




# BMJ Open Single-centre, open-label, randomised, trial to compare rapid molecular point-of-care streptococcal testing to standard laboratory-based testing for the management of streptococcal pharyngitis in children: study protocol

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## ABSTRACT

**Introduction** Streptococcal pharyngitis, which commonly occurs in children, should be treated with antibiotics. Clinical prediction rules to differentiate streptococcal pharyngitis from viral infection are not recommended in children. Rapid point-of-care (POC) antigen tests have limited sensitivity and so are not often used in Canadian paediatric emergency departments (EDs). Standard paediatric practice is to rely on laboratory-based testing, which often results in a delay before the results can be communicated to the patient; this may impede appropriate prescribing, decrease caregiver satisfaction and delay recovery. The objective of this study is to determine whether a novel rapid molecular POC assay for streptococcal pharyngitis leads to more appropriate antibiotic use in children seeking care in a paediatric ED than standard laboratory-based testing.

**Methods and analysis** A randomised, superiority, open-label, trial with two parallel groups. Children presenting to a tertiary paediatric ED at least 3 years of age who have a throat swab ordered for diagnosis of streptococcal pharyngitis will be eligible; those who have taken antibiotics within 72 hours prior to presentation and those with additional active infections will be excluded. The primary study outcome will be appropriate antibiotic treatment at 3–5 days postenrolment. Secondary outcomes include time to symptom resolution, caregiver satisfaction, caregiver/child absenteeism, number of subsequent healthcare visits, clinician satisfaction and incremental cost-effectiveness of POC testing. A total of 352 participants will be needed.

**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 trial 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** NCT04247243.

## Strengths and limitations of this study

- Randomised trial will enable more precise measurement of clinical benefits associated with the implementation of point-of-care streptococcal testing in a paediatric emergency department.
- An economic evaluation will be undertaken, which will permit the determination of whether the increased up-front testing costs are balanced by later cost savings during participant follow-up.
- Only a single-centre study so results may not be as generalisable.

## INTRODUCTION

### Background and rationale

Most pharyngitis is caused by viruses, for which treatment is not generally available. Group A Streptococcus (GAS) pharyngitis, in contrast, which accounts for 20%–40% of sore throat in children,<sup>1</sup> should be treated with antibiotics to prevent suppurative complications and rheumatic fever, to accelerate recovery and to diminish contagiousness and spread.<sup>1–3</sup> Unfortunately, viral and GAS pharyngitis have similar clinical presentations. As sore throat is one of the most common reasons for consulting a physician,<sup>4</sup> evidence-based approaches for the diagnosis/management of sore throat are needed. Clinical prediction rules do not obviate the need for microbiological testing in children<sup>1 5</sup> due to insufficient sensitivity (66%–94%) and specificity (40%–88%);<sup>6</sup> one large retrospective study did identify a small proportion of children at lowest risk, but this does not obviate the need for testing of the majority of cases.<sup>7</sup> Standard

laboratory-based diagnostic testing often takes at least 1 day, which makes timely and efficient antimicrobial prescribing challenging. Rapid point-of-care (POC) antigen tests have been around for decades but have limited sensitivity (65%–90%).<sup>8–10</sup> Given the increased prevalence of GAS pharyngitis and greater incidence of complications in paediatric populations, a negative rapid antigen test in children requires confirmatory testing by culture,<sup>1–9</sup> which greatly diminishes the utility of rapid antigen testing in an emergency department (ED).<sup>11</sup> Needless to say, the need to do back-up culture testing for all individuals testing negative for GAS pharyngitis at presentation will also increase the cost of this strategy.

Most paediatric EDs in Canada use standard laboratory-based GAS testing, which takes time: the swab must be transported to the lab, processed and the result then must be reported back to the requesting clinician. In practice, depending on the time/date that the patient presents and the particulars of the laboratory, it takes 24–72 hours to make the clinician aware of the result, who then has to contact the patient and arrange for treatment, if needed. Consequently, many ED clinicians discharge such patients with an antibiotic prescription to be held on to; if the swab is later found to be positive, the patient is telephoned and instructed to proceed to the pharmacy. This strategy, unfortunately, has some issues. Caregivers are not given a specific diagnosis, which reduces satisfaction<sup>12–13</sup> and promotes doctor-shopping; some caregivers will fill the prescription even if the culture is negative,<sup>14–15</sup> which incurs cost and potential drug-related harms; ED clinicians must spend time attempting to contact families whose children have positive test results, which diverts their attention from patients with acute illness; patients start treatment later, which delays clinical recovery<sup>16</sup> and potentially increases risk of spread; and many patients with positive cultures may not be reachable,<sup>11</sup> which increases the likelihood of sequelae.

