**ABSTRACT**

Evidence-based recommendations for paediatric community-acquired pneumonia (CAP) diagnosis and management are needed. Uncomplicated CAP is often caused by respiratory viruses, especially in younger children; these episodes self-resolve without antibiotic treatment. Unfortunately, there are no clinical criteria that reliably discriminate between viral and bacterial disease, and so the majority of children diagnosed with CAP are given antibiotics—even though these will often not help and may cause harm. We have developed a novel care pathway that incorporates point-of-care biomarkers, radiographic patterns, microbiological testing and targeted follow-up. The primary study objective is to determine if the care pathway will be associated with less antimicrobial prescribing.

**Methods and analysis**

A prospective, before–after, study. Previously well children aged ≥6 months presenting to a paediatric emergency department (ED) that have at least one respiratory symptom/sign, receive chest radiography, and are diagnosed with CAP by the ED physician will be eligible. Those with medical comorbidities, recently diagnosed pulmonary infection, or ongoing fever after ≥4 days of antimicrobial therapy will be excluded. In the control (before) phase, eligible participants will be managed as per the standard of care. In the intervention (after) phase, eligible participants will be managed as per the novel care pathway. The primary outcome will be the proportion of participants in each phase who receive antimicrobial treatment for CAP. The secondary outcomes include: clinical cure; re-presentation to the ED; hospitalisation; time to resolution of symptoms; drug adverse events; caregiver satisfaction; child absenteeism from daycare/school; and caregiver absenteeism from work.

**STRENGTHS AND LIMITATIONS OF THIS STUDY**

- Novel care pathway incorporates simple testing that is widely available in the higher-income country context.
- No individual-level randomisation or blinding of participants.
- Only a single-centre study so results may not be as generalisable.

**Ethics and dissemination**

All study documentation has been approved by the Hamilton Integrated Research Ethics Board and informed consent will be obtained from all participants. Data from this study will be presented at major conferences and published in peer-reviewed publications to facilitate collaborations with networks of clinicians experienced in the dissemination of clinical guidelines.

**Trial registration number**

NCT05114161.

**BACKGROUND AND RATIONALE**

In North America, up to 5% of preschoolers develop community-acquired pneumonia (CAP) every year. Pneumonia is the second-leading reason for paediatric hospitalisation in the US and may be the most common indication for antibiotic use in hospitalised children. In Canada, the annual incidence of paediatric CAP-related hospitalisation is 611 per 100 000 and approximately 20% of children hospitalised with CAP may need intensive care, which can result in significant morbidity.
Unfortunately, there are barriers to the optimal diagnosis and treatment of CAP. No symptoms or signs are specific for pneumonia, and there are no consensus criteria for its diagnosis. Although chest radiography (CXR) is widely assumed to be diagnostic, the inter-rater and intra-rater reliability for the identification of CXR infiltrates other than clear lobar consolidations is not good.

Furthermore, there are no features on history or physical examination that are highly specific for either viral or bacterial causes and validated radiographic criteria for reliably distinguishing between viral and bacterial pneumonia do not exist, (despite the fact that bacterial disease is more associated with consolidations), which makes the determination of the optimal management strategy for CAP challenging. Unlike adults, children commonly develop viral pneumonia or bacterial-viral coinfections, so a large study enrolling children hospitalised for CAP at 3 US centres showed that 66% had a respiratory virus detected and 26% had proven coinfections.

Consequently, even though recent randomized controlled trials (RCTs) have shown that short-course treatment is equally effective as longer courses of antibiotics for paediatric CAP, it seems likely that current treatment strategies are still resulting in a large proportion of children receiving antimicrobials that will do nothing to attenuate their illnesses. Failure to identify a bacterial pathogen, unfortunately, does not rule out an oral bacterial cause; diagnostics for respiratory viruses have excellent sensitivity and specificity, whereas those for bacterial pathogens are very limited. Therefore, a child with CAP whose nasopharyngeal swab (NPS) is positive for a virus could have a primary viral pneumonia or a viral infection complicated by a bacterial pneumonia.

