EUnetHTA Joint Action 3 WP4

Rapid assessment of other technologies using the HTA Core Model® for Rapid Relative Effectiveness Assessment

C-REACTIVE PROTEIN POINT-OF-CARE TESTING (CRP POCT) TO GUIDE ANTIBIOTIC PRESCRIBING IN PRIMARY CARE SETTINGS FOR ACUTE RESPIRATORY TRACT INFECTIONS (RTIS)

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Disclaimer

The assessment represents a consolidated view of the EUnetHTA assessment team members and is in no case the official opinion of the participating institutions or individuals.

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All authors, dedicated reviewers and external experts involved in the production of this assessment have declared they have no conflicts of interest in relation to the technology assessed according to the EUnetHTA Declaration of interest and confidentiality undertaking of interest (DOICU) statement form.

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LIST OF ABBREVIATIONS

ADR	adverse drug reaction
AMR	antimicrobial resistance
AOM	acute otitis media
AUC	area under the curve
BMI	body mass index
CAP	community-acquired pneumonia
CE	Conformité Européenne
CI	confidence interval
COPD	chronic obstructive pulmonary disease
CRP	C-reactive protein
CV	coefficient of variation
DOR	diagnostic odds ratio
DTA	diagnostic test accuracy
ECDC	European Centre for Disease Control
ERS	European Respiratory Society
ESAC	European Surveillance of Antimicrobial Consumption
ESCMID	European Society for Clinical Microbiology and Infectious Diseases
ESR	Erythrocyte sedimentation rate
GAS	Group A *Streptococcus*
GP	general practitioner
GRACE	Genomics to combat Resistance against Antibiotics in Community-acquired LRTI in Europe
HIV	human immunodeficiency virus
HRQOL	health-related quality of life
ICD	International Classification of Diseases
IVDR	EU Regulation 2017/746 on In Vitro Diagnostic Devices (the IVDR)
LRTI	lower respiratory tract infection
LTC	long-term care
OOH	out-of-hours
OR	odds ratio
MeSH	medical subject headings
NPV	negative predictive value
NNT	number needed to test
POC	point-of-care
POCT	point-of-care testing
PPV	positive predictive value
RADT	rapid antigen detection test

REA	relative effectiveness assessment
ROC	receiver operating characteristic
RCT	randomised controlled trial
RR	relative risk
RTI	respiratory tract infection
SD	standard deviation
SDI	social demographic index
SKUP	Scandinavian Evaluation of Laboratory Equipment for Point of Care Testing
SR	systematic review
URTI	upper respiratory tract infection

SUMMARY OF RELATIVE EFFECTIVENESS OF C-REACTIVE PROTEIN POINT-OF-CARE TESTING TO GUIDE ANTIBIOTIC PRESCRIBING FOR ACUTE RESPIRATORY TRACT INFECTIONS IN PRIMARY CARE

Scope

The scope of the assessment can be found here: Scope.

The aim of this collaborative assessment was to evaluate the relative effectiveness and safety of using C-reactive protein (CRP) point-of-care testing (POCT) to guide antibiotic prescribing in patients with acute respiratory tract infections (RTIs) in primary care settings. The relative effectiveness assessment (REA) sought to answer three questions by conducting three separate systematic reviews:

- Does the use of CRP POCT in primary care lead to a significant reduction in antibiotic prescribing without compromising patient safety? (SR1 – effectiveness and safety)
- What is the diagnostic test accuracy (DTA) of CRP in patients presenting with acute RTIs in primary care? (SR2 – DTA)
- How does the analytical performance of the commercially available CE marked CRP point-of-care tests marketed for use in primary care compare with standard laboratory CRP measurement and with each other? That is, are they are they interchangeable in terms of accuracy, precision and ease of use? (SR3 – analytical performance)

Introduction

Description of technology and comparators

Infection markers can be used to supplement the clinical diagnosis of an infectious disease. CRP is an acute-phase protein synthesised by the liver in response to infection or tissue inflammation. Normal serum or plasma CRP levels are below 5mg/L, but increase rapidly after an acute inflammatory response, peaking at 20 to 500mg/L after 48 hours. While raised levels of serum CRP often occur in bacterial infections (especially severe infections), typically only minor elevations are observed in viral infections. Traditionally CRP testing has been undertaken in the laboratory setting; CRP point-of-care testing (POCT) refers to testing at or near the site of the patient encounter with the result being available within minutes to inform decision-making. (B0001)

In the context of patients presenting to primary care with acute respiratory tract infections (RTIs), the aim of CRP POCT is to provide reliable test results which assist the clinician rule out a serious bacterial infection thereby supporting a decision not to prescribe an antibiotic to those who are unlikely to benefit from treatment. It may also help identify patients who could benefit from an antibiotic. (B0001) The test is indicated if, after clinical assessment, there is uncertainty as to whether an antibiotic should be prescribed. (B0002)

Fifteen CE marked CRP POCT systems were identified for inclusion in this REA. These could be broadly classified into quantitative (using an analyser to provide a quantitative CRP measurement) and semi-quantitative devices (using strips, dipsticks or single-use disposable tests) and are indicated for the measurement of CRP in human whole blood and in human serum and plasma. All are subject to EU Regulation 2017/746 on In Vitro Diagnostic Devices (the IVDR) and are intended for use by healthcare professionals. (A0020)

CRP POCT is suitable for use by non-laboratory-trained healthcare professionals in the primary care setting. (B0004) Basic training of healthcare professionals in the use of CRP POCT is re-

quired. Differences in the size, format, handling requirements and test performance time of the devices potentially contribute to differences in their acceptability and performance when used at the point-of-care. (B0009)

Health problem

RTIs are the most frequent infections encountered in primary care; most are viral, but a small proportion are caused by bacteria and may respond to antibiotics. Depending on the site of infection, RTIs may be classified as upper (pharyngitis, tonsillitis, laryngitis, rhinosinusitis, otitis media and the common cold) or lower (pneumonia, bronchitis, tracheitis and acute infective exacerbations of chronic obstructive pulmonary disease [COPD]). Influenza may affect both the upper and lower respiratory tract. (A0002)

Most RTIs are self-limiting. The natural course of upper respiratory tract infections (URTIs) is typically shorter (ranging from four days for acute otitis media to 2.5 weeks for acute rhinosinusitis) than for lower respiratory tract infections (LRTIs) (ranging from three weeks for acute bronchitis/cough to three to six months (to complete recovery) for community-acquired pneumonia [CAP]). (A0004) Worldwide, LRTIs, and in particular, pneumonia are associated with substantial morbidity and mortality. While the disease burden is lower in high-income countries, reflecting better access to vaccines and antibiotics, LRTIs still contribute to increased morbidity and mortality. (A0006)

Patient groups generally considered to be at the highest risk of acute RTI and their sequelae include: paediatric (<5 years) and geriatric (>70 years) patients, those with a pre-existing lung condition (such as COPD or asthma), immuno-compromised patients, and long-term care (LTC) residents of nursing homes. (A0003) For the purposes of this assessment, the population of interest is represented by patients of all ages who present with symptoms of acute RTI in primary care. (A0007) It is estimated that RTIs account for 15% of all consultations in primary care, with consultations for UTRI-related illnesses more than twice as common as those for LRTIs. (A0023)

Antimicrobial resistance (AMR) is a growing and significant threat to public health, and it is widely recognised that antibiotic resistance is driven by excessive and inappropriate antibiotic prescribing. Ecological studies have shown that increased antibiotic consumption correlates with increased antibiotic resistance, with countries that have moderate to high consumption of antibiotics also having high levels of AMR. However, a causal link between antibiotic consumption and resistance is difficult to establish. (A0002)

At the patient level, there is a clear link between antibiotic dose and duration and the emergence of antibiotic resistance. There is also evidence that patients who have been treated frequently with antibiotics are at greater risk of antibiotic resistance. (A0003) AMR results in increased morbidity and mortality from bacterial infections. It contributed to an estimated 33,000 deaths in the EU in 2015, with the highest burden in infants (aged < one year) and those aged 65 years or older [1]. AMR is estimated to cost the EU €1.5 billion each year due to extra healthcare costs for patients infected with multidrug resistant strains and productivity losses. Prudent use of antibiotics to prevent development of AMR is an important component of the 2017 EU action plan against antimicrobial resistance [2]. (A0006)

For URTIs, guidelines recommend clinical assessment should include a detailed clinical history and physical examination of the patient. Clinical prediction rules are used for some types of URTI to identify those patients most likely to benefit from antibiotic treatment. In uncomplicated cases of URTIs that do not exceed the expected durations of illness, a ‘no antibiotic’ prescribing strategy or a ‘delayed antibiotic’ prescribing strategy is generally recommended. For LRTI, the use of antibiot-

ics is recommended in patients with pneumonia and in those at higher risk of complications, but antibiotics are not otherwise recommended to treat acute bronchitis. A number of clinical guidelines recommend CRP measurement if, after clinical assessment, a diagnosis of pneumonia has not been made and there is uncertainty as to whether an antibiotic should be prescribed. Antibiotic-related adverse events are common. Treatment exposes patients to an increased risk of an adverse event, so the need for treatment must be considered relative to the potential for harm. (A0024) (A0025) Overprescribing of antibiotics for RTIs in primary care is common, with high levels of inappropriate prescribing documented in observational studies benchmarking antibiotic prescribing versus clinical guidelines. (A0025)

Recommendations around the use of CRP POCT for patients with suspected LRTIs have been included in guidelines in Norway, Sweden, the Netherlands, Germany, Switzerland, Czech Republic, Estonia and the United Kingdom. The use of CRP POCT varies substantially across Europe. Although recommended and available for use in many European countries, there are no reliable data on the current and/or expected annual usage of CRP POC tests in European countries. (A0011)

Methods

The selection of assessment elements was based on the EUnetHTA Core Model® Application for Rapid Relative Effectiveness (REA) Assessments Version 4.2. Additional elements were added from the HTA Core Model® Application for Diagnostic Technologies Version 3.0.

For the description and technical characteristics of technology (TEC) and health problem and current use of technology (CUR) domains, descriptive analyses of information from the various sources explored was carried out. Manufacturers of known commercially available CRP POC tests were contacted by the assessment team and requested to complete the Medical Devices Evidence Submission template. Manufacturers were asked to submit non-confidential evidence focusing on the technical characteristics and current use of the technology. The documentation provided was used along with material from company websites as a starting point to inform the TEC domain. The documentation provided was used in addition to the literature identified by the literature search to inform the TEC and CUR domains.

Systematic literature searches of various databases were carried out to identify primary studies fulfilling the inclusion criteria outlined in the scope of the assessment for each of the three systematic reviews. Detailed tables of the search strategies are included in Appendix 1. No limitations were applied with regard to study design or language. The search for the third systematic review (analytical performance) was limited to publications from 1990 onwards, as performance data from studies previous to this were considered unlikely to be of relevance to current commercially available POC tests. Clinical trial registries were assessed for registered ongoing clinical trials or observational studies. Two authors from HIQA independently reviewed titles and abstracts for each systematic review search. The full text of potentially eligible articles was reviewed by the two authors independently and studies were included or excluded based on predefined criteria (Scope). Studies that did not provide data on the relevant outcomes were excluded. Studies that reported on duplicate data were identified and excluded if no additional data were available in the secondary publication. Abstracts from conferences were also excluded. Any disagreement in study selection was resolved through discussion. Studies excluded at full-text review are listed in Appendix 1. Relevant data for the clinical effectiveness and safety domains were extracted and recorded in evidence tables independently by the two authors. These steps were also checked by the co-authors.

For the systematic review of clinical effectiveness and safety, studies considered clinically homogenous in terms of participants, interventions and outcomes were pooled for meta-analysis using RevMan5.3 software. Risk ratios were calculated for dichotomous variables. Heterogeneity was investigated using the I^2 statistic. Due to considerable heterogeneity across studies retrieved in both systematic review 2 and 3, meta-analysis of data was not appropriate. Results are described qualitatively.

Two reviewers independently assessed the quality or risk of bias of full-text articles included in the assessment using standardised critical appraisal instruments. The Cochrane risk of bias assessment approach was used to assess randomised controlled trials (RCTs) and cluster RCTs. For non-randomised controlled trials and observational studies, the Newcastle Ottawa quality assessment scale was used. The quality assessment of diagnostic accuracy studies (QUADAS-2) tool was applied to assess the risk of bias and applicability of diagnostic accuracy studies identified in systematic review 2 (diagnostic test accuracy). A modified QUADAS-2 tool was used to assess the risk of bias of studies in systematic review 3 (analytical performance). For the assessment of the strength of evidence, the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach was used. For the TEC and CUR domains, no quality assessment tool was used, but multiple sources (including national and European clinical guidelines, European surveillance data along with grey literature searches of HTA agency reports) were used in order to validate individual, possibly biased sources.

Potentially relevant patient organisations were contacted during the scoping phase in order to understand the patient's perspective, to identify possible additional outcomes of interest and to understand the relative importance of the outcomes identified. Input was provided by one patient advocacy organisation, Patient Focus (Ireland), with feedback provided based on the preliminary PICO and the draft project plan. The HTAi patient group submission template was used as the basis of a semi-structured telephone interview. The feedback provided was included in the discussions with the assessment team at the scoping e-meeting and was incorporated by the authors in their rating of the outcomes of interest through GradePRO.

Results

Clinical effectiveness

The systematic review of clinical effectiveness and safety (SR 1) included 12 studies, of which four studies were individual RCTs, three were cluster RCTs and five were non-randomised studies. Ten of the studies were carried out in Europe. All studies reported on at least one primary outcome. The studies identified as part of this systematic review related to only three of 15 CE marked CRP POC tests identified. Most studies only included adults; three included adults and children.

Seven RCTs with 5,320 patients were included in the meta-analysis for the primary prescribing outcome (antibiotic prescription at index consult). The pooled estimate for the RCTs showed a statistically significant reduction in antibiotic prescribing at index consultation in the CRP POCT group compared with usual care (relative risk (RR) 0.76, 95% CI: 0.67–0.86, I^2 = 70%). When grouped based on the method of randomisation (individual or cluster randomisation), the substantial heterogeneity in the pooled estimate (I^2 = 70%) reduced to 0% for cluster randomised trials (RR 0.68, 95% CI: 0.61, 0.75, I^2 = 0%; n=3). However, substantial heterogeneity remained in the individually randomised group (n=4; I^2 = 82%) which decreased to 5% with the removal of a Vietnamese study (RR 0.90 95% CI: 0.80, 1.02, I2 = 5%, n=3). Overall, the certainty of the evidence assessed with the GRADE approach was moderate for this outcome. Non-randomised studies

(n=4, 4,839 patients) show a similar effect of CRP POCT on antibiotic prescribing with a pooled RR of 0.61 (95% CI: 0.54–0.69, I^2 = 74%); GRADE certainty of evidence was very low. Five RCTs (2,744 patients) reported on the number of patients given antibiotic prescriptions within 28 days follow-up. All studies and the pooled estimate showed point estimates in favour of CRP POCT to reduce antibiotic prescribing within 28 days (RR 0.81, 95% CI: 0.74–0.88, I^2 = 21%); however, in three of the studies the difference was not statistically significant. (D0021)

Subgroup analysis was performed for upper versus lower RTIs for the outcome of antibiotic prescribing at index consultation. The pooled data from RCTs suggest a significant reduction in prescribing for patients presenting with URTI (RR 0.72, 95% CI: 0.58–0.90, I^2 = 0%); however, these findings are based on only two studies. Four RCTs provided data on LRTI. The pooled RR suggests that use of CRP POCT lowers antibiotic prescribing in patients with LRTI (RR 0.76, 95% CI: 0.61–0.94); however, there is substantial heterogeneity (I^2 = 59%), with only one study showing a statistically significant reduction compared with usual care. These results are supported by similar findings in non-randomised studies. (D0021)

Two studies (one RCT and one non-randomised study) provided information on whether antibiotics were prescribed for delayed or immediate use (n=378). No difference was reported in the number of patients provided with a delayed prescription between the CRP POCT and the usual care groups. However, one of the studies found significantly more prescriptions for antibiotics were redeemed in the usual care group (72% versus 23%). (D0021)

Three RCTs (n=1,264 patients) reported on the number of patients that made a substantial or complete recovery by day seven. The pooled estimate for the RCTs showed no significant difference in the number of patients making a substantial improvement or complete recovery beyond seven days (RR 1.03, 95% CI: 0.93–1.14, I^2 = 0%). In studies providing data regarding patient recovery beyond seven days, no significant difference was reported between the CRP POCT and usual care groups. In studies providing data in relation to time to resolution of acute RTI symptoms (n=4), all studies reported no significant difference between the CRP POCT and usual care groups. (D0005) (C0008)

Studies showed point estimates in favour of usual care when considering the number of patients re-consulting; however, the difference in reconsultation rates was not statistically significant in any study or in the pooled meta-analysis (RCTs: n=4,524, RR 1.09, 95% CI: 0.93–1.27 I^2 = 0%). (D0006)

None of the included studies reported on physician satisfaction with CRP POCT. Four studies reported on patient satisfaction (n=1,885). Patients were generally satisfied with the care received as part of the clinician visit. The results of the pooled analysis showed no significant difference between the CRP POCT and control groups (RCTs: RR 0.82 [95% CI: 0.55–1.21], I^2 = 48%). These findings were supported by the results of one non-randomised study. (D0017)

Three studies included children (n=1 age >1 year; n=2 all ages) in addition to adults. In the two studies for which data could be extracted for meta-analysis, the effect of CRP POCT on prescribing of antibiotics was similar in both adults and children. However, one study found a significant effect in both groups while the other reported no effect in both groups. It was not possible to do a planned sub-group analysis for older adults (≥65 years) as none of the retrieved studies assessed the effect of CRP POCT exclusively in this cohort. Only one study included an upper age limit (65 years).

Diagnostic test accuracy

The search of the literature retrieved 15 diagnostic test accuracy (DTA) studies (SR 2), all of which were carried out in Europe. The evidence retrieved in relation to children was limited, with only one study recruiting children aged between three months and 15 years of age. Only four studies used CRP POCT in primary care; two used the CRP POCT device in a laboratory while the remaining studies used standard laboratory equipment. A high level of heterogeneity was noted across studies, reflecting differences in the criteria used to define test positivity, diagnostic criteria (including use of CRP levels in isolation or as part of a clinical algorithm), patient populations and the absence of a universal reference standard for the diagnosis of RTIs requiring antibiotics. For the purposes of analysis, studies were grouped according to the types of RTI identified in the systematic review.

Two studies reported on the usefulness of CRP testing in diagnosing sinusitis. Both studies examined a range of thresholds and selected a threshold of 10 and 17 mg/L, respectively as suitable for ruling out a diagnosis of sinusitis [3, 4]. One study used CRP as part of a clinical decision rule, allowing half of the patients to be identified as low risk for sinusitis [3]. The other study examined CRP in combination with erythrocyte sedimentation rate (ESR) and found that the addition of ESR increased the sensitivity of the test [4]. (D1005, D1006)

Two studies sought to determine the optimal threshold for CRP testing in patients presenting with sore throats, with differing cut-points identified (6 mg/L versus 35 mg/L). However, these studies differed in their aim, with one study using CRP to distinguish between bacterial and non-bacterial pharyngitis[5], and the other to distinguish between GAS and non-GAS pharyngitis [6]. At a threshold of 35 mg/L, CRP was found to better at ruling in than ruling out bacterial pharyngitis and improved both sensitivity and specificity (0.78 [0.61-0.91] and 0.82 [0.73-0.88], respectively) compared with clinical diagnosis alone [5]. The authors subsequently used this threshold as part of a two-step clinical algorithm with approximately 30% of patients presenting with sore throat requiring a CRP measurement after clinical assessment [7]. The specificity of the algorithm was higher than the sensitivity (0.95 [0.88-1.00] versus 0.74 [0.53-0.88]). This two-step clinical algorithm requires further validation. At a threshold of 6 mg/L, CRP in combination with the Centor Score may be useful in ruling out GAS pharyngitis (Centor Score 1-4: sensitivity: 0.90; specificity 0.45), but only if RADT is not available (Centor Score 1-4: sensitivity: 0.90; specificity 0.97) [6]. The low specificity of this cut-point means that many false positives may be treated unnecessarily with antibiotics. (D1005, D1006)

Nine studies reported on the usefulness of CRP in LRTI and, or specifically in pneumonia. Five studies reported on the diagnostic accuracy of CRP at a specified threshold for diagnosing pneumonia. Four studies reported on a cut-point of 20 mg/L: three reported a sensitivity between 0.48 and 0.79 [8-11], while the fourth study reported a sensitivity of 100% at this cut-point [12]. One study (n=69) reported diagnostic accuracy at a lower threshold of 11 mg/L (sensitivity 0.82) [10], suggesting that some cases of pneumonia would be missed even at this lower threshold. At a threshold of 50 mg/L and 100 mg/L, specificity was between 0.84 and 0.96 and may be suitable for ruling in a diagnosis of pneumonia. Five studies investigated the diagnostic accuracy of CRP in combination with signs and symptoms for determining pneumonia in patients presenting with LRTIs. One study found the addition of CRP at a cut-point of 20 mg/L resulted in increased specificity, but reduced sensitivity compared with clinical judgement alone, suggesting it would have limited use in primary care unless the GP was trying to rule in a diagnosis of pneumonia [8]. Four other studies used CRP in combination with a signs and symptoms model to classify patients according to their risk of pneumonia. In these studies, addition of CRP testing to the prediction rule increased its discriminative power. Hopstaken et al. reported that, use of the rule could have

saved 41% of prescriptions for antibiotics with a 2.5% risk of missing a case of pneumonia [13]. In the study as part of the GRACE network, CRP was only useful in the intermediate risk category where there was clinical uncertainty, and allowed for the reclassification of around half of this group into high- or low-risk categories [14]. A further study by the GRACE consortium concluded that although CRP added diagnostic value to the signs and symptoms model, it had limited clinical utility in predicting a bacterial cause of LRTI [15]. (D1005, D1006)

Analytical performance

The systematic search for analytical performance studies returned 18 studies (SR 3) that provided data on 11 quantitative devices and two semi-quantitative devices. In all studies, the analytical performance of a CRP POCT device was compared with standard CRP measurement by trained laboratory staff using laboratory analyser equipment. Data on accuracy, precision and ease of use were extracted for each device from the included studies. There was considerable heterogeneity across studies in terms of the settings in which patient blood samples were obtained, the operator of the device, patient characteristics and how study outcomes were recorded. The included studies were generally found to be at high risk of bias in a number of domains.

Analytical performance refers to the ability of the assay to accurately measure CRP levels. Studies noted that there are few international guidelines that specify analytical quality requirements for CRP POCT devices. Scandinavian health bodies (Norway, Sweden and Denmark) suggest acceptable levels of accuracy for CRP POCT are a bias (the difference between the measured value and the true value) that is no greater than 15% (10% for some health bodies). The most common methods of reporting accuracy were agreement from a Passing Bablok regression, correlation from a Pearson or Spearman correlation coefficient or a mean difference from Bland-Altman plots. Precision is a measure of the random error in an assay and can presented as a coefficient of variation (CV); Scandinavian health bodies and other studies suggest a CV ≤10 % is acceptable. (D1001)

Only two studies evaluated semi-quantitative devices. The agreement between the reference test and the POCT was found to be moderate to good for the Actim® test (Kappa 0.53 to 0.93) and moderate for the Cleartest® (Kappa 0.56 to 0.61). The accuracy of the test was shown to decrease after the optimal read-time of five minutes. The main advantage of these devices was said to be their relative cost. The main disadvantages were the difficult pre-analytical handling, the accuracy, the time-critical nature of the tests, and that the results are not automatically entered into the patient record. In addition, the semi-quantitative tests included here (Actim® and Cleartest®) have an upper limit of 80mg/L. (D1001, D1008)

The majority of the evidence suggested acceptable performance for all eleven quantitative devices in the laboratory setting. Most of devices had a mean difference of <10 mg/L or <10% bias except at concentrations above 100 mg/L (Afinion™, NycoCard™, NycoCard™ Reader II, QuikRead® 101, Smart Eurolyser, iChroma™, Microsemi, AQT90 Flex). Precision was also acceptable in the laboratory for most of the devices (Afinion™, NycoCard™, QuikRead go®, QuikRead® 101, Microsemi, AQT90 Flex and ABX Micros), although CV values greater than 10% were reported in the laboratory setting in at least one study for the Smart Eurolyser, the NycoCard™ Reader II and the iChroma™ devices. This suggests that under idealised circumstances in the laboratory most of the devices are accurate and precise. (D1007)

When used at the point of care the results of accuracy and precision of the devices were more variable. In terms of accuracy, the Afinion™ reported <5% bias in two studies, while the bias for the NycoCard™, the QuikRead go®, and the iChroma™ were <15%. The accuracy was more

variable for QuikRead® and the Smart Eurolyser. Very little data were available on precision at the point of care. For the QuikRead® 101 and the spinit® devices the CV was <10% in all studies, while inconsistent results were reported for the Smart Eurolyser and the iChroma™ devices. (D1007)

Four studies compared multiple devices and provide a direct comparison of the devices [16-19]. Minnaard et al. concluded that four of the devices showed acceptable performance in the laboratory setting (Afinion™, NycoCard™ Reader II, QuikRead go® and QuikRead 101), while the Smart Eurolyser had unacceptably high imprecision. The Afinion™ and Smart Eurolyser were reported to be the easiest to operate [18]. Brouwer et al. compared six quantitative tests (Afinion™, QuikRead go®, Smart Eurolyser, iChroma™, Microsemi and AQT90 Flex) and concluded that the Afinion™ and Smart Eurolyser were the preferred analysers for CRP POCT based on a combination of their analytical performance and ease of use [16]. The Bukve et al. study compared six devices at the point of care (Afinion™, QuikRead go®, QuikRead® 101, iChroma™, NycoCard™ and ABX Micros); the Afinion™ and QuikRead® devices had the lowest systematic bias and the Afinion™, QuikRead® and QuikRead go® were associated with good participant performance in a quality assurance scheme [17]. The final study by Monteny et al., which compared the NycoCard™ device at the POC and the QuikRead® device in the laboratory setting, reported that the NycoCard™ device had better analytical performance [19] (D1007)

Four studies examined analytical performance of the devices in the laboratory setting and the primary care setting [20-23]. The Smart Eurolyser had acceptable accuracy and precision in the laboratory and at the POC, but had better performance in the laboratory. The other devices (ABX Micros, iChroma™ and QuikRead®) had acceptable analytical performance in the laboratory but unacceptable precision or accuracy in at least one primary care centre or at higher CRP levels [21]. Accuracy and precision therefore appear to be negatively impacted when the device is used at the point of care. (D1007)

In terms of ease of use, devices that are easier to use tend to have less pre-analytical handling and are designed in such a way that they are less susceptible to human error. The overall time taken for the test to be performed was an important factor, with times ranging from just over three minutes (QuikRead® 101) to over 13 mins (AQT90 Flex), but it is unclear from the literature what time period would be considered acceptable in the primary care setting. Participating in an external quality assurance scheme (EQAS) more than once; performing internal quality control at least weekly; the type of instrument used; having laboratory-qualified personnel performing the tests; and performing more than ten CRP tests per week were associated with good test performance. (D1007)

Safety

For the assessment of safety, all 12 studies identified for inclusion in SR1 (effectiveness) were considered.

None of the included RCTs or non-randomised studies reported the death of a patient. Five of the included RCTs specifically stated that there were no deaths during the study period. (D0011) (C0008)

No study reported specifically on reconsultations or hospitalisations due to an antibiotic-related adverse drug reaction (ADR). Five RCTs reported no hospitalisations during the follow-up period. One RCT reported a number of patient hospitalisations, but found no significant difference between the CRP POCT and control groups (RR 0.73, 95% CI: 0.25–2.09). A second study reported significantly more hospitalisations in the CRP POCT group relative to the control group; however,

after adjusting for all possible confounders the difference was no longer statistically significant (OR 2.91, 95% CI: 0.96–8.85, p = 0.060). (C0008) (D0011)

Ethical, organisational, patient and social and legal aspects (if applicable)

Potential ethical issues identified in relation to the implementation of CRP POCT included the potential for a small risk of harm to the patient or staff from blood-borne contamination. From an organisational perspective, it was noted that the introduction may lead to changes in the patient care pathway depending on who administers the test and communicates the results to the patient. Potential organisational issues may also arise relating to the development and implementation of a comprehensive quality assurance scheme to support testing in primary care. (Appendix 3)

Upcoming evidence

One planned trial evaluating the diagnostic test accuracy of a semi-quantitative CRP POCT device (FebriDx®) in patients being evaluated for acute community acquired febrile respiratory infection in primary care and urgent care outpatient offices and emergency departments was identified (Appendix 1 Table A11). This trial is scheduled to begin enrolling patients in April 2019. Feedback from an external expert identified that the 12-month follow-up to a large study included in SR1 (effectiveness and safety) has been accepted for publication.