The use of a molecular POC assay with accuracy comparable to the reference standard would obviate these problems by giving physicians a definitive result before ED discharge. Though the licensure of these assays<sup>17</sup> required verification of their performance characteristics, their implementation—and potential impact on patient-relevant outcomes—has never been evaluated extensively against a laboratory-based standard within the context of a randomised trial. The integration of a new POC assay into clinical pathways cannot be assumed to be simple. Furthermore, in addition to implementation considerations, cost is an important issue: the device itself, the consumable reagents and for the training of personnel to ensure this testing is conducted per the required standards. To be able to gauge whether these costs are bearable, we will need to establish whether implementation of the POC assay actually leads to better prescribing, quicker symptom resolution, and less healthcare utilisation. The proposed clinical trial will evaluate all potential benefits and costs of this novel care pathway.

## Objectives

The primary objective of this study is to determine whether rapid POC GAS testing for children aged 3–17 y with pharyngitis presenting to the ED leads to more appropriate antibiotic treatment at 3–5 days than laboratory-based testing, the reference standard. Secondary objectives are to determine whether rapid POC GAS testing is associated with more appropriate treatment by 7 days; quicker clinical recovery; less caregiver absenteeism; less child absenteeism; fewer healthcare visits; more caregiver satisfaction; more physician satisfaction; fewer household members with subsequent diagnoses of GAS pharyngitis; and less cost, from the payer perspective.

## METHODS

### Trial design

This study will be a randomised, superiority, open-label, trial with two parallel groups (1:1). Those randomised to the intervention arm will receive POC testing of their throat swab and their caregivers will be given testing results (and a prescription, if results are positive) prior to discharge. Those randomised to the control arm will receive standard care, which includes a throat swab processed by standard laboratory-based methods and a prescription at ED discharge that is not to be filled unless the positive results are communicated to the caregiver 24–72 hours later.

### Study setting and timing

The trial will be conducted in the ED of McMaster Children's Hospital (MCH), a tertiary care centre in Hamilton, Ontario. Enrolment began on 5 January 2021.

### Eligibility criteria

Any child presenting to the MCH ED aged 3+ years who has a throat swab ordered to diagnose GAS pharyngitis will be eligible to participate. We will exclude children who have taken any antibiotics within 72 hours prior to ED presentation, and those who are diagnosed with acute otitis media or bacterial pneumonia at the same visit, in order to ensure results are specific to the proposed intervention. There will be no exclusions for medical comorbidities, as both arms of this study will be receiving a validated test for GAS detection.

## INTERVENTIONS

### Explanation for the choice of comparators

There are several rapid POC GAS assays that are relatively simple to run.<sup>18</sup> The Abbott ID NOW Strep A2, approved by Health Canada for the detection of GAS in pharyngeal swabs, has been found to have a sensitivity of 98.5% (and a specificity of at least 93.4%) as compared with culture,<sup>17–19–20</sup> a positive result is signalled in ~3 min, and a negative result requires only 6 min to document, which is 10–15 min quicker than some of its competitors.<sup>21</sup>

TIMEPOINT	Child arrives in ED	Post Enrolment									
	Day 0	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 3-5	Day 7-10	
<b>Enrolment:</b>											
Eligibility screen	X										
Informed consent	X										
Baseline Data Collection	X										
Randomization	X										
<b>Allocation (randomized to one):</b>											
Point of Care Testing (Intervention)	X										
Standard Testing (Control)	X										
<b>ASSESSMENTS:</b>											
Caregiver Satisfaction	X								X	X	
Caregiver Diaries			X	X	X	X	X	X			
Follow-up contacts									X	X	

**Figure 1** Participant timeline. ED, emergency department.

The reference standard for GAS diagnosis has long been bacterial culture; classically, throat swabs are plated on sheep blood agar and incubated at 37°C for 18–24 hours.<sup>1 21</sup> Participants randomised to the control arm will have swabs processed for culture using the bioMérieux Walk Away Specimen Processor in the bacteriology laboratory.

