**SHORT-COURSE ANTIMICROBIALS FOR PAEDIATRIC PNEUMONIA**

**SHORT-COURSE ANTIMICROBIALS FOR THE TREATMENT OF PAEDIATRIC COMMUNITY-ACQUIRED PNEUMONIA**

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A Thesis Submitted to the School of Graduate Studies in Partial Fulfilment of the Requirements for the Degree Master of Science

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# ABSTRACT

Paediatric community-acquired pneumonia (CAP) is common in North America. It is often treated with beta-lactam antimicrobials targeting *S. pneumoniae*, the most important cause of CAP in young children. Current guidelines recommend 10 days of therapy for paediatric CAP, regardless of severity; in contrast, mild CAP in adults is routinely treated with only 5 days of antimicrobials. There have been no definitive studies of 5-day vs. 10-day therapy for CAP in children.

The objective of this thesis was to conduct a pilot RCT comparing 5 to 10 days of amoxicillin for the treatment of mild paediatric CAP and then design the multicentre follow-up trial.

Children aged 6 months - 10 years with no significant past medical history presenting to the McMaster Children's Hospital emergency department with mild CAP were eligible for enrollment. All participants were randomized to either 10 days high-dose amoxicillin (90 mg/kg/day divided bid) or 5 days of high-dose amoxicillin + 5 days placebo. The primary outcome was clinical cure at day 14-18 post-enrollment.

In total, 61 participants were recruited. The median participant age was 2.64 y. Only 60% of chest radiographs were reported by the radiologist as showing evidence of pneumonia. There were six treatment failures; one participant failed to defervesce on day 4, one participant had recurrent fevers leading to re-presentation to the emergency, and the other four participants did not meet clinical cure criteria but were essentially well at the time of follow-up. Study blinding has been maintained.

The majority of previously healthy children with mild CAP who are well enough to be treated as outpatients appear to do well, regardless of duration of antimicrobial treatment. Feasibility and safety of the trial protocol have been demonstrated; the follow-up multicentre trial is slated to begin in mid-2015.

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# PART 1: OUTLINE

The focus of this thesis was the design of a multicentre non-inferiority randomized controlled trial comparing short-course antimicrobial therapy to standard-duration therapy for the treatment of mild community-acquired pneumonia in children. After a review of the literature (Part 2), a pilot trial was designed (Part 4) and conducted using funds from the Hamilton Health Sciences New Investigator Award. The data and experience acquired from the pilot trial were reviewed prior to the design of the main multicentre trial (Part 3). Specific methodologic considerations relevant to the design of the pilot and main trial will be discussed last (Parts 5 and 6).

# PART 2: INTRODUCTION

*Burden of pneumonia in childhood*

Respiratory infection is the leading cause of death for children worldwide ([1](#_ENREF_1),[2](#_ENREF_2)). Up to 5% of preschoolers in North America and Europe develop community-acquired pneumonia (CAP) every year ([3](#_ENREF_3),[4](#_ENREF_4)). Paediatric hospitalization rates for CAP in the Western world are 1-4 per 1000/year, with pneumonia accounting for up to 20% of all paediatric admissions in some settings ([5](#_ENREF_5)). It should be noted that morbidity and mortality from lower respiratory tract infections is substantially higher in native and Northern populations in Canada and the United States ([6](#_ENREF_6)).

*Issues relating to the clinical diagnosis of pneumonia.*

Though physicians commonly diagnose CAP, there are no consensus criteria for its diagnosis. Its most common definition, “inflammation of the parenchyma of the lungs [caused by infection],” ([7](#_ENREF_7)) is not useful in practice, as there is no way for clinicians to objectively evaluate whether inflammation is present in the lung parenchyma of their patient prior to autopsy. Symptoms and signs of respiratory disease are not specific for pneumonia ([8](#_ENREF_8)); for example, tachypnoea and increased work of breathing are common presenting symptoms of bronchiolitis, an infectious syndrome involving primarily the small airways caused by viral pathogens. The absence of fever does not rule out pneumonia ([9](#_ENREF_9),[10](#_ENREF_10)); we note that fever was documented in only 18-26% of children admitted to intensive care units because of respiratory failure due to the emerging pathogen enterovirus-D68 in the summer of 2014 ([11](#_ENREF_11)).

Chest radiography is often assumed to be the ‘gold standard’ for the diagnosis of pneumonia; however, there are no consensus criteria for the interpretation of chest radiographs, though the World Health Organization attempted to establish criteria for pneumonia diagnosis in the context of epidemiologic studies ([12](#_ENREF_12)). A recent study enlisted 3 paediatric radiologists at both Boston Children’s Hospital and the Children’s Hospital of Philadelphia and provided them with a mix of chest radiographs (50 previously read as not having pneumonia, 25 previously read as having an alveolar infiltrate, 25 previously read as having an interstitial infiltrate, and 10 duplicates) taken from patients presenting with potential CAP to the emergency departments of these major children’s hospitals ([13](#_ENREF_13)). Inter-rater reliability was good for alveolar infiltrates (kappa 0.69 95% CI 0.60-0.78) but only slight for interstitial infiltrates (kappa 0.14 95%CI 0.05-0.23), a radiographic finding that is much more commonly found, and stratifying by institution had little effect on these estimates. Intra-rater reliability varied widely between the 6 respondents, with kappa 0.74-1.00 for alveolar infiltrates and kappa 0.21-1.00 for interstitial infiltrates. Please note that these estimates of inter-rater reliability are *between paediatric radiologists;* it has long been known that there are significant differences between the way radiologists and emergency physicians evaluate chest radiographs for pneumonia ([14](#_ENREF_14),[15](#_ENREF_15)). As the decision about whether a particular patient has CAP or not will generally be made by the emergency physician without consulting the radiologist, one might reasonably expect a dramatic decrease in overall inter-rater reliability for most chest radiographs. It should be emphasized that the ramifications of an emergency physician calling a given radiograph ‘negative’ for CAP and having the radiologist subsequently judging it to be ‘positive’ are much more significant than the converse, as the patient’s caregiver would have to be contacted to inform them of the ‘mistake’. Consequently, one could expect that emergency physicians will tend to judge more radiographs as ‘positive’ for CAP than radiologists.

To further complicate the diagnostic process, a recent study involving adults presenting to emergency departments with suspected pulmonary embolism who received both chest radiographs and chest computed tomography (CT) scans demonstrated that the sensitivity of chest radiograph for the detection of ‘opacities’ was only 43.5% compared to the gold-standard CT. Furthermore, specificity of chest radiograph was also poor; the positive predictive value of seeing an ‘opacity’ on chest radiograph was only 26.9% ([16](#_ENREF_16)). The authors did not define ‘opacity’ using strict guidelines – so it is possible that CT-visualized lesions not seen on radiography were trivial in size – but the low PPV of an opacity seen on chest radiography is certainly concerning.

It has recently been appreciated that perhaps ultrasound could be a useful modality for the detection of CAP, especially given that one might decrease the length of time patients spend in the emergency department through integration of bedside ultrasound into diagnostic protocols ([17](#_ENREF_17),[18](#_ENREF_18)). One recent trial in adults hospitalized with pneumonia found a sensitivity of 95% for ultrasound compared to the gold standard, which was the ‘[opinion of] an independent senior expert, based on the examination of the complete medical chart including initial clinical findings, emergency laboratory test, chest x-ray data, and the results of thoracic CT scan if available’; of the 23 participants who had ‘pneumonia’ documented on CT scan, all had a positive ultrasound, while only 12 had a positive chest radiograph ([18](#_ENREF_18)). Sensitivity of chest radiography was found to be only 67% and, unsurprisingly, specificity of ultrasound findings was lower than that of chest radiography (57% vs 76%). A previous trial in children presenting to the emergency department with suspected pneumonia compared bedside ultrasound to chest radiograph evaluation by paediatric radiologists blinded to physical examination and ultrasound findings. Ultrasound was found to have sensitivity of 86% and specificity of 89%; specificity increased to 97% for lung consolidation when positives restricted to sonographic air bronchograms exceeding 1 cm ([17](#_ENREF_17)).

Despite all of these issues, observational studies and clinical trials in upper-income countries often use somewhat similar definitions for ‘community-acquired pneumonia’ using fever, clinical signs of respiratory disease, and chest radiographic criteria, though, as noted above, none of these are sensitive or specific individually ([19-22](#_ENREF_19)). Though radiographic criteria have been proposed by the WHO for epidemiologic studies for the diagnosis of pneumonia, no such clinical criteria exist; consequently, most studies have slightly differing case definitions. Though the single most sensitive and specific test for the diagnosis of pneumonia would probably be thoracic CT scan, this diagnostic test involves too much ionizing radiation to use on a routine basis.

*Issues relating to the microbiologic diagnosis of pneumonia.*

It is even more difficult to make a bacteriologic diagnosis than a clinical one. In adults, Gram stain/culture of sputum can be useful in identifying pathogens that may not be treated adequately with typical empiric antimicrobials, as well as permitting de-escalation of broad-spectrum therapy, though the utility of this diagnostic test is balanced by the difficulties inherent in the collection, transport, processing, and interpretation of these specimens ([23](#_ENREF_23)). Unsurprisingly, it is orders of magnitude more difficult to obtain an adequate sputum specimen from a preschooler than from an adult, essentially rendering this diagnostic test useless in young children. A positive blood culture for a typical pathogen in a child with CAP makes the microbiologic diagnosis, but this occurs so infrequently that current guidelines actively discourage venipuncture in children with mild disease, as harm probably outweighs benefit; an example of typical ‘harm’ would include hospitalization and initiation of intravenous antibiotic therapy prompted by a ‘positive’ blood culture for a contaminant pathogen ([24](#_ENREF_24)).

Urinary pneumococcal antigen testing has been studied extensively in adults and is thought by many clinicians to be helpful in diagnosing CAP in older individuals. Sensitivity of this test was found to be 74.6% in a series of 350 immunocompetent adults with bacteraemic pneumococcal pneumonia ([25](#_ENREF_25)) and a meta-analysis reported an overall sensitivity of 68.5% (95% credibility interval 62.6-74.2%) and specificity of 84.2% (95% credibility interval 77.5-89.3%) compared to a composite of culture tests as reference standard ([26](#_ENREF_26)). Unfortunately, this test was found to have much less utility in children owing to high rates of positivity among controls with no significant respiratory symptoms ([27](#_ENREF_27),[28](#_ENREF_28)). A more recent report showed that there might be utility in performing urinary pneumococcal antigen testing in children suspected of having pneumonia who are first found to have elevated C-reactive protein or procalcitonin, but these results can only be called very preliminary due to the small size of the study ([27](#_ENREF_27)).

