Assessment and management of respiratory tract infections in primary care

Stefan Malmberg

General Practice/Family Medicine,
School of Public Health and Community Medicine,
Institute of Medicine, Sahlgrenska Academy,
University of Gothenburg
Gothenburg, Sweden, 2024

UNIVERSITY OF
GOTHENBURG

Cover illustration by Indra Bernlo 2024

Assessment and management of respiratory tract infections in primary care

stefan.malmberg@stfn.se

ISBN 978-91-8069-681-4 (PRINT)
ISBN 978-91-8069-682-1 (PDF)

Printed in Borås, Sweden 2024
Printed by Stema Specialtryck

Any sufficiently advanced technology
is indistinguishable from magic.

– Arthur C. Clarke,
Profiles of the Future: An Inquiry into the Limits of the Possible

Assessment and management of respiratory tract infections in primary care

Stefan Malmberg

General Practice/Family Medicine, School of Public Health and Community Medicine, Institute of Medicine, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden, 2024

Abstract

Background Respiratory tract infections (RTIs) are common causes of primary care visits. Most are harmless and self-limiting, but some can be severe and life-threatening, such as pneumonia, COVID-19, and Lemierre's syndrome. Overusing antibiotics leads to antimicrobial resistance, making treatments less effective. Therefore, it is essential to use objective metrics and evidence-based methods to determine the severity of RTIs to identify potentially life-threatening infections and avoid unnecessary antibiotic prescriptions. Researchers and experts compile and explain current scientific evidence in clinical guidelines for RTIs in primary care, but the link between national guidelines and physicians' perceptions of best management in different countries has not been clear. Antimicrobial stewardship programs (ASPs) are strategic efforts to educate clinicians on the clinical guidelines, promoting evidence-based systems for managing infections. The long-term impact of ASPs in primary care is believed to be beneficial, but the supporting evidence from randomized controlled trials has been ambiguous.

Aim To study the management of common respiratory tract infections in primary care, focusing on severity assessment, guidelines, and the impact of antibiotic stewardship programs.

Methods The **first paper** was a systematic review and meta-analysis to describe and quantify the association between Fusobacterium necrophorum (FN) and acute sore throat in primary care. The **second paper** was a randomized controlled trial investigating if a new ASP could increase compliance to guidelines for managing pharyngotonsillitis in primary care. The **third paper** was a cross-sectional survey in primary care to investigate the link between clinical management guidelines and medical practitioners' perceptions of optimal care for sore throat cases in five countries. The **fourth paper** was a clinical investigation of a medical device evaluating a camera-based system (method comparison) for measuring heart rate, oxygen saturation, respiratory rate, and blood pressure in patients with suspected COVID-19.

Results and conclusions Four studies were included in the **first paper**'s meta-analysis. The results indicate that FN may play a role in primary care patients with acute sore throat, but the association is much weaker compared to GAS. The **second paper** showed no significant differences between the intervention and control group at 6, 12, or 18 months from baseline for any of the outcome measures. In the **third paper**, the results showed that the guidelines for managing acute sore throat in primary care differed significantly between countries. Furthermore, primary care physicians' perception of how to best manage such cases were in line with their domestic guidelines. The results in the **fourth paper** showed that the camera-based measurements were, on average, close to the gold standard but with larger random variation. Hence, camera-based measurement of heart rate, oxygen saturation, respiratory rate, and blood pressure all seem to work, but accuracy and reliability need to be further technically improved and validated.

Keywords

Respiratory Tract Infections, Vital Signs, Patient Acuity, Biomedical Technology, Artificial Intelligence, Practice Guidelines as Topic, Guidline Adherence, Antimicrobial Stewardship, Fusobacterium Infections, Streptococcal Infections, Tonsillitis, COVID-19

Sammanfattning på svenska

Luftvägsinfektioner med symtom som ont i halsen, hosta och feber är bland de vanligaste anledningarna att uppsöka läkare i primärvården. I denna patientgrupp finns en stor andel självläkande och ofarliga infektioner. Samtidigt finns allvarliga och potentiellt livshotande tillstånd som kan börja med liknande symtom, till exempel lunginflammation (pneumoni), covid-19 och Lemierre's syndrom.

Överdriven användning av antibiotika och antivirala läkemedel främjar urvalet av resistenta stammar, vilket gör tillgängliga läkemedel mindre effektiva eller till och med värdelösa över tid. Därför är det nödvändigt att bedöma luftvägsinfektioners allvarlighetsgrad baserat på objektiva mått och tillgänglig vetenskaplig evidens för att kunna erbjuda effektiv behandling när det behövs och samtidigt undvika onödig antibiotikaförskrivning.

Forskare och experter inom klinisk handläggning av infektioner sammanställer och förtydligar det aktuella vetenskapliga läget i kliniska riktlinjer för vanliga luftvägsinfektioner i primärvården. Strategiska program för balanserad antibiotikaförskrivning (antibiotic stewardship programs, ASP) är insatser för att utbilda läkare och sjuksköterskor om de kliniska riktlinjerna, för att öka följsamhet till riktlinjer för diagnostik och behandling av infektioner.

I det **första delarbetet** undersöktes sambandet mellan Fusobacterium necrophorum (FN) och akut halsont i primärvården. FN är en bakterie som är mest känd för det livshotande Lemierres syndrom och halsböld, som ofta börjar med halsont. I den publicerade artikeln dras slutsatsen att FN kan orsaka akut halsont, men sambandet är mycket svagare jämfört med grupp A-streptokocker.

I det **andra delarbetet** genomfördes en randomiserad klinisk prövning (RCT) som studerar effekten av ett strategiskt program för rationell antibiotikaförskrivning (antibiotic stewardship program, ASP). Studien inkluderar 24 vårdcentraler som erhöll aktiv intervention och 25 vårdcentraler i kontrollgruppen. Studien syftade till att avgöra om en nyutvecklad mångfacetterad ASP kunde öka följsamheten till riktlinjer för handläggning av

halsfluss (faryngotonsillit). Den sex månader långa interventionen innehöll genomgång av aktuella riktlinjer vid halsfluss, reflekterande möten där läkarna fick återkoppling kring sin antibiotikaförskrivning vid halsfluss, diskussion av pedagogiska patientfall kring halsfluss och framtagande av lokala förbättringsinitiativ. Under interventionen erhöll läkarna upprepad individuell feedback i form av diagnoskopplad lab- och förskrivningsstatistik. Resultaten visade dock att ingendera gruppen ändrade följsamheten till riktlinjerna 6, 12 eller 18 månader från utgångsläget.

I det **tredje delarbetet** visade en enkät genomförd i fem länder att läkarnas uppfattningar om bästa praxis för handläggning av akut halsont stämde överens med deras nationella riktlinjer. Detta tyder på att primärvårdsläkare försöker lära sig och följa de aktuella riktlinjerna för att säkerställa evidensbaserad sjukvård. Men om riktlinjerna verkligen hade varit baserade på aktuell vetenskaplig evidens borde de vara samstämmiga i de studerade länderna, vilket inte var fallet. Skillnaderna skulle kunna tillskrivas att man prioriterar lokala handläggningstraditioner när man skapar riktlinjerna.

Det **fjärde delarbetet** flyttar fokus tillbaka till bedömning av allvarlighetsgrad i samband med luftvägsinfektioner. I detta arbete genomfördes en klinisk prövning av en ny kamerabaserad metod för att mäta vitalparametrar hos patienter misstänkt covid-19. Studien drar slutsatsen att kamerabaserad mätning av hjärtfrekvens, syremättnad, andningsfrekvens och blodtryck fungerar, men mätnoggrannhet och reliabilitet behöver förbättras och valideras ytterligare.

Avhandlingen utforskar handläggning av luftvägsinfektioner i primärvård, med fokus på bedömning av svårighetsgrad, kliniska riktlinjer, och strategiska program för rationell antibiotikaförskrivning, med målsättningen att bidra till förbättrade patientresultat och strategier för handläggning.

List of papers

I. **Malmberg S**, Petrén S, Gunnarsson R, Hedin K, Sundvall PD. *Acute sore throat and Fusobacterium necrophorum in primary healthcare: a systematic review and meta-analysis.* BMJ Open. 2021 Jun 4;11(6):e042816.

II. **Malmberg S**, Björk D, Hess-Wargbaner M, Åhrén C, Jacobsson G, Ulleryd P, Gunnarsson R, Sundvall PD. *"Acute sore throat in primary care - long term effect of a multifaceted antimicrobial stewardship program including audit and feedback"* Submitted, under review for publication.

III. Gunnarsson R, Ebell M H, Wächtler H, Manchal N, Reid L, **Malmberg S**, Hawkey S, Hay A D, Hedin, K. Sundvall, PD. *Association between guidelines and medical practitioners' perception of best management for patients attending with an apparently uncomplicated acute sore throat: a cross-sectional survey in five countries.* BMJ Open. 2020 Sep 17;10(9):e037884.

IV. **Malmberg S**, Khan T, Gunnarsson R, Jacobsson G, Sundvall PD. *Remote investigation and assessment of vital signs (RIAVS) — proof of concept for contactless estimation of blood pressure, pulse, respiratory rate, and oxygen saturation in patients with suspicion of COVID-19.* Infectious Diseases (Lond). 2022, Sep; 54:9, 677-686.

Content

Abbreviations

ASP	Antimicrobial Stewardship Program
CI	Confidence Interval
EPV	Etiologic Predictive Value
FN	Fusobacterium Necrophorum
GAS	Group A Streptococci (Streptococcus pyogenes)
P-EPV	Positive Etiologic Predictive Value
PCP	Primary Care Physician
PHC	Primary Health Care
PHCC	Primary Health Care Center
RADT	Rapid Antigen Detection Test
RCT	Randomized Controlled Trial
rPPG	Remote Photoplethysmography

Overview of the thesis

	TITLE	AIM
I	*Acute sore throat and Fusobacterium necrophorum in primary healthcare: a systematic review and meta-analysis.*	To describe and quantify the association between Fusobacterium necrophorum (FN) and acute sore throat in primary care.
II	*Acute sore throat in primary care - long term effect of a multifaceted antimicrobial stewardship program including audit and feedback.*	To investigate if a new Antimicrobial Stewardship Program (ASP) increases compliance with guidelines for managing pharyngotonsillitis cases in primary care.
III	*Association between guidelines and medical practitioners' perception of best management for patients attending with an apparently uncomplicated acute sore throat: a cross-sectional survey in five countries.*	To investigate the link between guidelines and medical practitioners' perception of optimal care for sore throat cases in five countries.
IV	*Remote investigation and assessment of vital signs (RIA-VS) — proof of concept for contactless estimation of blood pressure, pulse, respiratory rate, and oxygen saturation in patients with suspicion of COVID-19.*	To evaluate camera-based measurement of heart rate, oxygen saturation, respiratory rate, and blood pressure in patients with suspected Covid-19.

	METHODS	RESULTS	CONCLUSION
I	Systematic review and meta-analysis	Four studies were included in the meta-analysis. The cumulative positive predictive etiologic value (P-EPV) was 64% (95% CI 33% ↔ 83%) for FN and 93% (95% CI 83% ↔ 99%) for GAS.	FN may play a role in primary care patients with an acute sore throat, but the association was much weaker compared to GAS.
II	RCT in primary care	No significant differences between the intervention- and the control group at 6, 12, or 18 months from baseline for any of the outcome measures.	The ASP had no impact on guideline adherence in primary care.
III	International cross-sectional survey in primary care	Guidelines differed significantly between countries; primary care physicians' perceptions were in line with their domestic guidelines.	The differences between practitioners' perceptions of best management were associated with their national guidelines.
IV	Clinical investigation (method comparison)	The camera-based vital signs measurements were, on average, close to the gold standard but showed larger random variation.	Camera-based measurement of heart rate, oxygen saturation, respiratory rate, and blood pressure works, but accuracy and random variability need to be improved and validated.

Introduction

During my first years as a physician I had a chance to observe clinical practice in both hospitals and primary care settings. While doing so I started noticing common challenges in the management of respiratory tract infections (RTIs), which is a common health issue ranging from mild, self-limiting conditions to severe, even life-threatening illnesses. These observations inspired me to delve deeper into this field and explore new ways to tackle the challenges.

Encountering a dual problem sparked my initial curiosity: insufficient initial assessment of, and sometimes consequential, underestimation of the severity of infections, coupled with a noticeable deficiency in the documentation required for trend analysis and informed decision-making when re-assessing a patient. These observations have profound implications for patient safety, allocation of healthcare resources, and the rational use of antibiotics.

Respiratory tract infections present a diagnostic dilemma due to the overlap in symptoms across varying degrees of severity. This overlap makes the clinical decision-making process complex and highlights the necessity for precise and accurate assessment methodologies to distinguish between cases that require immediate and decisive intervention and those that can be managed conservatively. The prudent use of antibiotics and hospital resources emerges as a significant concern within this context, not only to mitigate the risk of antimicrobial resistance and minimize healthcare expenditures but also to avoid unnecessary side effects and negative patient outcomes.

Establishing Antibiotic Stewardship Programs (ASPs) and developing clinical guidelines based on the latest scientific evidence aim to address these challenges by promoting an evidence-based approach to treating RTIs. These initiatives emphasize the critical role of vital signs as a cornerstone in the severity assessment of infections, highlighting a significant area for improvement in current clinical practice.

However, I grew concerned that guideline compliance was suboptimal, and my clinical experiences and growing analysis of available literature indicated challenges in existing methodologies for measuring vital signs. These challenges affect the clinical management of patients and have broader implications for the efficacy of ASPs and adherence to clinical guidelines. Such observations

encouraged me to formulate research questions to enhance our understanding and management of RTIs.

Through this research I aim to make a meaningful contribution to developing more effective severity assessments and management strategies for RTIs, ultimately enhancing patient care and outcomes.

Respiratory tract infections are common and usually mild but severe cases present with similar symptoms

Respiratory tract infections are a common reason for attending primary care.[1] While typically mild and self-limiting RTIs range from the omnipresent common cold, mainly caused by rhinoviruses[2], to more severe conditions. Influenza, bronchitis, pharyngitis, tonsillitis, sinusitis, and otitis media typically present with manageable, mild to moderate symptoms and resolve with minimal intervention. However, these common RTIs have the potential for severe complications, albeit rare. A large European study recently demonstrated that 3.2% of RTI patients were classified as severe cases.[3]

Global perspective on mortality from infections

According to global statistics, three out of the top ten causes of death in 2019 were infectious diseases, and all communicable diseases combined accounted for 26% of all deaths worldwide in 2019.[4]

However, focusing on low-income countries paints an even darker picture. People in low-income countries are more likely to die from communicable diseases than noncommunicable ones. Six of the top ten causes of death in low-income countries are infectious diseases.[4]

Potentially life-threatening respiratory tract infections

RTIs include some diseases and conditions that, if not promptly and effectively managed, can progress to sepsis, which is a life-threatening organ dysfunction caused by infection.[5]

Bacterial pneumonia, primarily caused by Streptococcus pneumoniae, and COVID-19, caused by SARS-CoV-2, share common symptoms such as cough, dyspnoea, and fever. Similarly, tuberculosis typically presents with cough and fever, often accompanied by night sweats and fever. Lemierre's syndrome is a rare but severe complication following a bacterial sore throat, may present with sore throat and fever, followed by swelling and tenderness in the neck due to thrombophlebitis.

These RTIs can cause severe disease in different ways. Pneumonia and COVID-19 can impair gas exchange in the lungs due to mucus accumulation and inflammation, with severe cases leading to acute respiratory distress syndrome, sepsis, and multi-organ failure. Tuberculosis can cause extensive lung damage and disseminate to other organs. Lemierre's syndrome can lead to sepsis and thrombosis, which can cause widespread organ damage.

Diagnostic procedures typically involves a combination of clinical assessment (medical history, symptoms and signs), laboratory tests (such as CRP for bacterial infections), and imaging (such as chest X-rays for pneumonia or tuberculosis).[6] Molecular testing (polymerase chain reaction, PCR) and rapid antigen detection tests (RADTs) are used to identify specific viral and bacterial pathogens.

Management strategies for these RTIs focus on early recognition, accurate diagnosis, and prompt treatment to prevent progression to severe disease. Vaccination and education on hygiene and infection control are key components of prevention strategies in public health.

Fusobacterium necrophorum, sore throat and Lemierre's syndrome

Fusobacterium necrophorum (FN) is a gram-negative bacterium that sometimes causes Lemierre’s syndrome, a rare potentially lethal condition that starts with a sore throat.[7] FN is also a known pathogen in peritonsillar abscess.[8,9] Most current guidelines for managing patients with sore throat emphasize group A Streptococcus (GAS). However, some studies suggest that FN may cause a sore throat, especially in adolescents and young adults.[7–12]

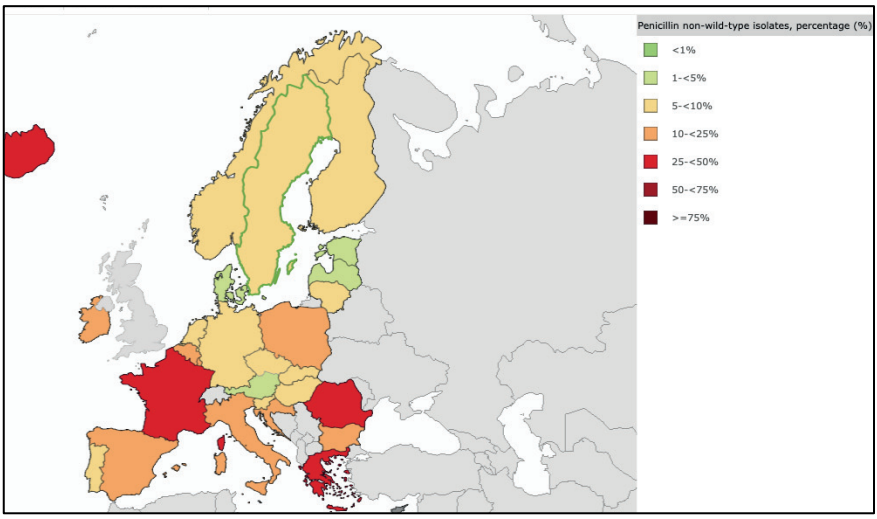
Previous literature reviews have not considered the rate of asymptomatic FN carriers, which is essential to estimate the clinical relevance of a throat swab indicating the presence of FN in a patient with an acute sore throat.[13–15]

To shed light on the role of FN in acute sore throat in primary care estimating the likelihood of an association between FN and uncomplicated acute sore throat while considering FN carriage rate in healthy individuals, would provide new insights. Additionally, comparing the FN and GAS association with an uncomplicated acute sore throat would clarify the significance. These topics are investigated in the **first paper** of this thesis.