Reimbursement

The use of CRP POCT in patients with suspected LRTI has been included in guidelines in the UK, Norway, Sweden, the Netherlands, Germany, Switzerland, Czech Republic and Estonia to determine severity of infection and to guide antibiotic prescribing. CRP POCT to inform prescribing in primary care was noted to have been indicated in 16 out of 19 countries for which data were provided, and to be reimbursed for this indication in nine of these countries. (A0021)

Table 1: Summary of findings table of the use of CRP POCT to guide antibiotic prescribing for patients presenting with acute RTI in primary care

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**CRP POCT**	**standard care**	**Relative (95% CI)**	**Absolute (95% CI)**		
Number of patients given antibiotic prescriptions for acute RTI at index consultation												
7	randomised trials	serious [a,b]	not serious	not serious	not serious [a,c]	none	1072/2702 (39.7%)	1432/2618 (54.7%)	**RR 0.76** (0.67 to 0.86)	**131 fewer per 1,000** (from 77 fewer to 181 fewer)	⊕⊕⊕◯ MODERATE	CRITICAL
Number of patients given antibiotic prescriptions for acute RTI at index consultation												
4	observational studies	not serious	not serious	not serious	serious [d]	none	1011/2326 (43.5%)	1784/2513 (71.0%)	**RR 0.61** (0.54 to 0.69)	**277 fewer per 1,000** (from 220 fewer to 327 fewer)	⊕◯◯◯ VERY LOW	CRITICAL
Number of patients given antibiotic prescriptions for acute RTI within 28 days*												
5	randomised trials	not serious	not serious	not serious	serious [c,d]	none	776/1368 (56.7%)	970/1376 (70.5%)	**RR 0.81** (0.74 to 0.88)	**134 fewer per 1,000** (from 85 fewer to 183 fewer)	⊕⊕⊕◯ MODERATE	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**CRP POCT**	**standard care**	**Relative (95% CI)**	**Absolute (95% CI)**		
Number of patients with substantial improvement or complete recovery at seven days follow-up												
3	randomised trials	not serious	not serious	not serious	not serious	none	324/627 (51.7%)	336/637 (52.7%)	**RR 1.03** (0.93 to 1.14)	**16 more per 1,000** (from 37 fewer to 74 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Number of patients with substantial improvement or complete recovery at 28-days follow-up*												
3	randomised trials	not serious	not serious	serious [e]	not serious	none	207/264 (78.4%)	199/263 (75.7%)	**RR 0.94** (0.69 to 1.28)	**45 fewer per 1,000** (from 212 more to 235 fewer)	⊕⊕⊕◯ MODERATE	CRITICAL
Patient mortality at 28-days follow-up*												
5	randomised trials	not serious	not serious	not serious	not serious	none	Out of 7,165 patients in 5 RCTs there were no reported deaths				⊕⊕⊕⊕ HIGH	CRITICAL
Number of patients given an antibiotic for delayed versus delayed + immediate												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CRP POCT	standard care	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	not serious		not serious		none	22/73 (30.1%)	29/81 (35.8%)	not pooled	see comment	-	IMPORTANT
Number of patients given an antibiotic for delayed versus delayed + immediate												
1	observational studies	not serious		not serious		none	10/27 (37.0%)	10/35 (28.6%)	not estimable		-	IMPORTANT
Time to resolution of RTI symptoms												
4	randomised trials	not serious	serious [f]	not serious	serious [f]	none	Studies were not pooled due to differences in the definition of the outcome. All four studies reported no significant difference in the time to resolution of symptoms between CRP POCT and usual care groups. Median time to resolution of symptoms in CRP POCT group ranged from 5 to 22 days. Median time in usual care group ranged from 4 to 22 days.				⊕⊕◯◯ LOW	CRITICAL
Number of patients reconsulting												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CRP POCT	standard care	Relative (95% CI)	Absolute (95% CI)		
4	randomised trials	not serious	not serious	not serious	not serious	none	272/2322 (11.7%)	230/2202 (10.4%)	**RR 1.09** (0.93 to 1.27)	**9 more per 1,000** (from 7 fewer to 28 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Number of patients reconsulting												
1	observational studies	not serious		not serious		none	14/60 (23.3%)	9/60 (15.0%)	not estima-ble		-	
Number of patients in need of hospitalisation												
5	randomised trials	not serious	serious [g]	not serious	not serious	none	Three studies reported no hospitalisation of patients. One study reported no significant difference in hospitalisation between CRP POCT group and usual care group. One study reported significantly more hospitalisations in the CRP POCT group, but after controlling for all confounders this difference was no longer significant.				⊕⊕⊕◯ MODERATE	CRITICAL
Patient satisfaction												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**CRP POCT**	**standard care**	**Relative (95% CI)**	**Absolute (95% CI)**		
3	randomised trials	not serious	not serious	not serious	serious [a]	none	794/894 (88.8%)	756/871 (86.8%)	**RR 0.82** (0.55 to 1.21)	**156 fewer per 1,000** (from 182 more to 391 fewer)	⊕⊕⊕◯ MODERATE	IMPORTANT
Patient satisfaction												
1	observational studies	not serious		not serious		none	51/60 (85.0%)	51/60 (85.0%)	not estima-ble		-	IMPORTANT

***** Not all studies had 28 days follow-up. Two studies had a follow-up period of 14 days and one had a 21-day follow-up period.
Abbreviations: CI: Confidence interval; **RR:** Risk ratio

Explanations

a. Heterogeneity.
b. Difference in effect estimate from cluster randomised RCTs and individually randomised RCTs.
c. 95% CI cross the line of no effect in a number of studies.
d. Moderate heterogeneity.
e. Follow-up was 14 days, 21 days and 28 days for the three studies, therefore the evidence for recovery at 28 days directly applies to only one study.
f. No attempt was made to pool data as different definitions were given for resolution of symptoms.
g. Effect of CRP POCT on hospitalisation differs substantially.

Table 2: Summary of findings table of the diagnostic test accuracy of CRP in patients presenting with acute RTI in primary care

Outcomes	Impact	№ of participants (studies)	Certainty of the evidence (GRADE)
CRP levels (mg/L) **	**Pharyngitis/Tonsillitis:** Reported mean CRP levels in patients were inconsistent (GAS [range 34.4-40 mg/L]; Non-GAS [range 15-29.9]). Studies differed in the spectrum of patients due to differences in inclusion criteria. **LRTI/Pneumonia:** Only one study reported mean CRP levels in children. In studies in adults, measured CRP concentrations were more consistent in patients without pneumonia (range 17-19 mg/L (n=2)) than in pneumonia patients (range 62-145mg/L (n=3)).	**Pharyngitis/Tonsillitis:** (n=2) **LRTI/Pneumonia:** (n=4)	**Pharyngitis/Tonsillitis:** ⊕◯◯◯ VERY LOW [a,b,c] **LRTI/Pneumonia:** ⊕⊕◯◯ LOW [c, d]
CRP optimal threshold**	**Sinusitis:** The optimal cut-off point ranged from 10-17 mg/L. **Pharyngitis/Tonsillitis:** The optimal threshold was derived from the patient sample. A cut-off point of 35 mg/L was used to distinguish between bacterial and non-bacterial pharyngitis (n=1). A threshold of 6 mg/L was used to differentiate between GAS and non-GAS patients (n=1). **Pneumonia/LRTI:** Optimal cut-off points were chosen rather than derived and were 11, 20, 50 100 mg/L.	**Sinusitis:** (n=2) **Pharyngitis/Tonsillitis:** (n=2) **RTI/Pneumonia:** (n=5)	**Sinusitis:** ⊕⊕⊕◯ MODERATE [e] **Pharyngitis/Tonsillitis:** ⊕⊕◯◯ LOW [f,g] **LRTI/Pneumonia:** ⊕⊕⊕◯ MODERATE [h]

Table 2: Summary of findings table of the diagnostic test accuracy of CRP in patients presenting with acute RTI in primary care

Outcomes	Impact	№ of participants (studies)	Certainty of the evidence (GRADE)
CRP alone at a specified threshold**	**Sinusitis:** CRP was significantly associated with a diagnosis of sinusitis at a cut-off point of 15 mg/L. At a threshold of 10 mg/L, CRP testing may be useful as a rule-out test. However, neither study recommended the use of CRP alone as a diagnostic tool. **Pharyngitis/Tonsillitis:** CRP testing was found to perform better in differentiating between bacterial and non-bacterial pharyngitis compared with clinical diagnosis only. **LRTI/Pneumonia:** At a cut-off point of 20 mg/L, in 3/4 studies the test demonstrated insufficient sensitivity to be used to reliably rule out pneumonia (sensitivity 0.48-0.79). At thresholds of 50 mg/L and 100 mg/L the test may be useful as a rule-in test (specificity 0.84-0.99).	**Sinusitis:** (n=2) **Pharyngitis/Tonsillitis:** (n=1) **LRTI/Pneumonia:** (n=5)	**Sinusitis:** ⊕⊕⊕◯ MODERATE [e] **Pharyngitis/Tonsillitis:** ⊕⊕⊕◯ MODERATE [g] **LRTI/Pneumonia:** ⊕⊕⊕◯ MODERATE [h,i]
CRP + signs and symptoms at a specified threshold**	**Sinusitis:** CRP testing in combination with other clinical tests (e.g. ESR measurement) or as part of a clinical decision rule may be useful in the diagnosis of acute sinusitis, particularly in identifying patients that are at low risk of acute bacterial sinusitis. **Pharyngitis/Tonsillitis:** CRP testing was found to be useful in identifying patients that would benefit from antibiotic treatment who were classified at intermediate risk of GAS pharyngitis based on a signs and symptoms model (n=1). However, a combination of the Centor Score and CRP was not found to be more accurate than other optional tests (i.e. RADT) (n=1). **LRTI/Pneumonia:** CRP testing + signs and symptoms model*** was found to be a better predictor of pneumonia than the signs and symptoms model alone and increased the discriminative power of the test.	**Sinusitis:** (n=2) **Pharyngitis/Tonsillitis:** (n=2) **LRTI/Pneumonia:** (n=4)	**Sinusitis:** ⊕⊕⊕◯ MODERATE [j] **Pharyngitis/Tonsillitis:** ⊕⊕◯◯ LOW [j,k] **Pharyngitis/Tonsillitis:** ⊕⊕◯◯ LOW [j, k]

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. Downgraded by one level for inconsistency: Studies were inconsistent with regard to the spectrum of patients included and CRP levels reported in non-GAS groups.
b. Downgraded by one level for imprecision: Wide 95% confidence intervals
c. Downgraded by one level for indirectness: Blood or serum CRP concentrations are not a direct measure of diagnostic test accuracy.
d. Downgraded by one level for inconsistency: Studies were inconsistent with regard to mean or median CRP levels reported in pneumonia patients.
e. Downgraded by one level for indirectness: CRP testing was used either in combination with other clinical criteria (i.e. erythrocyte sedimentation rate) or as part of a clinical prediction rule.
f. Downgraded by one level for inconsistency: Studies were inconsistent with regard to thresholds used to define test positivity.
g. Downgraded by one level for risk of bias: Current clinical guidelines recommend antibiotic treatment in patients with GAS pharyngitis only. The distinction between bacterial and non-bacterial pharyngitis may not be as useful.
h. Downgraded by one level for indirectness: 3/5 studies did not provide evidence or rationale for the cut-off points selected.
i. Downgraded by one level for inconsistency: Studies report widely varying measures of sensitivity.
j. Downgraded by one level for indirectness: Studies evaluated the diagnostic test accuracy of CRP POCT in addition to other diagnostic tools. The effect of CRP POCT alone for the diagnosis of RTI cannot be determined.
k. Downgraded by one level for inconsistency: Studies were inconsistent regarding the usefulness of CRP POCT in addition to a clinical score for the diagnosis of RTI infection.

**Measures of diagnostic test accuracy demonstrate clear threshold effects. That is, differences in accuracy are likely to be related to differences in the CRP cut-off point used in the study. It was therefore not appropriate to calculate summary estimates of accuracy for CRP POC tests as a group where a range of cut-off points have been used across studies. For this reason, the evidence is considered for each type of acute RTI identified in the systematic review.

***The signs and symptoms model is defined as a clinical prediction rule in which investigators identified the best combination of medical signs, symptoms, and other findings in predicting the probability of pneumonia with the aim of reducing uncertainty surrounding medical decision-making by standardising the collection and interpretation of clinical data.

Table 3: Summary of findings table of the analytical performance of CRP POCT compared with laboratory CRP testing for RTIs in primary care

Outcomes	Impact	№ of participants (studies)	Certainty of the evidence (GRADE)
Accuracy	There was no systematic methodology for assessing accuracy and there was heterogeneity between studies in regard to the setting and operator of the device. Two studies assessed accuracy of semi-quantitative devices; 17 studies assessed quantitative devices. The agreement with the reference standard for the semi-quantitative devices ranged from 0.53 to 0.93, this deteriorated if the test was read after the optimal 5 minutes. There was also evidence or inter-observer disagreement. The accuracy of most quantitative devices was acceptable under idealised laboratory conditions, but was poorer when used at the point of care. The accuracy of the devices tended to be poorer at high CRP concentrations (>100 mg/L), but this may not be clinically relevant.	(18 observational studies)	⊕◯◯◯ VERY LOW [a,b,c]
Precision	There was no systematic methodology for assessing precision. The acceptable level of imprecision was defined as a coefficient of variation less than 10%. The precision results were presented as within-day and between-day variation in the laboratory and primary care settings. Most devices reported acceptable precision in the laboratory setting (Smart Eurolyser, NycoCard™ Reader II & iChroma™ exhibited unacceptable precision [>10%] in at least one study). Only five studies had precision data measured at the point of care. Generally precision was comparable or poorer at the point of care.	(10 observational studies)	⊕◯◯◯ VERY LOW [a,b,c]
Ease of Use	There was no systematic methodology for assessing ease of use. The results were reported from laboratory and healthcare personnel. A survey or Likert scale was used or general statements were provided by participants. The overall time taken for the test was a major factor, but it was unclear from the studies what was considered an acceptable time period in the primary care setting. The Afinion™ and Smart Eurolyser were noted for their user-friendliness.	(8 observational studies)	⊕◯◯◯ VERY LOW [a,c,d]

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

Explanations

a. Using QUADAS 2, there was a risk of bias in a number of domains.
b. The evidence for analytical performance was not consistent between studies; this may have been due to the operator or the setting in which the device was used.
c. Some of the evidence is provided by studies in the laboratory setting with trained technicians as operators. These studies do not reflect the setting or operators that would use these devices in practice.
d. For some devices there were inconsistent reports regarding their ease of use.

Discussion

Clinical effectiveness and safety

The results suggest that CRP POCT, when used to guide management of patients who present with symptoms of acute RTI, leads to reduced antibiotic prescribing both at index consultation and up to 28 days follow-up. However, it is noted that these results are based on short-term data. Trials generally followed patients for 14 to 28 days. The average recruitment period across trials was 6.5 months, or 7.5 months from the recruitment of the first patient to completion of follow-up for the last patient. Based on the available evidence it is not known if the impact on GP prescribing behaviour persists over a longer period of time.

Subgroup analysis demonstrated that CRP POCT is effective at reducing antibiotic prescribing at index consultation in both URTI and LRTI; however, substantial heterogeneity was noted across studies, decreasing the strength of the evidence. It is not possible to state from this review what the impact of CRP POCT is on antibiotic prescribing in children with RTIs given the limited data and the lack of consistency in results. None of the retrieved studies assessed the effect of CRP POCT exclusively in older adults (≥65 years). Further studies are necessary to examine the effectiveness of CRP POCT in this cohort as they are recognised to be at high risk of RTI complications due to a high prevalence of co-morbidities. Nine of the eleven studies included in the meta-analysis were carried out in Europe. Therefore, while recognising that countries may differ in what standard care comprises and their antibiotic prescribing practices, the findings of this systematic review are believed to be transferable to the majority of European primary care settings. It is noted that a diverse range of interventions might be considered as part of antimicrobial stewardship and that these interventions may be used in tandem or in isolation. The mix of interventions offered and the sequence of their introduction may impact on their effectiveness.

The identified studies included in this systematic review related to only three of the 15 CE marked devices, all of which were quantitative devices. It is not certain if these data will apply to semi-quantitative devices given potential differences in their characteristics, performance and acceptability. There were very limited data on the number of antibiotics prescribed as a delayed prescription. Based on the findings of a single study, patients who receive a delayed prescription may be less likely to redeem it. If delayed prescriptions are common in cases where CRP levels are between 20 and 99 mg/L, our effect estimate could be lower than would be seen in practice given that a higher proportion of these prescriptions may not be redeemed.

The reduction in antibiotic prescribing does not appear to compromise patient safety. It is noted, that the outcomes reported in the trials may not capture all safety concerns. While serious adverse events that result in substantial morbidity or mortality are rare, antibiotic-related adverse events are common and may impact short-term health-related quality of life. However, it is also recognised that changes in the incidence of rare serious suppurative complications of RTIs (e.g., peritonsillar abscess, empyema, and intracranial abscess) arising from a failure to provide timely antibiotic treatment cannot be evaluated precisely in clinical trials. These data are provided by large long term cohort studies which suggest that substantial reductions in antibiotic prescribing can be safely achieved, although caution may be required in subgroups at higher risk of pneumonia. (A0006)

Diagnostic test accuracy

The evidence base for the diagnostic test accuracy of CRP testing in primary care is characterised by a high level of heterogeneity in patient populations, diagnostic criteria (including use of CRP levels in isolation or as part of a clinical algorithm), CRP cut-points, how the performance of the test is reported

and the absence of a universal reference standard for the diagnosis of RTIs requiring antibiotic treatment. Meta-analysis of the data was therefore not appropriate and a narrative review was presented. Planned subgroup analysis (children, older adults [≥65 years of age] patients attending out-of-hours (OOH) services and those in long-term care (LTC) facilities) were not possible due to limited data. Only one study included children (aged 3 months to 15 years) and no study specifically reported on CRP testing in older adults. Therefore no conclusions can be drawn on the diagnostic test accuracy of CRP testing in these subgroups and instead, results should be interpreted in terms of the general population. The results of this systematic review do provide important insights into the performance of CRP as a test to help identify patients who will benefit from antibiotic treatment and to aid decision-making for a number of conditions.

The evidence in relation to the diagnostic test accuracy of CRP in URTI is inconclusive. Limited evidence was found for the use of CRP testing in patients presenting with symptoms of acute sinusitis. Given this, and that current clinical guidelines do not generally recommend the use of antibiotics in acute sinusitis, it is unclear what the aim of CRP testing, on its own or as part of a clinical prediction rule, would be even if a suitable threshold could be established.

In pharyngitis/tonsillitis, treatment with antibiotics is generally only recommended in those with group A streptococcal (GAS) infection (5% to 30% of those presenting with sore throat). A cut-point of 35 mg/L CRP may be useful in discriminating bacterial from non-bacterial pharyngitis. One study suggests that at this threshold CRP may be useful as part of a clinical prediction rule in patients presenting with sore throats, whose diagnosis remains inconclusive after clinical examination; however this score required further validation. In contrast, at a threshold of 6 mg/L the use of CRP in combination with a clinical prediction rule to rule out GAS could lead to unnecessary prescribing of antibiotic. This study also reported that CRP POCT may not perform better than other available tests (i.e. RADT) in the detection of GAS infection. (D1002)

Current clinical guidelines recommend antibiotic treatment for pneumonia irrespective of the aetiology. With the exception of patients at higher risk of complications, antibiotics are generally not recommended for other LRTIs as these are generally considered to be self-limiting with limited clinical benefit from antibiotic treatment.

The high level of heterogeneity across studies evaluating the diagnostic test accuracy of CRP testing in pneumonia patients, mainly concerning the type of intervention and how performance of the test was reported, made comparison across studies difficult. Patients with pneumonia may present with low levels of CRP, therefore use of CRP levels in isolation may lead to cases of pneumonia being missed. At a CRP cut-point of 20 mg/L, three out of four studies found the sensitivity to be <0.75, and considered it too low to use as a rule-out threshold for pneumonia, while most studies found a CRP cut-point of 50 or 100 mg/L as sufficiently specific to use as a rule-in threshold for the diagnosis of pneumonia. Many of the DTA studies used CRP testing in combination with a clinical prediction rule, making it difficult to determine the effect CRP testing had on its own. While the value of CRP testing in addition to clinical signs and symptoms for the diagnosis of pneumonia in primary care is unclear, it appears most useful in patients where primary care physicians have diagnostic uncertainty. (D1005) (D1006)

A key finding of the review is that the sensitivity and specificity of the test was generally poor. It would be possible to pick a cut-point such that either the sensitivity or specificity was high, but not both. If a cut-point is chosen that ensures high sensitivity then the test may be better for ruling out, whereas setting it for high specificity is better for ruling in. The findings suggest that different cut-points might be suitable depending on the type of acute RTI with which the patient presents. However, the use of different cut-points could cause confusion, while the use of a universal cut-point would entail different

rates of misdiagnosis across RTI types. Taken at face value, based on the diagnostic test accuracy, CRP POCT is not a very good test for distinguishing between viral and bacterial RTIs. However, that finding is contradicted by the significant impact on antibiotic prescribing observed in the clinical effectiveness trials. It may therefore be that the accuracy of the test is of lesser importance, and what is more critical is that it facilitates a discussion between the clinician and the patient and perhaps a more conservative treatment approach to managing acute RTIs.

Only four studies related to CRP POCT in primary care; all other studies used CRP tests carried out by laboratory staff either using a CRP POCT device or standard laboratory equipment. Therefore, It is not certain if the findings are applicable to CRP POCT when performed at the point-of-care by the intended user. It is noted that one study reported that differences in CRP measurements obtained with POCT devices compared to standard laboratory measurement did not translate into clinically relevant differences in the diagnosis of radiographic pneumonia in adults presenting with acute cough in primary care.

The review was limited to patients presenting to primary care with symptoms of acute RTI. This criterion was strictly applied, so studies that included patients presenting to other treatment settings such as hospital emergency departments, urgent care centres and outpatient clinics were excluded unless the data specific to primary care could be extracted. The applicability of data from these settings to primary care was considered limited due to differences in staffing, access to diagnostic services and the spectrum of presenting patients. Data in relation to a number of CRP POC devices were therefore excluded from this systematic review. However, it is noted that the restriction may not be relevant to all countries, where certain outpatient clinics and urgent care centres may be considered part of the primary care system.

Analytical performance

A total of 18 studies evaluated the analytical performance of two semi-quantitative POCT devices and 11 quantitative POCT devices. The literature regarding the analytical performance of quantitative and semi-quantitative POC tests varied widely in terms of the study design, reported results and the quality of evidence presented. Analytical performance was presented as a measure of accuracy and or precision. Ten studies also include information on the ease of use of the device. There were three methodologies used in the included studies, with studies differing in the origin of the blood sample, the operator performing the test or the setting for the test (laboratory or primary care). Differences in the assessment of analytical performance as well as differences in the study methodology make direct comparison of the study data difficult.

The relevance of the accuracy and precision of CRP POCT devices in clinical decision-making can be seen by using the NICE guidelines for pneumonia as an example. These provide a recommendation that CRP POCT should be considered for patients with symptoms of LRTI in primary care if a diagnosis is unclear after clinical assessment, and that antibiotics should be prescribed based on the test result, that is, CRP <20 mg/L (no antibiotic required), a CRP ≥100 mg/L (immediate antibiotic prescription), and a CRP of 20–99 mg/L (consider a delayed antibiotic prescription). These are broad concentration categories and it could be argued that we are only interested to know if the analytical performance using CRP POCT is sufficient to ensure that the categorisation of patient samples is consistent with that which can be achieved with laboratory-grade testing. Therefore, while some of the devices have poorer performance in the lower (<2 mg/L) or upper (>100 mg/L) CRP concentrations, this may not be clinically relevant for the use of these devices for patients presenting with RTIs.

On the basis of the findings, it would appear that most of the devices are sufficiently accurate and precise under ideal laboratory conditions and could be used in the primary care setting, but training

would need to be put in place to ensure healthcare personnel who are likely to use the devices in practice are thoroughly trained. In addition, an external quality assurance scheme would need to be established to ensure adequate levels of accuracy and precision are being maintained over time. Core to a quality assurance scheme is the use of predefined levels for accuracy and precision so that those using CRP POCT in primary care can be assured that test results have an acceptable level of analytical performance. Although there are no universally recognised cut-points to indicate acceptable accuracy of a CRP POCT, Scandinavian health bodies (Norway, Sweden and Denmark) agree that greater than +/- 15% bias indicated poor performance [17, 23]. Further work would be needed to establish what is an acceptable level of accuracy within each county.

Conclusion

We are moderately confident that the use of CRP POCT leads to a significant reduction in the number of patients presenting to primary care with an RTI being given an antibiotic prescription at their index consultation. We are confident that this reduction is achieved without compromising patient safety. These findings are based on short-term data. It is not clear if the behavioural change is sustained over time or if the conditions in the trials (that is, ongoing use of CRP POCT to inform decision making) can be maintained. Given the high prescribing rate for acute RTIs, this reduction is likely to be clinically important as it reduces an individual's future risk of antibiotic resistance as well as reducing unnecessary antibiotic use for self-limiting RTIs when antibiotic-related harm is more likely that benefit,.

In terms of DTA, there is very limited evidence for the use of CRP to support antibiotic prescribing decisions in patients presenting with acute RTIs in primary care. In patients with ambiguous clinical findings, CRP testing may be useful when used in conjunction with clinical examination or as part of a clinical decision rule to identify those patients who are unlikely to benefit from an antibiotic, particularly where there is diagnostic uncertainty based on clinical examination alone. However, further validation of prediction rules incorporating CRP measurement is required.

The analytical performance of the CE marked quantitative CRP POCT devices evaluated in this assessment is broadly comparable to laboratory CRP testing when used in idealised circumstances. Performance may be poorer at extreme levels, but this is unlikely to impact decision-making in primary care where the decision to prescribe or not to prescribe an antibiotic applies to all values above or below a threshold. There is evidence of greater variability in performance when used by non-laboratory trained healthcare staff in primary care, with the variation most likely due to operator error. Devices that are easier to use may be associated with improved performance. To minimise the risk of operator error contributing to poor analytical performance, adequate training is necessary to ensure devices are used correctly and appropriately, along with a quality assurance programme to ensure that test performance is maintained over time.

Further research is required to validate the long-term effectiveness of CRP POCT to change prescribing behaviour and to validate its effectiveness and safety in specific sub-populations such as children and older adults (>65 years) and in different primary care settings (out-of-hours clinics and long-term care facilities) where the spectrum of patients may differ.

1 SCOPE

PICO for systematic review 1: Effectiveness of using CRP POCT to guide antibiotic prescribing in patients with acute RTIs in primary care settings

Description	Project scope
Population	The population of interest is represented by patients of all ages who present with symptoms of acute respiratory tract infection in primary care. Subgroups of particular interest include: children, older adults (≥65 years of age), patients attending out-of-hours (OOH) services and those in long-term care (LTC) facilities. ICD-10: J00 – J22 (upper and lower RTI), J40 (bronchitis not specified as chronic or acute), H65-H66 (otitis media). MeSH: C01.539.739, C08.730 (respiratory tract infection), C09.218.705.663 (otitis media), C07.550.781, C08.730.561, C09.775.649 (pharyngitis), C08.618.248, C23.888.852.293 (cough)
Intervention	CRP POC test for use in primary care setting (+/- communication training, +/- education component, +/- other biomarkers) in addition to standard care. Testing for CRP may assist the clinician in differentiating between bacterial and viral aetiology and therefore guide antibiotic prescribing. POC tests allow the test to be done at the time of consultation with results available within minutes. Twelve CE marked quantitative devices and three CE marked semi-quantitative methods will be considered in this assessment. The names of products and the corresponding manufacturers are: <u>Quantitative devices:</u> QuikRead® CRP for use on QuikRead® 101 instrument; QuikRead go® CRP for use on QuikRead go® instrument; QuikRead go® CRP+Hb for use on QuikRead go® instrument (Orion Diagnostica Oy) Alere Afinion™ CRP for use on Afinion™ AS100 analyser; NycoCard™ CRP test for use with NycoCard™ READER II (Abbott [Alere]) CRP assay for use with Cube S analyser (EuroLyser) CRP assay for iChroma™ instrument; AFIAS CRP for use with AFIAS 1 (Boditech Med) CRP assay run on AQT90 Flex (Radiometer Medical ApS) CRP assay run on Microsemi instrument (Horiba) spinit® CRP (Biosurfit) InnovaStar® instrument (DiaSys Diagnostic Systems GmbH) <u>Semi-Quantitative devices:</u> Actim® CRP (Medix Biochemica) Cleartest® CRP (Servoprax) FebriDx® (RPS Diagnostics) MeSH-terms: D12.776.034.145, D12.776.124.050.120, D12.776.124.486.157 (CRP), N04.590.874.500 (point of care tests)
Comparison	Standard care alone
Outcomes	**Primary outcomes:** <u>Prescribing outcomes</u> ➢ Number of patients given antibiotic prescriptions (delayed +immediate) for acute RTI (at index consultation and at 28-days follow-up) <u>Patient outcomes</u> ➢ Number of patients with substantial improvement or complete recovery at seven and 28-days follow-up ➢ Patient mortality at 28-days follow-up **Secondary outcomes:** <u>Prescribing outcomes:</u> ➢ Number of patients given an antibiotic prescription for immediate use versus delayed use

Description	Project scope
	➢ Number of patients who redeemed a prescription for an antibiotic Patient outcomes: ➢ Time to resolution of acute RTI symptoms ➢ ADR, including number of patients reconsulting or hospitalised due to ADR ➢ Number of patients with RTI complications resulting in reconsultation ➢ Number of patients with RTI complications in need of hospitalisation ➢ HRQOL ➢ Patient satisfaction ➢ Physician satisfaction Rationale: the included outcomes have been identified from systematic reviews [24, 25] MESH terms: D27.505.954.122.085 (antibacterial agents)
Study design	RCTs, cluster RCTs, non-randomised studies, observational studies

Abbreviations: ADR – adverse drug reactions; CRP – C-reactive protein; HRQOL – Health-related quality of life; LTC – long-term care; MeSH – medical subject heading; OOH – out-of-hours; RCT – randomised controlled trial; RTI – respiratory tract infection.

PICOS for systematic review 2: Diagnostic test accuracy of CRP in patients presenting with acute RTIs in primary care

Description	Project scope
Population	The population of interest is represented by patients of all ages who present with symptoms of acute RTI in primary care. Subgroups of particular interest include: children, older adults (≥65 years of age), patients attending out-of-hours (OOH) services and those in long-term care (LTC) facilities. ICD-10: J00 – J22 (upper and lower RTI), J40 (bronchitis not specified as chronic or acute), H65-H66 (otitis media), MeSH: C01.539.739, C08.730 (RTI), C09.218.705.663 (otitis media), C07.550.781, C08.730.561, C09.775.649 (pharyngitis), C08.618.248, C23.888.852.293 (cough)
Intervention	CRP POC test for use in primary care setting (+/- other biomarkers). Testing for CRP may assist the clinician in differentiating between bacterial and viral aetiology and therefore guide the prescription of antibiotics. POC tests allow the test to be done at the time of consultation with results available within minutes. Any CE marked CRP POC quantitative or semi-quantitative method will be considered in this assessment: MeSH-terms: D12.776.034.145, D12.776.124.050.120, D12.776.124.486.157 (CRP) , N04.590.874.500 (POC tests)
Comparison	For the diagnostic test accuracy review, the diagnostic standard used for comparison will be dependent on the acute RTI of interest (microbiological/laboratory/radiological confirmation). Each disease group will be analysed separately.
Outcomes	Primary outcomes: ➢ Sensitivity and specificity ➢ PPV and NPV ➢ Likelihood ratio ➢ Area under the ROC curve (AUC) ➢ DOR
Study design	Diagnostic test accuracy studies

Abbreviations: AUC – area under curve; CRP – C-reactive protein; DOR – diagnostic odds ratio; DTA – diagnostic test accuracy; LTC – Long term care; MeSH – medical subject heading; OOH – out-of-hours; NPV – negative predictive value; PPV – positive predictive value; RTI – respiratory tract infection; ROC – receiver operating characteristic.

