EVALUATION OF THE ORGANIZATIONAL CHALLENGES IMPLEMENTING C-REACTIVE PROTEIN POINT-OF-CARE TESTING

IN PRIMARY CARE FOR ADULTS WITH ACUTE COUGH IN BELGIUM

Project submitted in response to public tender by FOD project 'Evaluation of the organizational challenges of the implementation of POCT-CRP outside of hospital in adults with cough' (NAPAMR 2020-2024-POCT), supervised by Prof. dr. Jan Verbakel (KU Leuven, Department of Public Health and Primary Care).

CONTENTS

EXECUTIVE SUMMARY

Antimicrobial resistance (AMR) has been recognized by the World Health Organization as a major global health threat. In response, Belgium initiated a national action plan, "One World One Health," aimed at addressing AMR. One of the key strategies explored is the use of C-reactive protein (CRP) point-of-care testing (POCT) in general practice for managing acute cough, a condition often associated with inappropriate antibiotic prescriptions.

This report outlines the evaluation of four work packages (WPs) related to the implementation and assessment of CRP POCT devices:

1. Analytical Performance and linkage of devices (WP1): The study assessed the performance and user-friendliness of four POCT-CRP devices, focusing on analytical accuracy, precision, and traceability. Three out of four devices met the required criteria. The findings emphasized the need for strong quality assurance systems led by clinical laboratories to ensure reliable results.
2. End-user Training and Quality Assurance (WP2): Training of general practitioners and their staff was crucial for ensuring proper device usage. The report highlights the importance of ongoing quality assurance to maintain device accuracy and avoid negative public health consequences from incorrect usage.
3. Implementation Process and Stakeholder Engagement (WP3): A pilot implementation was conducted, and stakeholder feedback was gathered through interviews and focus group discussions. The findings revealed that the CRP tests were seen as valuable tools in clinical decision-making, particularly in reducing unnecessary antibiotic prescriptions. The study highlighted the importance of ease of use and proper integration into the clinical workflow for successful implementation.
4. Budget Impact Analysis (WP4): A budget impact analysis was conducted to assess the cost-effectiveness of implementing CRP POCT in Belgian general practice. The analysis projected an incremental cost of €14.8 million over five years compared to usual care, but it also highlighted the long-term benefits of reduced antibiotic use and improved AMR management.

The study concludes that while the implementation of CRP POCT devices in Belgian general practice is promising, careful consideration of organizational, financial, and training aspects is essential for large-scale adoption. The findings offer policymakers valuable insights into balancing the costs of implementation with the public health benefits of reducing AMR.

Abbreviations

AMR:	Antimicrobial resistance
BIA:	Budget impact analysis
CRP:	C-reactive protein
ECDC:	European center for disease prevention and control
HER:	Electronic health record
ETS:	Exponential smoothing
GP:	General practitioner
POCT:	Point-of-care testing
RTI:	Respiratory tract infection
APS:	Analytical Performance Specifications
ASZ:	Algemeen Stedelijk Ziekenhuis
CV:	Coefficient of variation
ERM:	European Reference Materials
IFCC:	International Federation of Clinical Chemistry
IRMM:	Joint Research Centre Institute for Reference Materials and Measurements
iQC:	Internal quality control
ISO:	International Organization for Standardization
LRTI:	Lower respiratory tract infections
MAU:	Maximum fit for purpose allowable MU
MU:	Measurement uncertainty
U_{ref}:	Uncertainty of reference materials
U_{cal}:	Uncertainty of calibrators
U_{rw}:	Random variability of measuring systems
NAPAMR:	National action plan on antimicrobial resistance
OLV	Onze-Lieve-Vrouw
r^2:	Coefficient of determination
rho or ρ:	Spearman's rank correlation
SKUP:	Scandinavian evaluation of laboratory equipment for point of care testing

BACKGROUND & OBJECTIVES

One of the main causes of antimicrobial resistance (AMR) is the use of antibiotics in human medicine. Antibiotic resistance is an important and growing problem and has a lasting impact on our medical care in the coming decades. In the ambulatory care, most antibiotics are prescribed by general practitioners (GP). Although acute respiratory tract infections are generally self-limiting, Belgian GPs often write an antibiotic for it. Despite great efforts to prevent inappropriate antibiotic prescribing in primary care in Belgium, the objectives, as described in the National AMR Action Plan, are not yet achieved.

Over the past decade, several interventions, such as point-of-care testing (POCT) were developed, launched and assessed, both in Belgium and in other (European) countries. But many of these interventions, including POCT, have not been widely implemented or evaluated in the Belgian context. Clinical studies in primary care (general practice) have demonstrated the use of CRP point-of-care testing (POCT) to direct antibiotic prescription resulting in a significant reduction of prescribing antibiotics without harming the patient. This intervention on adults with acute cough has also proven cost-effective, as well as effective in the longer term. In several European countries, POCT-CRP testing is part of the guidelines for good medical practice for acute cough/respiratory infections in general practice, for example in the Netherlands. Before POCT-CRP can be introduced nationally in Belgium, a number of organizational aspects need to be addressed.

1.1. Work package 1: Analytical performance and linkage between point-of-care setting and clinical lab environment

First step is to confirm analytical performance and precision of the POCT CRP devices, which will be done by the clinical laboratory and described in detail in this work package. Furthermore, an efficient supply chain is a fundamental requirement to ensure system reliability and reduce costs. Systems that can be applied to ensure the storage of test kits at the required temperature, guidelines that can control the correct disposal of test materials in a non-hazardous way and the impact on patient flow within the medical practice will be investigated. State of the art POCT hardware is equipped for patient and user identification, and for electronic data transfer of patient results to POCT middleware (already available in most hospital laboratories), to the laboratory information system (LIS) and to the electronic medical record (EMR). In this way, POCT results are made fully traceable in the LIS, available in the EMD and consultable via existing e-health platforms. The laboratory has expertise in establishing quality control of results and is familiar with the actions to be taken in case of discrepancies.

To this end, we will install the clinically validated (i.e. clinical performance as part of standard of care done by the clinical laboratory) POCT-CRP devices in GP practices and provide the necessary IT support, whereby linkage between the device and the lab information system is possible via middleware (Roche Cobas Infinity POC), after which the results can be medically validated (i.e. final semi-automated check of results by clinical biologist) by the clinical laboratory and re-structured in the GP's EMR through the calibrated channels.

1.2. Work package 2: End-user training and quality assurance

There is evidence that uncontrolled use of POCT can have far-reaching negative consequences for both individuals and public health. One aspect will be to consider systems that can be put in place to ensure that all personnel performing POCT have received

adequate training. This training will be provided by the manufacturer and clinical laboratory at a plenary meeting at the beginning of the implementation stage of this project. As user training is organised and monitored, the likelihood of pre-analytical errors is reduced and results will be more reliable. The laboratory and/or manufacturer will organise and certify training (state-of-the-art POCT equipment will only work if the user is identified and certified).

Imprecision as part of routine quality assurance will be evaluated in a subset of 15 practices (affiliated with the central lab of OLVZ Aalst) using a patient lithium heparin plasma pool (+/- 20 mg/L) in addition to manufacturer specific internal quality control (iQC) material with low and high CRP concentration.

1.3. Work package 3: Evaluation of the implementation process and stakeholder engagement

Meeting stakeholder expectations can ensure that one achieves the intended results. Identifying the different stakeholders and their expectations is crucial and provides a strategy to involve them. For example, appointing an implementation champion can help accelerate the process of adaptation of POCT-CRP, and national education campaigns can create the required awareness among patients to further embrace this new technology and support when (not) to use the test.
We will organise a survey of relevant stakeholders involved in this pilot project and the implementation of the POCT-CRP device using a survey and focus group discussions. From the experiences of the relevant stakeholders, we want to describe: how the implementation went in terms of organisation, evaluation of feasibility, feasibility, barriers and facilitators of implementation.
This study will also use focus group discussions to gauge experiences with the POCT-CRP devices in general practice. We will perform the focus group in person unless unforeseen circumstances prevent this. If necessary, the content and design of the focus group can be tested in advance with another physician who has experience in research.

1.4. Work package 4: Budget impact analysis to evaluate the feasibility and affordability of integrating CRP POCT into Belgian general practice for patients with acute cough

Beyond clinical considerations, economic evidence is essential when evaluating the implementation of a new healthcare intervention. A budget impact analysis (BIA) is a valuable tool for this purpose, as it examines the financial implications of introducing the new intervention compared to the existing situation. This analysis helps policymakers make informed decisions about the affordability and potential adoption of the intervention.

The objective of this study is to conduct a BIA to evaluate the feasibility and affordability of integrating CRP POCT into Belgian general practice for patients with acute cough. This evaluation involves establishing a future scenario based on literature and expert opinions as a reference, and comparing it to the current standard of care, under the assumption that CRP testing is not currently included in the Belgian guidelines for treating adults with acute cough.

WP1. ANALYTICAL PERFORMANCE AND LINKAGE OF POINT-OF-CARE DEVICES

GOAL:

(a) We aimed to confirm the analytical performance and user-friendliness of four POCT-CRP assays

(b) We then aimed to install the validated CRP POCT devices in 4 to 6 general practices and provide the necessary IT support, whereby a link between the device and the lab information system is possible via middleware, after which the results can be validated by the clinical laboratory and repeated via the usual pathways. structured in the EHR of the GP.

RESULTS:

(a) The analytical performance and user-friendliness of POCT-CRP devices varies among manufacturers, with 3 of the 4 POCT-CRP assays meeting our prespecified criteria regarding analytical performance, precision and user-friendliness.

(b) After obtaining formal **ethical approval** (dd 28th August 2023) from the UZ/KU Leuven Ethical Review Board, we have installed the **3** validated CRP POCT devices in **27** general practices and provided the necessary IT support, whereby a link between the device and the lab information system is possible via **middleware**, after which the results can be **validated** by the clinical laboratory and repeated via the usual pathways. structured in the **EHR** of the GP.

WP1a. Analytical performance and user-friendliness of four POCT-CRP assays

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1. SUMMARY

Introduction

Proper implementation of Point-of-Care testing (POCT) for C-reactive protein (CRP) in primary care can decrease the inappropriate use of antibiotics, thereby tackling the problem of growing antimicrobial resistance.

Objective

The analytical performance and user-friendliness of four POCT-CRP assays were evaluated: QuikRead go easy, LumiraDx, cobas b 101 and Afinion 2.

Materials and methods

Imprecision was evaluated using plasma pools in addition to manufacturer-specific control material. Trueness was assessed by verification of traceability to ERM-DA474/IFCC in parallel to method comparison towards the central laboratory CRP method (cobas c 503) using i) retrospectively selected plasma samples (n=100) and ii) prospectively collected capillary whole blood samples (n=50). User-friendliness was examined using a questionnaire.

Results

Between-day imprecision on plasma pools varied from 4.5% (LumiraDx) to 11.5% (QuikRead). Traceability verification revealed no significant difference between cobas c 503 CRP results and the ERM-DA474/IFCC certified value. cobas b 101 and Afinion achieved the best agreement with the central laboratory method. LumiraDx and QuikRead revealed a negative mean difference, with LumiraDx violating the criterion of >95% of POCT-CRP-results within ±20% of the comparison method. Regarding user-friendliness, Afinion obtained the highest Likert-scores.

Conclusion

The analytical performance and user-friendliness of POCT-CRP devices varies among manufacturers, emphasizing the need for quality assurance supervised by a central laboratory.

2. BACKGROUND

Point-of-Care testing (POCT) can be defined as a clinical diagnostic test performed in a health care setting outside a clinical laboratory, bedside or in proximity of the patient usually performed by non-laboratory-trained personnel [1-3]. POCT is widely used in hospital settings and routinely in primary care settings in several Scandinavian countries, the Netherlands and Switzerland. Interest in expanding to more general practice (GP) settings is increasing for C-reactive protein (CRP) testing to guide management of lower respiratory tract infections (LRTI), particularly. The overuse of antibiotics for LRTI is a widespread problem leading to antimicrobial resistance. POCT-CRP appears to be one of the top strategies to reduce inappropriate antibiotic prescribing and to combat increasing antimicrobial resistance in a cost-effective manner in adults [4-6]. The negative predictive value of CRP in combination with clinical signs and symptoms for serious infections can support physicians in clinical work-up, prescribing of antibiotics and follow-up of patients. Various European guidelines recommend POCT-CRP testing to guide treatment in LRTI to improve antimicrobial stewardship in primary care [7, 8]. In Belgium, the use of antibiotics in outpatient care is mainly prescribed by GPs and is higher than the European average. Unfortunately, there is currently no legal framework in place for the use of POCT outside the hospital in Belgium [6]. Therefore, the 'National Action Plan on Antimicrobial Resistance' (NAPAMR) study 2020-2024 "*Evaluation of the organizational challenges of out-of-hospital implementation of POCT-CRP in adults with cough"* was funded to evaluate the application and the economic feasibility of POCT-CRP outside hospitals and the creation of a legal framework with reimbursement for decentralized POCT-CRP in primary care. Evidently, POC-devices must generate accurate and robust results compared to laboratory testing and must comply to analytical performance specifications (APS) stated by (inter)national expert organizations [6, 9-13]. Therefore, patients' benefit and POCT reimbursement could only be provided and maintained when POCT is performed according to well-defined evidence-based guidelines and is integrated into a quality assurance program supervised by a certified, clinical laboratory [3, 6, 11, 14].

In this study, we aim to evaluate the analytical performance and user-friendliness of four different POCT-CRP assays based on POCT-specific international guidelines [11, 14, 15] and general and CRP-specific APS [9, 10, 16-18].

3. METHODS

The analytical performance study was executed by the POCT-team of the OLV Hospital Aalst, a Belgian secondary care hospital with 959 beds.

3.1. CRP measuring systems

Four quantitative POCT-CRP devices used in the FOD project '*Evaluation of the organizational challenges of out-of-hospital implementation of POCT-CRP in adults with cough'* were evaluated. An overview of the assay characteristics of the different POCT-CRP methods and the specific reagent lot numbers used (one for each POCT-CRP device) are summarized in Table 1. Every POCT-CRP method included in the study protocol, claims traceability to the currently available international CRP-standard, ERM-DA474/IFCC (Table 1) [19, 20].

The Tina-Quant CRP IV performed on cobas c 503 analyzer, routinely performed at the central laboratory of OLV Hospital Aalst and ISO (International Organization for Standardization) 15189 certified (Belgian accreditation system certificate 350-MED), was chosen as the comparison method.

3.2. Validation of the traceability of the comparison method

Measurement uncertainty (MU) of cobas c 503 was calculated towards ERM-DA474/IFCC using ISO 20914:2019 as a practical reference guide [21].
In addition, the traceability of the cobas c 503 CRP-method was verified by the analysis of the ERM-DA474/IFCC [19] in three runs during three consecutive days. The mean CRP result of the ERM, obtained on cobas c 503, is regarded as unbiased, if the combined expanded uncertainty of the certified value includes the difference between the certified value and the measurement result [19].

3.3. Analytical performance evaluation of POCT-CRP devices

3.3.1. TRACEABILITY POCT-CRP TOWARDS ERM-DA474/IFCC

Based on the mean cobas c 503 results of a 5-point dilution series of the ERM with 0.7% phosphate buffered saline, a regression line was calculated plotting the ERM theoretical results on the Y-axis and the cobas c 503 results on the X-axis. As the ERM-DA474/IFCC is not commutable to the POCT-CRP methods, verification of the traceability of the POCT-CRP devices was applied based on the results obtained by the method comparison study (see section 2.3.2). For CRP study results up to 41.2 mg/L (=certified value of the ERM-DA474/IFCC) [19], the c 503-ERM regression equation was used to recalculate the c 503 results of the study samples to more objective 'ERM' results.

3.3.2. METHOD COMPARISONS

Retrospectively, 100 left-over samples from lithium heparin plasma routinely sent to the central laboratory of OLV Hospital Aalst for CRP-analysis (Tina-Quant C-Reactive protein IV on cobas c 503 analyzer (Roche Diagnostics, Mannheim, Germany)), were purposively selected, to obtain CRP concentrations spread over the measuring range (e.g. 1 mg/L to 350 mg/L) of the different POCT-CRP devices [15]. Hemolytic, icteric or lipemic samples were excluded. All lithium heparin plasma samples were stored at 2-8°C for less than 5 days after sampling. After selection, all plasma samples were stored at -20°C and thawed prior to POCT-CRP analysis. CRP analyses were spread over at least 5 days for each POC device. Analytical performance was assured by daily iQC measurement.
Additionally, at least 50 capillary blood samples were prospectively collected from patients at the Pneumology and Gastroenterology ward of OLV Hospital Aalst and were immediately analyzed with the POCT-CRP device. All physicians and nurses from the Pneumology and Gastroenterology ward involved, were informed about the study design. The POCT-CRP samples were collected by the POCT-team and within a time frame of 30 minutes, a lithium heparin plasma sample was drawn from the same patient and sent to the laboratory for routine CRP analysis on the cobas c 503 (turnaround time less than 1 hour). All patients in whom capillary samples were collected, gave written informed consent before sample collection during the study period.

3.3.3.IMPRECISION

Imprecision was determined using the manufacturer specific internal quality control material (iQC) with low and high CRP concentration, a patient lithium heparin plasma pool with a low concentration of +/- 20 mg/L and a patient lithium heparin plasma pool with a high concentration of +/- 100 mg/L. All iQC samples and patient pools were measured during 10 consecutive days with each analyzer [17]. Every day a fresh frozen aliquot was used for the patient pools.

3.3.4.STATISTICAL ANALYSIS

Statistical analyses were performed with Excel-Analyse-It (Analysis Software, Ltd, UK) and MedCalc Statistical Software version 19.3 (MedCalc Software Ltd, Ostend, Belgium). Continuous variables are reported as mean value with a standard deviation (SD).

A Passing Bablok regression and Spearman's rank correlation was used to evaluate agreement between methods. Mean difference was examined using relative Bland–Altman plots for all POCT-CRP devices [13]. The 95% limits of agreement of the mean difference represents the 95% confidence interval [-1.96*SD;+1.96*SD].

3.3.5.ANALYTICAL PERFORMANCE SPECIFICATIONS (APS)

Based on the intended use of the POCT-CRP measuring systems in the FOD project '*Evaluation of the organizational challenges of out-of-hospital implementation of POCT-CRP in adults with cough*', the APS were set in concordance to the APS used by SKUP, an international and independent POCT expert organization [9, 13]. An acceptable accuracy is obtained when >95% of the CRP results measured on the POCT devices are within +/- 20% of the comparison method [9]. The criterion of an acceptable correlation between the POCT devices and the comparison method is defined as i) a slope and intercept not significantly differing from 1.0 and 0.0, respectively and ii) a Spearman's rank correlation rho ≥ 0.975. Regarding imprecision, a coefficient of variation (CV%) less than or equal to 10% is defined as acceptable [9].

3.4. User-friendliness

To include all stakeholders' objectives in the implementation of POCT, a user-friendliness survey was organized for on the one hand the POCT-experts of OLV Hospital Aalst/Asse (n=5/3) and Algemeen Stedelijk Ziekenhuis Aalst (ASZ) (n=2) and on the other hand non-experienced nursing personnel from the OLV Pneumology and Gastroenterology ward (n=6). After a professional instruction of the POCT-CRP device by the manufacturer or a qualified POCT-team member, a 7-point Likert scale (0-6) questionnaire was filled out, comprising questions related to the pre-analytical, analytical, and post-analytical phase. Twenty-three questions were bundled in the following topics: packaging and manipulation of pre-analytical device, blood collection, timespan between collection and analysis, duration of test and error codes. Based upon these categories, radar charts were created. For the POCT-team, 13 additional questions were asked concerning reagents conservation, risk of results misinterpretation and failure detection.

3.5. Ethical approval

The research related to human use complied with all the relevant national regulations, institutional policies and in accordance the Helsinki Declaration. The study has been

reviewed and approved by the local ethical committee of OLV hospital Aalst (Belgian registration number B1262023000002).

4. RESULTS

4.1. Validation of the traceability of the comparison method

Primordially, to be considered as a valuable comparison method, MU of cobas c 503 towards ERM-DA474/IFCC was calculated [21]. The estimated combined standard MU for cobas c 503 method was 5.18%, which is lower than the 'maximum fit for purpose allowable MU' (MAU) at minimum quality level of 5.64% [16, 18] (Supplemental data 1). In addition, the traceability of the cobas c 503 CRP-method was verified by the analysis of the ERM-DA474/IFCC (Supplemental data 2) [19]. The absolute difference (Dm) between this measured mean value (41.3 mg/L) and the certified value, i.e. 41.2 mg/L, was 0.1 mg/L, which was lower than the certified combined expanded MU of the material of 2.5 mg/L (Supplemental data 2). Therefore, at a confidence level of 95%, our results revealed no significant difference between the CRP result obtained with cobas c 503 and the certified ERM value [19].
Furthermore, based on the mean cobas c 503 results of a 5-point dilution series of the ERM with 0.7% phosphate buffered saline, a regression line was calculated plotting the ERM theoretical results on the Y-axis and the cobas c 503 results on the X-axis, revealing a very good coefficient of determination (r^2= 0.9993) (Supplemental data 2).

4.2. Analytical performance evaluation of POCT-CRP devices

4.2.1. TRACEABILITY POCT-CRP TOWARDS ERM-DA474/IFCC

For CRP study results up to 41.2 mg/L (=certified value of the ERM-DA474/IFCC), the c 503-ERM regression equation (y = 0.986x – 0.437) (Supplemental data 2) was used to recalculate the c 503 results of the study samples to more objective 'ERM' results. Results of the four POCT-CRP devices towards ERM-DA474/IFCC are presented in relative Bland-Altman and Passing Bablok plots in in Supplemental data 3 and Supplemental data 4. Overall, similar results were obtained as when compared directly with the cobas c 503 results (see section 3.2.2), with LumiraDx providing a marked and inaccurate underestimation of CRP values.