Results of different studies examining blood-based polymerase chain reaction (PCR) testing have been mixed, with most investigators finding many cases of culture-positive PCR-negative samples ([27](#_ENREF_27),[29-31](#_ENREF_29)). Culture or PCR of nasopharyngeal swabs (NPS) can readily detect *S. pneumoniae*, but there is little evidence suggesting that these techniques can distinguish between active infection and colonization; the latter is common in young children ([28](#_ENREF_28)). One group of investigators explored the utility of quantitative PCR for the diagnosis of pneumococcal CAP in HIV-positive adults aged > 18 years admitted to hospital in Soweto, South Africa ([32](#_ENREF_32)). They defined CAP as requiring either crackles or bronchial breathing on auscultation in the presence of 2 or more of cough, dyspnoea, pleuritic chest pain, or fever, in combination with ‘any new radiographic infiltrate’; in their population, a pneumococcal load of >8000 copies/mL had a sensitivity of 82% and specificity of 92% for the diagnosis of CAP. However, as for urinary pneumococcal antigen testing, this assay must be investigated in children prior to making any recommendations for its routine use in paediatrics. Additionally, it should be emphasized that pneumococcus-specific diagnostic tests will always give false-negative results for CAP cases caused by other pathogens, such as group A *Streptococcus*; these occur much more rarely than pneumococcus-associated CAP but do occur ([33](#_ENREF_33),[34](#_ENREF_34)).

*Mycoplasma pneumoniae,* an obligatory intracellular (“atypical”) pathogen, is a relatively common cause of CAP in older children ([35](#_ENREF_35)). In contrast, the role of atypical bacteria has never been well defined in young children. Canadian CAP management guidelines written in 1997 explicitly recommended treatment regimens (ie. macrolides) for young school-aged children that were active against these pathogens ([36](#_ENREF_36)). In contrast, newer 2011 Canadian and American guidelines strongly recommend routine usage of antimicrobials that have no activity whatsoever against atypical organisms ([24](#_ENREF_24),[37](#_ENREF_37)), though there have been no recent studies showing a change in the incidence or prevalence of respiratory infection with atypical pathogens in young children. *Mycoplasma* is not considered part of the normal respiratory flora, and so its detection in the nasopharynx via PCR is somewhat suggestive of causation ([35](#_ENREF_35)). It has been asserted that atypical pneumonia can be diagnosed on clinical and radiographic grounds ([23](#_ENREF_23),[24](#_ENREF_24)); however, a recent Cochrane review found no evidence to suggest that clinical diagnosis is reliable ([38](#_ENREF_38)), and *Mycoplasma* pneumonia has been shown to produce different radiographic patterns ([39](#_ENREF_39)). We note that a recent systematic review found that there is “insufficient evidence to support or refute treatment of *Mycoplasma pneumoniae* in [CAP]” ([40](#_ENREF_40)) and a recent Canadian guideline recommended against prescribing children azithromycin, the agent most often used for *Mycoplasma* treatment in adults ([41](#_ENREF_41)).

To complicate things further, it has long been presumed that preschoolers commonly develop viral pneumonia ([24](#_ENREF_24)). Diagnostics for viral respiratory pathogens are excellent and many centres routinely use multiplexed PCR panels that can detect almost all common important respiratory viruses in NPSs with high sensitivity and specificity ([42](#_ENREF_42)). However, it should be emphasized that the detection of a respiratory virus in a NPS does not rule out bacterial co-infection, a phenomenon that appears to be relatively common ([43](#_ENREF_43)). Clinically diagnosed CAP in a preschooler whose NPS is positive for a virus could indicate a primary viral pneumonia or a secondarily-infected bacterial pneumonia. Many clinicians have seen children with positive viral rapid tests who later are found to have positive blood cultures or who later develop features of severe pneumonia consistent with bacterial infection. Given the extreme difficulty in discerning between viral infection and viral and bacterial co-infection, it should not be surprising that radiographic criteria for distinguishing between viral and bacterial pneumonia have never been developed, though many clinicians would presume that a child who had an alveolar infiltrate on chest radiograph would have a bacterial pulmonary infection.

*Ramifications of these diagnostic uncertainties*

To summarize the previous two sections: there are no standardized, published, clinical criteria for the diagnosis of paediatric pneumonia, laboratory testing (such as complete blood counts and C-reactive protein measurement) is often unhelpful for the individual patient, observer interpretation of chest radiographs varies widely, and it is often difficult, if not impossible, to establish a microbiologic diagnosis. Antimicrobial treatment for typical bacteria (eg. *S. pneumoniae*) is quite different than that for atypical pathogens, and there is no specific therapy available for viruses beside influenza; consequently, though the natural history of CAP of *any* aetiology (including pneumococcal) is to spontaneously resolve, the results of a treatment trial may vary depending on which pathogens are infecting the study participants. There are two potential ways of dealing with this issue: create extremely stringent inclusion criteria, in the hope that the majority of participants have typical bacterial disease, or use more permissive inclusion criteria, enroll many participants, and later analyze subgroups based on the distribution of various covariates postulated to be associated with typical bacterial infection. The first strategy is best suited to individuals with severe disease, of whom the vast majority can be presumed to have bacterial infections; the second is the only way of conducting a clinical trial relevant to children without infection significant enough to warrant hospitalization.

*Current recommendations for treatment of paediatric CAP*

In August 2011, comprehensive guidelines for the diagnosis and treatment of paediatric CAP were published independently by the Infectious Disease Society of America (IDSA) ([24](#_ENREF_24)) and by the Canadian Paediatric Society (CPS) ([37](#_ENREF_37)). Neither could make definitive recommendations for the optimal duration of therapy due to a paucity of evidence. The IDSA guideline states “Treatment courses of 10 days have been best studied ([44](#_ENREF_44)), but shorter courses may be just as effective, particularly for more mild disease managed on an outpatient basis.” ([24](#_ENREF_24)) The CPS guideline states (without reference) that courses of 7-10 days are “standard” for mild pneumonia ([37](#_ENREF_37)). In contrast, in adults there is good evidence that 5 days of therapy is as effective as 7-10 days for CAP ([45](#_ENREF_45)), and so 5 days of therapy is generally recommended ([23](#_ENREF_23),[46](#_ENREF_46)). A recent survey of Canadian general paediatricians, emergency physicians, and infectious disease specialists showed that few use short courses of antimicrobials to treat paediatric CAP; 50% of all ED-based physicians using β-lactams treat mild pneumonia with 10 or more days of therapy ([34](#_ENREF_34)).

*The importance of optimizing the duration of antimicrobial therapy for CAP*

Despite the tremendous burden of CAP in children, the optimal duration of antimicrobial use for CAP in children is unknown, as noted in the previous section. Antimicrobial selection and duration should be determined based on clinical evidence, in order to avoid both under- and over-treatment. Infection persistence or recrudescence could result from under-treatment, whereas over-treatment could lead to harms such as increased rates of adverse drug reactions such as anaphylaxis ([47](#_ENREF_47)), elevated levels of antimicrobial-resistant bacteria circulating in the population ([46](#_ENREF_46)), and higher drug costs.

*Experience with short-course antimicrobial therapy – single trials*

Few trials have compared long- (10 day) and short-course (<7 day) therapy for paediatric CAP. Peltola et al. ([48](#_ENREF_48)) randomized hospitalized children with presumed bacterial infections to 4-day or 7-day courses of parenteral beta-lactam antimicrobials and found no difference between the two groups (short course treatment failure in 1/71, long course treatment failure in 0/50, confidence intervals not provided). Unfortunately, the majority of the study cohort was found to have either a viral infection or a syndrome of undetermined aetiology; it is not surprising that participants not suffering from bacterial infections did not have worse outcomes if they received shorter courses of antibacterials. In 1994-95, Harris et al. randomized 456 paediatric patients with CAP at 23 different US centres to either a 5-day course of azithromycin or to a 10-day regimen of either erythromycin or amoxicillin/clavulanate ([49](#_ENREF_49)). The 5-day arm was found to have similar rates of success (5-day 94.6% success, 10-day 96.2% success, confidence intervals and noninferiority margin not provided). However, macrolides are no longer the reference standard due to the increased prevalence of macrolide-resistant pneumococci today ([50-52](#_ENREF_50)) and, as previously noted, the CPS has advocated against the routine use of this agent ([41](#_ENREF_41)). Moreover, because the half-life of azithromycin is 68 hours, a 5-day course of azithromycin is in effect much longer than a 5-day course of most β-lactams (half life ~ 2 hours), so inferences about the potential success rate of short-course β-lactam therapy cannot be made on the basis of this trial. It should be noted that this trial was not designed as a non-inferiority trial; outcomes in the short- and standard-length antibacterial groups were compared and no statistically significant difference was found, so the results of this trial should properly be called ‘indeterminate.’ A recent randomized study in Israel compared 3-, 5-, and 10-day amoxicillin therapy for community-acquired pneumonia with alveolar consolidation in preschool children aged 6 – 59 months ([53](#_ENREF_53)). They found an increased failure rate in the 3-day group but no difference between the 5- and 10-day groups. Note that the investigators had initially estimated requiring a total sample size of over 120 but stopped the study early because they documented 0% failure rates in both 5- and 10-day treatment groups. It should be noted that the noninferiority margin was 10%, a sizable difference between standard and experimental treatments; many clinicians might not think that a short-course therapy for CAP with a potential failure rate of 10% was in fact ‘equivalent’ to standard therapy with a 0% failure rate. In addition, the results of this single-centre study are not necessarily generalizable to Canadian children today because the population was unvaccinated against *S. pneumoniae*, so the strains causing disease were very likely different, and the majority of participants came from a specific ethnocultural group, the Bedouin, living in the Middle East. This study also provided no information about when the participants were recruited, so it is very possible that many of the strains causing disease in this study were more susceptible to amoxicillin than those circulating today, overestimating the effects of short-course therapy. The overestimation of treatment effects in trials stopped early for benefit has also been well documented ([54](#_ENREF_54)).