**Intervention description and follow-up plans**

Participants randomised to the control arm will have their throat swabs (ESwab, flocked swabs with 1 mL Amies liquid medium, COPAN Diagnostics) processed as per standard care. Results, when available, are entered into

the laboratory electronic information system and paper results are also faxed back to MCH ED clinicians, who will call positive results back to study participants as per routine care (see figures 1 and 2).

Participants randomised to the intervention arm will have their throat swabs processed in the MCH ED by study personnel using the Abbott ID NOW and results will be provided back to the ED attending clinician. If an error occurs with the ID NOW processing, the result is indeterminate, or the participant is allergic to penicillin, the residual Amies solution from the swab will be sent to the bacteriology laboratory for processing as per standard care.

Study personnel will not be making treatment decisions for participants, regardless of group assignment; these will all be at the discretion of the attending ED physician. Participation in the study will only affect the diagnostic test used for the determination of whether GAS is detected on the swab.

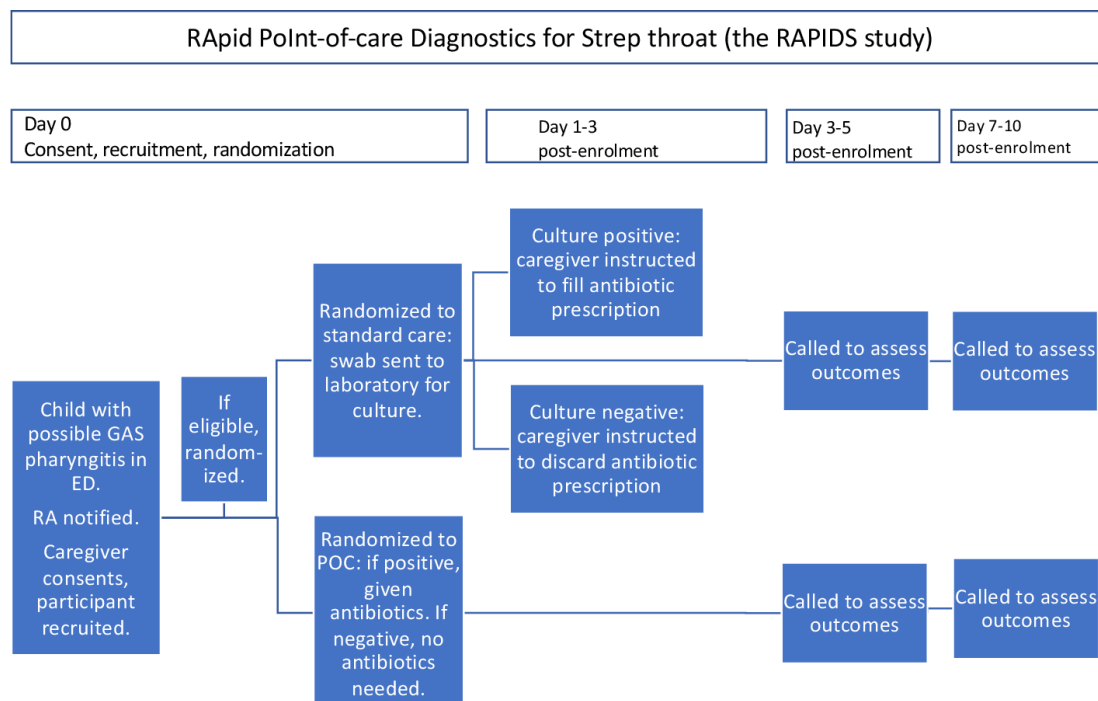
**Relevant concomitant care permitted or prohibited during the trial**

There are no restrictions to concomitant care during this trial. We will collect information about any antibiotics, antipyretics or other medications used.

**Outcomes**

**Primary outcome**

The primary study outcome will be the proportion of participants in each arm receiving appropriate antibiotic treatment (dichotomous outcome), measured by caregiver report at 3–5 days postenrolment. ‘Appropriate’ antibiotic treatment of the participant is defined as either:



**Figure 2** Flow chart. ED, emergency department; GAS, group A Streptococcus.

1. Throat swab is positive and participant receives antibiotics targeting (effective against) GAS.
2. Throat swab is negative and the participant does not receive antibiotics targeting (effective against) GAS.

All other combinations of throat swab results and antibiotic treatment scenarios will be deemed 'inappropriate.' To minimise social desirability bias, we will verify whether antibiotics were actually obtained at the patient's pharmacy (contact information taken at enrolment).