Biomarkers that could discriminate between bacterial and viral CAP have been long sought after but many, such as leucocyte counts, have not been found to be helpful. Increased C reactive protein (CRP) is associated with bacterial infection, but not sufficiently strongly to rule bacterial CAP in or out as a stand-alone test. Urinary pneumococcal antigen (UAg) testing was previously not specific for pneumococcal disease in children; however, this may no longer be true in the post-13-valent pneumococcal conjugate vaccine (PCV13) era with changes in S. pneumoniae colonisation patterns. Furthermore, a recent prospective cohort study of children hospitalised with CAP in Colombia (where pneumococcal vaccination rates are low) showed that only 18% had a positive UAg result (as compared with 8% of controls). UAg is modestly useful in the evaluation of adults with CAP and has been recommended to improve antimicrobial stewardship.

In a recent small prospective cohort of children hospitalised with respiratory infection at our institution, we found that UAg testing was moderately specific for probable bacterial CAP. Unfortunately, we know of no single assay that is both sufficiently accurate to either rule bacterial CAP in or out and simple enough to operationalise as a point-of-need test in the emergency department (ED) setting.

Since routine diagnostics do not reliably differentiate between bacterial and viral infection, it is not surprising that most children diagnosed with CAP at our institution are treated with antibiotics, a common practice in North America. Unfortunately, many of these children have primary viral infections and receive antibiotics that will not help but may cause harm. Minimising inappropriate antimicrobial prescribing is an important strategy to attenuate the increase in circulating antimicrobial resistance, which explains the interest in exploring the effectiveness of shorter courses of antimicrobials for numerous infections and subsequent changes to treatment guidelines. Antimicrobials routinely prescribed to children can produce problematic side effects and impact the ‘normal’ microbiota, which can influence the development of obesity, atopy and other disorders.

Our research question is: Will a novel care pathway to manage children aged ≥6 months diagnosed with non-severe CAP in the McMaster Children’s Hospital (MCH) ED lead to lower rates of antibiotic use as compared with current practice?

OBJECTIVES
The primary objective is to determine whether a novel care pathway for the management of paediatric non-severe CAP in the MCH ED will reduce antibiotic use.

The secondary objectives are to determine whether this care pathway will maintain comparable clinical outcomes (including clinical cure, time to resolution of all symptoms, representation to the ED, hospitalisation), decrease child and parent absenteeism, and improve caregiver satisfaction.

METHODS
Study design
The PIONEER study is a single-centre, before–after, cohort study at the MCH ED, a tertiary-care centre. Participants will not be randomly allocated to treatment groups; those who present in the control (before) phase will be managed as per routine care and those who present in the intervention (after) phase will be managed using the novel care pathway. This design was selected because of concerns that an individual-level RCT would easily become contaminated once ED clinicians saw the value of the novel pathway (and used aspects of the novel care pathway to participants randomised to the control group). This study will provide essential data for the design and future conduct of a multicentre trial.

The study began on 14 February 2022 and is expected to continue until 13 February 2024.

Eligibility criteria
Children aged 6 months – 18 years presenting to the ED who are diagnosed with CAP and are well enough to be
discharged home will be eligible. They must also have at least one of the following:
1. tachypnoea measured at triage (>60 beats/min for age<1 year, >50 beats/min for 1–2 years, >40 beats/min for 2–4 years, and >30 beats/min for >4 years);  
2. cough on exam or by history;  
3. increased work of breathing on exam; or  
4. auscultatory findings (eg, focal crackles, bronchial breathing) consistent with CAP.