Table 1: Summary of randomized trials of short-course vs. standard-course antibacterials for paediatric bacterial infections in upper-income countries

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Publication** | **Infection type** | **Experimental arm** | **Reference arm** | **Outcome** | **Comparison** |
| Peltola et al. ([48](#_ENREF_48)) | inpatients with pneumonia, sepsis, other bacterial infections with increased CRP | 4 days antibiotics | 7 days antibiotics | clinical recovery by end of treatment | not calculated |
| Harris et al. ([49](#_ENREF_49)) | CAP | 5 days azithromycin  | 10 days amoxicillin/ clavulanate (younger) or erythromycin (older) | clinical cure at day 15-19 post-enrolment | outcomes between groups not significant (chi-square p=0.74) |
| Greenberg et al. ([53](#_ENREF_53)) | CAP | 5 days amoxicillin | 10 days amoxicillin | clinical cure by 30 days | ARR = 0% |

*Systematic reviews of short-course antimicrobial therapy for paediatric CAP*

A Cochrane review ([55](#_ENREF_55)) summarized three randomized trials of reasonable quality comparing extremely short-course (3 days) vs short course (5 days) of antibiotic therapy for paediatric CAP in children aged 2-59 months in India ([56](#_ENREF_56)), Pakistan ([57](#_ENREF_57)), and Indonesia/Bangladesh ([58](#_ENREF_58)). No differences were found in clinical cure rate (RR 0.99; 95% CI 0.97-1.01), treatment failure (RR 1.07; 95% CI 0.92-1.25), or relapse rate (RR 1.09; 95% CI 0.83-1.42). Unfortunately, a meta-analysis showing that 3 days of therapy is non-inferior to 5 days of therapy for CAP is not relevant to Canadian physicians until it is shown that 5 days is non-inferior to 7-10 days, the current standard; it should also be emphasized that patient populations and algorithms for CAP diagnosis are very different in resource-limited settings ([59](#_ENREF_59)).

*Antimicrobial stewardship*

Optimizing antimicrobial prescribing, otherwise known as antimicrobial stewardship, has been noted to be the main strategy to deal with escalating antimicrobial resistance and has been called “a fiduciary responsibility for all healthcare institutions across the continuum of care.”([60](#_ENREF_60)) The Canadian Paediatric Society has said in a recent statement that “the implementation of antimicrobial stewardship initiatives…is regarded as a key step in reducing *Clostridium difficile* risk [in children].”([61](#_ENREF_61)) Many evidence-based guidelines published by Canadian and American authorities in the past ten years have sought to minimize the duration of systemic antimicrobials prescribed to both children and adults for the treatment of common infections such as acute otitis media ([62](#_ENREF_62)), acute rhinosinusitis ([63](#_ENREF_63)), acute otitis externa ([64](#_ENREF_64)), urinary tract infections ([65](#_ENREF_65)), and intra-abdominal infections ([66](#_ENREF_66)). Shortening an antimicrobial course by 2-5 days may not seem like much of a difference on an individual patient basis, but when these few days are multiplied by tens of thousands of cases per year, one can begin to appreciate the potential substantial benefits to society in terms of minimizing both population drug resistance and societal health care costs.

# PART 3: THE MAIN PROJECT

*1. Rationale*

Despite the tremendous burden of CAP in children, the optimal duration of antimicrobial use for CAP in children is unknown. The use of 5-day treatment regimens for CAP in adults is now commonplace ([23](#_ENREF_23),[67](#_ENREF_67)), but evidence to support similar practices in children is almost nonexistent; this has been acknowledged as a key knowledge gap in paediatric infectious diseases ([24](#_ENREF_24)). This trial will address this knowledge gap and provide key information to all Ontario physicians who treat children with CAP; optimization of management of paediatric CAP will benefit the children affected, their families, and all Canadians. This trial, as the first adequately-powered study investigating the utility of short-course β-lactam therapy for paediatric CAP in the developed world, would have a substantial and immediate impact on paediatric medicine.

*2. Research question*

In previously healthy children diagnosed with community-acquired pneumonia in the emergency department who are well enough to be treated as outpatients, does five days of oral high-dose amoxicillin lead to non-inferior rates of clinical cure at 14-18 days post-enrolment compared with the current standard, 10 days of oral high-dose amoxicillin?

*3. Objectives*

Our primary objective is to determine whether a short (5-day) course of oral high-dose amoxicillin, compared to a standard 10-day course of high-dose oral amoxicillin, will lead to non-inferior rates of early clinical cure in previously healthy children with mild community-acquired pneumonia.

Our secondary objectives are to evaluate the following epidemiological features in children diagnosed with mild CAP in the current era of universal vaccination with the 13-valent pneumococcal vaccine (PCV13) and include:

1. To establish the distribution of saliva C-reactive protein (CRP) values in a cohort of children meeting study criteria for CAP.
2. To determine what proportion of study participants have *Streptococcus pneumoniae* high-level colonization or *Mycoplasma pneumoniae* detected in nasopharyngeal swab (NPS) specimens.
3. To determine what proportion of study participants with alveolar consolidation documented on chest radiograph have NPS specimens positive for at least one virus.
4. To investigate whether the results of (2) and (3) differ substantially when stratified by age group (6-59 months vs. 5-10 years of age).
5. To explore whether any of the above factors appear to be more common in children who do not achieve early clinical cure.

*4. Methodology*

The current proposal is for a multicentre, randomized, controlled, double-blind, trial. Previously well children aged 6 months - 10 years presenting to the emergency departments (EDs) of McMaster Children’s Hospital (MCH) and the Children’s Hospital of Eastern Ontario (CHEO) with presumed CAP will be randomized to either a 10-day course of high-dose amoxicillin or a 5-day course of amoxicillin plus 5 days placebo.

*4.1 Study population*

*4.1.1 Inclusion criteria*

Children aged 6 months to 10 years presenting with CAP will be eligible. This age range was selected for the following reasons: the current incidence of pneumonia in North America is highest in preschool-aged children ([19](#_ENREF_19)), infants and young children are at higher risk for disease progression and hospitalization ([24](#_ENREF_24)), but children under the age of five are also more likely to have purely viral infection ([24](#_ENREF_24)). Other trials have enrolled only children under the age of five ([53](#_ENREF_53)); however, as many more children aged 5-10 years will have pneumococcal pneumonia, the exclusion of this population – despite their decreased risk of progression to severe disease – would be an unnecessary barrier to effective recruitment.

CAP will be defined as present if all four of the following numeric criteria are met:

1. fever (>37.5 C axillary, > 37.7 C oral, or >38 C rectal)([68](#_ENREF_68)) in the ED or recorded at home in the 48h prior to presentation;
2. **any one of**:
	1. tachypnoea on exam (as per age-specific norms ([69](#_ENREF_69)));
	2. cough on exam or by history;
	3. increased work of breathing on exam; or
	4. auscultatory findings consistent with pneumonia;
3. findings on chest radiograph consistent with bacterial CAP as judged by the ED physician;
4. the attending ED physician diagnoses the child with primary CAP (a patient with “asthma exacerbation with possible pneumonia” would not be eligible).

This definition is almost identical to the ‘reference standard’ in a recent study designed to investigate the accuracy of ICD-9-CM billing codes ([19](#_ENREF_19)) and very similar to those used in other clinical trials ([20-22](#_ENREF_20)). Many other studies of pneumonia simply use clinician diagnosis as a definition ([70-72](#_ENREF_70)); as detailed earlier, this approach is fraught with inaccuracies. The inclusion of fever as a necessary criterion will diminish the probability of recruiting participants with pertussis (which is much less likely to be associated with fever, ([6](#_ENREF_6))) or noninfectious conditions, neither of which would be expected to respond to amoxicillin. The necessity for participants to display a respiratory symptom or sign will diminish the probability of recruiting those with infections of other organ systems who are erroneously diagnosed with pneumonia. The requirement for participants to have a chest radiograph displaying a pneumonic infiltrate will likely increase the probability that they have an infection caused by a bacterial pathogen. Finally – since the aim of this pragmatic trial is to answer a real-world question asked by emergency physicians – it is important that all study participants are actually diagnosed with CAP.

To be included, participants must be well enough to be treated as outpatients (adequate volume status, able to tolerate oral medication, oxygen saturation >= 93%, no evidence of impending respiratory failure); obviously, if a child is ill enough to be admitted to hospital, it would be unwise to attempt short-course therapy. Additionally eligible participants must have no evidence of empyaema or necrotizing pneumonia, as routine management of these conditions would require parenteral antibacterials (and admission to hospital).

*4.1.2 Exclusion criteria*

Children will be excluded if they have any of the following: cystic fibrosis, anatomic lung disease, bronchiectasis, congenital heart disease, history of repeated aspiration or velopharyngeal incompetence or presence of tracheostomy, malignancy, conditions requiring treatment with immune suppressants (including organ or haematopoietic stem cell transplant, rheumatologic conditions, and inflammatory bowel disease, among others), primary immunodeficiency, advanced HIV infection; many clinicians would not treat any child with the aforementioned conditions with short-course antimicrobial therapy and, in many cases, would use more broad-spectrum antimicrobials due to key differences in potential infecting pathogens. Similarly, any child with prolonged admissions (>48 h) to hospital within the past 2 months, pneumonia previously diagnosed within the past month, or lung abscess diagnosed within the past six months would likely require a prolonged course of antimicrobials. Any participant treated with > 24 hours of beta-lactam antibiotics prior to presentation, that finished a course of amoxicillin < 72h prior to presenting to the ED, or received any intravenous cephalosporins or macrolide therapy in the ED would not be a suitable candidate for the study; receiving these medications in addition to the study antimicrobials could very well mask a ‘true’ difference in efficacy between long- and short-course therapy. Obviously, any child with a suspected allergy to penicillin or food colouring could not be ethically included in the study. Children who have previously been study participants will not be eligible to participate repeatedly, as their likelihood of treatment success or failure would likely be influenced by their success or failure at the time of their first enrolment.