4.2.2. METHOD COMPARISONS

The results of the four POCT-CRP devices towards the cobas c 503 comparison method are presented in relative Bland-Altman and Passing Bablok plots in Figure 1 and Table 2. Considering the whole measuring range, an acceptable agreement (rho ≥ 0.975) (Figure 1 A-D) and mean difference (Figure 1 E-H) towards the comparison method was obtained for all POCT-CRP devices. The highest relative mean difference was shown for LumiraDx, i.e. -13.66% [-36.68-9.37] (Table 2). The relative Bland-Altman plot elucidates (Figure 1 H) two groups of results, i.e. below 60 mg/L and higher than 6 mg/L, revealing a significantly higher mean difference for results below 60 mg/L. Consequently, LumiraDx obtained an unacceptable percentage of POCT-CRP results within the +/- 20% accuracy criterion, i.e. 66.3%, versus 97.8%, 100.0% and 97.5% for respectively cobas b 101, Afinion 2 and QuikRead go (Table 2).
Regarding the method comparison on capillary blood samples, cobas b 101, Afinion 2 and QuikRead go showed an acceptable agreement with the comparison method (rho ≥

0.975) (Figure 2 A-C), however LumiraDx had a lower Spearman's rho compared to the other devices (ρ=0.971) (Figure 2D; Table 3). cobas b 101 and Afinion 2 obtained the best correlation with the reference method as the slope and intercept are the closest to 1.0 and 0.0, respectively (Table 3). The slope of QuikRead go was 0.854, indicating a systemic underestimation of capillary blood CRP-levels. For all devices an acceptable relative mean difference towards the comparison method was obtained. QuikRead go had the highest relative mean difference, being -12.01% [-31.68-7.65] (Table 3). The percentage of POCT-CRP results within the +/- 20% accuracy criterion was 97.2%, 97.2%, 83.7% and 86.0% for respectively cobas b 101, Afinion 2, QuikRead go and LumiraDx (Table 3).

4.2.3.IMPRECISION

With CV% from 1.7% to 8.9% for the manufacturer's specific iQC samples, imprecision met the criterion of ≤10% for each POCT-CRP device (Supplemental data 5 and 6). In the iQC patient pools, CV% varied among the analyzers from 4.9% to 11.5%. Revealing CV% of 11.5% and 10.2%, QuikRead go exceeded the CV% criterion of 10% for both levels (not significantly, Chi^2-test p=0.8 and p=0.9, respectively; Table 4). Consecutively, the imprecision experiment was repeated, using a calibrated pipet for sample application instead of the QuikRead go specific sampling device; CV% significantly dropped to 5.9% and 4.9% for the low and high iQC level respectively.

4.3. User-friendliness

Overall, all POCT-CRP devices were scored user-friendly. QuikRead go easy CRP, Afinion 2 and cobas b 101 had comparable results, with mainly the analytical device, the duration of the test and the time span between the sampling and analysis being assessed as satisfactory (Figure 3). Scoring differences were mainly related to the packaging of reagents and the manipulation of the pre-analytical device, for which Afinion 2 clearly scored best (median Likert-score of 5.25). The ease of sampling was rated highest for Afinion 2 with a median Likert score of 5.75, thanks to its all-in-one system and capillary aspiration system. The sampling with the cobas b 101 disc was somewhat hampered by the protective sheath of the sampling device, only allowing a one-sided sample aspiration resulting in a lower median Likert score of 4.75. Overall, LumiraDx was rated less than the other devices, except for the error messages. However, since only a few error codes were encountered during the validation period, this category was often answered as 'nor agree, nor disagree' (median Likert-score of 3), which may have biased this result. The overall results of the POCT-survey were displayed in a radar chart (Figure 3 and Supplemental data 8).
Supplemental data 7 A-D provides the radar charts of every POCT-CRP device individually. The user-friendliness of cobas b 101, Afinion 2 and QuikRead go was scored similarly by all participants (14 for LumiraDx and Quikread go and 16 for Afinion 2 and cobas b 101). For the 'Aalst POCT' users however, the time span between sampling and analysis for Afinion 2 was scored lower (median Likert-score of 2). In contrast to the other instruments, this time span according to the manufacturer's instructions is limited to 1 minute (Table 1), necessitating the proximity of an Afinion 2 instrument during sampling. The ratings of LumiraDx were somewhat depending on the rating group; 'Aalst POCT' scored the clarity of the error messages and the time between sampling and analysis better than other participants (median Likert-scores of 5 and 3, respectively)

while the nurses and ASZ POCT scored the packaging and manipulation of the pre-analytical device higher (median Likert-scores of 5).

5. DISCUSSION

The usefulness of POCT-CRP in the diagnostic setting of LRTI is substantiated by its implementation in numerous European guidelines [7, 8]. In this setting, the patients' benefit is guaranteed by the integration of POCT-CRP in the quality assurance program supervised by a central clinical laboratory. Such a program ensures, but is not limited to, the monitoring of the analytical performance according to (inter)nationally available guidelines [2, 6, 9, 11, 14]. This implies the evaluation of measurement uncertainty of the total analysis process from sampling, by means of the collection material supplied by the manufacturer, to result interpretation. In Belgium, there is only a legal framework of the POCT application within hospitals [2, 11] and a proposal was recently submitted to the Ministry of Health to extend this to general practitioners, following the example of the Netherlands [6].

In the present study, we've evaluated the analytical performance of four POCT-CRP devices towards APS set by SKUP [9]. These criteria posed were less stringent than APS set for central lab CRP methods [12, 13], but justified considering the (i) specific clinical context in which the POC systems were intended to be used (in routine primary care), (ii) the variability observed in previous studies [22-26], (iii) the inherent biological variation of CRP [27, 28] and (iv) the clinical implications of CRP measurement within our patient population (adults with cough presenting to primary care) [29]. However, which APS to use is always a matter of discussion and we acknowledge that different APS could be preferred by other authors.

To ensure 'fit-for-purpose' of the cobas c 503 as a comparison method in our method validation section, we firstly confirmed that both the MU (Supplemental data 1) and verification of the traceability to the ERM-DA474/IFCC (Supplemental data 2) fulfilled the APS stated by (inter)national expert organizations [16, 18]. The cobas c 503's MU (5.18%) revealed to be lower than the minimum MAU goal of 5.64% as stated by Braga *et al*. [16]. The lack of selection bias due to the comparison method used was recently confirmed by Borrillo *et al*. showing that the harmonization of method specific CRP calibration material against this ERM-DA474/IFCC standard, reduces the inter-assay variability of central laboratory CRP methods to less than 10% [16].

As the ERM standard revealed incommutable for the different POCT-CRP instruments [19], traceability to the ERM was verified by a head-to-head comparison to re-calculated ERM test results, based on the cobas c 503-ERM regression equation (Supplemental data 3 and 4). In general, cobas b 101 and Afinion 2 displayed a better alignment with the ERM (for results up to 40 mg/L; Supplemental data 3 and 4) and with the cobas c 503 CRP method (for results covering the whole measuring range; Table 2 and Figure 1) than LumiraDx and QuikRead go, revealing low mean differences and regression equations with slopes and intercepts around 1.0 and 0.0, respectively. Although Brouwer *et al*. [30] described an underestimation of results obtained with Afinion 2, the findings of most other papers are in line with ours [22, 23, 31].

The imprecision of every device met the pre-established criterion of ≤ 10% [9], both for the manufacturer specific iQC materials (Supplemental data 5 and 6) as for the patient pools (Table 4). Bearing commutability aspects in mind, only the latter iQC materials ensure a correct imprecision evaluation among the different CRP methods. The higher

imprecision obtained by QuikRead go could be fully attributed to the imprecision of the sample applicator, as the imprecision significantly improved by performing the sample application using a calibrated pipette. Therefore, the device specific user training should primarily focus on the variability of the sampling.
In previous studies performed in children and adults, QuikRead go seems to provide reliable, precise results with a good agreement with central laboratory values [22, 24-26, 32]. In our method comparison, QuikRead go revealed a wider spread of results and a considerable negative mean difference ranging from -6.34% to -12.01% (Table 2 and 3). The finding of underestimation of CRP-results is concordant with a previous study of Brouwer and colleagues [30]. Similar to the findings of Monteny *et al.*[33], the mean difference increased for CRP-values < 40mg/L. The wide spread of results in the method comparison study using capillary samples, is reflected by the higher CV in the imprecision study (Table 4) and the lower percentage of samples, i.e. 83.7%, within the +/- 20% accuracy criterion (Table 3).
LumiraDx revealed the highest mean difference towards ERM-traceable results of -20.46% [-38.14;-2.78] (Supplemental data 3 and 4). The use of a calibrated pipette did not improve the underestimation of the results (data not shown), supporting the assumption of a systematic analytical error. Nevertheless, this negative difference was not retained in the prospective method comparison on capillary whole blood samples (Table 3). However, a greater spread of the data was observed, inherent to the larger sample volume required, which complicated sample collection, and resulted in a lower percentage of samples (86.0%) exceeding the +/- 20% accuracy criterion (Table 3). We acknowledge however that in our evaluation, only one reagent lot of test strips was used on two different devices. Additional tests will be performed to exclude any bias due to device and reagent variability. Nevertheless, due to the violation of the APS for both lithium heparin and capillary blood samples, the use of LumiraDx in the FOD project '*Evaluation of the organizational challenges of out-of-hospital implementation of POCT-CRP in adults with cough*' was temporally discontinued.
A shortcoming of our study is that we could not provide an estimated MU for the different POCT-CRP methods due to i) the unavailability of u_{cal} and ii) the limited u_{rw}, based on only a 14-day time period, a limited number (n=2) of instruments, one reagent lot and a trained POCT-team performing the analyses. A more representative u_{rw} should cover at least a six-month consecutive period, including most changes affecting measuring conditions, such as different lots of reagents, different calibrations, and different users [21]. For the u_{rw} of the cobas c 503 CRP method, the requested time frame was encountered (Supplemental data 1), but the results were based on a third-party quality control material instead of a commutable plasma pool, targeting a CRP concentration of 10 mg/L, indicative for detecting sub-clinical infection [16, 21].
Furthermore, all blood collections and analyses were performed by the POCT team of OLV Hospital Aalst. In routine practice, however, healthcare professionals will perform the POCT analyses. Therefore, although secondary to the analytical performance, the evaluation of the user-friendliness of a POCT method is an essential cornerstone in a POCT performance analysis. The user-friendliness survey showed that each device is acceptable for routine use. Overall, Afinion 2, cobas b 101 and QuikRead go received the highest Likert-scores. However, a (system-dependent) operating point was also retained for each device: e.g. the pre-analytical phase of QuikRead go was quite cumbersome because it consists of different steps, unlike cobas b 101 and Afinion 2, where the pre-

analytical device offers an all-in-one solution; the blood collection with cobas b 101 was somewhat difficult given the design of the disc; for Afinion 2, the time between blood collection and the analysis (1 minute) was experienced as too short if the device is not in the vicinity of the patient, which can be resolved by the use of an available appliance battery. LumiraDx obtained the lowest Likert-score within each of the categories. The main comments were related to the three minutes start-up time, a pre-heating time per analysis strip of two minutes, the need of constant proximity of the operator to complete intermediate steps and the larger sample volume needed, which is very difficult to apply from the finger directly on the strip and the capillary delivered is not very practical. Each of these working points were raised in a constructive feedback meeting with the various manufacturers.

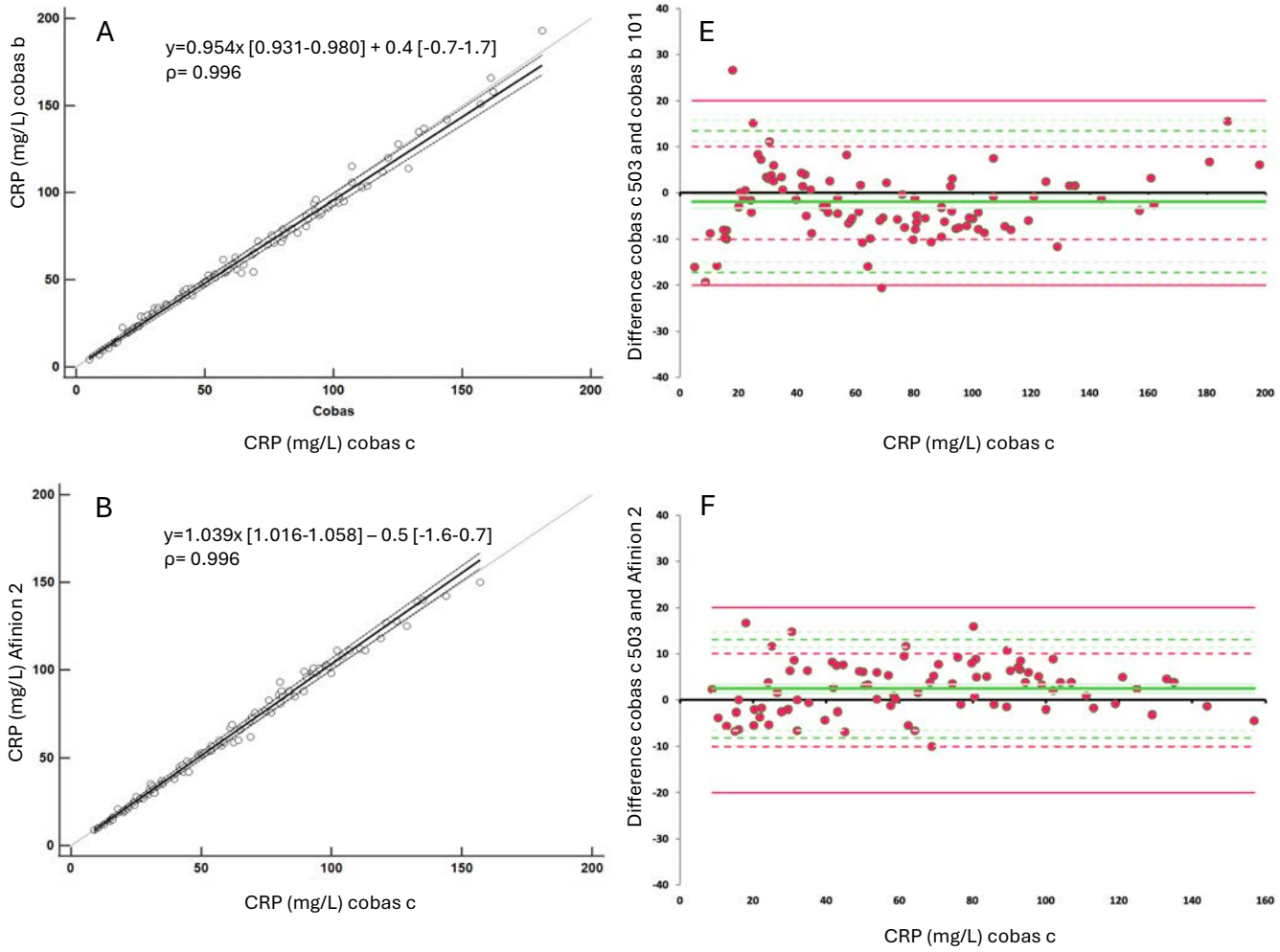
Previous studies have shown that point-of-care CRP testing can help reduce antibiotic prescribing and can be used in the ambulatory care setting [22, 29, 34]. Before widespread implementation can be recommended, the devices need to be fit-for-purpose and the analytical performance and user-friendliness should be verified. Especially at clinically relevant thresholds, imprecision and measurement uncertainty can lead to detrimental effects on clinical decision making and ultimately impact quality of care for patients in primary care. Therefore, manufacturers and lab specialists have a shared responsibility in realizing accurate POCT-CRP diagnostics, by, respectively, continuously improving the diagnostic performance of their in-vitro diagnostic medical devices based on increasing insights, and by maintaining a thorough quality assurance program on the devices routinely installed [6, 12, 13]

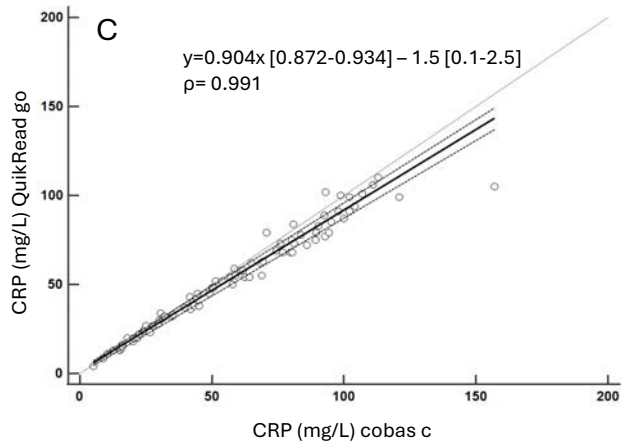
6. CONCLUSION

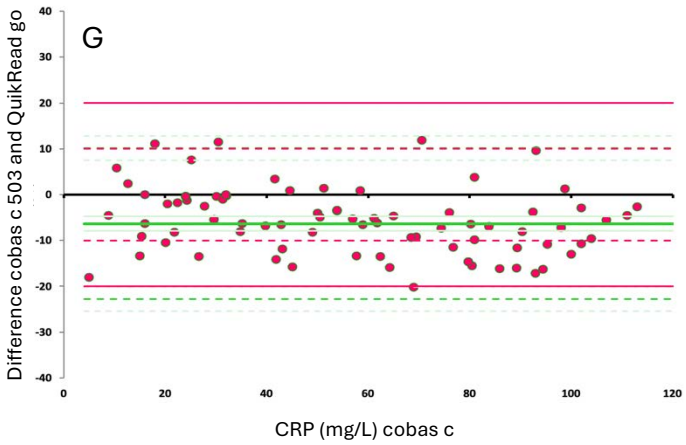
In conclusion, the analytical performance and user-friendliness of POCT-CRP devices varies among manufacturers, emphasizing the need for quality assurance supervised by a central laboratory.

7. FIGURES AND TABLES

Figure 1. Method comparison of lithium heparin plasma samples represented by a Passing Bablok (A-D) and relative Bland-Altman plots (E-H). A-D: the regression line, with corresponding regression equation and Spearman's ρ is represented by a solid line. The confidence interval for the regression is represented by the dashed lines and x=y is represented by the dotted line. E-H: The mean difference is represented by a solid green line, the 95% confidence interval of the bias by a dotted green line, the total acceptable error (+/- 20%) as solid red line and the acceptable CV (+/-10%) standard error as dotted red line.




C
y=0.904x [0.872-0.934] – 1.5 [0.1-2.5]
ρ= 0.991
CRP (mg/L) QuikRead go
CRP (mg/L) cobas c
0
50
100
150
200


G
Difference cobas c 503 and QuikRead go
CRP (mg/L) cobas c
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-10
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60
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100
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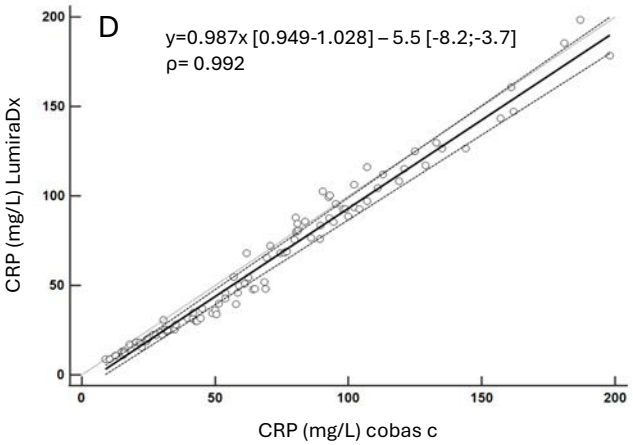
D
y=0.987x [0.949-1.028] – 5.5 [-8.2;-3.7]
ρ= 0.992
CRP (mg/L) LumiraDx
CRP (mg/L) cobas c
0
50
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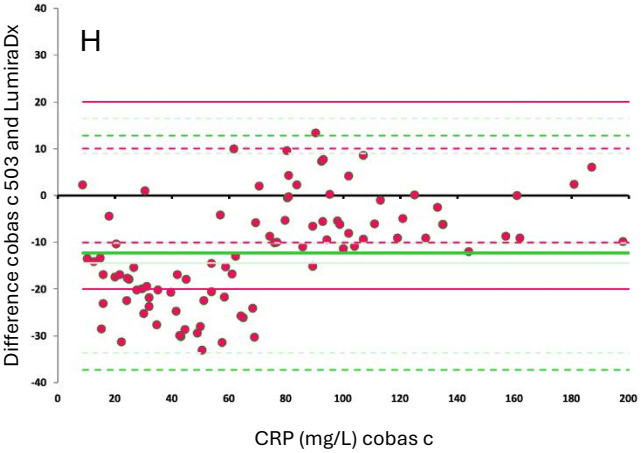
150
200


H
Difference cobas c 503 and LumiraDx
CRP (mg/L) cobas c
40
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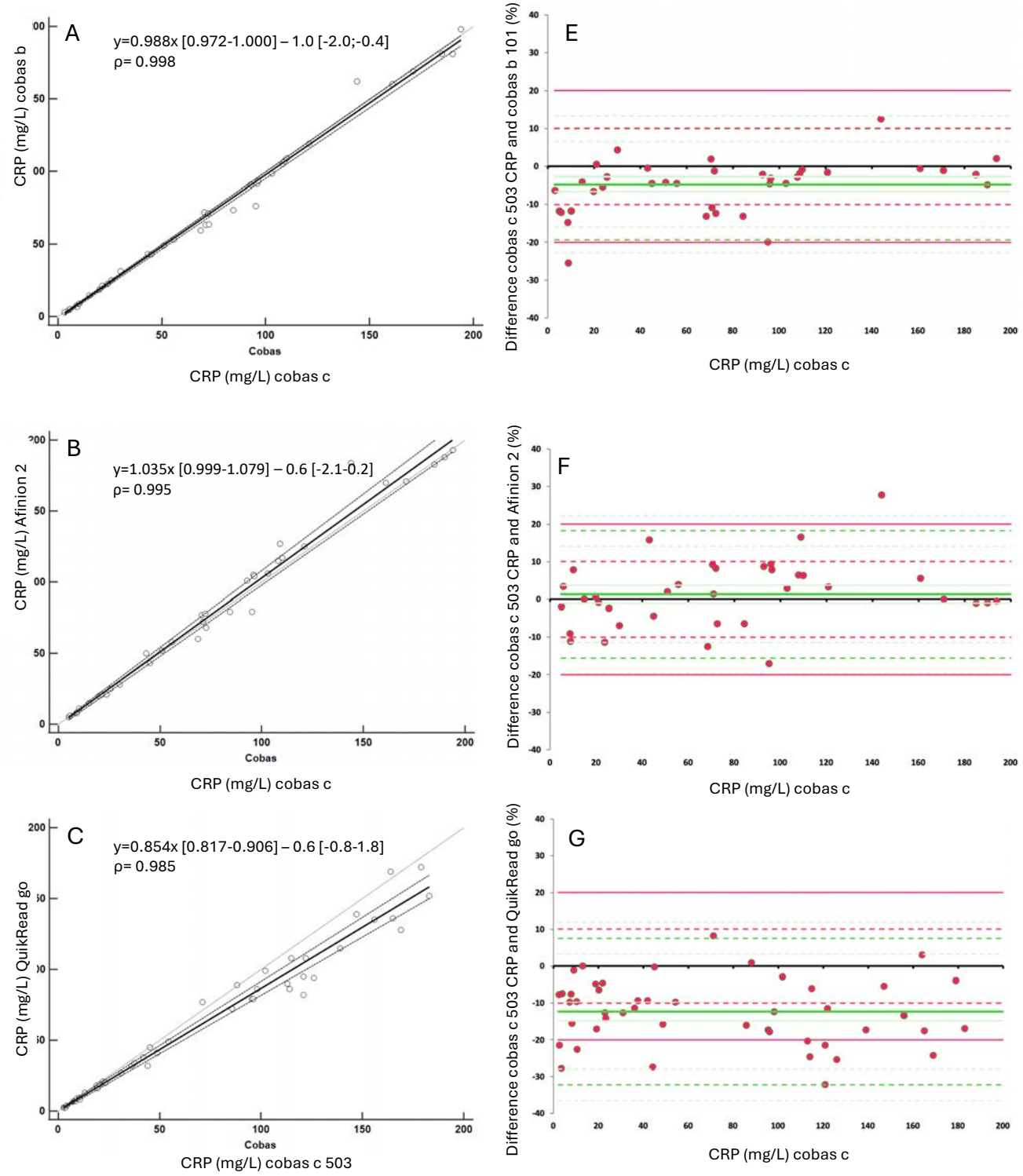
10
0
-10
-20
-30
-40
0
20
40
60
80
100
120
140
160
180
200

Figure 2. Method comparison of capillary blood samples (5-200 mg/L) represented by Passing Bablok plots (A-D) and relative Bland-Altman plots (E-H). A-D: the regression line, with corresponding regression equation and Spearman's ρ, is represented by a solid line. The confidence interval for the regression is represented by the dashed lines and x=y is represented by the dotted line. E-H: The mean difference is represented by a solid green line, the 95% confidence interval of the bias by a dotted green line, the total acceptable error (+/- 20%) as solid red line and the acceptable CV (+/-10%) standard error as dotted red line.