Overusing antibiotics is ineffective, causes unnecessary side-effects, and promotes antimicrobial resistance

In 2015, the World Health Organization introduced a Global Action Plan on Antimicrobial Resistance.[16] The primary aim of the plan is to raise awareness of antibiotic resistance, prevent infections, promote the optimal use of antibiotics, enhance knowledge through research and surveillance, and encourage the development of new antimicrobial drugs.

The use of antibiotics varies significantly between countries, and there is evidence of a correlation between antibiotic resistance and outpatient antibiotic use in Europe.[17–19] In different countries, the prescription of antibiotics is influenced by several factors, including the expectations of physicians and patients, institutional policies, reimbursement systems for healthcare providers, business practices of pharmacies, cultural influences, and corruption.[20–23] Studies suggest antibiotics are being overused for respiratory tract infections, which is a cause for concern.[22,24]



Proportion of penicillin-resistant (I/R) isolates of S. pneumoniae in Europe 2022.[19] Dataset provided by ECDC based on data provided by WHO and Ministries of Health from the affected countries.

Antibiotic prescriptions for respiratory tract infections have decreased over time in the Nordics, and compared to countries such as France, Greece, and Spain, Sweden has a low rate of antibiotic prescriptions.[19,25,26]

The emergence of antimicrobial resistance has led to the widespread ineffectiveness of conventional treatment options for infections previously treatable with multiple antimicrobial agents.[27] As a result, there is now an urgent need to improve surveillance and laboratory capacity, enhance infection prevention, promote strict treatment indications with (primarily) narrow-spectrum antibiotics (for human medicine and livestock), and to develop novel antimicrobial agents to battle these drug-resistant infections.[28,29]

Restrictive antibiotic prescribing is contingent on rigorous severity assessment

Antibiotics are still overprescribed for seemingly mild-moderate cases. Therefore, in the current situation, undetected severe cases have a good chance of being treated with antibiotics. A small reduction of antibiotic prescription rates from 54% to 51% in UK primary care settings seemed to slightly increase the incidence of pneumonia and peritonsillar abscess.[30] It is reasonable to raise concerns that a more considerable reduction of the antibiotic prescription rate could lead to an increase of severe infections. To further reduce antibiotic prescription,

severity assessment must be prioritized so that cases with a significant risk of progressing to a severe infection are still offered effective antibiotic treatments.

Systems for severity assessment - management guidelines and clinical decision rules

Guidelines and clinical scores and decision rules for infections are numerous. Some are diagnosis-specific, for example, PSI[31], CURB, and CURB-65 for pneumonia[32], Centor[33], McIsaac[34] and FeverPain[35] scores for sore throat, and Williams criteria[36] for sinusitis. Others are more general, such as SOS, MEWS and NEWS[37], for assessing severity.

In October 2023, three Swedish agencies and organizations (the Public Health Agency, the Medical Products Agency, and the Swedish Strategic Program Against Antibiotic Resistance) launched an updated collection of clinical decision rules for managing infections in primary care.[38] The first section explains that severe and uncommon infections can be challenging to recognize as they may show no specific signs, and identifying the indicators of a severe infection is essential for timely and appropriate treatment. It goes on to declare that thorough examination and history-taking are crucial for an accurate diagnosis, and in acutely ill patients, determining the severity of illness and assessing the risk situation is the first and most critical step for clinicians.

The purpose of these guidelines and clinical decision rules is to guide clinicians in managing infections in accordance with current scientific evidence – from assessing severity, investigating, diagnosing, selecting appropriate treatment, and planning follow-ups, to predicting outcomes, and communicating with other healthcare professionals.

Antimicrobial stewardship programs - enforcing guideline adherence

Strategic efforts to monitor and improve how antibiotics are prescribed by clinicians and used by patients are called antibiotic stewardship programs (ASPs). Behavioral science-based, multidisciplinary ASPs, including audit and feedback, have been shown to improve adherence to guidelines.[39–43]

Strama (The Swedish Strategic Program Against Antibiotic Resistance) aims to prevent antibiotic resistance by promoting the rational use of antibiotics. Since 1995, Strama has been successful in reducing antibiotic prescription rates by bringing authorities and healthcare providers together to surveil statistics on antibiotic prescribing, provide training, and help develop guidelines for hospitals and primary care facilities.[44]

Physicians often fail to adhere to guidelines and report uncertainty about correctly managing acute sore throat.[26,45–47] Studies have shown that some ASP activities are ineffective in improving guideline adherence.[39,48–50]

Due to suboptimal guideline adherence it is relevant to investigate how doctors' opinions of how to best manage RTIs harmonize with their domestic guidelines. Furthermore, the efficacy of ASPs for RTIs in primary care needs to be clarified. Therefore, it is desirable to scientifically evaluate well-defined and repeatable ASPs to determine their effect on guideline adherence and antibiotic prescribing. The **second and third papers** of this thesis examine these topics in detail.

The vital signs - which are they and how are they measured?

The five most essential physiological measurements are heart rate (pulse), respiratory rate, blood pressure, oxygen saturation (SpO2), and temperature, often recorded with an assessment of the level of consciousness.[51] Most of the above-mentioned clinical decision rules and guidelines for severity assessments rely on measuring several vital signs (PSI[31], CURB, CURB-65[32], SOS, MEWS, and NEWS[37]). A designated section below will delve into the specifics and challenges of measuring vital signs.

The vital signs

Respiratory rate, heart rate (pulse), blood pressure, body temperature and blood oxygen level ((saturation of oxygen in the peripheral blood, SpO2) are well-established vital signs, often accompanied by assessment of consciousness.[51,52]

Accurately assessing vital signs is a critical aspect of providing safe and high-quality healthcare. Vital signs provide valuable information that helps healthcare

providers understand the patient's condition, including how they respond to medical treatment and whether the patient's health is deteriorating.

Measuring the vital signs

A standard method for measuring vital signs involves utilizing multiple devices and recording the outcomes during the process. The patient should be seated comfortably, ideally with their arm supported on a flat surface.

Before taking blood pressure, the cuff must be measured to the appropriate size, as an incorrect cuff can produce inaccurate readings. Positioning the cuff correctly, just above the brachial artery on the upper arm, may require the patient to remove their shirt or roll up the sleeve. If an automatic blood pressure device is used it should be turned on, and enough time for the device to start and stabilize should be allowed before starting the measurement. A manual sphygmomanometer and stethoscope may be necessary for a more precise blood pressure reading. In that case, the clinician would position a manual cuff above the patient's upper arm. While keeping the stethoscope over the brachial artery, the cuff should be inflated to approximately 200 mmHg and then gradually deflated, listening for the Korotkoff sounds to record the systolic and diastolic readings.

Although many blood pressure devices display the pulse rate, they may not assess the rhythm, necessitating a one-minute manual pulse check to determine rate, rhythm, and consistency. The pulse can be detected at any site where an artery passes over a bone; the radial pulse is commonly assessed.

The pulse oximeter is an electronic device that measures the red blood cells' saturation of oxygen. Pulse oximeter sensors can be attached to a finger or toe, the forehead, nose, foot, or ear. The device requires 20-30 seconds to obtain a stable signal and display a consistent result.

Temperature measurements can be taken using devices such as tympanic, oral, or rectal thermometers. The tympanic thermometer, often used for convenience, involves placing a covered probe in the patient's ear until the device signals the completion of the reading. Positioning is crucial for accuracy.

Observing the respiratory rate can be challenging since it is best done covertly to avoid influencing the patient's breathing. After measuring the pulse, the clinician

may discreetly count the respiratory cycles by continuing to hold the patient's wrist and watching the patient's shoulder or chest movements with each breath.

While performing the vital sign measuring procedure the clinician would normally note the results on paper and later proceed to transfer the results to the patient's electronic health record.

Vital sign "inflation" - which signs are genuinely vital?

The term "vital sign" traditionally indicates functions essential for life that can be objectively measured. However, various conditions, symptoms, and psychosocial issues have been labelled vital signs[53], presumably aiming to emphasise their importance in health care, for example: sleep[54], pain[55], smoking[56], bowel movement[57], menstrual cycle[58], and (even) erection hardness[59]. Many of these so-called vital signs are subjective rather than objective and can hardly be considered "vital" for life.

Vital signs' measurement challenges

Despite the well-documented relationship between abnormal vital signs and impaired clinical outcomes, research has consistently shown that vital signs assessment is often neglected in hospitals[51], and there is no reason to assume that the situation is any better in primary care[60,61]. The insufficient measurement of vital signs could be attributed to various factors, including the nurses' and physicians' level of knowledge, clinical judgment, cultural and traditional practices, and the heavy workload that healthcare professionals often face.

Vital signs measurement accuracy

Depending on the clinicians' choice of measurement method, technique, training and skill, vital signs measurements can be more or less accurate. Anatomy and physiology also vary between subjects, affecting measurement results.

When comparing nurses' radial pulse measurements to ECG, one study showed a clinically significant difference with a SD of 14, and wide limits of agreement ±26,5 beats per minute and the difference increasing with tachycardia.[62]

Some studies have shown that respiratory rates are clustered around even numbers, such as 18 and 20 breaths per minute, suggesting that staff members measure respiratory rates over a shorter time than one minute and then multiply the results or estimate (guess?) respiratory rates based on the patient's overall appearance.[63–65] A considerable variation has been noted in respiratory rate measurements, with imprecise and unreliable results.[66–68] Similarly, blood pressure measurements have been shown to be inaccurate and highly dependent on the method and technique.[69,70] Peripheral thermometers (tympanic membrane, temporal artery, axillary, or oral) have shown unsatisfactory agreement when compared to central thermometers (pulmonary artery catheter, urinary bladder, esophageal, or rectal), with 95% limits of agreement outside the clinically acceptable range (± 0.5 °C).[71]

Time to measure vital signs

Measuring vital signs takes five to six minutes for a nurse[72,73], excluding time for cleaning and disinfecting the equipment, which would realistically add one to two minutes.[74] In hospitals, vital signs are not measured and recorded according to established protocols.[51]

Vital sign measurements are lacking

In primary care, vital signs are infrequently recorded in patients' medical records when suspecting an infection[60] - even when general practitioners have been explicitly instructed to measure and record vital signs when suspecting an infection.[61]

The role of vital sign measuring equipment in healthcare associated infections

Insufficient cleaning and disinfection of vital sign measuring equipment, such as blood pressure cuffs and pulse oximeter sensors, allows pathogens to survive on surfaces.[75,76] This could lead to the spread of bacteria from clinician to patient, from patient to clinician, and between patients, contributing to healthcare-associated infections.

New ways to measure vital signs

The challenges associated with measuring vital signs are concerning when considering their apparent significance in assessing the severity of infections. Therefore, it is essential to find ways to improve the current practices and investigate new methods that may reduce some of the shortcomings of the current methods. Before clinical implementation any new technology for measuring vital signs must undergo scientific evaluation and thorough testing. The fourth paper of this thesis evaluates a camera-based system for measuring vital signs.

PPG and rPPG - technologies for measuring physiology

Pulse oximeters use photoplethysmography (PPG), often in an alligator finger clip. PPG includes an LED on the skin that emits light and a sensor detecting reflected light. The amount of reflected light changes according to the pulsatile blood volume fluctuations in the tissue mirroring capillary dilation and constriction with each cardiac cycle's pulse wave.[77] Furthermore, the reflected wavelengths vary in sync with oxygen saturation.

Remote photoplethysmography (rPPG) works on the same principle as traditional PPG. However, instead of using an LED and sensor placed directly on the skin, rPPG uses a light source and a camera at a distance from the subject to achieve contactless measurement. RPPG creates a signal based on changes in red, green, and blue light reflected on the skin surface and subcutaneous tissues.[78] To optimize the signal for different vital sign measurements, digital signal processing and filtering techniques are deployed to create the signal from specific color hues. Vital sign measurements are based on the different rPPG signals.[79]

Remaining dilemmas

To better understand FN's role in acute sore throat cases in primary care, it is imperative to investigate the association while considering the FN carriage rate in healthy individuals and comparing it to the corresponding association for GAS.

The impact of Antibiotic Stewardship Programs (ASPs) for acute sore throat in primary care on antibiotic prescribing and guideline adherence is ambiguous and needs to be clarified.

Considering the insufficient guideline adherence it is relevant to investigate how physicians' perspectives on managing respiratory tract infections align with their domestic guidelines.

Since measuring vital signs is at the core of assessing the severity of infections, but current measurement methods are time-consuming, infrequent, inaccurate, and risk contributing to health-care associated infections, new technologies that could improve the measurement procedure should be studied.

Aims of the Thesis

Overall aim

To study the management of common respiratory tract infections in primary care, focusing on severity assessment, guideline compliance, and the impact of antibiotic stewardship programs.

Specific objectives

1. To describe and quantify the association between Fusobacterium necrophorum and acute sore throat in primary care. (**Paper I**)

2. To determine if an Antimicrobial Stewardship Program (ASP) could increase compliance with guidelines for diagnosing and treating pharyngotonsillitis in primary care. (**Paper II**)

3. To explore, in five countries, the association between national guidelines and medical practitioners' perception of optimal care for patients attending primary care with a sore throat. (**Paper III**)

4. To evaluate a new method for camera-based measurement of heart rate, oxygen saturation, respiratory rate, and blood pressure in patients with suspicion of COVID-19. (**Paper IV**)

Materials and Methods

Study populations

Paper I

The first paper was a systematic review and meta-analysis evaluating Fusobacterium necrophorum (FN) in patients presenting with an uncomplicated acute sore throat in primary healthcare settings.

Case-control studies describing FN prevalence in patients with an acute sore throat (cases) and healthy individuals (controls) were retrieved from the PubMed and SCOPUS databases. Papers describing case studies, studies including patients who received a prescription of antibiotics before the throat swab, and patients with immunosuppression, concurrent malignant disease, HIV infection, or another acute infection in addition to a sore throat were excluded.

Search strings for PubMed: ((("pharyngitis"[MH] OR "pharyngitis"[TIAB] OR "Lemierre Syndrome"[MH] OR "Lemierre Syndrome"[TIAB] OR "Necrobacillosis"[TIAB] OR "pharyngotonsillitis "[TIAB] OR "tonsillitis"[TIAB] OR "throat"[TIAB] OR "epidemiology"[TIAB]) AND ("fusobacterium necrophorum"[MH] OR "fusobacterium"[TIAB])) NOT "Case Reports"[pt]

Search string for Scopus: (TITLE-ABS-KEY ((pharyngitis OR "Lemierre Syndrome" OR necrobacillosis OR pharyngotonsillitis OR tonsillitis OR "Peritonsillar Abscess" OR throat OR epidemiology)) AND TITLE-ABS-KEY (fusobacterium)) AND DOCTYPE (ar) AND (LIMIT-TO (SUBJAREA , "MEDI ") OR LIMIT-TO (SUBJAREA , " IMMU ") OR LIMIT-TO (SUBJAREA , " BIO ")) AND (LIMIT-TO (LANGUAGE , "English ")) AND (EXCLUDE (EXACTKEYWORD , "Case Report"))

The screening process also involved checking each article's reference list for additional relevant publications. Only English language articles were considered. Two reviewers assessed the methodological quality of the studies independently (Table I), and disagreements were resolved through discussion within the review team.

Table 1 - Methodological quality assessment of included studies

	RISK		
	Low	**Intermediate**	**High**
Cases	Well defined (Centor criteria or similar).	At least two criteria mentioned in definition.	Not defined.
Controls	Asymptomatic.	Not asymptomatic.	---
Throat swab	Swabbed area described, transport and storage mentioned.	Swabbed area mentioned but not the transport or storage.	No mention of swab method.
Culture	Clear description of culture media, incubation time (or PCR if used).	Method described but not in detail.	Method not discussed.
Study type	Case control studies on FN.	Community surveillance studies mentioning FN prevalence.	Observational studies without well-defined cases and controls.
Geography and time	Cases and controls collected in the same area and time.	Cases and controls collected in the same area but over different time periods.	Cases and controls collected in different areas and time periods.

Paper II

The second paper was a randomized controlled trial in which all primary health care centers (PHCCs) in the Region Västra Götaland, western Sweden, were invited to participate, with 202 PHCCs being eligible in 2018.

Inclusion criteria for the PHCCs included being publicly funded, having at least three physicians employed, an electronic medical record compatible with the data extraction tool (MedRave Primary Care), and a license for the data extraction tool. The exclusion criterion was newly opened PHCCs active for less than one year.

Paper III

The third paper was a cross-sectional survey. The survey was conducted on primary care physicians working in primary healthcare facilities in five countries: Australia, Germany, Sweden, the United Kingdom, and the United States. Both senior physicians, such as General Practitioners (GPs) and consultants, and junior doctors undergoing training as residents and registrars, were invited to participate in the study.

Paper IV

The fourth paper describes a clinical investigation (method comparison) to evaluate camera-based measurements of heart rate, oxygen saturation, respiratory rate, and blood pressure in patients with suspected COVID-19.

Patients aged 18 years or older, who presented at the Sahlgrenska University Hospital, Östra Hospital emergency department for triage with typical COVID-19 symptoms, were fluent in Swedish and could provide informed consent, were invited to participate.

