

# **PRImary care Streptococcal Management (PRISM) study: in vitro study, diagnostic cohorts and a pragmatic adaptive randomised controlled trial with nested qualitative study and cost-effectiveness study**

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**Declared competing interests of authors:** Paul Little is a member of the NIHR Journals Library Board. James Raftery is a member of the HTA Editorial Board and NIHR Journals Library Editorial Group.

Published January 2014

DOI: 10.3310/hta18060

## Scientific summary

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Health Technology Assessment 2014; Vol. 18: No. 6

DOI: 10.3310/hta18060

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# Scientific summary

## Background

The overuse of antibiotics in primary care not only increases the risk of antibiotic resistance but exposes patients to side effects, and medicalises what are mostly self-limiting illnesses. Antibiotics are still prescribed for most patients attending primary care with acute sore throat, despite evidence from systematic reviews that there is modest benefit overall from antibiotics. Approaches to targeting antibiotics could facilitate more appropriate use of antibiotics, either targeting antibiotics using clinical scoring methods or using rapid antigen detection tests (RADTs). RADTs are very commonly used in many countries and are designed to detect the major bacterial pathogen Lancefield group A beta-haemolytic streptococcus (GABHS). However, there is debate about the importance of other major groups of streptococci (particularly Lancefield groups C and G). Furthermore, there is uncertainty about the variables that most clearly predict the presence of streptococci, and about the most appropriate RADTs to use in primary care. There is also very little robust trial evidence comparing management alternatives.

## Objectives

1. *In vitro study*: to assess in vitro validity and ease of use of several commercially available RADTs to detect GABHS and to explore the impact of using commercially available swabs instead of the swabs provided with the kits.
2. *Clinical diagnostic study*: to assess the incidence and clinical variables associated with streptococcal infections and develop a clinical score to help target antibiotic use.
3. *Randomised controlled trial*: to compare the targeting of antibiotics using a clinical score, or, alternatively, using a clinical score combined with a RADT, with empirical delayed antibiotic prescribing.
4. *Qualitative study*: to explore patients' and health-care professionals' (HCP) views of clinical scores and RADTs.
5. *Cost-effectiveness analysis*: to assess resource use and the health-related quality of life associated with clinical scores and RADTs and to show whether these can represent an efficient use of NHS resources.

## Methods

1. *In vitro study*: different concentrations and strains of GABHS and non-GABHS were assessed with OSOM<sup>®</sup> Ultra Strep A (Bio-Stat Limited, Stockport, UK), QuickVue<sup>®</sup> Dipstick Strep A test (TK Diagnostic, Oxford, UK), Streptatest<sup>®</sup> (DECTRA PHARM, Strasbourg, France), Clearview<sup>®</sup> Exact (Inverness Medical Professional Diagnostics, Bedford, UK) and IMI TestPack<sup>®</sup> Plus Strep A (Inverness Medical, Bedford, UK). Each kit was rated for ease of use. Test kit swabs were also compared with commercially available swabs.
2. *Clinical diagnostic study*: the variables significantly associated with the presence of pathogenic streptococci from throat swabs were assessed among patients aged  $\geq 5$  years presenting with acute sore throat in two cohorts of patients. Logistic regression was used to identify significant variables to incorporate in clinical prediction rules, and bootstrapping was used to estimate the area under the receiver operating characteristic (ROC) curve. Patients were recruited for a second cohort (cohort 2,  $n = 517$ ) consecutively after the first (cohort 1,  $n = 606$ ) from similar practices.
3. *Randomised controlled trial*: 1760 patients aged  $\geq 3$  years with acute sore throat were individually randomised using a web-based program to one of three structured approaches targeting antibiotic use according to (1) delayed antibiotic prescribing (control), (2) clinical score or (3) RADT use determined by a clinical score. The main outcomes were symptom severity, symptom duration and antibiotic use

(all of which were documented in > 80% of participants). The trial was not initially designed as an adaptive trial, but revision of the trial design and modification of the intervention were needed once it became clear that the first clinical score that was developed was not likely to be valid. The adaptive design was implemented once the change in design had been agreed with the funder.