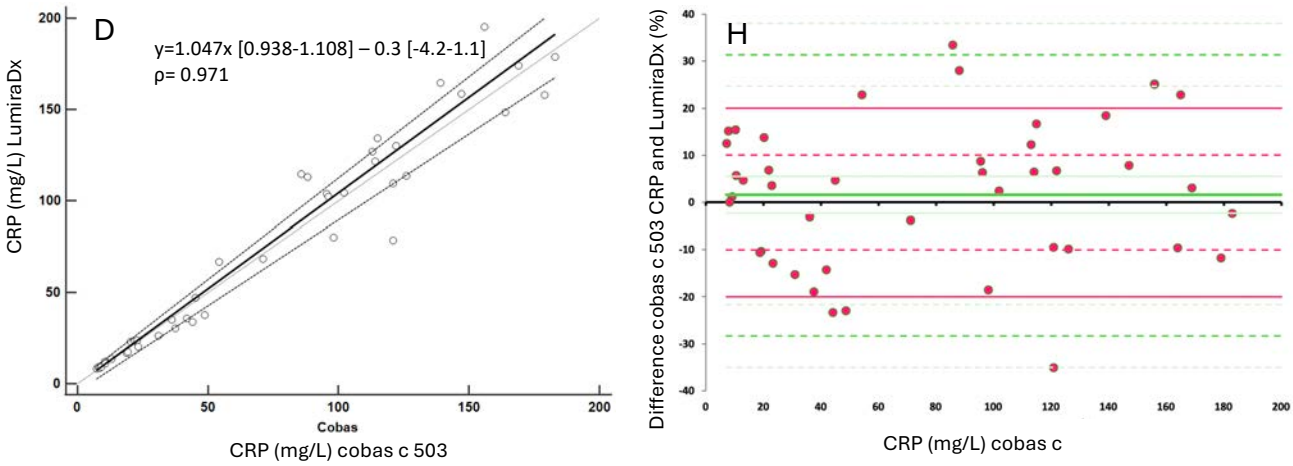


Figure 3. *Radar chart of the user-friendliness survey, comprising twenty-three questions covering following topics: packaging and manipulation of pre-analytical device, blood collection, timespan between collection and analysis, duration of test and error codes. The median Likert score obtained from 14 participants for LumiraDx (LumiraDx), and QuidRead go (Aidian Diagnostics) and 16 participants (cobas b 101 (Roche Diagnostics), Afinion 2 (Abbott)) is presented.*

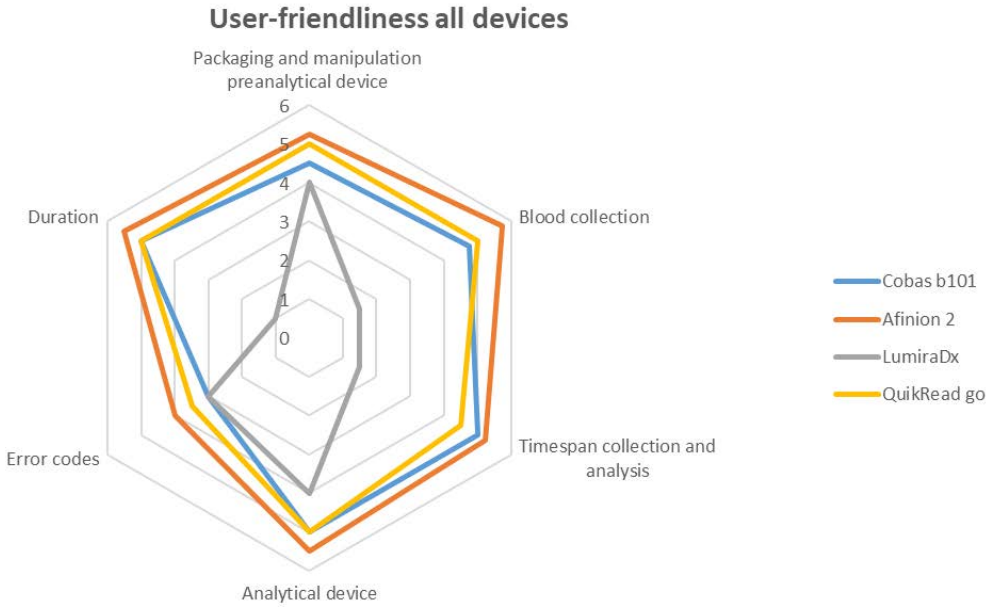


Table 1. Assay characteristics of the four POCT-CRP methods.

	QuikRead go (Aidian Diagnostics Espoo, Finland)	**Afinion 2 (Abbott, Oslo, Norway)**	**cobas b 101 (Roche Diagnostics, Mannheim, Germany)**	**LumiraDx CRP (LumiraDx, Stirling, UK)**
Test principle	Immunoturbi-dimetric assay	Solid phase, sandwich-format, Immunochemical assay	Immunoturbi-dimetric assay	Immunofluore-scent assay
Required sample volume	10 µL	2.5 µL	12 µL	20 µL
Measurement range whole blood	1-200 mg/L	5-200 mg/L	3-400 mg/L	5-250 mg/L
Measurement range plasma/serum	1-120 mg/L	5-160 mg/L	3-400 mg/L	5-250 mg/L
Max. time between collection and analysis	2 hours	1 min	2 min	Unspecified
Analysis time	2 min	3-4 min	3-4 min	4 min
Hematocrit correction	15%-75%	20%-60%	20%-60%	15%-55%
Traceability	ERM DA 474/IFCC	ERM DA 474/IFCC	ERM DA 474/IFCC	ERM DA 474/IFCC
Lot number iQC low / high	**1911044 / 1910072**	**10214493 / 10214494**	**020143-10 / 020143-20**	**1009000273000161 / 1009000274000162**
Lot number reagents	KT87-2	10220588	218151-01	50000752

Table 2. Lithium heparin plasma method comparison versus cobas c 503 (values 5-200 mg/L): results for Passing Bablok regression, Bland-Altman plot analysis (mean percentage difference) and the % of samples within the +/- 20% accuracy criterion.

	Number of samples	**Passing Bablok regression**			**Bland-Altman plot**	**% samples < +/- 20% mean difference**
		Slope [95% CI]	Intercept [95% CI]	Spearman's ρ [95% CI]	Mean difference (%) [95% CI]	
cobas b 101	93	0.954 [0.931-0.980]	0.4 [-0.7-1.7]	0.996 [0.994-0.997]	-2.58 [-17.19-12.04]	97.8
Afinion 2	87	1.039 [1.016-1.058]	-0.5 [-1.6-0.7]	0.996 [0.994-0.997]	2.53 [-8.21-13.28]	100.0
QuikRead go	81	0.904 [0.872-0.934]	1.5 [0.1-2.5]	0.991 [0.985-0.994]	-6.34 [-22.82-10.15]	97.5
LumiraDx	92	0.987 [0.949-1.028]	-5.5 [-8.2;-3.7]	0.992 [0.987-0.994]	-13.66 [-36.68-9.37]	66.3

Table 3. Capillary blood method comparison versus cobas c 503 (values 5-200 mg/L): results for Passing Bablok regression, Bland-Altman plot analysis (mean percentage difference) and the % of samples within the +/- 20% accuracy criterion.

	Number of samples	**Passing Bablok regression**			**Bland-Altman plot**	**% samples < +/- 20% mean difference**
		Slope [95% CI]	Intercept [95% CI]	Spearman's ρ [95% CI]	Mean difference (%) [95% CI]	
cobas b 101	36	0.988 [0.972-1.000]	-1.0 [-2.0;-0.4]	0.998 [0.995-0.999]	-5.22 [-20.29-9.86]	97.2
Afinion 2	36	1.035 [0.999-1.079]	-0.6 [-2.1-0.2]	0.995 [0.990-0.997]	1.50 [-15.50-18.49]	97.2
QuikRead go	43	0.854 [0.817-0.906]	0.6 [-0.8-1.8]	0.985 [0.972-0.992]	-12.01 [-31.68-7.65]	83.7
LumiraDx	43	1.047 [0.938-1.108]	-0.3 [-4.2-1.1]	0.971 [0.947-0.985]	1.68 [-28.52-31.88]	86.0

Table 4. Results of the between-day imprecision study for low- and high-level patient pools (n=10) performed on four POCT-CRP devices with mean and standard deviation (SD) in mg/L and CV in %.

	Low patient pool cobas c 503 (mg/L)	**Mean (SD) (mg/L)**	**CV (%)**
cobas b 101	18.6	20.6 (1.01)	4.91
Afinion 2		18.4 (1.39)	7.56
QuikRead go		18.1 (2.07)	11.5
LumiraDx		16.1 (1.45)	9.01
	High patient pool cobas c 503 (mg/L)	**Mean (SD) (mg/L)**	**CV (%)**
cobas b 101	98.6	93.1 (4.52)	4.86
Afinion 2		98.7 (7.59)	7.69
QuikRead go		88.8 (9.04)	10.2
LumiraDx		91.3 (4.44)	4.47

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WP1b. Linkage of three validated POCT-CRP assays

State of the art POCT hardware is equipped for patient and user identification, and for electronic data transfer of patient results to POCT middleware (already available in most hospital laboratories), to the laboratory information system (LIS) and to the electronic medical record (EMR). In this way, POCT results are made fully traceable in the LIS, available in the EMD and consultable via existing e-health platforms. The laboratory has expertise in establishing quality control of results and is familiar with the actions to be taken in case of discrepancies. The laboratory can provide support for technical problems (e.g. provision of back-up equipment) and can arrange contacts with manufacturers/distributors.

Point-of-care CRP Cartridges are for in vitro diagnostic use in the quantitative measurement of C-reactive protein (CRP) in human capillary (fingerstick) whole blood, and lithium-heparinized venous whole blood or plasma, using a point-of-care analyzer. The reagent cartridges are to be used by healthcare professionals at the point of care (POC) as well as in the clinical laboratory. The reagent cartridges are to be used as an aid in the decision to prescribe antibiotics in patients presenting with acute cough.

The point-of-care CRP devices are manufactured in accordance with IVDD regulations. A single use cartridge is used for the analysis of C-reactive protein in capillary whole blood. The point-of-care CRP devices have embedded software and a supporting service software application.

The clinically validated POC CRP devices are then prepared for transport by the respective manufacturers and performance will be confirmed using liquid quality control. Transport of the devices and installation together with the initial training of the end-users (GPs and GP staff) will be performed by the manufacturers. The device (i.e. analyzer) should be operated between 5-27 degrees C. Individual cartridges can be used at ambient temperatures (18 – 26 degrees C). There is no manual preparation required. All packaging and labelling is in accordance with IVDD regulations.

After obtaining formal **ethical approval** (dd28th August 2023) from the UZ/KU Leuven Ethical Review Board, we have installed the **3** validated CRP POCT devices in **27** general practices (**Figure 1)** and provided the necessary IT support, whereby a link between the device and the lab information system was possible via **middleware (Figure 2)**, after which the results were **validated** by the clinical laboratory and repeated via the usual pathways and structured in the **EHR** of the GP.

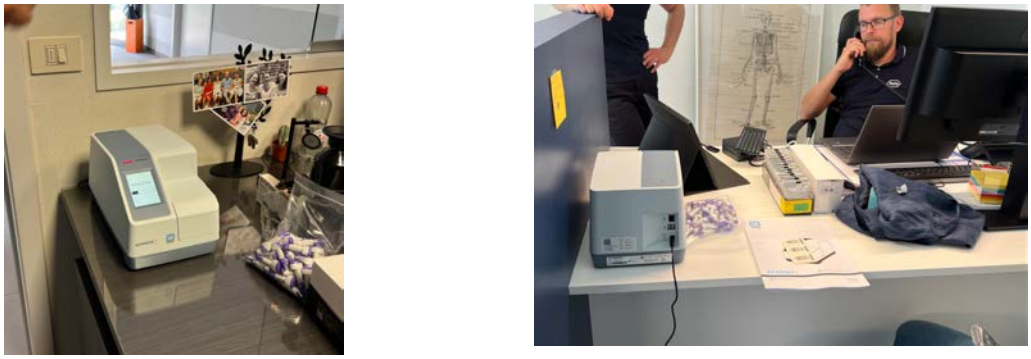

Figure 1: images of linkage of point-of-care CRP device in the clinical practices.

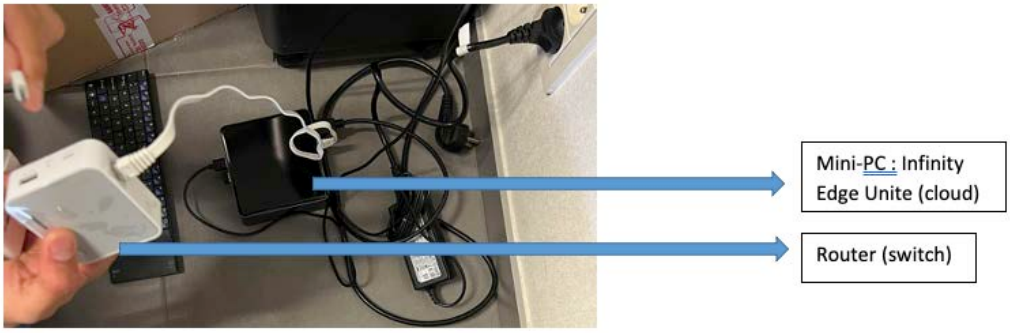

Figure 2: images of linkage of point-of-care CRP device in the clinical practices.

For each participating central laboratory (Klinisch Laboratorium OLV Ziekenhuis Aalst, Medisch Labo Medina Aalter, LHUB-ULB, Brussel en Laboratoires Cliniques St-Luc, Brussel), a subset of practices (3 to 5 per central lab), were provided with the middleware. All study-related activities (recruitment, informed consent, fingerprick blood sampling) were performed at the GP practices by the participating GPs and their staff.

WP2. ENDUSER TRAINING AND QUALITY ASSURANCE OF POINT-OF-CARE DEVICES

GOAL:
An important aspect was to consider systems that can be put in place to ensure that all personnel performing POCT have received adequate training. Clinical laboratories have mandatory procedures for monitoring the quality of diagnostic tests that will be applied in this pilot project (e.g. continuous internal quality control monitoring, external quality control, lot validation, lot reservation, reagent distribution, technical support). We wanted to provide enduser training and quality assurance of the validated POCT-CRP assays.

RESULTS:
We have organised a **launch event** on 5th September 2023 with **50 participants** where all 3 devices were represented by the respective companies and both the **clinical guidance** (60') **(Figure 1)** as well as a **hands-on training** was provided (30' per device) **(Figure 2)**. Lastly, the trial procedures were explained and the **protocol** and **informed consents** were provided.

1. BACKGROUND

There is evidence that uncontrolled use of POCT can have far-reaching negative consequences for both individuals and public health. One aspect will be to consider systems that can be put in place to ensure that all personnel performing POCT have received adequate training. This training was provided by the manufacturer and clinical laboratory at a plenary meeting at the beginning of the implementation stage of this project. As user training is organised and monitored, the likelihood of pre-analytical errors is reduced and results will be more reliable. The laboratory and/or manufacturer will organise and certify training (state-of-the-art POCT equipment will only work if the user is identified and certified).
Quality assessment on a regular basis is a prerequisite so that the treating physician and the patient can have confidence in the test result. One should consider how quality can be assessed by recognised professional bodies or by the government itself. Clinical laboratories were used to validate test results. Clinical laboratories have mandatory procedures for monitoring the quality of diagnostic tests that were implemented in this pilot project (e.g. continuous monitoring of internal quality control, external quality control, distribution of reagents, technical support).
Performing internal quality controls (IQC) at regular intervals is key to ensuring that POCT instruments are functioning properly and that POCT reagents are providing accurate patient results. Quality control material target concentrations should be chosen so that one falls within the reference interval or close to decision limits of the assay and one in the abnormal range (high or low). For qualitative tests, one of the selected QC material should be negative and one positive.

2. METHODS

Imprecision as part of routine quality assurance was evaluated in a subset of 15 practices (affiliated with the central lab of OLVZ Aalst) using a patient lithium heparin plasma pool (+/- 20 mg/L) in addition to manufacturer specific internal quality control (iQC) material with low and high CRP concentration. Each iQC sample was analysed at least 10 times per GP practice by the GP (staff), for each POCT-CRP device, spread over a period of 4 weeks each time. Imprecision was evaluated according to CLSI EP05-A3. The criterion for acceptable imprecision is defined as a coefficient of variation (CV%) less than or equal to 10%.

Additionally, capillary blood samples were prospectively collected from patients at the GP practices and were immediately analyzed with the POCT-CRP device. All physicians and nurses from the GP practices were informed about the study design. The POCT-CRP samples were collected by the certified practice staff. In all patients from whom capillary samples were collected, written informed consent was obtained from patients by the GPs and/or their staff before sample collection during the study period. It is generally to be expected that GPs will use the POCT-CRP at least 30 times per device.

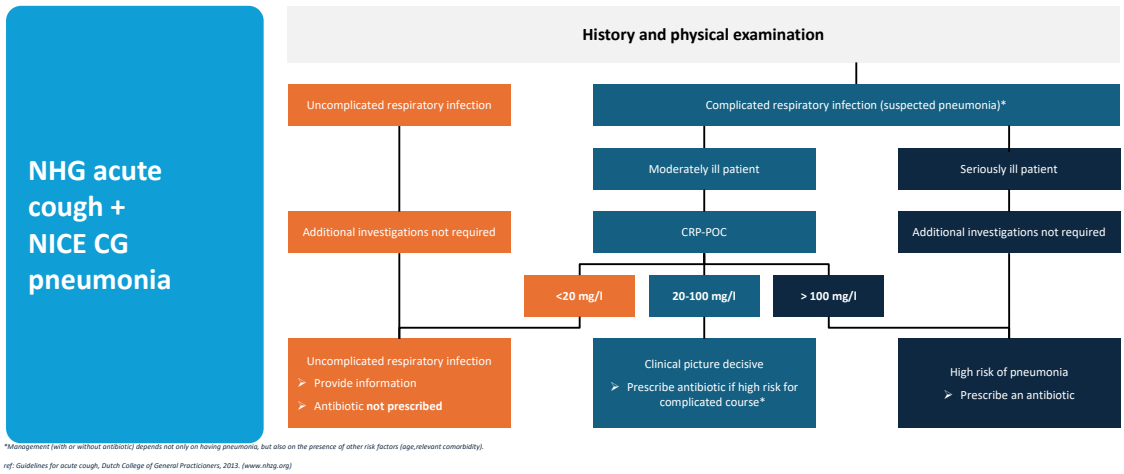

Figure 1: clinical guidance according the NHG (Dutch Society of Family Practice) guidelines.

3. RESULTS

We have organised a **launch event** on 5th September 2023 with **50 participants** where all 3 devices were represented by the respective companies and both the **clinical guidance** (60') **(Figure 1)** as well as a **hands-on training** was provided (30' per device) **(Figure 2)**. Lastly, the trial procedures were explained and the **protocol** and **informed consents** were provided.

Figure 2: images of hands-on training for the three validated POCT-CRP assays

WP3. EVALUATION OF THE IMPLEMENTATION PROCESS AND STAKEHOLDER ENGAGEMENT

GOAL:
We organized semi-structured interviews of the relevant stakeholders involved in this pilot project and the implementation of the CRP POCT device through a survey and focus conversations. Based on the experiences of the relevant stakeholders, we wanted to describe: how the implementation went in terms of organization, evaluation of feasibility, feasibility, barriers and facilitators of the implementation.