PICOS for systematic review 3: Analytic performance of commercially available CE marked CRP POCT

Description	Project scope
Population	The population of interest is represented by patients of all ages who present to primary care.
Intervention	CRP POC test for use in primary care setting (+/- other biomarkers) Twelve CE marked quantitative devices and three CE marked semi-quantitative methods will be considered in this assessment. The names of products and the corresponding manufacturers are: <u>Quantitative devices:</u> QuikRead® CRP for use on QuikRead® 101 instrument; QuikRead go® CRP for use on QuikRead go® instrument; QuikRead go® CRP+Hb for use on QuikRead go® instrument (Orion Diagnostica Oy) Alere Afinion™ CRP for use on Afinion™ AS100 analyser; NycoCard™ CRP test for use with NycoCard™ READER II (Abbott [Alere]) CRP assay for use with Cube S analyser (EuroLyser) CRP assay for iChroma™ instrument; AFIAS CRP for use with AFIAS 1 (Boditech Med) CRP assay run on AQT90 Flex (Radiometer Medical ApS) CRP assay run on Microsemi instrument (Horiba)) spinit® CRP (Biosurfit) InnovaStar® instrument (DiaSys Diagnostic Systems GmbH) <u>Semi-Quantitative devices:</u> Actim® CRP (Medix Biochemica) Cleartest® CRP (Servoprax) FebriDx® (RPS Diagnostics) MeSH-terms: D12.776.034.145, D12.776.124.050.120, D12.776.124.486.157 (CRP), N04.590.874.500 (POC tests)
Comparison	Standard laboratory CRP measurement or another CRP POCT instrument
Outcomes	<u>Primary outcomes:</u> ➢ Measures of accuracy (level of agreement between the result of one measurement and the true value) and precision (degree of reproducibility of the result) will be extracted for each CRP POCT device <u>Secondary outcomes:</u> ➢ Where available, information on ease of use and suitability for primary care POCT will also be collected and summarised for each device
Study design	Any study reporting on analytical performance

Abbreviations: CRP – C-reactive protein; MeSH – medical subject heading; POCT – point-of-care testing

2 METHODS AND EVIDENCE INCLUDED

2.1 Assessment Team

HIQA (lead authors):

- Developed the first draft of the EUnetHTA project plan
- Identified and contacted manufacturers
- Performed the literature search and study selection
- Conducted the assessment (extraction, analysis, synthesis and interpretation of findings)
- Developed the first draft of the relative effectiveness assessment (REA)
- Sent the first draft to dedicated reviewers, compiled feedback, answered comments and performed changes according to reviewers' comments

HVB (co-authors):

- Collaborated in the development of the EUnetHTA project plan
- Checked, provided input and endorsed all steps (e.g. collaboration in literature selection, data extraction, assessment of risk of bias)
- Checked, provided input and endorsed content of all domains. Collaborated on the writing of the discussion and conclusions, and endorsed same
- Reviewed drafts of the assessment, proposed amendments where necessary and provided written feedback

Dedicated reviewers:

- Reviewed draft project plan, proposed amendments where necessary and provided written feedback
- Rated the relevance of outcomes (GRADE method)
- Reviewed assessments, proposed amendments where necessary and provided written feedback

2.2 Scoping phase

During the scoping phase, the assessment team, external experts, manufacturers and a patient representative were consulted and asked to provide feedback regarding the population, intervention, comparator, patient-related outcomes, and study design (PICOS) for each of the three planned systematic reviews. A scoping meeting was organised before the start of the assessment to discuss the PICOS questions. This was attended by members of the assessment team, with external experts and the patient representative providing verbal feedback to the assessment team. The initial draft of the project plan agreed by the assessment team was circulated, developed and agreed upon by the authors and co-authors. In order to provide further transparency to the process, GRADE and GRADEpro (an electronic tool that allows and facilitates participation of panel members) were used to rate the importance of the outcomes identified.

2.3 Source of assessment elements

The selection of the assessment elements for each of the four domains – the description and technical characteristics of the technology, the health problem and current use of the technology, clinical effectiveness, and safety – was based on the assessment elements contained in the EUnetHTA Core

Model® Application for rapid relative effectiveness assessment (REA) Version 4.2 https://www.eunethta.eu/wp-content/uploads/2018/06/HTACoreModel_ForRapidREAs4.2-3.pdf [26]. Additionally, assessment elements from other HTA Core Model Applications (diagnostic technologies) were screened and included or merged with the existing questions if deemed relevant. General questions referring to selected issues were translated into specific answerable questions, which were either grouped together or answered individually, as appropriate.

2.4 Search

To identify relevant studies, systematic searches were carried out on the following databases:

- MEDLINE (OVID, Pubmed)
- Embase
- CINAHL (via EBSCOHost)
- The Cochrane Library

In addition, for systematic review 3 on analytical performance, OpenGrey and Scopus were searched as this type of study is more likely to be found in the grey literature. Hand searching of the literature was also undertaken including a cross-check of the reference list of included studies and relevant systematic reviews as well as citation tracking. Ad hoc internet searches were undertaken to identify other relevant grey literature. Finally, lists of relevant studies provided by manufacturers in their submission files were searched for additional studies. Submission files were submitted by three companies: Abbott (Alere), Orion Diagnostica Oy, and RPS Diagnostics. These files were used along with material from other company websites to inform the technology description domain. The following clinical trial registries were searched for registered ongoing clinical trials and observational studies: ClinicalTrials.gov and International Clinical Trials Registry Platform (ICTRP). Detailed tables can be found in the 'documentation of the search strategies' in Appendix 1. A separate search for clinical guidelines (G-I-N, National Guidelines Clearinghouse, hand searches) was also undertaken.

This REA comprises three systematic reviews that covered assessment elements for the clinical effectiveness and safety domains. The purpose of these reviews is to answer three research questions in relation to the use of CRP POCT to guide antibiotic prescribing in patients presenting with symptoms of acute RTI in primary care settings (Table 4).

Table 4: Research questions answered and the related systematic reviews

No.	Question	Systematic Review
1	Does the use of CRP POCT in primary care lead to a significant reduction in antibiotic prescribing without compromising patient safety?	Effectiveness and safety
2	What is the diagnostic test accuracy of CRP in patients presenting with acute RTIs in primary care?	Diagnostic test accuracy studies
3	Do the commercially available CE marked CRP POC tests marketed for use in primary care compare with standard laboratory CRP measurement and do they have comparable analytical performance? That is, are they interchangeable in terms of accuracy, precision and ease of use?	Analytical performance

Search strategies were designed for the various databases identified above for each of the three systematic reviews. Details of the search strategies are provided in Appendix 1.

At the time of the systematic literature searches, no limitations were applied with regard to study design or language. No limits were applied for the year of publication for the first two systematic reviews (clinical effectiveness and diagnostic test accuracy). The search for the third systematic review (analytical performance) was limited to publications from 1990 onwards as performance data from older studies were considered unlikely to be relevant to the current commercially available POC tests.

Two authors from HIQA independently reviewed titles and abstracts for each systematic review search. The full text of potentially eligible articles was reviewed by the two authors independently and the study included or excluded based on predefined criteria (see Section 1: Scope). Studies that did not provide data on the relevant outcomes were excluded. Studies that reported on duplicate data were identified and excluded if no additional data were available in the secondary publication. Abstracts from conferences were also excluded. Any disagreement in study selection was resolved through discussion. Studies excluded at full-text review are listed in Appendix 1. The study selection process for each of the three systematic reviews is described in Section 2.5 and Section 5.

Information to inform the description and technical characteristics of the technology (TEC) and current use (CUR) domains was obtained from relevant literature identified in the systematic reviews, the EUnetHTA submission files, clinical guideline sites, and hand searches including searches of manufacturer websites.

2.5 Study selection

As this REA comprises three systematic reviews on three related but separate research questions, to facilitate ease of reading, details of the studies selected for each of the three separate systematic reviews are included in Section 5.

2.6 Data extraction and analyses

Four review authors (KOB, KJ, LM, PM) independently extracted data using prepared data extraction forms developed for these three systematic reviews (SR 1: KOB and KJ; SR 2: PM and KJ; SR 3: KOB and LM). The authors resolved any discrepancy through discussion or with a fifth author (PH).

Measures of treatment effect are reported as a risk ratio with 95% confidence intervals for each dichotomised outcome. When results could not be pooled, they were presented qualitatively. Where it was appropriate to pool data, Review Manager 5 software was used to perform meta-analysis. Heterogeneity was investigated using the I^2 statistic. The choice between fixed and random effects meta-analysis was based on an assessment of the statistical and clinical heterogeneity across studies. Where substantial statistical heterogeneity was observed and sufficient studies were available, a meta-regression was considered to explore study characteristics that may be potential sources of heterogeneity. The following subgroup analyses were planned by:

- Study type: RCT versus cluster RCT versus observational studies
- Age group: children versus adults, younger adults (<65 years) versus older adults (≥65 years)
- Presenting symptoms: upper versus lower RTIs
- Setting: out of hours and those in long-term care

The sample size of cluster randomised controlled trials were modified as recommended in the Cochrane Handbook [27]. Design effect = 1 + (M-1) ICC, where M is the mean cluster size (that is, the average number of people in each cluster) and the ICC is the inter cluster correlation. For studies where the ICC was reported, the ICC was taken from the study. When it was not reported, the ICC was taken from the literature as recommended in the Cochrane handbook.

2.7 Quality rating

2.7.1 Quality appraisal for systematic review 1 (effectiveness and safety)

Two reviewers from HIQA independently assessed the quality or risk of bias of full-text articles included in the review using standardised critical appraisal instruments, with any disagreements resolved through discussion. As both randomised controlled trials and non-randomised studies were included, two separate methods were used to assess the risk of bias of included studies. The Cochrane risk of bias tool was used to assess RCTs and cluster RCTs https://methods.cochrane.org/bias/assessing-risk-bias-included-studies#The%20Cochrane%20Risk%20of%20Bias%20Tool [28]. This tool is used to assess the included studies for selection bias (random sequence generation and allocation concealment), performance bias, detection bias, attrition bias, reporting bias and any other sources of bias [28]. For non-randomised controlled trials and observational studies, the Newcastle Ottawa quality assessment scale was used. With this tool, the studies are assessed for selection bias, comparability and outcomes (https://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0078156/).

The quality of the body of evidence was assessed for each outcome using GRADE (Grading of Recommendations, Assessment, Development and Evaluation) [29]. External experts and members of the authoring, co-authoring and reviewing teams were involved in grading the importance of each of the outcomes identified. Feedback from the patient representative was included as part of the authors' review. The main findings of the review were presented in the 'Summary of findings' (SoF) table, created using the GRADE PRO tool (https://gradepro.org/). Primary review outcomes were listed with estimates of relative effects along with the number of participants and studies contributing data for each outcome. For each individual outcome, the quality of the evidence was assessed using the GRADE approach, which involves considering the risk of bias within studies (limitations in design, inconsistency, indirectness, imprecision and publication bias). Magnitude of the effect, dose-response effect and other plausible confounders were considered in relation to observational studies. Results are expressed as one of four levels of quality (high, moderate, low or very low), the definitions of which are outlined in Table 5.

Table 5: Definition of quality of evidence (GRADE)

Quality rating	Definition
High	"We are very confident that the true effect lies close to the estimate of the effect."
Moderate	"We are moderately confident in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different."
Low	"Our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect."
Very low	"We have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of the effect."

Source: GRADEpro handbook https://gdt.gradepro.org/app/handbook/handbook.html, Table 5.1

Relevant subgroup analyses were assessed for the most important outcomes. Evidence from observational studies was by default rated as low; however, the quality could be upgraded based on: 1) a strong or very strong association; 2) a dose-effect relationship; 3) if all plausible confounding may be working to reduce the demonstrated effect or increase the effect if no effect was observed.

2.7.2 Quality appraisal for systematic review 2 (diagnostic test accuracy)

The Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool was applied to assess the risk of bias in all studies identified in systematic review 2. This tool is designed for use in systematic reviews to evaluate the risk of bias across four domains (patient selection, index test, reference standard and flow of participants) and applicability across three domains (patient selection, index test and reference standard) and is guided by prompt questions. Two authors from HIQA independently assessed the risk of bias of included studies. Disagreements with regard to judgements were resolved through discussion.

2.7.3 Quality appraisal for systematic review 3 (analytical performance)

Standardised critical appraisal instruments to rate the quality of analytical performance studies are limited. As a result, a modified QUADAS-2 tool was used to assess the risk of bias of studies in systematic review 3. All questions from QUADAS-2 were retained. These related to patient selection, index test, reference test, and flow of participants. An additional question was added relating to the operator of the index test. Two authors from HIQA independently assessed the quality of the included studies. Disagreements in judgements were resolved through discussion.

Risk of bias and QoE

Details of the risk of bias of the studies included in systematic reviews (SRs) 1 (effectiveness and safety), 2 (diagnostic test accuracy) and 3 (analytical performance) are included in Sections 5.3, 5.8 and 5.9, respectively, and in Appendix 1.

2.8 Description of the evidence used

Details of the main characteristics of the studies included in systematic reviews (SRs) 1 (effectiveness and safety), 2 (diagnostic test accuracy) and 3 (analytical performance) are included in Sections 5.4, 5.5 and 5.9, respectively and in Appendix 1.

2.9 Patient involvement

Potentially relevant patient organisations were identified through an ad hoc search of the internet, national contacts and via European umbrella organisations. A standardised email was sent to these organisations and followed with further email and phone contact where appropriate. One patient advocacy organisation, Patient Focus (Ireland), identified through this process agreed to participate in the REA and signed the necessary DOICU form. This organisation was involved as part of the scoping phase in order to understand the patient's perspective, to identify possible additional outcomes of interest and to understand the relative importance of the outcomes identified. The preliminary PICO was provided to the organisation along with the draft project plan which provided additional background information. The HTAi patient group submission template was used as a basis of a semi-structured telephone interview. The feedback provided was included in the discussions with the assessment team at the scoping e-meeting and was incorporated by the authors in their rating of the outcomes of interest through GradePRO.

2.10 Deviations from project plan

While the scope of the assessment was not changed (that is, no change to the PICOS), additional assessment elements (AEs) were added from the diagnostic accuracy core model as they were more

relevant to the outcomes being described than the AEs in the REA model. Additional AEs added were: D0021 change in management, “How does use of the test change physicians' management decisions”; D1001 “What is the accuracy of the test against the reference standard”; D1003 “What is the reference standard and how likely does it classify the target condition correctly”; D1005 “What is the optimal threshold in this context”; D1006 “Does the test reliably rule in or out the target condition”; D1008 “What is known about the intra- and inter-observer variation in test interpretation”.

For SR2, a number of identified studies reported mean CRP levels in the sample population. Although this is not a measure of diagnostic test accuracy, it was included in the analysis to provide context in relation to the clinical usefulness of CRP cut-points.

Evidence from SR 3 (analytical performance) suggested the accuracy and precision of CRP POCT is sufficiently comparable to that of standard laboratory-based testing. For this reason, studies that measured CRP levels using CRP POCT devices (at the point of care or in the laboratory) or used standard laboratory CRP measumement were considered eligible for inclusion in SR 2 (diagnostic test accuracy). Clarity as to how CRP levels were measured is provided when reporting study results.

3 DESCRIPTION AND TECHNICAL CHARACTERISTICS OF TECHNOLOGY (TEC)

3.1 Research questions

Element ID	Research question
B0001	What is C-reactive protein (CRP) point-of-care testing (POCT)?
A0020	For which indications have each of the CRP POCT devices/methods received CE marking?
B0002	What is the claimed benefit of CRP POCT technology in relation to standard care for guiding antibiotic treatment in patients presenting to primary care settings with symptoms suggestive of an acute RTI? What might be the potential harms or risks of this technology in relation to standard care?
B0004	Who administers CRP POCT? In what context is it provided? In what primary care settings is it used (e.g. GP practices, out-of-hours clinics, long-term care facilities)?
B0009	What equipment, supplies and training are needed to implement CRP POCT in primary care?
B0003 A0021	What is the phase of implementation of CRP POCT in the various European countries participating in EUnetHTA? What is the reimbursement status of CRP POCT in primary care in the European countries participating in EUnetHTA?

3.2 Results

Features of the technology and comparators

[B0001] – What is C-reactive protein (CRP) point-of-care testing (POCT)?

Pathology test results inform diagnostic and treatment decisions that affect health outcomes. These tests have traditionally been performed in laboratories which have systems in place to ensure that the results obtained are comparable between different laboratories and of a consistent quality. Technological development has allowed some pathology testing to be performed near or at the site of the patient at the time of the consultation or encounter. This testing is usually performed outside a laboratory environment by health professionals including nursing and medical staff. Referred to as 'near patient testing' under Regulation (EU) 2017/746 on in vitro diagnostic medical devices (the IVDR) or more commonly as 'point-of-care testing (POCT)', it is intended to provide more rapid and accessible test results to inform patient care than can be achieved from laboratory settings [30]. For consistency, the term POCT will be used in this REA.

This REA is limited to the use of CRP POCT in patients who present with symptoms of acute RTI in the primary care setting. In the case of CRP POCT, the purpose of the test is to assist the clinician assess the likelihood of a serious bacterial infection as opposed to a less serious bacterial infection or viral infection, thereby supporting a decision whether or not to provide an antibiotic. CRP is one of the cytokine-induced acute-phase proteins produced by the liver, the levels of which rise during a general, non-specific response to various infectious and inflammatory triggers [31-35]. CRP combines with bacterial polysaccharides or phospholipids released from damaged tissue to become an activator of the complement pathway. In healthy people, the serum or plasma CRP levels are below 5 mg/L [36-

38]. A rapid increase in CRP can occur about six hours after an acute inflammatory stimulus, with CRP values peaking at approximately 20 to 500 mg/L after 48 hours [39, 40]. As elevated CRP levels may be associated with pathological changes, the CRP assay provides information for the diagnosis, therapy, and monitoring of infectious and inflammatory diseases [31, 35, 39, 40]. Raised concentrations of serum CRP often occur in bacterial infections; however, typically only minor elevations are observed in viral infections [41]. Therefore, when used in combination with clinical judgement, CRP POCT may aid the medical practitioner to rule out serious bacterial infections thereby supporting a decision not to provide an antibiotic to those who are unlikely to benefit from treatment.

Fifteen CRP POCT devices were identified for inclusion in this REA during the scoping phase. These can be broadly divided into two categories:

- Quantitative devices (devices comprising a test kit and analyser)
- Semi-quantitative devices (devices comprising strips, dipsticks or single-use disposable tests)

Table 6 provides an overview of the two different categories of CRP POCT devices, including their mechanism of action, similarities and differences.

Table 6: Overview of commercially available quantitative and semi-quantitative CRP POCT devices

Device type	Mechanism of action	Similarities	Differences
Quantitative assay kit and analyser instrument	Analysis using: Immunoturbidimetric measurement using fingerstick blood samples, whole blood, serum or plasma (n=6). Solid-phase immuno-chemical (or immuno-metric) assays (n=2). Fluorescence immunoassays (n=2) Solid-phase sandwich immunoassay (n=1). Multi-method immunoassay with haematology and clinical chemistry targets (n=1).	All tests: • Are CE marked • can detect whether CRP levels are low or high in a blood sample. • use relatively small volumes (2.5 to 20 µL of capillary blood. • time to result does not exceed 15 mins for any technology. • .	All 12 tests require an analyser. Quantitative CRP result. Time to result ranges from 4 to 13.5 mins across 12 analysers. Analytical range: 0.5 mg/L to 400 mg/L with all technologies covering 8 to 160 mg/L. Additional POCT assays are possible with all analysers.
Semi-quantitative test strips, dipsticks or single-use disposable test (SUDT)	Immunochromatographic assay test strip for CRP (n=2). Lateral flow immunoassay using direct sampling micro-filtration technology (n=1).		Tests do not require an analyser. Semi-quantitative result – categorised as low, medium or high for strips and low or high for SUDT. Time to result ranges from 7.5 to 15 mins across 3 tests. Analytical range for CRP in bands for semi-quantitative tests: 0 – >80 mg/L for strips and ≥ 20 mg/L for the single-use disposable device. One device co-tests for the viral biomarker MxA.

Abbreviations: n = number of tests with the specified mechanism of action

Quantitative tests require a small amount of whole blood, plasma or serum. The results are expressed in mg/litre (mg/L) with clinical guidelines typically recommending treatment with antibiotics when the CRP result is above a certain level. Certain analysers are suitable for use with other assays in addition to CRP; for example immunochemical faecal occult blood tests, urine albumin, glycated haemoglobin, urine albumin/creatinine ratio, D-dimer levels, lipoprotein A, total leucocytes, white blood cells, haematocrit and haemoglobin.

Semi-quantitative tests do not require an analyser. A small amount of capillary blood is applied directly to the test strip, or mixed with dilution buffer for a dipstick test, which then provides an indication of whether the patient has a low, medium or high CRP level. For one particular device, the CRP test is used in combination with a viral biomarker (that is, Myxovirus resistance protein A (MxA) in the FebriDx® test) to provide additional information regarding the likely aetiology (bacterial or viral) of the infection [34].

Table 7 provides the features of the 15 marketed CRP POCT devices in Europe relevant to this assessment. Data to inform this table were collected from the manufacturers and the literature review in the assessment process. Additional data were obtained from medtech innovation briefings on three of the CRP POCT devices: Alere Afinion™ CRP, QuikRead go® and FebriDx® undertaken by NICE in the UK [32-34].

Local, national and international clinical guidelines describe how CRP POCT may be used to inform prescribing decisions in primary care. For example, in the UK, NICE guidelines for the diagnosis and management of pneumonia in adults [42] recommend:

- the use of CRP POCT when it is not clear if antibiotics should be prescribed based on clinical assessment
- not routinely offering antibiotic therapy if the CRP concentration is less than 20mg/L
- considering a delayed antibiotic prescription (a prescription for use at a later date if the symptoms worsen) if the CRP concentration is between 20mg/L and 100mg/L
- offering antibiotic therapy if the CRP concentration is greater than 100mg/L.

It should be noted that semi-quantitative devices will narrow the CRP threshold choices available for clinical guidance on higher CRP cut-points.

The CRP POCT can be used in combination with communication training, an education component and/or tests for other biomarkers in addition to standard care to assist the treating clinician in differentiating between bacterial and viral aetiology, and thereby guide antibiotic prescribing. In order for the administration of CRP POCT to be most beneficial in the primary care setting, it must provide timely results to the medical practitioner, ideally within a number of minutes so, that they are available within the usual allotted consultation time.

Table 7: Features of the intervention

Technology					
	Quantitative CRP analysers				
Device type	**Assay kit & analyser**	**Assay kit & analyser**	**Assay kit & analyser**	**Assay kit & analyser**	**Assay kit & analyser**
Proprietary name	QuikRead go® CRP assay and QuikRead go® instrument	QuikRead go® CRP+Hb assay and QuikRead go® instrument	QuikRead® CRP assay and QuikRead® 101 instrument	Alere Afinion™ CRP assay and Alere Afinion™ AS100* or Alere Afinion™ 2**	NycoCard™ CRP assay and NycoCard™ Reader II
Manufacturer	Orion Diagnostica Oy	Orion Diagnostica Oy	Orion Diagnostica Oy	Abbott Diagnostic Technologies AS	Abbott Diagnostic Technologies AS
Reference codes	QuikRead go® CRP assay: 135171 (50 tests), 151461 (25 tests), 135174 (500 tests). Localised test versions: 133891, 145215,135172,135173,135283, 135174,125175 and QuikRead go® instrument: 133893. Localised versions: 135867,149915,145218,136196 QuikRead® CRP control: 68296 QuikRead go® CRP control High: 137071	QuikRead go® CRP+Hb assay: 140068 (50 tests) and QuikRead go Instrument: 133893. Localised versions: 135867,149915,145218,136196 QuikRead® CRP control: 68296 QuikRead go® CRP control High: 137071	QuikRead® CRP assay: 134191, 134193 (50 tests). Additional test versions: 67961, 128574,128577, 68798, 06160, 134194,134197,134195, 134198,128575,106161 and QuikRead® 101 instrument: 06040, 06078 QuikRead® CRP control: 68296	Alere Afinion™ CRP: 1116526, 1116522, 1116524, 1116023 (15 tests) and Afinion™ AS100 Analyser: 1116049 or Alere ™ 2 Analyser: 1116679, 1116680, 1116681 Alere Afinion™ CRP control: 1116057	NycoCard™ CRP: 1116078, 1116080 and NycoCard™ Reader II: 1116149 Alere Afinion™ CRP control: 1116057
Class/GMDN code	General Category IVD, CE marked in accordance with the IVD directive 98/79/EC; GMDN code 53705.	General Category IVD, CE marked in accordance with the IVD directive 98/79/EC; GMDN code 53705	General Category IVD, CE marked in accordance with the IVD directive 98/79/EC; GMDN code 53705	General Category IVD, CE marked in accordance with the IVD directive 98/79/EC; GMDN code 53707	General Category IVD, CE marked in accordance with the IVD directive 98/79/EC; GMDN code 53707

Technology					
	Quantitative CRP analysers				
Device type	**Assay kit & analyser**	**Assay kit & analyser**	**Assay kit & analyser**	**Assay kit & analyser**	**Assay kit & analyser**
Additional tests	Strep A, iFOB	Strep A, iFOB	iFOB, U-ALB	HbA1c, lipid panel, ACR	HbA1c, D-dimer, U-Albumin
Method	Immunoturbidimetric assay	Immunoturbidimetric assay	Immunoturbidimetric assay	Solid phase immuno-chemical assay	Solid phase immuno-metric assay
Sample size & type (+alternative materials)	20 µL capillary blood (venous whole blood, plasma or serum)	20 µL capillary blood (venous whole blood, plasma or serum)	20 µL capillary blood (venous whole blood, plasma or serum)	2.5 µL capillary blood (venous whole blood, serum or plasma)	5 µL capillary blood (venous whole blood, serum or plasma)
Analytical range (whole blood)	5 – 200 mg/L CRP	5 – 200 mg/L CRP 50 – 245 g/L Hb	8 – 160 mg/L CRP	5 – 200 mg/L CRP	8 – 200 mg/L CRP
Calibration	No – automatic	No – automatic	Yes – 15 sec	No – automatic	Yes – 15 sec
Haematocrit auto-correction	Yes[a]	Yes[a]	No	Yes[a]	No – calibrated to read 40% Ht
Special storage requirements for test (e.g. refrigeration)	CRP Reagent caps (in opened and unopened aluminium tube): 2-8°C (until expiry); 15-25°C; 24 hrs per day (1 month) & 7.5 hrs per day (3 months). Prefilled cuvettes in unopened foil pouches: 2-25°C (until expiry). It will take 15 minutes for an individual refrigerated prefilled cuvette to reach room temp.	CRP Reagent caps (in opened and unopened aluminium tube): 2-8°C (until expiry); 15-25°C; 24 hrs per day (1 month) & 7.5 hrs per day (3 months). Prefilled cuvettes in unopened foil pouches: 2-25°C (until expiry). It will take 15 minutes for an individual refrigerated prefilled cuvette to reach room temp.	CRP Reagent caps (in opened and unopened aluminium tube): 2-8°C (until expiry); 15-25°C; 24 hrs per day (1 month) & 7.5 hrs per day (3 months). Prefilled cuvettes in unopened foil pouches: 2-25°C (until expiry). It will take 15 minutes for an individual refrigerated prefilled cuvette to reach room temp.	Test Cartridge must reach an operating temperature of 15-30°C before use. Upon removal from refrigerated storage, leave the test cartridge in unopened foil pouch for at least 15 mins.	NycoCard™ test tube with dilution liquid is stored in refrigerator. It must be brought to room temperature before analysis.

Technology					
	Quantitative CRP analysers				
Device type	**Assay kit & analyser**	**Assay kit & analyser**	**Assay kit & analyser**	**Assay kit & analyser**	**Assay kit & analyser**
Analyser size and weight	14.5 x 15.5 x 27 cm 1.7 kg	14.5 x 15.5 x 27 cm 1.7 kg	8 x 14 x 22 cm 1.0 kg	17 x 19 x 34 cm and 5.0 kg* 20 x 19 x 33 cm and 3.4 kg**	20 x 17 x 7 cm instrument box 2.95 x 14.4 cm (reader pen) 0.54 kg
Analyser warm-up time	50 sec	50 sec	30 sec	Afinion™ AS100: 3 min Alere™ 2 Analyser: 1 min 30sec sec	25 sec
Performance time for pre- and actual analysis	4.5 min (= 2.5 min + 2 min)	4.5 min (= 2.5 min + 2 min)	5.5 min (= 2.5 min + 3 min)	Afinion™ AS100: 4.25 min (=30sec + 3.75min) Alere™ 2 Analyser: 3.30min (=30sec	8 min 35 sec (= 3 min 35 sec + 5 min)
Practical aspects of test	Pre-analytical handling: capillary with plunger, inner reagent cap pushed through while putting cap on cuvette.	Same as for QuikRead go® CRP assay. 2 results from a single sample in a single run.	Pre-analytical handling involves manual sample & reagent mixing performed prior to analysis on device.	Auto-self check with integrated error detection. Error codes possible due to small sample volume that may dry out after the 1min limit instructed in the package insert. Analyser cannot be moved if on.	Manual sample dilution, conjugate application and washing prior to analysis. Also need to manually adjust and white calibrate the reader pen of the battery-operated instrument.

Technology					
	Quantitative CRP analysers				
Device type	**Assay kit & analyser**	**Assay kit & analyser**	**Assay kit & analyser**	**Assay kit & analyser**	**Assay kit & analyser**
Connectivity	Yes to data transfer to electronic patient files. Measurement results can be sent to LIS.	Yes to data transfer to electronic patient files. Measurement results can be sent to LIS.	Yes to data transfer to electronic patient file and LIS/HIS using QuikRead® Quiklink.	Yes to data transfer to electronic patient files. Alere Afinion™ Data Connectivity Converter (ADCC) is also included for simple transfer of patient and controls results to LIS/HIS.	No to data transfer to electronic patient files.
Print function	Yes	Yes	No	Yes	No
Data storage on device	Yes	Yes	No	Yes	No
Device lifespan	Approx. 5 years or ≥ 50,000 measurements per device	Approx. 5 years or ≥ 50,000 measurements per device	Approx. 5 years or ≥ 50,000 measurements per device	Not reported	Not reported
Maintenance	Designed to be free of regular maintenance with built-in self-check operations.	Designed to be free of regular maintenance built-in self-check operations.	Designed to be free of regular maintenance built-in self-check operations.	Cleaning of cartridge chamber with a swab once a month.	The white calibration device, the pen tip and the pen ring of the instrument/pen should be inspected regularly and replaced if dirty or damaged.
Software updates	New software can be updated to the instrument with a USB stick.	New software can be updated to the instrument with a USB stick.	Software version 7.0 or newer shortens the assay reaction time. No detail on	USB stick upgrade process provides analyser with software	Not possible.