There was a 10-minute delay incurred by the study for each patient. To ensure the medical safety of the patients only those who were not at risk of experiencing any negative consequences due to a 10-minute delay were included in the study. Any patient in such a severe medical condition that even a 10-minute delay could worsen their medical condition was not included in the study to avoid potential harm. If deterioration was suspected and confirmed during the ten minutes of study activities the subjects were excluded from the study and immediately managed by the emergency department's nurses and doctors (who were in the same room).

Randomization and data collection

Paper I

Two reviewers assessed the methodological quality of the studies independently, and disagreements were resolved through discussion within the review team.

Initially, 490 publications were identified from the PubMed and Scopus database searches (258 from PubMed and 232 from Scopus). After removing duplicates and screening abstracts, 53 studies were read in full text for detailed assessment.

Paper II

PHCCs were asked to participate one at a time, and forty-nine PHCCs were randomly assigned to the intervention or control group, in a 1:1 ratio.

The intervention lasted six months, and the follow-up period was 18 months. The intervention was an ASP designed to improve the management of sore throat cases by promoting adherence to established guidelines, using a multifaceted approach that brought together medical practitioners through a series of meetings led by the local ASP physician (at baseline and after two, four, and six months).

A crucial aspect of the intervention was a comprehensive system of repeated audits and individual feedback with personalized reports highlighting laboratory results and antibiotic prescribing patterns in the context of sore throat management. These targeted insights enabled physicians to reflect on and refine their approach individually. Moreover, the physicians reviewed and discussed their PHCCs' aggregated laboratory results and antibiotic prescribing patterns.

The ASP physician extracted data at each PHCC. For the control group, the ASP physicians compiled data retrospectively after 18 months, including information from baseline, six, twelve, and 18 months. The intervention group saw a more frequent data collection regimen since the ASP physician presented the aggregated numbers for the PHCC, and handed out the personalized reports during intervention meetings. In addition to the same time points as the control group, they also gathered data at two and four months to facilitate discussions.

The data included the PHCCs' aggregated laboratory and antibiotic prescription statistics for patients with an acute sore throat:

- The proportion of antibiotic-prescribed pharyngotonsillitis cases:
    - with positive GAS-RADT
    - without GAS-RADT test
    - with first-line antibiotics (penicillin V according to the Swedish guideline)
- The proportion of GAS-RADT-negative pharyngotonsillitis cases prescribed antibiotic
- The proportion of pharyngotonsillitis cases with:
    - a CRP (c-reactive protein) test
    - a throat swab culture
    - a mononucleosis-RADT

Information regarding the PHCC's organization type (privately or publicly run), size, urban or rural location, adjusted clinical group (ACG), and care-need index (CNI) was also collected.

Paper III

Primary care physicians were requested to take part in this research study. They were given a concise survey, which was primarily distributed through in-person visits to their clinics by one of the researchers during their professional development meetings. In Germany, most surveys were sent by mail and followed up with a reminding phone call.

The survey consisted of a one-page questionnaire that first collected demographic information about the physicians, such as age, gender, year of graduation, and experience.

The survey inquired about factors influencing their decision to prescribe antibiotics for sore throat cases. The factors included indicative acute symptoms, history of comorbidities affecting immunity, physical findings at examination, the patient's wish to receive antibiotics, blood tests with erythrocyte sedimentation rate (ESR), high leucocyte count, C-reactive protein (CRP), fever above 38° Celsius (100.4 Fahrenheit), and findings from throat swabs.

Additionally, the questionnaire presented hypothetical case scenarios, asking participating physicians to indicate their likelihood of prescribing antibiotics

based on the results of throat swabs showing growth of specific bacteria, including Group A Streptococcus (GAS), Group C Streptococcus, Group G Streptococcus, Fusobacterium necrophorum, and Haemophilus influenzae. Respondents could answer using four Likert items ranging from 'yes, definitely' to 'definitely not'.

Paper IV

The new system that was investigated included a high-speed digital video camera, a digital radiometric infrared camera, LED lights, and a computer for recording data. The investigator positioned the equipment approximately one meter from the subject, and a video recording of the subject's face was captured. The video recording lasted 30 seconds and consisted of three ten-second parts, each with a different illumination setting: ambient light, visible red light, and invisible infrared light.

The reference method for measuring blood pressure was an automatic device with a selection of different-sized upper-arm cuffs (A&D UA-651). The heart rate measured by the blood pressure device was used as the reference for heart rate. The respiratory rate was manually measured by observing and counting the subject's respiratory cycles for 60 seconds. To measure SpO2, a portable pulse oximeter (Nellcor OxiMax N-65) was used with an alligator clip finger sensor. The pulse oximetry measurement was conducted for 30 seconds, from when the device gave a stabilized reading.

The data collection procedure for each included subject consisted of three steps:

1. First, all vital signs were measured using the carefully selected reference devices.
2. Secondly, the investigated new system recorded a 30-second video of the patient's face using high-speed and infrared cameras.
3. Finally, all vital signs were again measured using the same reference devices.

To minimize the impact of the initial delay caused by study activities, a copy of the standard reference method readings was given to those clinical professionals responsible for the medical care of each subject.

Later, after ending the data collection, specific software algorithms analyzed the collected 30-second video recordings to compute the vital signs at a different

location. Consequently, no measurement results from the new camera-based system were displayed or available in the clinical environment where the data was collected. Accordingly, the camera-based vital sign measurement results were never presented to the clinicians responsible for the subjects' medical care or stored in the subjects' electronic medical records.

Ethical considerations

Paper I

Ethical approval was not required since the study only used publicly available data from published articles, in which the ethical review process and mandated informed consent was obtained by the primary investigators in the original studies.

Paper II

The Ethics Review Board in Gothenburg determined that the Ethics Review Act did not apply to the study (application file number 1021-17, on December 12th, 2017). The committee stated in its advisory opinion that it had no objections to the study. Before the study began, the protocol was registered with ClinicalTrials.gov (ClinicalTrials.gov Identifier: NCT03408704).

Paper III

The study was approved by respective ethics committees in each of the five participating countries:

- Australia: Human Research Ethics Committee at James Cook University (reg number H6993).
- Germany: Ethik-Komission der Medizinischen Fakultät der Christian-Albrechts-Universität zu Kiel (reg number D 576/17).
- Sweden: Regional Ethical Review Board in Gothenburg (reg number 401-318).
- UK: Health Science Faculty Research Ethics Committee (reg number 58742).
- USA: University of Georgia Institutional Review Board.

To uphold privacy, PCPs were requested to provide only non-sensitive and anonymous data. Guidelines were publicly available in the public domain.

Paper IV

Approval from ethical authority and medical products agency

The research underwent a thorough review process and was deemed ethically sound and safe for participants by the Swedish Ethical Review Authority (registration numbers 2020-01936 and 2020-02723), and the Swedish Medical Products Agency (registration number 5.1-2020-36817).

Informed consent

Before participating in the study all patients had to review and sign an informed consent form, which provided them with detailed information about the study's procedures, objectives, and potential risks and benefits. This ensured that each patient was fully informed about the study and had the opportunity to ask questions and clarify any concerns before agreeing to participate.

Independent study monitoring

Throughout the course of the study, Scandinavian CRO closely monitored and oversaw the implementation of ISO14155:2011, ICH-GCP, and other relevant regulations to ensure that all aspects of the research complied with international standards for clinical research.

Study protocol registration

The study was registered with Universal Trial Number (UTN) U1111-1251-4114 and ClinicalTrials.gov Identifier NCT04383457, providing transparency in research conduct and reporting.

Disclosure and conflict of interest

The fourth paper of this thesis has been published, and in the paper, it was disclosed that two of the authors hold shares in Detectivio AB, the biotech company responsible for developing the RIA-VS device. The author of this thesis was one of two authors who declared this conflict of interest. It is worth noting that the other authors had no conflicts of interest.

Because of this conflict of interest, the statistical calculations were not performed by the author of this thesis, but by one of the supervisors. To further mitigate this conflict of interest, the supervisors of this thesis, who themselves have no conflict of interest, took extra measures to ensure objectivity.

Statistical methods

Paper I

Prevalence in cases and controls - chi-square

The pooled difference in the prevalence of Fusobacterium necrophorum (FN) between cases (patients with acute sore throat) and healthy controls was compared using the χ^2 (chi-square) test.

Positive etiologic predictive value

The study's primary statistical method was the Positive Etiologic Predictive Value (P-EPV). This method determines the probability of a true etiologic association between a symptom (such as sore throat) and a finding (such as the presence of FN in the throat), while also taking into account the presence of healthy carriers. This method was selected because it provides a straightforward percentage (between 0% and 100%) that indicates the likelihood of a true connection between FN and sore throat symptoms.

The study also compared P-EPV for FN with P-EPV for Group A Streptococcus (GAS) using data from the same patients and publications to provide a comprehensive understanding of the role of these bacteria in acute sore throat cases.

Paper II

Outcome measures

The primary outcome was the change in the proportion of antibiotic-prescribed pharyngotonsillitis cases with positive GAS-RADT. Secondary outcomes included changes in the proportions of GAS-RADT negative pharyngotonsillitis cases prescribed antibiotics, cases with first-line antibiotic prescriptions, and cases with a C-reactive protein (CRP) test taken. The national goals for these outcomes were also considered in the analysis.

Comparative statistics at baseline

Depending on the variable type, chi-square tests, and t-tests were used to identify any baseline differences between the intervention and control groups.

Estimation of change

For each PHCC we calculated changes between the baseline and follow-up periods at six, twelve, and eighteen months for the outcome measures described in the study.

Regression analysis

Multiple linear regression was used to compare changes in outcomes between the intervention and control groups. This analysis was made for each outcome measure at the six, twelve, and eighteen-month follow-up periods. Change in outcome measures compared to the baseline was used as the dependent variable, with group affiliation (intervention or control group) as an independent variable. Additional independent co-variables included baseline data for the number of registered patients, location (urban or rural), Care-need index (CNI), Adjusted Clinical Group (ACG), and type of PHCC (private or public).

Paper III

Dichotomized Likert items

The study used 5-grade Likert items to ask participants about the perceived importance of different diagnostic tests, including throat swabs and blood tests. The Likert items were split into two categories (dichotomized) to analyse the responses for each question. For example, 'strongly agree' and 'agree' were merged and coded as '1', while 'neutral', 'disagree', and 'strongly disagree' were coded as '0'.

Multivariable binary logistic regression

Two multivariable binary logistic regressions were conducted to investigate the factors influencing medical practitioners' perceptions. One analysis focused on the significance of throat swabs, while the other examined the significance of blood tests as dependent variables. The independent variables were practitioners' age, gender, seniority (senior or under training), and country.

Outcome comparison

The study compared the results of the regression analyses with the guidelines of each country. Adjusted Odds Ratios (ORs) with 95% Confidence Intervals (CIs) were presented, and a significance level of 0.05 was used.

Paper IV

Gold standard comparison

The average of the first and second reference measurements was used as the gold standard against which the RIA-VS was validated. Pre-defined thresholds for acceptable tolerance limits were set for blood pressure, pulse, respiratory rate, and SpO_2.

Random variability estimation

The variance of the difference between RIA-VS and the first reference measurement was calculated and compared to the variance between the two reference measurements to assess random variability.

Mean error and Bland-Altman plots

The mean error, its 95% confidence interval, its range, and the proportion of measurements within the acceptable tolerance error was calculated for validation. These differences were visually represented using Bland-Altman plots.

Leave one out cross-validation

Leave One Out cross-validation was used for SpO2 and blood pressure estimation. This means that the artificial intelligence (machine learning) algorithms were trained on all patient data except for one patient, and then tested on the excluded patient's data. This cycle was repeated until each patient had been the excluded patient tested on, to ensure unbiased prediction results.

Results

Paper I: Fusobacterium necrophorum may play a role in primary care patients with an acute sore throat

Four medium- to high quality studies

Searches in PubMed and Scopus databases found 490 publications. After removing duplicates and screening abstracts, 53 studies were assessed in detail. Out of the 53 studies which were read in full text, 37 were excluded for various reasons, such as focusing on different patient categories or lacking a control group. This left 16 studies that potentially met the inclusion criteria. However, after further evaluation, only four of these studies were found to be of high or medium quality and were therefore included in the meta-analysis (Table 2).

A narrative synthesis was produced for each included study, highlighting the study methodology, target population characteristics, outcomes, and methodological quality assessment.

After aggregating the numbers from the four papers, the meta-analysis was based on 1138 cases and 707 controls.

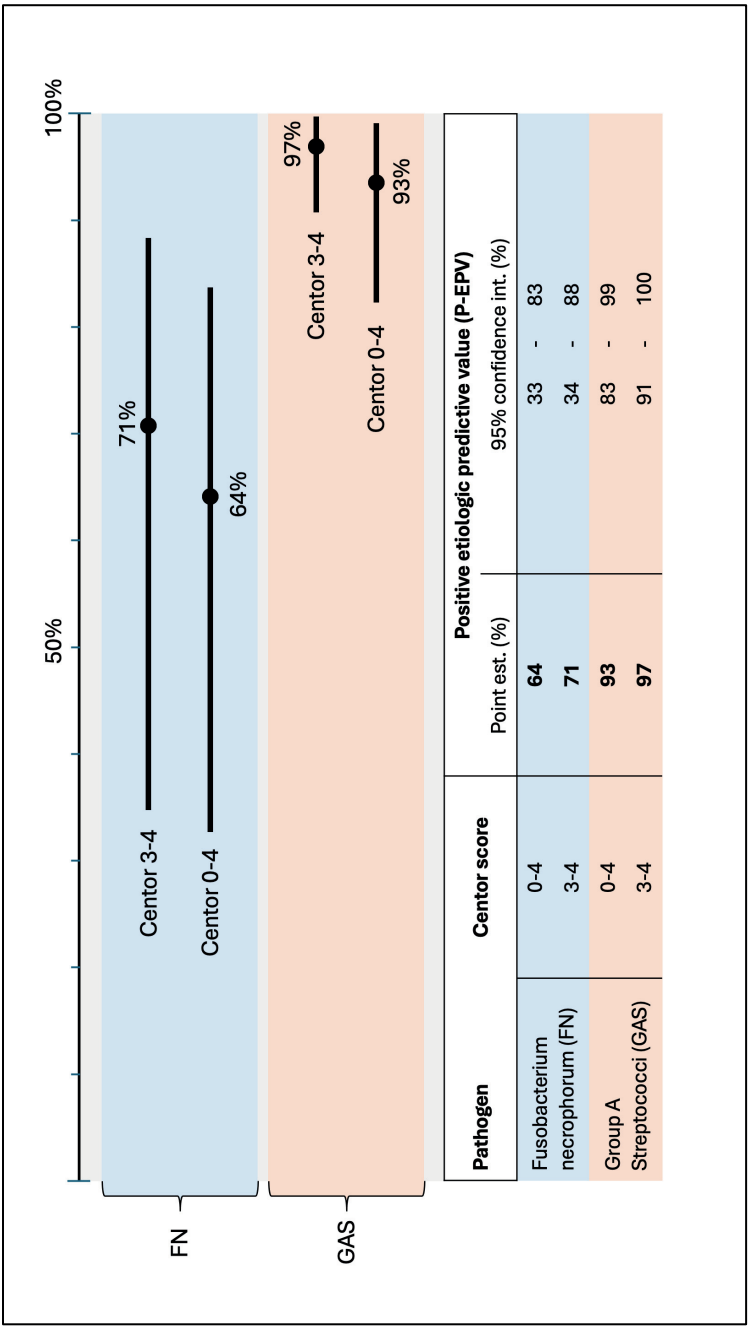
Positive etiologic predictive value of fusobacterium necrophorum for acute sore throat in primary care

The positive etiologic predictive value (P-EPV), which reflects the probability of a true connection between the sore throat and the pathogens, was 64% (95% CI 33 ↔ 83%) for FN and 93% (95% CI 83 ↔ 99%) for GAS (Table 2and Figure 1). When focusing on patients with higher Centor scores (3-4), the P-EPV increased to 71% (95% CI 34 ↔ 88%) for FN and 97% (95% CI 91 ↔ 100%) for GAS (Table 2and Figure 1). These results demonstrate a definitive link between FN and acute sore throat, albeit weaker compared to GAS, with a noticeably narrower CI.

Table 2– Case-control studies examining Fusobacterium necrophorum and group A streptococcus in patients with an acute uncomplicated sore throat in primary care

			Age, years (range)		Number of cases and controls			% FN detected (n)			% GAS detected (n)		
			Cases	Controls	Cases		Controls	Cases		Controls	Cases		Controls
Study [ref]	**Design**	**Method**			Centor 0-4	Centor 3-4		Centor 0-4	Centor 3-4		Centor 0-4	Centor 3-4	
Hedin 2015[11]	Pro	Culture	33 (15–48)	31 (16-46)	220	85	128	15% (33)	19% (16)	3.1% (4)	30% (66)	49% (42)	2.3% (3)
Centor 2015[10]	Pro	PCR	22 (15-30)	24 (15-30)	312	64	180	21% (64)	23% (15)	9.4% (17)	10% (32)	16% (10)	1.1% (2)
Kjaerulff 2015[84]	Pro	Culture	28 (15-40)	29 (15-40)	100	29	100	16% (16)	21% (6)	9.0 % (9)	26% (26)	48% (14)	3.0% (3)
Hayakawa 2018[85]	Pro	PCR + culture	29 (25-37)	33 (26-36)	44	19	31	14% (6)	21% (4)	6.5% (2)	11% (5)	16% (3)	0.0% (0)
SUBTOTAL (low & medium risk for bias)					***676***	***197***	***439***	***18% (119)***	***21% (41)***	***7.2% (32)***	***19% (129)***	***35% (69)***	***1.8(8)***
Jensen 2007[86]	Pro	PCR + culture	25 (18-32)	22 (18-32)	105	-	92	51% (54)	-	21% (19)	5.7%* (6*)	-	-
Jensen 2015[12]	Retro	Culture	19 (10-40)	22 (10-40)	179	-	176	24% (43)	-	5.7% (10)	3.9%* (7*)	-	0% (0)
SUBTOTAL (high risk for bias)					***284***	-	***268***	***34% (97)***	-	***11% (29)***	***4.6%* (13*)***	-	-
TOTAL (ALL SIX ARTICLES)					**960**	**178**	**707**	**23% (216)**	**21% (37)**	**8.6% (61)**	**15%* (142*)**	**39% (69)**	**1.1% (8)**

**GAS-tonsillitis was excluded (by PCPs using RADT) in the two articles by Jensen et al.; thus, those results for GAS were irrelevant for the purpose of this meta-analysis.*



Pathogen	Centor score	Positive etiologic predictive value (P-EPV) Point est. (%)	95% confidence int. (%)
Fusobacterium necrophorum (FN)	0-4	**64**	33 - 83
	3-4	**71**	34 - 88
Group A Streptococci (GAS)	0-4	**93**	83 - 99
	3-4	**97**	91 - 100

Figure 1 - Probability of a true link between sore throat and a positive FN test compared to GAS based on studies with data from both patients and healthy controls.