4. *Qualitative study*: Semi-structured face-to-face and telephone interviews were conducted with general practitioners (GPs) and nurse practitioners (NPs) from general practices across Hampshire, Oxfordshire and the West Midlands.
5. *Cost-effectiveness analysis*: A cost-utility study [cost/quality-adjusted life-year (QALY)] and a cost-effectiveness study (cost/change in symptom severity) were carried out as part of the randomised controlled trial. Resource use data were obtained from GP case notes and from study clinicians. QALYs were estimated by means of EQ5D scores obtained from the 14-day diary.

## Results

1. *In vitro* study: The IMI test was the easiest to use. Sensitivity increased with higher streptococcal concentration: at high concentrations sensitivity ranged from 62% [Clearview; 95% confidence interval (CI) 51% to 72%] to 95% (OSOM and IMI; 95% CI 88% to 98%). All tests were specific (100%). Most kits performed well independent of what swab was used, but Clearview was much more sensitive with polyester swabs than the kit swabs and rayon swabs.
2. *Clinical diagnostic study*: A, C or G beta-haemolytic streptococci were found in 40% of participants in cohort 2 and 34% in cohort 1. There was variation in the items that were significant in multivariate analysis in both cohorts. The clinical features predicting the presence of these streptococci in multivariate analysis in both cohorts were as follows: short prior duration of illness (attend rapidly in  $\leq 3$  days; multivariate-adjusted odds ratio 1.92 cohort 1, 1.67 cohort 2); fever in the last 24 hours (1.69, 2.40); and doctor's assessment of severity (severely inflamed pharynx/tonsils) (2.28, 2.29). Absence of coryza or cough and purulent tonsils were also significant predictive variables in univariate analysis in both cohorts and in multivariate analysis in at least one cohort. A five-item score based on Fever, Purulence, Attend rapidly ( $\leq 3$  days), severe Inflammation and No cough or coryza (acronym FeverPAIN) had moderate predictive value (bootstrapped estimates of area under ROC curve 0.73 cohort 1, 0.71 cohort 2) and performed well in identifying a substantial number of participants at low risk of streptococcal infection (38% in cohort 1 and 36% in cohort 2 scored  $\leq 1$ , associated with streptococcal percentages of 13% and 18%, respectively). A Centor score of  $\leq 1$  identified 23% and 26% of participants with streptococcal percentages 10% and 28%, respectively.
3. *Randomised controlled trial*: A preliminary score to predict streptococcal infection (score 1;  $n = 1129$ ) was replaced by a more valid score (FeverPAIN,  $n = 631$ ) in an adaptive trial design. There were no significant differences between groups for score 1, and it performed significantly less well than FeverPAIN for the key outcomes. For FeverPAIN, symptom severity was documented in 80% of patients [delayed 168/207 (81%); clinical score 168/211 (80%); RADT 166/213 (78%)]. Severity was lower in the clinical score group than in the delayed prescribing group ( $-0.33$ ; 95% CI  $-0.64$  to  $-0.02$ ;  $p = 0.039$ ; equivalent to one in three rating sore throat a slight rather than moderately bad problem), and a similar reduction was observed for the RADT group ( $-0.30$ ;  $-0.61$  to  $-0.00$ ;  $p = 0.053$ ). Moderately bad or worse symptoms resolved significantly faster (30%) in the clinical score group (hazard ratio 1.30; 95% CI 1.03 to 1.63) but not in the RADT group (1.11; 95% CI 0.88 to 1.40). In the delayed group, 75/164 (46%) used antibiotics, and 29% fewer used antibiotics in the clinical score group (risk ratio 0.71; 95% CI 0.50 to 0.95;  $p = 0.018$ ) and 27% fewer in the RADT group (0.73; 95% CI 0.52 to 0.98;  $p = 0.033$ ). No significant differences in complications or reconsultations were found.
4. *Qualitative study*: Fifty-one participants took part in the study. Of these, 42 were HCPs (29 GPs and 13 NPs) and nine were patients. HCPs could see a positive role for RADTs in terms of reassurance, as an educational tool for patients and for aiding inexperienced practitioners, but also had major concerns about RADT use in clinical practice. A particular concern was the tension and possible disconnect with clinical experience and intuition – a concern which was also raised about clinical scores. Other issues included the validity of the tests (the role of other bacteria, and carrier states), the issues of time and

resource use, and the potential for medicalisation of self-limiting illness. In contrast, however, experience of using RADTs over time seemed to make some participants more positive about using the tests. Moreover, patients were much more positive about the place of RADTs in providing reassurance and in limiting their antibiotic use.