Technology					
	Quantitative CRP analysers				
Device type	**Assay kit & analyser**	**Assay kit & analyser**	**Assay kit & analyser**	**Assay kit & analyser**	**Assay kit & analyser**
Quality checks	QuikRead® CRP control (68296) and QuikRead® go CRP control High (137071) are intended for routine quality control of CRP assays by the QuikRead® go instrument. Low and high conc. approx. 30 and 85 mg/L. Self-diagnosis operational checks	QuikRead® CRP control (68296) and QuikRead® go CRP control High (137071) are intended for routine quality control of CRP assays by the QuikRead® go instrument . Low and high conc. approx. 30 and 85 mg/L. Self-diagnosis operational checks	QuikRead® CRP control (68296) is intended for routine quality control of CRP assays by the QuikRead® 101 instrument. Target control conc. approx. 50 mg/L	Alere Afinion™ CRP Control from Alere is recommended for routine quality control testing with each new lot or delivery of new CRP test kits.	Alere Afinion™ CRP Control is recommended for routine quality control testing with each new lot or delivery of new CRP test kits.
Training & support	Additional costs associated with training. No details provided.	Additional costs associated with training. No details provided.	Additional costs associated with training. No details provided.	Manufacturer provides online learning videos and on-site training at no extra cost.	Manufacturer provides online learning videos and on-site training at no extra cost.
Warranty	2 years	2 years	2 years	12 months	12 months

	Technology				
Semi-/quantitative	**Quantitative CRP analysers**				
Device type	**Assay kit & analyser instrument**	**Assay kit & analyser instrument**	**Assay kit & analyser instrument**	**Assay kit & analyser instrument**	**Assay kit & analyser instrument**
Proprietary name	Eurolyser CRP assay and Cube S Analyser	iChroma™ CRP test cartridge and iChroma™ Reader	AFIAS™ CRP test cartridge and AFIAS 1™	AQT90 Flex CRP assay and AQT90 Flex analyser	Microsemi CRP reagent unit and Microsemi
Manufacturer	Eurolyser Diagnostica	Boditech Med	Boditech Med	Radiometer Medical ApS	Horiba Ltd
Reference codes	Eurolyser CRP assay: ST 0100 CRP test kit (32 tests) ST 0102 CRP test kit with integrated capillary (32 tests) ST 1000 CRP control kit (2 x 2ml)(low/high) Cube S analyser: CA 0110	iChroma™ CRP test cartridge for use with iChroma™ Reader Reference codes not reported.	AFIAS™ CRP for use with AFIAS 1™ Analyser	AQT90 Flex CRP Reagent pack (capacity for 200 separate tests and waste disposals) AQT90 Flex immunoassay analyser 393-838 Reference code from 2008 CE declaration (March 2015)	Microsemi CRP Reagent Unit (50 tests per cartridge, 2 cartridges per box) Microsemi analyser
Class/GMDN code	General Category IVD, CE marked in accordance with the IVD directive 98/79/EC	General Category IVD, CE marked in accordance with the IVD directive 98/79/EC	General Category IVD, CE marked in accordance with the IVD directive 98/79/EC	General Category IVD, CE marked in accordance with the IVD directive 98/79/EC; GMDN code 53705	General Category IVD, CE marked in accordance with the IVD directive 98/79/EC
Additional tests	Microalbumin, D-Dimer, Ferritin, iFOB, K^+ , Lipoprotein A, Troponin I, ASO, CRP, hsCRP, Cystatin C (GFR), Hb, HbA1c, PT (INR)	Troponin I, CK-MB, myoglobin, hsCRP, PSA, AFP, HbA1C, cortisol, malaria, reumafactor IgM, D-dimera, CEA[b], TSH[b], T4[b], FSH[b], hCG[b], LH[b], prolactin[b], testosterone[b], ferritin[b], iFOB[c], microalbumin[c]	Quantitative testing possible using c-tip for TSH, PCT, and HbA1c	D-dimer, beta-hCG, troponin I, troponin T, CK-MB, myoglobin, NT-proBNP	WBC, RBC, Hb, Ht, platelets, lymphocytes, monocytes, granulocytes (calculated: MCV, MCH, MCHC, RDW, PDW, MPV)

	Technology				
Semi-/quantitative	**Quantitative CRP analysers**				
Device type	**Assay kit & analyser instrument**	**Assay kit & analyser instrument**	**Assay kit & analyser instrument**	**Assay kit & analyser instrument**	**Assay kit & analyser instrument**
Method	Immunoturbidimetric assay	Fluorescence sandwich immunoassay	Fluorescence immunoassay	Solid phase sandwich immunoassay	Immunoturbidimetric assay
Sample size & type (+alternative materials)	5 µL capillary blood sample (venous blood/ serum)	10 µL capillary blood sample (venous blood/ plasma/serum)	10uL or 50uL capillary blood sample from finger or heel (whole blood/ plasma/serum)	2 mL venous blood sample (plasma)	18 µL capillary blood sample + dead volume in the tube to 100 µL. (venous blood)
Analytical range (whole blood)	2.0 – 240 mg/L CRP	2.5 – 300 mg/L CRP	0.5~200 mg/L CRP	5 – 500 mg/L CRP	2.0 – 230 mg/L CRP
Calibration	No – automatic	No	Yes. ID Chip recorded once for each specific lot.	Yes. Adjustment needed when using a new lot no. reagent pack (time needed: 48 mins).	No
Haematocrit auto-correction	Yes[a]	No	No	Yes[a]	Yes[a]
Special storage requirements for test (e.g. refrigeration)	Storage in refrigerator (2-8°C). Allow single test at least 10 mins to warm up to room temperature.	Storage in refrigerator (2-8 °C). Allow detection buffer (DB) tube to attain room temperature for 30 mins before performing test. 2-8ºC for DB / 4-30ºC for cartridge.	Storage in refrigerator (2-8°C).	No special storage requirements. Closed analysis system.	No special storage requirements stated on company brochure.
Analyser size and weight	Instrument: 16 x 13 x 14.5 cm 2.4 kg	18.5 × 8 × 25 cm 1.3 kg	32 x 20 x 18 cm 3.9 kg	45 × 46 × 48 cm 35 kg	43 × 26 × 45 cm 19 kg

	Technology				
Semi-/quantitative	**Quantitative CRP analysers**				
Device type	**Assay kit & analyser instrument**	**Assay kit & analyser instrument**	**Assay kit & analyser instrument**	**Assay kit & analyser instrument**	**Assay kit & analyser instrument**
Analyser warm-up time	Not reported	Not reported	Not reported	Not reported	Not reported
Performance time for pre- and actual analysis	5 min (= 1 min + 4 min)	5 min (= 2 min + 3 min)	5 min (= 2 min + 3 min)	13.5 min (= 30 sec + 13 min) Add 4 mins to install reagent pack if necessary	4.5 min (= 30 sec + 4 min)
Practical aspects of test	Automated, maintenance-free analysis with pre-set calibration curves & auto-self-test routine. Integrated capillary not always easily filled with blood.	Allow detection buffer tube to attain room temperature for 30 mins before performing test. Relatively complicated preanalytical handling using sample with detection buffer. Requirement to shake 10 times and discard first 2 drops before adding 2 drops to test cartridge. Portable analyser.	Semi-automatic immunodiagnostic device which uses all-in-one cartridges; it automatically mixes and dispenses samples when user loads sample only. Desktop analyser (but easy to carry). Empty the C-tip waste box daily.	The system minimises pre-analytical sample handling and utilises a closed sample system for reagent mixing and measurement. No contact with blood or waste. Needs venous blood samples and involves considerable time for analysis. Up to 15 cartridges placed in inlet with up to 16 tests each.	CRP measurement only possible in combination with haematology parameters. All-in-one: 3 reagents in the same cartridge and no need for cartridge removal after use.
Connectivity	Yes. Eurolyser CUBE is suited for connecting to eHealth services due to its internet and network capable android application on the tablet PC.	Yes. Online connection indirectly possible with LIS.	Yes. LIS / HIS communication.	Yes. Online connection possible with HIS and LIS.	Yes. Online connection possible with LIS.

	Technology				
Semi-/quantitative	**Quantitative CRP analysers**				
Device type	**Assay kit & analyser instrument**	**Assay kit & analyser instrument**	**Assay kit & analyser instrument**	**Assay kit & analyser instrument**	**Assay kit & analyser instrument**
Print function	Seiko DPU-414 thermal printer & Seiko Label Printer 650 SE are optional accessories	Printer (optional)	Data output via Internal Printer	Hardware includes 4" thermal-sensitive printer	Integrated thermal printer
Data storage on device	Yes. Data transfer is possible to external devices	No details reported	Yes. 5,000 patient results	Yes. 2,000 patient results	Yes. 180 patient results
Device lifespan	Not reported	Not reported	Not reported	Not reported	Not reported
Maintenance	Designed as maintenance-free. Instrument is calibrated at the factory and has an internal self-check procedure during every measurement.	No details reported	No details reported	No details reported	Refer to "zero-maintenance" concept applicable to the technology.
Software updates	Embedded software and new versions are released for free when new features or functionality improvements are added. Updated via the CUBE app.	No details reported	No details reported	No details reported	No details reported

	Technology				
Semi-/quantitative	**Quantitative CRP analysers**				
Device type	**Assay kit & analyser instrument**	**Assay kit & analyser instrument**	**Assay kit & analyser instrument**	**Assay kit & analyser instrument**	**Assay kit & analyser instrument**
Quality checks	The CUBE system uses single-use reagents, and internal measurements are to be performed once a week. Integrated QC system.	No details reported	No details reported	Built in quality control for continuous analyser performance evaluation. Liquid quality control (LQC) materials for the AQT90 FLEX analyser help estimate the precision of test results and detect systematic analytical deviations that may arise from reagent or analyser variation.	Quality control target values uploaded by flash card.
Training & support	Online video tutorials for analyser set up and training.	No details reported	No details reported	No details reported	No details reported
Warranty	No details reported	No details reported	No details reported	No details reported	No details reported

	Technology				
Semi-/quantitative	**Quantitative CRP analysers**		**Semi-quantitative CRP tests**		
Device type	**Assay kit & analyser instrument**	**Assay kit & analyser instrument**	**CRP test strips**		**Single-use disposable test**
Proprietary name	spinit® CRP disposable disc and spinit® instrument	CRP IS™ test kits and Innovastar™analyser	Actim® CRP dip sticks	Cleartest® CRP strips	FebriDx®
Manufacturer	Biosurfit	DiaSys Diagnostic	Medix Biochemica	Servoprax	RPS Diagnostics
Reference codes	spinit® CRP disposable disc (20 test kit size) Reference codes not reported	CRP IS™ test kits 270699910761 (50 determinations per test kit) 270699910760 (100 determinations per test kit) and Innovastar™analyser	Actim® CRP kit 31031ETAC (20 CRP test packs)	Cleartest® CRP strips C3 4050 (10 and 20 CRP test packs)	FebriDx® BP0036 (25 CRP test kit)
Class/GMDN code	General Category IVD, CE marked in accordance with the IVD directive 98/79/EC	General Category IVD, CE marked in accordance with the IVD directive 98/79/EC	General Category IVD, CE marked in accordance with the IVD directive 98/79/EC	General Category IVD, CE marked in accordance with the IVD directive 98/79/EC	General Category IVD, CE marked in accordance with the IVD directive 98/79/EC; GMDN: 64042.
Additional tests	Hb1Ac and other blood components (total leucocytes, white blood cells and haematocrit)	Glucose, haemoglobin, HbA1c	No	No	MxA
Method	Multi-method combination of immunoassay, haematology and clinical chemistry targets in a disposable test panel	Immunoturbidimetric test	Immunochromatographic	Immunochromatographic	Lateral flow immunoassay

	Technology				
Semi-/quantitative	**Quantitative CRP analysers**		**Semi-quantitative CRP tests**		
Device type	**Assay kit & analyser instrument**	**Assay kit & analyser instrument**	**CRP test strips**		**Single-use disposable test**
Sample size & type (+ alternatives)	5 µL capillary blood sample (whole blood (venous and capillary), serum and plasma)	10 µL capillary blood sample (whole blood and plasma)	10 µL capillary blood sample (can also sample from anti-coagulated whole blood)	10 µL capillary blood sample (can also sample from anti-coagulated whole blood)	5 µL capillary blood sample
Analytical range (blood)	2 – 180 mg/L CRP	5 - 400 mg/L CRP	0 – >80 mg/L CRP	0 – >80 mg/L CRP	Qualitative thresholds: CRP ≥ ~ 20 mg/L MxA ≥ ~40 ng/mL
Calibration	No	No – precalibrated tests. But original calibration stability for 9 months only. To ensure measuring accuracy of the parameter reagent lot in use, recalibration is recommended.	N/A	N/A	N/A
Haematocrit auto-correction	No	Yes[a]	No	No	No
Special storage requirements for test (e.g. refrigeration)	Storage in refrigerator (2 - 8 °C)	Ready-to-use unit dose test. Shelf life 18 months from production.	Storage at 2 to 25 °C. Stored unopened, Each component can be used until the expiry date marked on the component.	Storage at 2 - 30 °C.	No refrigeration or special storage conditions required. The shelf-life for the test kits is 2 years at room temperature.
Analyser size and weight	24 x 22 x 31 cm 4 kg	20 x 15 x 17 cm 4 kg	N/A	N/A	N/A

	Technology				
Semi-/quantitative	**Quantitative CRP analysers**		**Semi-quantitative CRP tests**		
Device type	**Assay kit & analyser instrument**	**Assay kit & analyser instrument**	**CRP test strips**		**Single-use disposable test**
Analyser warm-up time	No details reported	No details reported	N/A	N/A	N/A
Performance time for pre- and actual analysis	5 min (= 1 min* + 4 min) (*however wait-time of at least 3 mins after fridge removal before opening pouch)	8 min (= 1 min + 7 min)	7.5 min (= 2.5 min + 5 min)	7.5 min (= 2.5 min + 5 min*) (*analysis time should not be later than 10 min)	10 min (= performance + time to result). Analysis time should not exceed 3 hours of the results being displayed.
Practical aspects of test	Must remove disc from refrigerator and wait at least 3 minutes before opening pouch.	Fully automated system – no manual steps required during measurement. Single cartridge containing all reagents needed for testing. Precalibrated tests – no time-consuming calibration.	Relatively complicated pre-analytical handling, semi-quantitative, inter-observer variation, cut-off at 80 instead of 100 mg/L.	Relatively complicated pre-analytical handling, semi-quantitative, inter-observer variation, cut-off at 80 instead of 100 mg/L.	FebriDx® does not require any additional ancillary equipment. FebriDx® “high CRP” reading suggests ≥ 20mg/L.
Connectivity	Yes. LIS / HIS communication	No details reported	N/A	N/A	N/A
Print function	Print-out of test results in standard labels with printer (optional accessory)	No details reported	N/A	N/A	N/A
Data storage on device	Yes	50 results			Results display for 3 hours.

	Technology				
Semi-/quantitative	**Quantitative CRP analysers**		**Semi-quantitative CRP tests**		
Device type	**Assay kit & analyser instrument**	**Assay kit & analyser instrument**	**CRP test strips**		**Single-use disposable test**
Device lifespan	Not reported	Not reported	Single-use strip	Single-use strip	Single-use disposable test. Shelf life of 2 years at room temperature.
Maintenance	No maintenance as per manufacturer website	No details reported	N/A	N/A	N/A
Software updates	No details reported	Link to IS Software for software download and update instructions	N/A	N/A	N/A
Quality checks	A self-check is performed automatically when running a test	No details reported	N/A	N/A	External controls are available.
Training & support	No details reported	No details reported	Not reported	Not reported	Training provided through UK distributor as well as RPS Detectors.com or FebrDx.com (NICE MIB July 2017)
Warranty	No details reported	No details reported	N/A	N/A	N/A

Abbreviations: ACR (Albumin/creatinine ratio); AFP (Alpha-fetoprotein); ASO (Anti-Streptolysin-O); CEA (oncofetal glycoprotein); CK-MB (Creatine Kinase either muscle or brain type); FSH (follicle-stimulating hormone); GMDN (Global Medical Device Nomenclature); Hb (haemoglobin); HbA1c (glycated haemoglobin); hCG (human chorionic gonadotropin); HIS (Hospital Information System); hsCRP (high-sensitivity CRP); Ht (haematocrit); iFOB (faecal immunochemical test for haemoglobin); IVD (in vitro diagnostic); K+ (Potassium); LH (Luteinising hormone); LIS (Laboratory Information System); MCH (mean corpuscular haemoglobin); MCHC (mean corpuscular haemoglobin concentration); MCV (mean corpuscular volume); MPV (mean platelet volume); MxA Myxovirus resistance protein A); N/A (not applicable); NT-proBNP (N-terminal pro b-type natriuretic peptide); PCT (Procalcitonin); PDW (platelets distribution width); PSA (prostate specific antigen); PT(INR) Prothrombin Time (international normalized ratio) ; RBC (red blood cell); RDW (red blood cells distribution width); Strep A (*Streptococcus pyogenes*); T4 (Thyroxine); TSH (thyroid stimulating hormone); U-ALB (quantitative test for albumin in urine samples); WBC (white blood cell).

Footnotes: a. If the Hct value is outside the range 20-60 %, no CRP test result will be reported and an information code will be displayed). In these cases serum or plasma samples are recommended for CRP analysis; b. Only in serum/plasma, centrifuge step necessary; c. Urine/faeces.

Sources included: Brouwer (2015)[16] ; Minnaard (2013) [18]; NICE Medtech Innovation Briefing reports for QuikRead® [33], Alere Afinion™ [32] and FebriDx® [34]; dossier submissions from Orion, Abbott, Medix Biochemica and RPS Diagnostics, and available information from manufacturers' websites.

[A0020] – For which indications have each of the CRP POCT instruments/methods received CE marking?

A summary of the regulatory status of the identified CRP POCT devices is provided in Table A16 in Appendix 2. Orion Diagnostica was the first to launch a fully quantitative CRP POCT system (QuikRead®) in 1993. This original device has been followed by newer-generation quantitative devices from Orion Diagnostica and competing manufacturers in the in vitro diagnostic medical device market. The tests are indicated for the quantitative determination of CRP in human whole blood and in human serum and plasma. The measurement of CRP provides information for the detection and evaluation of infection, tissue injury, inflammatory disorders and associated diseases. These tests are CE marked in accordance with the IVD Directive (98/79/EC) and are classified as general category IVDs. The CE marking process for this class of IVDs involves the manufacturer self-declaring that the device is in conformity with the IVD Directive. Semi-quantitative CRP test strips, Actim® and Cleartest®, are also CE marked in accordance with the IVD directive.

The first semi-quantitative CRP and viral biomarker co-test was CE marked in September 2014: FebriDx® is a CE marked rapid in vitro immunoassay for the semi-quantitative measurement of CRP and qualitative measurement of Myxovirus resistance protein A (MxA) in peripheral whole blood. An updated version of the device that included an all-in-one built-in safety lancet, calibrated blood collection and transfer system, and integrated push-button buffer delivery mechanism to help prevent user-related errors and improve test performance has since been developed.

All these IVD medical devices are intended for use by a healthcare professional. The CRP system is indicated for use in patients when it is not clear if antibiotics should be prescribed based on clinical assessment alone.

CRP POCT devices are subject to EU Regulation 2017/746 on In Vitro Diagnostic Devices (IVDR) which came into force at the end of May 2017 [30]. The regulations will have a staggered transitional period, with full application after five years. These regulations replaced a number of existing directives and are intended to strengthen the current regulatory system by providing:

- clearer requirements for clinical data on IVD medical devices, and their assessment
- more specific product requirements, such as a unique identifier for IVD medical devices
- improved pre-market assessment and post-market surveillance of all high-risk devices
- increased control and monitoring of Notified Bodies by the National Competent Authorities and the Commission
- more stringent requirements for POCT (near-patient tests)
- enhanced traceability for IVDs.

One of the key changes under the IVDR relates to the conformity assessment procedures required of manufacturers prior to an IVD being placed on the market. Requirements vary based on the risk classification of the device, that is, for low-risk (Class A) up to high-risk (Class D). Assessment and certification by a notified body for medical devices will be required for those IVD devices in Classes B, C and D. Class A devices placed on the market in a sterile condition shall also require notified body involvement, limited to the sterile aspects of the product. Devices for POCT (near patient testing) are classified in their own right under Rule 4(b) Annex VIII of the 2017 IVDR regulations. Depending on the intended purpose specified by the manufacturer, CRP tests will likely be in Class C (under Rule 3)

or Class B (under Rule 6). This represents a significant change to the existing regulatory system, where the majority of IVDs are self-declared by the manufacturer rather than being assessed by a notified body. Detailed requirements for the performance evaluation of IVDs are outlined in the IVDR. Under the IVDR, IVDs for POCT must perform appropriately for their intended purpose taking into account the skills of the intended user and the potential variation in the user's technique and environment, with sufficient information provided in order for the user to be able to correctly interpret the result provided. It is recognised that the enhanced regulatory burden arising from implementation of the IVDR may impact the number and range of IVDs on the market.

Within each country, the organisation designated as the Competent Authority for medical devices has a role is to ensure that all medical devices sold into the market comply with the relevant legislation. This means that a medical device must achieve the performance criteria specified by the manufacturer and in doing so must not compromise the health and safety of patients, service providers and any other persons. In their role as a Competent Authority, these organisation must operate a vigilance system for medical devices. Vigilance issues include adverse incidents and field safety corrective actions (FSCAs). Reporting includes voluntary reporting systems for users of medical devices, healthcare professionals or any other person who identifies a medical device safety issue. There is a mandatory requirement for manufacturers to report vigilance issues to the appropriate national Competent Authority. The European guidelines for a medical devices vigilance system are outlined in MEDDEV 2.12/1 [16, 43].

A field safety corrective action (FSCA) is an action taken by a manufacturer to reduce a risk of death or serious deterioration in the state of health associated with the use of a medical device that is already placed on the market. Such actions, whether associated with direct or indirect harm, should be reported and should be notified via a field safety notice (FSN). The FSCA may include, for example: the return of a medical device to the supplier; device modification; advice given by manufacturer regarding the use of the device and/or the follow up of patients, users or others. It is very important that providers of CRP POCT have adequate traceability systems in place in the event of a field safety corrective action necessitating, for example, a review of results or the recall of patients for repeat testing.

[B0002] – What is the claimed benefit of CRP POCT technology in relation to standard care for guiding antibiotic treatment in patients presenting to primary care settings with symptoms suggestive of an acute RTI? What might be the potential harms or risks of this technology in relation to standard care?

The aim of the CRP POCT technology is to provide reliable CRP test results, which allow physicians to differentiate between mild and severe RTIs, and to rule out potentially serious bacterial infections, when it is not clear if antibiotics should be prescribed based on clinical assessment alone. The physician follows diagnostic and treatment guidelines, basing antibiotic treatment decision(s) for the patient (of no antibiotic therapy, delayed antibiotic prescription or offering antibiotic therapy) on whether CRP results fall below or above explicit thresholds as outlined earlier.

The technology should therefore have a moderating influence on the need for the physician to issue an immediate prescription for antibiotics. The test result should be available in minutes during patient consultation to support an immediate treatment decision in primary healthcare settings, eliminating the delay in receiving laboratory results (which can often take hours or even days to arrive) and speeding up patient referral to secondary care if required. By assisting physicians to make immediate treatment decisions, the technology is intended to enhance patient safety and compliance with clinical guidelines for the management of RTI, as well as physician and patient satisfaction. CRP

POCT conducted during the patient visit has been found to increase patient satisfaction and understanding of when antibiotics are and are not needed [44].

Debate over the accuracy of POC tests and their effect on antibiotic prescribing is ongoing. Some studies have found the analytical performance of POCT comparable to laboratory testing, while others have reported that certain pieces of equipment are more accurate and precise than others [18, 45]. The ability of CRP POCT to aid in the diagnosis of serious bacterial RTIs is unclear, with some studies finding it useful in primary care [46], while others have reported it to have limited utility [47]. The subsequent effect of CRP POCT on the prescription of antibiotics has shown conflicting results, with some studies finding it significantly reduces antibiotic prescribing [24, 48], while others have found it has little effect [46, 49] or may even lead to an increase in antibiotic use [50] and hospitalisation rates [24]. CRP POCT can produce false positive as well as false negative results, leading to the possibility of over- or under-treatment of RTIs [24].Some commonly prescribed medications (such as, lipid-lowering agents, ACE inhibitors, ARBs, anti-diabetic agents, anti-inflammatory and anti-platelet agents, and beta- adrenoreceptor antagonists) are known to lower CRP levels, and this should be taken into account during the patient consultation, as a low CRP test result may carry a risk of inappropriate treatment choices by the clinician [51]. Over-treatment can lead to avoidable adverse reactions to antibiotics and contribute to antimicrobial resistance; while under-treatment due to a failure to prescribe timely antibiotic therapy could potentially lead to increased morbidity or mortality.

The safety and effectiveness and diagnostic test accuracy of CRP POCT in patients presenting with acute RTI as well as the analytical performance of the commercially available CE marked tests is assessed in detail in the safety and effectiveness domains of this report.

[B0003] – What is the phase of development and implementation of the technology and the comparator(s)? Overlaps with:

[A0021] – What is the reimbursement status of CRP POCT in primary care in the European countries participating in EUnetHTA?

The use of CRP POCT in patients with suspected LRTI has been included in guidelines in the UK, Norway, Sweden, the Netherlands, Germany, Switzerland, Czech Republic and Estonia to determine severity of infection and to guide antibiotic prescribing [42, 52]. Leading adopters of the technology include the Netherlands and the Scandinavian countries [18]. The UK NICE guidelines for the diagnosis and management of pneumonia in adults (2014) have issued a non-mandatory recommendation that CRP POCT should be considered for people with symptoms of LRTI in primary care if a diagnosis is unclear after clinical assessment, and that antibiotics should be prescribed based on the result.

In many European countries, healthcare is budget-driven rather than reimbursement-driven. These countries appear not to provide direct reimbursement for the use of CRP POCT in primary care. The reimbursement estimate per test was estimated from data provided by one of the five manufacturers who engaged in the REA, and from data shared by the WP4 partner from the relevant country. A summary of the reimbursement recommendations and implementation phase for CRP POCT in Europe is provided in Table A17 in Appendix 2.

[B0004] – Who administers CRP POCT? In what context is it provided? In what primary care settings is it used (e.g. GP practices, out-of-hours clinics, long-term care facilities)?

As indicated in A0020, the identified CRP POCT devices are intended for use by healthcare professionals and are suitable for use in primary care. The suggested use of CRP POCT is in patients presenting with symptoms of acute RTI where the clinical assessment of the infection type (bacterial or viral) is inconclusive, and it is unclear if antibiotics should be prescribed. Depending on the clinical guideline or care pathway developed, the test may be administered by the GP, practice nurse, healthcare assistant or pharmacist [53]. Primary care settings may include GP practices, out-of-hours clinics, long-term care facilities and community pharmacies. Commercially available CRP POCT analysers intended for use in primary care range in size and weight (from 1kg to 35kg) with some considered to be portable instruments that can be easily moved to the point-of-need, for example if a GP is providing care in a number of settings including out-of-hours clinics or long-term care facilities. However it is noted that moving instruments could impact their analytical performance.

[B0009] – What equipment, supplies and training are needed to implement CRP POCT in primary care?

The type of equipment required for implementing CRP POCT in primary care depends on whether the technology adopted is a quantitative test (that is, assay with analyser) or semi-quantitative test (that is, strip or single-use disposable device). The features of the commercially available CE marked technologies identified in this REA are listed in Table 7. [B0001]

For certain brands of CRP POCT analyser and assay vial system, scanners and barcode label printers may be required to facilitate information transfer of the batch and lot number of the assay vial to the electronic health record of the patient. The facility to either scan or directly upload results into the clinical record and laboratory information management system could be considered beneficial when considering potential wide-scale implementation of the technology within a healthcare system.

Lancets and capillary sticks are needed for the capillary blood sample for all tests, with the exception of the FebriDx®, which has an integrated lancet and capillary in the single-use disposable device.

When providing POCT, suitable facilities are required for sample collection, execution of the point-of-care tests, storage of instrumentation (if any), safe disposal of sharps and clinical waste, and to ensure that consumables such as test kits and reagents are stored under the appropriate conditions as defined by the manufacturer. Relevant regulations include the European Union (Prevention of Sharps Injuries in the Healthcare Sector) Regulations 2014 [54].

Refrigeration of test kits at 2-8°C is required for a number of the assay tests identified, with a specification that the kits be brought to room temperature prior to use. The unique storage details specific to each device are listed in Table 7.

Given the requirement for a blood, serum or plasma sample, usual local and national infection prevention and control guidelines will apply to minimise the risk of the patient acquiring a preventable healthcare-associated infection and also to protect staff from acquiring an infection in the workplace. Disposable gloves should be worn for all activities that carry a risk of exposure to blood or body fluids.

The disposal of all samples and other test materials should follow usual official regulations. Consumables such as lancets, disposable strips, cartridges, patient samples, and any used cuvettes, capillaries and plungers if required for the analyser type, should be handled and disposed of as appropriate for potentially infectious (bio-hazardous) waste. Waste receptacles must be of sufficient

size and volume to accommodate the waste generated, including sharps bins where relevant. When used in accordance with good laboratory practice, good occupational hygiene and the instructions for use, the reagents supplied with these tests should not present a hazard to health. Some of the assays minimise the exposure to test reagents as they use all-in-one test cartridges (with the reagent included), while one analyser (AQT90) uses a closed-sample system for reagent mixing.

Basic training of healthcare professionals is required to use CRP POCT in primary care. The level of training involved will depend on whether the technology adopted is a quantitative test (that is, assay with analyser) or semi-quantitative test (that is, test strip, dipstick or single-use disposable device). Training in preanalytic handling including machine calibration is required for quantitative tests; training in the interpretation of the tests is required for both quantitative and semi-quantitative tests. The practical aspects of using the available tests and the level of training support available from manufacturers (where provided) are detailed in Table 7. In addition, support may be needed from laboratories to provide advice on quality assurance, external quality control and training in tandem with that provided by the manufacturers.

In some countries, national guidelines for the implementation of POCT in primary care are available that detail the requirements for staff training in the use of POCT. For example, the "Guidelines for Safe and Effective Management and Use of Point of Care Testing in Primary and Community Care in Ireland (2009)" [55], state that:

"It is imperative that all staff performing POCT are trained and competent in the use of the test. This training may be conducted by the manufacturer or authorised representative. Relevant professional organisations may also provide training on certain tests. It is important to agree the detail and level of training to be provided by the manufacturer or his representative at the time of purchase of the POC test and to ensure that this training is completed and recorded prior to implementation of the POCT service. Training records should be kept in each testing location. Where appropriate, trainers should be designated and such individuals should receive extra training. A training record template is included in Appendix 7.5. The competency of the individual performing POCT should be assessed on an ongoing basis and supplementary training provided if required.

A training programme should be put in place and should include the following elements:

- *Instructions on safe working practices*
- *Principles of operation of the device*
- *Review of the manufacturer's instructions for use (IFU), limitations of the device, interferences*
- *Review and understanding of error messages, interpretation, and appropriate responses*
- *Calibration and quality control requirements, including acceptable limits, appropriate record keeping and required actions for failed results*
- *Patient preparation, sample collection and handling according to the manufacturer's stated requirements and health and safety regulations*
- *Interpretation and recording of patient results and appropriate patient referral and follow-up*
- *Training of new recruits and periodic refresher training for service providers"*

There may also be a healthcare policy requirement to include communication training and/or an education piece for physicians and patients around the link between antibiotic prescribing and anti-microbial resistance.