The primary outcome was selected because of its objective nature, important in the context of an open-label study, and its relevance to both patients and healthcare providers. We estimate that standard diagnostic pathways are associated with appropriateness rates of approximately 85%<sup>14,22</sup> and suggest that an absolute improvement in prescribing of at least 10% would be clinically relevant, especially given that the only significant disadvantage of the intervention is cost.

### Secondary outcomes

1. Appropriate antibiotic treatment by day 7 postenrolment.
2. Time to resolution of both participants' throat pain and fever in each arm, censored at day 10.
3. 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), censored at day 10.
4. The number of days that participants miss school/daycare in each arm, censored at day 10.
5. The number of healthcare visits for pharyngitis or related conditions for participants in each arm within 7 days.
6. Caregiver satisfaction in each arm, measured at three time points: discharge, day 3–5 and day 7–10.
7. The satisfaction of ED physicians who clinically manage the participants in each arm, measured within 48 hours of participant enrolment.
8. The satisfaction of ED physicians who do or do not have to make a call to participants to inform them of reference (culture) testing results, measured between 24 and 72 hours after participant enrolment.
9. The number of family members in each arm subsequently diagnosed with GAS pharyngitis within 7 days.
10. The incremental cost-effectiveness of POC testing, measured from the point of view of the healthcare system. The major costs will include the cost of testing, costs of medications, and costs of healthcare visits within 7 days; this will, therefore, be reported as the increased cost (if applicable) for each additional person treated appropriately with antibiotics.

### Sample size

We predict conservatively<sup>22</sup> that 85% of participants randomised to standard care will be treated appropriately. Given that a prospective open-label study found that 97.1% of participants undergoing rapid molecular testing for GAS pharyngitis were treated appropriately

with antibiotics,<sup>14</sup> we hypothesise that the intervention will be associated with a 10% absolute increase in appropriate treatment. To detect this change using  $\chi^2$  testing with 80% power, alpha=0.05, 160 participants/arm are needed. To account for 10% lost to follow-up, we will enrol a total of 352 participants.

### Recruitment

MCH ED physicians and nurses will inform study staff when they identify a participant of the appropriate age with a reasonable suspicion of streptococcal pharyngitis, especially if the ED physician orders a swab for GAS testing. There will also be documentation available so that caregivers of potential participants can independently obtain information about the study. If a potential participant is eligible, a study research assistant (RA) will obtain informed consent and the swab specimen will be randomised.

### Sequence generation, allocation concealment and randomisation

Participants will be randomly assigned 1:1 to intervention or control using a computer-generated randomisation schedule using variable block sizes. The randomisation schema was developed by personnel who will not be involved with participant recruitment. Randomisation will be accomplished using a web-based system (Research Electronic Data Capture, REDCap) which will not release the treatment allocation until eligibility has been verified and the patient has been recruited into the trial. The RAs who obtain informed consent will be the individuals who interface with the randomisation programme and receive the treatment allocation.

### Blinding

The nature of the intervention precludes blinding of participants/caregivers or of the study outcome assessors.

### Patient and public involvement

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

### Data collection and management

#### Plans for assessment and collection of outcomes

At recruitment, baseline clinical data collection will be minimal to encourage recruitment, minimise caregiver burden, and disrupt ED flow as little as possible. Age, gender, self-described race/ethnicity, medical comorbidities, symptoms at presentation (throat pain/fever/headache/other), duration of illness, number of family members, daycare/school attendance, Canadian Triage and Acuity Score (CTAS) score, McIsaac score, and time of ED triage will be recorded.

### Data management

Data will be collected on paper and entered into a secure online data management system (REDCap). Data will serve as source documentation and audit checks will be performed on all entered data to ensure accuracy.

## Confidentiality

Personal information for study participants required for follow-up will be collected on paper and stored in a secured location, available only to study personnel. No personal data will be entered into the online data collection forms in order to protect confidentiality.

## Data collection methods

### Primary outcome

GAS testing results will either be noted by the RA on the day of enrolment (for those randomised to the intervention arm) or will be abstracted from the MCH laboratory information system (for those randomised to the control arm) 24–72 hours after enrolment. The primary outcome will then be assessed by contacting the caregiver at day 3–5 postenrolment to determine whether the participant took antibiotics targeting (ie, effective against) GAS pharyngitis; this response will be compared with the testing result to determine appropriateness of treatment. Dispensing of antibiotics will be verified through contact with the participant's pharmacy.