RESULT:
After obtaining formal ethical approval, the participants have been informed were contacted in November 2023 to be able to organize semi-structured interviews of the relevant stakeholders involved in this pilot project and the implementation of the CRP POCT device through a survey and focus conversations. Findings indicate that tailored implementation of POC CRP-tests in Belgium can be successful if ease of use, workflow integration, and decision-making support are prioritized, with the goal of reducing prescriptions and enhancing antimicrobial stewardship.

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1. SUMMARY

Background: Despite self-limiting nature of acute respiratory tract infections, Belgian GPs often prescribe antibiotics. Studies show CRP point-of-care testing significantly reduces antibiotic use and can be cost-effective with long-term efficacy in adults with acute cough. Before national implementation in Belgium, organizational aspects must be addressed.
Aim: This study used focus group discussions to assess stakeholder experiences in a pilot project using POCT-CRP devices in general practice for adults with acute cough.
Methods: Four semi-structured focus groups were conducted among Belgian GPs and relevant stakeholders. Transcripts were analyzed using reflexive thematic analyses.
Results: 31 participants contributed. Five themes emerged:

(i) **Help tackle their diagnostic uncertainty:** The point-of-care CRP test serves as an objective tool that complements clinical judgement in situations where diagnostic uncertainty arises.

(ii) **Proper integration in their existing workflow:** While most GPs required some time to adjust to the device, once they became accustomed to it, they frequently incorporated its use into their multitasking during consultations.

(iii) **Ease-of-use is considered crucial:** The speed, ease of use, and minimal blood sample required were highlighted as the most critical features of the CRP device

(iv) **A decision-making tool at their fingertips:** Whether confirming their gut feeling or producing unexpected results, GPs found the CRP test valuable for explaining to patients why antibiotics were unnecessary, which helped reduce delayed prescriptions and promote more appropriate prescribing.

(v) **They care about quality and support:** GPs emphasized the need for robust quality control and ongoing support from the lab and device manufacturers to address installation and technical issues during large-scale CRP device implementation.

Discussion: Findings indicate that tailored implementation of POC CRP-tests in Belgium can be successful if ease of use, workflow integration, and decision-making support are prioritized, with the goal of reducing prescriptions and enhancing antimicrobial stewardship.

2. BACKGROUND

Antimicrobial resistance, commonly referred to as AMR, poses a significant and enduring threat to public health both presently and in the years resulting in infections becoming difficult or impossible to manage. This exacerbates the risk of disease transmission, severe illness, disability, and death (1). In Europe and around the world, several initiatives have been put in place to combat AMR. The European Observatory has contributed to a public debate on the EU's future health priorities, resulting in a report aimed at keeping health at the top of the political agenda in Europe and worldwide. Their recent work has focused on antimicrobial resistance, global health policies and social prescriptions (2). On a global scale, the World Health Organization (WHO) and its partners have launched the International Pathogen Surveillance Network (IPSN). This network aims to connect countries and regions to improve the collection and analysis of pathogen samples. The data obtained are key tools for researchers, policy-makers and health-care workers to rapidly identify and respond to outbreaks or the emergence of drug-resistant strains (3). Belgium has been proactive in combating AMR, initiating a national plan aligned with the "One World, One Health" strategy. This plan emphasizes shared responsibility across all sectors to ensure optimal care for people and animals, safe food, and a healthy environment for all its citizens (4).

In Europe, 80% to 90% of all antibiotics are prescribed in primary care, primarily by general practitioners (GPs), with most being prescribed for respiratory tract infections (5–7). In Belgium, general practitioners still prescribe antibiotics unnecessarily too often, particularly for respiratory tract infections, despite national initiatives aimed at improving guidelines and public awareness campaigns (5,8,9). Furthermore, primary care settings are usually the first point of contact for patients and often the first places where new or previously controlled diseases are detected and treated. This highlights the essential roles of primary care in the early detection and management of infectious diseases, as well as in combating antimicrobial resistance by promoting the judicious use of antibiotics (5,10)

Acute cough from an upper respiratory tract infection or acute bronchitis is usually caused by a viral infection. Most of these infections, including acute bronchitis, are estimated to be viral in 85% to 95% of cases, and antibiotics are not usually needed (11). A key challenge in managing acute cough is identifying which patients need antibiotics. Due to often low poor predictive value of clinical assessments, there is a tendency to overprescribe antibiotics unnecessarily (12) The benefits of rapid test, point-of-care C-reactive protein (POCT-CRP), are now undeniable. CRP is a predictor for serious infections, especially for serious bacterial infections (13,14). POCT-CRP tests can be a valuable addition to primary care by improving antibiotic targeting and offering a cost-effective solution to managing respiratory infections. Adoption of POCT-CRP and subsequent antibiotic prescription was tested without compromising patient safety, indicating that many acute respiratory infections cases did not require antibiotics and could be managed effectively with CRP guidance (15,16). Its use is part of practice guidelines and is implemented in primary care practice in countries such as the Netherlands and England, to guide antibiotic management for acute cough. In the Netherlands, these tests are widely used and reimbursed, supported by good integration of health services. In England, despite recommendations in guidelines, funding issues and poor integration of services limit their use and reimbursement (17,18).

Although clinical studies have shown that using CRP POCT results in significant reductions of antibiotic prescribing, few studies have focused on the actual implementation process through enduser involvement. By conducting focus group discussions involving key stakeholders, this study aims to assess the feasibility and identify barriers and facilitators related to the implementation of POCT-CRP devices within general practice settings. By doing so, this study aims to identify the important drivers to integrate POCT-CRP devices

into Belgian primary healthcare practices, while also characterizing the necessary organizational adjustments required for broader national implementation.

3. METHODS

3.1. Study design and setting

This research employs a qualitative approach, using semi-structured focus groups with key stakeholders for the implementation of POCT-CRP tests in primary care. Stakeholders included general practitioners (GP), GP trainees, representatives of companies distributing POCT-CRP devices and clinical biologists. Stakeholders were involved in a pilot project where clinically validated POCT-CRP devices (QuikRead go easy CRP test (Aidian Diagnostics, Espoo, Finland), Cobas b101 (Roche Diagnostics, Mannheim, Germany) CRP test and Afinion 2 (Abbott, Oslo, Norway) CRP test) were installed in 22 GP practices with necessary IT support. These GP practices were situated across Flanders and Brussels (Belgium) and related to one of four central clinical laboratories: Klinisch Laboratorium OLV Ziekenhuis Aalst, Medisch Labo Medina Aalter, LHUB-ULB, Brussel and Laboratoires Cliniques St-Luc, Brussel. The linkage of the device and the lab information system was achieved via middleware (Roche Cobas Infinity POC), which was provided to a subset of practices (3-5 per central lab). The clinical laboratory medically validated the results, which were then re-structured into the GP's EMR through the calibrated channels. The pilot project started with the training of end-users at a plenary meeting provided by the study team, manufacturers and clinical laboratories. During the session, a presentation was given regarding the use of POCT-CRP within routine clinical decision making, the study process and how to use the devices, followed by a hands-on practice session. After the installation of the devices, all study-related activities were performed by the GPs and their staff. This included recruiting adult patients with acute cough who met the eligibility criteria, obtaining the informed consent form from the patients and/or their legally authorized representatives, finger prick blood sampling, performing the CRP-test and explaining the results to the patient. Also, regular quality controls (QC) were performed by the GPs or practice staff. One to three different POCT-CRP devices were used by the GPs during a period of approximately three months, from September to December 2023.
Four focus groups were conducted to explore stakeholders' experiences with the CRP-devices, following the methodology outlined by Krueger et al. Methods and findings are reported in accordance with the Consolidated Criteria for Reporting Qualitative Research (COREQ) checklist (Additional file 1, I). The study protocol is included in Additional file 1 (II).

3.2. Recruitment and selection of participants

We contacted participants in the pilot project via email. Based on their location and the central clinical laboratory they were associated with, we invited participants to attend a focus group at the nearby clinical laboratory in one of three Belgian cities: Aalst, Aalter, or Brussels. Due to the large number of participants in Aalst, two focus groups were organized for this region, one of which was organized online (as a result of unforeseen weather conditions). The representatives of companies distributing POCT-CRP devices could choose in which focus group they participated. Each focus group included a convenience sample of 6-12 participants, with a total of 36 participants. An e-mail was sent to the focus group participants post-hoc to gather demographical information.

3.3. Focus group discussions

Four focus groups were conducted between January and March 2024, took place in 3 cities in Belgium and online via Microsoft Teams, and lasted 45 min to 1.5 hours each. The three Dutch-speaking groups (Aalter, Aalst) were moderated by SG, with AD as an observer and the French-speaking group (Brussels) was moderated by MD with SG as an observer.

The focus groups were semi-structured according to the interview guide (Additional file 1, III) to ensure that all critical areas were addressed, while still providing participants with the opportunity to discuss topics that were personally meaningful to them. The topic guide was initially created in Dutch based on previous research. Several authors of this paper, with diverse professional expertise, worked on refining the final version of the topic guide, which was subsequently translated and reviewed with French-speaking researchers. The following topics were covered: (1) overview of the purpose and rationale for the focus group and signing of the informed consent form, (2) participants introducing themselves, (3) discussion of prior experiences with a POCT CRP-device and the facilitators and barriers to its use, (4) discussion of the installation, organization and feasibility of the devices, (5) discussion of their experience with technical problems and point of contact in such cases, (6) discussion of when and why the device was used. The interview guide was created in Dutch and then translated and discussed with the French speaking researcher.

3.4. Data analysis

All focus groups were audio-recorded, transcribed verbatim using Amberscript (details not available), checked and pseudonymised prior to being translated into English using Deepl GmbH Pro (Berlin, Germany), since results analysis was carried out in English.

Reflexive thematic analysis within a realist and constructionist framework was used to analyse the transcripts (Braun and Clarke) (19,20). The overall aim of this kind of analysis is to build an explanatory framework for understanding stakeholders' experiences with the implementation process of POCT-CRP devices in general practice. First, AD, MD, SG, FW and LV familiarised themselves with the data. Then, each of the four focus groups was analyzed individually, followed by a team meeting between each analysis. During this process, the research team was aware that their personal experiences could influence and potentially delimit how they interpreted the data. Remarks or discrepancies were discussed in the in-between meetings to help them separate the participants' experiences from her own and to ensure the integrity of the analysis.

Focus groups conducted in Dutch were coded by three Dutch principal coders, while one of the reviewers was French speaking. For the French focus group, the lead coder was French-speaking, while two other coders and reviewers were Dutch-speaking. The role of each coder changed between the different focus groups, thereby ensuring a comprehensive and balanced approach to coding. During the meetings, AD coordinated and revised the coding before moving on to the following focus group analysis. From the second focus group onwards, the research team involved in analyzing the results constructed themes inductively through collaborative discussions. This process was supported by a codebook containing definitions and examples. The resulting codebook was then used to code the subsequent focus groups. Both the codebook and themes were iteratively reviewed and refined. All analyses were performed using QSR NVIVO software version 14 (QSR International Pty Ltd, Melbourne, Australia).

After analysis, we performed a member check. Focus group participants were asked via e-mail to score the list of final themes on a 6-point Likert scale, from strongly disagree to strongly agree. They were also given the opportunity to provide additional comments in a free text-format (i.e., participant checking). X of the X participants provided feedback and X of them agreed with the final themes. Detailed results are shown in Additional file 1 (IV).

Dutch and French quotes were translated to English with DeepL software. The English quotes were translated back to Dutch or French so that the researchers could check whether the translation correctly reflected what the participants really meant.

3.5. Reflexivity statement

AD (MSc.) and MD (MSc., PhD) are both females with a background in biomedical sciences. AD is born in Belgium and is currently working as a PhD researcher. MD is born in Belgium and is currently working as a post-doc researcher. As outsiders to the group under study, AD and MD do not have direct experience with EHRs or POCT-CRP devices. Therefore, their insights are shaped primarily by a research-focused perspective, which may differ from practical clinical practice. SG, FW, LV (MD) are female GPs in training, all born in Belgium. JV (prof., MD) is a male GP with 16 years of clinical experience, also born in Belgium. Prior to the start of the study, AD, MD, FW and JV already had experience with qualitative research methods. SG and LV did not have any experience in qualitative research yet but attended other focus groups to observe, followed pertinent lectures and reviewed relevant literature. There was no relationship established prior to study commencement between the researchers and the participants.

3.6. Surveys

In addition to the focus groups, we organized a survey of relevant stakeholders involved in this pilot project and the implementation of the POCT-CRP device. After the testing period, all participants received a survey regarding the device(s) used during the last period (up to 3 surveys per physician for up to 3 devices in total). The survey contained questions about the implementation of the POCT-CRP device in general practice, the feasibility of the procedure and the barriers and facilitators they faced during the implementation process. Scores were used per question ranging from completely agree and agree to neutral, disagree and completely disagree.

3.7. Ethical approval

The study protocol and associated documentation was approved by the Ethics Committee Research of UZ/KU Leuven on August 31st, 2023 (S67992).

4. RESULTS

Over 150 stakeholders were contacted, of which 41 expressed interest in the focus groups and confirmed their participation, and ultimately 36 took part. Reasons for non-participation included: unsuitable timing (x), forgetting to put it in the agenda (1), personal reasons (2), not finding a babysitter (1), or participation in a previous focus group (1). Among the 36 participants across the four focus groups, 19 were GP's, 8 represented companies selling the CRP-devices and 9 were from the clinical laboratories.

The analysis produced four intersecting themes (Figure 1). The full coding tree and Dutch quotes can be found in Additional file 1 (VI, VII).

4.1. Theme 1: Rationale for using CRP POCT: Tackling Diagnostic Uncertainty and Improving Patient Communication

4.1.1. CRP Test as an Objective Tool to facilitate therapeutic decision making

Doctors frequently described the CRP test as an objective tool that can be used as an additional argument to consider alongside gut feeling and clinical examination. According to the physicians, the two complement each other well. The CRP-value enables the GP to differentiate between viral and bacterial infections and facilitates therapeutic decision-making in patients who express their symptoms differently or have varying perceptions of illness.

And at clinical level, well ... in fact that, ... I think it gives us something very objective that in general practice, it's true that we're very good at gut feeling and clinical examination, ... and

also to really feel a little how people feel, and that allows a certain objectification of things, depending on the CRP
But also vice versa that you have someone with you that you say, he is really sick to death right now and that it's not that bad and thought, okay, that's the difference in the way people experience an illness, too.
is it here still a postviral or is it here really still something atypical that could be underlying it.

4.1.2. CRP is Used in Cases of Diagnostic Uncertainty and to Improve Patient Communication

Two reason that were frequently mentioned for performing the test were cases of diagnostic uncertainty or the need for an extra argument to convince the patient that antibiotics were not necessary. Doctors mentioned that they most commonly used the test when they were stuck in their diagnostic process, had diagnostic doubts, or wanted to reduce the differential diagnostic landscape. They referred to these situations as "the grey zone." The test was particularly useful in cases of uncertainty between a viral or bacterial infection and hesitating whether to prescribe antibiotics. Additionally, doctors used the test when they had a gut feeling that something might be wrong or when they sought confirmation or reassurance. When clinical examination and the CRP test pointed in the same direction, this reassured the doctors.
I think with me especially if I kind of came to a kind or at a moment in my, in my diagnostic process that I didn't really get out that way immediately or if I felt like I was a bit stuck in the sense of: What extra argument can I still make here to convince people to then go in the direction of no antibiotics all or if da was my assessment at da moment or on the other hand if I had the feeling of is da now something that I do want to give antibiotics for moe myself but then still have doubts in order to have for my self then also sometimes I think a bit of extra arguments. Uhm, so yes, so a little bit in a, in a euhm not immediately decided diagnostic process and da I or the patient needed another extra convincing factor.
For me, it was as soon as I saw that I had some sort of doubt, and I said to myself "would I use an antibiotic? or rather not? It was precisely my clinical examination, my history-taking, which I did completely and which brought me to doubt, that I had this argument, there, in addition, when I had a doubt.
Actually positively, yes, I think it did really add value for um certain cases. Uhm, yes, actually mainly I think a bit from all or how that I personally used it mainly, I think is a bit twofold. On the one hand mainly from uhm an optic to sometimes convince people not to take antibiotics all or if there was a demand for antibiotics to be able to throw a kind of extra argument euh into the fray and on the other hand sometimes in borderline cases where that I clinically euh feared a bit for a, for a serious infection to have there or not an exclusion or a confirmation of my euhm, of my clinical sense or of my clinical assessment euhm. So da was a bit ambivalent.
Another reason frequently mentioned by doctors for performing the test was to reassure or convince the patient of the non-necessity of antibiotics. When a patient insists on antibiotics, the CRP value is easier to explain to patients than simply saying, "it's a viral infection." Moreover, patients feel that the doctor has acted and has no doubts. However, doctors emphasized that this should not be the sole reason for conducting the test.
Host: Does it help you communicate? MG 4: Unquestionably, it saves lives. And when you've got fifteen patients and by the sixteenth you've still got to fight, to tell him no antibiotics at some point, I honestly admit that there are times when I don't fight. So this machine is going to help me not to fight and is going to fight in my place. It's going to say "it's under 5, no discussion" and people are, as you say, convinced straight away. MG 5: I really agree.
I think that is very quickly something you can do in between. That actually... I think you spend longer discussing with the patient why that they don't need antibiotics or do need antibiotics than the result of den test takes.

also for your patient, if you explain very clearly beforehand look, if it's low, it's viral, if it's high, it's bacterial and you come back and you say: look, it's low, then they have more confidence in it
F1P9: On the one hand, I did find it useful to use it when patients really absolutely want antibiotics themselves to then show that it's not necessary.
F3P2: Benefits, lots of benefits (everyone laughs), (unintelligible) policy. In itself yes, tis handy hehe or so with people who are fans of antibiotics (laughs) anyway, allee easier to convince, or so have something objective. People who can't just get away with 'it's a viral infection', who then somehow don't just take your word for it or something, or just don't just... (being interrupted, overstanding)

4.1.3.CRP Should Be Used over and above Clinical Examination

According to doctors, it remains important not to rely solely on the CRP value but to continue assessing the patient thoroughly. The CRP value should be interpreted with clinical examination in mind. If a patient appears seriously ill but has a low CRP value, it is important to follow up and encourage the patient to return if symptoms worsen, as there can be some delay in the CRP response, according to the doctors. In any case, the clinical examination is considered essential, and the CRP test is an additional tool that complements the clinical assessment, but does not replace it. If the clinical examination was clear, there was no need to use the CRP device, according to the doctors.

Yes, and I think that this CRP was also, it was an additional argument, but just like my clinical examination was also an additional argument. It's not my CRP that's going to do everything and that's going to take care of me. But yes, when I was between the two, it was also me and what I felt and what I had examined, what I had objectified and who made that decision. So that's an argument in addition to all the other arguments I had. But the medical history, the clinical examination and this, it's just another weapon (LAUGHTER).
Yes, the only drawback is roof still, yes in itself always a bit with your delay of course he of CRP. It is sometimes (gasps), all the time, that the clinic is still (laughs) important, of course, and the follow-up, because you can still have a normal CRP at an early stage, and then it goes up anyway. We shouldn't blind ourselves to it or anything, think especially that a bit (people confirm muttering).
Yes, because I think that general medicine is also ... I think that this relationship with the patient, the discussion, the clinical examination, ... it's so important that I don't want general medicine to be overrun by biology machines and stuff.

4.1.4.CPR can be used for various clinical indications and in diverse contexts

Although many doctors frequently mentioned that they were fans of the device and appreciated its added value, there were also cases where they consciously decided not to perform the CRP test. For instance, when the diagnosis was clear to both the doctor and patient, in cases of early fever or cough, when running behind schedule, or when more information than just the CRP value was needed, leading to performing a general blood test. Doctors stated that within the context of the study, they most often used the test for adults with prolonged cough or when the cough sounded unusual, but clinical findings were limited. The test was particularly useful during the period from November till December for these cases. They repeatedly emphasized that they did not use the test for all patients with a cough. Only one doctor indicated that he used the test for every patient with acute cough, as this was the scope of the study, but also stressed that this often felt unnecessary.
Notably, doctors had also used the test for various indications outside the scope of the study, such as erysipelas, urinary tract infections, pneumonia, diverticulitis and appendicitis. They also used the CRP-test in the context of nursing homes (with use less than expected), home visits (when rapid diagnosis is needed), and in children.

There's no point in using a machine for all the people who cough, for whom there is some sort of clinical evidence.
MG 4: So for administrative reasons sometimes I didn't do it, because it took an extra three, four, seven minutes. I was already very late.
So especially the idea of euhm, that person is coughing and that cough doesn't sound so okay, but we don't hear that much clinically, euhm da was pretty much an addition to know is there here, is da here still a postviral or is da here really still something atypical that could be behind it. So that did help me a bit in choosing whether to start antibiotics or not.

4.1.5. CRP Test Instead of General Blood Test in Children

The use of the test in children was discussed in every focus group. According to the doctors, the test was particularly valuable for children due to more diagnostic uncertainty and the importance of quickly deciding whether to refer the child to the hospital. Even when the doctor did not suspect anything serious, it could help reassure parents, they said. A CRP test is easier to perform in children compared to a general blood test, due to the minimal amount of blood required. Additionally, the result is available immediately, allowing for quick decision-making without the need to call the patient back.
F3P2: All, because I think also just really often antibiotics are given in children just because of that diagnostic uncertainty and surely you don't want to miss something in a child or so all, yes.
F3P7: Well yes, tis da, tis da. And with children it can also go two ways I think uhm a super sick child with such an equal ne CRP that is negative or a child whereda you think, tis still cava and then suddenly such a super high CRP because clinical is very often more difficult in a child (several confirm). All in all, I think that's where the greatest added value lies.
I think: yes, now we have focused on adults with coughs. I think the added value with children is huge, because then you don't have to do heavy blood sampling, which da they don't like. They don't like a finger prick like that.
F3P2: Yes, on the other hand, there are also, yes, parents of young children who do sometimes go to the paediatrician specifically for the CRP shot. And if you manage that yourself, I think that's an advantage. It's more accessible that way, so you don't necessarily have to go to the paediatrician or something like that or even sometimes send them yourself.
F4P2: Gosh yes I did take out 2 kids uhm under 6 months with ne UWI. Me CRP of 100, 120. So kwas glad I had da.
F3P9: Yes, or the people who da you would otherwise take blood from that you can then already immediately say, ge have so not that: ah call back tonight or call back tomorrow so you can immediately link a policy to it
F4P2: People liked that they didn't have to have a whole blood sample taken then, people who were afraid of needles allowed it. Then you have something huh.
F3P2: And also for parents, all das da go over myself now, but for other parents it is too.
unknown: For reassuring them

4.2. Theme 2: Smooth Collaboration with Companies and Labs and Proper Implementation in Existing Workflow, Facilitated by Ease of Use, Speed, and Minimal Blood Requirement

Installation, adaptation, cooperation, frequency of use and quality control
Most doctors needed some time to get used to the device, but once familiar, most doctors found it easy to use. Interestingly, general practice trainees were often quicker to adapt to the device and implement it into their workflow. They also used it more frequently and stated they would greatly miss it if it were no longer available. More experienced doctors were sometimes less likely to use the device as quickly, since they are used to work without the device.