The workflow at the testing site may need to be reconsidered if POCT has not previously been used in the primary care setting (that is, who will perform the test and report the result to the patient). For quantitative tests, the number of analysers required will depend on the number of practitioners performing the test and the layout of the practice setting.

Independent accreditation is an important and often mandatory requirement for pathology laboratories as part of their quality assurance processes. International standards for POCT have been developed by the International Standards Organization (ISO) in the form of ISO 22870: 2016 [56]. This document gives specific requirements applicable to POCT and is intended to be used as a companion to ISO 15189: 2012 *Medical Laboratories – Requirements for Quality and Competence Standard*. The ISO 22870 standard specifies requirements for competence and quality in POCT performed in hospitals, clinics and healthcare organisations providing ambulatory care; it excludes patient self-testing in a home or community setting. National guidelines in some countries recommend that any POCT service in primary care be ISO accreditable [55, 57]. These guidelines may recommend any site providing a POCT service to undergo a relevant accreditation procedure in order to provide assurance of the validity of the point-of-care results taking into account clinical context and patient safety [57]. Examples of organisations that provide external quality assurance include SKUP (www.skup.org), a Scandinavian cooperation between agencies in Denmark, Norway and Sweden for evaluation of near-patient laboratory equipment, which publishes independent evaluations of the analytical performance of CRP POCT equipment; and Weqas in Wales (www.weqas.com), which is supporting roll-out of CRP POCT to inform antibiotic prescribing in Wales.

3.3 Discussion

CRP POCT devices are indicated for the quantitative determination of CRP in human whole blood and in human serum and plasma. The measurement of CRP provides information for the detection and evaluation of infection, tissue injury, inflammatory disorders and associated diseases.

The aim of the CRP POCT technology is to provide reliable test results, which allow physicians to differentiate between mild and severe RTIs, and to rule out potentially serious bacterial infections, when it is not clear if antibiotics should be prescribed based on clinical assessment alone. The test is therefore expected to be used as a rule-out tool and have a moderating effect on the prescribing of antibiotics.

CRP POCT can be used in combination with communication training, an education component and/or tests for other biomarkers in addition to standard care to assist the treating clinician in differentiating between bacterial and viral aetiology, and thereby guide antibiotic prescribing. It is proposed that use of CRP POCT enhances patient safety and compliance with clinical guidelines, as well as physician and patient satisfaction. There is a risk, however, that CRP POCT can produce false positive as well as false negative results, leading to the possibility of over- or under-treatment of RTIs. Over-treatment can lead to avoidable adverse reactions to antibiotics; while in those who are under-treated, there is the potential risk of increased rates of morbidity or mortality.

Fifteen CE marked CRP POCT devices (that is, devices that are declared to be in conformity with the IVD directive) were identified for inclusion in this REA. These could be broadly classified into one of two categories: quantitative methods (that is, analysers using either capillary or venous blood) and semi-quantitative methods (that is, strips, dipsticks or single-use disposable tests using capillary

blood). These technologies differ in a number of respects, including the size and portability of the analyser devices; the requirement for calibration and the extent to which pre-analytical handling is required; analyser warm-up and performance times; and the degree to which test data can be stored on the device, printed and/or transferred to electronic patient files. These differences may impact the acceptability and performance of the various devices for the intended user (that is, healthcare staff who are not laboratory specialists working in the primary care setting) and their use could have implications for practice management and workflow.

There must be confidence in the CRP results delivered from CRP POCT in primary care. Doctors require accurate and reliable technology that will deliver CRP results that their patients can trust. ISO accreditation of the CRP POCT sites addresses issues relating to clinical governance, risk management, user competence training, internal quality control and external quality assurance of testing, with national guidelines in some countries recommending that any POCT service should be ISO accreditable.

Use of CRP POCT in the management of patients with suspected LRTI has been included in guidelines in the UK, Norway, Sweden, the Netherlands, Germany, Switzerland, Czech Republic and Estonia, with the Netherlands and Scandinavian countries being leading adopters of the technology in primary care. At least 18 European countries have CRP POCT technology available to medical practitioners for use in patients in primary, outpatient and/or ambulatory care settings, although reimbursement status and policy differs between countries.

4 HEALTH PROBLEM AND CURRENT USE OF THE TECHNOLOGY (CUR)

4.1 Research questions

Element ID	Research question
A0002	What conditions do acute RTIs comprise and how are these defined? What is antimicrobial resistance and how is it related to antibiotic prescribing patterns?
A0003	What are the known risk factors for acute RTIs? What factors increase the prevalence of antimicrobial resistance in the population?
A0004 **Overlaps with** **A0005**	What is the natural course of acute RTIs? (As RTIs are a collection of specific diagnoses, each diagnosis will be discussed briefly, e.g. pneumonia, pharyngitis.) What are the symptoms and burden of disease of an acute RTI for the patient? (Again, as RTIs are a collection of specific diagnoses, each diagnosis will be discussed briefly, e.g. pneumonia, pharyngitis.)
A0006	What are the consequences of acute RTIs for society? What are the consequences of antimicrobial resistance for society?
A0007	What is the target population of this assessment?
A0024 **Overlaps with** **A0025**	How are acute RTIs currently diagnosed according to published guidelines from European countries? How are acute RTIs currently managed according to guidelines from European countries? How are they managed in practice?
A0023	What is the epidemiology of RTIs across the European Union in primary care settings?
A0011	To what extent is CRP POCT currently used in Europe to guide antibiotic prescribing?

4.2 Results

Overview of the disease or health condition

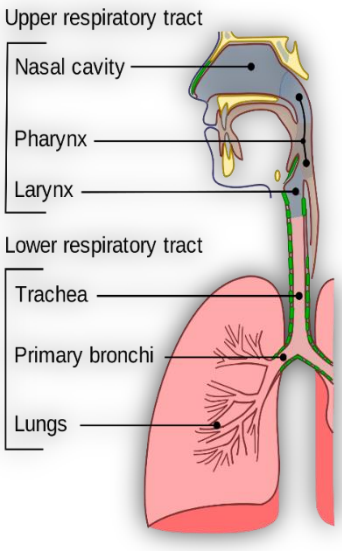
[A0002] – What conditions do acute RTIs comprise and how are these defined?

Respiratory tract infections (RTIs) are the most frequent infections encountered in primary care; most are viral, but a small number are caused by bacteria and may respond to antibiotics. Symptoms of RTI include cough, discoloured and/or increased sputum production, pain, fever, blocked and/or runny nose, respiratory distress, loss of voice, feeling unwell, or combinations of focal and systemic symptoms. RTIs may be classified as upper or lower respiratory tract infections, the boundary of which is typically the larynx. Upper respiratory tract infections (URTIs) include pharyngitis, tonsillitis, laryngitis, rhinosinusitis, otitis media and the common cold [24]. Lower RTIs (LRTIs) include pneumonia, bronchitis, tracheitis and acute infective exacerbations of COPD. Influenza may affect both the upper and lower respiratory tract. The pragmatic definition of a LRTI adopted in the 2011 guidelines produced by the European Respiratory Society (ERS) in collaboration with the European Society for Clinical Microbiology and Infectious Disease (ESCMID) is as follows: *'an acute illness (present for 21 days or less), usually with cough as the main symptom, with at least one other lower*

respiratory tract symptom (sputum production, dyspnoea, wheeze or chest discomfort/pain) and no alternative explanation (for example, asthma)' [58].

The distinction between the upper and lower respiratory tract is illustrated in Figure 1. The definition of the different types of acute RTIs, their associated symptoms, and burden of disease, along with the natural course of the illnesses at an individual patient level, are detailed in Table A4 (Appendix 1).

Figure 1: Anatomy of the respiratory tract



In the majority of cases of RTI, no pathogen is identified, primarily because the organism is missed, or as in the case of patients presenting in primary care, testing is not performed because of challenges obtaining samples, limited access to diagnostics, and the limited clinical utility in obtaining results subsequent to the requirement for an empirical treatment decision to be made. A potential pathogen was identified in 59% of adults presenting to primary care with LRTI in a large EU-funded prospective case-control diagnostic study (n=3,104) undertaken in eleven European countries by the GRACE (Genomics to combat Resistance against Antibiotics for Community-acquired lower respiratory tract infection (LRTI) in Europe) consortium. Overall, a bacterial pathogen was identified in 21% of patients and a viral pathogen was identified in 48% of patients; both bacterial and viral pathogens were identified in 10% of cases [59]. The most common bacterial pathogens isolated were *Streptococcus pneumoniae* (5.5%) and *Haemophilus influenzae* (5.4%), while the most common viral pathogens isolated were human rhinovirus (20.1%), influenza virus (9.9%) and human coronavirus (7.4%). This evidence is consistent with the literature reported in the 2011 European Respiratory Society (ERS)/ European Society for Clinical Microbiology and Infectious Diseases (ESCMID) guidelines which noted that viruses are isolated in up to 60% of community-acquired LRTIs. The most common bacterial pathogens isolated are *Streptococcus pneumoniae* and *Haemophilus influenza*, although published estimates vary, ranging from 3% to 30% and from 3% to 14%, respectively, of community-acquired LRTI cases [58].

The aetiology of a subset of LRTI, specifically community-acquired pneumonia (CAP) in adults presenting to primary care, was also reported in the prospective study by the GRACE consortium. CAP was diagnosed in 4.5% of adults (6.4% of those >65 years) presenting with LRTI in primary care. Potential bacterial pathogens were significantly more likely to be identified in those with CAP, with a bacterial pathogen identified in 30% of cases. Viral pathogens were identified in 37% of cases, while

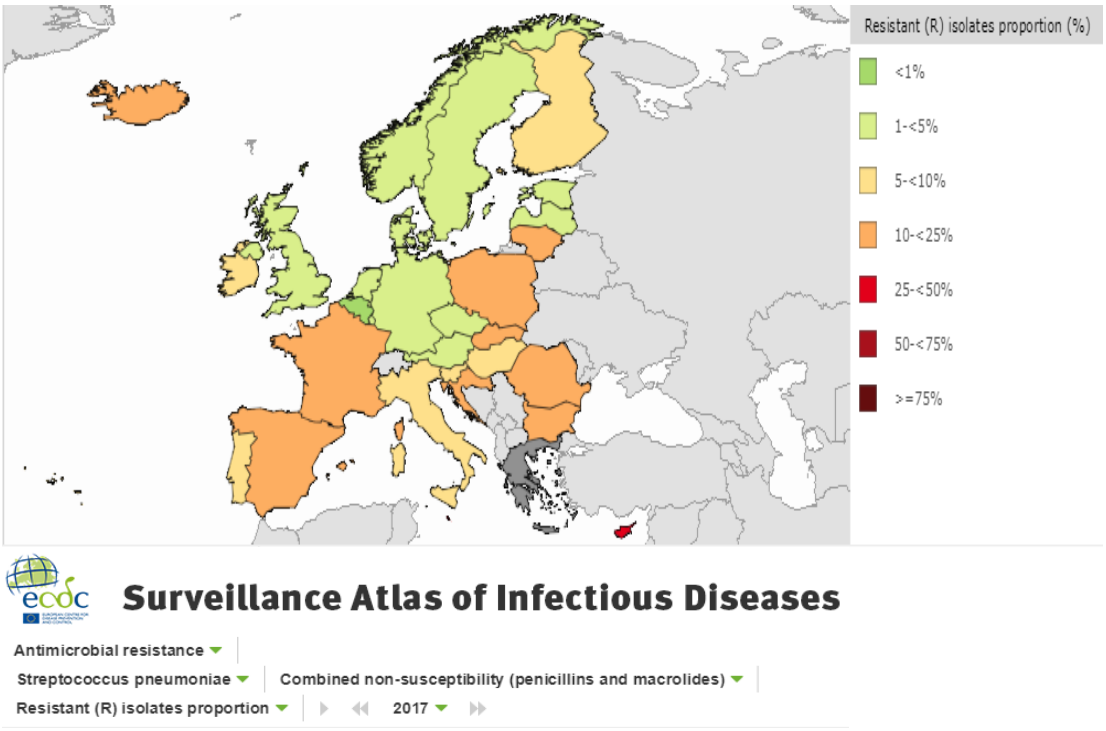
both bacterial and viral pathogens were identified in 7% of cases. No pathogen was identified in 40% of CAP cases. Again, the most common bacterial pathogens isolated were *Streptococcus pneumoniae* (9.2%) and *Haemophilus influenzae* (14.2%) [59]. This evidence is also consistent with other literature including that reported in the 2011 ERS/ESCMID guidelines which noted that viruses are involved in up to 30% of CAP, again with Streptococcus pneumoniae and *Haemophilus influenzae* being the most common bacterial pathogens [58, 60, 61].

What is antimicrobial resistance and how is it related to antibiotic prescribing patterns?

Antimicrobial-resistant organisms are found in people, food, animals, plants, and the environment (in water, soil, and air) and they can move between ecosystems [62]. Antimicrobial resistance (AMR) occurs naturally and over time when microorganisms (such as bacteria, fungi, viruses, and parasites) are exposed to antimicrobial substances [62]. As a result, treatments become ineffective and infections persist in the body, increasing the risk of spread to others [62]. However, new AMR mechanisms are emerging and spreading globally, threatening our ability to treat infectious diseases, resulting in prolonged illness, disability, and death, and increasing the cost of healthcare. Although the emergence of AMR is a natural phenomenon, the misuse and overuse of antimicrobials is accelerating this process [63].

The European Antimicrobial Resistance Surveillance Network (EARS-Net) has documented the changing epidemiology of bacteraemias in Europe, highlighting the emergence and spread of totally or almost totally resistant bacteria in European hospitals [64]. Of note, however, is the fact that the primary care setting accounts for 80% to 90% of all antibiotic prescriptions [65]. In 2017, the European Centre for Disease Control (ECDC) Surveillance Atlas of Infectious Disease reported high levels of *Streptococcus pneumoniae* with combined non-susceptibly to penicillins and macrolides in Bulgaria, Cyprus, Croatia, France, Iceland, Lithuania, Poland, Romania, Slovakia and Spain (Figure 2).

Figure 2: Antimicrobial resistance (combined non-susceptibility for penicillins and macrolides) versus *Streptococcus pneumoniae* in EU/EEA countries, 2017

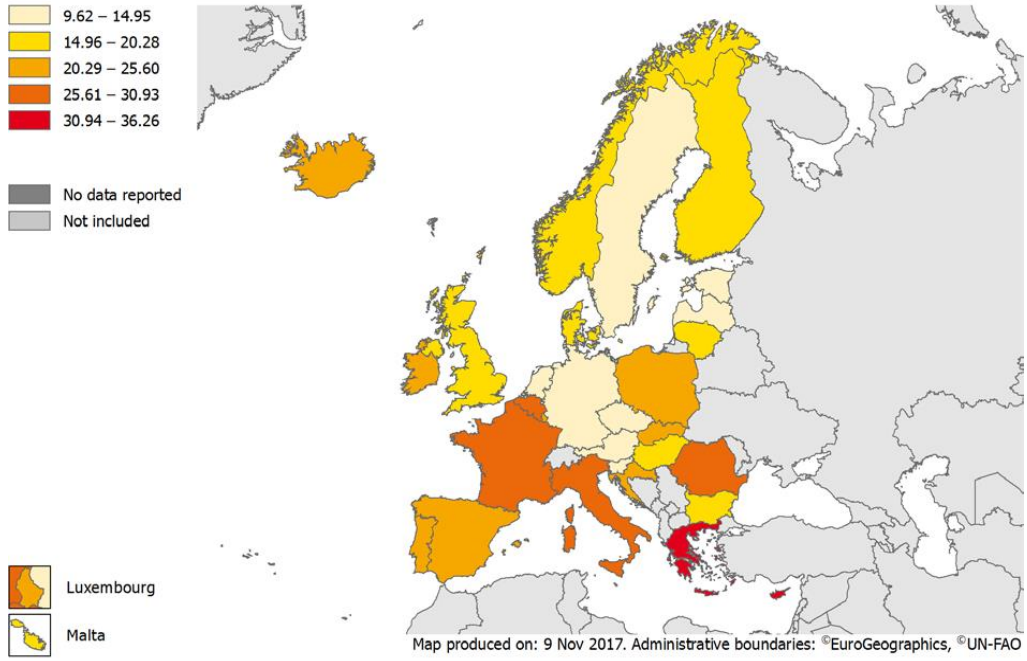


Source: The European Centre for Disease Control (ECDC).

During the same period, high levels of carbapenem-resistant *Klebsiella pneumoniae* were reported in Cyprus, Greece, Italy, and Romania. This trend indicates higher rates of antimicrobial resistance in southern and eastern European countries.

The European Surveillance of Antimicrobial Consumption Network (ESAC-Net) collates data for the EU and EEA countries on community-level antibiotic consumption for systemic use. Data for 2016 indicate an EU/EEA population-weighted mean consumption of 21.9 DDD per 1,000 inhabitants per day. Although consumption was noted to be lower than in previous years, overall antibiotic consumption in the community showed no significant decreasing trend for the period 2012–2016 [66]. There is substantial inter-country variation with consumption ranging from 10.4 (the Netherlands) to 36.3 (Greece) DDD per 1,000 inhabitants per day (Figure 3). A number of countries, specifically Finland, Luxembourg, Norway and Sweden (Northern Europe), showed a decreasing trend in consumption during the 2012–2016 period, whereas increases were noted in Greece and Spain (Southern Europe) [66].

Figure 3: Consumption of antibiotics for systemic use in the community, EU/EEA countries, 2016 (expressed as DDD per 1 000 inhabitants per day)



Source: The European Centre for Disease Control (ECDC) Summary of the latest data on antibiotic consumption in the EU (November 2017) [66].

This correlation between increased antibiotic consumption (which can be interpreted as a proxy for antibiotic prescribing patterns) and increased antibiotic resistance has been observed in a number of ecological studies. These studies have identified countries in the south and east of Europe that have moderate to high consumption of antibiotics as also having high rates of antimicrobial resistance [67]. Quality appraisal of antibiotic use is also undertaken by ESAC using twelve different quality indicators based on the type of antibiotic consumed (n=5), the relative proportions of these types (n=4), the use of broad versus narrow spectrum antibiotics (n=1), and seasonal variation in consumption (n=2). The 2012 ESAC quality appraisal of antibiotic use in an outpatient setting between 2004 and 2009 also

showed an important north-south divide when the quality of antibiotic use is considered, with northern countries more likely to be rated as having high-quality use [68].

While antibiotic use is widely associated with antibiotic resistance, demonstrating causality is difficult because of population-based confounders and because there is wide variation in the effects of antibiotics that are within the same class on the selection of resistant organisms [69]. However, several case reports of fluoroquinolone-associated *Clostridium difficile* diarrhoea have been published [70]. A systematic review and meta-analysis of a large set of studies (n=243) found that antibiotic consumption is associated with the development of antibiotic resistance at both the individual and community level. This link was reported to be particularly strong for countries in Southern Europe [71]. At the patient level, there is a clear link between antibiotic dose and duration and the emergence of antibiotic resistance; there is also evidence that patients who have been treated frequently with antibiotics are at greater risk of antibiotic resistance [67, 71]. As mentioned previously, the EARS-Net has noted the emergence and spread of totally or almost totally resistant bacteria in European hospitals [64]. Of note, however, is that the primary care setting accounts for 80% to 90% of all antibiotic prescriptions [65]. However, it is noted that due to difference in molecular mechanisms of resistance and associated fitness costs (transmissibility), the persistence of resistance differs between antibiotics. For example, compared with the newer macrolides azithromycin and clarithromycin, persistence of resistance selection following amoxicillin therapy in patients with community-acquired LRTI is significantly shorter [69].

[A0003] – What are the known risk factors for acute RTIs?

The respiratory tract is vulnerable to infection from bacteria or viruses. RTIs are seasonal and tend to be more common during the winter. Children tend to acquire more URTIs than adults. This is due to the lack of immunity to the multiple viruses that can cause colds. Most RTIs are self-limiting. However, extra care and additional treatment may be required for people who are more vulnerable to the effects of opportunistic infections. The following factors, which include individual characteristics and behaviours, patient disease states and medications, and environmental exposures, are associated with a higher risk of RTI [72]:

- Aged < five years or >70 years
- Smokers
- Pre-existing lung condition (such as COPD or asthma)
- Immuno-compromised (such as HIV positive patients)
- Immuno-suppressive medication regimen (such as tacrolimus)
- Long-term care residents of nursing homes
- Under-nutrition in children
- Indoor and ambient air pollution.

The risk factors for complicated influenza should also be noted for select populations [73]:

- Aged < six months or >65 years
- Morbid obesity (BMI ≥40)
- Pregnancy (including up to two weeks post-partum)
- Neurological, hepatic, renal, pulmonary and chronic cardiac disease
- Diabetes mellitus
- Severe immunosuppression.

The 2015 Global Burden of Disease Study of LRTIs detected a relationship between incidence and mortality from LRTIs and the Social Demographic Index (SDI) [74]. Mortality from LRTIs decreased

rapidly when transitioning from low to middle SDI countries. This association with socio-demographic issues is particularly evident for children aged less than five years where the burden of LRTI remains high. This may have implications for subsets of socially-deprived populations within European countries.

The risk of complications in a primary care patient with LRTI was also assessed by the Joint Task Force of the European Respiratory Society (ERS) and European Society for Clinical Microbiology and Infectious Diseases (ESCMID) [58]. They recommend that patients with an elevated risk of complications should be monitored carefully and referral to hospital should be considered. In patients aged 65 years of age and older, the following characteristics are associated with a complicated course [58]:

- presence of chronic obstructive pulmonary disease (COPD), diabetes or heart failure
- previous hospitalisation in the past year
- taking oral corticosteroids
- antibiotic use in the previous month
- general malaise
- absence of upper respiratory symptoms
- confusion/diminished consciousness
- abnormal vital signs, including tachycardia (heart rate >100), fever (>38°C), tachypnoea (respiratory rate >30) or hypotension(blood pressure <90/60)
- when the primary care physician diagnoses pneumonia.

In patients aged less than 65 years, the task force reported that diabetes, a diagnosis of pneumonia and possibly also asthma are risk factors for complications. For all age groups, serious conditions such as active malignant disease, liver and renal disease and other disorders that are relatively rare in primary care, but which affect immunocompetence, also increase the risk of complications.

What factors increase the prevalence of antimicrobial resistance in the population?

The major drivers behind the occurrence and spread of antimicrobial resistance (AMR) are the use of antimicrobial agents and the transmission of antimicrobial-resistant microorganisms between humans, between animals, and between humans, animals and the environment. While antimicrobial use exerts ecological pressure on bacteria and contributes to the emergence and selection of AMR, poor infection prevention and control practices and inadequate sanitary conditions favour the further spread of these bacteria [75]. Globalisation, the rapid and frequent traveling and the increasing international market exchange of foods and feeds, and modern healthcare will increase the spread and selection of resistant bacteria favouring the persistence of multi-resistant bacteria [76].

As discussed in section A0002, other factors that may affect the development of AMR in patients include the dose, duration of treatment and class of antibiotic (selective pressure), disease transmission and exposure rates, host susceptibility (such as vaccination status), and transmissibility (fitness cost) of the pathogen [77]. Currently, approximately 40% of *Streptococcus pneumoniae* isolates are penicillin-resistant in several countries that lack significant conjugate vaccine coverage [78].

Recent antibiotic use has been identified as the foremost risk factor for the development of resistance among invasive pneumococcal disease cases, but other risk factors include age (particularly children aged less than five years), female gender, hospitalisation, living in an urban area, attending day care, paediatric serotypes (that is, serotypes found commonly in children), HIV infection, and immunosuppression. Studies have found that previous use of beta-lactam antibiotics, extremes of age

(for example, children aged less than five years and the elderly), and child care attendance were associated with penicillin-non-susceptible pneumococcal infections [78]. Antimicrobial resistance may also result from indiscriminate or poor use of antibiotics; for example, the early termination of antibiotic treatment by the patient when the initial symptoms of the infection have improved [54].

The English Surveillance Programme for Antimicrobial Utilisation and Resistance (ESPAUR) report of 2018 also provides data linking trends in antibiotic use with the proportion of common isolates resistant to key antibiotics. The robustness of some resistance reporting has been questioned due to the use of specific automated antibiotic susceptibility testing devices by some laboratories which may over-estimate particularly intermediate resistance levels [79]. An electronic database study in Oxfordshire (1999–2011) demonstrated a link between increased use of co-amoxiclav with an increased incidence of *Escherichia coli* bacteraemia attributable to co-amoxiclav-resistant isolates. The increasing proportion of co-amoxiclav resistant isolates was preceded by change in antibiotic policy from second- and third-generation cephalosporins towards co-amoxiclav with gentamicin as the empirical treatment for sepsis in response to rising *Clostridium difficile* infection rates [80].

The rapid seasonal decrease in resistance associated with markedly reduced antibiotic use suggests that drug-resistant *Pneumococci* may pay a fitness cost [81]. The observed fitness cost of resistance genes/mutations is a prerequisite for reversibility of antibiotic resistance by reduced antibiotic use [76]. However, so far the clinical evidence for reversibility is limited [82, 83]. The potential of reversing antibiotic resistance through the reduction of antibiotic use will depend on the fitness cost of the resistance mechanism, the epidemic potential of the bacteria/strain, and the transmission route of the species [76].

Effects of the disease or health condition

[A0004] – What is the natural course of acute RTIs? Overlaps with**:**

[A0005] – What are the symptoms and the burden of disease of an acute RTI for the patient?

As detailed in A0002, RTIs comprise a collection of specific diagnoses which can be broadly classified as upper and lower RTIs, the boundary of which is typically the larynx. The definition and symptoms of each of these conditions, along with the burden of the disease and the natural course of the illness in the individual patient, are detailed in Table A4 (Appendix 1). The natural course of URTIs is typically shorter (ranging from four days for acute otitis media to 2.5 weeks for acute rhinosinusitis) than for LRTI (ranging from three weeks for acute bronchitis/cough to three to six months (to complete recovery) for community-acquired pneumonia [CAP]).

LRTIs with a bacterial aetiology are often assumed to result in a different illness course than non-bacterial causes, but evidence of actual difference is lacking. The illness course of a bacterial LRTI in a large study population (n=1,021) of adult patients presenting to primary care with symptoms of acute cough for whom pneumonia was not clinically suspected was evaluated as part of a secondary analysis of a multicenter European trial by the GRACE consortium. While a slightly worse course of disease was observed in those for whom a bacterial origin was identified, the relevance of this difference was not found to be clinically meaningful. The authors concluded that, similar to non-bacterial LRTI, the illness course of bacterial LRTIs (where clinical pneumonia is not suspected) is generally mild and self-limiting [84].

The Global Burden of Disease study of LRTIs focused on the burden associated with pneumonia and bronchitis in 195 countries during 2015 [72]. It estimated that LRTIs were the fifth leading cause of death (of 249 causes) and the leading infectious cause of death worldwide. LRTIs were the second-

leading cause of disability-adjusted life years (DALYs) globally in 2015 after ischaemic heart disease. Globally, pneumonia remains the most common cause of death in children younger than five years of age, causing 1.6 million deaths annually. A proportion of RTIs are vaccine-preventable, with variation in access to and uptake of vaccines contributing to differences in disease burden. For example, while the pneumoccocal vaccine is recommended for children by the World Health Organization (WHO), global coverage was estimated at only 25% in 2013, with estimates that pneumococcal disease is responsible for over 30% of deaths from vaccine-preventable diseases in children [85]. The Global Burden of Disease study also highlights the burden of LRTIs in the elderly population, with nearly 700,000 deaths in patients aged older than 70 years due to pneumococcal pneumonia worldwide [72]. Among high-income countries (21 of the 34 of which are European), LRTIs were responsible for 486,408 deaths (that is, 45.5 per 100,000) and 5.1 million DALYs in 2015; a 21.6% increase in deaths and 9% increase in DALYs was noted between 2005 and 2015 [72].

The number of deaths due to LRTI in children aged younger than five years in the high income countries was estimated at 3.4 per 100,000 in 2015; this represented a decrease of 34.9% between 2005 and 2015 [72]. Data from 14 hospital-based studies estimate the incidence of admissions for severe acute LRTI in Europe in 2010 was approximately 14 episodes per 1,000 children per year in children aged 0-11 months, and approximately seven episodes per 1,000 children per year in those aged 0-59 months. This translates to approximately 553,000 episodes per annum in children aged younger than five years in Europe [86].

As noted in A0005, patients with COPD are at increased risk of acute RTIs and their sequelae. UK estimates of inpatient mortality attributable to exacerbations of COPD range from 4% to 30% [87]. The wide variation in these estimates results from the fact that studies investigated different subgroups of patients. The factors contributing to frequent exacerbations remain unclear, but viral infections appear to be a major cause of exacerbations. The Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) cohort study identified a distinct “frequent exacerbator” group, who were more susceptible to exacerbations of COPD irrespective of their disease severity [88]. These patients could be identified by a previous history of two or more exacerbations per year. Patient mortality has been shown to be significantly related to the frequency of these severe exacerbations requiring hospital care [89]. There are also data on mortality following discharge from hospital after treatment for an acute exacerbation of COPD. In the UK it has been reported that death occurred in 14% of cases (184/1,342) within three months of admission [90]. COPD exacerbations were responsible for more than 0.9% of all 11.7 million hospital admissions and 2.4% of the 4.2 million acute medical admissions in England for 2003/2004. Most of these admissions are on an emergency basis, with the mean length of stay remaining almost unchanged at about ten days [87].

[A0006] – What are the consequences of acute RTIs for society?

The societal consequences of acute RTIs focuses on the substantial burden of these infections on healthcare utilisation in primary care.

As documented in A0004, data from the Global Burden of Disease study, LRTI are associated with substantial morbidity and mortality. These data are limited to LRTIs and are primarily based on data from hospital in-patient databases. No European-equivalent database was identified relevant to the burden of RTIs in primary care. The General Practice Research Database (now part of the Clinical Practice Research Datalink, a publicly funded research data service) in the UK has been widely used for pharmacoepidemiological research. It comprises anonymised electronic data submitted by general practitioners covering approximately 5% of the total UK population. Using these data, a 2007 study looking at the health burden of influenza in England and Wales estimated that 779,000 to 1,164,000 general practice consultations, 19,000 to 31,200 hospital admissions and 18,500 to 24,800 deaths

annually are attributable to influenza infections [91]. These data on GP consultations tally with the seasonal mean estimate of 789,219 influenza-attributable GP episodes between 1995 and 2009 in the UK [92]. In an average season during this time period, 2.4% of children aged less than five years and 1.3% of elderly patients aged over 74 years had a GP episode for respiratory illness attributed to influenza A. The corresponding figures for influenza B were 0.5% and 0.1%, respectively. The study noted that while the bulk of the burden in primary care falls on those aged less than 45 years, elderly patients are more likely to be hospitalised and to die [92]. Annual influenza epidemics are estimated to cause between 12,000 and 13,800 deaths in the UK [73].

