps – Agilent 401425

Taq – Invitrogen 11785-200

Pipettes

ALL WORK PERFORMED IN FUME HOOD

**Protocol**

- DNA is extracted from 200 µl of the NW bacterial pellet stored in STGG using the QIAamp DNA mini kit and the Centers for Disease Control protocol
- The pellet is then resuspended in 200 µl TE buffer containing 0.04 g/ml lysozyme and 75 U/ml mutanolysin (Sigma) and incubated at 37°C for 1 hr. Vortex the sample
- Add 20 µl of proteinase K and 200 µl of Buffer AL to the sample and then incubate at 56°C for 30 min
- Centrifuge briefly and add 260 µl of ethanol. Then follow the manufacturer's instructions for all further steps.
- DNA is eluted in 100 µl of QIAGEN elution buffer and stored at -20°C
- Colonisation density is determined by targeting the pneumococcal autolysin *lytA* gene
- Include a no-template control, a negative extraction control (parallel extraction of TE buffer) and a *S. pneumoniae* (BHN418) positive control in each run.
- Amplify DNA with the Mx3005P system (Stratagene) and the data should be analysed using the instrument software
- A sample is considered positive if both duplicates had a cycle threshold ($C_T$) value below a mean 35. Values of >8000 copies/ml should be considered clinically relevant. Our (lower) limit of detection (LLD) is 40 copies.

**Reading/References**


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2. CDC: http://www.cdc.gov/ncidod/biotech/files/pcr-body-fluid-DNA-extract-strep.pdf. Accessed August 2013.
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## Appendix C

Contains emergency patient information leaflets (PILs):

- HOME FIRST Feasibility PIL
- HOME FIRST Pilot PIL
- PCV EHPC Vaccination PIL
- PCV EHPC Inoculation PIL

Do you have any of the following?

List of symptoms to prompt contact

- Fever (>38 ˚C)
- Increasing drowsiness
- Worsening cough or sputum
- Coughing up blood
- Increasingly unwell
- Feeling faint
- Vomiting – unable to keep antibiotics down

YES

**Call HOME FIRST**

- Via ACTRITE - weekdays 09.00 - 20.00 0151 7062047
- Via ACTRITE - weekends 09.00 - 18.00 0151 7062047
- Direct to HOME FIRST research team weekdays 09.00 – 16.30 0151 7064860 or 07810354171
- Outside office hrs - 24 hr emergency contact - 0151 7062000 and ask for the on-call HOME FIRST Doctor OR
- Attend AED/call 999

**HOME FIRST**

[HOME Followed-up by Infection Respiratory Support Team]

LSTM
LIVERPOOL SCHOOL OF TROPICAL MEDICINE

Patient Information Sheet

**EMERGENCY CONTACT**

- Via ACTRITE - weekdays 09.00 - 20.00 0151 7062047
- Via ACTRITE - weekends 09.00 - 18.00 0151 7062047
- Direct to HOME FIRST research team weekdays 09.00 – 16.30 0151 7064860 or 07810354171

At all other times phone

**0151 706 2000**

Hospital Switchboard

11/NW/0670

# THINGS YOU SHOULD KNOW.....

Discharge home

You will be transferred home using a hospital taxi and accompanied by the study nurse. All your discharge medications (TTO's) will be dispensed by pharmacy prior to discharge. Meals-on-wheels will be arranged as needed. You have been provided with a lifeline (pendant alarm) +/- home portable observations machine.

Follow-up

You must complete your antibiotic course as directed by the HOME FIRST staff. Your patient visit diary will list all the times & dates when the HOME FIRST team will visit your home. Additional dates may be arranged as needed, depending on how quickly you are recovering. You will also have clinic appointments at 1 and 6 months after discharge from hospital.

What should I look out for?

If you feel generally unwell or have any of the following:

- **Fever (>38 ˚C)**
- **Increasing drowsiness**
- **Worsening cough or sputum**
- **Coughing up blood**
- **Increasingly unwell**
- **Feeling faint**
- **Vomiting – unable to keep antibiotics down**

## What should I do?

You should also contact the HOME FIRST research team immediately. **Outside office hours** - ask the Hospital switchboard - for the **on- call HOME FIRST Doctor**. They will be available by telephone 24 hours a day for advice.

## What if I feel very unwell?

In the event you feel very unwell we advise you to immediately phone the emergency research team. Or alternatively in the event of an emergency attend the Emergency Department, NHS Walk-in centre or call 999.

## What do I tell the doctor?

**If, for any reason you have to attend your doctor or the hospital you need to inform them that:**

**You have ..... and are being cared for at home by HOME FIRST – a supported early discharge team for patients with respiratory infection as part of a pilot research study.**

11/NW/0670

Do you have any of the following?