*4.2 What are the planned trial interventions?*

*4.2.1 Screening, enrolment, and intervention assignment.*

Education will be provided to ED staff (MDs, RNs, trainees) to inform them of the rationale and objectives of the study. These ED staff will then notify the research assistants (RAs) when a child is diagnosed with CAP; at CHEO, an organized network of volunteers will also participate in ED surveillance. Gift cards ($5) will be given to ED healthcare providers that notify study staff of potential study participants in order to incentivize notification; this strategy has worked well in the pilot at McMaster. Reviews and meta-analyses of strategies to improve retention in trials have consistently identified monetary incentives as being associated with higher rates of follow-up ([73-75](#_ENREF_73)); smaller incentives provided to all participants have been found to be generally more effective than larger incentives only provided to a few participants via a lottery system ([73](#_ENREF_73)). (Many of these studies were done to determine whether financial incentives increased the rate at which study participants returned survey questionnaires, but many of the conclusions are likely generalizable to our context.) The amount of money that generates the maximum incremental benefit per dollar will probably depend on the study population; however, somewhat counter-intuitively, multiple studies have not shown a significant dose-response relationship with financial incentives, with smaller incentives often leading to a similar response rate compared to larger incentives ([73](#_ENREF_73)).

After quickly obtaining some screening information over the phone, the RAs will then proceed to the ED to recruit the participant. All participants will be given an initial 5 days of amoxicillin. For potential participants who present at a time when an RA is not available, the attending ED physician will prescribe amoxicillin at the study dose and obtain consent for subsequent RA contact and potential enrolment at the participant’s home within 24 hours after ED discharge.

*4.2.2 Experimental (short course antimicrobials).*

Those randomized to the intervention will receive amoxicillin 90 mg/kg/day divided twice daily for 5 days (‘medication series A’) followed by placebo twice daily for 5 days (‘medication series B’). The placebo will be identical in appearance to the amoxicillin given as ‘medication series B’ to the control group and will be packaged identically.

It was decided that five days of antibacterials was the most appropriate duration to test in the experimental arm, for the following reasons:

1. 5 days of antibacterials has been shown to be non-inferior to 10 days for the treatment of CAP in adults ([45](#_ENREF_45))
2. 5 days of antibacterials has been shown to be non-inferior to 10 days for the treatment of bacterial meningitis in children, a *much* more severe infectious syndrome than mild CAP ([76](#_ENREF_76))
3. 3 days of antibacterials are routinely used for CAP treatment in lower-resourced settings. However, if a trial found that 3 days of treatment was inferior to the reference standard, this would not obviate the possibility that 5 days might be as effective as 10 days; it seems more practical (and ethical!) to us to conduct a trial comparing 5 days to 10 days *first*, and then address the issue of whether 3 days would be sufficient. Additionally, a similar trial found higher rates of treatment failure from 3-day courses of antibacterials than with 10 days of therapy ([53](#_ENREF_53)).
4. Many clinicians already use 7 days of therapy for mild CAP; we note that the CPS guideline states that 7-10 days of treatment is ‘standard’, despite a lack of evidence for this recommendation ([37](#_ENREF_37)). It would therefore be a suboptimal use of resources to formally demonstrate the non-inferiority of 7 days compared to 10 days if this will not lead to any significant change in practice, especially if we suspect that 5 days of therapy will also be non-inferior.

*4.2.3 Control (standard course).*

Children presenting with study-defined CAP randomized to the control group will receive standard therapy, ie. amoxicillin 90 mg/kg/day divided twice daily for 5 days (‘medication series A’) followed by a second (altered in colour and consistency) course of amoxicillin 90 mg/kg/day divided twice daily for 5 days (‘medication series B’). Both arms require a distinct ‘medication series B’ to avoid unblinding since pharmacy is not able to precisely match the taste of liquid placebo to the amoxicillin of ‘medication series A.’

*4.2.4. Lab testing at enrollment.*

For study participants who have blood work drawn as part of routine care (as per the attending ED physician), a complete blood count and serum C-reactive protein (CRP) will be sent. Though these laboratory investigations are not sensitive or specific enough to rule CAP in or out in a given participant, their levels have been found to be proportional to the probability of having a bacterial infection, enabling stratification of participants in sensitivity analyses ([77](#_ENREF_77)). For all other patients, a saliva CRP will be sent. This particular test has not been studied in the context of acute paediatric lower respiratory tract infection; consequently, at this stage, one cannot predict whether higher salivary CRP levels will be seen in children with bacterial pneumonia. However, we have received funding and are about to begin a prospective cohort study enrolling hospitalized children with viral bronchiolitis, bacterial complicated pneumonia, and community-acquired pneumonia (possibly bacterial) in whom salivary CRP will be assayed. It will therefore be known whether salivary CRP is truly higher in children with bacterial pneumonia prior to the analysis of this proposed multicentre randomized trial.

All patients will have nasopharyngeal swabs collected and tested for respiratory viral pathogens. The multiplex respiratory virus polymerase chain reaction (PCR) testing panel in clinical use at McMaster Children’s Hospital detects parainfluenza 1/2/3, influenza A/B, RSV A/B, adenovirus, human metapneumovirus, rhinovirus, and enterovirus. Should the epidemiology of viral infections in Ontario change significantly during the study period we will also have access to the Luminex xTag RVP testing panel, which also detects coronaviruses. All NPS specimens will also have incidence density of *Streptococcus pneumoniae* (target is *lytA*) measured using a quantitative PCR assay; “high-level” colonization will be defined as > 10 000 genome equivalents/mL specimen. To detect ‘atypical’ organisms, a loop-mediated isothermal amplification (LAMP) assay will be used to simultaneously detect *Mycoplasma pneumoniae, Chlamydophila pneumoniae,* and *Legionella pneumophila*. It will be critically important to document what respiratory pathogens are present in each of the study participants both to expand our knowledge of the epidemiology of mild paediatric CAP in the current era as well as to permit sensitivity analyses; it is common to have viral-bacterial pulmonary coinfection, but logic would dictate that the probability of bacterial infection is higher in a child with no viral/atypical pathogens detected than in a child with a positive NPS for a viral pathogen.

*4.3 Randomization and group allocation.*

Dr. Thabane’s Biostatistics Unit at St Joseph’s Healthcare Hamilton will organize participant randomization using a centralized computer system accessible by phone 24 hours per day, 7 days per week. A randomization list stratified by centre will be generated such that participants can be assigned at random to one of the two study groups in a 1:1 ratio. The randomization will be blocked using random block sizes of 2, 4, and 6. The blocks will be of random sizes to provide another layer of protection to the blinding process, so that neither the RAs nor the investigators know into which groups the participants are randomized.

*4.4 Proposed methods for protecting against other sources of bias*

To reduce the possibility of selection bias, all children who are diagnosed with CAP in the EDs of MCH and CHEO will be screened and approached to participate. It will be substantially harder to recruit potential participants who present in the middle of the night; this may introduce bias if those children are different than those who present during the day and early evening. We will attempt to minimize this threat to validity by contacting potential participants who present during the night at home the next day. Randomization and allocation will proceed as described above. As it is impossible to precisely match the taste and appearance of the placebo to the amoxicillin suspension, we have planned a two-series medication system (‘series A’ and ‘series B’) to prevent unblinding by ensuring that all participants change medications after 5 days.

*4.5 Participant follow-up*

*4.5.1 Frequency and duration of follow-up.*

Outcome data will be collected both by the participants’ caregivers in a symptom diary (previously pilot-tested) and by the RA. Diary forms will inquire to symptoms and signs relevant to the secondary outcomes (see 4.6.2, ‘Secondary outcomes’, below); caregivers will be asked to fill out a diary form daily for the 10 days post-enrolment. The RA will contact the participants three times (day 3-5, day 7-10, and one month after enrollment) to verify clinical stability, to reinforce adherence to the diary, and to troubleshoot problems. The first telephone contact is critical to ensure that no participants with persistent fever might possibly be randomized to short-course therapy; parents will also be reminded to contact the RA should they develop fever after day 4 and any participant with persistent/recrudescent illness will be invited to be assessed by a co-investigator. As noted above, any study participant with persistent fever >72h after beginning the study medication will be re-assessed as necessary and will complete at least 10 days of (open-label) amoxicillin. The phone call at 7-10 days will be used to verify the absence of recrudescent illness and to collect data in the event that the caregiver does not fully complete the symptom diary. Participants will return to the hospital for a visit between day 14-18 to deliver the symptom diaries, all medication containers, and to permit assessment by a physician or nurse either in the ED or a paediatric outpatient clinic.

*4.6 Proposed outcome measures.*

*4.6.1 Primary outcome - early clinical cure*

The primary outcome, early clinical cure, will be defined by meeting all of the following criteria: 1) significant improvement in dyspnoea and increased work of breathing, and no recorded tachypnoea, at the day 14-18 follow-up visit; 2) no more than 1 fever spike (as noted in the definition of CAP) as a result of bacterial respiratory illness from day 4 up to and including the day 14-18 follow-up visit; and 3) lack of a requirement for additional antibacterials or admission to hospital because of persistent/progressive lower respiratory illness during the 2 weeks after enrollment. This definition of clinical cure is similar to that used in other studies of 5-day CAP therapy in children ([49](#_ENREF_49)) and adults ([45](#_ENREF_45)).

Our definition was created using explicit criteria to ensure transparency and maximize the generalizability of the results. However, to optimize the appropriateness of the definition, the criteria are somewhat complex; this is to ensure that ‘failure’ in the trial would be associated with a clinical scenario that would merit a change in overall management, even if that change was as little as a requirement for additional follow-up by the treating clinician.

The first criterion of the definition states ‘significant improvement’ in respiratory symptoms; this will be assumed to be present if the participant’s caregiver opines that the child has no functional limitation resulting from any residual dyspnoea/increased work of breathing. This was written in this way because the first iteration of this criterion in the pilot study stated ‘complete resolution’; there was one child who had very mild increased work of breathing at the follow-up visit and as such was judged to have ‘failed therapy’, though no further antimicrobials or follow-up was deemed necessary by the treating clinician. The second criterion notes that more than a single spike of fever is required for ‘failure’ to avoid erroneous conclusions resulting from an errant thermometer reading; two participants in the pilot ‘failed’ therapy because of a single spike of fever not leading to any management change. Fevers of unknown aetiology will be presumed to be associated with bacterial respiratory illness, but participants with fevers due to other discernible causes, whether viral (new respiratory illness documented by a NPS positive for a virus not present at the time of initial enrolment, clinical croup, stomatitis/herpangina, hand-foot-mouth disease, gastroenteritis with positive stool results, conjunctivitis, meningoencephalitis, viral hip synovitis, peri-or myocarditis, hepatitis) or bacterial (cellulitis and other soft tissue infections, septic arthritis/osteomyelitis, meningitis, urinary tract infection with positive urinalysis, or cholecystitis) would be considered to have met clinical cure criteria. Clearly, admission to hospital – even if antimicrobial treatment does not need to be changed – is not conducive to short-course therapy and merits a decision of treatment ‘failure.’