In total, it is estimated that there are 5.5 million consultations each year for acute respiratory illness in England and Wales [91]. However, the majority of such consults often relate to other RTIs, including specifically acute cough or bronchitis and URTIs, such as acute otitis media (AOM), sore throat/ pharyngitis/tonsillitis, rhinosinusitis and the common cold, which are largely self-limiting and complications are likely to be rare if antibiotics are withheld [93]. The safety of reducing antibiotic prescribing for self-limiting RTIs in primary care was examined in a cohort study of registered patients with 45.5 million person years of follow-up data between 2005 and 2014 from 610 UK general practices [94]. It was reported that slightly higher rates of pneumonia and peritonsillar abscess were reported in general practices with lower antibiotic prescribing rates for RTIs. This translated into potentially one additional case of pneumonia each year and one additional case of peritonsillar abscess each decade in a general practice with an average list size of 7,000 patients that reduced the proportion of RTI consultations with antibiotics prescribed by 10%. It was noted that that complications could be fewer if GPs stratify antibiotic prescribing according to the level of risk. There was no evidence found that mastoiditis, empyema, meningitis, intracranial abscess, or Lemierre's syndrome were more frequent in the low prescribing practices. Achieving such reductions in antibiotic prescribing would be expected to reduce the risks of antibiotic resistance, the side effects of antibiotics, and the medicalisation of largely self-limiting illnesses [94].

Antibiotic treatment of RTIs can expose patients to an increased risk of an adverse event or an episode of drug-associated toxicity. Common side-effects of antibiotics are gastrointestinal symptoms, skin rashes, and thrush; specific effects with particular antibiotic classes include nephrotoxicity associated with aminoglycosides, teeth staining attributable to tetracyclines, and tendonitis and tendon rupture with fluoroquinolones. New restrictions on the use of fluoroquinolone antibiotics have been recommended by the EMA Committee for Human Medicinal Products (CHMP) due to their association with certain prolonged, serious, disabling, and potentially irreversible drug reactions [95]. The relative merit of the benefits and harms of antibiotic treatment can be considered in the context of the numbers needed to treat and to harm. For example, in the case of acute bronchitis the numbers needed to treat (NNT) to benefit is six based on the outcome of abnormal lung exam, and eleven based on the outcome of a clinician's global assessment [96]. For the same indication, the number needed to harm (NNH) is 24. That is, 24 patients need to be treated for one to experience a harm. By contrast, for acute otitis media the NNT is 24 and the NNH is 13 [97]. For acute sinusitis, the NNT ranges from seven to 20 depending on the outcome measure, and the NNH is 10 [98]. It is clear that harm may be a more likely outcome than benefit, depending on the choice of outcome. It should be borne in mind that the benefits and harms may not be considered of equal importance. The key point is that harms from antibiotic consumption are common in patients with acute RTIs.

Consequences of antimicrobial resistance for society

The consequence of antimicrobial resistance is increased mortality and morbidity from bacterial infections, as well as an increased economic burden on the healthcare sector in the treatment and care of patients infected with multidrug resistant strains, and a loss of productivity in society [99, 100].

If resistance to currently available antibiotics becomes widespread, this will adversely impact on the delivery of effective medical care in a wide range of clinical settings. A risk assessment study of antibiotic pan-drug-resistance in the UK indicated that there is an approximately 20% chance of such a situation arising in the UK over a five-year timeframe. The impact of such an event, were it to occur, would be very significant in clinical and public health terms, with marked increases in morbidity and mortality [100].

The societal costs in Europe of selected antibiotic-resistant bacteria were estimated to be about €1.5 billion a year in 2007 [101]. Antimicrobial resistance kills around 50,000 people a year in the US and Europe, and is estimated to kill more than 700,000 people globally [63]. Predictive macroeconomic models, which found that if resistance is not addressed, the world will produce around $8 trillion USD less per year by 2050, and a cumulative $100 trillion USD would be wiped off the world's production over the next 35 years [63]. However, this review on antimicrobial resistance only estimates lost economic output, and does not take into account any increased associated healthcare costs.

Antimicrobial resistance increases the cost of healthcare with lengthier stays in hospitals and more intensive care required [62]. It complicates treatment and can result in additional antibiotic courses and outpatient visits, excess hospitalisations and work loss [78]. Specific to antibiotic-resistant pneumococcal pneumonia, a 2014 study by Reynolds et al. found that resistance led to 32,398 additional outpatient visits and 19,336 additional hospitalisations, accounting for $91 million USD (4%) in direct medical costs and $233 million USD (5%) in total costs, including work and productivity losses [102]. In adults, increased costs due to penicillin non-susceptible pneumonia and bacteremia were due to prolonged hospitalisations and the use of more expensive antibiotics [78]. Data from the US estimated that 55% of all antibiotics prescribed for acute RTIs in outpatients are probably not needed, leading to a waste of $732 million (1999 dollar values) of $1.32 billion spent [77].

Current clinical management of the disease or health condition

[A0024] [A0025] – How is the disease or health condition currently diagnosed and managed according to published guidelines and in practice?

RTIs are commonly encountered in primary care, with data suggesting that they account for around 60% of antibiotic prescriptions issued within primary care [93]. However, as previously noted, acute RTIs are often viral, self-limiting and do not require an antibiotic [93, 96, 103]. A number of European and national guidelines for the diagnosis and management of acute RTIs are summarised in Table A5 (Appendix 1).

There are commonalities in the care pathways for the diagnosis and management of acute RTIs across Europe. URTIs (common cold, acute sore throat/acute pharyngitis/acute tonsillitis, acute otitis media (AOM) and acute rhinosinusitis) are characterised as self-limiting, and often viral in aetiology. For these URTIs, the guidelines recommend that a clinical assessment should include a history (presenting symptoms, use of over-the-counter or self-medication, previous medical history, relevant risk factors, relevant co-morbidities) and a physical examination to identify relevant clinical signs [93]. For acute sore throat, pharyngitis and tonsillitis, there is a preference for using clinical prediction rules (such as the Fever PAIN, McIsaac or Centor scores) to identify those patients likely to benefit from antibiotics, rather than routinely conducting a pharyngeal swab for group A *Streptococci* (GAS) [93, 104-107]. A diagnosis of AOM is generally made on the basis of conventional otoscopy, and there is little evidence that antibiotics reduce complications from AOM. For acute sinusitis, patients present with symptomatic inflammation of the mucosal lining of the nasal cavity and paranasal sinuses (<four weeks' duration). Unilateral symptoms and purulence make bacterial aetiology more likely. In

uncomplicated cases of URTIs that do not exceed the expected durations of illness, a no-antibiotic prescribing strategy or a delayed antibiotic prescribing strategy is generally recommended for patients [93, 98]. The guidelines suggest advice should be given to patients about the typical duration of illness and how to manage symptoms, including using analgesics for pain and antipyretics for fever. Antibiotics are generally only recommended for patients who are systemically very unwell, for patients with signs or symptoms of a more serious illness and/or complications, and for patients who are at high risk of complications due to a pre-existing co-morbidity. Select patient groups (such as those immunocompromised or with severe co-morbidities) may require immediate antibiotic treatment.

Seasonal influenza is a vaccine-preventable disease and annual Influenza vaccination remains the most effective preventive strategy for severe influenza. While the ECDC recommend the vaccine for all Europeans, it is noted to be especially important for those at higher risk of serious influenza complications: individuals with specific chronic medical conditions, pregnant women, and children aged 6-59 months, the elderly and healthcare workers [108].

Guidelines for the management of LRTI and specifically community-acquired pneumonia (CAP) in adults have been published by a number of European countries in addition to consensus guidelines published by a joint taskforce of the European Respiratory Society (ERS) and the European Society for Clinical Microbiology and Infectious Disease (ESCMID) [58]. The guidelines distinguish between cough (or acute bronchitis) and pneumonia. The use of CRP measurement is recommended if after clinical assessment a diagnosis of pneumonia has not been made and it is unclear if antibiotics should be prescribed. Use of antibiotics is recommended in patients with a diagnosis of pneumonia and in those with LRTI with risk factors for complications (such as co-morbidities), but not in other patients who are less unwell including those with acute bronchitis.

Acute LRTI is a broad description of a group of disease entities, encompassing acute bronchitis, pneumonia and exacerbations of chronic lung disease. In primary care, it can be difficult to differentiate between those different conditions without doing extensive additional diagnostic tests due to the substantial overlap in presenting symptoms. As noted, patients can present with cough, sputum production, dyspnoea, tachypnoea, fever, chest discomfort /pain, wheezing and auscultatory abnormalities [58]. Reports indicate that around 5–12% of patients presenting in primary care with symptoms of a LRTI are diagnosed with CAP [109, 110] and 22–42% of these patients are admitted to hospital [42]. The Dutch College of General Practitioners (NHG) guidelines provide recommendations regarding the use of CRP levels to help inform antibiotic prescribing in patients who present with signs and symptoms of pneumonia and in those patients with acute cough who have other risk factors for complications due to their age (<3 months or >75 years) or relevant comorbidities. A prospective observational study evaluated the use of CRP POCT with these guidelines, and found that differences in antibiotic prescription rates among GPs were most obvious in patients who presented with CRP values between 20 and 100 mg/L. Most GPs followed the NHG guidelines and did not prescribe antibiotics to patients with low (that is, less than 20mg/L) CRP values [111].

Interestingly, in cases of acute cough studied in 13 countries in Europe, the variation in clinical presentation of patients did not explain the considerable variation in antibiotic prescribing, with such variation not being associated with clinically important differences in recovery [112]. Without access to CRP POCT, there may be “defensive over-prescribing of antibiotics” by doctors for patients presenting with symptoms of LRTI, especially where the clinical assessment is inconclusive and the need for antibiotics is unclear. A 2015 observational study from the Netherlands of the (antibiotic) management of patients with RTIs, whose care was benchmarked to the prescribing guidelines for acute otitis media (AOM), acute sore throat, rhinosinusitis or acute cough, reported an overall

antibiotic prescription rate of 38%. Of these prescriptions, 46% were not indicated by the guidelines. Relative overprescribing was highest for throat (including tonsillitis) and lowest for ear consultations (including AOM). Absolute overprescribing was highest for LRTIs (including bronchitis). Overprescribing was highest for patients between 18 and 65 years of age, when GPs felt patients' pressure for an antibiotic treatment, for patients presenting with fever and with complaints longer than one week [113].

A 2018 US retrospective study examining the adherence to guidelines from the Infectious Disease Society of America (IDSA) for the testing and treatment of children with pharyngitis found that 28% of the antibiotics prescribed for pharyngitis in the cohort were not indicated for the specified condition [114].

The efficacy of antibiotics in the treatment of adults presenting with acute LRTI, in whom pneumonia was not suspected clinically, was assessed in an international (12 European countries) randomised placebo-controlled trial by the GRACE consortium (n=2,061). There was no clear evidence of benefit seen with amoxicillin therapy. Compared with placebo, the use of amoxicillin was not associated with a difference in symptom severity or the duration of symptoms rated "moderately bad" or worse in the first few days of infection (HR 1.06 [95% CI: 0.96–1.18]), neither overall nor when limited to patients aged 60 years or older. While new or worsening symptoms were significantly less common in the amoxicillin group (15.9% versus 19.3%, p=0.043), the number needed to treat (NNT) was high (NNT=30) and was matched by a similarly sized number needed to harm for side effects (NNH=21) [103]. Similar estimates were reported by a 2017 updated Cochrane review examining the efficacy of antibiotics in the treatment of acute bronchitis [96]. In many cases, the use of antibiotics will not be beneficial to the patient's recovery and will expose them to potential side effects.

Given concern around persistent high rates of inappropriate prescribing, quality indicators have been developed to identify ideal or acceptable antibiotic prescribing rates for a range of RTIs in primary care. A study by the ESAC elicited expert opinion from 40 experts from 25 countries across seven dimensions on three quality indicators (percentage prescribed an antibiotic, recommended antibiotics and use of quinolones) [115]. The recommended ideal antibiotic prescribing proportions was between 0 and 20% for a range of URTIs, while it was 90 to 100% for CAP. A similar study in the UK that elicited the expert opinion of 14 academic experts from the UK, and validated the estimates through an online survey of 43 practising prescribers in primary care reported broadly consistent ideal or acceptable antibiotic prescribing rates [74].

Target population

[A0007] – What is the target population of this assessment?

This is defined in the project Scope. However, the size of the target population for this intervention is difficult to estimate.

[A0023] – What is the epidemiology of RTIs across the European Union in primary care settings?

No international studies were identified that reported European-level data for patients presenting with RTI in primary care. As noted in section A0006, the Global Burden of Disease study reports international data for RTIs, but these data do not include incidence data from primary care.

In the absence of similar epidemiological data limited to patients presenting to primary care, the data reported in this section relies heavily on published studies and surveillance data from a limited

number of European countries, in particular the Netherlands and the United Kingdom for which large-scale studies based on primary care data were identified.

Estimates from the Second Dutch National Survey of General Practice (2000-2002) [116] report that 15% of all episodes in general practice related to RTI illness. In total, 4.2% of those presenting to primary care were diagnosed with a RTI with an incidence rate of 144 per 1,000 person-years. On average, URTI and LRTI accounted for 100 and 44 GP consultations per 1,000 person-years, respectively. If signs and symptoms were added to the total incidence figures, the incidence of GP consultations for RTI was 215 per 1,000 person-years. The median age of patients presenting to a GP with at least one episode of RTI was 31 years (range 0 to 105) and 44% were male. A subset of patients had at least three episodes of GP-diagnosed RTI in one year (42 per 1,000 total patient population). The incidence of URTI was significantly higher in children aged less than five years than in other year-cohorts (392 per 1,000 child-years; relative risk (RR) 4.9 (95% CI: 4.8–5.0)), and with the exception of acute otitis media (15 versus 16/1,000; RR 0.9, 95% CI: 0.85–0.95), incidences were higher for females than for males (103 versus 74 per 1,000; RR 1.4 (95%CI: 1.35–1.45). Among patients presenting to primary care, the four most common URTIs diagnosed were rhinitis, acute sinusitis, acute otitis media and acute tonsillitis with incidence rates of 51.0, 22.7, 15.6 and 10.2 per 1,000 person-years, respectively. A U-shape association was observed between age and LRTI with a higher incidence observed in children aged 0 to 4 years (78 per 1000) and adults aged 75 years and older (70 per 1,000) compared with the other age categories (23 per 1,000). This U-shape association was also evident when restricted to diagnoses of pneumonia with incidence rates of 16.6 and 21.6/1,000 person years in those aged 0-4 years and adults aged 74 years and older, respectively. The incidence of both upper and lower RTI was significantly higher in patients with chronic lung disease (209/1,000 [RR: 1.5] and 156/1000 person years [RR 5.2], respectively) compared with the total patient population. LRTIs were also noted to be significantly more common in patients with diabetes mellitus (RR: 2.2) and cardiovascular disease (RR: 2.2) [116].

Using data from the UK General Practice Research Database which, as noted in A0006, has been widely used for pharmacoepidemiological research, Millett et al. estimated the incidence of community-acquired LRTI and pneumonia among older adults (age ≥65 years) over a 14-year study period (1997-2011). The crude overall LRTI incidence in primary care was 122.93 episodes/1,000 person years. Incidence increased with increasing age from 92.21 episodes/1,000 person-years (65-69 years) to 187.91 episodes/1,000 person-years (85-89 years), and was noted to be higher in males than females. Incidence was also noted to be higher in patients with a history of COPD. The overall incidence of CAP was 7.99/1,000 person years, was higher in males than females, and was noted to increase significantly with increasing age (from 2.81 to 21.81 episodes/1,000 person-years in those aged 65-69 years and 85-89 years, respectively) [117].

The substantial burden associated with RTIs was also confirmed in a more recent study of respiratory and communicable disease incidence from a primary care sentinel network in England. The 2014-2015 mean weekly incidences of the common cold, acute otitis media (AOM), pneumonia and influenza-like illness were 105.09, 25.95, 2.48, and 9.77 cases per 100,000 population, respectively; there was evidence of seasonal variation for all four conditions. A U-shape association was again observed for pneumonia: after controlling for other factors, multivariate logistic regression analysis showed that compared with those aged 0-4 years, the odds of a pneumonia were significantly lower for those aged 5 to 24 years (OR 0.33) and those aged 25 to 49 years (OR 0.57) and highest for those aged 75 years and older (OR 6.37) [118].

A proportion of RTIs are vaccine-preventable, with variation in vaccination policy, and access to and uptake of vaccine, contributing to differences in disease burden. As noted in (A0025) seasonal

influenza is a vaccine-preventable disease and annual influenza vaccination remains the most effective preventive strategy for severe influenza. However, the substantial burden associated with influenza in primary care is also evident in a study using data from the UK Clinical Practice Research Datalink (CPDR) and surveillance data that tracked GP episodes for respiratory illness, otitis media and antibiotic prescriptions attributable to influenza during 14 seasons (1995-2009). Seasonal mean estimates of influenza-attributable GP episodes were 857,996 corresponding to 1.5% of the total population, with a wide inter-seasonal variability. In an average season, 2.4% of children aged less than five years and 1.3% of those aged 75 years and older had a GP episode for respiratory illness attributed to influenza A; while 0.5% and 0.1% respectively had episodes related to influenza B. Of note, two-thirds of influenza-attributable GP episodes were estimated to result in a prescription of antibiotics [92].

As noted, no large-scale international studies were identified that reported European level data for patients presenting with RTI in primary care. However, one retrospective observational study of primary care databases from Belgium, the Netherlands and Sweden reported on the incidence of consultations for seven acute infections (URTI, sinusitis, tonsillitis, otitis media, bronchitis, pneumonia and cystitis) in 2012 and the antibiotic prescriptions corresponding with these diagnoses. For the six RTI diagnoses under study, consultation incidences were 162, 173 and 296 per 1,000 registered patients per year for Sweden, the Netherlands and Belgium, respectively. Consultation incidence for the diagnoses of URTI and bronchitis in Belgium were twice as high as those observed in the Netherlands and Sweden. In the Netherlands, the consultation incidence for sinusitis was higher than in the other countries, while the consultation incidence for tonsillitis in Sweden was twice that of the Netherlands. High consultation incidences were associated with high antibiotic prescription rates, with GPs in the Netherlands and Sweden noted as prescribing fewer antibiotics for RTIs than those in Belgium [119].

While data have been collected on GP visits for influenza-like illness in different countries, given the wide rates of national case definitions, differences in consultation behaviour, vaccination coverage and obligatory doctor visits for absence from school or work, the estimated consultation rates differ between countries. A large community study on influenza in the UK, the Flu Watch cohort study, which has been used by the European Influenza Surveillance Network (EISN) to estimate the burden of influence in Europe, reported age-group specific and overall estimates of the rates of symptomatic influenza disease. Seasonal and pandemic influenza over five successive cohorts (England 2006-2011) were tracked. The proportion of illnesses resulting in at least one GP consultation was 11.6%, 15.3% and 21% for those with any respiratory illness, influenza-like illness with, and without, confirmed fever, respectively [120].

[A0011] – To what extent it is CRP POCT currently used in Europe to guide antibiotic prescribing?

As outlined in A0021, CRP POCT testing for patients with suspected LRTI has been included in guidelines in Norway, Sweden, the Netherlands, Germany, Switzerland, Czech Republic and Estonia and the United Kingdom [42, 52]. The Scandinavian countries in particular have been leading adopters of the technology [18]. Although recommended and available for use in many European countries, there are no reliable data on the current and/or expected annual usage of CRP POC tests in the respective European countries, or the extent to which practitioners adhere to the clinical guidelines regarding their use. An international cross-sectional survey reported on the use of POC tests by primary care clinicians in Australia, the USA and Europe (Belgium, the Netherlands and the UK) [121]. CRP POCT was carried out by 48% of the Dutch primary care clinicians, which contrasted with a usage of 3% reported for Belgium and 15% for the UK. In the survey, clinicians from Belgium

and the UK expressed a desire to use CRP POCT (75% and 61%, respectively) that was higher than their current use of the tests. This latent demand for access to CRP POCT is suggestive of an unmet clinical need in primary care to assist prescribing decisions for patients presenting with RTIs. As outlined in A0021, the CRP POCT technology is being used in a wide range of European countries. Many European countries also appear not to provide direct reimbursement of the technology in the primary care setting.

4.3 Discussion

RTIs are the most frequent infections encountered in primary care. No international studies were identified that reported European-level data on the burden of RTIs in this setting therefore estimates used in this report rely heavily of published studies and surveillance data from a limited number of European countries for which large-scale studies based on primary care data were identified. These confirmed the substantial burden of RTIs, with estimates that 15% of all episodes in primary care relate to RTIs, with consultations for URTI-related illness more than twice as common as those for LRTI. Given differences in consultation behaviour, vaccination coverage and obligatory doctor visits for absences from school or work, consultation rates for RTIs are likely to differ between countries. While consultation rates may vary, there is broad consistency in clinical guidelines in the care pathways for diagnosis and management of acute RTIs. URTIs are characterised as self-limiting and often viral in aetiology with a no-antibiotic or delayed antibiotic prescribing strategy generally recommended in uncomplicated URTIs that do not exceed the expected durations of illness. Immediate antibiotic therapy is typically only recommended for URTIs in patients who are systemically very unwell and for those patients who are at high risk of complications due to a pre-existing co-morbidity. In respect of LRTI, there is also broad consistency in guidelines for the diagnosis and management of LRTI and specifically CAP. Studies suggest that around 5–12% of patients presenting in primary care with symptoms of a LRTI are diagnosed with CAP. Given the substantial morbidity and mortality associated with CAP and the higher probability of a bacterial aetiology, antibiotics are recommended in all patients with a clinical diagnosis of pneumonia and in those with LRTIs with risk factors for complications (such as co-morbidities). Antibiotics are not recommended in those patients who are less unwell including those with acute bronchitis, with European guidelines recommending use of CRP measurement if after clinical assessment a diagnosis of pneumonia has not been made and it is unclear if antibiotics should be prescribed.

European surveillance data indicate a greater than threefold variation between countries in the consumption of antibiotics for systemic use in the community, with a trend towards higher antibiotic consumption in southern and eastern European countries. Given the substantial burden of acute RTIs in primary care and despite the broad consistency between national guidelines for RTIs, much of this variation may relate to variation in actual antibiotic prescribing practices for these conditions in primary care. Over-prescribing of antibiotics is common in this setting, with high levels of inappropriate prescribing documented in observational studies benchmarking antibiotic prescribing versus guidelines. Prescribing an unnecessary antibiotic will potentially expose the patient to needless adverse effects without aiding recovery. Furthermore, there is the major societal concern about the increasing emergence of antimicrobial resistance (AMR), a major driver for which is the misuse and overuse of antibiotics. European surveillance data has documented substantial inter-country variation in the prevalence of antimicrobial resistant strains including penicillin-resistant *Streptococcus pneumoniae*, with a trend towards higher rates of antimicrobial resistance in southern and eastern European countries.

While antibiotic use is widely associate with antibiotic resistance, demonstrating causality is difficult because of population-based confounders and wide variation in the effects of antibiotics that are

within the same class on the selection of resistant organisms. There is very limited evidence that a reduction in the overall rates of antibiotic prescribing leads to reversal or an overall reduction in AMR. At a patient level, however, there is a clear link between antibiotic dose and duration and the emergence of antibiotic resistance with evidence also that patients who have been frequently treated with antibiotics are at greater risk of AMR.

The use of CRP POCT to inform prescribing for patients with suspected LRTI in primary care has been included in national guidelines in several European countries. A survey of EUnetHTA partners suggests that CRP POCT is available for use in at least 17 European countries with confirmation that the technology is reimbursed when used in primary care for this indication in Denmark, Hungary, the Netherlands, Norway, Poland, Slovenia and Switzerland.

5 CLINICAL EFFECTIVENESS (EFF)

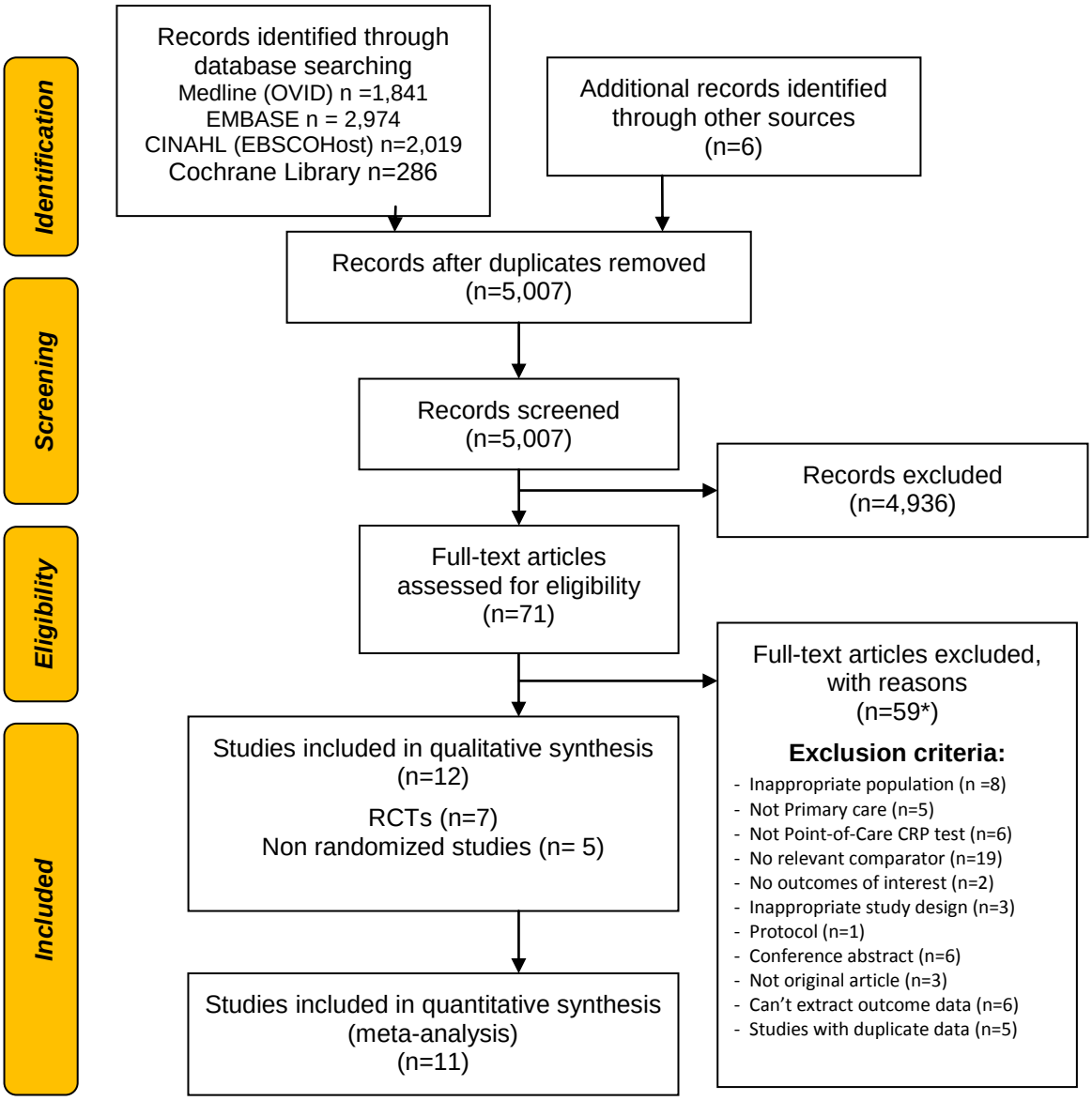
5.1 Research questions – Systematic review 1

Element ID	Research question
Change in Management (AE from Diagnostic core model)	
D0021	How does use of CRP POCT change physicians' management decisions?
Effectiveness (REA AEs)	
D0001	What is the expected beneficial effect of the intervention on mortality? Overlaps with C0008 – patient safety.
D0005	How does the technology affect symptoms and findings (severity, frequency) of the disease or health condition? Overlaps with C0008 – patient safety.
D0006	How does the technology affect progression (or recurrence) of the disease or health condition? Overlaps with C0008 – patient safety.
D0011	Does the use of CRP POCT to guide antibiotic prescribing lead to reduced adverse events as a result of lower antibiotic prescribing rates compared with standard care?
D0012	What is the effect of CRP POCT on health-related quality of life?
D0013	What is the effect of CRP POCT on disease-specific quality of life?
D0017	Were patients satisfied with the use of CRP POCT to guide antibiotic prescribing for their RTI?

5.2 Study selection

Literature search and study selection process for systematic review 1 (effectiveness and safety)

Figure 4: Flow chart systematic review 1 (effectiveness and safety)



* Some studies were excluded for more than one reason and therefore 64 reasons were given for full-text exclusion for 59 studies.

A total of 5,007 articles were identified through database searching and manufacturers' submissions. After title and abstract screening, 71 articles were identified as being potentially relevant. Of these, 59 articles were subsequently excluded due to the reasons listed in Figure 4. The most common reason for exclusion was the lack of a relevant comparator group. The majority of these studies were observational studies that reported on CRP POCT versus no CRP POCT, but upon reading the full text of

the article it was clear that all physicians had access to CRP POCT, but that some chose not to use it. These studies were excluded as it was unclear if the non-use of CRP POCT was because these physicians never used it in their practice to inform a decision or because following clinical examination of the individual patients they felt it was unnecessary. Five studies were identified that presented duplicate data of studies that were already included [122-126]. This left 12 studies for inclusion in systematic review 1 [127-138], of which 11 studies were included in the meta-analysis [127, 129-138]. The twelfth study met our inclusion criteria, but did not present enough information in the paper to allow data to be extracted for meta-analysis; attempts to contact the author were unsuccessful [128]. This study (Bjerrum et al. 2004) only reported on the primary outcome (the number of patients given an antibiotic prescription at the index consultation) and the results from this study have been included in the narrative for this outcome.

The search also identified seven relevant systematic reviews [24, 48, 49, 139-142]. These studies were checked for additional references. One systematic review [48] included four additional studies, two of which had been excluded in this study as they were duplicate studies [124], and two studies were excluded as the testing was undertaken in an emergency department and therefore did not meet the inclusion criteria [143, 144]. In the scoping phase of this assessment, we identified a relevant Cochrane review by Aabenhaus et al. from 2014 [24]. A decision was made at that time not to directly update this review as our review included additional outcomes of interest and it included more study types (observational studies in addition to RCTs); however, we did base our review on the Aabenhaus review. The references of included studies were also searched for additional relevant articles, but none were identified. Manufacturers' submissions were also checked for additional studies; six were identified that appeared to be relevant, but on full-text review all were excluded.