List of symptoms to prompt contact

- Fever (>38 ˚C)
- Increasing drowsiness
- Worsening cough or sputum
- Coughing up blood
- Increasingly unwell
- Feeling faint
- Vomiting – unable to keep antibiotics down

YES

**Call HOME FIRST TEAM**

- Direct to HOME FIRST research team weekdays 09.00 – 16.30 0151 706 3381
- Outside office hrs - 24 hr emergency contact - 0151 706 2000 and ask for the on-call HOME FIRST Doctor OR attend AED/call 999

**HOME FIRST PILOT STUDY**

[HOME Followed-up by Infection Respiratory Support Team]

LSTM
LIVERPOOL SCHOOL OF TROPICAL MEDICINE

Emergency Patient Information Sheet

**EMERGENCY CONTACT**

**Weekdays 08.00 – 16.00 on 0151 706 3381**

**At all other times phone on 0151 706 2000**

**Hospital Switchboard**

**Ask for the on-call HOME FIRST Doctor**

12/NW/0731

# THINGS YOU SHOULD KNOW.....

Discharge home

You will be transferred home using a hospital taxi and accompanied by the study nurse. All your discharge medications (TTO's) will be dispensed by pharmacy prior to discharge. Meals-on-wheels will be arranged as needed.

Follow-up

You must complete your antibiotic course as directed by the HOME FIRST staff. Your patient visit diary will list all the times & dates when the HOME FIRST team will visit your home. Additional dates may be arranged as needed, depending on how quickly you are recovering. You will also have a clinic appointment arranged for you for 4-6 weeks time.

What should I look out for?

If you feel generally unwell or have any of the following:

- **Fever (>38 °C)**
- **Increasing drowsiness**
- **Worsening cough or sputum**
- **Coughing up blood**
- **Increasingly unwell**
- **Feeling faint**
- **Vomiting – unable to keep antibiotics down**

## What should I do?

You should also contact the HOME FIRST research team immediately.

**Outside office hours** - ask the Hospital switchboard - for the **on-call HOME FIRST Doctor**. They will be available by telephone 24 hours a day for advice.

## What if I feel very unwell?

In the event you feel very unwell we advise you to immediately phone the emergency research team. Or alternatively in the event of an emergency attend the Emergency Department, NHS Walk-in centre or call 999.

## What do I tell the doctor?

**If, for any reason you have to attend your doctor or the hospital you need to inform them that:**

**You have ..... and are being cared for at home by HOME FIRST – a supported early discharge team for patients with respiratory infection as part of a pilot research study.**

Vaccination Leaflet

## Hepatitis A Vaccine (Avaxim)

Hepatitis A is a viral infection that causes acute inflammation of the liver. It typically acquired through food or water contaminated by human faeces. Foods that grow close to the ground such as strawberries and lettuce or shell fish are particular risks.

It is also possible to contract the disease directly through close personal contact, in conditions of poor faecal hygiene. This mode of transmission may occur between children, and during certain sexual practices.

The Hepatitis A vaccine is given by intra muscular injection and provides protection for one year, the booster is given 6-12 months after the first injection providing protection against the virus for 20 years.

If you receive the Hepatitis A vaccine, around 10% of people who receive this vaccine experience mild reactions. These usually occur in the first few days after vaccination and usually disappear spontaneously within a few days.

**Mild Reactions**

The most commonly reported adverse reactions include headache, mild fever and muscle ache. Other commonly reported adverse reactions are nausea, vomiting, diarrhoea, abdominal pain, tiredness, influenza-like illness and injection site reactions (redness, hardening, swelling and itching).

**Severe Allergic Side Effects**

As with all vaccines, there is a very rare possibility (approximately one in a million doses) of this vaccine causing a severe allergic reaction called anaphylaxis. All health professionals responsible for vaccination are trained to deal with the recognition and treatment of anaphylaxis.

Vaccination Leaflet

## Pneumococcal Conjugate Vaccine (Prevenar-13)

Prevenar-13 is used to protect against pneumococcal infections in "at risk individuals" (children under 5 years and adults over 50 years).

Pneumococcal bacteria are responsible for infections including otitis media (ear infections), sinusitis, pneumonia, meningitis and sepsis.

The bacteria are passed between individuals through close contact.

If you receive the Prevenar-13 vaccine, around 10% of people who receive the vaccine experience mild reactions. These usually appear in the first few days after vaccination and usually disappear spontaneously within a few days.

**Mild Reactions**

The most commonly reported adverse reactions include swelling and redness at the injection site (10%) and low-grade fever (1%).
Other mild side effects include slightly raised temperature, sickness, diarrhoea, loss of appetite and poor quality sleep. No serious side effects have been reported.