Paper II: Ambitious antibiotic stewardship program produced no significant differences between intervention- and the control groups

Primary health care centres enrolment and groups

A total of 49 Primary Health Care Centers (PHCCs) were assessed for eligibility, with 24 randomized to the intervention group and 25 to the control group. Although there were some losses to follow up, data was successfully retrieved from 36 PHCCs (16 in the intervention group and 20 in the control group).

There were more privately than publicly run PHCCs in the intervention group; otherwise, there were no baseline differences between groups. Overall, the number of antibiotic prescriptions among the PHCCs participating in the study was similar to that of all PHCCs in the studied region of Sweden.

The intervention started in Jan-Mar 2018 and was completed between Jul-Sep 2018, with follow-up continuing until Sep 2019.

Baseline adherence to acute sore throat guidelines

At baseline, pharyngotonsillitis was managed according to Swedish guidelines in two-thirds of cases. The primary outcome measure (proportion of antibiotic-prescribed pharyngotonsillitis cases with a positive GAS-RADT at the PHCC) was 2/3 for the intervention group and slightly less
for the controls.

Changes over time

There were no significant differences between the intervention and control groups in terms of changes in proportions for the outcomes (antibiotic-prescribed cases with positive GAS-RADT, GAS-RADT-negative cases prescribed antibiotics, cases prescribed first-line antibiotics, and cases with a CRP test taken) at six, twelve, and eighteen months from baseline.

Paper III: Acute sore throat guidelines differed significantly between countries and physicians' perception of best management were in line with their domestic guidelines.

Survey distribution and response

Of the 969 surveys that were distributed to physicians in primary care in Australia, Germany, Sweden, the UK, and the USA, a total of 713 were returned, resulting in a response rate of 74%. Out of these, 680 forms contained adequate information to be analysed, which represented a response rate of 70%. Thirty-three surveys had to be excluded from the analysis due to incomplete or insufficient information.

Guideline inconsistencies between five countries - Australia, Germany, Sweden, the United Kingdom, and the United States

The guidelines for managing acute sore throat in primary care differed considerably between the participating countries. For example, using throat swabs to detect GAS was recommended (under certain conditions) in Sweden and the USA, mentioned as an option in German guidelines, and discouraged in the UK but not mentioned in the Australian guidelines. Furthermore, the countries' recommendations on when to consider prescribing antibiotics were inconsistent. The guidelines in Australia, Germany, and the UK recommended relying predominantly on clinical grading of the tonsillitis signs and symptoms, while the Swedish and US guidelines stressed confirmation of GAS using RADT tests as a prerequisite.

Physicians' perceptions of best management in line with domestic guidelines

The study found significant differences in the perceived importance of throat swabs and blood tests for guiding antibiotic prescribing. For instance, physicians in Australia, Germany, and the UK were less likely to agree that throat swabs are essential than their counterparts in Sweden and the USA (Figure 2). German practitioners, in particular, placed a higher emphasis on the clinical value of

blood tests. UK practitioners were more likely to prescribe antibiotics if a throat swab showed no growth of potentially pathogenic bacteria, indicating a variance in practice across countries.

Figure 2 shows the percentage of practitioners who consider throat swabs important when deciding on the prescription of antibiotics: USA (88%), Sweden (87%), Australia (70%), Germany (61%), and the UK (52%).

GPs from the United Kingdom exhibited a notable lack of awareness regarding FN. The physicians in Australia and the UK were more inclined to administer antibiotics to patients who exhibited growth of group C and group G Streptococci.

The study revealed that older physicians tended to attach greater significance to blood tests such as leukocyte counts, erythrocyte sedimentation rate, or CRP. GPs and specialist consultants tended to perceive blood tests or throat swabs as less important compared to their counterparts still in training.

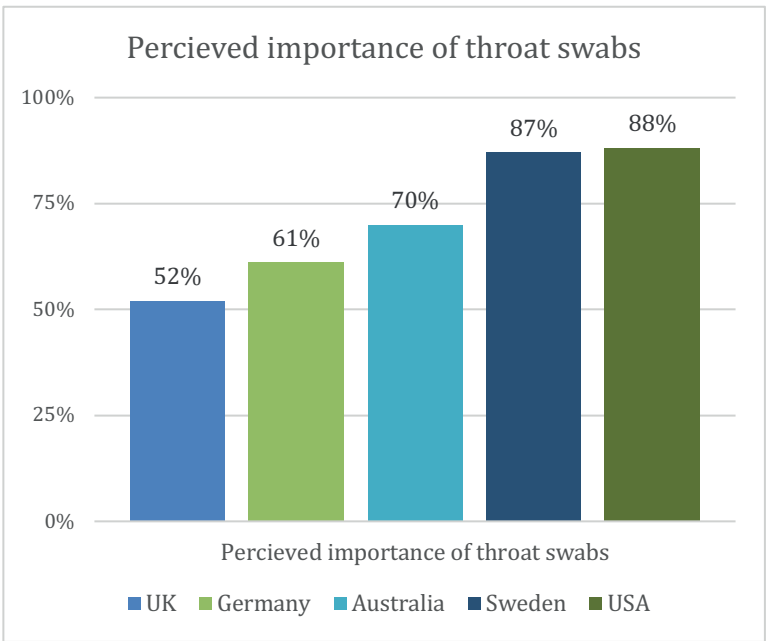


Figure 2: The perceived importance of throat swabs for guiding antibiotic prescribing among physicians in primary care.

Paper IV: Camera-based vital signs measurements were close to the gold standard but less consistent

From June to October 2020 214 patients were enrolled in the study, with an average age of 44 years. Most were female (61%), and their Fitzpatrick skin types ranged from 1 to 4. Included subjects had wide ranges in reference vital signs measurements, including systolic blood pressure (73–210 mmHg), diastolic blood pressure (44–115 mmHg), pulse (52–161 beats/min), respiratory rate (9–40 breaths/min), and oxygen saturation (67–100%).

Camera-based vital sign measurement shows promise but varies more than standard methods

The camera-based measurements of vital signs (systolic and diastolic blood pressure, pulse, respiratory rate, and oxygen saturation) were, on average, close to the gold standard reference measurements (defined as the average of two reference measurements). However, the camera-based measurements had considerably greater random variation than the reference methods (when comparing the two reference measurements). Furthermore, the RIA-VS technology tended to normalize the measurements, meaning high values were underestimated while low values were overestimated.

Blood Pressure

The new RIA-VS device's measurements of systolic and diastolic blood pressure (SBP and DBP) were close to the gold standard on average. Initially, the mean error (ME) between the RIA-VS device and the gold standard was, on average, ±3.2 and ±2.4 mmHg, respectively for SBP and DBP. After AI training, these errors were reduced to ±0.069 and ±0.13 mmHg, respectively (Figure 3 and 4). Of the RIA-VS results, 53% for SBP and 68% for DBP were within the pre-defined tolerance range (±10 mmHg, Figure 5). Corresponding numbers for the reference measurements were 71% for SBP and 92% for DBP (Figure 5). However, the random variation was more significant for the RIA-VS camera than the reference methods: 3.9 times higher for SBP and 3.3 times higher for DBP.

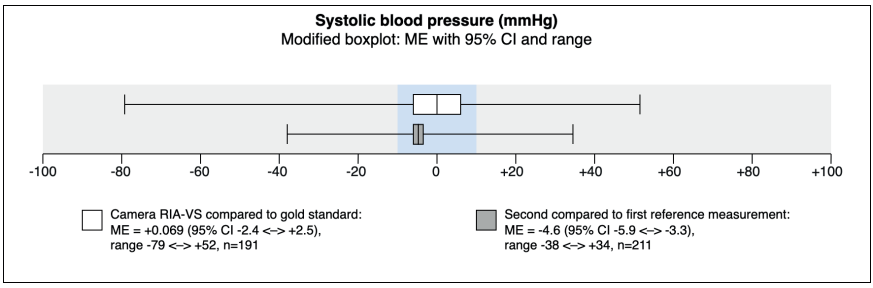


Figure 3: Modified boxplot showing results for systolic blood pressure with mean error (ME), 95% CI, and range, for the camera RIA-VS compared to the gold standard and the second reference measurement compared to the first. The blue area shows the predefined tolerance range.

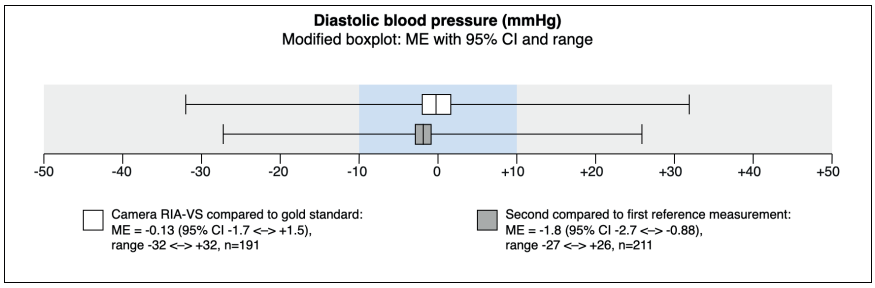


Figure 4: Modified boxplot showing results for diastolic blood pressure with mean error (ME), 95% CI, and range, for the camera RIA-VS compared to the gold standard and the second reference measurement compared to the first. The blue area shows the predefined tolerance range.

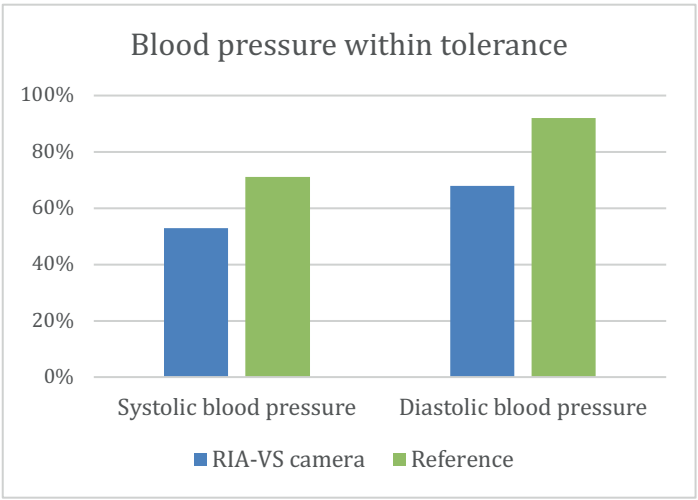


Figure 5: Blood pressure, proportion within tolerance range (±10 mmHg) for the RIA-VS camera compared to gold standard, and the second reference measurement compared to the first.

Heart rate (pulse)

The study found that the pulse measurements using RIA-VS had only a slightly higher random variation (1.4 times higher) than the standard reference method, indicating a relatively accurate pulse rate estimation. The ME for pulse was +1.4 beats per minute (95% CI +0.27 ↔ +2.5), with a -43 ↔ +18 range and 79% within the predefined tolerance error range. Comparing the second reference measurement to the first showed an ME of -0.97 beats per minute (95% CI -2.0 ↔ +0.023), with a -51 ↔ +44 range, and 93% within the predefined tolerance error range. (Figures 6 and 7)

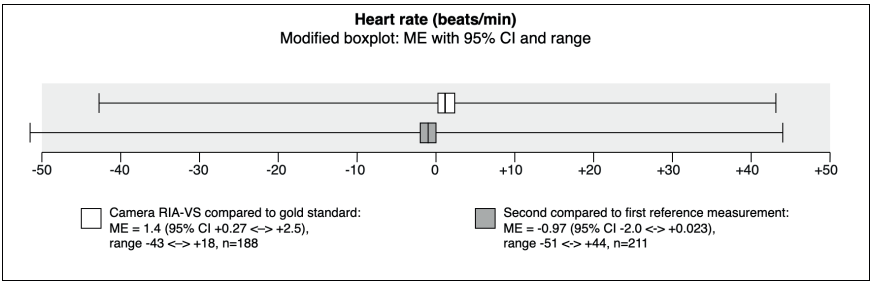


Figure 6: Modified boxplot showing results for heart rate (pulse) with mean error (ME), 95% CI, and range, for the camera RIA-VS compared to the gold standard and the second reference measurement compared to the first.

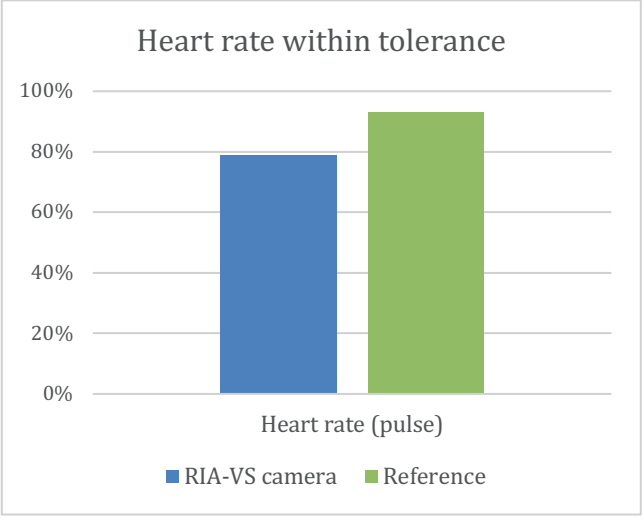


Figure 7: Heart rate (pulse), proportion within tolerance range (±10 mmHg) for the RIA-VS camera compared to gold standard, and the second reference measurement compared to the first.

Respiratory rate

The ME for respiratory rate was +1.1 breaths per minute (95% CI +0.14 ↔ +2.0) with a -19 ↔ +16 range (Figure 8) and 59% of results within the predefined tolerance error range (Figure 9). However, the random variation for respiratory rate measurements by RIA-VS was significantly higher (4.7 times) than the reference method, suggesting more significant discrepancies in measuring this vital sign.

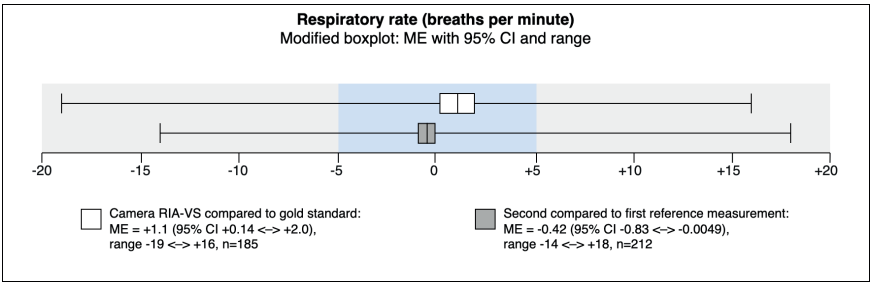


Figure 8: Modified boxplot showing results for oxygen saturation (SpO2) with mean error (ME), 95% CI, and range, for the camera RIA-VS compared to the gold standard and the second reference measurement compared to the first. The blue area shows the predefined tolerance range.

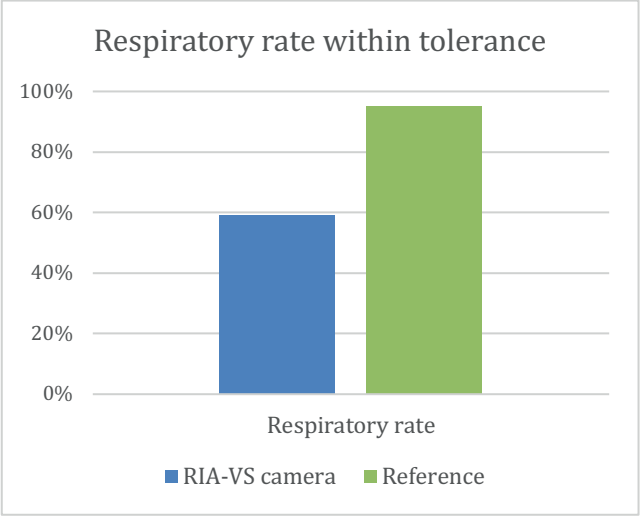


Figure 9: Respiratory rate, proportion within tolerance range (±5 breaths per minute) for the RIA-VS camera compared to gold standard, and the second reference measurement compared to the first.

Oxygen saturation (SpO2)

The RIA-VS device was more accurate at estimating SpO2 using ambient light than a fixed algorithm aided by infrared and red LED light. The ME for ambient light SpO2 was -0.049% (95% CI +-0.35 ↔ +0.26, Figure 10) with a -5.0 ↔ +6.9 range and 71% within the predefined tolerance error range (Figure 11). The random variation in SpO2 measurements using ambient light was 2.0 times higher, and for infrared and red light, it was 6.7 times higher compared to the reference method.