5.3 Quality rating

Details of the quality of the evidence included in this systematic review are included in Appendix 1.

5.4 Results

5.2.1 Effectiveness and safety of using CRP POCT to guide antibiotic prescribing in patients with acute respiratory tract infections (RTIs) in primary care settings (Systematic Review 1)

Included studies

The systematic review retrieved 12 studies that assessed the effectiveness and safety of using CRP POCT to guide antibiotic prescribing in patients presenting to primary care with acute RTIs (Table 8). Four studies were individually randomised RCTs (n=3,345) [130-132, 138], three were cluster RCTs (n=4,874, modified sample size n=1,975) [127, 129, 135] and five were non-randomised studies (n=8,998 for four studies included in meta-analysis) [128, 133, 134, 136, 137]. A detailed description of the twelve studies is found in Appendix 1 (Table A6). The sample size of cluster RCTs was modified as described in section 2.6.

Table 8: Main characteristics of studies included

Author and year or study name	Study type	Number of patients	Intervention(s)	Main endpoints	Included in clinical effectiveness and/or safety domain
SR 1: Effectiveness and safety					
RCTs					
Andreeva 2014	Cluster RCT	179	CRP POCT (Afinion™ test system)	Antibiotic Rx at index consultation, Antibiotic Rx at 28 days F/U, Substantial improvement/complete recovery at 7 and 28 days, Mortality, Reconsultations	Effectiveness Safety
Cals 2009	Cluster RCT	431	CRP POCT NycoCard™ II reader	Antibiotic Rx at index consultation, Antibiotic Rx at 28 days F/U, Substantial improvement/complete recovery at 7 and 28 days, Mortality, Time to resolution of RTI symptoms, Reconsultations, Patient satisfaction	Effectiveness Safety
Cals 2010	RCT	258	CRP POCT QuikRead® CRP	Antibiotic Rx at index consultation, Antibiotic Rx at 28 days F/U, Substantial improvement/complete recovery at 7 and 28 days, Mortality, Antibiotic Rx for delayed used, Time to resolution of RTI symptoms, Reconsultations, Patient satisfaction	Effectiveness Safety
Diederichsen 2000	RCT	812	CRP POCT NycoCard™ reader	Antibiotic Rx at index consultation, Substantial improvement/complete recovery at 7 and 28 days	Effectiveness Safety
Do 2016	RCT	2,037	CRP POCT NycoCard™ analyser with NycoCard™ II reader	Antibiotic Rx at index consultation, Antibiotic Rx at 28 days F/U, Mortality, Time to resolution of RTI symptoms, Reconsultations, Hospitalisations, Patient satisfaction	Effectiveness Safety
Little 2013	Cluster RCT	4,264	CRP POCT QuikRead® CRP	Antibiotic Rx at index consultation, Mortality, Time to resolution of RTI symptoms, Reconsultations, Hospitalisation	Effectiveness Safety
Melbye 1995	RCT	239	CRP POCT NycoCard™ Reader	Antibiotic Rx at index consultation, Antibiotic Rx at 28 days F/U, Substantial improvement/complete recovery at 7 and 28 days	Effectiveness Safety

Author and year or study name	Study type	Number of patients	Intervention(s)	Main endpoints	Included in clinical effectiveness and/or safety domain
Non-randomised studies					
Bjerrum 2004	Observational study	367 GPs	CRP POCT	Antibiotic Rx at index consultation	Effectiveness
Jakobsen 2010	Observational	803	CRP POCT NycoCard™ CRP QuikRead® CRP	Antibiotic Rx at index consultation	Effectiveness
Kavanagh 2011	Pilot cross-sectional study	120	CRP POCT QuikRead® CRP	Antibiotic Rx at index consultation, Antibiotic Rx for delayed used, Reconsultations, Patient satisfaction	Effectiveness Safety
Llor (a) 2012	Non-randomised before-after study	3,356*	CRP POCT NycoCard™ CRP	Antibiotic Rx at index consultation	Effectiveness
Llor (b) 2012	Non-randomised before-after study	560*	CRP POCT NycoCard™ CRP	Antibiotic Rx at index consultation	Effectiveness

*Only those patients who received the full intervention were included.

Abbreviations: CAP – community acquired pneumonia; CRP – C-reactive protein; DTA – diagnostic test accuracy; F/U – follow-up; LRTI – lower respiratory tract infection; POCT – point-of-care testing; RCT – randomised controlled trial; Rx – prescription

Ten of the studies were carried out in Europe, one in Russia [127], and one in Vietnam [132]. The length of follow-up varied from no follow-up to 28 days. All included studies reported on at least the primary outcome, that is, antibiotic prescribing at the index consultation. Presenting symptoms and inclusion criteria differed between studies, with some studies including only patients with LRTIs [127, 137, 138], others patients with URTI only (in particular sinusitis) [128, 134, 136], while others included both URTI and LRTI [129-133, 135]. Some studies included patients with exacerbations of chronic obstructive pulmonary disease (COPD), while others excluded patients with chronic disease. Most studies only included adults, while three included adults and children [128, 131, 132]. The studies tended to include more woman than men (RCT range 57-72% female) (Appendix 1, Table A6). Three studies received funding from the manufacturers of the CRP POCT devices [130, 134, 138]. The identified studies included in this relative effectiveness assessment (REA) related to only three of the 15 CE marked devices (QuikRead® CRP kit/QuikRead® 101, Alere Afinion™ CRP, and NycoCard™ CRP for use with NycoCard™ II Readers). All three of these devices are quantitative devices.

The non-randomised studies differed substantially from the RCTs in a number of ways and as a result have been analysed separately. Not only did they differ in terms of study design, but they also differed in terms of access to the intervention. In the RCTs, all patients in the intervention group received the intervention, while no patients in the control group received it. In the non-randomised studies, the intervention group had access to CRP POCT, but the clinicians may or may not have used it, while the control group had no access to CRP POCT.

As there was clinical heterogeneity due to the spectrum of RTIs included in each study (Table A6), a random effects model was used for meta-analysis unless otherwise stated.

Change in management

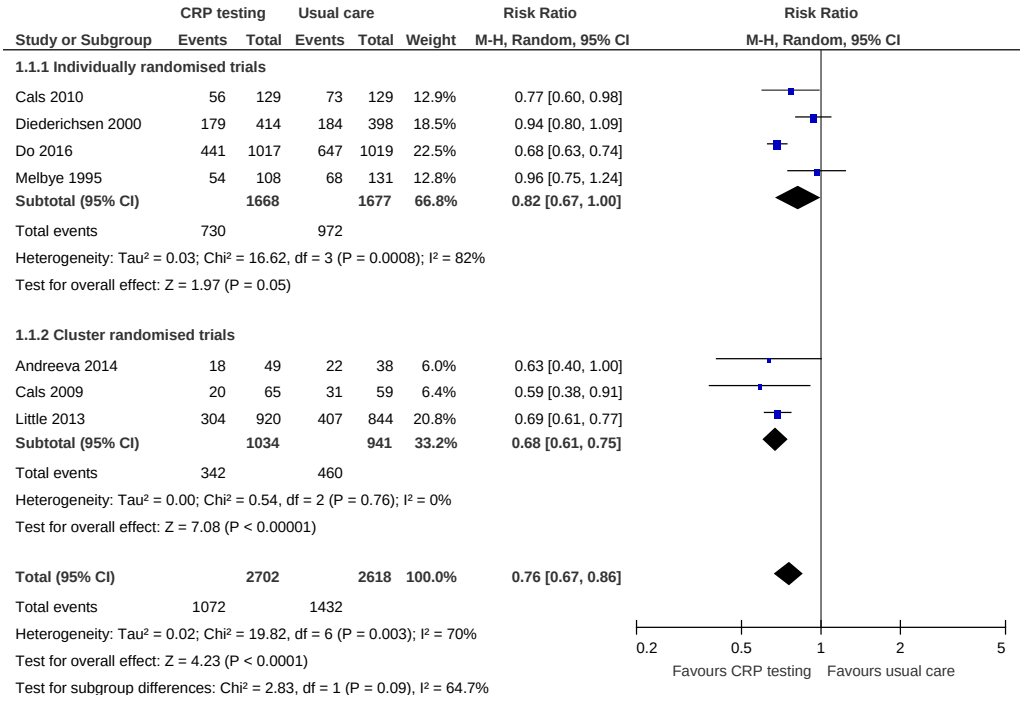
[D0021] – How does use of the test change physicians' management decisions?

Number of patients given an antibiotic prescription at the index consultation

All 12 studies (randomised n=7; observational n=5) reported on this outcome [127, 129-138]. In the meta-analysis, the seven RCTs (individually randomised studies n=3,345; cluster randomised trials with modified sample size n=1,975) and four non-randomised studies (n=4,839) all showed point estimates in favour of CRP POCT to reduce antibiotic prescribing; however, in four studies the difference was not statistically significant (Figure 5) [127, 131, 134, 138].

The pooled estimate for the RCTs showed a statistically significant reduction in antibiotic prescribing in the CRP test group, compared with usual care (RR 0.76, 95% CI: 0.67–0.86, I^2 = 70%) (Figure 5). There was substantial heterogeneity in this pooled estimate (70%). This could not be attributed to differences in trial type, as even in our planned subgroup analysis, grouping the trials based on type of randomisation used (individual or cluster), there was substantial heterogeneity in the individually randomised group (I^2 = 82%, n=4), but not in the cluster randomised group (I^2 = 0%, n=3). When performing a sensitivity analysis, much of the heterogeneity observed in the individually randomised subgroup was due to the 2016 study by Do et al. (I^2 decreases from 82% to 5% when this study is removed) [132]. The study by Do et al. differs from the other studies as it was carried out in Vietnam, while the other studies were carried out in Europe or Russia. It also reported a high level of antibiotic prescribing in the usual care arm, even though they excluded patients with severe RTIs. Inclusion of the study by Do et al. in the meta-analysis of individually randomised trials produced a pooled effect of CRP POCT on antibiotic prescribing of RR 0.82 (95% CI: 0.67, 1.00, I^2 = 82%, n=4) while removing this trial produces an RR of 0.90 (95% CI: 0.80, 1.02, I^2 = 5%, n=3). Removal of this study from the pooled analysis makes only a small difference to the overall pooled effect estimate (RR 0.78 95% CI: 0.66, 0.92, I^2 = 68%, n=6). In the cluster randomised trials, there was a statistically significant reduction in antibiotic prescribing in the CRP POCT group compared with usual care (RR 0.68 95% CI: 0.61, 0.75, I^2 = 0%). However, it should be noted that two of these three studies (Cals 2009 [129] and Little 2013 [135]) used a factorial design and included a communications component that was shown by the authors to have a significant effect on lowering antibiotic prescriptions at the index consultation both on its own and when used in combination with CRP POCT. Removal of these studies from the meta-analysis had only a small effect on the pooled estimate (RR 0.80, 95% CI: 0.67, 0.96, I^2 =77%).

Figure 5: Forest plot: Antibiotic prescribing at index consultation (RCTs and Cluster RCTs)

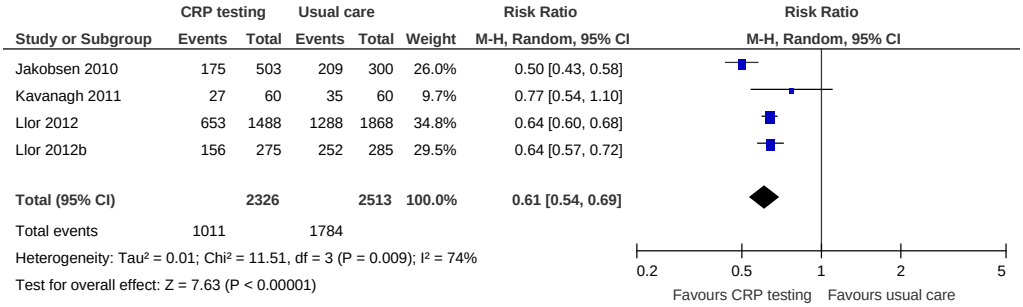


The observational studies show a similar effect of CRP POCT on antibiotic prescribing with a pooled RR of 0.61 (95% CI: 0.54–0.69) (Figure 6). There was substantial heterogeneity in the pooled estimate with an I^2 = 74%. In a sensitivity analysis, it was identified that the 2010 study by Jakobsen et al. was the source of the heterogeneity. When this trial was removed from the meta-analysis, the effect of CRP POCT on antibiotic prescribing remained, but the heterogeneity decreased (RR 0.64, 95% CI: 0.61–0.68, I^2 = 0%, n=3). The study by Jakobsen et al. compared antibiotic prescribing in Norway and Sweden, where CRP POCT is often used in routine consultation, to Wales in the UK where it is not available to GPs. As Sweden and Norway and the UK have different health systems and patients may have different expectations about receiving an antibiotic, this control group may not have been a suitable comparator [133]. The 2004 study by Bjerrum et al. also reported a significant difference in prescribing between their CRP POCT group and the usual care group, but the data were not available in a format where it could be extracted for meta-analysis (OR 0.43, 95% CI: 0.33–0.58) [128].

The number needed to test (NNT) using CRP POCT to save one antibiotic prescription was calculated and ranged between 3 and 20 people, depending on the study type. That is:

- RCTs (all), NNT 10.0 (95% CI: 4.8–151.5)
- RCTs (without Do 2016), NNT 19.8 (95% CI: 9.0–102.0)
- Cluster RCTs, NNT 6.3 (95% CI: 5.0–8.6)
- RCTs + Cluster RCTs, NNT 7.6 (95% CI: 5.2–14.4)
- RCTs + Cluster RCTs (without Do 2016), NNT 9.0 (95% CI: 5.6–22.4)
- Observational studies, NNT 3.5 (95% CI: 2.9–4.6)

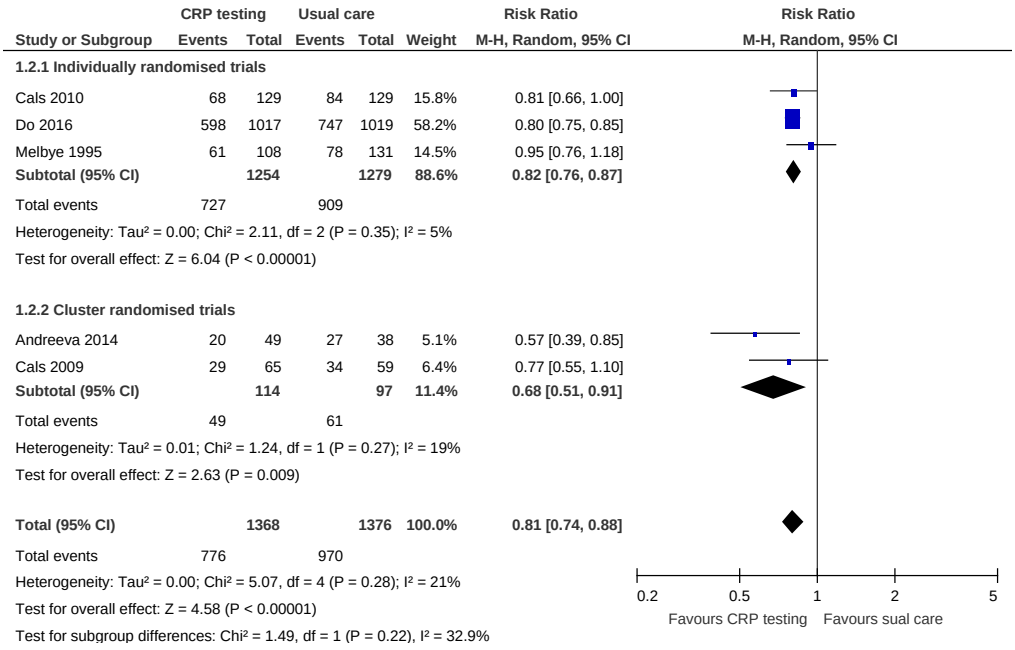
Figure 6: Forest plot: Antibiotic prescribing at index consultation (Non-randomised studies)



Number of patients given an antibiotic prescription within 28 days follow-up.

Five RCT studies reported on this outcome (Figure 7) [127, 129, 130, 132, 138], of which three were individually randomised studies (n=2,533) and two were cluster randomised studies (modified sample size n=211). No observational studies reported on prescribing beyond the index consultation. All included studies showed point estimates in favour of CRP POCT to reduce antibiotic prescribing within 28 days (RR 0.81, 95% CI: 0.74–0.88, I^2 = 21%); however, in three of the studies the difference was not significant. Not all of the studies had a follow-up period of 28 days: the study by Melbye et al. had a 21-day follow-up period [138], while the studies by Do et al. and Andreeva et al. had a 14-day follow-up period [127, 132]. There was no indication that more patients subsequently received an antibiotic during the follow-up period in the CRP POCT group compared with usual care.

Figure 7: Forest plot: Antibiotic prescribing within 28 days (RCTs and Cluster RCTs)



Planned subgroup analysis

Subgroup analysis was performed for upper (sinusitis, sore throat, etc.) versus lower RTIs (bronchitis, acute exacerbations of COPD, pneumonia, cough, etc.) for the outcome of antibiotic prescribing at the index consultation. Eight studies (three RCTs [130, 135, 138], one cluster RCT [127] and four non-randomised studies [133, 134, 136, 137]) provided data on either LRTI or URTI or both (Figure 8 and Figure 9).

Figure 8: Forest plot: Antibiotic prescribing at index consultation in LRTI and URTI (RCTs and Cluster RCTs)

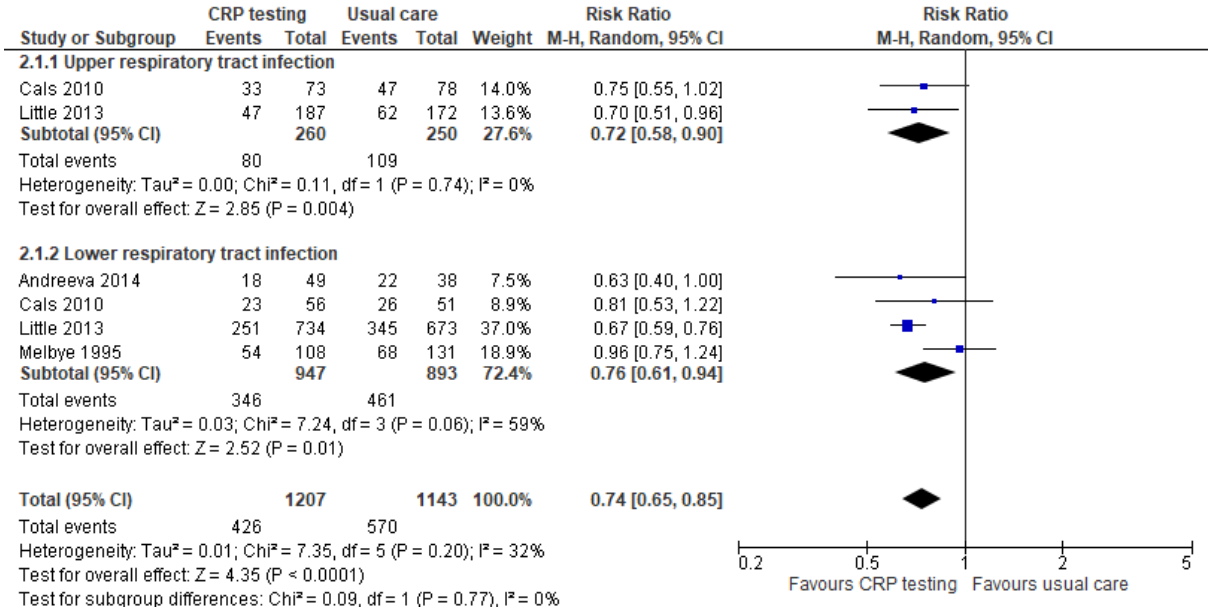
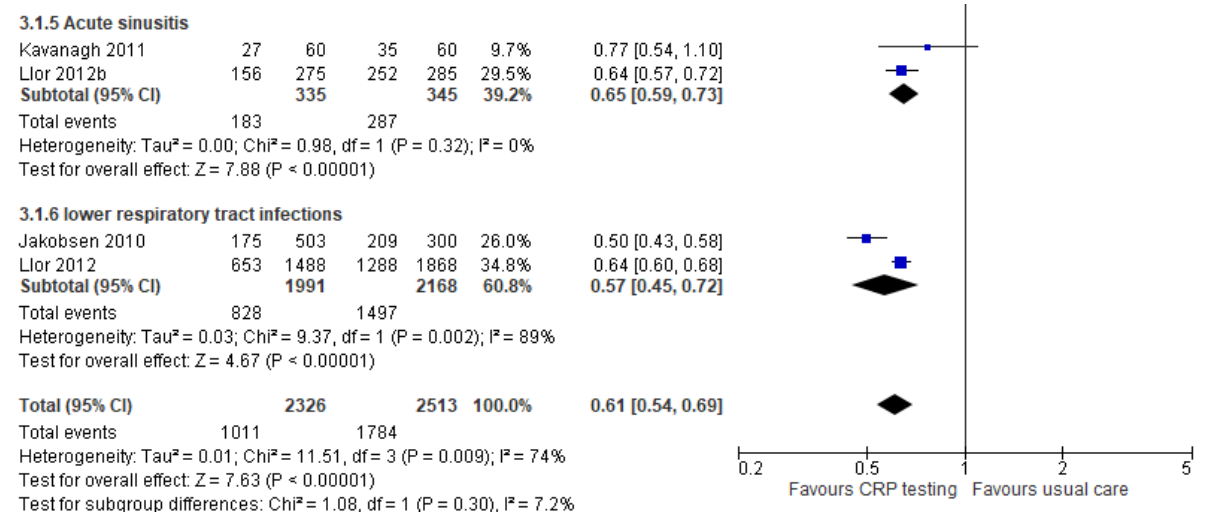


Figure 9: Forest plot: Antibiotic prescribing at index consultation in LRTI and URTI (Non-randomised studies)



Two RCTs provided data on URTI [130, 135]. Overall, the pooled estimate shows a significant reduction in antibiotic prescribing between the CRP POCT group and the usual care group for URTI in both RCTs (RR 0.72, 95% CI: 0.58–0.90, I^2 = 0%). The non-randomised studies show a similar finding, both studies have a point estimate favouring CRP POCT, but the difference is not statistically significant in the Kavanagh et al. study but is significant in the Llor 2012 study. Overall, the pooled estimate

shows a significant reduction in antibiotic prescribing between the CRP POCT group and the usual care group (RR 0.65, 95% CI: 0.59–0.73, I^2 = 0%).

Four RCTs provided data on LRTI [127, 130, 135, 138]. Three of the studies had a non-significant reduction in antibiotic prescribing in the CRP POCT group compared with the usual care group [127, 130, 138], while one study showed significant difference [135]. The pooled RR suggests CRP POCT does lower antibiotic prescribing in patients with LRTI (RR 0.76, 95% CI: 0.61–0.94), however there is substantial heterogeneity (I^2 = 59%). This finding is backed up by two non-randomised studies (Llor 2012 and Jakobsen) with a pooled estimate of RR 0.57 (95% CI: 0.45–0.72, I^2 = 89%).

Two RCTs [131, 132] included adults and children. The study by Do et al. found a similar and significant effect of using CRP POCT on antibiotic prescribing with children and adults (children n=1,028, RR 0.69, 95% CI: 0.62–0.78; adults n=1,008, RR 0.67, 95% CI: 0.60–0.76; combined cohort n=2,036, RR 0.68, RR: 0.63-0.74). The study by Dierderichsen et al. also included adults and children in their study. While they did not report the antibiotic prescribing separately for adults and children, the Cochrane review by Aabenhaus et al. used unpublished data to calculate the effect of CRP POCT in children and adults separately for this study and reported that CRP POCT did not have a significant effect on the prescribing of antibiotics in either group (children n=139, RR 1.09, 95% CI: 0.70–1.71; adults n=673, RR 0.91, 95% CI: 0.78–1.07)[24]. As noted previously, the effect of CRP POCT on antibiotic prescribing in the combined cohort in this study was not significant (children and adults n=812, RR 0.94, 95% CI: 0.80 to 1.09).

Although it was not possible to do a subgroup analysis based on CRP cut-points, there was an option to undertake subgroup analysis of studies where there was a clear recommendation to the GP on the basis of specified CRP levels, specifically if CRP is < 20 mg/L not to prescribe antibiotics, to prescribe antibiotics when CRP is > 100 mg/L and to use clinical judgement when CRP is between 20 and 99 mg/L as per NICE guidelines for pneumonia. Four studies fit this criteria (see Table 9 for a description of algorithms used in each study), two individually randomised RCTs [130, 132], one cluster RCT [135] and one non randomised study [137]. Combining the RCTs (using modified sample size for cluster RCT) produces a pooled estimate of RR 0.69 ([95% CI: 0.65, 0.74], I^2 = 0%). The non-randomised study by Llor et al. agreed with the pooled estimate (0.64 [0.60, 0.68]), suggesting that providing GPs with clear cut-points based on clinical guidelines may enhance the effect of CRP POCT on antibiotic prescribing.

Table 9: Algorithms used in studies

Author	Year	Algorithm, if used
Studies with clear recommendation to the GP		
Cals	2010	Advice was given based on CRP test values. No antibiotics if CRP <20mg/L, immediate antibiotics of CRP >100 mg/L and consider a delayed prescription for CRP levels between 20 and 99 mg/L. Physicians could deviate from the advice at any time
Do	2016	Recommend that antibiotics should not be prescribed if CRP ≤20 mg/L for patients aged 6–65 years and if CRP ≤10 mg/L for patients aged 1–5 years. Adults with CRP ≥100 mg/L and children with CRP ≥50 mg/L should generally receive antibiotics and hospital referral should be considered. Between these thresholds no specific recommendation was given and clinicians were advised to use their clinical discretion.

Llor	2012	Advice based on CRP cut-points. GPs were advised to use CRP test only in cases of doubt, and not as a standalone test, withholding antibiotic therapy for CRP values <20 mg/L and prescribing an antibiotic for values >100 mg/L.
Little	2013	Recommended cut-points for CRP. CRP ≤ 20 mg/l – self-limiting LRTI, withhold antibiotics. CRP 21-50 mg/L – majority of patients have self-limiting LRTI, assessment of signs, symptoms, risk factors and CRP is important, withhold antibiotics, in most cases. CRP 51-99 mg/L – assessment of signs, symptoms, risk factors and CRP is crucial, withhold antibiotics in the majority of cases and consider delayed antibiotics in the minority of cases. CRP ≥ 100 mg/L – severe infection, prescribe antibiotics
Other Algorithms used in studies		
Andreeva	2014	GPs were told that antibiotics were usually not needed when the CRP value was below 20 mg/L and that a prescription could be indicated for CRP values above 50 mg/L, taking into account the duration of illness, but that giving antibiotics should be decided on a case-by-case basis.
Bjerrum	2004	None reported.
Cals	2009	CRP <20 – pneumonia extremely unlikely. CRP 20 to 50 – pneumonia very unlikely. CRP 50 to 100 – clear infection, most likely bronchitis possibly pneumonia, combining clinical findings and CRP very important. CRP >100 – severe infection, pneumonia more likely.
Diederichsen	2000	Advice was given to the GPs that a normal CRP value (<10mg/L) and a CRP value <50 mg/L was seldom the result of bacterial infection.
Jakobsen	2010	None reported.
Kavanagh	2011	Based on CRP cut-points. CRP value of <20 was considered indicative of a viral or self-limiting infection. A value of 20 to 50 was taken to indicate a 'borderline' level (at which advice would usually be given to observe symptoms over 48 hours with explanation in relation to red flag symptoms and signs, and the possible issue of a delayed antibiotic prescription). A level of >50 was considered to be indicative of a bacterial infection.
Llor	2012	The GPs were informed about the evidence regarding CRP use in RTIs and it was emphasised that the test result should always be interpreted in combination with patient history recording and clinical examination. A CRP test result >40 mg/L was interpreted as a support for the decision to prescribe antibiotics, while a CRP test result <10 mg/L supported the decision on no antibiotic prescribing.
Melbye	1995	Disease duration 0-24 hours: CRP <50 mg/L – no change in clinical decision. Give antibiotics at CRP ≥50 mg/L. Disease duration 1-6 days: Do not give antibiotics at CRP <11 mg/L, CRP 11-49 mg/L no change in clinical decision, give antibiotics at CRP ≥50 mg/L. Disease duration seven days or more: Do not give antibiotics at CRP <11 mg/L, CRP 11-24 mg/L no change in clinical decision, give antibiotics at CRP ≥25 mg/L.

Number of patients given an antibiotic prescription for immediate use versus delayed use and redemption of prescriptions

One RCT [130] and one non-randomised study [134] included information on whether the prescribed antibiotic was delayed or for immediate use. Delayed antibiotic prescribing is a strategy of providing a patient with a prescription for an antibiotic, but advising them not to fill the prescription unless their symptoms persist or worsen, or if laboratory results (if requested) subsequently indicate a bacterial infection. These studies (by Cals et al. 2010 and Kavanagh et al. 2011), showed no difference in the number of patients provided a delayed prescription between the CRP group and the usual care groups (RR 0.84, 95% CI: 0.53–1.33 and RR 1.30, 95% CI: 0.63–2.66, respectively). However, the study by Cals et al. 2010 also looked at how many patients redeemed their delayed prescription, and found significantly more redeemed prescriptions in the usual care group compared with the CRP POCT group (72% versus 23%). As the study by Cals et al. 2010 showed no significant difference in recovery at seven days between the CRP POCT group and the usual care group ([D0005], [C0008]), this might suggest that patients were more reassured that they did not need an antibiotic when the findings from the clinical examination were supported by their CRP test result. Further qualitative studies would need to be done to explore the reasons for redemption of delayed prescriptions. Other than the study by Cals et al. 2010, no study provided information on the number of patients who redeemed a prescription for antibiotics.

Mortality

[D0001] – What is the expected beneficial effect of the technology on mortality?

As this AE overlaps with C0008, results will be presented in Section 6.2 (Safety). In brief, out of 7,165 patients (CRP test group n=3,696, usual care group n= 2,469), there were no reported deaths. It is therefore unlikely that the use of CRP POCT will have any beneficial or detrimental effect on mortality.

Morbidity

[D0005] – How does the use of CRP POCT to guide antibiotic prescribing affect symptoms and findings (severity, frequency) of RTI?