**Severe Allergic Side Effects**

As with all vaccines, there is a very rare possibility (approximately one in a million doses) of this vaccine causing a severe allergic reaction (bronchospasm [wheezing and breathlessness) and facial swelling) called anaphylaxis. All health professionals responsible for vaccination are trained to deal with the recognition and treatment of anaphylaxis.

**What to do if you have a reaction.**

Is it **mild?**

- Headache
- Muscle ache
- Nausea
- Rash
- Flu-like illness
- Swelling, itching, hardening at the injection site

Inform the research team by phone on:

**07919 480 736**

Is it **severe?**

- Hives
- Swelling of the throat
- Swelling of the mouth
- Breathlessness/ wheeze

**IMMEDIATELY**
Attend Accident and Emergency in Hospital
AND
Inform the research team by phone on:
**07919 480 736**

Vaccination Leaflet

**RANDOMISED CONTROLLED TRIAL OF PCV AND HEP A VACCINE ON EXPERIMENTAL CARRIAGE OF PNEUMOCOCCAL BACTERIA**

LSTM
LIVERPOOL SCHOOL OF TROPICAL MEDICINE

Information Sheet

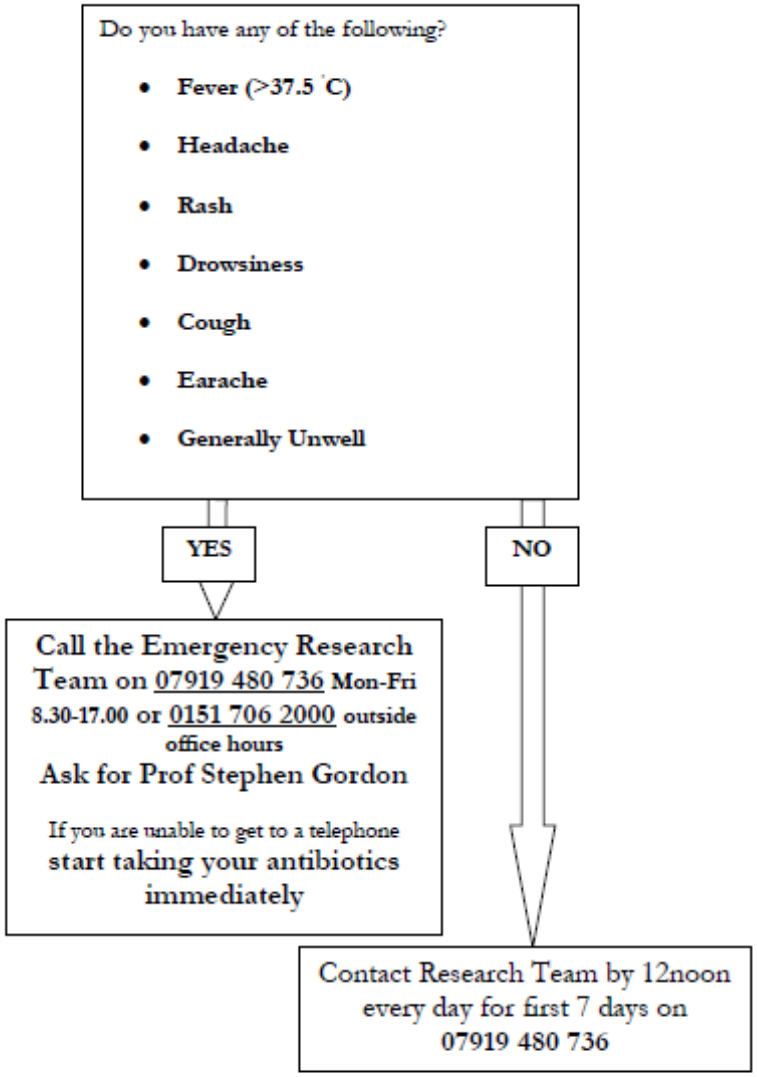
**EMERGENCY RESEARCH TEAM**

**07919 480 736**

**Mon-Fri 09.00-17.00**

**At all other times phone**

**0151 706 2000**
**Hospital Switchboard**




# PNEUMOCOCCAL CONJUGATE VACCINE AND EXPERIMENTAL HUMAN PNEUMOCOCCAL CARRIAGE STUDY

LSTM
LIVERPOOL SCHOOL OF TROPICAL MEDICINE

Information Sheet

**EMERGENCY RESEARCH TEAM**

**07919 480 736**

**Mon-Fri 08.30-17.00**

**At all other times phone**

**0151 706 2000**

**Hospital Switchboard**

## What should I do?

If you have any of the above symptoms we would ask that you should contact the research team on the following numbers without delay

07919 480 736 **Mon - Fri 08.30-17.00hrs**

0151 706 2000 **outside office hours** Hospital switchboard - ask for Prof Stephen Gordon. He will be available by telephone 24 hours a day for advice.