Yes, at home it still takes a bit of intellectual adjustment, at least on my part. It's true that we're so used to doing things without it that, from the moment the consultation starts saying "ha, it would be nice to do that as well"... So, for me, it's something that I still have a little, a little lack of reflex to say "ha, I'll do it", but it's true that if the machine is installed as it should be here or as it already is, it's... You just have to get into the habit of doing it, in the end.
F3P9: No, with us that actually went very smoothly too, and a bit similar also because it was with that acute cough, we started with that and then so gradually, once you get used to using it, we did use it a lot, yes.
F1P8: Well, I actually also have a bit of the same experience that you have to look at the patient anyway. That is perhaps also because, if I compare with the HAIO. She has, of course, she started as HAIO on 1 October, so she actually started with the presence of a CRP device and I have been working without a CRP device for 20 years. So I do notice that she would immediately follow this up much more and that I have to think about it once, I'll check it, I'll maybe check it once, but I also have the feeling that you know, that, but that you do find out that someone who is very ill can still be relatively low CRP and that you have to make an agreement with the patient that if you become really ill, then you have to get back in touch.
I also notice that in my practice especially the younger doctors used it a lot, albeit I used it the most, I think (everyone laughs). Also because of that diagnostic uncertainty and that the slightly older doctors have used it a little less and gone on their experience earlier.

The frequency of device use varied significantly among doctors. Some used it rarely, others daily, and some up to 7-8 times a day. One participant wondered aloud whether so many tests were performed because the machine was available or because it was genuinely necessary. However, many doctors indicated that they would miss the device if it were no longer available.
And once they got the hang of it, they couldn't stop. I think I called two or three times to say: we need stock again, stock, ... (LAUGHS) when they started using it, it's like everyone else, it takes a while to get going, but when you do, it's 7 or 8 times a day sometimes. It was reassuring, so frankly it was a great project.
What I think is that it's not at all at the beginning, and then too much, and then the right balance comes along. It's a bit like logic: you discover an object, you take a while to use it. Then when you do use it, you use it a bit too much, and then you discover its limits and its advantages, and then you find the right balance, and it's fine after that. I think it took us a while to get started with the ROCHE machine. We were more critical of you (look at Firm 1) because it was the first machine we had. And then, after a while, we got used to it and we got too used to it. And then the last one was perfect. I think it was a bit more like that.
Euh, how that I personally experienced it, euhm, I think I didn't use it very often per se (questioning tone), ma da in the cases that I used it, that I did find it an added value. Hyper-intensive use, so it's always a question of whether we did a lot of tests because there was a machine or because there was a real need to do tests. That's the question we always ask ourselves.

The installation and implementation of the devices was described by almost all doctors as very smooth. If there was an issue, it was quickly resolved by the companies and labs, accessible by phone and email. This prompt support was highly appreciated by the doctors. The most common problems were IT and network issues, connectivity problems between the lab and the device, error messages, the device being too warm or cold, etc. Other participants emphasized that they encountered no technical issues. The lab also provided quality control (QC) supervision and extra materials if needed.
Frankly, those who came were right at home, it was impressive. They came, set up, did things and left. They arrived, they left and apart from the colour of the machine changing. People would say to me "yes, they came, then they left" (LAUGHS). It was magical

MG 4: Firms are very responsive, let's be honest. It's impressive. They have the resources, they have staff who are very responsive. Frankly, I still use a device. When I have a problem, I send an email. I get an answer very quickly. "We're on our way" or frankly, it's...
We had three points of contact. We had the companies' points of contact. I had to call them for small details, to get into the menus and sub-menus, and we got an immediate response. Then there were XX and XX for the LUB, where I think I sent a few messages to help. And then there's your colleague from Roche who looks after the connectors and who was very, very valuable. It's clear that if these machines are going to be there, we need to have these invaluable people with us.
and I have to admit that I found it very reassuring. And if we had a breakdown, we had a telephone number, which I didn't hesitate to use on several occasions. (LAUGHTER)
We never had any problems with any of the devices, only one or two error messages in the beginning. But that was it, so yes, we had no negative experiences with it.
So that way, you spend a lot of time on something that then works in the end and certainly if you have already explained it to the patient and it doesn't work, you see a lot of disappointment (laughs). But yes, that was the main thing, especially that last device, that error message we just couldn't get rid of.
MG 1: Here at home, I think there are still some small logistical, IT and network problems that haven't yet been 100% resolved. Let's just say that once it's ... once it's up and running, we'll be able to do it more easily, I think.

According to a lab representative, too few QC tests were performed, even within the current study framework. For instance, the device could be set to block after a certain number of tests and only become usable again after a QC test. General practitioners confirmed that they did not always perform QCs because it was too much hassle or simply forgotten. Other doctors noted that it took some time getting used to it initially, but once familiar, it was easy to carry out. Some general practitioners delegated QC tests to their practice assistants.
F3P7: Alleja ik snap da he, ultimately those devices t'should actually be made so da you just block the device after x number of term. And that you actually have to carry it out. I don't know to what extent there will be a high QC policy if it's completely independent of the lab. QC products are also really not cheap, for example. You might pay 150 euros for 1 box, but in the end you won't get anything out of it. I think this is also an important, practical point in the implementation.
It's important if we want to guarantee that the doctor can have confidence in the result, that he interprets it, that he has this quality environment around... it's not just a test.
Aloes, in general medicine you have to be aware every time whether the results you get are reliable or not because you've set up this calibration that you tend not to do every time. I've just recommended it here, because I don't have your equipment any more. So I've had to recalibrate and each time I say to myself "tomorrow, tomorrow, tomorrow" and then a patient comes in and we have to do this one again, ... and then, ... but we lose reliability because we don't have the staff that you have, that other laboratories have, the rigour that laboratories have.
Calibrating the machine is not really complicated. You just have to be rigorous enough to do it, but it's so useful on a daily basis that I think you can take the time to do it. It's quick, frankly. After that, you might find it all a bit complicated, but frankly here it's really easy and it helps.
Experiences with the connection between laboratories and the EMR, and with the encoding of CRP results in the EMR, are variable, with some preferring manual encoding of results and others an automatic system in the EMR.

4.2.1.Integration of the CRP-test in the GP's workflow

All doctors agreed that the test is best performed during the consultation, after the clinical examination, but before explaining the diagnosis and treatment.

F3P3: After the clinical examination (two answers at once: also F3P1) and then before you give your explanation. That you say: look, I'm in doubt a bit, I'm going to do that test first, explain a bit about the test, wa da da is right, while you (being interrupted)
F4P2: With me always after the clinical examination, da I did always do the clinic first and then if I had any doubts in that, then indeed ne CRP or if I did not have any doubts before, but had the feeling of the patient is not yet fully along and da would help extra then euhm ma I did always do clinical examination first.
The finger prick blood sampling was done by the doctor or nurse. Some doctors had also occasionally performed a rapid test from a global blood sampling. The result was read by the doctor or relayed by the nurse or secretary. Many doctors did not find the test's waiting time (2 to 3 minutes) disruptive to the consultation. Often, this time was used to explain things to the patient, prescribe other medication, write certificate for work, perform other tests, engage in small talk with the patient, or take a brief moment of rest for the doctor. However, some doctors felt that the waiting time could be shorter. Experience was a key factor in integrating the test smoothly into the consultation. With frequent use, doctors learned the best time to use the test and what to do while waiting.
F4P1: So then he actually does make that I think, all, I think the more da you are also familiar with it to use in your workflow, the easier that integrates into your consultation.
but sometimes also really at a later, at a later time. Uhm, that of course meant that the consultation sometimes dragged on a bit because, of course, the earlier you do it, the more it can fit into your consultation.

By multitasking, most doctors did not feel that the test added extra time to the consultation but rather that the time was integrated into the process. However, a few doctors noted that, despite the test being quick, it still disrupts the consultation due to the need for taking a sample and waiting for the result. Some attributed this disruption to the timing of the test, while others linked it to the device's location or wanting to see results too soon.
I think that even if these tests are extremely fast, interrupting a consultation, taking a sample and waiting for a result, even if it's not very long, is still in.... a busy consultation, it's still time that's wasted in inverted commas. Well, you can always say to the patient: "I'll take a patient and then I'll come and see the result with you" and make them wait in the waiting room. But it's true that in the future things will go faster and faster, but I find that the current time, even if it's short, is a little bit prohibitive.
But indeed ge did your allé, and your tests in the meantime.... Early on I already had to prescribe something else from antibiotics, allé antibiotics, I had to prescribe something else from medication. There are other things though or their attestations for the work you are making. And by then den test is known.
I'll come back to that. I don't think anyone in our group felt that this time was a problem... but that's .... because, well, it's integrated into a discussion time, afterwards with the patient, letting the... In fact, as the machine wasn't in the surgery, we weren't waiting for the result to arrive. We'd run it, talk to the patient, consider other things, do other tests if necessary, and then go and get the result, which we'd pass on. So that didn't pose many problems for us.
F3P2: It goes so smoothly, I never really felt like I had to necessarily wait or anything (several confirm).
Until you take it off and when you offer it and then take it off and know the result, it might take longer than we realise, because you do other things in the meantime.
I don't think anyone in our group felt that this time was a problem... but that's .... because, well, it's integrated into a discussion time, afterwards with the patient, letting the... In fact, as the machine wasn't in the surgery, we weren't waiting for the result to arrive. We'd run it, talk to the patient, consider other things, do other tests if necessary, and then go and get the result, which we'd pass on. So that didn't pose many problems for us.
Basically, five minutes at the most. But with a time that we can also share because the administrative part we do during the administrative part, the sampling part we did during the

examination, the test part we go and look for something, it takes...and we go and look for the result afterwards, it's not five minutes that we have to add to the consultation. It's five minutes that need to be incorporated into a consultation. Sometimes it saves time, when you have to explain afterwards why you didn't give antibiotics, and then you get an immediate answer. Sometimes it requires further explanation. But that's okay, it's all part of the game.

4.2.2. Most Important Factors for Optimal Integration in Workflow

Doctors emphasized that the location of the CRP device plays a crucial role in the test's ease of use. A shared space with the CRP device, where you do not have to disturb other doctors if you wish to perform the test, promotes its use. Also, the environment should have an adequate temperature (not too hot, not too cold) to ensure correct device operation. Some doctors indicated they had some problems, due to the device being in a cold kitchen or under a heater. According to doctors, it is important that the test is as user-friendly as possible, as quick as possible, and requires as little blood as possible. Some doctors also noted that it would be helpful if samples could be preserved longer (up to 2 hours), allowing for processing samples from home visits.

think that each machine, since I've had the opportunity to test all three, has its advantages and disadvantages: the volume of samples taken, the speed or delay between sampling and analysis, which can be a problem, and the environment in which the machine is used.

What you need is a dedicated place, I think, at least when there are several of us, to avoid having to interrupt colleagues and having the machine in a colleague's office. And the dedicated area needs to have a fridge so that we can leave the reagents that we're not using, take them out... make sure that there are always some outside, because if they're, ... if they come out of the fridge straight away, we can't use them and the machine doesn't get cold in the winter, we could make a sort of little incubator for them...

F4P1: I think (being interrupted) I think uhm, ge can be the, the only thing da ge have no influence on of course is. Is the turnaround time of your, of your device he, you can be very fast in taking in and get better at that. But of course never train the device to pass its test faster than it needs time. I think that's an important factor. Because you can, I think you can with any sampling method, if you do it long enough, you'll get better at it I think. (F4P2 talks unintelligibly through it) But of course the turnaround time of the device, you can't really get around that, so I think it's a determining factor in that. Yes especially in a consultation that is sometimes quite clenched in time.

And indeed, the advantage of you being able to keep that for two hours is that we also did it once at home visit and I thought that was an added value.

Yes, I especially liked the speed. If I wanted to know before, I would take a blood test and then you would have to wait five or six hours before you got the result. So yes, in that area anyway.

F3P9: Yes, I can actually agree with that (laughs). A little bit has already been said, but I think also especially the speed, you can link your policies immediately he. Da makes it, yes, does save you a lot of time.

What we found very interesting was having the results immediately. We were talking about Friday evening, but even on Monday evening, we take the sample at 5 p.m., send it to the laboratory, some laboratories may be on the ball, let us know at 9 p.m., and then we have to contact the patient again. It's complicated, but now that we have the information directly, we can also look at the patient's follow-up in a completely different way. So I think it's really very useful.

I think it's the ease of use. We're not lab assistants, so it's true that it has to be easy. Coming back to what I said earlier, I think it's important that it's quick and simple.

4.3. Theme 3: Impact/Consequences: Tool to Support Decision-Making

4.3.1. Interpretation of the (surprising) outcome of the CRP test, leading to co-consulation

Doctors reported that the test results sometimes surprised them in two ways. Sometimes a patient appeared seriously ill, but the CRP-value was very low; other times, they suspected nothing serious, but the CRP-value was very high. Otherwise, they might have probably seen the latter patient again in a few days, but now they could provide immediate assistance. Other times, the test confirmed their gut feeling or intuition, providing reassurance.

We obviously discussed this a lot amongst ourselves. I don't think it only served to reassure us. I think that some therapeutic decisions were made thanks to these tests, decisions that would probably not have been made simply on the basis of a good clinical examination and a good medical history

Yes, possibly, in addition to all the regard? How shall I put it agree it is indeed you sometimes scare in the two sides that you think of okay, this won't be too bad but we'll still check once, because it already takes a bit longer for example and then you have a sky-high CRP. But also vice versa that you have someone with you that you say, he is really sick to death right now and that it's not that bad and thought, okay

On the other hand, in such a very sick patient, where you don't hear anything on the lungs, for example, to be sure that the CRP is not suddenly very high,

when you had a very low CRP, that reassured me

Doctors emphasized that one must be cautious of false reassurance. You should not let the CRP value fully guide your decision. It remains important to observe the patient and trust your intuition, they mentioned.

We shouldn't let it fully guide us, but it is indeed han... (hesitates) All right, it gives you more, or maybe even a reassurance, that you're thinking in the right direction.

Maybe still one afterthought but it's just been, I think, very case-specific. We had a patient who seemed very, very sick, in retrospect probably was very sick. But the CRP actually falsely reassured us at the time. We then measured a CRP of less than three, but unfortunately she was admitted two days later with septic shock with pneumonia on nen influenza so all yes, that was somewhere then, for us it was. But maybe allee I think without that CRP had, it was just for us a bit more of a confirmation of oh no it's really okay, whereas then maybe falsely yes that felt like that. But I think with or without CRP the situation had turned out just the same huh, we wouldn't have done anything differently I don't think, but it got us.... (being interrupted)

But I do have another case that indeed CRP was completely normal on Monday and then two days later he had a CRP of over 200. Yes and he had symptoms for more than 24 hours, so sometimes it can indeed be false reassurance ... (not understood) the exceptions I think.

I, yes, I immediately see a lot of added value as well. And it's true though, you have to keep looking at your patient and even if your test is okay.... Saying if it gets worse then come back.

Yes, the only drawback is roof still, yes in itself always a bit with your delay of course he of CRP. It is sometimes (gasps), all the time, that the clinic is still (laughs) important, of course, and the follow-up, because you can still have a normal CRP at an early stage, and then it goes up anyway. We shouldn't blind ourselves to it or anything, think especially that a bit (people confirm muttering).

Sometimes during the focus groups, discussions or confusion arose about the cut-off values of the CRP test. Some doctors mentioned the NICE guidelines with cut-off values of 20 and 100. Other doctors used different cut-offs. However, the doctors agreed that the test is most useful when the result is either very low or very high. In these cases, the follow-up actions are clear.

F3P5: The NICE guidelines and the the guidelines, the guidelines from the Netherlands for acute cough that already exist that do the cut-off 20 and 100 for adults. Da you say below 20, let's say, viral. Between 20 and 100 deferred antibiotic prescription. And above 100 anyway. But there are no specific guidelines in Belgium today. Da are more the UK, the NICE

guidelines and then the Netherlands guidelines that exist now and are actually being extended a bit to countries like here and dast the reason.
Yes, when I had a CRP of 5 or less, I used to say "it's OK, it's a virus, next week you'll be back in great shape" so...

The challenge arises when the result falls within the grey zone, typically described by the doctors as between 30-60. In such cases, many doctors sought advice from colleagues. In this way, the CRP test stimulated co-consultation and discussion among different doctors, according to the participants. Some participants also described the CRP device as a "meeting place" for the various doctors.
MG 5: What I found interesting was that it prompted a lot of ... counting, co-consulting.
MG 4: what does that mean?
GP 5: Well, in other words, my colleague was doing a test, she had a test that was doubtful between ... she had 27 and still found that the patient wasn't very well, so "can you come and listen?", "give me your opinion?". I found that very interesting.
MG 4: And that's the same medicine, I think. When you start sharing it. And the machine served as a meeting place like a coffee machine in big companies (LAUGHTER). The CRP machine was our coffee machine (LAUGHTER). He'd explain the story to me and frankly, "Don't even take the test! Or "yes, you did", "ha and I'm curious to see the result! And it was very interesting to see that, as he says, what I like about medicine is the co-consultation.
F4P2: Well, talking about it in practice does make us critical. So it is useful to hear from colleagues we are not always there, so I am more careful with that. But it (unintelligible) is just like that if it's a CRP of what should I do here now. But if it's nothing like that it's good, and if it's a lot it's also good. But something between the two is annoying. So somewhere that keeps you thinking about it a bit more, like if I do it, what will it help me with in the end?

4.3.2. Consequences of the Test for GPs and Patients

Besides confirming or disproving the doctor's intuition, the test influenced whether or not to prescribe antibiotics. Some doctors mentioned that the CRP test allowed them to prescribe fewer antibiotics with confidence, even though they initially expected to encounter many high CRP levels, which would lead to more prescriptions. One doctor mentioned that in the past, they might made a delayed antibiotic prescription for the weekend, but now they felt confident enough to make no prescription at all if the CRP was low. When you explain to the patient beforehand that no antibiotics are needed if the CRP is low, it is easier for patients to accept. Doctors reported that the CRP test was well-received by patients. Patients appreciated that an additional test was done and were pleasantly surprised to receive the result immediately, rather than having to wait until the next day.
I think there's a demand from patients too. I think that general medicine has its limits compared to specialist medicine because people say to us, "my doctor, the specialist does this to me, ... he asks for this...". And our profession is completely based on probabilities, on experience, on anamnesis, on the clinic. And there's nothing we can do about it, machines like this must become indispensable
Um, so yes, but also the other way round as my colleague said, uhm it also reassures you a little bit somewhere of uhm there is no infection at all and it's okay and that also helps people to then uhm me go home with a peace of mind or something and also have the feeling of uhm the doctor did the right thing and have no more doubts.
F4P2: Yes, people are fans of it too I have the impression. Euh sure, amai you know that already right now (smile in the background) and uh yes, I notice that they do too, that they find it handy so yes, pro
and I also found it as a starting GP sometimes a bit of a test for my own clinical research, when I heard crepitations or something like that I thought aaaah huh, then I would have started antibiotics earlier without the CRP device and then I sometimes found it interesting to add an extra parameter so objectively.

So that did help me a bit in choosing whether to start antibiotics or not. Uhm, da did make me prescribe less antibiotics especially, da feeling I did.
Certainly if we want to meet our target, targets for antibiotics a little bit and get those prescriptions down. Yes, surely that's a way to do that in a, in a more reassuring way, where both the patient and you yourself are more reassured to say anyway of: look, we're not going to do it. And also vice versa.
and I also found it as a starting GP sometimes a bit of a test for my own clinical research, when I heard crepitations or something like that I thought aaaah huh, then I would have started antibiotics earlier without the CRP device and then I sometimes found it interesting to add an extra parameter so objectively.
But euh yes, it's not that I, because I was afraid I might have high CRP's, so I would start antibiotics sooner, but that wasn't really the case. Sometimes, though, I thought, ow, ah, that's high here, and I still sometimes think that the treshhold above 40, you can still have viral infections I think with 50-60 (everyone confirms) that the clinic still takes precedence, but you can (interrupted
Then in the past I might have tried more quickly once from a deferred prescription. There then now, if that CRP is indeed low, that I just don't make a prescription then lol. So yes. Because I'm more on the patient side, and I find that really reassuring, because we know that a doctor doesn't have absolute knowledge and can't always be sure, not in all cases in any case. So when you're on the patient's side and the doctor's opinion is corroborated by a small CRP, it's extremely reassuring that, yes, you're not going to take antibiotics for nothing. It's... I,... from the patient's point of view, I find it really very interesting.
and that also helps people to then uhm me go home with a peace of mind or something and also have the feeling of uhm the doctor did the right thing and have no more doubts.
So I think it's definitely an extra added value when starting antibiotics, also for your patient, if you explain very clearly beforehand look, if it's low, it's viral, if it's high, it's bacterial and you come back and you say: look, it's low, then they have more confidence in it. Than to say otherwise: no no, you don't need antibiotics. So that's a bonus for them too, I think,
So and the patient also experiences that as very positive that that is also known immediately. That they don't have to wait until the next day for their result, or so they say.
MG 5: I can only answer for myself because we haven't talked about it with colleagues, honestly. Not only that, it was extremely well received by the patients, "Oh, you're going to do a study", but it's not so much the study that's interesting. Here, we have the opportunity to carry out an examination which, in any case, I'll eventually have you do by taking a full blood sample. We'll get the answer straight away: "Is it right for you? I wonder if it wasn't the patients who were sadder than we were to no longer have ... (LAUGHS)
But I think that we, as doctors, forget that there are patients. And the few times we've been patients, we realise the limits of human beings and we don't want the guy in front of me to like me and want to talk to me, I'm happy, but I want to leave in good health. That we don't miss out on anything; sometimes machines do too, not just human beings, but I think the two would make a good couple. Whether it's human beings or machines, it would still stress me sometimes from personal experience.
I also think it has a condition that you give much less delayed antibiotic prescriptions now. I didn't do that much either because I don't believe in it very much. But indeed, if you have someone on Friday. And you have a CRP that's really low and it's not that someone is deathly ill eh, then I think you're less likely to give a deferred prescription than if you don't have a value, if you have to do it on the off-chance.