### Secondary outcomes

The RA will note the time that informed consent is signed and collect demographic information from the caregiver at enrolment. Daily diaries will be distributed to all caregivers either on paper (at enrolment) or via email so that caregiver-report measures can be collected daily. Thermometers will be offered to all participants. Participants will be contacted at 3–5 days and at 7–10 days postenrolment.

Secondary outcomes will be measured as follows:

1. Antibiotic treatment by 7 days will be measured via caregiver report at the 7–10 day contact.
2. Time to resolution of symptoms will be measured using caregiver diaries; if these are not completed, the RA will measure this at the 3–5 days contact or the 7–10 days contact, as appropriate. Fever will be defined as  $\geq 38^{\circ}\text{C}$  oral or  $\geq 37.5^{\circ}\text{C}$  axillary and pain will be measured by the FACES scale.<sup>23</sup>
3. Number of days of missed school/daycare (participant) or work (caregivers) will be measured using caregiver diaries (self-report on a daily basis). If these are not completed, the RA will measure this by caregiver report at the 3–5 days contact and/or the 7–10 days contact, as appropriate. If work has already been disrupted by public health measures related to the COVID-19 pandemic, caregivers will be asked to judge how many days of work would have been disrupted had these measures not been in place. If school has already been disrupted by public health measures related to the COVID-19 pandemic, caregivers will be asked to judge how many days of school would have been missed had these measures not been in place.
4. The number of healthcare visits that the study participant has for pharyngitis or sinopulmonary infections (ie, acute otitis media, sinusitis or pneumonia) within 7 days will be assessed by the RA by caregiver report at the 7–10 days contact.
5. Caregiver satisfaction will be measured at enrolment (just prior to discharge from the ED) and again at each of the 3–5 days and 7–10 days follow-ups. This will be done by asking the following questions (previously used and validated in a similar context<sup>24–26</sup>):
  - a. 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)
  - b. How satisfied are you with the doctor's diagnosis? (extremely satisfied/very satisfied/moderately satisfied/slightly satisfied/not very satisfied/not at all satisfied)
  - c. How satisfied are you with the antibiotic treatment plan? (extremely satisfied/very satisfied/moderately satisfied/slightly satisfied/not very satisfied/not at all satisfied)
6. Attending ED physician satisfaction will be assessed at the time of enrolment in person by the RA or by email within 48 hours of enrolment. This will be done by asking the following question:
  - a. How helpful was the GAS testing method that you used today for your overall management plan? (Extremely so/very much so/moderately so/not very much/not at all)
7. The satisfaction of the ED clinician who has to make the follow-up call for testing results or the ED clinician who has to make calls on the day subsequent to participant enrolment (in the event that the participant was randomised to POC testing), will be assessed on that day in person by the RA, or by email within 48 hours of that time. This will be done by asking the following question:
  - a. How disruptive was it to you today to follow-up the study participant to inform them of testing results? (Extremely so/very much so/moderately so/not very much/not at all)
8. To determine the impact of having to make follow-up calls on the ED clinician's time, the number of phone call attempts required to contact the participant will also be recorded.
9. Caregivers will be asked about the number of household contacts subsequently diagnosed with GAS pharyngitis by the RA at the time of the 3–5 days and 7–10 days contacts.
10. The following data will be recorded for all participants as part of the economic evaluation:
  - a. Time between signing informed consent and official ED discharge time on the day of enrolment (noted by the RA during/after enrolment).
  - b. Method of diagnosis (standard GAS culture or POC testing, present in randomisation database).
  - c. Cost of antibiotics prescribed (information acquired from pharmacy after 7–10 days RA phone call).
  - d. Number and type of healthcare visits in the 7 days after enrolment.

## Retention

The study intervention is very brief and follow-ups are done remotely soon after enrolment, so we predict less than 10% lost to follow-up.

## Data management

In this study, source documentation will be primarily paper-based. All forms will be kept securely at a research office at MCH. A study master list linking names and direct identifiers to study ID codes will be kept separately from study source documentation. Data will then be uploaded to a secure REDCap database, where data rules, range checks, and valid values can be periodically checked/enforced, to optimise accuracy and fidelity of data entry. All modifications to the database will be tracked and users will all have specific privileges with respect to data handling. Source documentation will be kept for a total of 10 years.