## What if I feel very unwell?

In the unlikely event you feel very unwell we advise you to start taking the antibiotics immediately and phone the emergency research team (07919 480 736 or 0151 706 2000). In the unlikely situation that you are unable to make contact with the team we recommend you attend your nearest Emergency department.

## What if I am not near a phone?

If for any reason you are unable to make contact with the emergency research team we would advise that you start taking your antibiotics straight away. This is one tablet (500mg) of AMOXICILLIN to be taken three times per day. If you have any concerns we recommend you attend your nearest Emergency Department.

## What do I tell the doctor?

**If, for any reason you have to attend your doctor or the hospital you need to inform them that:** *You have had live Streptococcus pneumoniae inoculated into your nose on __/__/____ as part of a randomised control trial into nasal carriage and vaccination. The bacteria you carry are fully sensitive to amoxicillin and you have no history of allergy to this antibiotic.*

## Do I need to do anything if I feel well?

We ask that for the **first 7 days** you text or phone **Dr Andrea Collins** and **Sr. Angela Wright** by 12noon every day on the following number: **07919 480 736** .

This is to ensure that you are not experiencing any problems. If we do not hear from you by 12noon we will contact you to make sure you are not experiencing any problems. In the event that we cannot contact you, your next of kin will be contacted.

## Things you should know.....

## Following inoculation with pneumococcus

After the pneumococcus is put into your nose it is possible that it may cause an infection. Although this is very unlikely it is sensible that you familiarise yourself with symptoms or signs that may indicate infection to make sure they are recognised and treated early.

**Keep your thermometer, antibiotics and contact numbers with you at all times during the study.**

WHAT SHOULD I LOOK OUT FOR?

If you feel generally unwell or have any of the following:

- **Fever (temp>37.5 ˚C)**
- **Shivering**
- **Headache**
- **New rash**
- **Drowsiness**
- **Cough**
- **Earache**

If you have any of the symptoms or signs marked in bold please call the emergency number immediately.

**07919 480 736 (Mon-Fri 08.30-17.00)**

**At all other times phone 0151 706 2000 and ask for Prof Stephen Gordon**

# Appendix D

Contains outcome measures from the HOME FIRST studies:

- Telephone Satisfaction Questionnaire (Patient)
- Telephone Satisfaction Questionnaire (NOK, carer, consultee)
- CAPSYM Questionnaire
- SF-12 Questionnaire
- RECRI Questions

**HOME FIRST Telephone Patient Satisfaction Questionnaire**

| | | | | | |
|---|---|---|---|---|---|
| **Q1** | **I have been treated with kindness and respect by staff** | Strongly agree | Agree | Disagree | Strongly disagree |
| **Q2** | **The staff attended well to my personal needs** | Strongly agree | Agree | Disagree | Strongly disagree |
| **Q3** | **I was able to talk to the staff about any problems that I might have had** | Strongly agree | Agree | Disagree | Strongly disagree |
| **Q4** | **I received all the information I wanted about the cause and nature of my illness** | Strongly agree | Agree | Disagree | Strongly disagree |
| **Q5** | **The doctors and nurses have done everything they can to make me well again** | Strongly agree | Agree | Disagree | Strongly disagree |
| **Q6** | **I am happy with the amount of recovery I have made** | Strongly agree | Agree | Disagree | Strongly disagree |

(adapted from Wilson et al, B.J. Gen Pract 2002)

**HOME FIRST Telephone Carer / Next of Kin / Consultee Satisfaction Questionnaire**

| | | | | |
|---|---|---|---|---|
| **They have been treated with kindness and respect by staff** | Strongly agree | Agree | Disagree | Strongly disagree |
| **The staff attended well to their personal needs** | Strongly agree | Agree | Disagree | Strongly disagree |
| **I was able to talk to the staff about any problems/ questions that I might have had** | Strongly agree | Agree | Disagree | Strongly disagree |
| **I received all the information I wanted about the cause and nature of their illness** | Strongly agree | Agree | Disagree | Strongly disagree |
| **The doctors and nurses have done everything they can to make them well again** | Strongly agree | Agree | Disagree | Strongly disagree |
| **I am happy with the amount of recovery they have made** | Strongly agree | Agree | Disagree | Strongly disagree |

(Adapted from Wilson et al, B.J. Gen Pract 2002)

## HOME FIRST CAPSYM Questionnaire

Patients with pneumonia sometimes experience symptoms or problems which we are evaluating as part of the study in which you are currently participating. We would therefore like to ask you a few questions about your own current experience in that respect. I am going to read you a list of symptoms or problems. For each of them, I will ask you the extent to which the symptom/problem has bothered you in the past 24 hours: not at all, a little, moderately, quite a bit or extremely. If you have not had the symptom/problem in the past 24 hours, please let me know.