4.4. Theme 4: Challenges of Large-Scale Implementation: Care About Quality and Support

During the various focus groups, doctors frequently emphasized certain challenges that might arise with large-scale implementation.

The representative stressed that stricter monitoring would be necessary for wider implementation. Maintaining quality controls is difficult depending on the type of practice/GPs, but they agree that they are needed to guarantee the reliability of results, and that a system must be in place to guarantee them.

5. DISCUSSION

This focus group study has several strengths. First, the focus groups were performed according to best practices. The focus groups consisted of seven and five participants respectively, which ensured adequate diversity, a diverse range of opinions and sufficient interaction. The interview guide was discussed with a GP with expertise in qualitative research to optimize the research process. After transcribing the focus groups, coding was done independently by two researchers. They individually performed all qualitative analyses and, subsequently, results were compared, reducing the risk of bias in this process. Also, this qualitative research was reported in line with the COREQ-checklist, which improves transparency, enhances replication possibilities, and increases usability of findings.
Secondly, focus groups can provide in-depth information on a particular topic, allowing researchers to gain a more comprehensive understanding of the attitudes, opinions, and experiences of the participants. This can provide rich and nuanced insights that are difficult to obtain through other research methods such as surveys. We did focus on the implementation of CRP-devices in a particular clinical area, namely adults with acute cough in general practice, which provided a more in-depth analysis of the topic.
Third, focus groups can reveal how people interact with one another and how they respond to different opinions and ideas. This can provide valuable insights into group interactions, non-verbal communication and social dynamics. It can provide additional insights into the research topic and help to contextualise the data. By involving GPs, people from the lab and people from the companies, we gained more insight into the similarities and differences in opinions among the different physician groups.
This study also has some limitations.
In the first place, we limited our study to ambulatory care physicians in the Flemish part of Belgium, using an EMR, so results reported by our study may be less representative of the wider physician population. Our sample size was relatively small (12 physicians) and limited to a subset of the physicians in the country. As a result, this group represents only a small sample of the target group, questioning the generalizability of our findings. Nevertheless, physicians were purposively sampled to obtain variation in clinician characteristics, resulting in a diverse group, which corresponds quite well to the general population of ambulatory physicians in Belgium. Further, participants were partially recruited based on ongoing professional relationships with the research center, which may have resulted in a group of participants that are already interested in CDSS and were therefore more motivated to participate in the focus group (i.e., selection bias). This may influence generalizability of the results, as physicians who are less motivated may have varying preferences regarding the use of the system.
Second, although the interview guide was developed with the input of a GP with research background, it was not pilot tested prior to the initial focus group. Conducting a pilot test of the guide before initiating the actual focus groups can improve its overall quality. On the other hand, this also means that the participants involved in the pilot test cannot participate in the subsequent focus groups anymore. Also, since there were insufficient participants willing to come to Leuven, the second focus group was performed online (Microsoft Teams). This conversation also led to interesting insights, but there was slightly less interaction among the participants and longer monologues were held.
Furthermore, preferences for the use of a CDSS mentioned by the physicians may not accurately reflect their actual preferences, because of biased or inaccurate recollection of

their past experiences or preferences. For example, there may be additional preferences for the use of a CDSS that were not recalled by the physicians (i.e., recall bias).
Moreover, participants in focus groups may be influenced by social desirability bias, which means they may tend to provide socially desirable responses or responses conform to perceived expectations, rather than their true opinions or experiences. Responses that do not accurately reflect their true opinions, can limit the accuracy and validity of the data collected. We tried to minimize this by assuring confidentiality and emphasizing the importance of their true experiences at the beginning of the focus groups.
As a final point, reflexivity is an important concept in qualitative research. In the context of focus group discussions, reflexivity refers to the researcher's ability to reflect on their own biases, assumptions, and values, and how these might affect the way they moderate the discussion, and the way they interpret the data. HD and AD, who designed, performed and moderated the focus group discussions have backgrounds in biomedical sciences which might cause a more analytical way of thinking. Despite having less experience in qualitative research, they tried being mindful of their own biases and assumptions to minimize the impact of these factors and to produce more valid and reliable data.

6. CONCLUSION

The findings revealed that the CRP tests were seen as valuable tools in clinical decision-making, particularly in reducing unnecessary antibiotic prescriptions. The study highlighted the importance of ease of use and proper integration into the clinical workflow for successful implementation.

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WP4. BUDGET IMPACT ANALYSIS

GOAL:
The financial implications of the proposed testing strategy should also be examined through a budgetary impact analysis, as such estimates are a crucial requirement for policy makers before a healthcare technology is widely adopted.

RESULTS:
We have first performed a preliminary budget impact analysis based on previous data from published literature to assess the financial implications of the proposed testing strategy. The final budgetary impact analysis was performed at the end of this pilot project on the basis of the available information from this study and available data from public databases in Belgium on the use of healthcare services at population level.

Report prepared by:
Erinn D'hulster, Salima Azahaf, Margo Van Genechten, Prof. Jan Verbakel, Prof. Jeroen Luyten have significantly contributed to the realization of this report. Data collection was assisted by Tibo Wynant and Thaddee Ding.

1. BACKGROUND

Antimicrobial resistance (AMR) is a natural process in which microorganisms acquire the ability to withstand antimicrobial treatments, such as antibiotics, through genetic mutations following exposure (1,2). In 2018, the World Health Organization (WHO) identified AMR as one of the top ten threats to public health, emphasizing its global prevalence as a major obstacle in treating common infectious diseases (2,3).

The overuse and misuse of antibiotics significantly accelerate the emergence and spread of AMR (2). In primary care, inappropriate prescribing is particularly concerning, with approximately one-third of all antibiotic prescriptions being unnecessary (4). In Belgium, general practitioners (GPs) account for 76.6% of total antibiotic consumption, corresponding to a higher-than-average rate of antibiotic use in the ambulatory sector compared to other European countries (3).

The treatment of patients presenting with acute cough is a leading reason for GP visits, significantly contributing to excessive antibiotic prescribing (5). In many cases, antibiotics are prescribed despite the underlying cause being a self-limiting, uncomplicated infection that would naturally resolve without treatment (6). This inappropriate prescribing not only provides no therapeutic benefit but also poses risks of adverse side effects. According to current guidelines for managing acute cough in adults in the Netherlands, antibiotics should be restricted to patients with confirmed or suspected bacterial pneumonia or those at elevated risk of developing complications (7).

A potential strategy to address inappropriate antibiotic prescribing and limit the spread of AMR is the implementation of C-reactive protein (CRP) point-of-care testing (POCT) in primary care settings (6,8). This approach aims to promote more targeted and evidence-based prescribing practices.

CRP is a biomarker used to assess infection. While CRP levels are typically low (<20 mg/L), they can rise significantly in bacterial infections. The distinct elevation of CRP levels in bacterial versus viral infections can assist GPs in determining whether antibiotic treatment is warranted (6,8,9). Devices have been developed to measure CRP levels at the point of care, offering rapid diagnostic information during consultations. This facilitates prompt medical decision-making without requiring central laboratory testing.

Several studies in primary care settings have demonstrated that CRP POCT is an effective decision support tool for significantly reducing antibiotic prescriptions without compromising patient safety (6,8). The impact of this approach could be further enhanced by providing GPs with communication training, equipping them to clearly explain the rationale behind antibiotic prescribing decisions to patients (8). Such training could help manage patient expectations regarding antibiotics, a factor often contributing to unnecessary prescriptions (10). Given the robust evidence supporting the efficacy of CRP POCT in reducing unnecessary antibiotic use and its successful implementation in other high-income countries, it is reasonable to consider its adoption in the Belgian healthcare context.

Beyond clinical considerations, economic evidence is essential when evaluating the implementation of a new healthcare intervention. A budget impact analysis (BIA) is a valuable tool for this purpose, as it examines the financial implications of introducing the new intervention compared to the existing situation (11). This analysis helps policymakers make informed decisions about the affordability and potential adoption of the intervention (12).

1.1. STUDY OBJECTIVES

The objective of this study is to conduct a BIA to evaluate the feasibility and affordability of integrating CRP POCT into Belgian general practice for patients with acute cough. This evaluation involves establishing a future scenario based on literature and expert opinions as a reference, and comparing it to the current standard of care, under the assumption that CRP testing is not currently included in the Belgian guidelines for treating adults with acute cough.

1.2. REFERENCE SCENARIO

The scenario suggested for the base analysis follows practices seen in other countries that have implemented CRP POCT. It also incorporates recommendations from an expert group that developed a framework for organizing POCT outside of hospitals in Belgium (13). Key aspects of this scenario are illustrated in **Figure 1**.

FIGURE 1: Key assumptions of the reference scenario

- **Application of NHG guideline**: The Dutch NHG guideline for acute cough is adopted within the Belgian context.
- **Service-level agreement**: A service-level agreement between the clinical laboratory and general practice is established, with the laboratory managing all logistical aspects and the installation of the device.
- **Training:** Online e-learning modules on CRP testing and rational antibiotic prescribing are offered as part of the accreditation system in which physicians are required to earn credit points.
- **Phased Implementation**: A gradual rollout over three years is planned to closely align with real-world conditions, with a maximum uptake of 64% in line with the Dutch situation.

FIGURE 1: Key assumptions of the reference scenario

In this established base case scenario, it is assumed that the Dutch NHG guideline on acute cough, which promotes the efficient use of CRP POCT, will be adopted in the Belgian context (7, 14). A summary of this NHG guideline is shown in **Figure 2**. The approach begins with a thorough patient history to assess the patient's condition. For uncomplicated infections, no further tests are performed, and antibiotics are not prescribed. For moderate symptoms with suspected pneumonia—considering factors such as age over 75, comorbidities, fever lasting more than 7 days, or abnormal auscultation (15)—patients are classified as intermediate risk, and a CRP test is conducted to aid in diagnosis. If the CRP level is below 20 mg/L, pneumonia is unlikely, and antibiotics should not be prescribed. Conversely, if the level exceeds 100 mg/L, there is a high probability of pneumonia, justifying antibiotic prescription. For intermediate CRP values, further clinical evaluation is needed, considering whether the patient is at risk for complications. In cases of severe symptoms indicative of pneumonia, antibiotics are prescribed based on established guidelines without additional testing.

To reflect real-world practice more accurately, we acknowledge that some physicians may deviate from this guideline. Based on Dutch experience, we assume that even if the CRP value is below 20 mg/L, some physicians might still prescribe antibiotics (16). We do not consider deviations from the guidelines for CRP values between 20 and 100 mg/L because it is difficult to determine the appropriateness of antibiotic prescribing in this range. Nor do we account for scenarios where deviations from the guidelines might occur if a CRP value above 100 mg/L is measured, as this would imply a non-prescription, which is deemed highly unlikely.

Moreover, as proposed by Van Hoof et al. (13), the reference scenario will adopt a '*Scandinavian model*'. This model involves a service-level agreement between the clinical laboratory and general practice. Under this partnership, the laboratory will manage logistics, including ordering and distributing reagents, monitoring lot numbers, evaluating new lots, ensuring the provision of quality control materials, and installing the device. Additionally, the laboratory will facilitate electronic results transfer, validate test results, provide technical support, and more. This arrangement enables the GP to benefit from the laboratory's existing infrastructure, expertise, and network, including access to contacts with manufacturers and distributors if needed.

Furthermore, each general practice will be equipped with one CRP device. In practices with multiple healthcare providers (e.g., GPs or practice assistants/nurses), the device will be centrally located to ensure accessibility for all relevant staff. According to the service-level agreement, these devices will be provided to GPs without ownership; they will be purchased in bulk at the national level by laboratory services, which will then distribute them to primary care practices on a loan basis.

In this base case scenario, no compensation is provided to GPs for conducting and interpreting CRP tests. The time investment required for administering the test is expected to be largely offset by a reduction in future consultations for acute cough (17). This reduction is anticipated due to the supportive role that CRP POCT can play in educating patients about the self-limiting nature of most respiratory tract infections (RTIs) and the frequent unnecessary use of antibiotics for these conditions.

Training on CRP testing, rational antibiotic prescribing, and communication techniques related to antibiotics will be available online through an e-learning module, as part of the accreditation system requiring GPs to earn a minimum number of credit points by participating in continuing education activities over a specified period. Laboratories will provide certification and, once approved, will manage the installation of devices in practices. To ensure the ongoing clinical effectiveness of CRP POCT in reducing antibiotic prescriptions, refresher training should be provided. The frequency of these refresher sessions should be decided by policymakers.

We anticipate a gradual implementation over three years, as immediate adoption appears unrealistic (18). This phased approach will help manage the substantial initial investment required for equipment and software.

In addition to this reference scenario, we will explore other scenarios to develop comprehensive policy recommendations.

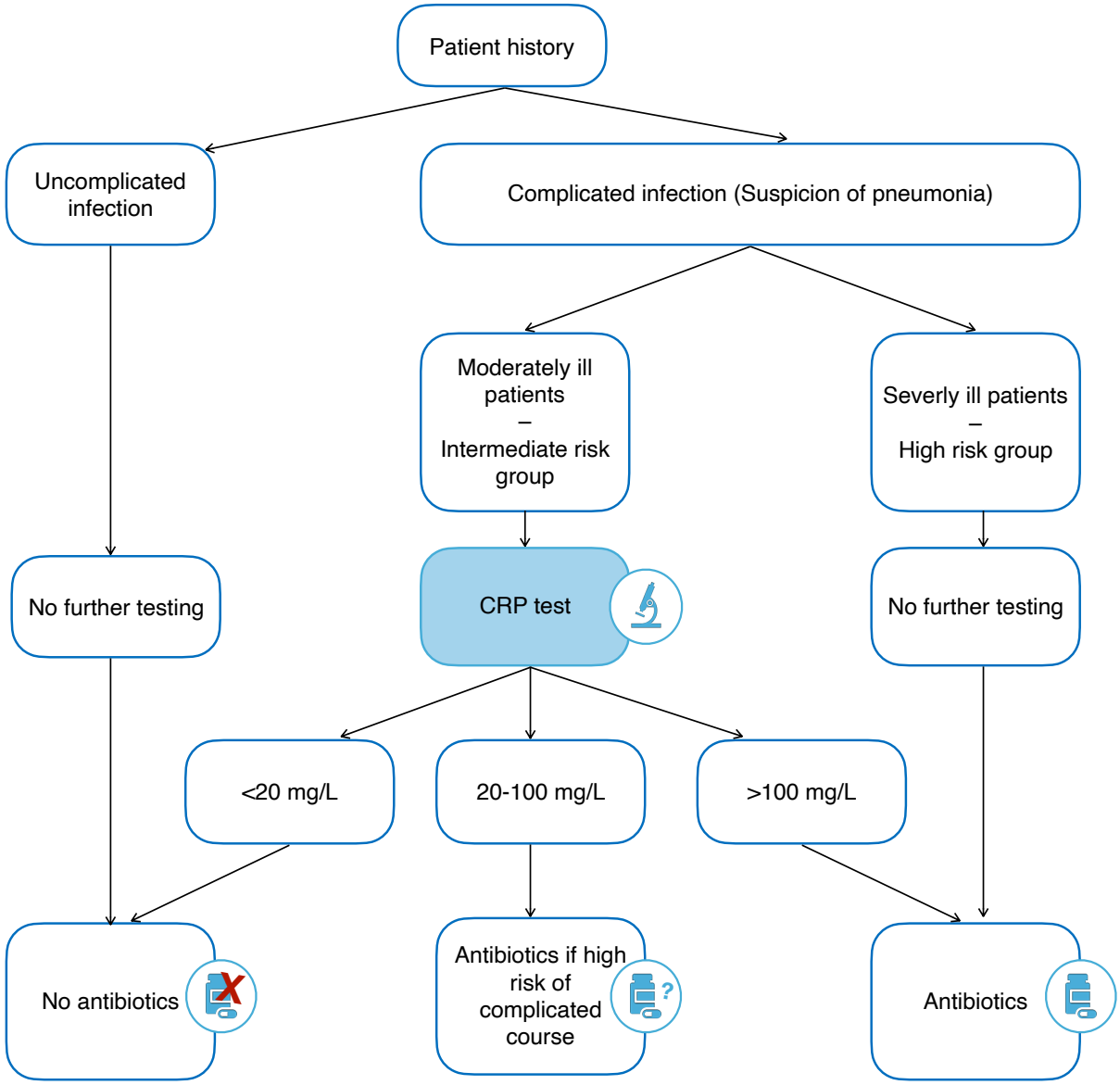

FIGURE 2: Summary Dutch acute cough guidelines

2. METHODS

This study adheres to the guidelines established by the Belgian Health Care Knowledge Centre (KCE) for conducting a BIA (19). A decision tree model is used to estimate the incremental budgetary impact of the CRP POCT intervention compared to usual care. The incremental approach focuses on assessing the additional costs or savings directly attributable to the intervention, relative to the current standard of care.

2.1. SETTING AND TARGET POPULATION

The study focuses on adult patients with acute cough who seek treatment from GPs in Belgium's primary care system.

2.2. STUDY PERSPECTIVE, TIME HORIZON & DISCOUNT RATE

In accordance with KCE guidelines (19), this analysis adopts the perspective of healthcare payers. This perspective includes payments out of the federal government's and the communities' health care budget as well as patients' co-payments. Indirect costs borne outside the health care sector, such as productivity losses and travel expenses, were not considered as these costs are consistent with a broader perspective.

The model utilizes a five-year time horizon to estimate future costs related to the implementation of CRP POCT. A one-year cycle length was applied in the decision tree, with prescribing probabilities assessed during the index consultation. The five-year period corresponds to the usage duration of the CRP device as estimated by experts, although the device's actual lifespan may extend beyond this period. Therefore, this study adopts a conservative approach in evaluating the budgetary impact of CRP POCT implementation.

Discounting reflects the preference for immediate benefits and deferring costs. However, because a BIA concentrates on the actual financial impact of an intervention rather than the present value of future costs, Belgian guidelines advise against applying a discount rate in this type of analysis (19).

2.3. COMPARATOR

The comparator in this analysis is usual care, which entails the management of acute cough in adults by GPs without the routine application of the NHG guidelines including CRP POCT.

2.4. DECISION-ANALYTIC MODEL: DECISION TREE

The decision tree used to calculate the incremental budgetary impact of implementing CRP POCT compared to usual care for adults with acute cough in Belgian primary care is illustrated in **Figure 3**. The decision tree is read from left to right. The blue square represents the decision point between the two strategies. Green circles are probability nodes, representing uncertain events with branches showing possible outcomes and their probabilities. Probabilities of branches emanating from the same node, sum to one. The red triangles are terminal points representing the final outcomes. The vertical line in the decision tree model indicates that the subsequent subtrees follow the same structure and are therefore not shown in detail.

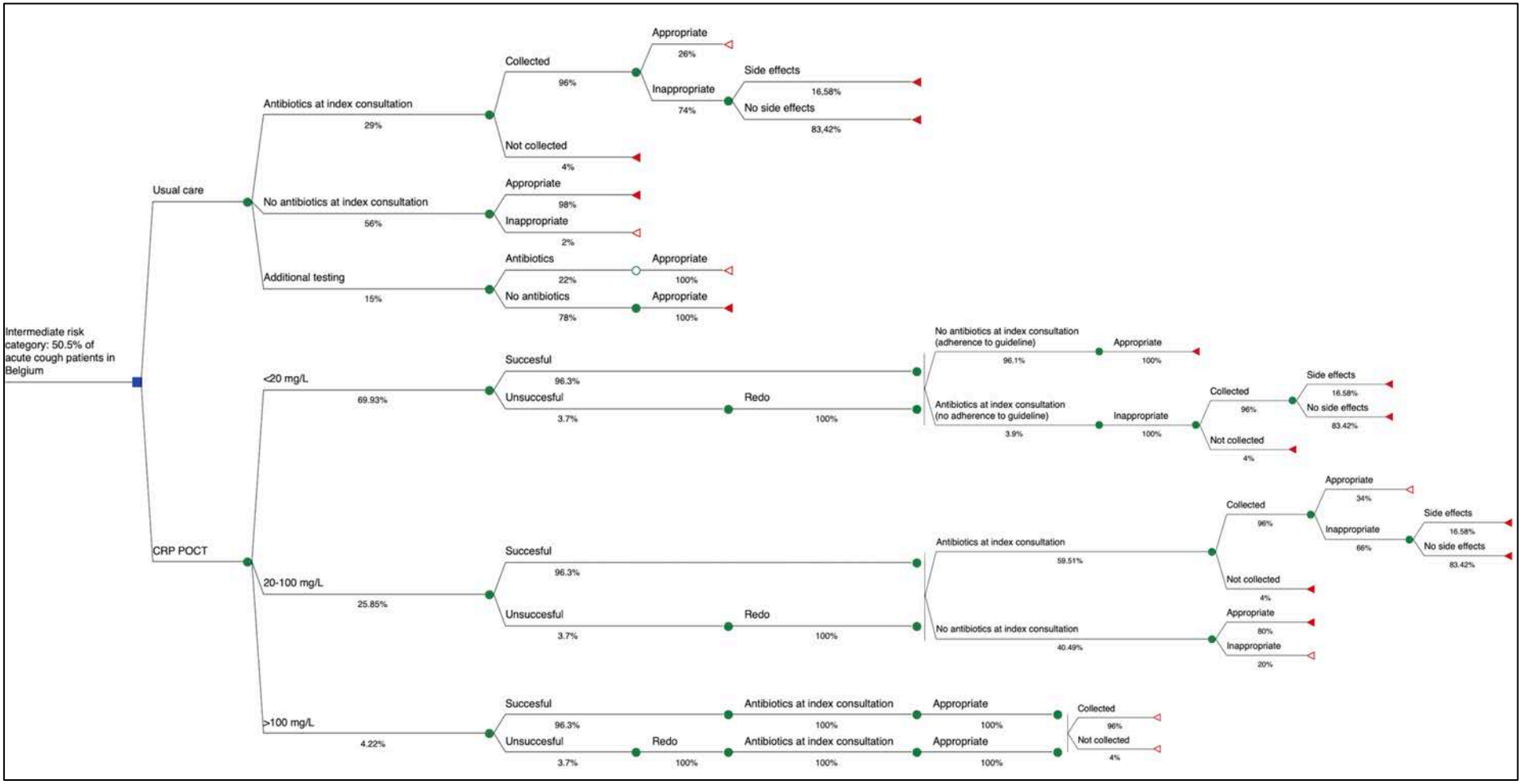

FIGURE 3: Decision tree structure – *CRP POCT (C-reactive protein Point-of-care testing)*

2.4.1. MODEL STRUCTURE

The upper main branch of the model represents the scenario of usual care without CRP POCT, with subsequent pathways stemming from this strategy. In contrast, the lower main branch illustrates the scenario involving CRP testing as per the NHG guidelines.