For the measurement of the primary outcome, a physician or nurse, blinded to treatment allocation, will assess temperature, respiratory rate, and evident increased work of breathing in person using standardized protocols; these physical examination findings are the most important when assessing response to therapy. Lack of fever at home will be verified through assessment of the symptom diaries. Medical visits for persistent respiratory illness will be assessed by directly asking the participant’s caregiver; though caregiver report is not an entirely reliable modality, we believe that the sensitivity and specificity of the question ‘Did your child see another health professional because of a concern about respiratory illness within the past ten days?’ should be adequate.

*4.6.2 Secondary outcomes*

Secondary outcomes will include:the number of days the participant is absent from school; the total number of caregiver-days that their work is disrupted to care for the child; the number of days of mild drug adverse reactions; the incidence of severe drug adverse reactions (including anaphylaxis); participant adherence to the study medications; and recurrence of respiratory illness in the month after enrollment that leads to an ED visit or another antimicrobial course.We feel that these outcomes are important to children and their caregivers, especially for mild illness with an excellent prognosis. These will all be participant- or caregiver-report measures, and will be measured through participant documentation in the diaries; there will also be secondary verification by the research assistant at telephone contact on days 3-5 and 7-10 after enrollment. The symptom diary will include the following: temperature, dyspnoea (older participants), increased work of breathing, school attendance, caregiver absenteeism, days of mild diarrhoea, abdominal discomfort, vaginitis, rash) and severe (anaphylaxis) drug adverse reactions, and the number of missed medication doses. The caregivers will be instructed how to take their child’s temperature and assess increased work of breathing.

Measuring adherence is a trial setting is not a simple matter. There are direct and indirect methods of assessing adherence; of these, direct methods are much more accurate. These include directly observed therapy or measurement of drug levels in blood, both of which are impractical for a study such as this, and would likely cause substantial inconvenience and/or pain to the study participants. Indirect methods include patient (or caregiver) (self-)report; pill counts; patient diaries; electronic medication monitors; rates of prescription refills; assessment of the patient’s clinical response; and measurement of physiologic markers ([78](#_ENREF_78)). Of these seven, we plan to use the first three, and the last four are not appropriate for the study (monitors are expensive, no refills are needed, and, in this case, neither patient assessment nor measurement of physiologic markers will inform adherence). Some investigators state that patient self-report is “simple, inexpensive, and the most useful method in the clinical setting,” though they note that the results are “easily distorted by the patient”; these same authors note that pill counts are “objective, quantifiable, and easy to perform,” again noting that participants can dump medication to conceal nonadherence ([78](#_ENREF_78)). In the proposed trial, adherence with medications will be assessed from the diaries but will also be measured by checking the (returned) medication containers; any left-over medication will be weighed.

*4.7 Sample size*

We estimate the baseline failure rate of standard therapy to be ~5%; this estimate is consistent with previous studies in children ([49](#_ENREF_49)), is less than that found in similar adult studies ([45](#_ENREF_45)), and was the approximate rate seen in the pilot study. We will use a noninferiority margin of an additional 7.5%, for a total acceptable failure rate in the experimental arm of 12.5%; a 2008 survey of infectious disease physicians found the median acceptable failure rate in treatment of community-acquired pneumonia to be 13.5% ([79](#_ENREF_79)). Setting α at 5%, with 80% power, 135 participants in each arm will be required for this trial(PASS software package, NCSS LLC, Kayesville, UT); as we will have accrued ~ 60 subjects in the pilot to be ‘rolled-over’, an additional 210 participants will be required*.*

*4.8 Anticipated recruitment rate*

The pilot has had very low rates of loss to follow-up (2/61, 3%) presumably due to the acute nature of the problem and the fact that many caregivers appreciate the clinical service provided. We anticipate enrolling ~60 participants per year at McMaster Children’s Hospital, based on the pilot results. As CHEO has many more children presenting to their ED, we predict conservatively that we will be able to enroll at least 75 per year at that site. All estimates below are based on data from CHEO ED census Mar 2011 – Apr 2013.

Children (aged 6 mos. – 10 y) with CAP to CHEO ED: 1442/year

As above, restricted to those arriving 10 am – 10 pm: 986/year

Projected enrolment with MCH ineligibility/success rates: 124/year

Detailed review of 50 randomly selected charts of children aged 6 months – 10 years diagnosed with CAP at the CHEO ED in 2013 demonstrated that 22 (44%) met all inclusion and exclusion criteria. Assuming McMaster rates of missing/refusal of approach/refusal of consent, estimated enrolment would be 986\*0.44\*(55/(55+56+38+9)) = 151 participants/year.

Overall, it is very likely that we will be able to recruit 50-75 participants/year at McMaster Children’s and 75-100 participants/year at the Children’s Hospital of Eastern Ontario.

*4.9 Data analysis.*

We will adopt CONSORT criteria in reporting the trial. The principal analysis will be per-protocol, as is recommended for noninferiority trials ([80-82](#_ENREF_80)). The principal analysis is not intention-to-treat (ITT) simply because the effect of ITT analysis is to reduce the difference seen between treatment groups; in a superiority trial, this functions to buttress a conclusion of superiority, but in a non-inferiority trial, ITT analysis could lead to a false conclusion of non-inferiority by masking a true difference between treatment arms.

 The baseline characteristics will be analyzed using descriptive statistics reported as mean (standard deviation) or median (first quartile, third quartile) for continuous variables depending on the distribution and count (percent) for categorical variables. As the primary outcome is binary, the chi-square test will be used; secondary outcomes will be analysed using chi-square or t-test depending on the distribution of the outcome variable. As this is a non-inferiority trial, the crucial statistical comparison will be between the 95%CI of the difference between the failure rate of the experimental arm and the standard therapy arm; should the upper bound of this difference be smaller than 7.5%, a conclusion of non-inferiority will be reached. Descriptive analyses will be used to compare rates of viral and atypical co-infections in the entire study population and between groups, stratified by age. We will use the t-test or chi-squared test to analyze secondary outcomes as appropriate (former for continuous variables, latter for dichotomous variables). These analyses will be exploratory. The following sensitivity analyses are planned:1)intention-to-treat analysis; 2) strict per-protocol analysis including only those participants whose radiographs were reported by a radiologist to have alveolar infiltrates; 3) per-protocol analysis stratified by whether the saliva CRP was greater than the 75%ile; and 4) per-protocol analysis stratified by whether a virus, an atypical pathogen, or high-level *S. pneumoniae* colonization was found in the NPS. If evidence is found of effect modification or confounding related to the above parameters additional analyses will be undertaken. The results of all analyses will be reported as estimate of effect, corresponding 95% confidence interval and associated p-values. All p-values will be reported to three decimal places with those less than 0.001 reported as p<0.001. The criterion for statistical significance will be set at alpha = 0.05.

*4.10 Anticipated results*

Given our clinical experience, as well as the results of the small Israeli trial ([53](#_ENREF_53)), we expect to find that 5 days of amoxicillin are non-inferior to 10 days for the treatment of mild CAP; put otherwise, a short course will result in a clinically acceptable cure rate while minimizing cost and adverse events. We also expect to find viral infections more often in preschoolers, that the prevalence of *Mycoplasma* infection is correlated with age, and that coinfections are not associated with higher failure rates.

*4.11 Potential problems and alternative strategies*

Our inclusion criteria are not specific for bacterial infection, and the inclusion of patients with purely viral disease might mask a true difference between short- and long-course therapy for the treatment of bacterial CAP. The secondary analyses will be designed to target specifically those with more severe bacterial infections. However, this is a pragmatic RCT, and as such is designed to answer a real-world question that clinicians must ask every time they are confronted with a child with pneumonia; consequently, the results of the trial will be useful for ED-based physicians, who are never able to distinguish reliably between viral and bacterial pneumonia. In order to optimize adherence to study medications, we have chosen to dose amoxicillin twice daily instead of three times daily; the latter is better from a pharmacodynamic standpoint but the former has been judged to be acceptable ([24](#_ENREF_24)). We will measure adherence by collecting used medication bottles and determining how many doses were taken; this method is not foolproof but is acceptable ([78](#_ENREF_78)) and appropriate for this trial.

*5. Trial management*

*5.1 Data Safety and Monitoring Board (DSMB).*

This committee, comprised of two clinical experts and a biostatistician, guided by a charter to be created, will be responsible for safety oversight of the study, including monitoring of adverse reactions. The DSMB will be responsible for making recommendations on safety issues, premature trial termination, and unblinding of study groups. The DSMB, which will be blinded to study group, will be asked to review safety data on an biannual basis for each arm of the study. If safety concerns arise, more frequent meetings will be initiated. The DSMB will receive immediate notification and reports of serious adverse reactions.There are no plans for an interim analysis as the estimated risk of harm associated with this trial is low.

*5.2 Risks to the safety of trial participants*

Both arms of the trial will be given amoxicillin, the first-line agent for the treatment of paediatric CAP. The main theoretical risk to those in the short-course group will be relapse due to potential under-treatment, which will be minimized by maintaining close contact with all participants. As discussed above, although the CPS guideline states (without reference) that 7-10 days of antibiotic therapy for paediatric CAP is ‘standard’ for uncomplicated pneumonia ([37](#_ENREF_37)), the IDSA guidelines explicitly say that it is likely that shorter courses will be just as effective and that further studies are needed ([24](#_ENREF_24)). These studies have already been done in adults, in whom the standard is now five days of therapy for uncomplicated pneumonia ([45](#_ENREF_45)); additionally, a randomized controlled trial published in the Lancet demonstrated non-inferiority for five days versus ten days of antimicrobials for bacterial meningitis, an infection that is far more severe and difficult to treat than uncomplicated pneumonia ([76](#_ENREF_76)). It is for these reasons that it is critical to conduct a study such as this, in an effort to optimize the way we care for children. It should be noted that close monitoring will mitigate any of the possible risks of short-course therapy. For example, the research assistant, at the time of the first contact 3-5 days after enrollment, will ensure that the participant has defervesced; should this not be the case, blinding will be broken and the participant will be given a 10-day course of amoxicillin. We will also ensure that caregivers have detailed instructions outlining which medical professionals at McMaster Children’s Hospital to contact in the event of a clinical deterioration during the study period at all hours to facilitate re-evaluation of the participant and appropriate medical management. Overall, given that study participants will likely have much closer follow-up than non-participants, that medications will be provided free of charge, and that they will be guaranteed to receive appropriate antibiotic therapy, study participants stand to directly benefit from participating in the study. We note as well that a similar recently published study, though under-powered and terminated early for benefit, showed no difference in failure rate between 5- and 10-day therapy ([53](#_ENREF_53)).