Children will be excluded if they have any of the following: cystic fibrosis, anatomic lung disease, bronchiectasis, congenital heart disease (requiring treatment or with exercise restrictions), history of repeated aspiration/velopharyngeal incompetence, malignancy (current or past), immunodeficiency (primary, acquired, or iatrogenic), pneumonia previously (clinically) diagnosed within the past month, or lung abscess diagnosed within the past 6 months. Children who present with ongoing fever after ≥4 days of beta-lactam therapy active against *S. pneumoniae* (ie, amoxicillin, amoxicillin-clavulanate, cefprozil, cephalexin, cefadroxil, levofloxacin/moxifloxacin, or doxycycline) will not be eligible. Children will not be eligible to participate more than once.

**Interventions**

The novel care pathway intervention will incorporate multiple factors to determine who is at low (vs appreciable) risk of bacterial CAP. At recruitment, specific radiographic findings and point-of-care (POC) CRP testing will identify those who are at appreciable risk and will receive antibiotic treatment on that day (figure 1). The next day, results of multiplex respiratory pathogen

![Decision tree for novel care pathway (day of enrolment). CRP, C reactive protein; PCV13, pneumococcal conjugate vaccine.](image_url)
and UAg testing (optional) will be used to determine if any participants initially judged to be low risk have moved into the appreciable-risk category and should be prescribed antibiotics (figure 2).

**Explanation for the choice of comparators**

The comparator in this study, used in the control phase, will be standard treatment. This is defined as antibiotic management at the discretion of the ED physician who assesses the participant. We will be providing education to ED clinicians supporting 3–5 days of amoxicillin for children with uncomplicated CAP, given recent randomised trials demonstrating the non-inferiority of short-course antibiotics in this context.\(^{20–22}\) We will also remind ED clinicians that most paediatric CAP is associated with viral pathogens and that the Infectious Disease Society of America states that antibiotic treatment of non-severe CAP in young children is not obligatory.\(^{16}\) However, during the course of the study, we will not actively work to change CAP prescribing practices through audit and feedback.

**Follow-up plan**

The research assistant (RA) will contact caregivers at day 2–5, day 14–21 and day 30 post enrolment for outcome ascertainment. Caregivers will be asked to complete a daily diary for 7 days that will include the following: temperature, dyspnoea (older participants), increased work of breathing, and both mild (days of mild diarrhoea, abdominal discomfort, rash) and severe (eg, anaphylaxis) drug adverse reactions. Caregivers will also be instructed on how to assess increased work of breathing and to take their child’s temperature; all will be offered thermometers. All participants whose symptoms do not progressively improve will be encouraged to return to the ED to be reassessed, as per standard of care.

**Intervention description**

After consent, in the intervention (after) phase, the caregiver will be introduced to the concept of antimicrobial stewardship and the rationale for the novel care pathway will be explained. The participant will have a NPS and a rapid POC blood CRP. (The RA will perform the POC CRP testing, which will take 3–6 min.) UAg will be done by a study lab technician and NPS testing will be done by the Hamilton Regional Laboratory Medicine Program to detect common respiratory viruses (ie, RSV, influenza A/B, parainfluenza I–III, adenovirus, enterovirus, rhinovirus, SARS-CoV-2) and *Mycoplasma pneumoniae*; these results will be available the day after enrolment. For those participants who are unable to produce urine at recruitment, a sample can be taken after discharge but within 24 hours of enrolment. These diagnostic tests will determine management using the novel care pathway.

