# A randomized controlled trial to investigate whether a multifaceted Antimicrobial Stewardship Program can improve adherence to guidelines for diagnosis and treatment of uncomplicated pharyngotonsillitis in primary care

# Abstract

**Background:** In order to achieve a rational use of antibiotics and slow down the development of antibiotic-resistant bacteria, it is important to develop and scientifically evaluate Antimicrobial Stewardship Programs (ASP), the purpose of which is to reduce unnecessary use of antibiotics. Pharyngotonsillitis (sore throat) is one of the most common causes of antibiotic prescription in primary care. Since adherence to guidelines on diagnosis and treatment of pharyngotonsillitis is insufficient, a well-defined, repeatable and scientifically evaluated ASP needs to be developed for this purpose.

**Aims and objectives:** To develop an ASP for pharyngotonsillitis and evaluate whether this intervention can increase compliance with guidelines for the diagnosis and treatment of pharyngotonsillitis in primary care.

**Study Methods:** A randomized controlled trial in which 50 primary health care centres (PHCCs) in Västra Götaland are randomized either to an intervention group implementing the newly developed ASP for pharyngotonsillitis or to a control group.

The intervention lasts for six months, including both doctors and nurses and involving reflective meetings on guidelines, didactic patient cases, identification of local improvement opportunities, the establishment of an action plan and recurrent feedback in the form of a lab- and diagnosis-linked prescription statistic for pharyngotonsillitis.

Antibiotic prescription for pharyngotonsillitis is followed up in relation to a rapid antigen detection test (RADT) for group A streptococci (GAS). Primary outcome measure: the proportion of patients with antibiotic-treated pharyngotonsillitis who have a positive RADT for GAS. Change in outcome measures will be compared between the control group and the intervention group at 6, 12 and 18 months.

**Expected Results:** If the trial shows that this ASP leads to increased adherence to guidelines for pharyngotonsillitis, the implementation of this ASP could lead to more rational use of antibiotics.

# Background

Antibiotic-resistant bacteria are becoming more common and constitute one of the biggest threats to our future health [1, 2]. To slow down this development, it is important not to prescribe antibiotics unnecessarily [3]. Pharyngotonsillitis (sore throat) is one of the most common causes of antibiotic prescribing in primary health care centres (PHCCs) [4, 5]. In the clinical everyday life, general practitioners (GPs) experience uncertainty about the treatment of patients with pharyngotonsillitis [6], and adherence to guidelines on diagnostics and treatment of pharyngotonsillitis needs to be improved [4, 7]. The single most important rule-of-thumb in primary care is to normally only prescribe antibiotics for pharyngotonsillitis when a positive rapid antigen detection test (RADT) for beta-haemolytic streptococci group A (GAS) is presented [8, 9].
It is important for GPs to have the opportunity to reflect on their own antibiotic prescribing, to have regular interdisciplinary discussions at the PHCC about antibiotics and guidelines to increase knowledge and understanding of the guidelines and thus feeling confident in the clinical everyday life [10-14]. Structural factors at the PHCC such as the manager's involvement and nurses' work on telephone counselling and on triage reception are also important in achieving a rational use of antibiotics [10]. Antimicrobial Stewardship Programs (ASP) are structured multifaceted interventions to reduce unnecessary antibiotic use and have in many cases led to more rational use of antibiotics within inpatient care [15-17]. There is largely no evidence showing which ASPs are effective in PHCCs, at least from a Swedish perspective since we have a comparatively low rate of antibiotic prescribing [17, 18].
Since pharyngotonsillitis is common and adherence to guidelines is insufficient, there is a need for a well-described, repeatable and scientifically evaluated ASP for pharyngotonsillitis.

# Aims and Objectives

To scientifically develop and evaluate an ASP to see if this intervention can increase adherence to guidelines for the diagnosis and treatment of pharyngotonsillitis in primary care.

# Research questions

Is there a difference between PHCCs randomized to ASP intervention or control in change from baseline and measurements after 6, 12 and 18 months regarding the following outcomes:

1. the proportion of patients with pharyngotonsillitis prescribed antibiotics (J01 excluding methenamine) having a positive RADT for GAS? (Pharyngotonsillitis is a collective term that covers several diagnostic codes (ICD-10 codes))?
2. the proportion of patients with pharyngotonsillitis and a negative rapid test for GAS prescribed antibiotics (J01 excluding methenamine)?
3. the proportion of patients with pharyngotonsillitis prescribed recommended first-line antibiotics (in Sweden phenoxymethylpenicillin = PcV)?
4. the proportion of patients given a diagnosis of pharyngotonsillitis where CRP was analysed?