Overall, the interview will only take a few minutes and the questions are simple to answer. Please remember that you should answer in reference to what happened in the past 24 hours. Thank you very much in advance for your participation.

*Please read each item to patient and circle the number that corresponds to how much the patient has been bothered by the symptom/problem IN THE PAST 24 HOURS.*

| **In the past 24 hours, how much have you been bothered by:** | | | | | | |
|---|---|---|---|---|---|---|
| | **Patient did not have the symptom/problem** | **Patient had the symptom/problem and it bothered him/her...** | | | | |
| | | **Not at all** | **A little** | **Moderately** | **Quite a bit** | **Extremely** |
| *1. Coughing? | 0 | 1 | 2 | 3 | 4 | 5 |
| *2. Chest pains? | 0 | 1 | 2 | 3 | 4 | 5 |
| *3. Shortness of breath? | 0 | 1 | 2 | 3 | 4 | 5 |
| 4. Coughing up phlegm/sputum (secretion from the chest)? | 0 | 1 | 2 | 3 | 4 | 5 |
| 5. Coughing up blood? | 0 | 1 | 2 | 3 | 4 | 5 |
| *6. Sweating? | 0 | 1 | 2 | 3 | 4 | 5 |
| *7. Chills? | 0 | 1 | 2 | 3 | 4 | 5 |
| *8. Headache? | 0 | 1 | 2 | 3 | 4 | 5 |
| *9. Nausea? | 0 | 1 | 2 | 3 | 4 | 5 |
| 10. Vomiting? | 0 | 1 | 2 | 3 | 4 | 5 |
| 11. Diarrhea? | 0 | 1 | 2 | 3 | 4 | 5 |
| 12. Stomach pain? | 0 | 1 | 2 | 3 | 4 | 5 |
| *13. Muscle pain? | 0 | 1 | 2 | 3 | 4 | 5 |
| *14. Lack of appetite? | 0 | 1 | 2 | 3 | 4 | 5 |
| *15. Trouble concentrating? | 0 | 1 | 2 | 3 | 4 | 5 |
| 16. Trouble thinking? | 0 | 1 | 2 | 3 | 4 | 5 |
| *17. Trouble sleeping? | 0 | 1 | 2 | 3 | 4 | 5 |
| *18. Fatigue? | 0 | 1 | 2 | 3 | 4 | 5 |

* Indicates items that are included in the CAP-Sym 12.

**HOME FIRST SF-12® Patient Questionnaire**

Examination date (circle):
Day 0 Day 2 Day 7 1 mth clinic appt 6mth clinic appt

This information will help your doctors keep track of how you feel and how well you can do your usual activities. Answer every question by placing a check mark on the line in front of the appropriate answer. If you are unsure about how to answer a question, please give the best answer you can and make a written comment beside your answer.

1. In general, would you say your health is:
_____ Excellent (1)
_____ Very good (2)
_____ Good (3)
_____ Fair (4)
_____ Poor (5)

The following two questions are about activities you might do during a typical day. Does YOUR HEALTH NOW LIMIT YOU in these activities? If so, how much?

2. MODERATE ACTIVITIES, such as moving a table, pushing a vacuum cleaner, bowling, or playing
golf:
_____ Yes, limited a lot (1)
_____ Yes, limited a little (2)
_____ No, not Limited at all (3)

3. Climbing SEVERAL flights of stairs:
_____ Yes, limited a lot (1)
_____ Yes, limited a little (2)
_____ No, not limited at all (3)

During the PAST 4 WEEKS have you had any of the following problems with your work or other regular
activities AS A RESULT OF YOUR PHYSICAL HEALTH?

4. ACCOMPLISHED LESS than you would like:
_____ Yes (1)
_____ No (2)

5. Were limited in the KIND of work or other activities:
_____ Yes (1)
_____ No (2)

During the PAST 4 WEEKS, were you limited in the kind of work you do or other regular activities AS A RESULT OF ANY EMOTIONAL PROBLEMS (such as feeling depressed or anxious)?