## Statistical methods

### Statistical methods for primary and secondary outcomes

This trial will be reported as per the Consolidated Standards of Reporting Trials guideline. Baseline characteristics will be described and reported by group using count (%) for categorical variables, and mean (SD) or median (IQR) for continuous variables, depending on the distribution of the variable in question. All analyses of outcomes will be intention to treat; those who are randomised to the intervention arm but who have errors in POC testing necessitating laboratory-based culture will be analysed in the intervention group. We will use logistic or binomial regression to analyse binary outcomes (including the primary outcome) with results reported as OR or relative risk, corresponding 95% CI and associated p value (see [table 1](#)). We expect to have sufficient events for logistic regression based on the rule of thumb of 10–15 events for each degree of freedom to avoid overfitting.<sup>27</sup> For time to resolution, we will use Cox regression analysis and use Kaplan-Meier curves to display the data. Comparisons between groups will be based on the log-rank test with the effect estimate reported as hazard ratio (95% CI and associated p value). For count outcomes, we will use Poisson regression and report the results as incidence rate ratio, corresponding 95% CI and p value. For satisfaction outcomes, we will use non-parametric methods (such as the Mann-Whitney U test). Economic evaluation will be conducted by comparing outcomes and costs between arms; measures will be incremental cost per effect ratio between arms (with estimated 95% CI around ratios), with appropriate treatment being the main effect indicator. We hypothesise that the point estimate for the magnitude of improvement in appropriateness in prescribing (the primary outcome) in the intervention arm as compared with the control arm will be higher in participants with more prior visits to healthcare professionals and in participants with higher baseline fevers, so we have planned those subgroup analyses. We will perform sensitivity analyses to assess the robustness of the results to variations

in key assumptions and the subgroup of participants who have a MacIsaac score of 2 or greater. Although we do not foresee the likelihood of missing data, we will use multiple imputation to account for missing data as a sensitivity analysis should this arise. All analyses will be performed using SAS V.9.4.

## Oversight and monitoring

### Adverse event reporting and harms

We do not expect any significant harms associated with the intervention or study procedures, given that we are not taking any additional samples from participants and not prescribing additional or different treatments. However, we will record all adverse events (AEs) experienced by study participants that occur after enrolment until the final follow-up visit (phone call at days 7–10). AEs are defined as any untoward occurrence in a study participant, regardless of causality or relation to study procedures. We expect that most participants found to have streptococcal pharyngitis, regardless of whether they are assigned to the intervention or control arms, will be treated with amoxicillin or other antibiotics. Specific AEs associated with amoxicillin and other antibiotic therapy include rash, nausea, diarrhoea, candidiasis and, rarely, anaphylaxis. We would expect that participants will be counselled about the risk of these AEs by their treating physician and will encourage all study participants to seek medical care (either at the MCH ED or with their family physicians) should they develop these drug-related AEs. We will report all AEs that appear to be caused by or related to study procedures to the Hamilton Integrated Research Ethics Board, as per standard operating procedures.

### Data monitoring committee and interim analyses

In this randomised trial, the risks associated with the intervention are very small. As a result, we will not be doing interim analyses, and we do not feel that a data monitoring committee is warranted.

## Ethical considerations

The protocol, the consent forms, and all participant-facing study materials have been reviewed and approved by the Hamilton Integrated Research Ethics Board (approval #2020–8067) to verify adherence to Good Clinical Practice regulations. Informed consent will be obtained by research staff from all caregivers; additionally, assent will be required from all participants aged 7–15 years and consent will be required from all participants aged 16 and over.

## Dissemination plans

The principal knowledge translation goal of this study will be to facilitate integration of trial results into current Canadian guidelines and disseminate the information to the healthcare community. Should POC GAS testing be shown to confer significant benefit at a reasonable cost, we would expect that this would become standard of care at the MCH ED and envision that this testing would be