The following research questions will not estimate change but rather focus on a description of numbers during the baseline period:

5. the proportion of patients with pharyngotonsillitis prescribed antibiotics where no throat swab was taken

6. the proportion of patients given a diagnosis of pharyngotonsillitis where throat swab culture was analysed?
7. the proportion of patients given a diagnosis of pharyngotonsillitis where a rapid test for mononucleosis was analysed?

Is there a correlation between any change in the proportion of patients with antibiotic-treated (J01 excluding methenamine) pharyngotonsillitis with a positive RADT for GAS and the structural factors in the intervention group:

- the size of the PHCC (number of enlisted patients) and the age profile of enlisted patients?
- the number of patients with pharyngotonsillitis per 1000 enlisted patients and year?
- geographical location (large or mid-sized city versus small village)?
- Adjusted Clinical Group (ACG; a measure for evaluating the enlisted population's state of health)?
- Care-need index (CNI, socio-economic variables)?
- Type of PHCC: private/public?
- staffing (proportion of permanent-employed GPs, Residents, interns and locum tenens)?

# Study Methods

## Target and Study Population

50 PHCCs in the southwest of Sweden (Västra Götaland Region), volunteering to participate in this project, are randomized either to an intervention group, implementing the newly developed ASP for pharyngotonsillitis, or to a control group.

### Inclusion criteria:

- PHCCs located in Västra Götaland with an agreement with Region Västra Götaland (there are about 200 such PHCCs).
- The PHCC has at least 3 medical practitioners (required for reflective meetings to be meaningful).
- The PHCC has an electronic medical record compatible with the data extraction tool MedRave Primary Care.
- The PHCC has a license for the data extraction tool MedRave Primary Care.

### Exclusion criteria:

- Newly opened PHCCs that have been in existence for less than one year (excluded because reliable measurement cannot be made at baseline)

### Calculation of sample size (power calculation)

Assuming linear regression where the independent variable is the group affiliation (control or intervention), an effect size (Cohen's d) of 0.3, a significance level of 0.05 and a power of 0.95. Under these assumptions, 45 primary care centres are required. In order to have a safety margin, we will strive to include 50 primary care centres.

## Study Design

## PHCCs randomized to the intervention group

Any PHCC in Region Västra Götaland, Sweden, are required to have a dedicated contact GP to Strama Västra Götaland in order to be eligible for public funding: “The PHCC must have knowledge of current antibiotic resistance data, its adherence to treatment guidelines for infections in primary care and antibiotic prescription. The primary care centre must also appoint ASP physicians who cooperate with, and together with the operations manager, report to Strama Västra Götaland in these areas.”
These physicians, who already have a deep understanding of the issues around antibiotic stewardship, will be responsible for the ASP on their respective PHCC (called “ASP physicians”).

In order to be able to carry out the intervention, the ASP physicians at the PHCCs randomized to the intervention will receive training to lead workshops about diagnosis and treatment of pharyngotonsillitis at their PHCC. The workshops will include a Powerpoint presentation on current guidelines for pharyngotonsillitis, a discussion on a case study of pharyngotonsillitis with didactic questions and a tutor manual, present lab- and diagnosis-linked prescribing statistics of pharyngotonsillitis to their colleagues at the PHCC, to identify areas of potential improvement and to create an action plan based on this, which is then followed up at the PHCC as described below. Strama prepares and provides all the required materials for these workshops. The PHCCs' ASP physicians are trained during the month before the intervention commenced and the training will be held by the project manager and Strama Västra Götaland. Several training opportunities will be offered so that all ASP physicians at the PHCCs in the intervention group will be able to attend the training.