The novel care pathway will follow a decision tree to stratify patients into risk categories (see figure 1). Patients with large radiographic lobar consolidation (ie, consolidation of an entire lobe of a lung or the majority thereof) detected by radiograph, ultrasound or CT scan, OR POC CRP >60 mg/L will be deemed ‘appreciable risk’ while patients with CRP <20 mg/L will be deemed ‘low risk’. ‘Radiographic lobar consolidation’ will be defined as per WHO standards,\(^{54}\) namely: ‘...confluent alveolar infiltrate that may encompass an entire lobe or a large segment, fluffy, mass-like, cloud-like density...’. Given that the inter-rater reliability for the identification of lobar consolidation is good,\(^{14–15}\) and large consolidations are more likely to be associated with bacterial infection,\(^{13,15}\)
we feel empiric treatment of these participants with antibiotics is warranted. The CRP cut-offs of 20 mg/L and 60 mg/L were selected after reviewing the literature; we sought a lower cut-off with increased sensitivity and a higher cut-off with increased specificity. A 2011 systematic review recommended a cut-off of 20 mg/L for CRP to rule out serious bacterial infections (sensitivity 80%, specificity 70%) and a later large prospective cohort study found very similar results. Another meta-analysis found that bacterial CAP was associated with serum CRP values greater than 35–60 mg/L. A small prospective study of children hospitalised with CAP found that a CRP of >40 mg/L had 94.6% sensitivity to rule out pneumonia and it has been suggested that its absence can be used to help exclude pneumonia. Infants are more likely to have serious bacterial infections than older children and will not have received a full PCV13 course; and wheezing is more specific for bronchiolitis.

Appreciable-risk participants will be given a prescription for 3–5 days of antibiotics. This will be high-dose amoxicillin unless the participant has a severe penicillin allergy, in which case the ED clinician will be asked to select an alternative (eg, cefprozil, levofloxacin). Low-risk participants will be discharged without antibiotics. On the day after enrolment, additional results will be reviewed, and the further management of initially ‘low-risk’ children will proceed as follows (figure 2):

- if respiratory virus positive (and both UAg negative and Mycoplasma negative), the family will be contacted and reassured.
- if respiratory virus negative (and both UAg negative and Mycoplasma negative), the participant will be asked to return to the ED for reassessment on day 2–3 if fever does not resolve and symptoms do not abate.

All participants who have not defervesced by day 4–5, or who worsen at any time in the opinion of the caregivers, will be asked to return to the ED for reassessment.

Relevant concomitant care permitted or prohibited during the study
No medications or care will be prohibited during the study for either phase.

Outcomes
Primary outcomes
The primary outcome is the proportion of participants that are treated with antibiotics in the first 14 days after enrolment for the purpose of treating CAP. For measurement of the primary outcome, the enrolment date study source documentation will be used to determine if antibiotics were prescribed initially; furthermore, an RA will phone the caregiver at day 2–5, day 14–21, and day 30 to ascertain if any antibiotic prescriptions were given by another healthcare provider, and if so, the associated rationale.

Secondary outcomes
The secondary outcomes are:
1. Clinical cure by the time of the day 14–21 outcome assessment, as defined by all of the following:
   1. Improvement of respiratory symptoms, according to the caregiver. (Persistent or lingering cough, improved from baseline, would be consistent with clinical cure.)
   2. Lack of hospitalisation for CAP.
   3. Lack of receipt of additional antimicrobials, beyond those prescribed on the day of enrolment in the MCH ED (either control or intervention phase) or the subsequent day as part of the study (intervention phase), by any healthcare provider for suspected persistent or progressive CAP.
   4. Treatment with broad-spectrum antibiotics for CAP (ie, amoxicillin/clavulanate, cephalosporins, azithromycin, fluoroquinolones).
   5. The occurrence of drug-related adverse events.
   6. Unscheduled ED or urgent care visits before day 30 post enrolment.
   7. Unscheduled visits to primary care (family MD, nurse practitioner, physician assistant) before day 30 post enrolment.
8. Hospitalisation for CAP before day 30 post enrolment.
9. The development of complicated CAP (ie, pleural effusion or PICU admission) before day 30 post enrolment.
10. The number of days that participants’ caregivers in each arm miss work (for those who work outside the home) or have work disrupted (for those who work within the home), before the day 14–21 outcome assessment.
11. The number of days that participants miss school/daycare before the day 14–21 outcome assessment.
12. The acceptability of the care plan from the caregiver’s perspective on day 0 and 30 (using a previously validated scale).
13. Failure to achieve clinical cure in those who have CRP<20 mg/L.