6. ACCOMPLISHED LESS than you would like:
_____ Yes (1)
_____ No (2)

7. Didn't do work or other activities as CAREFULLY as usual:
_____ Yes (1)
_____ No (2)

8. During the PAST 4 WEEKS, how much did PAIN interfere with your normal work (including both work outside the home and housework)?
_____ Not at all (1)
_____ A little bit (2)
_____ Moderately (3)
_____ Quite a bit (4)
_____ Extremely (5)

The next three questions are about how you feel and how things have been DURING THE PAST 4 WEEKS. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the PAST 4 WEEKS –

9. Have you felt calm and peaceful?
_____ All of the time (1)
_____ Most of the time (2)
_____ A good bit of the time (3)
_____ Some of the time (4)
_____ A little of the time (5)
_____ None of the time (6)

10. Did you have a lot of energy?
_____ All of the time (1)
_____ Most of the time (2)
_____ A good bit of the time (3)
_____ Some of the time (4)
_____ A little of the time (5)
_____ None of the time (6)

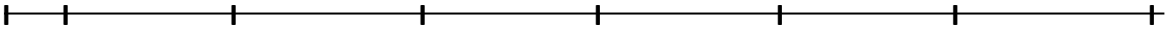
11. Have you felt downhearted and blue?
_____ All of the time (1)
_____ Most of the time (2)
_____ A good bit of the time (3)
_____ Some of the time (4)
_____ A little of the time (5)
_____ None of the time (6)

12. During the PAST 4 WEEKS, how much of the time has your PHYSICAL HEALTH OR EMOTIONAL PROBLEMS interfered with your social activities (like visiting with friends, relatives, etc.)?

_____ All of the time (1)
_____ Most of the time (2)
_____ A good bit of the time (3)
_____ Some of the time (4)
_____ A little of the time (5)
_____ None of the time (6)

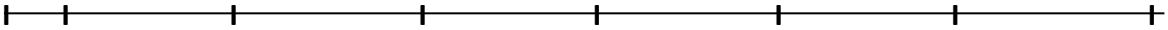
**Functional RECovery from Respiratory tract Infection Questionnaire (RECRI).**

1. When (if at all) did your sleep return to normal?



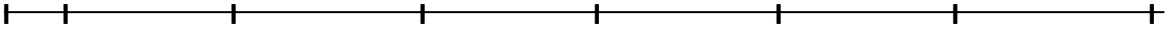
**1 day 1 week 2 weeks 3 weeks 4 weeks 5 weeks 6 weeks**

2. When (if at all) did your diet/appetite return to normal?



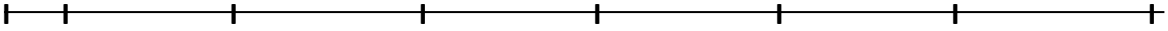
**2 day 1 week 2 weeks 3 weeks 4 weeks 5 weeks 6 weeks**

3. When (if at all) did your (pre-defined on day of recruitment) exercise capacity return to normal?



**1 day 1 week 2 weeks 3 weeks 4 weeks 5 weeks 6 weeks**

4. When (if at all) did your capacity to work/socialise (delete as appropriate) return to normal?



**1 day 1 week 2 weeks 3 weeks 4 weeks 5 weeks 6 weeks**

**Appendix E** contains miscellaneous HOME FIRST documents:

- HOME FIRST Pilot Staff Roles and Responsibilities
- HOME FIRST DMSC Terms of Reference

**HF Staff Roles and Responsibilities.**

| Role | Dr responsible | Nurse responsible | Details |
|---|---|---|---|
| **Recruiting** | X | x | Both nurse and doctor recruited, it was anticipated that this would most commonly be the Doctor's role as they may be better placed to discuss the patient's potential discharge with fellow medical colleagues. The recruitment log was completed by the nurse. Clinical exam (both); blood tests (both); TTO's (Doctor) discharge letter (Doctor), ambulance/liaising with family or NH (both), checking bloods (both) and discharge checklists (ward staff). |
| **Ward / department teaching** | X | x | Disseminated information about the study during planned teaching sessions (wards), at consultants meeting on A&E, and ad hoc whilst screening. |
| **Advertising** | | x | Arranged with hospital communications team for ethically approved posters to be placed in hospital; communication – paper and intranet. Posters were laminated and placed in clinical and patient areas in the hospital. |
| **Screening** | X | x | Nurse checked inpatient status on IPM (or similar) [especially on Mondays] before planning ward based re- reviews. Those discharged / missed were updated on the screening log. The ward location of patient was confirmed (if previously in AMAU / A&E). Doctor screened all relevant hospital areas and delegated screening wards to nurse. |
| **Screening log** | X | x | • Completed paper screening logs on a daily basis for screened patients<br>• Patient location changes were updated |