## The ASP physician leads a workshop at the PHCC with the following content:

All permanently employed doctors who are on duty at the PHCC will attend the reflective meeting as well as the practice manager of the PHCC's. The reflective meeting is led by the ASP physician. At least one representative of the nurses participates, if possible, all nurses participate in the meetings and also the PHCC's laboratory staff. The reflective meeting includes:

- A PowerPoint presentation, prepared by Strama Västra Götaland, which illustrates guidelines on diagnosis and treatment for pharyngotonsillitis in primary care including a short patient case.
- An extensive discussion around hypothetical cases of patients with pharyngotonsillitis. Didactic questions are posed to facilitate discussion. The discussion is led by the ASP physician who uses a supervisor manual to facilitate the discussion.
- The ASP physician will, before the reflective meeting, extract lab- and diagnosis-linked prescription statistics for pharyngotonsillitis during the past year (using the “tonsillitis module” in the software “Medrave4 Primary care”). These statistics are prepared for the PHCC as a whole and for each individual doctor in the primary care centre to form the basis for self-reflection. The ASP physician presents this data at the workshop. Based on the statistics, the PowerPoint presentation and the discussion of the patient cases, the participants identify which opportunities for improvement are available at their PHCC. This is summarised in a structured form, which is also part of the CRF (Case Report Form). Individual doctors' prescriptions form the basis for self-reflection but are not reported in CRF, where only the PHCC's combined diagnosis-linked prescription statistics are reported for pharyngotonsillitis.
- Based on identified improvement opportunities, the workshop continues with a discussion about suitable measures at the PHCC, in order to improve. The practice manager participates in this discussion. The resulting action plan is documented in the CRF.

### Follow-up meetings on primary care centres in the intervention group:

- Every two months, during the intervention process (six months), the ASP physician extracts the PHCC's lab- and diagnosis-linked prescription statistics for pharyngotonsillitis for the last two months. The statistics are presented in a doctor meeting or staff meeting to follow up on the action plan. This statistic is extracted for the PHCC as a whole and for each individual doctor to form the basis for self-reflection. Based on the result, the continued work is adjusted as needed and the ASP physician notes a summary in the PHCC's CRF.
- If questions arise during the intervention, the ASP physician can consult with Strama Västra Götaland.

# The control group

PHCCs that are randomized to the control group do not receive any study-related active intervention and the doctor who is responsible for reporting antibiotic prescription statistics to Strama at these PHCCs do not receive the above mentioned ASP training. The PHCCs in the control group, like all other PHCCs in Västra Götaland, participate in the activities that Strama Västra Götaland carries out regardless of this project.

# Data collection

### Collected data for all PHCCs (intervention group + control group)

The following data is collected for all PHCCs, both in the intervention group and the control group; at the start of the study (when the intervention starts at the PHCCs = baseline), as well as 6, 12 and 18 months after the date when the PHCCs in the intervention group begin the intervention with reflective meetings around pharyngotonsillitis.

**Quality indicators for pharyngotonsillitis - measurement period last six months:**

- the proportion of patients prescribed antibiotics (J01 excluding methenamine) for pharyngotonsillitis having a positive rapid test for GAS
- the proportion of patients prescribed antibiotics (J01 excluding methenamine) for pharyngotonsillitis having a negative rapid test for GAS
- the proportion of patients prescribed antibiotics (J01 excluding methenamine) for pharyngotonsillitis given first line antibiotics (PcV) according to the national Swedish guidelines
- the proportion of positive rapid test for GAS of all analysed rapid test for GAS among patients with a formal diagnosis of pharyngotonsillitis
- the proportion of patients with a formal diagnosis of pharyngotonsillitis where CRP was analysed
- the proportion of patients with a formal diagnosis of pharyngotonsillitis where throat swab culture was analysed
- the proportion of patients with a formal diagnosis of pharyngotonsillitis where a rapid test for mononucleosis has been analysed

This data is extracted (for the last six months) using the software “Medrave4 Primary care ®” at baseline and after 6, 12 and 18 months. Virtually all PHCCs in Västra Götaland have this software and regularly use it for monitoring quality at the PHCC. In addition, all PHCCs included in this project will check that the rapid test for GAS is registered in the electronic medical record in such a way that the software “Medrave4 Primary Care ®” can identify this.

**Structural data required in CRF:**

- Staffing at the present time: Number of permanent-employed GPs, Residents, interns, and locum tenens, respectively divided into short-term (<3 months of service) and long-term (≥ 3 months of service) locum tenens.
- The number of patients with pharyngotonsillitis per 1000 patients enlisted at the PHCC at baseline.