Sample size
We expect that at least 95% of participants will be treated with antibiotics in the control phase, given current ED prescribing patterns. To have 80% power to detect an absolute 15% reduction in prescribing in the intervention phase, assuming 5% loss to follow-up, and to be able to adjust for up to 2 potential confounders (eg, presence of asthma and season), we will need 77 participants in each phase (alpha=0.05). In 2018–2019, there were 429 children diagnosed with CAP in the MCH ED, so our target of 154 is feasible.

Recruitment
Recruitment will be carried out in the MCH ED by RAs. The following data will be collected at recruitment for each participant: gender, self-described ethnicity, age, temperature at triage, duration of fever in the last 7 days, clinical features consistent with pneumonia in the last 48 hours (cough, tachypnoea, auscultatory findings, respiratory rate at triage), presence of wheezing on exam, antibiotic use within the last 90 days (type of antibiotic, length of course, date taken), hospitalisation within the past 90 days, date of presentation to the ED, triage level (measured using the Canadian Triage and Acuity Scale), radiologist interpretation of chest X-ray, and PCV13 vaccination history. See figure 3.

Patient and public involvement
The public was not involved in the design of this study.

Data collection and management
After obtaining informed consent, the RAs will recruit the participant in the ED and complete the relevant documentation. Paper forms will be kept on-site in a secure room and will be later digitised by the research staff. The study database has been created using Research Electronic Data Capture (REDCap) software, whose servers are securely housed in an on-site limited access data centre at McMaster University; all web-based information transmission is encrypted.

Data collection methods
Primary outcome
The primary outcome will be ascertained by reviewing recruitment source documentation; follow-up with the caregiver at day 2–5; and follow-up with the caregiver at day 14–21.

Secondary outcomes
These will be measured as follows:
1. Clinical cure will be determined by caregiver report at the day 14–21 contact.
2. Treatment with broad-spectrum antibiotics for CAP will be determined by caregiver report at the day 2–5 contact, the daily diaries and the day 14–21 contact.
3. Drug-related adverse events will be ascertained by caregiver report at the day 2–5 contact, the daily diaries and the day 14–21 contact.
4. Mycoplasma positivity in the NPS will be verified through study source documentation. Treatment with Mycoplasma-active antibiotics for CAP will be determined by caregiver report at the day 2–5 contact, the daily diaries and the day 14–21 contact.
5. Time to resolution of CAP symptoms will be determined by caregiver report at the day 2–5 contact, the daily diaries and the day 14–21 contact.
6. Unscheduled ED or urgent care visits before day 30, unscheduled visits to primary care before day 30, hospitalisation for CAP before day 30 and the development of complicated CAP before day 30 will be ascertained by caregiver report at the 30-day contact.
7. Caregiver absenteeism and child absenteeism will be measured by caregiver report in the daily diaries.
8. Caregiver satisfaction will be measured at enrolment (just prior to discharge from the ED) and again at day 30. This will be done by asking the following questions (previously used and validated in a similar context):
   1. How satisfied are you with your child’s overall care tonight? (extremely satisfied/very satisfied/moderately satisfied/slightly satisfied/not very satisfied/not at all satisfied).
   2. How satisfied are you with the doctor’s diagnosis? (extremely satisfied/very satisfied/moderately satisfied/slightly satisfied/not very satisfied/not at all satisfied).
   3. How satisfied are you with the antibiotic treatment plan? (extremely satisfied/very satisfied/moderately satisfied/slightly satisfied/not very satisfied/not at all satisfied).
9. The proportion of participants with initial CRP<20 mg/L who later fail to achieve clinical cure will be calculated using source documentation.