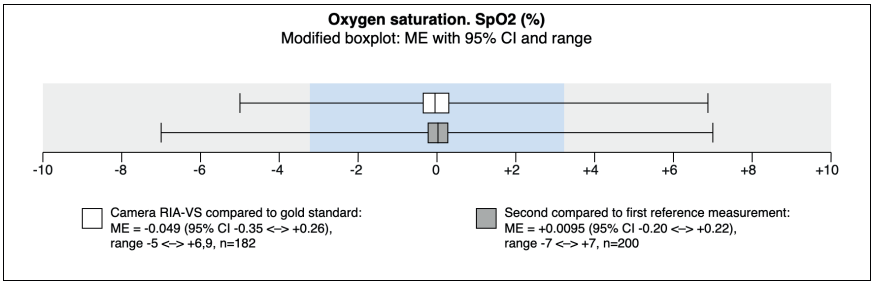


Figure 10: Modified boxplot showing results for oxygen saturation (SpO2) with mean error (ME), 95% CI, and range, for the camera RIA-VS compared to the gold standard and the second reference measurement compared to the first. The blue area shows the predefined tolerance range.

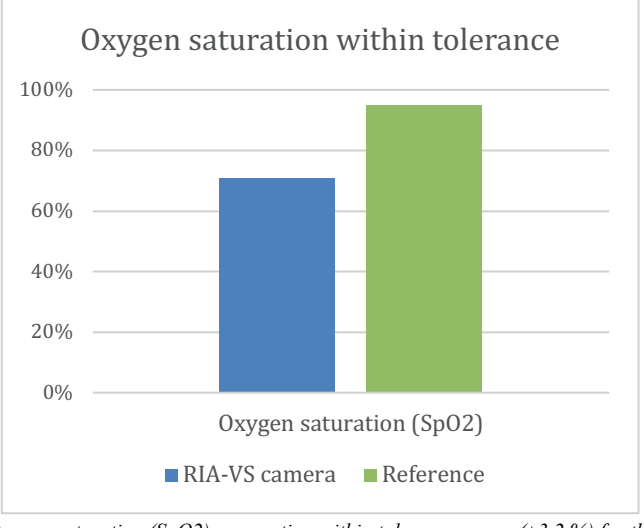


Figure 11: Oxygen saturation (SpO2), proportion within tolerance range (±3,2 %) for the RIA-VS camera compared to gold standard, and the second reference measurement compared to the first.

AI training improved usability and accuracy of camera-based blood pressure and oxygen saturation measurements

Initially, only 70 out of 214 videos were usable for blood pressure measurement. However, after training the AI on the complete patient dataset this number increased to 191. The mean error in systolic and diastolic blood pressure between RIA-VS and the gold standard improved significantly after AI training. The AI algorithm measuring blood oxygen saturation in ambient light could successfully analyze only 39 out of 214 attempts, increasing to 182/214 after AI training. The ambient light SpO2 AI algorithm was more accurate than the fixed algorithm aided by infrared and red LED light.

Discussion

Main findings

The positive etiologic predictive value (P-EPV), which reflects the probability of a true connection between the sore throat and pathogens, was 64% (95% CI 33↔ 83%) for Fusobacterium necrophorum (FN) and 93% (95% CI 83↔ 99%) for Group A Streptococci (GAS). When focusing on patients with higher Centor scores (3-4), the P-EPV increased to 71% (95% CI 34↔ 88%) for FN and 97% (95% CI 91↔ 100%) for GAS. These results demonstrate a definitive association between FN and acute sore throat, albeit weaker compared to GAS (Paper I).

A six-month antibiotic stewardship program (ASP), added to pre-existing and long-running stewardship efforts, had no impact on antibiotic prescribing and managing of acute sore throat cases in primary health care centres (PHCCs). Over the follow-up period, there were no significant changes between the intervention and control groups in the proportion of cases prescribed antibiotics (whether with positive or negative GAS-RADT results), those prescribed first-line antibiotics, or cases with a CRP test conducted. (Paper II)

Guidelines for managing acute sore throat in primary care vary considerably across countries and primary care physicians' practices align with their respective national guidelines in Australia, Germany, Sweden, the UK, and the USA. Key differences were noted in the perceived importance of throat swabs and the reliance on clinical signs versus confirmatory tests such as RADTs for prescribing antibiotics. (Paper III)

The camera-based approach shows promising results for contactless measurement of blood pressure, pulse, respiratory rate, and SpO2. The technology must be refined before use in medical care, considering the normalization tendencies and more considerable random variation compared to the reference methods. (Paper IV)

Strengths and limitations of the thesis

Methodological diversity is a noteworthy strength of this Ph.D. thesis, as the four independent papers have distinct objectives and study designs: a systematic review and meta-analysis (Paper I), a randomized controlled trial (Paper II), an international cross-sectional survey (Paper III), and a clinical investigation (method comparison) of a medical device (Paper IV).

A systematic review with meta-analysis allows for a comprehensive synthesis of existing data, as in this case, where the method provides a higher level of evidence regarding FN's role in primary care patients with a sore throat. Combining results from multiple studies enhances the generalizability and reliability of the findings compared to the individual studies included in the review.

The RCT is the gold standard in clinical research design, enabling a controlled and unbiased assessment of an intervention's efficacy. Investigating if a clearly defined and repeatable ASP increases pharyngotonsillitis guideline adherence in primary care, this RCT helps inform those making current and future strategic efforts to improve guideline adherence.

The international survey of primary care doctors offers a perspective on clinical practices and sore throat guidelines across diverse healthcare systems. This breadth of data uncovers multinational trends and revealed unexpected differences and universal challenges in medical practice.

A clinical investigation comparing a new medical device against established methodologies demonstrates a commitment to innovation and translational research. In addition to the rigorous ethical review encompassing all clinical research, a comprehensive approval process with the Swedish Medical Products Agency was required to initiate the project. The study contributes to evaluating and implementing new technology by validating its usefulness and accuracy in a clinical setting.

Methodological issues

Methodological strengths and limitations of Paper I

Structured review process, comprehensive search strategy, and rigorous quality assessment

The review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement[80], ensuring a structured and standardized review process. This approach enables reproducibility and comparison with similar studies. A detailed search strategy was employed across PubMed and SCOPUS without time limitations, ensuring a broad and thorough search for relevant studies. The methodological quality assessment of included studies was carried out using defined criteria, which helped identify and include studies with medium to high methodological quality for the meta-analysis.[81] Before initiating any study activities, a research protocol listing these important methodological aspects was published in Prospero[82], a database specifically for reviews.

The use of positive etiologic predictive value (P-EPV) for the meta-analysis allows for a more nuanced understanding

Applying P-EPV in the meta-analysis provides a more sophisticated approach to assessing the probability of FN being a causative agent in sore throat cases since it takes into account the prevalence of FN in healthy controls. Furthermore, the comparative data on the prevalence of FN and GAS across various Centor scores offer valuable insights into their respective roles in pharyngotonsillitis in primary care.

Wide P-EPV confidence intervals for FN – apply caution when interpreting findings

The wide CIs for P-EPV for FN indicate that while the study provides valuable insights into the association between FN and acute uncomplicated sore throat in primary healthcare settings, the precision of these estimates is relatively low. This uncertainty needs to be considered when assessing the clinical relevance of

FN in patients presenting with an acute sore throat compared to the more established GAS, where the CIs in this meta-analysis were narrower.

Positive etiologic predictive value (P-EPV) and random effect models

Unlike typical random effects models, the P-EPV method, used in the **first paper**, does not directly account for variation between studies. However, the between-study variation statistics (I^2) used in random effect models are unreliable when a small number of publications are included, as in this case (four studies).

P-EPV is considered more clinically useful and easier to understand, particularly for clinicians unfamiliar with research statistics. The most significant advantage is that it takes asymptomatic carriage into account. P-EPV was deemed more appropriate for the study's goal to assess the clinical relevance of FN in acute sore throat cases. However, in other contexts or with a different study design, traditional random-effects models could be more suitable.

Limited number of case-control studies included in the review

One significant limitation was the limited number of available case-control studies presenting the proportion of Fusobacterium necrophorum (FN). This limitation restricts the breadth of evidence available for analysis and may affect the generalizability of the findings. While excluding studies with methodological limitations can be seen as a strength, it also limits the scope of the review. Some excluded studies may have provided relevant data but were not considered for various reasons, such as a lack of a control group or a focus unaligned with the scope of the review.

The screening and selection process could introduce bias

Two reviewers independently screened and selected studies for inclusion, but disagreements were resolved through discussion with the entire study team. While this is standard practice, it inherently involves subjective judgment, which could introduce bias into the study selection process.

GAS, Fusobacterium necrophorum, and antibiotics

The conclusion drawn from **Paper I** suggest a notable association between FN and acute sore throat, particularly in patients with higher Centor scores, although to a lesser extent (and wider CIs) than the association with GAS. This observation makes a valuable contribution to understanding the aetiology of sore throats and may influence clinical decision-making. However, while the association is statistically significant, the clinical relevance of FN in acute sore throat, compared to GAS, remains to be fully determined.

Antibiotic treatment for GAS-positive cases is commonly recommended in acute sore throat management due to its efficacy in reducing symptom duration and intensity and preventing rare but severe complications, such as rheumatic fever and glomerulonephritis.[83] The potential benefits of such treatment justify its use despite the risk of contributing to antibiotic resistance.

Given the similarity in clinical presentation and the potential severity of FN-related complications (Lemierre's syndrome and peritonsillar abscess), a case can be made for treating FN-positive tonsillitis with antibiotics based on the assumption that antibiotic therapy would provide a clinical benefit comparable to that observed in GAS treatment by reducing the acute symptoms and potentially preventing deterioration and complications.

It is important to note that while GAS is a well-recognized pathogen in pharyngotonsillitis, and its complications are well-documented, FN has not been historically targeted in standard sore throat management. However, the presented recognition of FN's role in sore throat may warrant a re-evaluation.

It is a substantial leap from identifying an association to suggesting antibiotic treatment — the hypothesized benefits of antibiotic treatment for FN-positive sore throat cases are speculative until proven by rigorous clinical trials. RCTs would be needed to investigate whether antibiotic treatment of FN-positive sore throat cases is safe and effective, keeping these perspectives in mind. The research should include a comprehensive risk-benefit analysis, weighing the risk of contributing to antibiotic resistance against the potential benefits of treating FN infections.

Methodological strengths and limitations of Paper II

Well-defined and scalable intervention

The ASP physician at each PHCC led the activities during the six-month intervention. All material needed for the ASP was prepared, and the software for extracting the laboratory- and prescribing statistics for sore throat patients was readily available. If the results had shown a meaningful change in the intervention group, indicating that the intervention was effective, the intervention could be rapidly implemented at many more PHCCs.

Individualized reports on laboratory- and prescribing statistics

As part of the intervention, each physician could evaluate their statistics showing how they had used laboratory tests and prescribed antibiotics when managing sore throat patients in recent months. Furthermore, they repeatedly met to discuss their PHCCs aggregated statistics. This allowed for repeated evaluation of the guideline adherence on both individual and aggregated levels.

Baseline comparison indicates appropriate randomization

The study collected comprehensive baseline data, including laboratory and prescription statistics, organizational characteristics of the PHCCs, and detailed adherence records during the intervention. Both groups had similar overall adherence to the national guideline at baseline, indicating a well-balanced randomization process.

Lack of blinding and inconsistent adherence to the intervention

The study was not blinded, allowing the possibility of bias. Clinicians in the control group could learn about the intervention, and their behavior might have been influenced by the Hawthorne effect (awareness of being observed). Furthermore, there was inconsistent adherence to the intervention, as individual diagnosis-linked prescription statistics were not distributed as instructed in several PHCCs.

Dependence on individuals and loss of participating PHCCs

The intervention's success was highly dependent on a single individual at each PHCC (the ASP physician), making it vulnerable to personnel changes. Eight PHCCs in the intervention group withdrew from the study, possibly indicating that some participants perceived the intervention as too ambitious or of insufficient value.

Methodological strengths and limitations of Paper III

The first multinational study connecting guidelines to practitioners' perceptions shows a high response rate

A noteworthy strength of the study is the novel approach of connecting specific guideline differences with medical practitioners' perceptions of best management for patients with an acute sore throat. The high response rate suggests the findings could be generalizable to a broader population. Despite known challenges in surveying medical practitioners, this high participation rate indicates strong engagement and relevance.

Limitations from the cross-sectional design

The cross-sectional study design is a limitation because it restricts the possibility of determining the causality or direction of relationships between guidelines and practitioner perceptions. Put another way: Are practitioners influenced by national guidelines, or vice versa? While the study aims for broad applicability, its findings are most directly relevant to high-income countries, as noted in the discussion of guidelines and their influence on medical practice.

Perceptions instead of actual performance

The study measured medical practitioners' perceptions of optimal management rather than actual clinical practices. This approach may not accurately reflect real-world prescribing behavior.

Potential selection bias

Recruiting participants primarily through educational meetings could introduce a selection bias since it represents a convenience sample rather than a random sample. However, the effect of such bias is likely less significant today compared to the past due to changes in how practitioners attend educational events. The potential selection bias is further discussed under the headline "Ethical considerations" below.

Methodological strengths and limitations of Paper IV

Inclusion of real-world patients

A major strength of the study is the inclusion of actual patients in an emergency department with suspected COVID-19 patients exhibiting a wide range of abnormal vital signs. This enhances the authenticity and applicability of the findings to clinical scenarios.

Testing the learning potential of AI

The study's design highlights the potential of machine learning algorithms to improve the accuracy and robustness of medical devices over time. The software in the RIA-VS device, powered by AI, estimated blood pressure and oxygen saturation with greater accuracy after being trained and successfully analyzed 2.7 times more blood pressure samples and 4.7 times more blood oxygen saturation samples than before. This is a clear example of how AI-powered software can improve with more data.

Limited generalizability

The study explicitly aimed to evaluate the new RIA-VS method in patients presenting with typical COVID-19 symptoms, and critically ill patients were not included. The study findings are most applicable to similar clinical scenarios and patient populations. Although there was some diversity in the population sampled, the study did not include patients of all skin types, particularly those with

Fitzpatrick skin types 5 and 6. As a result, the generalizability of the study's results across different demographic groups is limited.

Study environment constraints

The study was conducted in an emergency department setting, which adds a layer of complexity due to the variability in patient conditions, the stress of the environment, and the potential influence of these factors on the measurement accuracy of the new device. At the time, the initial severity assessment of all patients with suspected COVID-19 took place in a temporary triage station located just outside the emergency department entrance. The triage station was hastily built by placing two shipping containers with the long sides parallel, cutting open the adjacent container walls to create a single "room", covering the gap in the roof with a tarp and the floor with wooden plates. The containers were combined outdoor and indoor environments since the doors were always open, with frequent visits from birds and insects. The construction represented an unusual working environment for modern healthcare, including, for example, rats living under it, rain sometimes pouring like a waterfall in the middle of the room (between the two containers), tangled cables taped to the floor, walls, and roof, and temperatures ranging from a few degrees Celsius to above 40 degrees on sunny days. Sawdust and used nicotine pouches in every corner were clues of previous use and revealed that the "room" was never cleaned.

Due to constraints on the operational environment set by the manufacturers of reference measurement devices and some components in the new RIA-VS device, data collection had to be paused occasionally. The stressful environment made it harder for subjects to remain still during video recording, and environmental factors, such as reflections from windows in nearby buildings and shadows from people passing by, may have reduced the quality of recorded videos, which may have negatively affected the results.

Camera-based vital signs measurements - pros

A system that utilizes a camera to capture vital signs by briefly scanning the patient's face would provide several benefits over current methods of measuring vital signs. Eliminating the need for physical contact between the equipment and the patient reduces the risk of infection transmission and improves patient comfort. A camera-based system would simplify the vital sign measuring procedure,

which could help improve the frequency and completeness of measurements. Clinicians could measure vital signs quickly and efficiently, reducing the time and effort required for assessment. This could also reduce stress among healthcare workers and increase the reliability of risk-stratifying patients. Furthermore, a refined and validated future camera-based system could improve vital sign measurement accuracy, as some currently used devices have suboptimal precision, and obtaining vital signs depends on clinicians' knowledge, skill, and technique.

Camera-based vital signs measurements - cons

A camera-based technology may not be suitable for all patients. For instance, some patients may have facial hair or skin conditions that could interfere with accurate readings. In such cases, additional tests or measurements may still be required to assess vital signs accurately. Another limitation is that environmental factors such as lighting and backdrop may affect the camera-based system. These factors could impact the measurements' accuracy. Additionally, the accuracy of the vital sign measurements may be impacted by patient movement.

A camera-based system requires calibration and testing to ensure accurate readings across different patient populations. Factors such as age, sex, and ethnicity could affect the reliability of the measurements, and the system may require ongoing calibration to ensure accuracy for all patients. Another factor is that implementing any new technology necessitates investment in infrastructure and training, incurring cost.

Ethical considerations

Ethical approval and patient consent in data analysis

Paper I used publicly available data from published articles where the primary investigators of the original studies obtained informed consent from participants.[10,11,84,85] Therefore, there was no need for separate ethical approval for this secondary analysis of previously obtained data.

Only published and aggregated data on the group level were used (acute sore throat or healthy asymptomatic controls) and the aim of Paper I aligns with the aims of the papers included in the study.

Participant dropout and study continuity

Participant dropout is expected in clinical research, emphasizing the importance of respecting participant autonomy. However, this ethical cornerstone can conflict with the scientific aim of obtaining complete data sets.

Paper II faced significant participant dropout, particularly among PHCCs in the intervention group, which could introduce bias and affect the representativeness and validity of the study outcomes. The research team tried to minimize dropout rates by clearly communicating the study's benefits and burdens and trying to establish trust with participants.

In this case, the dropout rate in Paper II's intervention group could illustrate how ASPs may never get a chance to prove their benefits if they fade away in the clinical reality of competing demands, stress, and limited resources. Furthermore, no trends were observed in the intervention group, indicating that no statistically significant effect would be realistically expected even if the few PHCCs that dropped out happened to be the ones were the ASP made a real impact.

Ensuring transparency in reporting and implementing rigorous statistical methods are crucial for preserving scientific validity and ethical principles while managing dropouts.