*6. Knowledge translation plan*

The nature of the proposed trial is strongly toward the pragmatic end of the clinical trial spectrum ([83](#_ENREF_83)); consequently, the results of the trial will be positioned for rapid integration into clinical practice by Canadian physicians. To that end, both integrated and end-of-grant KT methods will be employed to facilitate communication of study results to healthcare practitioners – the main knowledge users for this study. The principal KT goal of the project will be, subsequent to the determination of whether short-course antimicrobial therapy is noninferior to the standard of care, to facilitate integration of trial results into current Canadian CAP guidelines and disseminate the information to the healthcare community. To do this, research team members will collaborate with established networks of clinicians experienced in the dissemination of clinical guidelines to healthcare practitioners, i.e. the Canadian Paediatric Society, Association of Medical Microbiology and Infectious Disease Canada, Infectious Disease Society of America, Canadian Association of Emergency Physicians, and Pediatric Emergency Research Canada (PERC). Given that PERC, a highly successful research network involving 15 children’s hospitals, represents a key group of knowledge users for this study, the executive was invited to the table in the design phase to ensure that the study objectives were relevant to Canadian emergency physicians and the study protocol was structured in such a way to optimize both internal and external validity. PERC has since unanimously endorsed the proposed study as one deserving of its support; furthermore, the study protocol was presented to the wider PERC community for more feedback at its annual meeting in 2014. The above-noted collaborations will be stimulated though presentation at major Canadian and American meetings (Pediatric Academic Societies, Canadian Paediatric Society, etc.); healthcare decision makers will be provided a one page synopsis of the results and invited to meet with study team members to discuss the implications. The end-of-grant KT strategy will also focus on publication of results in a peer-reviewed open-source journal (preferably a general paediatric journal because of the broad audience), oral and poster presentation at local and national meetings, and leveraging dissemination through the diverse professional networks of the research team members (the applicant and co-investigators are trained in disciplines including paediatric infectious disease, adult infectious disease, medical microbiology, clinical epidemiology, and paediatric emergency). In all cases, messages will be tailored to ensure relevance to the target audience.

# PART 4 – THE COMPLETED PILOT TRIAL

The design of the pilot trial was very similar to that of the main follow-up study described in detail in Part 2. This section will outline aspects specific to the pilot and will describe problems encountered in the conduct of the pilot trial, with specific reference to design features that were modified for the main follow-up study; design features of the pilot that were not changed for the multicentre trial will not be listed, to avoid redundancy. Preliminary clinical and microbiologic results will be presented.

*Objective*

The main objective of the pilot trial was to investigate feasibility of the follow-up multicentre trial. The feasibility criteria of the pilot were:

1. to enrol at least 70 participants during the 9-month study period;
2. to complete the enrolment process within 90 minutes for >90% of participants;
3. to ensure appropriate blood and respiratory specimens get sent in >90% of participants;
4. to ensure >90% of participants complete the symptom diaries correctly;
5. to contact >98% of participants at day 3-5 post-randomization;
6. to ensure that 100% of contacted participants who do not defervesce by day 4 post-randomization are unblinded and are continued on a full 10 days of amoxicillin;
7. tocontact >95% of participants at day 7-10 post-randomization;
8. to reassess >90% of participants at MCH at day 14-18 post-randomization;and
9. to contact >90% of participants at ~ 1 month post-randomization.

These feasibility objectives were constructed with reference to a seminal work on pilot studies ([84](#_ENREF_84)). Our primary concern was the ability of a research assistant to contact, recruit, and enroll sufficient numbers; consequently, the majority of feasibility criteria were drawn from the ‘resource projections’ domain (see section on ‘feasibility criteria’ in Part 5). As the only potential disadvantage of short-course antimicrobial therapy would be an increased risk of treatment failure, there are also feasibility criteria specifying minimum rates of loss to follow-up and/or switches to rescue standard-course therapy. There were no feasibility criteria addressing the appropriateness of the study population or that of the appropriateness of the selected outcomes; the revisions to the primary outcome that occurred over the course of the trial will be covered in detail below.

The trial enrolled 61 participants over a 14-month period. We had predicted a higher number of potentially eligible participants on the basis of reviewing previous McMaster Children’s Hospital emergency department (ED) data; the difference between predicted and actual enrolment is due in large part to the vagaries of coding for children with lower respiratory tract infection and the differences in the way different clinicians diagnose ‘pneumonia’ (please see the relevant sections detailing issues with the clinical and microbiologic diagnosis of pneumonia in Part 1). However, the fact that we recruited fewer than 70 participants in a nine-month period will not preclude proceeding with the main trial; it will simply lead to a modification of expectations (and consequent budgetary changes). Recruitment for the first 12.5 months of the trial (21 Dec 2012 – 11 Jan 2014) can be summarized as follows:

Diagnosed with mild CAP, aged 1-10 years: 435

Ineligible: 277

came to ED already on β-lactam: 89

 no fever on history or exam: 65

 asthma flare or Hx severe asthma: 28

 pneumonia dx in past month: 24

 allergy to penicillin: 21

 no resp symptom or sign: 14

 got ceftriaxone or macrolide in ED: 13

 significant PMHx: 11

 no CXR done: 06

 recent admission to hospital: 02

 previously in study: 02

 unimmunized: 01

 from another region (visiting): 01

Remainder eligible: 158

Missed: 56

Refused approach: 9

Refused consent: 38

Enrolled: 55

Feasibility criterion #2 was established because of concerns from ED staff that recruitment and enrolment would interfere with flow in the ED; however, no problems were encountered, primarily because the recruitment process took approximately half an hour. It was therefore assumed that this feasibility criterion was met, though detailed time records were not kept.

We did not foresee that only 7 of 61 participants would have blood work drawn by the attending ED physician. This is in contrast to clinical practice described at other sites conducting trials in optimizing treatment for paediatric CAP ([53](#_ENREF_53)) and resulted in a subtle change to the original inclusion criteria (see below). This is a perfect example of the importance of establishing feasibility criteria for pilot trials; we are currently investigating the utility of saliva-based C-reactive protein measurement and plan to use this diagnostic test in the main follow-up study. Fifty-seven of 61 participants (93%) had nasopharyngeal swabs that were received and processed by the microbiology laboratory.

Five of 61 participants (8%) did not return the symptom diaries, which would suggest that feasibility criterion #4 was met. However, the wording of this feasibility objective was somewhat vague; we note that participant caregivers occasionally made errors in the completion of the forms. This occurred most often with the measurement of child respiratory rate, which led to the omission of this item from later versions of the symptom diaries.

There was little problem ensuring appropriate follow-up. Every participant was contacted at day 3-5 post-randomization and both participants who did not defervesce by day 4 were transitioned successfully to 10 days of open-label amoxicillin. These criteria (#4 and #5) were probably the most important of all, as they dealt with participant safety, the only conceivable disadvantage of short-course antimicrobial therapy. There were two participants whose caregivers chose to withdraw them from the study; all other participants were contacted at day 7-10, had the primary outcome measured at day 14-18, and were successfully contacted ~ 1 month post-randomization.

*Study population*

The original definition of CAP was the same as that used for the multicentre trial with one minor difference; the first ‘systemic illness’ criterion was originally defined as fever OR an abnormal peripheral white blood cell count (<4 or >15 x 109 cells/L). This criterion was originally written this way because an abnormal peripheral WBC count has been included in other definitions of pneumonia ([19](#_ENREF_19),[53](#_ENREF_53)). As the vast majority of participants did not have blood work drawn, we simplified the definition for the follow-up trial by omitting the peripheral WBC component. The original eligibility criteria included children aged 1-10 years; however, as children aged 6-12 months are similar to other preschoolers in terms of CAP aetiology, clinical features, treatment, and prognosis ([24](#_ENREF_24)), we revised the inclusion criteria partway through the trial to permit enrolment of these infants. The exclusion criteria were not changed.

*Laboratory testing at enrolment*

The necessity of changing the protocol to include saliva-based C-reactive protein sampling (because of the rarity of venipuncture in these relatively well children) has already been discussed.

*Randomization*

As the pilot trial was based at a single centre, the study pharmacy was in charge of randomization; phone-based randomization was not used. At enrolment in the ED, all participants were given a five-day supply of amoxicillin. The study pharmacy then randomized the patient and provided either five more days of amoxicillin (different formulation) or five days of placebo; the participants returned to McMaster before day 5 to obtain the second set of medications. Clearly, this system will not work with multiple sites, and so it was modified for the main study.

*Proposed outcome measures*

The primary outcome in the pilot, composed of three separate items, was very similar to that described for the multicentre study, and was defined as follows:

1. Complete resolution of dyspnoea, increased work of breathing, and tachypnoea, PLUS
2. Persistent afebrile state from day 4 up to and including the day 14-18 follow-up visit, PLUS
3. Lack of a requirement for additional antibacterials or admission to hospital because of persistent/progressive lower respiratory illness during the 2 weeks after enrolment.

It was modified slightly, however, as a few children who were essentially well at the time of follow-up were counted as ‘failures’, unnecessarily introducing noise into the analysis. Clinical trials should use outcomes that are relevant to individuals and clinicians; a definition of ‘failure’ that does not involve any requirement for a change of management or a change in prognosis should be modified. Item 1 was changed from ‘complete resolution’ to ‘significant improvement’, as there was one child who had mild residual increased work of breathing at day 14-18 but did not require any other medication and was normal at 1-month followup. Item 2 was expanded upon so that children with a documented new respiratory viral infection or an obvious alternate cause of fever would not be judged to have ‘failed’ antimicrobial therapy; the requirement for >1 fever spike was also added as there were two participants who had a single isolated fever spike during the second 5 days of therapy and were entirely well at day 14-18 follow-up. The effect of these changes will be to make antimicrobial failure more rare – and therefore increase the sample size requirements for the main study – but will decrease the ‘noise’ in the analysis, as non-meaningful ‘failures’ might occur by chance more commonly in one arm than another and produce spurious results in the main trial.