Statistical methods
Statistical methods for primary and secondary outcomes
Descriptive statistics will be used to describe baseline characteristics. Continuous variables such as age and duration of fever will be presented as either median with first to third quartiles.
third quartiles (Q1,Q3) or mean with SD depending on the distribution. Normality will be assessed visually. Categorical variables such as gender, clinical features (fever, presence of tachypnea, cough, wheezing, increased work of breathing, or auscultatory findings consistent with pneumonia) will be presented as a count (%). The primary outcome and secondary outcomes will be analysed using regression analysis. Linear regression will be used for continuous outcomes, logistic regression will be used for binary outcomes, ordinal regression will be used for ordinal variables and cox regression will be used for time-to-event analysis (see table 1). For all regression analyses, confounding will be accounted for by including the variables (eg, presence of asthma and season) in the models. Multiple imputation will be used to handle missing data and sensitivity analyses will be performed on the imputed data. If the data are missing not at random (informative missing), then we will consider pattern mixture modelling which is joint modelling of the outcome along with the probability of response. All statistical tests will be performed using two-sided tests at 0.05 level of significance. The results will be reported as an estimate of OR, HRs or mean difference with corresponding 95% CIs and p values. All analyses will be performed using R V.4.0.4 (R Core Team 2021) and SPSS V.26.

**Limitations of the study**
As previously mentioned, we will not be randomising at the individual level. Despite the fact that we believe that this will be a net benefit to study validity (by preventing control-group contamination), this will obviously increase the possibility of bias if there are differences

### Figure 3  Schedule of events and follow-up.

| CONTROL PHASE (STANDARD CARE) | Enrolment | Post-enrolment |
|--------------------------------|-----------|----------------|
| TIMEPOINT                      | Day 2 – 5 | Day 14 – 21    | Day 30          |
| Eligibility screen            | X         |                |                |
| Informed consent              | X         |                |                |
| Outcome assessment            | X         | X              | X              |

| INTERVENTION PHASE (NOVEL CARE PATHWAY) | Enrolment | Post-enrolment |
|----------------------------------------|-----------|----------------|
| TIMEPOINT                              | Day 1     | Day 2 – 3     | Day 2 – 5     | Day 14 – 21 | Day 30 |
| Eligibility screen                     | X         |                |                |             |       |
| Informed consent                       | X         |                |                |             |       |
| Nasopharyngeal swab (NPS)              | X         |                |                |             |       |
| Imaging                                | X         |                |                |             |       |
| Point of care CRP                      | X         |                |                |             |       |
| Urine pneumococcal antigen (UAq, optional) | X         |                |                |             |       |
| Antibiotic prescription                |           |                |                |             |       |
| Outcome assessment                     | X         | X              | X              | X            |       |

| Appreciable risk patients             |           |                |                |             |       |
| Low risk patients                     |           |                |                |             |       |
| Review of additional results (prescription may be given) | X         | X              |                |             |       |
| Outcome assessment                     |           |                | X              | X            | X     |
| UAq result (If applicable)             | X         |                |                |             |       |
| NPS result                             | X         |                |                |             |       |
| Imaging result                         | X         |                |                |             |       |
between the prognosis, treatment, or outcome ascertainment (since there is no blinding) of participants enrolled in the control phase as compared with those enrolled in the intervention phase. With the current study design, we will be unable to draw a causal conclusion with high certainty even if participant outcomes are better in the work phase, due to the risk of residual confounding; we will only be adjusting for two of the most important confounders that can be measured.

In this type of before–after study, results could be biased if there are significant temporal trends, such as an extreme change in the epidemiology of paediatric CAP over the time-course of the study. Some changes have been observed recently; the institution of non-pharmaceutical interventions (chiefly restrictions in movement and assembly) to mitigate the impact of the COVID-19 pandemic was associated with a dramatic drop in the incidence of both respiratory viral disease and