Data collection methods and response rates for surveys

The data collection method can significantly influence the quality and quantity of the data. **Paper III**'s researchers opted for a direct approach, physically disseminating and retrieving forms at educational meetings for PCPs, which tends to yield higher response rates. This stands in contrast to the less personal, albeit more efficient, method of email surveys, which allows for an impressive reach but usually suffers from lower response rates.

Bias and representativeness

Selection bias occurs when recruited participants do not represent the entire target population, potentially skewing the research results. In **Paper III**, the recruitment strategy – sourcing participants primarily through educational meetings – could have introduced such a bias. This method may disproportionately represent physicians who are more active in staying up-to-date with developments in their field or have specific interests that align with the theme of a particular educational meeting.

However, the growing acceptance of continuous training and education for physicians throughout their careers has likely diluted the effect of this selection bias. With more practitioners obligated to attend educational activities, the participant pool should become more representative of the general PCP population, reflecting a broader range of practices and attitudes toward sore throat management. Furthermore, the topics for the educational meetings where the survey was distributed were not RTIs or acute sore throat but other primary care associate themes, such as diabetes or ischemic heart disease.

Clinical research on novel technology during the covid-19 pandemic

The **fourth paper** of the thesis was conducted during the initial wave of the COVID-19 pandemic in 2020. The research involved patients with suspected COVID-19 and aimed to explore the efficacy of contactless vital signs measurements. At face value, the decision to test this novel technology on a vulnerable patient population during a high-stress period may appear inappropriate, even irresponsible, raising questions about the potential risk to patients and researchers alike.

Clinical evaluation amidst COVID-19 – weighing risks against benefits

One might question the rationale behind not initially testing a healthier cohort since the research activities could introduce delays in emergency care for patients in critical need. Moreover, the risk to researchers was not insignificant, conducting the study at a time when understanding of COVID-19 was still evolving. The decision by the emergency department to participate in the study while struggling to manage a surge of infected patients also presents an ethical dilemma.

The justification for proceeding with the study during the pandemic was anchored in the potential benefits of contactless vital sign measurement. The methodology was potentially a faster and safer way to assess patient health, which could be invaluable in overwhelmed emergency settings.

Studies with the potential to improve pandemic management fast-tracked by Swedish authorities requiring rigorous patient safety measures

Given the circumstances, all other non-essential clinical research was suspended, and the authorities had implemented a "fast track" for approving studies that could positively impact pandemic management. Recognizing the potential benefits and the urgent need the Swedish Ethical Review Authority and the Medical Products Agency prioritized and approved the project. The emergency department's management and medical leaders agreed to collaborate and determined that the research project had an appropriate process to protect patient safety.

Extensive precautions were taken to protect patients, and the inclusion criteria ensured that only those with no apparent severe illness were recruited. Participation required fluency in Swedish (reading, writing, conversational) and capability of understanding and giving informed consent. A research nurse and physician explained the study and provided written information (approved by authorities). They were also available to answer questions, ensuring all participants were informed about the study and its objectives. An independent monitor audited all documentation and repeatedly reviewed the research site to ensure adherence to international standards for clinical trials.

Despite the strict precautions, there were instances where patients proved to be more severely ill than their appearance revealed, as indicated by their reference vital sign measurement results. Research activities were immediately stopped in these situations, and clinicians promptly attended to the patients. One could speculate that participation in the study inadvertently reduced the waiting time in these cases.

The balance between advancing medical knowledge and ensuring patient and researcher safety, particularly during a public health crisis highlights the complex decision-making processes inherent in conducting important clinical research in high-risk circumstances. The research team proceeded with a deep sense of

responsibility and urgency, operating within the ethical and regulatory framework set by supervising authorities and with a commitment to patient safety.

Disclosing study funding and author ownership in tech firm behind RIA-VS device to maintain transparency

Two of the authors, Stefan Malmberg and Taha Khan, disclosed owning shares in the medical technology company developing the RIA-VS device. This disclosure ensures transparency regarding potential conflicts of interest. The other authors, Ronny Gunnarsson, Gunnar Jacobsson, and Pär-Daniel Sundvall, had no conflicts of interest to declare. Additionally, the published paper contains information about how the study was funded, which provides transparency about the financial support for the research. The medical technology company provided the RIA-VS device and technical support but no financial contributions to the study.

Findings in relation to literature

Fusobacterium necrophorum and acute sore throat in primary care

Asymptomatic carriage is relevant for assessing the association between FN and acute sore throat in primary care

Previous research has shown that there are healthy carriers of FN, and some studies have indicated that FN may cause sore throat, especially in adolescents and young adults.[10–12,84–86] However, none of the three most recent systematic reviews considered healthy carriers when assessing FN's significance in primary care pharyngotonsillitis cases.[13–15]

Agerhäll et al. have further emphasized the significance of asymptomatic carriage rates for FN, as their paper underscores the high incidence of asymptomatic carriage among adolescents and young adults aged 16-25 (9.2% with PCR).[87] The study also demonstrated a significantly higher detection rate with PCR, suggesting that FN might be present more frequently in the pharyngeal mucosa of healthy adolescents and young adults than previously identified by traditional culturing methods.[87] This could explain the comparatively lower incidence of FN amongst controls in **Paper I**, which includes two studies using swab culture[11,84] and the remaining two studies using PCR[10,85].

Adding to the evidence, Nygren et al.'s research investigated the geographical differences in tonsillar carriage rates of FN among healthy participants aged 15-25 years in Sweden and Zambia.[88] The study found that tonsillar carriage was significantly more common in Sweden (21%) than in Zambia (3%), suggesting significant geographical differences in the prevalence of FN, with implications for understanding the pathogen's role in pharyngotonsillitis and potentially guiding the interpretation of tonsillar findings in patients with this condition. Such geographical differences should be considered when comparing guidelines for managing acute sore throat in different countries, creating a link to **Paper II**. Guideline differences may stem from geographical variations in the prevalence of different pathogens, which have yet to be uncovered by science.

Clinical significance of FN

Using the P-EPV[89] as an innovative statistical approach, Paper I affirms FN's clinical relevance in acute sore throat in primary care, suggesting a nuanced interpretation alongside established pathogens such as GAS.

Despite the increasing clinical information on this bacterium, there is a lack of consensus on its clinical importance and how to appropriately manage an FN-positive acute sore throat. In a recent review article, Centor et al. highlighted the need for guidance in treating infections caused by FN.[90] The review emphasizes the significance of FN in causing bacterial pharyngotonsillitis and its association with severe septic and suppurative complications, particularly in the 15-30 age group.

This discussion illustrates that, although FN has been recognized for its contribution to severe throat infections, such as Lemierre's syndrome and peritonsillar abscess, its presence in both uncomplicated acute sore throat cases and healthy individuals (asymptomatic carriers) requires us to reevaluate its clinical significance, taking into account the complex nature of pathogenicity in the respiratory tract microbial community.

ASP for acute sore throat in primary care

Despite the multifaceted intervention design of the RCT described in **Paper II**, the study did not observe an increase in guideline adherence among PHCCs in the Region of Västra Götaland, Sweden. The study's methodology and findings contribute to a growing body of literature illustrating the challenges of improving antibiotic prescribing practices.

ASP interventions, including audit and feedback, are supported by clinical evidence and sometimes work

Sometimes, straightforward interventions provide remarkable results. For example, sending a single peer-comparison letter to high-prescribing PCPs in Ontario, Canada, led to statistically significant reductions in total and prolonged-duration antibiotic prescriptions.[42] Even less complicated, displaying a poster-sized letter in examination rooms, informing patients on the clinicians' commitment to appropriate use of antibiotics has been shown to reduce inappropriate antibiotic prescriptions.[91]

The ASP investigated in **Paper II** implemented most, if not all, of the 15 suggestions of intervention design features associated with effective feedback interventions presented in a paper by Brehaut et al. investigating practice feedback interventions.[43] For example, the recommended actions were consistent with established goals and priorities, specific, and under the recipient's control. There were multiple instances of feedback, individually and for the physicians in aggregate at each PHCC, with scheduled meetings to minimize cognitive load for recipients. The meetings led by the ASP physician at each PHCC allowed feedback through social interaction, ensured that the information came from a trusted local champion[44], and enabled guided constructive reflection with colleagues.

Similarly, in a recent paper, King et al. evaluated outpatient ASP interventions and considerations and concluded that using multiple complementary intervention strategies is more likely to be effective.[40] From the identified intervention strategies, the ASP in **Paper II** included point-of-care testing, clinical decision support, audit and feedback with peer comparison, and clinician education. However, the intervention did not explicitly include patient education, communication skills training (for clinicians), public commitment posters, and accountable justification.

In a trial involving PHCCs in Boston and Los Angeles clinicians were randomized to receive zero, one, two, or three interventions over 18 months.[92] At the start, all clinicians were educated on antibiotic prescribing guidelines. The three interventions were (1) *suggested alternatives* (automatic "pop-up" message suggesting non-antibiotic treatment when diagnosing an RTI), (2) *accountable justification* (encouraging clinicians to justify each antibiotic prescription, with their free text response added to the patient's medical record as an "antibiotic justification note"), and (3) *peer comparison* (emails to physicians that compared their individual antibiotic prescribing rates with "top performers"). The results showed that accountable justification and peer comparison effectively reduced rates of inappropriate antibiotic prescribing for acute RTIs.

Hence, compared to the ambitious audit and feedback activities in **Paper II**'s ASP, with multiple meetings, comprehensive statistics on antibiotic prescribing, and peer discussion to agree on improvement plans, the Meeker et al. study's accountable justification and peer comparison interventions were more effective. Perhaps the ASP's 18-month duration was instrumental to the results. Alternatively, the improvements were linked to focusing on personal accountability and

competitiveness. Do physicians modify their prescribing behavior more when competing against peers than when comparing with quality control goals?

ASP interventions are not always effective in changing primary care antibiotic prescribing

A study in Germany conducted by Wächtler et al. investigated the impact of implementing a guideline and an additional GAS-RADT on antibiotic prescriptions for sore throat.[50] The results showed that the intervention did not significantly reduce the antibiotic prescription rates, which remained about three times higher than the GAS prevalence.

Hemkens et al. examined the effect of a nationwide ASP on antibiotic use among PCPs in Switzerland.[39] The intervention involved quarterly personalized antibiotic prescription feedback to physicians for two years. The ASP did not significantly change antibiotic prescribing across all patients. However, over part of the intervention period a decrease in antibiotic prescribing in older children, adolescents, and younger adults was observed, but only temporarily.

Aghlmandi et al. evaluated the effect of a quarterly antibiotic prescription audit and feedback on PCPs in Switzerland with medium to high antibiotic prescription rates.[48] Despite the intervention, there was no significant reduction in antibiotic prescribing rates. The study highlights the challenges of reducing antibiotic prescriptions in a setting with already low prescription rates compared to other European countries. Notably, the **Paper II** study's context in Sweden – a country recognized for its strategic efforts against antibiotic resistance[44] – provides a similar setting where incremental gains in guideline adherence might be increasingly difficult to achieve due to pre-existing high levels of awareness and practice among healthcare professionals.

The lack of significant effect from the ASP intervention described in **Paper II** aligns with the findings in the studies by Hemkens et al., Wächtler et al., and Aghlmandi et al., as these three studies were unsuccessful in improving physicians' antibiotic-prescribing behaviors through
their respective interventions.[39,48,50]

An underlying theme across these studies is that providing feedback or training on guidelines might not be sufficient. These similarities indicate a need to reassess how interventions are designed. In order to impact antibiotic prescribing

habits in primary care settings, more engaging, context-specific, and multifaceted interventions may be necessary, tailored to specific clinical scenarios, national or regional professional traditions, and existing levels of guideline adherence.

Should pharmacies and pharmacists or primary health care clinics and physicians attend to acute sore throat patients?

A different approach to reducing inappropriate antibiotic prescribing would be to step back, reconsider care pathways, and consider whether general practitioners should always decide when to recommend and prescribe antibiotics.[83,93] Rebalancing primary care services by transferring the management of minor ailments, such as uncomplicated cases of acute sore throat, to community pharmacies can offer patients more accessible pathways and free PCPs to manage more complex cases.

A test-and-treat service for sore throat was introduced in selected community pharmacies in Wales. The service screened sore throat cases (pharmacy customers) using FeverPAIN/Centor scores, offered RADT to detect GAS if appropriate, and the pharmacist supplied antibiotics if indicated. A comprehensive evaluation concluded that the Welsh test-and-treat service represents a scaleable and reliable pathway to promote the appropriate use of GAS-RADT and antibiotics while substantially reducing the workload of PHCCs.[94] Similar results had been observed in an English study with a similar design.[95]

However, as described earlier in the section on FN and acute sore throat, severity assessment and patient safety are key challenges to address and investigate before definitively reorganizing the management of acute sore throat in a way that shifts extensive responsibilities to pharmacies and pharmacists instead of PHCCs and PCPs. Furthermore, supposing resident and junior physicians no longer encounter uncomplicated sore throat cases in the PHCCs, how will they learn and expand their experience to improve their assessment and examination skills?

Guidelines and primary care physicians' perception of acute sore throat management

Paper III provides insights into sore throat management in the primary care context by investigating three main topics: (I) describing and comparing national

sore throat guidelines in five countries, (2) surveying physician's perceptions and attitudes towards best management of sore throat cases, and (3) comparing physicians' perceptions and attitudes with their national guideline.

International consensus on managing uncomplicated acute sore throat in low-risk patients

As demonstrated by the variability in national guidelines and the diverse perceptions of primary care physicians documented in **Paper III**, an international unified approach to best practice is lacking. These differences complicate clinical decision-making and potentially impact patient care quality and outcomes.

The most pronounced differences lie in the guidelines' recommendations on using throat swabs and identifying etiological agents for which antibiotic therapy may be considered necessary. Is the lack of an international consensus on these critical points warranted by geographical differences in the prevalence or virulence of pathogens or genetic differences in the populations? Or is it simply a reflection of varying traditions and attitudes that are formalized and maintained through national recommendations and guidelines?

These findings signal a need for an international guideline that would offer a standardized approach to managing uncomplicated acute sore throat cases in patients at low risk for rheumatic fever. This guideline should critically evaluate and integrate evidence on the efficacy of throat swabs in diagnosing relevant etiological agents and summarize clear criteria for when antibiotic therapy may be appropriate.[83,90]

An international consensus guideline recommended across many high-income countries would be a monumental step forward in achieving these goals.[93]

Guidelines and clinical practice

While **Paper III** outlines the variability of national guidelines for sore throat management across five countries, a factor that deserves deeper exploration is the actual use and implementation of these guidelines in clinical practice. Birgand et al. compared 15 international infection prevention and control (IPC) guidelines and found that barriers to successful implementation are often multiple and interconnected.[96] Such barriers may include the guidelines themselves,

the implementation process, and social, cultural, and local organizational factors. Francke et al.'s investigation into guideline implementation demonstrates that physicians' real-world application and adoption of guidelines can vary significantly and are related to several factors, for example, guideline characteristics (complexity), implementation strategies, work environment, physicians' personal beliefs, and perceived patient expectations.[97]

Adding to this line of thought Kurotschka et al. provide a perspective surveying general practitioners and outpatient pediatricians regarding antimicrobial treatment, investigating another critical dimension affecting guideline implementation: knowledge of guideline recommendations and confidence in antibiotic therapy.[98] The results highlight a paradox where practitioners exhibit high guideline knowledge scores, but antibiotic prescribing statistics show that guideline recommendations are frequently ignored.

The connection between evidence-based guidelines and individual clinical judgment adds another layer to the discussion on guideline implementation, suggesting that achieving agreement between guidelines and practice is not just a matter of spreading knowledge but also involves reconciling these guidelines with personal clinical experience and patient-specific factors.

Camera-based measurements of vital signs

Several technical challenges remain before declaring camera-based vital signs measurements fully developed for clinical use

A systematic review by Vinothini Selvaraju et al. explores the advancements and challenges in measuring vital signs through camera-based methods.[79] The study analyzes articles published between January 2018 and April 2021, emphasizing the technologies' performance, factors affecting them, and their application in addressing various health issues. The review identifies significant research gaps in dealing with large and heterogeneous populations, real-time scenarios, moving subjects, and BP and SpO2 measurement accuracy.

Several studies point to a promising future for camera-based technology for measuring vital signs

A paper by Edem Allado et al. investigated the accuracy and reliability of heart rate measurement using imaging photoplethysmography (rPPG), comparing it to the gold standard electrocardiogram (ECG) across a large patient cohort in a hospital setting.[99] The study found a strong correlation between the rPPG and ECG measurements, establishing the method's accuracy at 96.2%. Factors such as age, gender, and skin phototype were considered, with the study highlighting that the rPPG system's accuracy did not significantly differ across these variables. However, similarly to **Paper IV**, the sample size for darker skin tones (Fitzpatrick skin types 5 and 6) was too small for conclusive results.

Consistent rPPG signal quality across skin types is required for camera-based measurements' clinical relevance

Confirming rPPG signal consistency and measurement accuracy across all hues of skin pigmentation is crucial for the camera-based technology to be implemented in clinical use. The rPPG signal is the key to achieving accurate measurement results since it is the basis for quantifying heart rate, blood pressure, oxygen saturation, and respiratory rate. Research efforts and technological development give reason for optimism, and recent research results seem promising.[100,101]

Direct measurement based on the rPPG signal

Software methods that quantify vital signs directly from physiological signals, such as heart rate or blood oxygen level from rPPG signals, offer a more precise and immediate reflection of the individual's current health status. These methods analyze the raw, unfiltered data provided by the body's physiology, ensuring that the measurements are directly correlated with the individual's actual physiological state at the moment of measurement. The RIA-VS devices investigated in **Paper IV** uses this direct approach, which allows for more accurate monitoring and assessment of vital signs, as external predictors or averaged data do not influence it. Relying on real-time data these methods can quickly detect variations in vital signs, providing immediate feedback crucial for timely intervention in acute medical situations.