**Table 1** Variables, hypotheses, outcome measures and analysis methods

Variable/outcome	Hypothesis	Outcome measure	Method of analysis
<b>Primary</b>			
Appropriateness of antibiotic treatment	Better in intervention arm than control arm	Comparison of swab testing result and caregiver report of whether participant given antibiotics (dichotomous)	Logistic or binomial regression
<b>Secondary</b>			
Time to resolution of throat pain and fever	Shorter in intervention arm than control arm	Daily diary records, caregiver report (time to event)	Cox regression
No of days of missed school/daycare by participant	Fewer in intervention arm than control arm	Daily diary records, caregiver report (count)	Poisson regression
No of days of missed work by participant's caregivers	Fewer in intervention arm than control arm	Daily diary records, caregiver report (count)	Poisson regression
No of healthcare visits that the participant has for pharyngitis or sinopulmonary infection within 7 days	Fewer in intervention arm than control arm	Caregiver report (count)	Poisson regression
Caregiver satisfaction at enrolment	Higher in intervention arm	Caregiver report (ordinal)	Mann-Whitney U test
Caregiver satisfaction at day 3–5	Higher in intervention arm	Caregiver report (ordinal)	Mann-Whitney U test
Caregiver satisfaction at day 7–10	Higher in intervention arm	Caregiver report (ordinal)	Mann-Whitney U test
Attending ED physician satisfaction at recruitment	Higher in intervention arm	ED physician report (ordinal)	Mann-Whitney U test
Attending ED physician satisfaction at the time of call-back	Higher in intervention arm	ED physician report (ordinal)	Mann-Whitney U test
No of household contacts subsequently diagnosed with GAS pharyngitis	Fewer in intervention arm	Caregiver report (count)	Poisson regression
<b>Subgroup analyses</b>			
Participants with >1 visit to a healthcare provider before presentation compared with those with one or less visits	Magnitude of improvement of appropriateness in intervention arm as compared with control arm increased in subgroup with >1 visit	Appropriateness of antibiotic treatment	Logistic or binomial regression
Participants with highest temperature >39.4°C (102.9°F) in 24 hours prior to enrolment compared with those with highest temperature of 39.4°C (102.9°F) or lower	Magnitude of improvement of appropriateness in intervention arm as compared with control arm increased in subgroup with initial highest temperature >39.4°C (102.9°F)	Appropriateness of antibiotic treatment	Logistic or binomial regression
<b>Sensitivity analyses</b>			
Only participants with MacIsaac score of 2+	Results will remain robust	Appropriateness of antibiotic treatment	Logistic or binomial regression
Inclusion of participants with missing data	Results will remain robust	Appropriateness of antibiotic treatment	Logistic or binomial regression with multiple imputation for missing data

ED, emergency department; GAS, group A Streptococcus.



considered for implementation at other similar EDs across Canada. To accomplish this goal, research team members will collaborate with established networks of clinicians experienced in the dissemination of clinical guidelines to healthcare practitioners; these collaborations will be stimulated through presentation at major conferences. The KT strategy will also focus on publication of results in a peer-reviewed high-impact journal.

## DISCUSSION

The proposed study will evaluate all important benefits of a POC GAS assay so that improvements in antibiotic administration, caregiver satisfaction, and clinician satisfaction can be measured accurately—so that these predicted benefits can be weighed against the increased costs of implementing POC diagnostic testing.

There will be limitations to this study. It will only be at a single centre; consequently, it is possible that the types of patients who present with suspected GAS pharyngitis at MCH are not comparable to those who present to other children's hospitals, let alone community hospitals, either in Canada or other high-income countries. The benefit of rapid POC testing could be attenuated in settings where patients are more likely to trust their physician and/or adhere to their recommendations; conversely, the benefits of rapid POC testing would likely be greater in settings where it is easier for patients to 'doctor-shop' and/or where there is increased baseline prescribing of antimicrobials for respiratory infections.

The cost of rapid POC testing is not limited to the device and consumables. Medical laboratory licensing is contingent on ongoing quality assurance and quality control, with which laboratory personnel—but likely not ED-based clinicians—are very familiar. There will be costs, primarily related to training and maintenance of competence, related to the implementation of another POC diagnostic test that will not be measured in this study.

Having said that, this intervention under study in the proposed trial is one of the few that offers real benefit to both patients and clinicians, with the only real impediment to implementation being a moderate increase in cost. Consequently, we feel that this study is critical to undertake as part of our vision of improving paediatric ED-based care in Canada. This trial will also gather important data that will serve to inform a multicentre implementation study, which will address the previously-mentioned limitations as related to external validity.

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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. FS, AJK, MSm, SK, MSu and LT revised the funding application and protocol critically. AB, QD and DMG revised the protocol critically.

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**Competing interests** None declared.

**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.

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