| Variable/outcome | Hypothesis | Outcome measure | Method of analysis |
|------------------|------------|-----------------|--------------------|
| **Primary**      |            |                 |                    |
| Antibiotic therapy for CAP | Less frequent in intervention (after) phase than control (before) phase | Caregiver report and source documentation (dichotomous) | Logistic or binomial regression |
| **Secondary**    |            |                 |                    |
| Clinical cure    | Comparable in intervention (after) phase as compared with control (before) phase | Caregiver report (dichotomous) | Logistic or binomial regression |
| Treatment with broad-spectrum antibiotics for CAP | Comparable in intervention (after) phase as compared with control (before) phase | Caregiver report (dichotomous) | Logistic or binomial regression |
| Occurrence of drug-related adverse events | Less frequent in intervention (after) phase than control (before) phase | Daily diary records, caregiver report (dichotomous) | Logistic or binomial regression |
| Treatment with Mycoplasma-active antibiotics for those in whom Mycoplasma is detected | More frequent in intervention (after) phase than control (before) phase | Source documentation and caregiver report (dichotomous) | Logistic or binomial regression |
| Time to resolution of difficulty breathing and fever | Comparable in intervention (after) phase as compared with control (before) phase | Daily diary records, caregiver report (time-to-event) | Cox regression |
| Unscheduled ED or urgent care visits before day 30 | Comparable in intervention (after) phase as compared with control (before) phase | Caregiver report (dichotomous) | Logistic or binomial regression |
| Unscheduled primary care visits before day 30 | Comparable in intervention (after) phase as compared with control (before) phase | Caregiver report (dichotomous) | Logistic or binomial regression |
| Hospitalizations before day 30 | Comparable in intervention (after) phase as compared with control (before) phase | Caregiver report (dichotomous) | Logistic or binomial regression |
| Development of complicated CAP before day 30 | Comparable in intervention (after) phase as compared with control (before) phase | Caregiver report (dichotomous) | Logistic or binomial regression |
| Number of days of missed work by participant’s caregivers | Comparable in intervention (after) phase as compared with control (before) phase | Daily diary records, caregiver report (count) | Poisson regression |
| Number of days of missed school/daycare by participant | Comparable in intervention (after) phase as compared with control (before) phase | Daily diary records, caregiver report (count) | Poisson regression |
| Caregiver satisfaction at enrolment | Comparable in intervention (after) phase as compared with control (before) phase | Caregiver report (ordinal) | Mann-Whitney U test |
| Caregiver satisfaction at day 30 | Comparable in intervention (after) phase as compared with control (before) phase | Caregiver report (ordinal) | Mann-Whitney U test |
| Failure to achieve clinical cure in participants whose initial CRP is<20mg/L | Very infrequent | Source documentation |

CAP, community-acquired pneumonia.
invasive pneumococcal disease. However, we believe that the potential effect size of the intervention is so large (since overprescribing for paediatric CAP is so common, given how commonly viruses cause disease) that—even if this were to recur during the course of the study—we would still be able to observe some benefit associated with the intervention (or postulate that there would still have been benefit even if the pandemic restrictions not occurred). We also note that a simple increase or decrease in a particular respiratory virus or bacterial pneumonia pathogen would likely not have a significant effect on study results; only a change in the proportion of children with bacterial CAP (which seems unlikely to occur) would have a marked impact on conclusions about the effectiveness of the study intervention. Mycoplasma pneumoniae outbreaks have been documented within the past decade in North America, which would be slightly problematic should one occur in only the ‘before’ or ‘after’ phase. However, the measurement of Mycoplasma CAP is one of the secondary outcomes and is explicitly built into the design of the intervention, so an outbreak should not pass unnoticed; we also note that this is much more likely to occur in older children, who are less likely to present to the study site. It is also possible that other entities (eg, Ontario Medical Association) could initiate antimicrobial stewardship interventions (eg, new social media campaign to discourage inappropriate antibiotic use) in our region during the study period that might influence the study’s ability to draw conclusions about the effectiveness of the intervention, although we know of none that are currently being planned.

The components of the novel care pathway are implementable in the context of a Canadian ED but would not be in other outpatient settings (such as in a clinic where diagnostics are either not available or costly to patients); consequently, the generalisability of this study is limited, especially given that it is a single-centre study.