Adding layers of information introduces risk for advanced "guesstimation"

In contrast, models that include subject information like age and BMI, especially those that generate synthetic data to fill gaps in collected data, may not reflect actual physiological changes.

Incorporating information such as BMI and age into algorithms for estimating vital signs can lead these models to rely heavily on statistical norms and averages.[102] This approach may result in advanced "guesstimation," where the estimated vital sign readings are influenced more by the demographic group the individual belongs to rather than their specific physiological state. This is because they are partially based on statistical averages and assumptions that may not apply to every individual, particularly when affected by disease or injury, as rapid fluctuations in vital signs can occur. Reliance on synthetic data for missing BMI and age combinations further exacerbates the issue, as the generated data might not accurately represent the diverse physiological conditions in different individuals. Consequently, the model risks becoming inaccurate at the extremes of blood pressure, which is critical for patient safety and effective management.[103]

While models incorporating subject information such as age and BMI can offer valuable insights into general trends in population health, they are unfit for measuring vital signs on individual patients. Software methods that quantify vital signs directly from physiological signals provide a more accurate, responsive, and individualized measurement approach.

Primary care perspectives

The **first and fourth papers** relate to identifying potentially severe infections in primary care. In **Paper I**, the described association between FN and uncomplicated acute sore throat raises the question of whether expanding the indication for antibiotic treatment to include FN could prevent peritonsillitis and Lemierre's syndrome. **Paper IV** shows that a new camera-based method for measuring heart rate, oxygen saturation, respiratory rate, and blood pressure works, but accuracy and random variability need to be improved and validated. A future improved version could simplify vital sign measurements, save time, and improve severity assessments in primary care and other clinical scenarios.

The **second and third papers** are linked to whether management guidelines and antibiotic stewardship programs influence primary care practices. Adding an ambitious six-month ASP (regarding acute sore throat) to ongoing long-term stewardship activities was ineffective, according to the findings in **Paper II**. Therefore, such an ASP is not advisable in areas where substantial antibiotic stewardship activities are already in place. Nonetheless, this intervention may yield more positive results in settings with fewer prior stewardship interventions. **Paper III** showed differences between countries in primary care guidelines for managing acute sore throat, and physicians' perceptions of best management practices aligned with their domestic guidelines. Giving local management traditions an influential impact on the contents of RTI management guidelines may undermine the original intention of promoting an evidence-based method.

Conclusion

The findings from **Paper I** indicate a statistically significant but clinically uncertain association between Fusobacterium necrophorum (FN) and acute sore throat. This association is more pronounced in patients with higher Centor scores but not as strong as the association with Group A Streptococcus (GAS). While these results enhance our understanding of sore throat etiology, the wide confidence intervals call for a careful interpretation of the data.

Whether antibiotic treatment for FN-positive sore throats could diminish symptom duration and severity and potentially prevent serious complications such as peritonsillitis and Lemierre's syndrome remains a hypothesis with insufficient scientific evidence. Expanding the indication for antibiotic treatment must be approached cautiously, weighing the potential benefits against the risks of contributing to antibiotic misuse and resistance. A rigorously designed randomized controlled trial (RCT) would be necessary to explore the safety and efficacy of treating FN-positive sore throat cases with antibiotics and preferably include a thorough risk-benefit analysis to ensure that the potential advantages of antibiotic therapy do not contribute to the growing issue of antibiotic resistance.

Paper II highlights the complexity of modifying physician behavior regarding antibiotic prescribing. Despite implementing an extensive antibiotic stewardship program prescribing practices remained the same. This underlines the difficulty in creating effective antibiotic stewardship programs, the challenges in generating change in clinical practice, and the possibility that other factors beyond guidelines and education influence prescribing habits.

The findings in **Paper III** demonstrate a notable variation in the management of acute sore throat internationally, with physician practices closely mirroring their respective national guidelines. This suggests that local clinical culture and national recommendations significantly influence decision-making in primary care, which may affect the uniformity of care provided to patients with acute sore throat. However, it could also indicate the opposite - that local guidelines mirror established clinical practices.

Paper IV presents a step forward with developing camera-based technology for vital sign measurements. While promising, the technology's current limitations, including a tendency to normalize readings and more significant random

variation compared to reference measurements, highlight the need for further refinement before it can be integrated into routine clinical practice. Once reliability and accuracy are adequate and validated, the technology could enable quicker and more frequent vital sign measurements, promoting quality of care and improving patient outcomes.

To summarize, these four studies stress the importance of considering different bacterial pathogens in sore throat assessments, the resilience of established prescribing patterns in the face of educational interventions, the impact of national guidelines on clinical practice, and the potential of emerging technologies to improve vital sign measurement and severity assessment, pending further development and validation.

Future Perspectives

Paper I revealed that FN is a noteworthy pathogen for patients experiencing an uncomplicated acute sore throat in primary care. Therefore, exploring the prospect of using antibiotic treatment to reduce the intensity and duration of symptoms associated with FN-associated sore throat is relevant. Furthermore, it would be intriguing to investigate whether administering antibiotics to patients who have tested positive for FN and are experiencing an uncomplicated sore throat could prevent the development of Lemierre's syndrome and peritonsillitis.

In light of the findings in **Paper II**, that an ambitious ASP targeting primary care physicians had no impact on antibiotic prescribing or guideline adherence, alternative strategies must be considered. One possible route would be to study different types of nudging techniques that have the potential to impact physicians' behavior. For example, deploying a digital notification function that prompts physicians to confirm their decision and provide a reason for deviating from the recommended antibiotic management could prove effective. By using this approach physicians may be inspired to consider their decision-making process more actively, which could lead to better outcomes.

Directing antimicrobial stewardship programs (ASPs) toward physicians alone may not be optimal for improving guideline adherence, particularly in uncomplicated sore throat cases. An area worth exploring could be the possibility of entrusting the care of healthy patients with an uncomplicated acute sore throat not only to primary care physicians, but also to nurses or pharmacists, who could manage their condition independently. This could lead to more efficient and cost-effective healthcare practices while ensuring that patients receive the appropriate level of care they require.

While the **fourth study** provides valuable insights into the potential of contactless measurement of vital signs, its results and limitations suggest that further research is needed to validate it across a broader range of patient populations, health conditions, and clinical settings. Expanding the scope of future studies to include a wider variety of patients and settings would help assess the technology's generalizability and practical applicability more comprehensively. Furthermore, technological improvements are necessary to meet the rigorous performance and reliability requirements of clinical decision-making.

Acknowledgements

I extend my most profound gratitude to **Pär-Daniel Sundvall**, my principal supervisor. Since you convinced me to embark on this Ph.D. journey, you have generously shared knowledge and experience in science and research. Your help in planning, navigating grant applications, making introductions, and providing support has been crucial. Thank you for the discussions and for being an exceptional mentor on my academic voyage.

I sincerely thank my co-supervisor, **Ronny Gunnarsson**, for stimulating conversations with refreshing perspectives. Your conviction in finding solutions to complex challenges has inspired me to approach research with resilience and optimism. I am grateful for your exceptional support and generous sharing of wisdom from the statistical domain, which has guided me through the complexities of medical research. Thank you, Ronny, for your trust and support.

My sincere appreciation goes to **Gunnar Jacobsson**, my co-supervisor, for adding new perspectives and thought-provoking questions to my research journey. Your ability to challenge preconceptions has cultivated my critical thinking and curiosity. Thank you for your invaluable contributions to my academic growth.

My heartfelt thanks to all my teachers, colleagues, and friends at the **Swedish National Research School in General Practice** led by **Anna Myleus**, **Carl Johan Östgren**, and **Lars Hjalmar Lindholm**. Thank you for the enriching education, stimulating discussions, invaluable inspiration, and networking opportunities.

Gratitude to **Taha Khan** for sharing profound insights into artificial intelligence and research and for the shared vision of transforming research outcomes into impactful medical technology products to enhance healthcare.

I extend my appreciations to my colleagues at **HälsoBrunnen** PHCC for their support and understanding, which were crucial in affording me the time needed. A special thanks to **Björn Almén**, who initially endorsed and encouraged my research ambitions.

Thank you, **Susanna Petrén** for your patient collaboration in conducting our systematic review and meta-analysis, which was demanding yet stimulating.

I thank all my co-authors for their invaluable collaboration and contributions to our shared research projects.

Thank you, **Katarina Hedin**, for generously sharing expertise and experience in our collaboration on Paper I and III.

Thank you, **Sofia Sundvall**, for your dedication as a research nurse, assisting in the meticulous parsing of numbers and double-checking details, ensuring precision in our work.

Thank you, **Bledar Daka** for contagious positivity in providing feedback, inspiration, and encouragement.

Thank you, **Hanna Laukkanen**, for sharing the absurd data collection endeavor in the COVID-19 triage shipping container with me.

Thank you, **Lena Nordeman**, for leading the inspiring and supportive work at VGR R&D primary healthcare in Borås.

Thank you, **Péter Boda**, for the deep conversations that helped me discover the exciting territories where medical technology, human-machine interaction, user experience, and design thinking peacefully coexist.

Thank you, **Mark Rosenfeld**, for meticulously checking the English language and aiding in the enhancement of my scientific writing skills.

Additionally, I would like to express my gratitude to **SweGRIN**, **Strama**, the **Region Västra Götaland Research, Education, Development & Innovation in Primary Health Care**, and **CARe** (the Centre for Antibiotic Resistance Research at the University of Gothenburg).

Thanks for your patience, love and encouragement, dear **family** and **friends**.

Last but not least, I wholeheartedly extend my gratitude to my astonishing wife **Anneli** and remarkable children **Neo** and **Indra** for restricting my bad habit of sneaking research and work into many evenings, weekends, vacations, and destinations – enriching my life with well-needed perspective, laughs, play, and love.

References

1. Larsen L, Wensaas KA, Emberland KE, Rortveit G. Respiratory tract infections in Norwegian primary care 2006–2015: a registry-based study. *Scand J Prim Health Care*. 2022;40(2):173-180. doi:10.1080/02813432.2022.2069711
2. Passioti M, Maggina P, Megremis S, Papadopoulos NG. The Common Cold: Potential for Future Prevention or Cure. *Curr Allergy Asthma Rep*. 2014;14(2):413-. doi:10.1007/s11882-013-0413-5
3. Velden AW van der, Pol AC van de, Bongard E, et al. Point-of-care testing, antibiotic prescribing, and prescribing confidence for respiratory tract infections in primary care: a prospective audit in 18 European countries. *BJGP Open*. 2022;6(2). doi:10.3399/BJGPO.2021.0212
4. The top 10 causes of death. Published online December 9, 2020. Accessed December 16, 2023. https://www.who.int/news-room/fact-sheets/detail/the-top-10-causes-of-death
5. Reinhart K, Daniels R, Kissoon N, Machado FR, Schachter RD, Finfer S. Recognizing Sepsis as a Global Health Priority — A WHO Resolution. *N Engl J Med*. 2017;377(5):414-417. doi:10.1056/NEJMp1707170
6. Moberg A. *Diagnosing Pneumonia in Primary Care.* Linköpin University; 2020.
7. Riordan T. Human Infection with Fusobacterium necrophorum (Necrobacillosis), with a Focus on Lemierre's Syndrome. *Clin Microbiol Rev*. 2007;20(4):622-659. doi:10.1128/CMR.00011-07
8. Wikstén J, Kaltiainen E, Pitkäranta A, Blomgren K. Renewal of peritonsillar abscess: Impact of the bacterial species of the infection and clinical features of the patient—A prospective comparative aetiological study. *Clin Otolaryngol*. 2017;42(6):1358-1362. doi:10.1111/coa.12893
9. Powell EL, Powell J, Samuel JR, Wilson JA. A review of the pathogenesis of adult peritonsillar abscess: time for a re-evaluation. *J Antimicrob Chemother*. 2013;68(9):1941-1950. doi:10.1093/jac/dkt128
10. Centor RM, Atkinson TP, Ratliff AE, et al. The Clinical Presentation of Fusobacterium-Positive and Streptococcal-Positive Pharyngitis in a University Health Clinic. *Ann Intern Med*. 2015;162(4):241-247. doi:10.7326/M14-1305
11. Hedin K, Bieber L, Lindh M, Sundqvist M. The aetiology of pharyngotonsillitis in adolescents and adults – Fusobacterium necrophorum is commonly

found. *Clin Microbiol Infect*. 2015;21(3):263.e1-263.e7. doi:10.1016/j.cmi.2014.08.020

12. Jensen A, Hansen TM, Bank S, Kristensen LH, Prag J. Fusobacterium necrophorum tonsillitis: an important cause of tonsillitis in adolescents and young adults. *Clin Microbiol Infect*. 2015;21(3):266.e1-266.e3. doi:10.1016/j.cmi.2014.09.020

13. Marchello C, Ebell MH. Prevalence of Group C Streptococcus and Fusobacterium Necrophorum in Patients With Sore Throat: A Meta-Analysis. *Ann Fam Med*. 2016;14(6):567-574. doi:10.1370/afm.2005

14. Holm K, Bank S, Nielsen H, Kristensen LH, Prag J, Jensen A. The role of *Fusobacterium necrophorum* in pharyngotonsillitis – A review. *Anaerobe*. 2016;42:89-97. doi:10.1016/j.anaerobe.2016.09.006

15. Klug TE, Rusan M, Fuursted K, Ovesen T, Jorgensen AW. A systematic review of Fusobacterium necrophorum-positive acute tonsillitis: prevalence, methods of detection, patient characteristics, and the usefulness of the Centor score. *Eur J Clin Microbiol Infect Dis*. 2016;35(12):1903-1912. doi:10.1007/s10096-016-2757-y

16. World Health Organization. Global action plan on antimicrobial resistance. Accessed February 7, 2024. https://www.who.int/publications-detail-redirect/9789241509763

17. Bruyndonckx R, et al. Exploring the association between resistance and outpatient antibiotic use expressed as DDDs or packages - Gothenburg University. *J Antimicrob Chemother*. 2015(70):1241-1244.

18. Goossens H. Antibiotic consumption and link to resistance. *Clin Microbiol Infect*. 2009;15(3):12-15. doi:10.1111/j.1469-0691.2009.02725.x

19. Surveillance Atlas of Infectious Diseases. Accessed February 7, 2024. https://atlas.ecdc.europa.eu/public/index.aspx

20. Collignon P, Athukorala P chandra, Senanayake S, Khan F. Antimicrobial Resistance: The Major Contribution of Poor Governance and Corruption to This Growing Problem. *PLOS ONE*. 2015;10(3):e0116746. doi:10.1371/journal.pone.0116746

21. Jacobsson G, Carlsson F. God samhällsförvaltning viktig i kampen mot antibiotikaresistens. *Läkartidningen*. 2015(112).

22. Butler CC, Hood K, Verheij T, et al. Variation in antibiotic prescribing and its impact on recovery in patients with acute cough in primary care: prospective study in 13 countries. *BMJ*. 2009;338:b2242. doi:10.1136/bmj.b2242

23. Blaser MJ, Melby MK, Lock M, Nichter M. Accounting for variation in and overuse of antibiotics among humans. *BioEssays*. 2021;43(2):2000163. doi:10.1002/bies.202000163

24. Dekker ARJ, Verheij TJM, van der Velden AW. Inappropriate antibiotic prescription for respiratory tract indications: most prominent in adult patients. *Fam Pract*. 2015;32(4):401-407. doi:10.1093/fampra/cmv019

25. Skajaa N, Gehrt L, Nieminen H, et al. Trends in Antibiotic Use in Danish, Finnish, Norwegian and Swedish Children. *Clin Epidemiol*. 2022;14:937-947. doi:10.2147/CLEP.S362262

26. Tyrstrup M, Beckman A, Mölstad S, et al. Reduction in antibiotic prescribing for respiratory tract infections in Swedish primary care- a retrospective study of electronic patient records. *BMC Infect Dis*. 2016;16(1):709. doi:10.1186/s12879-016-2018-9

27. Laxminarayan R, Duse A, Wattal C, et al. Antibiotic resistance—the need for global solutions. *Lancet Infect Dis*. 2013;13(12):1057-1098. doi:10.1016/S1473-3099(13)70318-9

28. Dadgostar P. Antimicrobial Resistance: Implications and Costs. *Infect Drug Resist*. 2019;12:3903-3910. doi:10.2147/IDR.S234610

29. Kameron S, Carolynn EP. Bacterial Antibiotic Resistance: on the Cusp of a Post-antibiotic World. *Curr Treat Options Infect 2019 1142–57*. 2019(11):42-57. doi:10.1007/s40506-019-0181-4

30. Gulliford MC, Moore MV, Little P, et al. Safety of reduced antibiotic prescribing for self limiting respiratory tract infections in primary care: cohort study using electronic health records. *BMJ*. 2016;354. Accessed February 6, 2024. https://www.jstor.org/stable/26946154

31. Fine MJ, Auble TE, Yealy DM, et al. A Prediction Rule to Identify Low-Risk Patients with Community-Acquired Pneumonia. *N Engl J Med*. 1997;336(4):243-250. doi:10.1056/NEJM199701233360402

32. Aujesky D, Auble TE, Yealy DM, et al. Prospective comparison of three validated prediction rules for prognosis in community-acquired pneumonia. *Am J Med*. 2005;118(4):384-392. doi:10.1016/j.amjmed.2005.01.006

33. Centor RM., Witherspoon JM, Dalton HP, Brody CE, Link K. The Diagnosis of Strep Throat in Adults in the Emergency Room. *Med Decis Making*. 1981;1(3):239-246. doi:10.1177/0272989X8100100304

34. McIsaac WJ, White D, Tannenbaum D, Low DE. A clinical score to reduce unnecessary antibiotic use in patients with sore throat. *CMAJ Can Med Assoc J*. 1998;158(1):75-83.