### Structural data for each participating PHCC

These are obtained from Munin (a quality monitoring software for Primary care in Västra Götaland):

- Type of PHCC: run privately or public?
- the size of the PHCC (number of enlisted patients) and age profile of enlisted patients?
- geographical location (large or mid-sized city versus small village)?
- the number of patients with pharyngotonsillitis per 1000 enlisted patients and year?
- Adjusted Clinical Group (ACG); a measure for evaluating the enlisted population's state of health)?
- Care-need index (CNI); socio-economic index of patients enlisted at the PHCC

# Data processing

## Descriptive statistics

Descriptive statistics (a measure of central tendency and probability distribution) will be presented for the all previously stated research questions at the start of the study (when the intervention starts at the PHCCs = baseline) and after 6, 12 and 18 months.

## Comparisons at baseline

Comparative statistics (chi-two tests and t-tests pending on variable type) will be performed to identify differences between the intervention group and the control group at baseline.

## Estimation of change

Any change between the data for the 6 months prior to the intervention (when the intervention starts at the PHCCs = baseline) and measurement after 6, 12 and 18 months, respectively, is calculated for each PHCC regarding the following outcome measures:

**Primary outcome measure**

1. the proportion of patients with antibiotic-treated (J01 excluding methenamine) pharyngotonsillitis having a positive rapid test for GAS

**Secondary outcome measures**

2. the proportion of patients with pharyngotonsillitis and a negative rapid test for GAS prescribed antibiotics (J01 excluding methenamine)
3. the proportion of antibiotic-treated (J01 excluding methenamine) patients with pharyngotonsillitis treated with recommended antibiotic according to guidelines (PcV)
4. the proportion with pharyngotonsillitis diagnosis where CRP was analysed
5. the proportion of patients with pharyngotonsillitis prescribed antibiotics where no throat swab was taken
6. the proportion with pharyngotonsillitis diagnosis where throat swab culture was analysed
7. the proportion with pharyngotonsillitis diagnosis where a rapid test for mononucleosis has been analysed.

### Regression analysis

***A) Investigate if the intervention is effective***

To investigate whether a change in outcome measure 1-4 differs between the intervention group and the control group, linear regression is performed where adjustment is made for any variables that differ at baseline. A regression is performed for each individual outcome measure at follow-up after 6, 12 and 18 months. Change in the respective outcome measures compared to baseline is used as a dependent variable. Group affiliation (intervention group or control group) will be used as an independent variable. Independent variables will also be the following covariates taken from baseline measurement:
the number of enlisted patients at baseline, location in cities versus small villages, Adjusted Clinical Group (ACG), Care-need index (CNI) and type of PHCC (private/public).

***B) Investigate if structural factors are associated with maintaining the effect of the intervention***

To study if there is a relationship between more permanent change in the proportion of patients with antibiotic-treated (J01 excluding methenamine) pharyngotonsillitis who had a positive rapid test for GAS (primary outcome measure) and structural data in the intervention group, regression analysis will be done.

Change between baseline and follow-up data (18 months after initiation of intervention) for the proportion of patients treated with antibiotics for pharyngotonsillitis who have had a positive rapid test for GAS is used as a dependent variable. The following independent variables will be used:
the number of patients with pharyngotonsillitis per 1000 enlisted patients and year, the proportion of PHCCs located in cities versus small villages, Adjusted Clinical Group (ACG), Care-need index (CNI) and type of PHCC: (private/public), at baseline.

# Expected results and significance

This study is expected to shed light on whether a well-defined ASP intervention can increase adherence to guidelines for the diagnosis and treatment of pharyngotonsillitis in primary care. If so, the implementation of this ASP could lead to improved diagnostics and more rational use of antibiotics in pharyngotonsillitis in primary care. In order to be able to slow down the increasing trend with an increasing proportion of resistant bacteria, it is important to avoid unnecessary antibiotic treatments.

The intervention will be well described so that it can be repeated elsewhere if the evaluation shows that the intervention is effective. The planned intervention is time-efficient in that the Strama group educates one ASP physician from each PHCC so that they, in turn, carry out the intervention at their respective PHCC.

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