Oversight and monitoring

Adverse event reporting and harms

The novel care pathway will likely result in fewer antibiotic prescriptions, and so could potentially be associated with recrudescence of CAP and symptoms associated with this (eg, fever, cough)—although these symptoms can also occur because of new (intercurrent) respiratory viral infection, which is not uncommon. We will be actively seeking evidence of potentially recrudescent infection and any participant with new or worsening respiratory symptoms will be asked to come back to hospital for evaluation at the ED or an in-hospital clinic. The prognosis of paediatric CAP is so good that we would doubt that any significant or life-threatening sequelae would result from the withholding of antibiotics for a short period of time in any child initially categorised as ‘low-risk’.

We do not expect any AEs associated with study-related specimen collection. NPS are done routinely at our institution as part of the work-up of children with CAP given how commonly it is caused by viral pathogens. Neither the POC CRP (finger-poke capillary testing) nor the UAg are expected to cause any AEs. Though we do not expect any adverse events related to study procedures, should an AE be thought to be ‘related’ or ‘possibly related’ to study activities, they will be documented fully.

Data monitoring committee and interim analyses

Given the low-risk nature of this study, we do not foresee the need for a data monitoring committee. The study will not conduct any interim analyses.

Ethical considerations

The protocol, the consent forms, and all participant-facing study materials have been approved by the Hamilton Integrated Research Ethics Board (#2021-13270) to verify adherence to Good Clinical Practice regulations. Informed consent will be obtained from the parent/legal caregiver of all participants and assent will be obtained from children aged 7–15 years old.

Dissemination plans

We expect that our novel care pathway will greatly improve care for children with non-severe CAP. End-of-grant KT methods will focus on presentations at local and national meetings and publication in major paediatric journals. Our research team includes leadership at the Hamilton Regional Laboratory Medicine Program (MS), which should facilitate post-study implementation, if appropriate.

The next stage in the research process would be to verify the generalisability and implementability of the novel care pathway in diverse EDs across Canada in a multicentre randomised trial. Research team members currently collaborate with established networks experienced in the conduct of multicentre randomised trials and dissemination of clinical guidelines, including the Association of Medical Microbiology and Infectious Disease Canada Clinical Research Network and Pediatric Emergency Research Canada (PERC). PERC involvement comes hand in hand with a direct knowledge translation follow through via Translating Emergency Knowledge for Kids, a sister network that disseminates evidence-based knowledge from PERC to community EDs across the country.

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Contributors JMP conceived the study, designed the study, wrote and revised the funding application, drafted the protocol, and revised the protocol critically. AJK and ME revised the funding application and protocol critically, with specific expertise.
relating to the management of children in the ED; they will also oversee ED implementation issues. SK, JW and DM revised the funding application and protocol critically, with specific expertise relating to the diagnosis and management of infectious diseases and the implementation of antimicrobial stewardship initiatives. DMG, FS, MS and ML revised the funding application and protocol critically, with specific expertise relating to the development and use of microbiological diagnostics; they will also oversee laboratory-based implementation issues. JE and LJ revised the funding application and protocol critically, with specific expertise relating to statistical analysis. MS revised the funding application and protocol critically, with specific expertise relating to the pharmacology of antibiotics. All authors have revised the final manuscript.

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**Competing interests** JMP’s institution has received grant funding from MedImmune for an RSV research study. ML is on the WHO EML Working group, a Paladin Labs advisory board, and a Sunovion Pharmaceuticals advisory board.

**Patient and public involvement** Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

**Patient consent for publication** Not applicable.

**Ethics approval** This study involves human participants and was approved by Hamilton Integrated Research Ethics Board 2021-13270-GRA. Participants gave informed consent to participate in the study before taking part.

**Provenance and peer review** Not commissioned; externally peer reviewed.

**Data availability statement** Data are available upon reasonable request. Data relating to the primary outcome will be made available upon reasonable request. These will be made available after study completion and publication.

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