The decision tree focuses on patients within the intermediate-risk group, as this is the only group recommended for CRP testing according to the NHG guidelines (7, 14) and thus the only group where incremental impact compared to the usual care scenario is anticipated. The intermediate-risk group comprises 50.5% of the total patient population in this study (20). The low- and high-risk groups, which are excluded from the decision tree analysis, account for 31.7% and 17.8% of the total population, respectively (20). Prescription rates for antibiotics in these groups are approximately 21% for the low-risk group and 46% for the high-risk group (20).

The decision tree classifies antibiotic prescribing into two categories: appropriate and inappropriate. Antibiotics are considered appropriate when prescribed for pneumonia. Due to the lower positive predictive value of CRP POCT, it is expected that the use of CRP POCT will not substantially influence the rate of appropriate antibiotic prescribing (21). Additionally, because inappropriate non-prescribing occurs infrequently, no significant impact is anticipated in this category either. Again, following the incremental analysis approach, the focus will be on branches where changes in patient numbers are expected. Given the high negative predictive value of CRP POCT (using a cutoff value of 20 mg/L) (21,22), these branches are where inappropriate prescribing and appropriate non-prescribing might occur. All relevant pathways end in fully filled terminal points (red triangles), while non-relevant pathways end in half-filled terminal points.

Furthermore, the model considers the potential side effects associated with antibiotic prescriptions, distinguishing among acute gastrointestinal symptoms, skin rash, and severe Clostridium difficile infection.

The model also accounts for whether patients actually collect their prescribed medication, acknowledging that having a prescription does not guarantee consumption. No follow-up costs are included for patients who do not pick up their prescriptions, based on the assumption that these individuals are likely recovering autonomously and therefore did not retrieve the medication.

In the usual care scenario, the model accounts for the possibility of further testing, including blood samples for CRP and leukocyte analysis or a chest X-ray. Adopting a conservative approach, if antibiotics are prescribed based on these additional test results, it is assumed that the prescription is appropriate.

In the CRP scenario, again, all pathways of interest conclude at fully filled terminal points, while non-relevant pathways terminate at half-filled ones. In this segment of the tree, the cost of CRP POCT is applied uniformly to all patients, given that each will undergo testing. It is anticipated that a portion of the tests may not be successful on the first attempt—potentially due to factors such as insufficient blood volume or expired cartridges—necessitating a second test. It is further assumed that this subsequent test will always be successful.

As mentioned, the model accounts for imperfect adherence to the NHG guideline by assuming that some physicians may prescribe antibiotics even if the CRP value is below 20 mg/L. Based on Dutch data, we estimate that 3.9% of CRP measurements below this threshold still lead to antibiotic treatment (16).

The model did not simulate the risk of subsequent respiratory tract infections (RTIs) due to insufficient evidence indicating that the risk of further RTIs varies by the initial treatment strategy (17). Moreover, the model's timeframe is too narrow to capture potential reductions in

future RTI consultations; additionally, the evidence on this potential effect remains inconclusive (17).

The model was replicated over five cycles (one cycle per year) in the base case analysis, with all patients modeled simultaneously in each cycle.

2.4.2. MODEL PARAMETERS

- **POPULATION DATA**

The NHG guideline, including CRP POCT, targets the management of acute cough in patients aged 18 years and older, with acute cough defined as lasting up to three weeks (7). To estimate the size of the relevant patient group for this analysis, data from the Intego database (23)—a Flemish general practice registry with weekly data collections—was used, following several key steps.

First, the proportion of initial consultations within a three-week episode for diagnoses where acute cough is a possible symptom was calculated, considering ICPC-2 codes R05, R72, R74, R75, R76, R77, R78, R80, and R81. It was estimated that there are approximately 29 consultations per 100 patients with at least one GP contact annually, where the reason for the consultation may be acute cough.

Given that 80% of the adult Belgian population has at least one GP contact per year (24), this translates to an estimated 2,203,286 relevant consultations annually in Belgium. Of these, 50.5%, or 1,112,659 consultations, are recommended for CRP testing, as these patients fall into the intermediate-risk group according to NHG guidelines (16,20).

Finally, as outlined in the reference scenario, it is assumed that the implementation of the CRP testing strategy will occur gradually, with a cumulative one-third increase each year, and that not all GP practices will ultimately adopt the strategy. Based on Dutch experience, the maximum adoption rate is expected to be 64% (25). This results in approximately 237,367 patients entering the decision tree in year 1, 477,734 in year 2, and 712,102 in years 3, 4, and 5.

- **COST INPUTS**

This analysis focuses exclusively on the costs associated with pathways in the decision tree that are impacted by either the CRP POCT strategy or usual care, in line with the incremental approach. All cost estimates are presented for the reference year 2024, expressed in euros, and are inclusive of VAT. Prices were adjusted using the healthcare index (26).

Opportunity costs, such as those arising from the increased consultation time when conducting CRP POCT, are not included, as this BIA focuses on capturing the actual financial flows within the healthcare system. In line with the study's perspective, indirect costs, such as those related to lost productivity due to illness or absenteeism, are also excluded. The cost components considered in this analysis are summarized in **Table 1** below.

Cost inputs based on the number of patients	Estimate (€)
Cost of inappropriate antibiotics	13.57
Acute gastrointestinal symptoms treatment cost	0.57
Skin rash treatment cost	0.23

Severe clostridium difficile infection treatment cost	2,811.58
Cost of additional testing	20.36
Predicted average yearly AMR cost due to S. pneumoniae (Usual care)	4.595.300.00
Predicted average yearly AMR cost due to S. pneumoniae (CRP POCT) over 5 years	4.359.752,46
Cost inputs based on the number of tests	
Test cartridge	5.25
⇒ Succesful CRP POCT	5.25
⇒ Unsuccesful CRP POCT	10.50
Cost inputs based on the number of devices	
CRP device cost	1,986.00
Transport cost per CRP device	6.00
Cost of initial set-up, including technical training	120.00
Quality control per year	396.00
Validation of test results and incoming batches, along with technical support	60.00

TABLE 1: Cost inputs

Cost of Antibiotics

The BAPCOC Belgian guide for anti-infective treatments in outpatient practice recommends amoxicillin 1 g, taken three times daily for 7 days, as the first-choice treatment for pneumonia (27). This treatment costs the Belgian healthcare system €13.57.

Cost of Side Effects

Given the anticipated reduction in antibiotic use due to CRP POCT, a corresponding decrease in the incidence of side effects associated with antibiotic therapies and their related costs is also expected. This analysis focuses on acute gastrointestinal symptoms, skin rash, and severe Clostridium difficile infections caused by antibiotic intake.

For treating acute diarrhoea caused by antibiotics therapy, the use of probiotics is recommended (28). From the perspective of Belgian healthcare payers, the cost of probiotics is €10.32 (29). Based on expert opinion, probiotics are used in 1-10% of cases. Taking the average of this range, the cost per patient is approximately €0.57.

For skin rash side effects, an antihistamine such as cetirizine is typically administered to relieve itching (30). The cost of a small package of 10 mg cetirizine tablets is €4.14 (31). Again, considering expert opinion that 1-10% of patients use medication for this side effect, the average cost per patient is €0.23.

Lastly, severe Clostridium difficile infections may occur, requiring hospitalization. The associated cost for treatment is €2,811.58 (32).

Cost of Additional Testing (Usual Care)

In the usual care arm, additional testing may be done, either by sending a blood sample to the lab for CRP and leukocyte analysis, which costs €23.11 (33), or by conducting a chest X-ray, which costs €17.61 (33).

Cost of AMR

Ignoring AMR in economic analyses can lead to misleading conclusions, especially in large-scale interventions, due to their substantial indirect clinical and economic effects on resistance levels (34,35). Therefore, accurately assessing the budget impact of such interventions necessitates incorporating AMR considerations. To estimate the cost of AMR, several steps were undertaken.

First, future levels of AMR and antibiotic consumption without any intervention were projected using a methodology employed in a previous study (36). Historical data from the European Centre for Disease Prevention and Control (ECDC) database was utilized for this purpose (37,38). Forecasting was carried out with an Exponential Smoothing (ETS) model with an additive damped trend in RStudio (39). To mitigate the impact of COVID-19, the forecast was based on data from 2005 to 2019. The projections for 2024 to 2028 are visualized in **Figures 4** and **5**.

To estimate the cost impact of rising AMR levels, it was assumed that 8% of AMR in Belgium is attributable to resistance in *Streptococcus pneumoniae* (40). Based on an estimated cost of AMR in Belgium of €24 million in 2019 (1), the cost attributed to *S. pneumoniae* resistance was calculated to be €1.92 million in 2019. Assuming a linear relationship between AMR levels and costs, this would amount to €3.8 million by 2024, according to the forecasts.

With the implementation of CRP POCT, a reduction in antibiotic consumption and, consequently, in AMR is anticipated. To evaluate this impact, we calculated elasticity, which measures the responsiveness of AMR to changes in antibiotic consumption. Specifically, it quantifies the percentage change in AMR resulting from a one-percent change in antibiotic consumption. To estimate this elasticity, we used a panel dataset from all available countries in the ECDC database for the same period. Elasticity was determined through Ordinary Least Squares regression analysis, and the midpoint elasticity e was computed using the formula:

$$e = \frac{\frac{R_2 - R_1}{(R_2 + R_1)/2}\ x\ 100}{\frac{C_2 - C_1}{(C_2 + C_1)/2}\ x\ 100}$$

In this formula, R_1 and R_2 represent the AMR levels at two specific points, while C_1 and C_2 represent the corresponding levels of antibiotic consumption.

For the intermediate risk group, a 23% decrease in antibiotic prescriptions is expected (6). Given that this group represents 50.5% of the relevant patient population, with 64% of all GPs expected to adopt the intervention and 76.6% of prescriptions occurring in primary care (3,20,25), a total decrease of 5.7% in broad-spectrum penicillin consumption is anticipated.

With an elasticity of 0.8744 and a corresponding AMR decrease of 4.98% compared to the usual care scenario, the forecasted AMR costs associated with resistance in *S. pneumoniae* for the period 2024-2028 are presented in **Table 2** and **Table 3**. These tables compare the usual care scenario with the scenario of implementating of the NHG guideline.

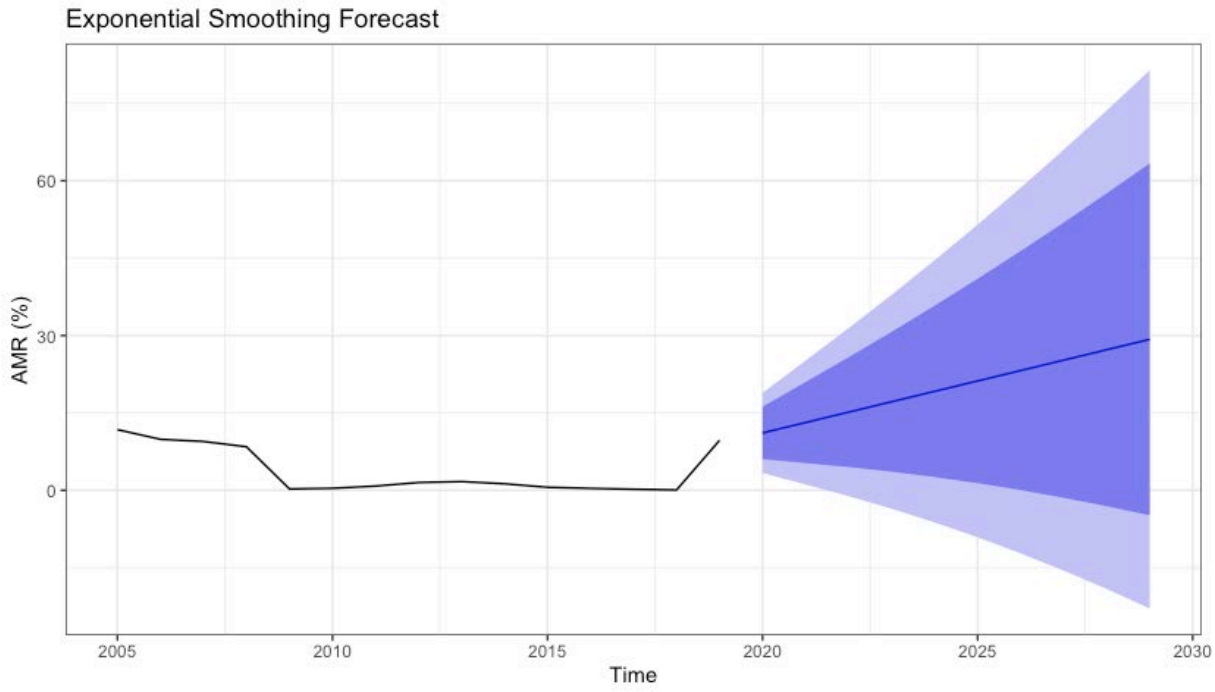

FIGURE 4: Exponential smoothing forecast AMR levels Belgium

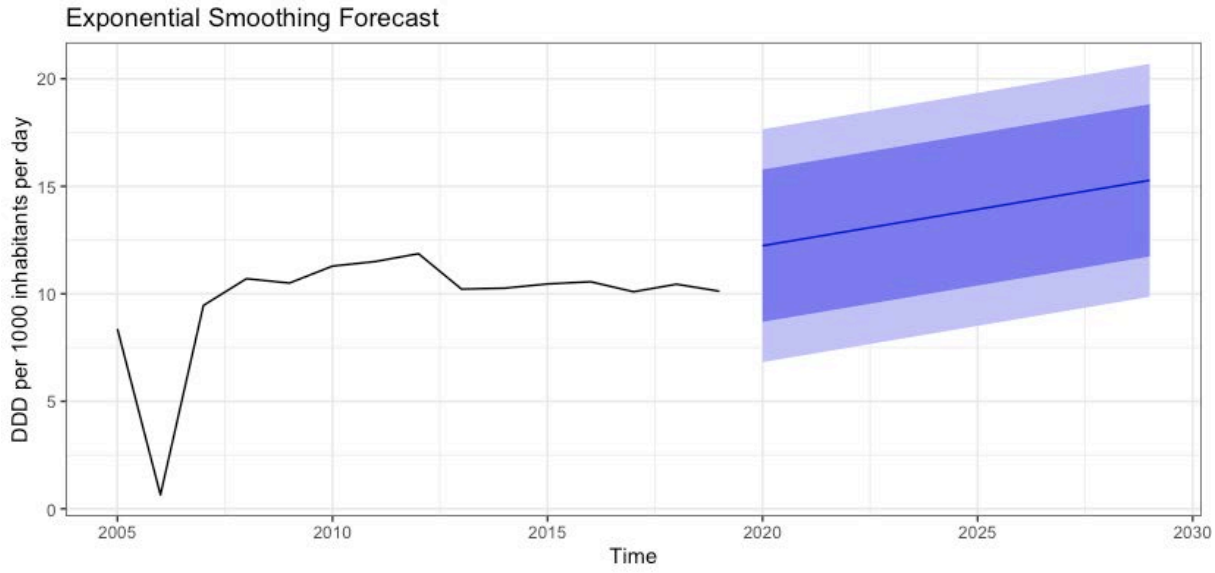

FIGURE 5: Exponential smoothing forecast antibiotics consumption levels Belgium

The dark purple line represents the mean point estimate, while the surrounding shaded areas indicate the uncertainty, calculated using the `forecast` package in R. This package estimates uncertainty by analyzing the forecasting errors from the ETS model. It then computes the conditional variance of future values, with uncertainty increasing as the forecast horizon extends. This variance is used to generate prediction intervals, reflecting the expected range of future values. These intervals are displayed as shaded areas in the graph, with wider margins indicating greater uncertainty in the predictions.

	Consumption of broad-spectrum penicillin *DDD per 1000 inhabitants per day*	**AMR S. Pneumoniae** *Isolates (%)*	Cost of AMR (€)
2024	13.59	19.18	3,800,000.00
2025	13.93	21.19	4,197,650.00
2026	14.26	23.21	4,595,300.00
2027	14.60	25.22	4,992,950.00
2028	14.94	27.24	5,390,600.00

TABLE 2: Forecasts of broad-spectrum penicillin consumption and AMR levels (Usual care)

	Consumption of broad-spectrum penicillin *DDD per 1000 inhabitants per day*	**AMR S. Pneumoniae** *Isolates (%)*	Cost of AMR (€)
2024	12.81	18.23	3,611,113.02
2025	13.13	20.13	3,985,432.74
2026	13.45	22.04	4,359,752.46
2027	13.76	23.94	4,734,072.18
2028	14.08	25.85	5,108,391.90

TABLE 3: Forecasts of broad-spectrum penicillin consumption and AMR levels (NHG guideline)

Cost of CRP POCT

The costs associated with CRP POCT encompass both variable costs, which fluctuate with the number of tests conducted, and fixed investment costs related to each device.

For fixed costs, the estimate for each CRP POCT device is based on the number of accredited general practices in Belgium, which totals 6,624 as of 2024 according to IMA Atlas (41). Costs related to laboratories are based on 194 labs in Belgium (42). Costs per GP are based on the 13,980 active GPs in Belgium affiliated with accredited practices as reported by RIZIV, excluding trainees (43).

Similar to practices, we anticipate a maximum adoption rate of 64% for both laboratories and individual GPs, applied gradually.

Cartridge costs are based on catalog prices from three manufacturers involved in this project: Aidian® (Finland), Roche® Diagnostics (Switzerland), and Abbott® Laboratories (USA), with an unweighted average price of €5.25 per cartridge. For tests that fail on the first attempt and require a second cartridge, the total cost is €10.50. No additional cost is allocated for the delivery of cassettes, as this can be included with regular transport activities, and thus does not incur extra expenses.

The cost of quality assessment for CRP POCT is based on monthly testing for both high and low values. This requires two control fluid flacons and two cartridges, resulting in an

estimated monthly cost of €33.00. This estimate might be an overestimation, as it does not account for the possibility of reusing control vials after opening or sharing them among different practices to reduce costs, due to the logistical challenges associated with these options.

No reimbursement is included for performing these quality checks in the reference scenario, as this task is typically carried out by staff within the general practice.

Quality control can be either internal, with solutions provided by the manufacturer, or external, with solutions provided by an independent third party. It is assumed that a combination of these methods will be used, but the costs are considered equivalent in this analysis.

Additional costs include those for device installation, transportation, validation of test results, technical support from the laboratory, and lot validation.

In the reference scenario, CRP POCT training is integrated into the accreditation system and does not include monetary compensation (only credit points). The development cost of an online training module for this could not be determined and is not included in this analysis.

Furthermore, costs associated with the administrative and governance structure of the CRP POCT program are not included either. No clear structure or cost estimates for these activities could be identified.

- **PROBABILITY INPUTS**

The probabilities incorporated into the decision tree were derived from the Intego database, relevant literature, and data gathered specifically for this project (23). Estimates for these probability inputs, along with their sources, are provided in **Table 4**.

Parameter	Estimate (%)
General probabilities	
Estimated adoption rate of CRP POCT	64.00
Prevalence of patients with acute cough in Belgian practices	29.00
Antibiotics collected	96.00
Proportion of patients with acute cough classified as moderate risk	50.50
Acute gastrointestinal symptoms	10.00
Skin rash	6.67
Severe Clostridium Difficile infection	0.75
Proportion of patients receiving antibiotics at first consultation (usual care)	29.00
Inappropriate prescriptions of antibiotics (usual care)	74.00
Additional testing requested at first consultation (usual care)	15.00
Failure rate of tests	3.70
Test results <20 mg/l	69.93

Test results 20-100 mg/l	25.85
Test results >100 mg/l	4.22
Antibiotic prescription for 20-100 mg/l	59.51
Proportion of patients with CRP <20 mg/L still receiving antibiotics	3.90
Inappropriate prescriptions of antibiotics (CRP POCT)	66.00

TABLE 4: Probability inputs

In the usual care scenario, data from the Intego database indicate that antibiotics are prescribed at the initial consultation in 24% of cases (23). By applying the ratio between the prescription rates for the intermediate-risk group and the overall prescription rate (37/31) reported by Minnaard et al. (15), the prescription rate for the intermediate-risk group in the Belgian context is estimated to be 29%. Of these prescriptions, 74% are considered inappropriate (44). Additionally, in 15% of consultations within the usual care scenario, additional testing is done (23).

In the NHG guidelines scenario, the probabilities for the test result categories are set at 69.93% for values below 20 mg/L, 25.85% for values between 20 and 100 mg/L, and 4.22% for values exceeding 100 mg/L (15). Additionally, it is assumed that 3.9% of CRP values below 20 mg/L still result in an antibiotic prescription (16). Based on a relative risk of 0.77 for prescribing with CRP testing compared to usual care, as reported in a recent Cochrane review, the prescription rate for the group with CRP values between 20 and 100 mg/L is estimated to be 59.51% (6). The appropriateness of these prescriptions is evaluated based on the redistribution of patients from the usual care scenario and the assumed appropriateness of prescriptions for test results less than 20 mg/L and greater than 100 mg/L. Consequently, it is assumed that 21% of prescriptions for intermediate test results are appropriate.