| | | | |
|---|---|---|---|
| | | | • Nurse confirmed the location of each patient previously on AMAU & A&E prior to repeat review<br>• Notes made on A4 paper, then transcribed onto the screening log<br>• Nurse uploaded data onto electronic screening log (usually) on a weekly basis |
| **OSIRIS or similar** | | x | Database of all those recruited, visits and when they completed the study. Monitored by RD&I. |
| **Demographics database** | | x | Completed spreadsheets for:<br>• Demographics with a summary of each patient / learning outcome, clinical results, LOS etc<br>• CAPSYM: -30, day 0 & 6 weeks<br>• SF12: day 0 & 6 weeks<br>• RECRI: 6 weeks<br>• Patient satisfaction questionnaire<br>• Carer/NOK/relative satisfaction questionnaire |
| **Electronic site file** | | x | Maintained by nurse. An electronic replica of the physical site file was available and was password protected, on the shared drive. |
| **Home visits** | x | x | Wherever possible they occurred before midday – in order that if a patient was unwell, results from clinical blood samples were back before 4pm. Green bag and CRF were taken to the property, and completed. The following documents were followed, completed and referenced as needed:<br>• Escalation & readmission flow chart<br>• Telephone contact chart (in and out of hours)<br>• Review criteria and flowchart for discharge<br>During a home visit clinical examination was performed and the study team checked for any issues – they spent time talking to care |

| | | | |
|---|---|---|---|
| | | | giver / family - particularly for care home patients when required. Routine planned bloods such as INR or as required bloods depending on clinical picture were to be taken. Catheters inserted or removed as needed. The study team ensured equipment had been delivered / ensures supplied / meal on wheels food delivered. It was not the team's responsibility to liaise with landlords or deal with other non-clinical issues. All home visits were discussed with a study Doctor the same day, either face to face, via text / telephone or email. A management plan was then agreed. |
| **Paper site file** | | x | Maintained by nurse. Doctor emailed relevant documents as needed or when received. |
| **BP equipment** | | x | Arranged for equipment to be calibrated regularly and added certificates to electronic and site file. Spare batteries were kept in green bag. |
| **Green bag** | | x | Used contents checklist to ensure maintained in date stock. Nurse arranged regular calibration of equipment with supplier. |
| **CRF / recruitment packs** | | x | Made up recruitment packs. Nurse ensured blood results and investigations section on CRF and all questionnaires (day – 30; day 0, 6 weeks) and databases were completed. |
| **Ordering case notes** | | x | Ordered case notes via IPM (or similar system) clinic appointments and stored in locked office. |
| **Arranging remuneration payments** | | x | Bank details were collected during recruitment. Information was stored on a secure database, and any paperwork was shredded. Nurse gave bank payment forms to finance department at LSTM. Occasionally cash payments were made if absolutely necessary. |
| **Updating database for OPD dates** | | x | A database recorded all of the above information. This allowed the team to see at a glance where each patient was up to in the study. |
| **GP letters posted** | | x | |

| | | | |
|---|---|---|---|
| **Ward thank you gifts** | x | x | Study team gave final thank you to ward staff after recruitment had closed. |
| **Annual progress report** | | x | This was completed using an RD&I template. After being signed by PI, it was emailed to REC/ RD&I / LCRN/ PI. Stored in site file and electronically. |
| **End of study declaration form** | | x | Completed at the end of the study. |
| **Final report** | x | x | Completed within 12 months of the end of the study. |
| **SAE reporting** | x | x | Completed necessary documentation and submitted it to RD&I (sponsor). The study was put on holding pending investigation/review as needed. |
| **Delegation log** | | x | Nurse ensured delegation log was up to date. Nurse ensured research team's CVs and GCP all up to date and in paper and electronic site file. |
| **Chest XR** | x | x | Ordered repeat CXR and any other investigations at 6/52 OPD as needed. Nurse documented radiology reports on demographic database |
| **DMSC** | x | | Updated DMSC on a weekly basis by email – highlighted any relevant issues. |
| **Time data** | x | x | Doctor and nurse recorded all time spent on screening and home visits and travel time to enable a health economic assessment, this was cross checked by an independent assessor. |
| **Telephone numbers to switch** | x | x | List of all relevant telephone numbers and names was made and given to switch. On call flowchart was used as required. Forwarding the on call mobile was usually the simplest and safest solution. |
| **LOS** | | x | Calculated using online tool http://www.timeanddate.com/date/duration.html. Data was stored on demographic database. |