5. *Cost-effectiveness analysis*: As score 1 had not been shown to be effective but FeverPAIN appeared to be effective, the cost-effectiveness results are only presented for the second part of the trial, when FeverPAIN was used. There were 499 individuals who had both symptom severity and cost data from case notes review. Costs for the initial visit and for the 1-month follow-up were similar at £51, £44 and £52 for the delayed, clinical score and RADT groups, respectively. The clinical score group dominated both other groups for both the cost/QALY and cost/change in symptom severity analyses, being both less costly and more effective. Cost-effectiveness acceptability curves indicated the clinical score method to be the most likely to be cost-effective in both cases.

## Conclusions

1. *In vitro study*: The IMI TestPack was suitable for use with high sensitivity, specificity and ease of use.
2. *Clinical diagnostic study*: Non-group A strains commonly cause streptococcal sore throats, and present with similar symptomatic clinical features to group A streptococci. The variables that are predictive of streptococcal infection vary between cohorts, and thus the conventional approach of a single development cohort and then a subsequent validation cohort may not identify the optimal variables to test in a clinical prediction rule. From the two cohorts, a five-item score (acronym FeverPAIN) is likely to be valid (Fever during the last 24 hours, Purulent tonsils, Attend rapidly ( $\leq 3$  days), very Inflamed pharynx, No cough/coryza), but further validation is required.
3. *Randomised controlled trial*: Targeting antibiotic using a clinical score (FeverPAIN) improves control of symptoms and reduces antibiotic use. A rapid antigen test combined with a clinical score provides similar benefits for antibiotic use, but no clear advantages over using a clinical scoring method alone.
4. *Qualitative study*: It is unlikely that RADTs will have a comfortable place in clinical practice in the near future until health professionals' concerns are met, and they have direct experience of using them. The routine use of clinical scoring systems for acute upper respiratory tract illness also faces barriers related to clinicians' perceptions of their utility in the face of clinician experience and intuition.
5. *Cost-effectiveness study*: Using a clinical score appears to be an efficient use of health-care resources compared with either delayed antibiotic prescribing or the use of a RADT combined with a clinical score.

## Overall conclusion

Rapid antigen detection tests that are inexpensive, accurate and easy to use are potentially widely available for use in primary care. Although they will detect Lancefield group A streptococci, they are not designed to detect non-group A strains that commonly cause streptococcal sore throats, and present with a similar illness to group A streptococci. The variables that are predictive of streptococcal infection vary between different samples, but from the two cohorts of patients a five-item score (acronym FeverPAIN) is likely to be valid, but further validation is required. Targeting antibiotic using a clinical score (FeverPAIN) improves control of symptoms, reduces antibiotic use and is very cost-effective. Using a rapid antigen test in addition to using the clinical score provides no clear benefits for patients over using the clinical score alone, and is more costly, less cost-effective and faces several barriers from clinicians. The implementation of clinical scoring methods in everyday practice will require health professionals' issues related to the perceived utility of clinical scores in the face of clinical experience and intuition to be addressed.

## Suggestions for further research

This study has demonstrated the limitation of using one data set to develop a clinical score. FeverPAIN, derived from two data sets, appears to be valid and its use improves outcomes, but diagnostic studies to confirm the validity of FeverPAIN in other data sets and settings are needed.

Experienced clinicians need to identify barriers to the use of clinical scoring methods. Implementation studies that address perceived barriers in the use of FeverPAIN are needed.

## Trial registration

This trial is registered as ISRCTN32027234.

## Funding

Funding for this study was provided by the Health Technology Assessment programme of the National Institute for Health Research.

ISSN 1366-5278 (Print)

ISSN 2046-4924 (Online)

Five-year impact factor: 5.804

*Health Technology Assessment* is indexed in MEDLINE, CINAHL, EMBASE, The Cochrane Library and the ISI Science Citation Index and is assessed for inclusion in the Database of Abstracts of Reviews of Effects.

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## This report

The research reported in this issue of the journal was funded by the HTA programme as project number 05/10/01. The contractual start date was in October 2006. The draft report began editorial review in August 2012 and was accepted for publication in January 2013. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the reviewers for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

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