Additionally, it is assumed that 3.7% of CRP tests must be redone due to initial errors, such as insufficient blood in the capillary or the use of expired cartridges. This figure reflects the error rate observed in this project.

Finally, both strategies compared—usual care and CRP POCT—consider potential side effects from antibiotic consumption and the fact that not all patients prescribed antibiotics actually consume them. The decision tree includes the following probabilities for side effects: acute gastrointestinal symptoms occur in 10% of cases (45), skin rash in 6.7% of cases (45), and severe Clostridium difficile infection in 0.75% of cases (46).

The proportion of patients who do take the prescribed antibiotics is estimated at 96%, based on Spurling et al. (47)

2.4.3 SENSITIVITY ANALYIS

To ensure the robustness of the results in response to variations in input data, different types of sensitivity analyses were conducted.

- **UNIVARIATE SENSITIVITY ANALYSIS**

Univariate sensitivity analysis was performed to evaluate the effect of uncertainty in each individual parameter on the overall results. This deterministic sensitivity analysis involved varying each parameter to the extremes of its defined range while keeping all other parameters fixed at their baseline values.

For this analysis, input parameter ranges were determined by applying a ±20% interval to most estimates. Certain parameters had tailored intervals: for cartridge costs, the range was set between €4.00 and €6.50, reflecting the lowest and highest catalogue prices identified. For devices, the interval spanned from €1,390.00 to €3,250.00, also corresponding to the lowest and highest catalogue prices for the different devices in this project.

The outcomes of the univariate sensitivity analysis are presented in a Tornado diagram.

- **PROBABILISTIC SENSITIVITY ANALYSIS: MONTE CARLO SIMULATION**

In accordance with KCE guidelines, a probabilistic model with 10,000 iterations was employed to account for uncertainty in the model parameters. The parameters were varied simultaneously throughout the simulations, according to predefined probability distributions. For these probability distributions, the ranges from the univariate sensitivity analysis were utilized as uniform distributions.

The results of the probabilistic sensitivity analysis are presented as the mean budget impact along with the 95% credibility interval.

- **SCENARIO ANALYSIS**

In addition to the reference scenario, we explored alternative organizational models and assessed their impact on the overall incremental cost of implementation over the specified time horizon. The following scenarios were considered:

SCENARIO ANALYSIS

Scenario 1: On-site monthly quality control by laboratory staff

In the focus groups conducted as part of this project (Work Package 3), some physicians expressed reluctance to perform routine quality control checks themselves. Therefore, we have included a scenario in which a laboratory staff member conducts these checks on-site each month. It is estimated that this task will require approximately 15 minutes per practice, at an hourly rate of €60.00, resulting in a monthly cost of €15.00 per practice, or €180.00 annually. We have not accounted for additional travel costs, as it is assumed that this visit can be combined with other routine visits, such as sample collection or delivery of materials.

Scenario 2: GP fee-for-service compensation for testing and interpretation

In this scenario, GPs receive a fee-for-service compensation of €8.72 per CRP test conducted and interpreted, based on compensation rates for PCR tests during the COVID-19 pandemic (33). This fee-for-service model may potentially lead to overuse of the tests.

Scenario 3: Compensation through practice premium

In this scenario, physicians who use the device are compensated through a flat-rate model via '*de geïntegreerde praktijkpremie*'—a fixed annual amount provided to GPs to support their practice and the use of electronic services (48)—instead of a fee-per-item model. As of 2024, the practice premium amounts to €6,000.00 based on eight criteria. We assume that, proportionally, an additional €750.00 would be allocated for a ninth criterion (the use of the CRP POCT device), resulting in a total practice premium of €6,750.00 per year per GP.

SCENARIO ANALYSIS

Scenario 4: On-site training by laboratory staff

In this scenario, clinical training on CRP POCT, communication techniques, and appropriate antibiotic prescribing is provided on-site by laboratory staff, instead of through a centralized e-learning module as proposed in the reference scenario. This training is assumed to be conducted concurrently with the installation and technical explanation of the device. Furthermore, it is assumed that the training necessitates a dedicated visit, which incurs separate transportation costs because it cannot be combined with routine tasks, such as sample collection, due to the need to schedule the training session when the GPs are available. A total of 3 hours is allocated for clinical and technical training, as well as device installation, at a rate of €60.00 per hour, resulting in a total cost of €180.00 per device. As in the reference scenario, refresher training is provided within the 5-year period. This one-hour refresher training will also be conducted on-site by a laboratory staff member. The cost for this refresher training is estimated at €60.00 for the session, plus an additional €6.00 to cover transportation expenses.

Scenario 5: Device per individual GPs

In this scenario, a CRP testing device is provided to individual active GPs in Belgium, excluding GPs in training ("HAIOs"). As of 2022, there are 13,980 active GPs in Belgium affiliated with accredited practices (43). With an anticipated maximum uptake rate of 64%, devices will be gradually distributed to approximately 8,947 GPs over a period of three years.

Scenario 6: Traceability of patient results

In this scenario, we analyze the incremental costs associated with implementing an IT system designed to ensure the connectivity and traceability of CRP POCT results. This involves equipping each CRP device with cloud technology, with an estimated annual recurrent cost of €1,000 per device.

Additionally, middleware, which is central laboratory software intended to maintain connectivity within the lab, may also be utilized. However, because this middleware can serve multiple types of devices beyond CRP devices and accurately allocating its costs to CRP devices was not feasible within the scope of this project, this scenario is limited to the costs associated with the cloud solution that supports data transfer in the context of general practice.

3. RESULTS

3.1. REFERENCE SCENARIO

Based on the decision tree, we calculated the relevant variable costs in both main arms of the analysis. A detailed breakdown of these calculations is provided below. **Table 6** presents the total incremental costs of implementing CRP POCT over a five-year period.

Total variable costs are calculated for each cost parameter by multiplying the number of patients by the respective probabilities and unit costs. The probabilities are calculated by multiplying the probabilities from the decision tree structure (**Figure 3**) at each decision node along the pathway, from the initial decision point to the terminal outcome. The model includes a total of 712,102 patients. These patients are gradually introduced into the model according to an incremental rate of 33.33% per year. By year 3, the full cohort of 712,102 patients enters the model each year. Therefore, the variable costs for years 3 to 5 are identical on a per-year basis.

Cost parameters	Patients	Probability	Cost (€)	Total (€)
Usual Care				
Year 1				
Inappropriate antibiotics	712,102	33.33%*29%*74%*96%	13.57	663,526.57
Acute gastrointestinal symptoms	712,102	33.33%*29%*74%*96%*10%	0.57	2,787.10
Skin rash	712,102	33.33%*29%*74%*6.67%*96%	0.23	750.12
Severe Clostridium Difficile infection	712,102	33.33%*29%*74%*0.75%*96%	2811.58	1,031,074.81
Cost of additional testing	712,102	33.33%*15%	20.36	724,847.34
Year 2				
Inappropriate antibiotics	712,102	(2*33.33%)*29%*74%*96%	13.57	1,327,053.14
Acute gastrointestinal symptoms	712,102	(2*33.33%)*29%*74%*10%*96%	0.57	5,574.21
Skin rash	712,102	(2*33.33%)*29%*74%*6.67%*96%	0.23	1,500.24
Severe Clostridium Difficile infection	712,102	(2*33.33%)*29%*74%*0.75%*96%	2811.58	2,062,149.63
Cost of additional testing	712,102	(2*33.33%)*15%	20.36	1,449,694.69
Years 3-5				
Inappropriate antibiotics	712,102	29%*74%*96%	13.57	1,990,778.78
Acute gastrointestinal symptoms	712,102	29%*74%*10%*96%	0.57	8,362.15
Skin rash	712,102	29%*74%*6.67%*96%	0.23	2,250.59
Severe Clostridium Difficile infection	712,102	29%*74%*0.75%*96%	2811.58	3,093,533.80
Cost of additional testing	712,102	15%	20.36	2,174,759.51
CRP testing				
Year 1				
Inappropriate antibiotics	712,102	(33.33%*25.85%*59.51%*66%*96%) + (33.33%*69.93%*3.9%*96%)	13.57	401,176.55

Acute gastrointestinal symptoms	712,102	(33.33%*25.85%*59.51%*66%*10%*96%) + (33.33%*69.93*3.9%*10%*96%)	0.57	1,672.82
Skin rash	712,102	(33.33%*25.85%*59.51%*66%*6.67%*96%) + (33.33%*69.93%*3.9%*6.67%*96%)	0.23	450.22
Severe Clostridium Difficile infection	712,102	(33.33%*25.85%*59.51%*66%*0.75%*96%) + (33.33%*69.93%*3.9%*0.75%*96%)	2,811.58	618,850.10
Cost CRP POCT	712,102	33.33%*96.3%	5.25	1,199,949.89
	712,102	33.33%*3.7%	10.5	92,207.99
Year 2				
Inappropriate antibiotics	712,102	[(2*33.33%)*25.85%*59.51%*66%*96%] + [(2*33.33%)*69.93%*3.9%*96%]	13.57	803,523.09
Acute gastrointestinal symptoms	712,102	[(2*33.33%)*25.85%*59.51%*66%*10%* 96%] + [(2*33.33%)*69.93%*3.9%*10%*96%]	0.57	3,345.64
Skin rash	712,102	[(2*33.33%)*25.85%*59.51%*66%*6.67%* 96%] + [(2*33.33%)*69.93%*3.9%*6.67%*96%]	0.23	900.45
Severe clostridium difficile infection	712,102	[(2*33.33%)*25.85%*59.51%*66%*0.75%* 96%] + [(2*33.33%)*69.93%*3.9%*0.75%*96%]	2,811.58	1,237,700.20
Cost CRP POCT	712,102	(2*33.33%)*96.3%	5.25	2,399,899.78
	712,102	(2*33.33%)*3.7%	10.5	184,415.97
Years 3-5				
Inappropriate antibiotics	712,102	(25.85%*59.51%*66%*96%) + (69.93%*3.9%*96%)	13.57	1,205,405.18
Acute gastrointestinal symptoms	712,102	(25.85%*59.51%*66%*10%*96%) + (69.93%*3.9%*10%*96%)	0.57	5,018.95
Skin rash	712,102	(25.85%*59.51%*66%*6.67%*96%) + (69.93%*3.9%*6.67%*96%)	0.23	1,350.80
Severe clostridium difficile infection	712,102	(25.85%*59.51%*66%*0.75%*96%) + (69.93%*3.9%*0.75%*96%)	2,811.58	1,856,735.97
Cost CRP POCT	712,102	96.3%	5.25	3,600,209.69
	712,102	3.7%	10.5	276,651.63

TABLE 5: Detailed calculations of variable costs for Usual care and CRP POCT

Cost components	CRP POCT (€)	Usual care (€)	Incremental cost (€)
Incremental impact in year 1			**3,492,126.21**
CRP device	2,806,368.42		2,806,368.42

Transport CRP device	8,478.45	0.00	8,478.45
Initial set-up, installation and training	169,569.09	0.00	169,569.09
Validation of test results and incoming batches, along with technical support	119,181.68	0.00	119,181.68
Quality control	559,577.99	0.00	559,577.99
Cost of AMR	1,203,583.97	1,266,540.00	-62,956.03
Cost of CRP POCT	1,292,157.94	0.00	1,292,157.94
Cost of inappropriate antibiotics	401,761.57	663,526.60	-261,765.04
Cost of S.E.	620,973.17	1,034,612.09	-413.638.92
Cost of additional testing	0.00	724,847.38	-724,847.38
Incremental impact in year 2			**3,984,284.49**
CRP device	2,806,368.42	0.00	2,806,368.42
Transport CRP device	8,478.45	0.00	8,478.45
Initial set-up, installation and training	169,569.09	0.00	169,569.09
Validation of test results and incoming batches, along with technical support	238,363.36	0.00	238,363.36
Quality control	1,119,155.99	0.00	1,119,155.99
Cost of AMR	2,656,955.16	2,798,433.33	-141,464.03
Cost of CRP POCT	2,584,315.88	0.00	2,584,315.88
Cost of inappropriate antibiotics	803,523.13	1,327,053.20	-523,530.07
Cost of S.E.	1,241,946.34	2,069,224.19	-827,277.84
Cost of additional testing	0.00	1,449,694.76	-1,449,694.76
Incremental impact in year 3			**4,461,038.46**
Incremental impact in year 4			**1,453,292.22**
Incremental impact in year 5			**1,429,961.94**
CRP device	2,806,368.42	0.00	2,806,368.42
Transport CRP device	8,478.45	0.00	8,478.45
Initial set-up, installation and training	169,569.09	0.00	169,569.09
Validation of test results and incoming batches, along with technical support	357,580.80	0.00	357,580.80
Quality control	1,678,901.87	0.00	1,678,901.87

mCost of AMR in year 3	4,359,752.46	4,595,300.00	-235,547,54
Cost of AMR in year 4	4,734,072.18	4,992,950.00	-258,877,82
Cost of AMR in year 5	5,108,391.90	5,390,600.00	-282,208,10
Cost of CRP POCT	3,876,861.51	0.00	3,876,861.51
Cost of inappropriate antibiotics	1,205,405.24	1,990,778.88	-785,373.65
Cost of S.E.	1,863,105.82	3,104,146.69	-1,241,040.87
Cost of additional testing	0.00	2,174,759.62	-2,174,759.62
Total incremental budget impact			**14,820,703.32**

TABLE 6: Total incremental costs of implementing CRP POCT over a five-year period

3.2. SCENARIO ANALYSIS

Scenario	Description	Total budget impact (€)	Difference with reference scenario (€)
1	On-site monthly quality control by laboratory staff	17,873,175.86	3,052,472.54
2	GP fee-for-service compensation for testing and interpretation	39,658,201.35	24,837,498.03
3	Compensation through practice premium	41,661,632.28	26,840,928.96
4	On-site clinical training by laboratory staff	15,354,950.05	534,246.73
5	Device per individual GPs	24,168,960.35	9,348,257.03
6	Traceability of patient results	31,779,308.06	16,958,604.74

TABLE 7: Five-year budget impact of the different scenarios

3.3. UNIVARIATE SENSITIVITY ANALYSIS

The Tornado diagram in **Figure 6** illustrates the results of the univariate sensitivity analysis, highlighting that the prescription rate of antibiotics in the usual care scenario exerts the greatest influence on costs, with potential variations in the five-year budget impact of up to €4.50 million more at the lower bound (if fewer antibiotics are prescribed) and a decrease of approximately €4 million at the upper bound. The next most significant impact comes from variations in the CRP device cost, followed by the cost per CRP POCT and the adoption rate. Additionally, the number of patients undergoing additional testing, and the associated costs also have a considerable influence the five-year budget impact. In contrast, fluctuations in the cost of initial set-up of the devices and technical training, as well as the failure rate of tests, have the least effect on overall cost variation.

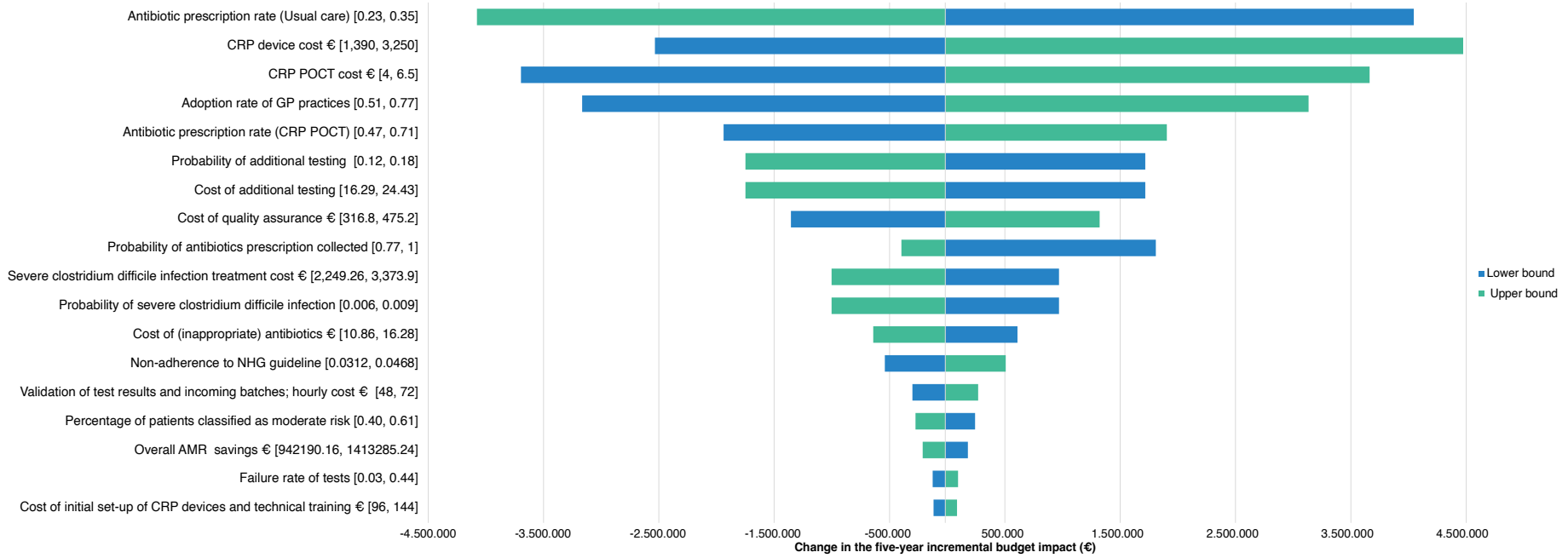

FIGURE 6: Tornado diagram

3.4. PROBABILISTIC SENSITIVITY ANALYSIS

The results of the Monte Carlo simulation (10,000 iterations) yielded a mean budget impact of €14,793,522.80, with a 95% credibility interval ranging from €14,679,879.98 to €14,907,165.61. The narrowness of this interval demonstrates the robustness of the results.`

4. DISCUSSION

The aim of this analysis was to calculate the budgetary impact over a 5-year time horizon for an implementation of CRP rapid tests in Belgian general practice. The analysis showed that this budgetary impact over 5 years amounts to € 14,820,703.32 in the reference scenario.

Different scenarios were considered in the analysis. The budgetary implications of on-site monthly quality control by laboratory staff were calculated, prompted by feedback from physicians in focus groups conducted as part of Work Package 3 of this project, who expressed reluctance to perform quality control themselves. Moreover, the analysis examined the effects of different financing models. Beyond the financial implications, it is crucial for decision-makers to consider how the selected financing system may influence both overutilization and underutilization. Finally, the analysis assessed the impact of varying the number of devices and the influence of installing connectivity and traceability systems to provide a comprehensive understanding of the budgetary impact.

The findings of this study are subject to several limitations that should be considered when interpreting the results.

First, the potential growth of the patient population over time was not accounted for, given the relatively short timeframe of 5 years, despite KCE guidelines recommending this. This omission may have led to an underestimation of the total incremental costs.

Secondly, an incremental approach was adopted for reasons of efficiency. By focusing on areas where an impact from CRP POCT was anticipated, other associated costs might have been overlooked. For instance, the analysis primarily considered the impact on the index consultation, potentially neglecting longer-term effects. It was assumed that CRP would be used only once, whereas CRP POCT could be used multiple times during a single illness episode to monitor CRP levels. Additionally, the potential use of CRP POCT for other indications beyond acute cough or in different patient populations, such as children, was excluded, which might lead to an underestimation of its positive impact.

Thirdly, the analysis considered only costs related to CRP POCT, without accounting for other factors necessary to ensure a successful implementation. These factors might include conducting a public awareness campaign to inform patients about the reasons for CRP POCT and its potential benefits at both the individual and societal levels. Additionally, CRP POCT is most effective in reducing antibiotic prescriptions when integrated within a broader set of initiatives aimed at tackling AMR, which were not addressed in this analysis either.

The accuracy of estimates for certain cost parameters in this study could also be improved. For instance, the number of GP practices was estimated based on available information from IMA Atlas, but this remains an approximation. Additionally, the estimate of AMR costs is inherently uncertain, as it was derived from an OLS regression model assuming a linear relationship between AMR and antibiotic consumption, whereas the real situation is more complex, involving non-linear effects and delays. Furthermore, the estimate of AMR costs is based on data that encompasses a broader healthcare context, as specific data for primary care settings is limited and the complexity of AMR makes it challenging to isolate these costs within first-line care. Additionally, catalog prices were used in the analysis, whereas policymakers might be able to negotiate lower prices. This could lead to an overestimation of the budgetary impact.

The assumption of a maximum uptake rate of 64% has a substantial impact on the final results. However, this estimate is highly uncertain and dependent on various factors, including the potential reimbursement rate for administering the test. This uptake rate was analogously applied to the number of laboratories, assuming that larger laboratories are more likely to adopt the test, while smaller laboratories might encounter higher initial costs that could impede their adoption. This assumption for laboratories is also highly uncertain and contributes to the overall uncertainty of our analysis.

Finally, the distribution of costs among different healthcare payers was not analyzed. This omission stems from the lack of clarity regarding how costs will be allocated among stakeholders in the Belgian primary care setting, specifically concerning which costs will be borne by laboratories under service level agreements, which will be the responsibility of practices, and which will be covered by the government. Consequently, the potential impact of cost-sharing on the number of tests performed was not addressed either.

5. CONCLUSION

This study found that implementing CRP POCT in Belgian primary care would result in an incremental budgetary impact of approximately €14.8 million over a five-year period, based on the reference scenario. This scenario included the provision of one analyzer per GP practice, online training as part of the accreditation system, and logistical and technical support from clinical laboratories to ensure quality. It also assumed a maximum adoption rate of 64% with a gradual implementation over three years.

Alternative scenarios were evaluated to examine the effects of deviations from the reference scenario. Different financing models were explored, which revealed significant impacts on the overall results.

These findings can assist policymakers in weighing the incremental budgetary impact of CRP POCT implementation against the public health implications of rising antimicrobial resistance. Policymakers should aim to balance the promotion of CRP POCT adoption with strategies to prevent overuse.

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