*Sample size*

The sample size was selected in order to test study procedures, protocols, and resources, in an effort to verify that the feasibility criteria could be achieved. We did not calculate a sample size in order to estimate the variance of treatment failure for sample size calculations in the main follow-up study; please note that much of the literature on this topic has been developed for interval/ratio covariates that have normal distributions (see ‘Sample size considerations’ in Part 5).

*Pilot trial results (clinical)*

Blinding has been maintained; the following consist of the results in aggregate. The median age of participants was 2.64 years (Q1-Q3 1.64 – 4.33 y). As previously noted, only seven participants underwent venipuncture; the median peripheral WBC count was 13.5 x 109 cells/L (Q1-Q3 10.3 – 16.7 x 109 cells/L) and the median serum C-reactive protein level was 34.3 g/L (Q1-Q3 30.3 – 44.5 g/L). Though all participants were required to have a consolidation on chest radiograph as judged by the ED physician, only 60% of chest radiographs of study participants were reported to have findings consistent with pneumonia by the attending paediatric radiologist.

Six children (10%) did not achieve clinical cure, as defined *a priori.* Two participants experienced significant clinical problems; one developed worsening respiratory symptoms and was hospitalized on the 4th day after enrolment and the other had persistent fever as so was given open-label amoxicillin to finish 10 days of therapy. The other four participants who did not achieve cure had less significant clinical illness: one had residual very mild work of breathing at day 14-18, one had recrudescent respiratory symptoms on day 8 and so was prescribed additional antibacterials (but had a new respiratory viral infection documented on repeat nasopharyngeal sampling), one had a single spike of fever on day 11 (but was well at followup), and one had a single spike of fever or day 17 (but was well at followup). Were we to follow the recommendations set out by Cocks and Torgerson, despite the fact that their theory was developed for use with interval/ratio outcome measures, the only scenario that would preclude proceeding with the main follow-up study would be if all 6 ‘failures’ occurred in the short-course antimicrobial treatment arm, as the risk difference would be 0.2 (lower bound of 80% CI 0.11, higher than the selected margin of 0.075) ([85](#_ENREF_85)). However, as two-thirds of these ‘failures’ were not clinically significant, and we have subsequently modified the definition of the primary outcome, we feel justified in continuing with the multicentre trial.

*Pilot trial testing results (microbiologic)*

Of 57 NPS specimens from participants in the pilot available for analysis, 33 (58%) were positive for at least one virus, with 2/30 positive for 2 viruses. Over half the samples (n=31, 55%) had high-level *S. pneumoniae* colonization (> 4 log copies/mL); this positivity rate is very similar to that seen in a recent observational study of children with CAP defined using clinical and radiographic parameters ([21](#_ENREF_21)). Just under half (15 of 31, 48%) specimens with high-level *S. pneumoniae* colonization were also positive for a virus.

Unsurprisingly, only 2 (4%) were positive for *Mycoplasma pneumoniae.* Both of these were also positive for a virus, and neither of these were accompanied by high-level *S. pneumoniae* colonization. Not a single specimen was positive for the other atypical pathogens found more commonly in adults (*Chlamydophila* and *Legionella* spp). There were 8 (14%) NPS specimens that were not positive for any respiratory pathogens tested for in the study.

*Other problems encountered in the pilot trial*

If enrolment is to be optimized, missing potentially eligible participants and refusal of consent need to be kept to a minimum. Missing participants was extremely common in the early stages of the pilot, primarily because all recruitment was dependent on ED staff notifying the research assistant that a potential participant was present in the department; not only were there not sufficient resources to enable the permanent presence of a study team member in the ED, but all potential participants must be diagnosed by an ED physician as having CAP to be eligible. Optimizing ED-study team communication was achieved by repeatedly approaching the numerous health care professionals (attending staff, nurses, trainee MDs, etc.) who work in the ED, posting relevant notices, and feeding back missed notifications. The original protocol was also clarified and expanded to permit the research assistant to approach potential participants in their homes after being discharged home on amoxicillin given by the ED physician; this was most useful for children who were discharged in the early hours of the morning.

The most common reason for refusing consent was an unwillingness to return for the measurement of the primary outcome, especially for those who did not live in proximity to the hospital; there were also parents concerned that fewer days of antibiotics would have decreased efficacy. Unfortunately, there was nothing that could be done about the former, as it would be extremely difficult to induce physicians to visit participants in their home for a three-minute clinical examination. There is also little to be done about the latter, as there is still a widespread assumption among both health-care professionals and laypeople that taking an antimicrobial is essentially a zero-risk medical intervention, despite mounting evidence to the contrary. We are currently planning another trial exploring methods to better communicate the adverse events (including perturbation of the microbiome and colonization with resistant pathogens, among others) associated with antibacterial therapy to caregivers; however, the results from this trial will not be ready by the time the larger follow-up trial begins.

# PART 5 – SELECTED METHODOLOGIC CONSIDERATIONS FOR NON-INFERIORITY STUDIES

*Assay sensitivity*

The issue of assay sensitivity (proper design of a trial, enabling it to distinguish an effective intervention from an ineffective one) is critical but often underappreciated in the appraisal of non-inferiority studies. A ‘successful’ superiority study that demonstrates that one treatment is superior to another has, by definition, adequate assay sensitivity ([81](#_ENREF_81)). A superiority study that does not demonstrate that one treatment is superior to another may or may not have sufficient assay sensitivity; this study is properly referred to as having an ‘indeterminate’ result and the conclusions drawn from it depend on study characteristics, most importantly on whether or not the study was adequately powered to detect a clinically significant difference ([86](#_ENREF_86)). In contrast, a ‘successful’ non-inferiority study that demonstrates no difference between one treatment and the reference standard may or may not have sufficient assay sensitivity and therefore may or may not be valid. This is clearly a major issue as poor assay sensitivity essentially invalidates a non-inferiority study, regardless of the care taken designing all other aspects of the trial. The draft guidance of the United States Food and Drug Administration (FDA) notes that “[it is critical] to know…that the active control had its expected effect in the trial” and indicates that one should reference previous placebo-controlled studies of the reference treatment ([81](#_ENREF_81)). This same document notes that – if only a single non-inferiority study is to be completed – setting alpha at 0.001 constitutes additional evidence suggesting that a false conclusion of non-inferiority is unlikely ([81](#_ENREF_81)).

It is difficult to guarantee assay sensitivity for our proposed trial. As described extensively in the background, there is substantial inter-observer variability in the diagnosis of pneumonia and – even when this diagnosis is made – it is even harder to reliably determine if the infection is caused by a bacterial pathogen. This issue is important because the inclusion of too many participants with purely viral CAP would dramatically lower assay sensitivity, as neither short- nor standard-course antimicrobials have any effect on non-bacterial infections. We have attempted to optimize assay sensitivity by creating a definition of CAP with adequate face validity and that is consistent with others previously used in the literature. The other method that will be used to ensure study validity will be the use of sensitivity analyses; as noted in the protocol, comparisons will be made between short- and standard-course antimicrobial therapy in subgroups of participants who would be most likely to have bacterial infections (ie. alveolar infiltrates on chest radiograph, elevated C-reactive protein values, high-level pneumococcal colonization in nasopharyngeal specimens). The only way to absolutely guarantee that all participants had bacterial infections would be to include only those with blood cultures positive for CAP-causing pathogens; this would not only be infeasible (due to the extreme rarity of concomitant bacteraemia) but would result in the necessity of including those with more severe disease – who would not be eligible for short-course antimicrobial therapy anyway.

The potential inclusion of children without bacterial infections is not the only threat to assay sensitivity. As the FDA states, it is important to compare the efficacy of the reference treatment in the trial to past RCTs ([81](#_ENREF_81)); however, there are no known placebo-controlled trials of antibiotics for paediatric CAP in the literature. It is not even known what proportion of untreated paediatric bacterial CAP will self-resolve in the current era. There are records documenting mortality and morbidity from pneumonia in the pre-antibiotic era, but to use those to estimate baseline antibiotic efficacy would undoubtedly greatly exaggerate the impact of these medications, as the baseline health of children is much better today than in the early twentieth century.

*Determination of the non-inferiority margin*

It is obvious that the selection of the non-inferiority margin has a significant impact on trial outcome. It is also clear that clinical considerations should inform the determination of the margin; if the margin is judged as unacceptably wide to clinicians, a ‘successful’ non-inferiority trial will have little impact on practice. However, selection of the margin based solely on the clinical experience of the principal investigator should probably be avoided, despite how commonly this has been done in the past ([87](#_ENREF_87)).

The FDA draft statement also provides guidance relating to statistical considerations affecting the selection of the non-inferiority margin; note that its main concern seems to be – if the experimental treatment is found to be non-inferior to the standard therapy – that there is sufficient evidence to be reasonably confident the experimental treatment is also superior to placebo ([81](#_ENREF_81)). If the margin was greater than the predicted effect of the standard treatment, for example, a trial could successfully demonstrate non-inferiority for an experimental treatment that is not superior to placebo. The FDA draft guideline first instructs investigators to review meta-analyses of clinical trials of the standard therapy compared to placebo to discern the pooled estimate of efficacy; if only single trials are available, they can be used, but obviously there will be much less precision in the estimates of efficacy. In the ‘fixed margin method’, the key parameter M1 is then identified as the upper bound (ie. most conservative estimate, which for the risk difference is the least negative value, and for the relative risk is the value closest to unity) of the 95% CI surrounding the point estimate of either the risk difference or the relative risk ([81](#_ENREF_81)). This assumes, of course, that the effect of standard therapy in trial participants will be comparable to that in past placebo-controlled RCTs, and that the non-inferiority trial will be of comparable quality to these past trials (as ‘noise’ in less well-designed trials can obscure the ‘signal’ of effect). The upper bound of the CI is used instead of the point estimate because “half of all trials, even if the historical estimate is correct, would be expected to have a smaller effect, so that one could not be reasonably sure such an effect of the control was present” ([81](#_ENREF_81)). The noninferiority margin, M2, can then be calculated after determining what proportion of effect of the standard therapy is to be ‘preserved’. The suggested default proportion is 50%; some authors have recommended that greater proportions (resulting in smaller noninferiority margins) should be used when standard therapies have greater effects and when outcomes are serious and/or irreversible (eg. death), whereas smaller proportions can be used when the experimental treatment is expected to be safer or cheaper than standard treatment ([88](#_ENREF_88)). The formulae for determining M2 are the following ([88](#_ENREF_88)):