35. Little P, Moore M, Hobbs FDR, et al. PRImary care Streptococcal Management (PRISM) study: identifying clinical variables associated with Lancefield group A β-haemolytic streptococci and Lancefield non-Group A streptococcal throat infections from two cohorts of patients presenting with an acute sore throat. *BMJ Open*. 2013;3(10):e003943. doi:10.1136/bmjopen-2013-003943

36. Williams JW, Simel DL, Roberts L, Samsa GP. Clinical Evaluation for Sinusitis. *Ann Intern Med*. 1992;117(9):705-710. doi:10.7326/0003-4819-117-9-705

37. Khwannimit B, Bhurayanontachai R, Vattanavanit V. Comparison of the accuracy of three early warning scores with SOFA score for predicting mortality in adult sepsis and septic shock patients admitted to intensive care unit. *Heart Lung*. 2019;48(3):240-244. doi:10.1016/j.hrtlng.2019.02.005

38. [Treatment recommendations for common infections in outpatient care] Behandlingsrekommendationer för vanliga infektioner i öppenvård 2023. Published online 2019.

39. Hemkens LG, Saccilotto R, Reyes SL, et al. Personalized Prescription Feedback Using Routinely Collected Data to Reduce Antibiotic Use in Primary Care: A Randomized Clinical Trial. *JAMA Intern Med*. 2017;177(2):176-183. doi:10.1001/jamainternmed.2016.8040

40. King LM, Fleming-Dutra KE, Hicks LA. Advances in optimizing the prescription of antibiotics in outpatient settings. *BMJ*. 2018;363. Accessed February 27, 2024. https://www.jstor.org/stable/26964050

41. Gerber JS. Improving Outpatient Antibiotic Prescribing: Another Nudge in the Right Direction. *JAMA*. 2016;315(6):558-559. doi:10.1001/jama.2016.0430

42. Schwartz KL, Ivers N, Langford BJ, et al. Effect of Antibiotic-Prescribing Feedback to High-Volume Primary Care Physicians on Number of Antibiotic Prescriptions: A Randomized Clinical Trial. *JAMA Intern Med*. 2021;181(9):1165-1173. doi:10.1001/jamainternmed.2021.2790

43. Brehaut JC, Colquhoun HL, Eva KW, et al. Practice Feedback Interventions: 15 Suggestions for Optimizing Effectiveness. *Ann Intern Med*. 2016;164(6):435-441. doi:10.7326/M15-2248

44. Mölstad S, Löfmark S, Carlin K, et al. Lessons learnt during 20 years of the Swedish strategic programme against antibiotic resistance. *Bull World Health Organ*. 2017;95(11):764-773. doi:10.2471/BLT.16.184374

45. Gröndal H, Hedin K, Strandberg EL, André M, Brorsson A. Near-patient tests and the clinical gaze in decision-making of Swedish GPs not following current guidelines for sore throat – a qualitative interview study. *BMC Fam Pract*. 2015;16:81. doi:10.1186/s12875-015-0285-y

46. Sundvall PD, Skoglund I, Hess-Wargbaner M, Åhrén C. Rational antibiotic prescribing in primary care: qualitative study of opportunities and obstacles. *BJGP Open*. 4(4):bjgpopen20X101079. doi:10.3399/bjgpopen20X101079

47. Andre M, Gröndal H, Strandberg EL, Brorsson A, Hedin K. Uncertainty in clinical practice – an interview study with Swedish GPs on patients with sore throat. *BMC Fam Pract*. 2016;17:56. doi:10.1186/s12875-016-0452-9

48. Aghlmandi S, Halbeisen FS, Saccilotto R, et al. Effect of Antibiotic Prescription Audit and Feedback on Antibiotic Prescribing in Primary Care: A Randomized Clinical Trial. *JAMA Intern Med*. 2023;183(3):213-220. doi:10.1001/jamainternmed.2022.6529

49. Lampi E, Carlsson F, Sundvall PD, et al. Interventions for prudent antibiotic use in primary healthcare: an econometric analysis. *BMC Health Serv Res*. 2020;20(1):895. doi:10.1186/s12913-020-05732-2

50. Wächtler H, Kaduszkiewicz H, Kuhnert O, et al. Influence of a guideline or an additional rapid strep test on antibiotic prescriptions for sore throat: the cluster randomized controlled trial of HALS (Hals und Antibiotika Leitlinien Strategien). *BMC Prim Care*. 2023;24(1):75. doi:10.1186/s12875-023-01987-w

51. Kellett J, Sebat F. Make vital signs great again – A call for action. *Eur J Intern Med*. 2017;45:13-19. doi:10.1016/j.ejim.2017.09.018

52. Elliott M. The global elements of vital signs' assessment: a guide for clinical practice. *Br J Nurs*. 2021;30(16):956-962. doi:10.12968/bjon.2021.30.16.956

53. Draves J, Tekiner H, Yale E, Mazza J, Yale S. A Comprehensive Assessment of The Eight Vital Signs. *EuroBiotech J*. 2022;6(3):133-146. doi:10.2478/ebtj-2022-0014

54. McCarthy M, Murphy P, Rosenberg R, Orford C. The overlooked vital sign: The importance of measuring sleep in drug development studies. *Drug Discov Today*. 2022;27(3):690-696. doi:10.1016/j.drudis.2021.12.003

55. Mularski RA, White-Chu F, Overbay D, Miller L, Asch SM, Ganzini L. Measuring Pain as the 5th Vital Sign Does Not Improve Quality of Pain Management. *J Gen Intern Med*. 2006;21(6):607-612. doi:10.1111/j.1525-1497.2006.00415.x

56. Rothemich SF, Woolf SH, Johnson RE, et al. Effect on Cessation Counseling of Documenting Smoking Status as a Routine Vital Sign: An ACORN Study. *Ann Fam Med*. 2008;6(1):60-68. doi:10.1370/afm.750

57. Bowel Movement: The Sixth Vital Sign. Accessed February 29, 2024. https://oce-ovid-com.ezproxy.ub.gu.se/article/00004650-201405000-00006/PDF

58. American Academy of Pediatrics, Committee on Adolescence, American College of Obstetricians and Gynecologists, Committee on Adolescent Health Care. Menstruation in Girls and Adolescents: Using the Menstrual Cycle as a Vital Sign. *Pediatrics*. 2006;118(5):2245-2250. doi:10.1542/peds.2006-2481

59. Washmuth NB, Queen T, Simpson W, Clark BH, Elliott SD. Using Erection Hardness as a Vital Sign. *Phys Ther*. 2023;103(1):pzac130. doi:10.1093/ptj/pzac130

60. Blacklock C, Haj-Hassan TA, Thompson MJ. When and how do GPs record vital signs in children with acute infections? A cross-sectional study. *Br J Gen Pract*. 2012;62(603):e679-e686. doi:10.3399/bjgp12X656810

61. Loots FJ, Smulders D, Giesen P, Hopstaken RM, Smits M. Vital signs of the systemic inflammatory response syndrome in adult patients with acute infections presenting in out-of-hours primary care: A cross-sectional study. *Eur J Gen Pract*. 27(1):83-89. doi:10.1080/13814788.2021.1917544

62. Opio MO, Kellett J. How Well Are Pulses Measured? Practice-Based Evidence from an Observational Study of Acutely Ill Medical Patients During Hospital Admission. *Am J Med*. 2017;130(7):863.e13-863.e16. doi:10.1016/j.amjmed.2017.01.033

63. Badawy J, Nguyen OK, Clark C, Halm EA, Makam AN. Is everyone really breathing 20 times a minute? Assessing epidemiology and variation in recorded respiratory rate in hospitalised adults. *BMJ Qual Saf*. 2017;26(10):832-836. doi:10.1136/bmjqs-2017-006671

64. Semler MW, Stover DG, Copland AP, et al. Flash Mob Research: A Single-Day, Multicenter, Resident-Directed Study of Respiratory Rate. *Chest*. 2013;143(6):1740-1744. doi:10.1378/chest.12-1837

65. Hooker EA, O'Brien DJ, Danzl DF, Barefoot JAC, Brown JE. Respiratory rates in emergency department patients. *J Emerg Med*. 1989;7(2):129-132. doi:10.1016/0736-4679(89)90257-6

66. Brabrand M, Hallas P, Folkestad L, Lautrup-Larsen CH, Brodersen JB. Measurement of respiratory rate by multiple raters in a clinical setting is unreliable: A cross-sectional simulation study. *J Crit Care*. 2018;44:404-406. doi:10.1016/j.jcrc.2017.12.020

67. Drummond GB, Fischer D, Arvind DK. Current clinical methods of measurement of respiratory rate give imprecise values. *ERJ Open Res*. 2020;6(3). doi:10.1183/23120541.00023-2020

68. Lim WS, Carty SM, Macfarlane JT, et al. Respiratory rate measurement in adults—how reliable is it? *Respir Med*. 2002;96(1):31-33. doi:10.1053/rmed.2001.1203

69. Ray GM, Nawarskas JJ, Anderson JR. Blood Pressure Monitoring Technique Impacts Hypertension Treatment. *J Gen Intern Med*. 2012;27(6):623-629. doi:10.1007/s11606-011-1937-9

70. Sebo P, Pechère-Bertschi A, Herrmann FR, Haller DM, Bovier P. Blood pressure measurements are unreliable to diagnose hypertension in primary care. *J Hypertens*. 2014;32(3):509-517. doi:10.1097/HJH.0000000000000058

71. Niven DJ, Gaudet JE, Laupland KB, Mrklas KJ, Roberts DJ, Stelfox HT. Accuracy of Peripheral Thermometers for Estimating Temperature. *Ann Intern Med*. 2015;163(10):768-777. doi:10.7326/M15-1150

72. Zeitz K. Nursing observations during the first 24 hours after a surgical procedure: what do we do? *J Clin Nurs*. 2005;14(3):334-343. doi:10.1111/j.1365-2702.2004.01071.x

73. Dall'Ora C, Griffiths P, Hope J, et al. How long do nursing staff take to measure and record patients' vital signs observations in hospital? A time-and-motion study. *Int J Nurs Stud*. 2021;118:103921. doi:10.1016/j.ijnurstu.2021.103921

74. Scott D, Kane H, Rankin A. 'Time to clean': A systematic review and observational study on the time required to clean items of reusable communal patient care equipment. *J Infect Prev*. 2017;18(6):289-294. doi:10.1177/1757177417714046

75. Davis C. Blood pressure cuffs and pulse oximeter sensors: A potential source of cross-contamination. *Australas Emerg Nurs J*. 2009;12(3):104-109. doi:10.1016/j.aenj.2009.03.004

76. Garrido-Molina JM, Márquez-Hernández VV, García-Viola A, Rodríguez-Maresca MÁ, del Águila JG, Gutiérrez-Puertas L. What is essential remains invisible to the eyes? Blood pressure cuffs colonized by bacterial diversity. *Int Microbiol*. 2023;26(2):389-396. doi:10.1007/s10123-022-00308-y

77. Yoon G, Lee JY, Jeon KJ, et al. Multiple diagnosis based on photoplethysmography: hematocrit, SpO2, pulse, and respiration. In: *Optics in Health Care and Biomedical Optics: Diagnostics and Treatment*. Vol 4916. SPIE; 2002:185-188. doi:10.1117/12.482947

78. Sinhal R, Singh K, Raghuwanshi MM. An Overview of Remote Photoplethysmography Methods for Vital Sign Monitoring. In: Gupta M, Konar D, Bhattacharyya S, Biswas S, eds. *Computer Vision and Machine Intelligence in Medical Image Analysis*. Vol 992. Advances in Intelligent Systems and Computing. Springer Singapore; 2020:21-31. doi:10.1007/978-981-13-8798-2_3

79. Selvaraju V, Spicher N, Wang J, et al. Continuous Monitoring of Vital Signs Using Cameras: A Systematic Review. *Sensors*. 2022;22(11):4097. doi:10.3390/s22114097

80. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. *PLoS Med*. 2009;6(7):e1000097. doi:10.1371/journal.pmed.1000097

81. SIGN Methodology checklist 4: case-control studies. Accessed May 18, 2018. https://www.sign.ac.uk/what-we-do/methodology/checklists/

82. The likelihood that Fusobacterium necrophorum is linked to uncomplicated pharyngotonisillitis in primary care patients - a systematic with meta analysis. Published online September 5, 2018. https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42018106800

83. Gunnarsson R, Orda U, Elliott B, Heal C, Del Mar C. What is the optimal strategy for managing primary care patients with an uncomplicated acute sore

throat? Comparing the consequences of nine different strategies using a compilation of previous studies. *BMJ Open*. 2022;12(4):e059069. doi:10.1136/bmjopen-2021-059069

84. Kjærulff AMG, Thomsen MK, Ovesen T, Klug TE. Clinical and biochemical characteristics of patients with Fusobacterium necrophorum-positive acute tonsillitis. *Eur Arch Otorhinolaryngol*. 2015;272(6):1457-1463. doi:10.1007/s00405-015-3535-7

85. Hayakawa K, Nagashima M, Kanehisa E, et al. Real-time PCR investigation of the prevalence of Fusobacterium necrophorum in patients with pharyngitis in Japan. *J Infect Chemother*. 2018;24(12):969-974. doi:10.1016/j.jiac.2018.09.008

86. Jensen A, Hagelskjær Kristensen L, Prag J. Detection of Fusobacterium necrophorum subsp. funduliforme in tonsillitis in young adults by real-time PCR. *Clin Microbiol Infect*. 2007;13(7):695-701. doi:10.1111/j.1469-0691.2007.01719.x

87. Agerhäll M, Henrikson M, Johansson Söderberg J, et al. High prevalence of pharyngeal bacterial pathogens among healthy adolescents and young adults. *APMIS*. 2021;129(12):711-716. doi:10.1111/apm.13179

88. Nygren D, Brorson E, Musonda M, Wasserstrom L, Johansson Å, Holm K. Geographical differences in tonsillar carriage rates of *Fusobacterium necrophorum* – A cross-sectional study in Sweden and Zambia. *Anaerobe*. 2021;69:102360. doi:10.1016/j.anaerobe.2021.102360

89. Taube A. The predictive value of microbiologic diagnostic tests if asymptomatic carriers are present. Ronny K. Gunnarsson and Jan Lanke, Statistics in Medicine 2002; 21:1773–1785. *Stat Med*. 2003;22(7):1201-1202. doi:10.1002/sim.1476

90. Centor RM, Atkinson TP, Xiao L. *Fusobacterium necrophorum* oral infections – A need for guidance. *Anaerobe*. 2022;75:102532. doi:10.1016/j.anaerobe.2022.102532

91. Meeker D, Knight TK, Friedberg MW, et al. Nudging Guideline-Concordant Antibiotic Prescribing: A Randomized Clinical Trial. *JAMA Intern Med*. 2014;174(3):425-431. doi:10.1001/jamainternmed.2013.14191

92. Meeker D, Linder JA, Fox CR, et al. Effect of Behavioral Interventions on Inappropriate Antibiotic Prescribing Among Primary Care Practices: A Randomized Clinical Trial. *JAMA*. 2016;315(6):562-570. doi:10.1001/jama.2016.0275

93. Gunnarsson RK, Ebell M, Centor R, et al. Best management of patients with an acute sore throat – a critical analysis of current evidence and a consensus of experts from different countries and traditions. *Infect Dis*. 2023;55(6):384-395. doi:10.1080/23744235.2023.2191714

94. Mantzourani E, Wasag D, Cannings-John R, Ahmed H, Evans A. Characteristics of the sore throat test and treat service in community pharmacies

(STREP) in Wales: cross-sectional analysis of 11 304 consultations using anonymized electronic pharmacy records. *J Antimicrob Chemother*. 2023;78(1):84-92. doi:10.1093/jac/dkac358

95. Thornley T, Marshall G, Howard P, Wilson APR. A feasibility service evaluation of screening and treatment of group A streptococcal pharyngitis in community pharmacies. *J Antimicrob Chemother*. 2016;71(11):3293-3299. doi:10.1093/jac/dkw264

96. Birgand G, Johansson A, Szilagyi E, Lucet JC. Overcoming the obstacles of implementing infection prevention and control guidelines. *Clin Microbiol Infect*. 2015;21(12):1067-1071. doi:10.1016/j.cmi.2015.09.005

97. Francke AL, Smit MC, de Veer AJ, Mistiaen P. Factors influencing the implementation of clinical guidelines for health care professionals: A systematic meta-review. *BMC Med Inform Decis Mak*. 2008;8:38. doi:10.1186/1472-6947-8-38

98. Kurotschka PK, Tiedemann E, Wolf D, et al. Management of Common Infections in German Primary Care: A Cross-Sectional Survey of Knowledge and Confidence among General Practitioners and Outpatient Pediatricians. *Antibiotics*. 2021;10(9):1131. doi:10.3390/antibiotics10091131

99. Allado E, Poussel M, Moussu A, et al. Accurate and Reliable Assessment of Heart Rate in Real-Life Clinical Settings Using an Imaging Photoplethysmography. *J Clin Med*. 2022;11(20):6101. doi:10.3390/jcm11206101

100. Zhang X, Hu M, Zhang Y, Zhai G, Zhang XP. Recent Progress of Optical Imaging Approaches for Noncontact Physiological Signal Measurement: A Review. *Adv Intell Syst*. 2023;5(9):2200345. doi:10.1002/aisy.202200345

101. Ernst H, Scherpf M, Malberg H, Schmidt M. Optimal color channel combination across skin tones for remote heart rate measurement in camera-based photoplethysmography. *Biomed Signal Process Control*. 2021;68:102644. doi:10.1016/j.bspc.2021.102644

102. Wu BF, Chiu LW, Wu YC, Lai CC, Cheng HM, Chu PH. Contactless Blood Pressure Measurement Via Remote Photoplethysmography With Synthetic Data Generation Using Generative Adversarial Networks. *IEEE J Biomed Health Inform*. 2024;28(2):621-632. doi:10.1109/JBHI.2023.3265857

103. Tarassenko L. Is the 'Lifelight' app adequately validated for blood pressure measurement? The Centre for Evidence-Based Medicine. Accessed March 16, 2024. https://www.cebm.net/covid-19/question-is-the-lifelight-app-adequately-validated-for-blood-pressure-measurement-answer-no/