| | | | |
|---|---|---|---|
| **Patient summaries** | x | x | Brief summary of anything interesting or unusual about each case was completed i.e. future learning points. |
| **Reliance device** | x | x | Nurse received a monthly report from Reliance. Used by all staff at all home visits |
| **Taxis** | | x | Booked via local taxi company by nurse if needed. The process at RLBUHT was as follows:<br>• Nurse confirmed taxi required<br>• Phoned taxi to get quote<br>• Phoned / emailed LSTM to raise purchase invoice<br>• Phoned taxi and gave purchase invoice number, then proceeded with booking. |
| **Booking OPDs and home visits on calendar** | | x | Referred patient for OPD and booked slot. If patient was unable to attend the 6 week OPD a home visit was arranged. All OPDs and home visits were booked on at least 2 staff calendars with patient's initials / address/ post code/ phone number included for safety purposes. I.e. if no contact with doctor or nurse at set time, the police were informed where the nurse/doctor was last known to be. |
| **Independent telephone questionnaire** | | x | Performed by an administration clerk after training from nurse. Training included: reminding volunteer about the study they took part in when they were in hospital, telling volunteer that they were an independent assessor; explaining the questionnaire; negotiating more convenient times to complete it if volunteer / carer was too busy<br>Notes were made by nurse on reverse of questionnaire to assist caller i.e. if volunteer was in HF or SHC arm, date interview due / volunteer details / carer details / telephone numbers<br>Results were uploaded onto a database by nurse |
| **Contacts list** | x | x | Maintained by nurse with a list of useful and important contacts. |

# Data Monitoring and Safety Committee Terms of Reference

## HOME FIRST PILOT STUDY

**Short title:** HOME FIRST PILOT STUDY

**REC Ref:** 12/NW/0731

**Chief Investigator**: Stephen Gordon
Chair in Respiratory Medicine
3rd Floor CTID Building
Liverpool School of Tropical Medicine
Pembroke Place
Liverpool
L3 5QA
(0151) 705 3169

**Sponsors:** Royal Liverpool and Broadgreen University Hospital NHS Trust and Liverpool School of Tropical Medicine

1. Introduction

The HOME FIRST (early supported discharge scheme for patients with lower respiratory tract infection) originally began in winter 2011-2012 with the feasibility study. Results of this feasibility study have been published (BMC Pulmonary Medicine 2014) and presented in appropriate international meetings (BTS winter meeting 2012). The pilot study began recruiting in October 2014. In total 15 patients have been recruited and 187 patients have been screened. There have been 2 readmissions from the HOME FIRST arm. The North-West REC has approved this study.

2. Remit & Responsibilities

The DMC will provide the independent review of safety data for this study. To carry out this function, the DMC will:

a) Review emerging safety data from the study. Data will be presented to the committee by spreadsheet weekly during the duration of the study. Responses are copied to all by email. This system has proved effective in our other research projects (such as experimental carriage models)
b) Review, evaluate and make recommendations to the Investigators and the Trust as to whether to modify, suspend, terminate or extend the study.
c) Be notified of any SUSAR without delay. DMC will also review SAEs/AEs on a regular basis and in particular review the causality assessments of all adverse events with regards to the patient selection criteria.

3. Membership

The DMC will comprise three members who will include one clinician and one statistician. Also in attendance will be the Chief Investigator and Lead Research Nurse, a member of the Trust's RD & I Department will also be invited to attend. Only the three members of the DMC will be involved in decision making, which may be carried out in closed sessions as needed.

4. Attendance & Frequency of Meetings

Meetings will be held by email circulation. At a minimum there will be one meeting prior to recruitment of 30 patients and one when recruitment is completed or a decision is made that sufficient patient numbers have been screened. Other meetings may take place at the discretion of the members. Other external panel members may also be invited to attend meetings to discuss specific topics.

5. Quorum

All three members of the DMC will constitute a Quorum. A Chair plus one member may be quorate providing the third member confirms by email that he/she agrees to all decisions recorded in the minutes of the meeting.

6. Reporting Arrangements
    a. Prior to each meeting a report will be prepared by the Chief Investigator and Research Nurse/Doctor.
    b. Individual patient data will be available if required.
    c. Minutes shall be formally recorded and submitted to the RLUH RD & I Department.

## Agreement to be a Member of the DMC

I have read the Data Monitoring Committee Charter for the above study, and I am willing to abide by this charter and serve as a member of the DMC. I declare my interests below, and agree to provide details of any future conflicts of interests, should they arise.

**1. Name:** Rebecca Bancroft

**Title:** Consultant Physician RLBUHT

**Signed:** **Date:**

**I declare the following interests**

**2. Name:** Arthur Ricky Kang'ombe

**Title:** Lecturer/Biostatistician, Liverpool School of Tropical Medicine

**Signed:** **Date:**

**I declare the following interests**

**3. Name:** Sasha Shepperd

**Title:** Professor of Health Services Research, Oxford University

**Signed:** **Date:**

**I declare the following interests**

**4. Name:** Stephen Gordon

**Title:** Chief Investigator

**Signed:** **Date:**

**I declare the following interests**