1. If comparing absolute risk reductions, M2 = (1-preserved effects)\*M1\*(-1)
2. If comparing relative risks, M2 = eln(1/M1)(1-preserved effects)

(It should be noted that these methods will often lead to the generation of different non-inferiority margins. Absolute risk reductions (presented as number needed to treat) can be more useful for decision-making by clinicians, though relative risks are less susceptible to variation between studies.) If it is assumed that the failure rate of standard therapy is 5% and that of no therapy is 25% (ie. 75% of mild bacterial CAP in children will resolve of its own accord without any treatment), then the risk difference for standard therapy is -0.2; if 50% of the effect is desired to be preserved, then M2 for the proposed trial should be 0.1. However, there are no data to support this estimate of a 25% failure rate for no treatment; if the true failure rate was only 15%, then the M2 for the proposed trial would be 0.05. Estimates of child CAP-specific mortality from the pre-antibiotic era cannot be used to generate M1 since this would without doubt overestimate CAP-specific mortality in children today, leading to a far-too-large estimate of M1. We note the FDA draft statement explicitly states “where there is uncertainty about the historical effect size [of standard treatment]…it will usually be necessary to have more than one non-inferiority study to support effectiveness”, ([81](#_ENREF_81)) though its primary concern appears to be for ensuring appropriate approval of new drugs.

Interestingly, the FDA draft statement notes that – because of the way that M2 is calculated – if the 95% CI for the point estimate of the effectiveness of the experimental treatment crosses M2, it does not necessarily mean that this therapy is clearly inferior to the control treatment. (In contrast, if the CI crosses M1, there is no evidence that the experimental therapy is superior to placebo.) It seems to endorse the post-hoc logic in some instances of, for example, “assuring 48% retention [of the control effect]” since the *a priori* selection of 50% retention of effect is entirely arbitrary ([81](#_ENREF_81)). This would seem to be somewhat dangerous, especially given the repeated concern about methodologic problems leading to a type I error in non-inferiority studies (rather than a type II error in superiority studies).

# PART 6 – SELECTED METHODOLOGIC CONSIDERATIONS FOR PILOT STUDIES

There is no one accepted definition for a ‘pilot’ or ‘vanguard’ study, but most would agree that this type of smaller study is important prior to embarking on a large and expensive randomized clinical trial. There are innumerable reasons for conducting a pilot study, most of which aim to verify that the study as designed is appropriate and that the investigators have a realistic estimate of resources (both human and otherwise) needed to complete the main follow-up study ([89](#_ENREF_89)). However, it is important to realize what the results of a pilot study can and should be used for.

*Feasibility criteria*

As the primary goal of a pilot study is to usually determine the feasibility of the follow-up main trial, these studies should usually have predetermined explicit feasibility criteria that will inform the decision to proceed with the larger trial. Interestingly, the importance of stating clear feasibility criteria has been highlighted in relatively few publications ([84](#_ENREF_84)). Additionally, we have not been able to find published literature (Thabane L, personal communication) addressing related methodologic questions that would appear to be critical, such as: how should feasibility criteria be selected? Are there certain key feasibility domains that should always be represented among the criteria for *every* pilot study? If a particular feasibility criterion is not achieved in a pilot trial, is there any way of objectively assessing whether planned modifications could result in a successful follow-up larger trial (or are there certain types of failures that would preclude any further application for funding). This lack seems quite curious, given that anecdotal experience would suggest that pilot data are essentially required to successfully receive significant amounts of funding for a randomized trial. Building upon a previously-established paradigm ([84](#_ENREF_84)), it seems reasonable to propose that pilot RCTs should all include feasibility criteria drawn from the following list:

1. *Appropriateness of study population.* Do the inclusion and exclusion criteria adequately describe the population of interest? Are there participants who are technically eligible (or ineligible) that should not be?
2. *Appropriateness of outcomes.* Is the primary outcome truly important? Are the instruments designed to measure the primary outcome able to be used efficiently and appropriately in the study population?
3. *Recruitment rate.* Based on the eligibility criteria, is it reasonable to suppose that sufficient numbers will be recruited in a practical time-frame in order to assess a difference in the primary outcome between groups? If not, are there other outcomes that are important but more frequent? Can eligibility criteria be relaxed and yet still include only the population of interest?
4. *Resource projections.* Will the resources – both human and otherwise – be sufficient to successfully conduct the trial or was the pilot obviously under-budgeted for? Is the infrastructure (especially information technology-related) adequate and workable in the study setting? Can study procedures actually take place within an appropriate time-frame? Are the co-investigators able to actually carry out their assigned tasks?
5. *Safety and ethics.* Have any new safety problems been identified? Have any ethical issues arisen that were not foreseen?

*Sample size considerations*

Please note that the list in the previous section did not explicitly include feasibility criteria related to sample size projections. Some authorities would suggest that it is preferable to design the main study using parameters present in the literature, as point estimates of treatment effects in small studies can vary widely ([84](#_ENREF_84)). However, many authors have attempted to promulgate statistically appropriate ways of using pilot data to inform the sample size decision-making for the larger follow-up study. Some of these apply to ‘internal’ pilot studies, otherwise described as statistical analysis partway through a large study in an effort to gauge if original sample size calculations (ie. variance of the outcome of interest) were correct, and some apply to ‘external’ pilot studies, which are entirely separate from and precede the larger follow-up trial.

Wittes and Brittain suggested that large trials should – halfway through enrollment – recalculate the variance of the outcome of interest; should the variance be higher than the original estimates, the overall sample size would need to be increased to maintain nominal power ([90](#_ENREF_90)). Sandvik et al. developed a formula to calculate appropriate internal pilot trial size for normally-distributed outcomes; this size is at minimum 20 and potentially much larger, as it depends on the estimates of the standard deviation (SD) of the outcome variable in the literature, sizes of previous trials, etc. ([91](#_ENREF_91)) They note that their procedure – as for that of Wittes and Brittain – will affect the final estimate of treatment variance, which will change the significance level of the result ([91](#_ENREF_91)). This effect was expected to be ‘small’; a later work by Friede and Kieser attempted to quantify the projected magnitude of this effect for different study designs ([92](#_ENREF_92)).

Some authors have proposed simpler ways of calculating the appropriate size of a pilot study, either internal or external, with the ultimate goal of predicting SD/variance of the main follow-up study. Lancaster *et al.* referred to the (unreferenced) ‘rule of thumb’ stating that an n=30 is often sufficient for pilot trials ([93](#_ENREF_93)); Julious suggested that including 12 participants per treatment arm would be sufficient to gauge the projected variance in the larger follow-up trial ([94](#_ENREF_94)). Sim and Lewis did not overtly find fault with these recommendations but demonstrated quite elegantly the variability inherent in estimating SDs using small samples and alluded to the potential utility of an **inflation factor**, “the factor by which the SD derived from the pilot study should be increased to be x% confident of achieving at least the nominal power in the main study”; this is simply the ratio of the upper x% CI of the estimate of the pilot SD and the observed pilot SD ([95](#_ENREF_95))**.** Interestingly, one of the foundation concepts of their manuscript – that one should project the SD of the follow-up study to be close to the upper limit of the CI of the SD of the pilot study – was articulated almost 20 years earlier by Browne ([96](#_ENREF_96)). Sim and Lewis concluded by noting that using slightly different methodologies, pilot sample sizes of at least 55 are likely to be optimal for generating reliable estimates for the follow-up trial if the outcome variable is interval/ratio and potentially many more patients may be required when the outcome of interest is nominal or ordinal ([95](#_ENREF_95)).

The foundation of the approach espoused by Cocks and Torgerson is different; they recommend selecting a pilot trial sample size large enough to produce a reasonably precise estimate of the treatment effect ([85](#_ENREF_85)). Their method involves construction of a one-sided 80% CI around the point estimate of effect and, if the upper limit for a superiority study excludes a *clinically* significant difference, proceeding with the main follow-up study would not be indicated ([85](#_ENREF_85)). They note that this procedure is only feasible if the variance of the main outcome variable is known; one might hypothesize that this would be true for only a minority of situations. After working through examples, they conclude that an appropriate ‘rule of thumb’ would be 9% of the projected sample size of the main study, or 20 participants, whichever is larger ([85](#_ENREF_85)).

# PART 7 – CONCLUSIONS AND FUTURE DIRECTIONS

Community-acquired pneumonia is clearly an important problem for Canadian children, their caregivers, and clinicians. The proposed trial will likely provide important information relating to the optimal duration of therapy for mild CAP – however, as detailed in the previous sections, many relevant questions remain unanswered. Refining the criteria for diagnosis of pneumonia is critically important for clinicians, trialists, and epidemiologists. Almost all of the many additional modalities outlined in detail in previous sections require additional evaluation in diagnosis- or outcome-based studies to better gauge their potential contributions to the management of children with suspected CAP. We are about to begin one such study to systematically investigate the performance characteristics of both salivary C-reactive protein measurement and nasopharyngeal pneumococcal genomic loads in children with lower respiratory tract infections admitted to hospital; we have postulated that both of these indices will be higher in children with bacterial pneumonia than in those with viral bronchiolitis, but this hypothesis requires experimental verification. Additionally, even if high-level nasopharyngeal pneumococcal colonization is ‘in truth’ associated with pneumococcal CAP, it will not help to diagnose paediatric bacterial CAP caused by other organisms, such as group A *Streptococcus* – should assays be developed to measure these other pathogens as well?It seems quite reasonable to suppose that optimization of CAP diagnosis will be accomplished through a combination of clinical judgment, laboratory investigations (such as CRP and pneumococcal nasopharyngeal genomic load) and radiologic imaging (whether chest radiography or ultrasound). An appropriate evaluation of all of these modalities – plus practical combinations in series – will require a large (multicentre) cohort of children with presumed CAP whose treatment is standardized and whose outcomes are precisely documented. The proposed trial will be important to ensure that ‘standardized treatment’ is optimized prior to proceeding. There is much work to be done to improve our ability to diagnose and treat paediatric community-acquired pneumonia – best to start soon!

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