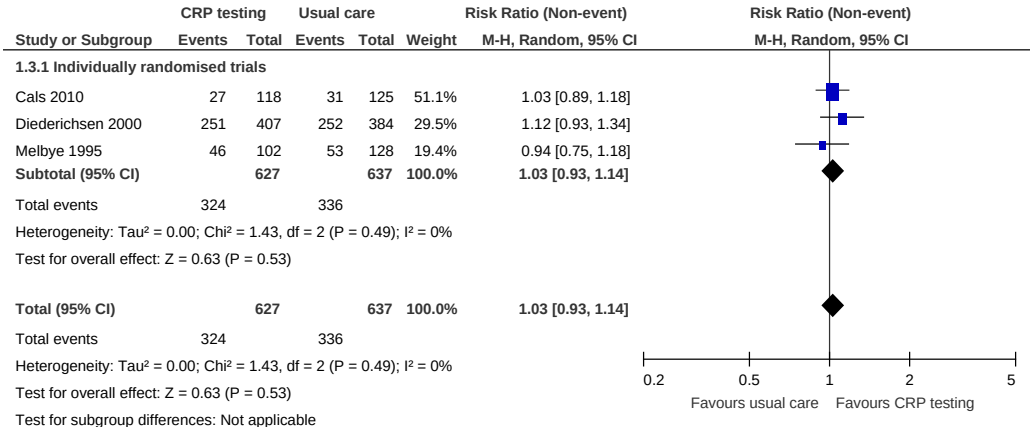
This AE overlaps with C0008**.**

Number of patients with substantial improvement or complete recovery at seven days and 28 days

Three RCTs (n=1,264 patients) reported on the number of patients that made a substantial or complete recovery by day seven (Figure 10) [130, 131, 138]. The study by Diederichsen et al. did not include this information in their paper, but the author had provided this information for the Cochrane review by Aabenhaus et al. and this data was extracted directly from the Aabenhaus review [24]. There was no difference in the number of patients making a substantial or compete recovery between the CRP POCT group and the usual care group at seven days (RR 1.03, 95% CI: 0.93–1.14, I^2 = 0%). Of note, the study by Cals et al. 2009 (n= 388 patients) also reported that there was no significant difference in clinical recovery between the groups at seven days, but the data were not extractable for meta-analysis [24, 129].

Three studies (one individually randomised RCT [138] and two cluster RCTs [127, 129]) reported on recovery beyond seven days: Andreeva et al., Melbye et al. and Cals et al. reported on clinical recovery at 14 days, 21 days and 28 days, respectively. Cals 2009 data was extracted directly from the Aabenhaus et al. review [24] as this data was not available in the study paper. In all three studies, there was no difference in recovery beyond seven days between the CRP POCT group and the usual care group (n=527, with modified sample sizes for cluster RCTs. RR 0.94 [95% CI: 0.68–1.28], I^2 = 0%).

Figure 10: Forest plot: Recovery by day seven (RCTs and Cluster RCTs)



Time to resolution of acute respiratory infection symptoms

Four studies (two individually randomised RCTs [130, 132] and two cluster randomised RCTs [105, 129]) reported on the time to resolution of symptoms (Table 10) [129, 130, 132, 135]. All four studies reported the median time to resolution of symptoms; however, no attempt was made to pool these data as the definition of resolution of symptoms differed between studies. All of the studies reported no significant difference in the time to resolution of symptoms between the CRP POCT and usual care groups, even when one group had received more antibiotics than the other group.

Table 10: Median time to resolution of symptoms

Author (year)	Patients	Median time to symptom resolution in CRP group (days)	IQR (days)	Median time to symptom resolution in usual care group (days)	IQR (days)
Do (2016)	All patients	5	4 to 7	5	4 to 7
	Children	5	3 to 7	5	4 to 7
	Adults	6	4 to 10	5	4 to 8
Cals (2010)	Rhinosinusitis	14	10 to 28	14	7 to >28
	LRTI	15.5	9.5 to 28	20	13.3 to >28
Cals (2009)	All patients	22	14 to 28	22	14 to 28
Little (2013)	All patients	5	3 to 9	5	3 to 9
	URTI	5	3 to 7	4	3 to 8
	LRTI	6	3 to 9	5	3 to 9

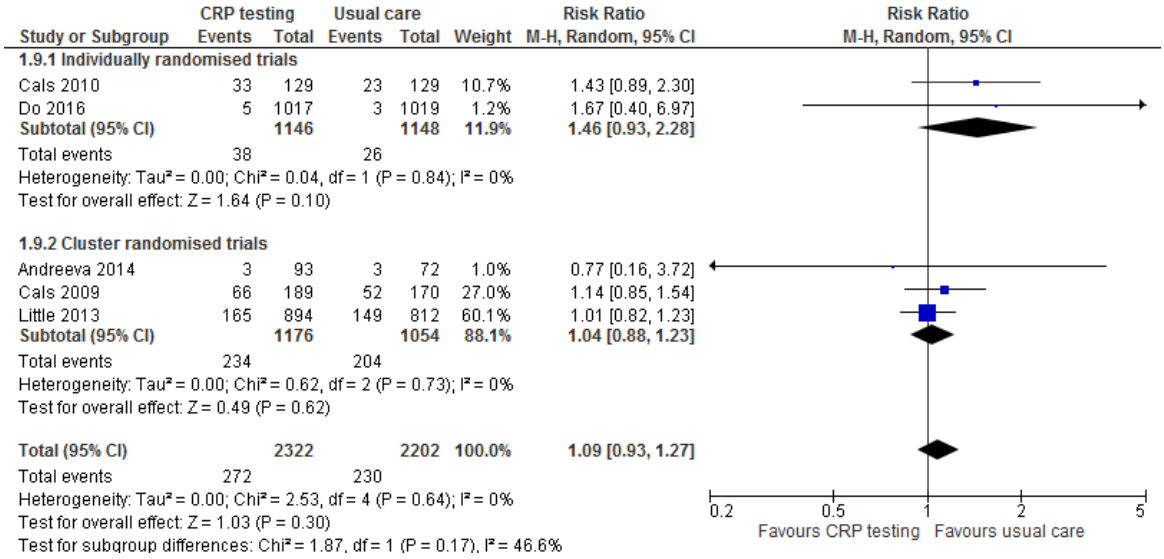
[D0006] – How does CRP POCT affect progression (or recurrence) of the RTIs?

This AE overlaps with C0008 and is also discussed in the Safety domain.

Number of patients reconsulting

Six studies reported on reconsultations – five RCTs (of which two were individually randomised and three were cluster randomised trials) and one non-randomised study (Figure 11) [127, 129, 130, 132, 134, 135]. While the point estimates for reconsultation exceeded that of the usual care group in all but one study, this difference was not statistically significant in any study. The difference in reconsultation rates between the CRP POCT group and the usual care group was not statistically significant in the pooled meta-analysis (RCTs n=4,524, RR 1.09, 95% CI: 0.93–1.27 I^2= 0% and non-randomised study n=120, RR 1.56, 95% CI: 0.73–3.32).

Figure 11: Forest plot: Reconsultations (RCTs and Cluster RCTs)



[D0011] – Does the use of CRP POCT to guide antibiotic prescribing lead to reduced adverse events as a result of lower antibiotic prescribing rates compared with standard care?

This AE overlaps with C0008 and is reported in the Safety domain.

Health-related quality of life

[D0012] – What is the effect of the technology on generic health-related quality of life?

There were no studies that reported on health-related quality of life (HRQoL).

[D0013] – What is the effect of the technology on disease-specific quality of life?

There were no studies that reported on disease-specific quality of life.

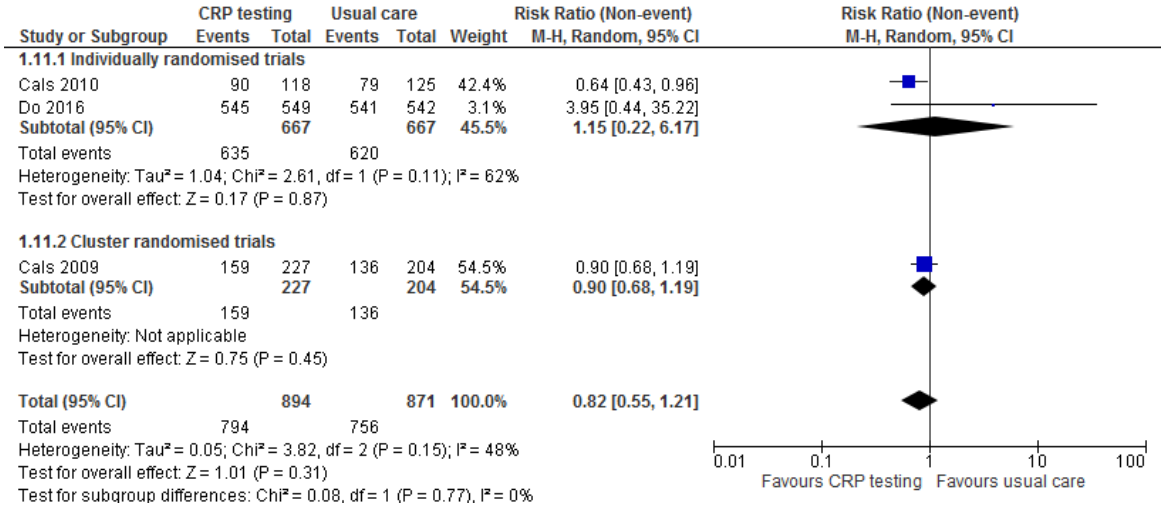
Satisfaction

[D0017] – Were patients satisfied with the technology?

Patient and physician satisfaction

None of the included studies reported on physician satisfaction with CRP POCT. Four studies in total reported on patient satisfaction (n=1,885). In three of these studies satisfaction with their clinician visit was measured using a Likert scale: one individually randomised study [130], one cluster randomised study [129] and one non randomised study [134]. The fourth study was an RCT and the authors used a scale of 1 to 10 to measure patient satisfaction regarding participation in the trial [132]. The patients were generally satisfied with the care received and there was no significant difference between the CRP POCT group and the control group (RCTs RR 0.82 [95% CI: 0.55, 1.21], I^2 = 48%; non-randomised study Kavanagh et al. RR 1.00, 95% CI: 0.86–1.16). Although in one study, Cals et al. 2010, patients were more often satisfied in the CRP POCT group than in the usual care group (Figure 12).

Figure 12: Forest plot: Patient satisfaction, satisfied (RCTs and Cluster RCTs)



5.5 Discussion

Overall, our results suggest that CRP POCT, when used to guide management of patients who present with symptoms of acute RTI, leads to reduced antibiotic prescribing both at index consultation and up to 28 days follow-up. All studies showed a point estimate that favours the use of CRP testing in reducing antibiotic prescribing, but in some studies this difference was not significantly different to usual care. There was substantial heterogeneity in the pooled results for the individually randomised RCTs and the non-randomised studies. A sensitivity analysis showed that most of the heterogeneity in the individually randomised RCTs was due to one study by Do et al., which was carried out in Vietnam [132]. The study had a high level of prescribing in the usual care arm (63.5%), even though they excluded anyone presenting with severe acute RTIs and therefore may have been different to the other studies. Removal of this study from the RCT analysis results in a non-significant reduction in antibiotic prescribing in the CRP POCT group with much lower heterogeneity (I^2 = 5%). In the non-randomised studies, the effect of CRP POCT on reducing antibiotic prescribing remains, but the heterogeneity is reduced (I^2 = 0%) with the removal of one study that used a control group from a different country to the intervention group [133]. This reduction in antibiotic prescribing in the CRP POCT group does not appear to lead to a significant difference in clinical recovery or reconsultation rates.

Delayed prescribing is a method whereby a prescription is issued to the patient for use at a later date if their symptoms do not improve. Only two studies reported on the use of delayed prescriptions [130, 134] and there appears to be no significant difference in the use of delayed prescriptions between the CRP POCT group and the usual care group. The use of delayed prescriptions has been shown to be a very effective method of reducing antibiotic prescription redemption [145]. In both of these studies, the algorithm given to the GPs in the CRP POCT group suggested the use of a delayed prescription if the CRP levels were intermediate. As a result, one might expect more delayed prescribing in the group receiving the CRP POCT; however, in both of these studies it appeared that GPs were already using delayed prescribing in their usual care. Of note, Cals et al. also looked at redemption rates for the delayed prescriptions and found it to be significantly lower in the CRP POCT group. While it is not possible to draw a conclusion based on a single paper, this could suggest that knowing their CRP POCT result provides patients with greater assurance that an antibiotic is not warranted.

In the studies that reported on patient satisfaction [129, 130, 132, 134], the patients were mostly satisfied and there was no difference in satisfaction between the CRP POCT group and the usual care group, suggesting that the provision of CRPPOCT neither improves nor disimproves their consultation experience.

In addition to the outcomes we had identified as important, one study [127] reported on referral to radiography and found there was a significantly lower rate of referral in the CRP POCT test group compared with the usual care group (55.5% versus 96% p=0.004). Although no conclusions can be drawn from this, if CRP POCT leads to a reduction in referrals for further testing it could lead to substantial savings for the healthcare system without negatively impacting on patient safety.

A number of the studies [129, 135-137] included an educational or communications component in their intervention with CRPPOCT. This may have enhanced the effect of CRP POCT on antibiotic prescribing, but the removal of Little 2013 and Cals 2009 from the RCT meta-analysis only changes the pooled risk ratio a small amount and still leads to the conclusion that CRP POCT leads to a significant reduction in antibiotic prescribing (RR 0.80, 95% CI: 0.67–0.96).

Due to a lack of studies, we were unable to carry out all of our pre-planned subgroup analysis. From the 2014 Cochrane review by Aabenhaus et al. [24] we expected heterogeneity by study type. Therefore we planned subgroup analysis for individually randomised and cluster randomised trials; non-randomised (observational) studies were analysed separately due to the difference in quality of this study type. There were sufficient studies to analyse URTI separately to LRTI and in all study types antibiotic prescribing was significantly lower in the CRP POCT group (Figure 5, Figure 6) suggesting that CRP POCT is useful for both upper and lower RTIs. However, there was substantial heterogeneity, particularly in the non-randomised studies. Only three studies included children, and in the two studies for which data could be extracted for meta-analysis, the effect of CRP POCT on prescribing of antibiotics was similar in both adults and children [24, 125, 132]. However, one study found a significant effect in both adults and children while the other reported no effect in both groups. In light of the limited data including children and the lack of consistency in results, it is not possible to state from this review what the impact of CRP POCT is on antibiotic prescribing in children with RTIs.

Although most studies included adults of all ages, there was no separation of results for younger adults (<65 years) versus older adults. More studies involving CRP POCT would be useful in older adults as older adults often have co-morbidities and may be on multiple medications, and it is currently unclear what effect this may have on CRP POCT and on GP prescribing. There were no studies that met our inclusion criteria that included patients from long-term care facilities or out-of-hours clinics, so it was not possible to look at these populations separately.

Our study shows similar results to other published systematic reviews in the area [24, 48, 139, 142], with the conclusion that although some studies show no significant difference between CRP POCT and usual care in terms of antibiotic prescribing, when combined, the pooled estimates suggest CRP POCT does have a significant effect on prescribing. We included both RCTs and observational studies in our review to ensure the review reflected the findings from a range of study types and not just clinical trials where GPs might be more motivated to follow the suggested algorithms and limit their antibiotic prescribing.

The studies included in the systematic review were all characterised by patient follow-up periods of no more than four weeks. The average recruitment period across trials was 6.5 months, or 7.5 months from the recruitment of the first patient to completion of follow-up for the last patient. One study has subsequently published data with 3.5 years follow-up that gives some evidence in relation to the sustained impact of CRP POCT for RTIs. These limited data suggests that the initial introduction of CRP POCT might be associated with behavioural change that leads to reduced consultation by patients for subsequent episodes of RTI. A key question is whether the availability of CRP POCT within a general practice continues to impact on antibiotic prescribing over the longer term. That impact could be initiated through raised awareness among both patients and clinicians, and that the associated behavioural change might be sustained. Whether those behavioural changes require ongoing access to CRP POCT is not known, and it is possible that behaviours could revert to those in place prior to its introduction.

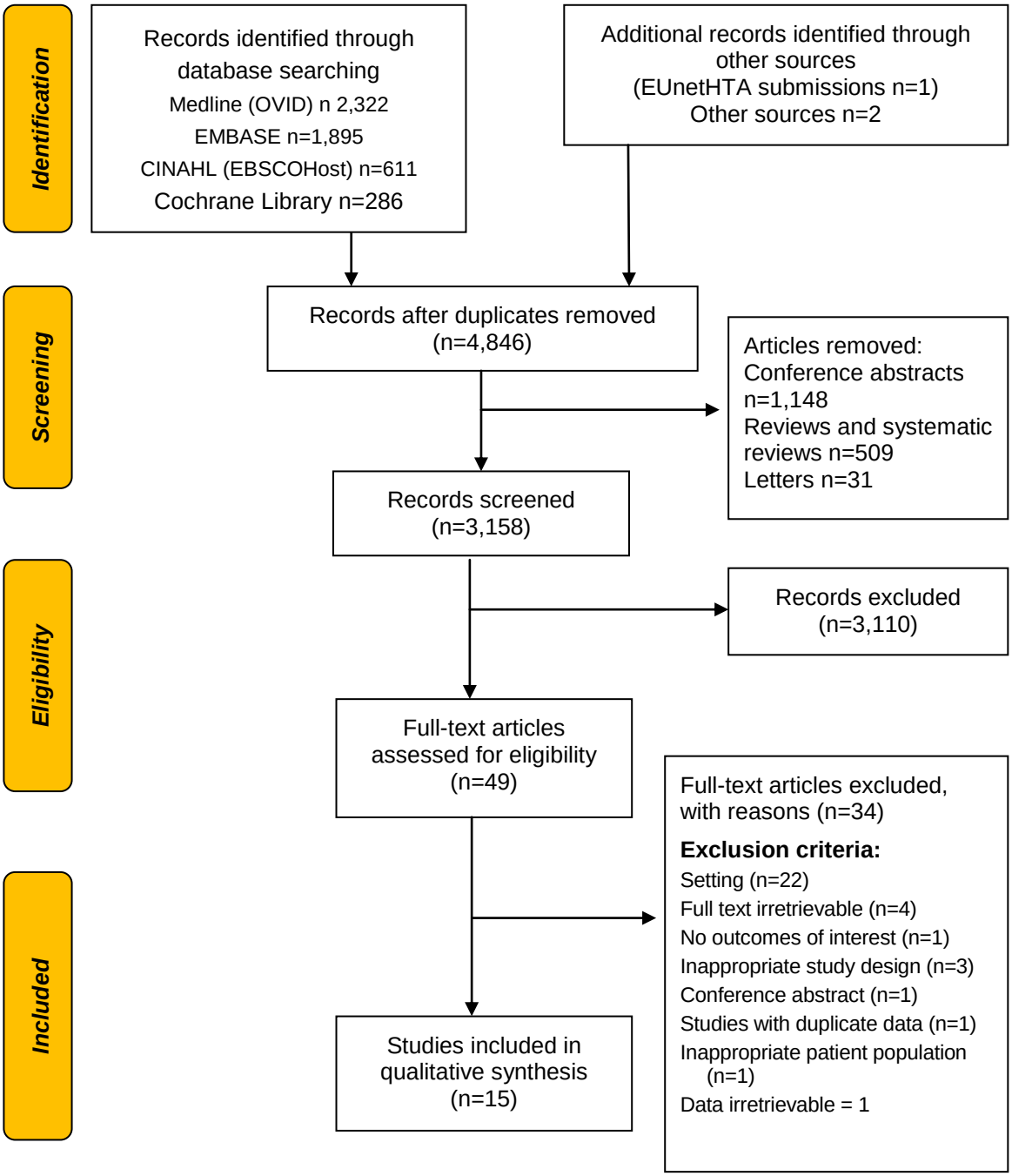
5.6 Research questions – Systematic review 2 (Diagnostic test accuracy)

Element ID	Research question
Diagnostic core model	
D1002	How does the test compare to other optional tests in terms of accuracy measures?
D1003	What is the reference standard for acute RTI and how likely does it classify the target condition correctly?
D1005 Overlaps with **D1006**	What is the optimal threshold value in this context? Do CRP levels reliably rule in or rule out the target condition?

5.7 Study selection

Literature search and study selection process for systematic review 2 (diagnostic test accuracy)

Figure 13: Flow chart systematic review 2 (diagnostic test accuracy)



A total of 4,846 studies were identified through searches of the selected databases and the grey literature. Following screening, 49 articles were identified as being potentially relevant. Of these, 35 studies were later excluded. Reasons for exclusion are documented in Figure 13. The most common reason for exclusion was inappropriate setting, that is, the study was not limited to patients presenting to a primary care setting. Following an eligibility assessment, 15 studies were included in the analysis.

The search also identified three relevant systematic reviews [47, 146, 147] and one meta-analysis [25]. A cross-check of the references included in these papers resulted in one potentially relevant paper being identified [148]. The paper was excluded following contact with the author as data relating to primary care patients excluding those presenting to outpatient clinics were not available.

5.8 Quality rating

Details of the quality of the evidence included in this systematic review are included in Appendix 1, Figures A2 and A3.

5.9 Results

Included studies

The search of the literature retrieved 15 diagnostic test studies that evaluated the diagnostic test accuracy of CRP in patients presenting with acute RTIs in primary care (Table 11).

Table 11: Main characteristics of studies included in systematic review of DTA

Author and year or study name	Study type	Number of patients	Intervention(s)	Main endpoints	Included in diagnostic test accuracy domain
Sinusitis					
Ebell 2017	DTA (Acute rhinosinusitis)	175	Standard CRP laboratory measurement	DOR	Effectiveness
Hansen 1995	DTA (Acute rhinosinusitis)	168	NycoCard™ CRP	DOR, sensitivity, specificity, PPV, NPV	Effectiveness
Pharyngitis/Tonsilitis					
Calvino 2014	DTA (Acute pharyngitis)	149	CRP POCT QuikRead go®	Mean CRP level	Effectiveness
Christensen 2014	DTA (Acute tonsillitis)	100	Standard CRP laboratory measurement	Mean CRP level, Sensitivity, Specificity, AUC	Effectiveness
Gulich 2002	DTA (Acute pharyngitis)	265	NycoCard™ CRP	Sensitivity, Specificity, PPV, NPV, AUC	Effectiveness
Gulich 1999	DTA (Acute pharyngitis)	161	NycoCard™ CRP	Sensitivity, Specificity, PPV, NPV	Effectiveness
Pneumonia					
Heiskansen-Kosma 2000	DTA (Acute pneumonia)	193	Standard CRP laboratory measurement	Mean CRP level,	Effectiveness
Holm 2007	DTA (LRTI)	364	Standard CRP laboratory measurement	Sensitivity, specificity, PPV, NPV, DOR	Effectiveness
Hopstaken 2003	DTA (LRTI)	243	Standard CRP laboratory measurement	AUC, DOR	Effectiveness

Hopstaken 2009	DTA (LRTI)	95	Standard CRP laboratory measurement	Sensitivity, specificity, PPV, NPV, AUC	Effectiveness
Lagerström 2006	DTA (CAP)	82	CRP POCT device (NycoCard™ reader) in laboratory	Median CRP levels	Effectiveness
Melbye 1988	DTA (CAP)	69	Standard CRP laboratory measurement	Sensitivity, specificity, NPV, LR	Effectiveness
Minnaard 2015	DTA (acute pneumonia)	200	CRP POCT device (Afinion™, NycoCard™ reader II, Eurolyser Smart 700/340, QuikRead go®, QuikRead® 101) in laboratory	Sensitivity, specificity, PPV, NPV	Effectiveness
Teepe 2016	DTA (acute cough)	3,104	Standard CRP laboratory measurement	AUC, PPV, NPV	Effectiveness
Van Vugt 2013	DTA (acute cough)	2,820	Standard CRP laboratory measurement	Sensitivity, specificity, PPV, NPV, LR, AUC, DOR	Effectiveness

Abbreviations: CAP – community acquired pneumonia; CRP – C-reactive protein; DTA – diagnostic test accuracy; F/U – follow-up; LRTI – lower respiratory tract infection; POCT – point-of-care testing; RCT – randomised controlled trial; Rx – prescription; PPV – positive predictive value; NPV – negative predictive value; LR – likelihood ratio; AUC – area under the curve; DOR – diagnostic odds ratio

All fifteen studies were carried out in Europe [3-7, 9-12, 14, 15, 149-153]. The studies evaluated the utility of CRP testing across a range of RTIs including pharyngitis, acute tonsillitis, sinusitis and LRTI including pneumonia. The majority of included studies enrolled patients aged 15 years and older [3-7, 9-12, 14, 151-153]. One study recruited children aged between three months and 15 years of age only [150]. The utility of CRP levels in the evaluation of patients presenting with signs and symptoms of RTI was assessed using cut-points ranging from 6 to 100 mg/L. CRP levels were measured using commercially available POCT devices suitable for use in primary care in four of the 15 studies [4, 5, 7, 153]. Two studies used a CRP POC test; however, the analyses were carried out by a laboratory technician [9, 11]. The remaining studies used standardised laboratory testing for CRP [3, 6, 10, 12, 14, 15, 150-152]. Two studies received research funding from manufacturers of CRP POCT devices [11, 14]. A detailed description of the 15 studies is provided in Appendix 1 (Table A7).

Diagnostic test accuracy may vary between patient subgroups. For the purposes of analysis, studies have been grouped according to the type of RTI identified in the systematic review. There was a high level of heterogeneity across studies, reflecting differences between studies in the criterion used to define test positivity, diagnostic criteria, patient populations, and due to the absence of a universal reference standard for the diagnosis of RTIs requiring antibiotics. For this reason, meta-analysis of the data was not appropriate. Due to the inconsistency of effect measures and positivity thresholds reported by individual studies, a narrative summary of the reported diagnostic test accuracy outcome measures is provided. As noted, details of study, population, intervention and comparator characteristics are provided in Appendix 1 (Table A7). A number of identified studies reported mean CRP levels in the sample population. Although this is not a measure of diagnostic test accuracy, it is included in

the analysis to provide context in relation to the clinical usefulness of CRP cut-points. Measurement of patient CRP levels is not intended to reflect the diagnostic test accuracy of CRP POC tests. In the majority of the included studies sensitivity and specificity data were reported and presented. To aid with the interpretation of these data, additional tables have been included in the appendix that report the likelihood ratios (LR) for studies for which it was possible to extract or calculate these values (Appendix 1, Table A9, Table A10 and Figure A1).

Evidence in relation to two assessment elements ([D1005] and [D1006]) was identified for three RTI types: sinusitis, pharyngitis or tonsillitis and LRTIs or pneumonia. As there is substantial overlap between the AEs, the evidence is presented sequentially for the three conditions to facilitate ease of reading.

Sinusitis

[D1005] – What is the optimal threshold value in this context? Overlaps with:

[D1006] – Do CRP levels reliably rule in or rule out acute sinusitis requiring antibiotic therapy?

Two studies were identified for inclusion, an overview of which can be found in table Appendix 1 (Table A7).

A 2017 paper by Ebell et al. reported the results of a univariate logistic regression analysis of the association between CRP levels and acute maxillary rhinosinusitis across a range of cut-points (10 mg/L, 15 mg/L and 20 mg/L). The authors reported that at a CRP threshold of >15 mg/L, the diagnostic odds ratio (DOR) of acute sinusitis was 4.75 (95% CI: 2.50–9.02), when using the presence of purulent or mucopurulent fluid from antral puncture as the reference standard (Table 12). A clinical decision rule incorporating signs, symptoms and CRP testing at a cut-point of ≥17 mg/L classified almost half of patients as low risk, allowing clinicians to rule out acute bacterial rhinosinusitis in these patients and to treat them symptomatically without prescribing antibiotics [3].

A 1995 paper by Hansen et al. assessed the usefulness of CRP testing using the NycoCard™ CRP POCT device for the prediction of acute maxillary sinusitis across a range of CRP thresholds (<11 mg/L, 11-24 mg/L, 25-49 mg/L, >49 mg/L), using the presence of purulent or mucopurulent fluid from antral puncture as the reference standard [4]. A cut-point of 10 mg/L was found to be the most appropriate threshold above which most patients were likely to have acute maxillary sinusitis. Sensitivity and specificity were reported to be 0.73 and 0.6, respectively, at this threshold, suggesting that at this cut-point CRP POCT may be most useful as a rule-out test to identify patients who do not require antibiotic therapy for resolution of symptoms (Table 12; Appendix 1, Table A9). The addition of erythrocyte sedimentation rate (ESR) increased the sensitivity of the test, but not its specificity (0.82 and 0.57, respectively).

Table 12: Diagnostic test accuracy of CRP for acute maxillary sinusitis

Author year	Sensitivity	Specificity	PPV	NPV	DOR (95% CI)
Ebell 2017 (n=175, sinusitis* 52%, bacterial sinusitis** 35%)					>10mg/L*: 4.29 (2.27-8.11) >15mg/L*: 4.75 (2.50-9.02) >20mg/L*: 3.92 (2.02-7.61) >10mg/L**: 2.56 (1.32 – 4.97)

					>15mg/L**: 2.75 (1.42-5.33) >17 mg/L**: 2.75 (1.42-5.33) >20mg/L**: 2.43 (1.28-4.6)
Hansen 1995 (n=174, sinusitis 53%)	10 mg/L: 0.73 25 mg/L: 0.52 50 mg/L: 0.33 CRP 10 mg/L + ESR: 0.82	10 mg/L: 0.6 25 mg/L: 0.78 50 mg/L: 0.9 CRP 10 mg/L + ESR: 0.57	CRP 10 mg/L + ESR: 0.68	CRP 10 mg/L + ESR: 0.74	11-24 mg/L: 2.7 (1.2-6.1) 25-49 mg/L: 3.5 (1.4-8.6) >49 mg/L: 7.4 (3.1-18)

***Reference standard:** Antral puncture revealing purulent or mucopurulent fluid.

****Reference standard:** Positive bacterial culture of antral puncture fluid.

Pharyngitis and tonsillitis

[D1005] – What is the optimal CRP threshold value in this context? Overlaps with:

[D1006] –Do CRP levels reliably rule in or rule out pharyngitis and tonsillitis requiring antibiotic therapy?

Four studies published between 1999 and 2014 were identified. A summary of the studies is included in Appendix 1 (Table A7).

CRP levels in patients with pharyngitis or tonsillitis

Calvino et al. investigated the use of CRP POCT to identify patients with GAS infection among those presenting to primary care with acute pharyngitis who met all four Centor criteria (clinical signs and symptoms that indicate a higher likelihood of isolating *Streptococcus*: absence of cough, tonsillar exudates, history of fever, tender anterior cervical adenopathy) [153]. Using throat culture as the reference standard, the prevalence of bacterial pharyngitis and GAS were high (80.4% and 55.7%, respectively). There was no statistically significant difference in mean CRP concentrations between GAS infection (34.4 mg/L [95% CI: 25.6–43.3]) and non-GAS infection (29.9 mg/L [95% CI: 19.7–40.2]). Mean CRP levels were noted to be higher in patients with group C *Streptococcus* (n=13, mean 56.3 mg/L) compared with GAS infection. Mean CRP levels were comparable for patients with GAS infection and patients for which no bacterial cause of pharyngitis could be identified (n=29, 27.9 mg/L) (Table 13). On this basis, the authors concluded that CRP levels are not useful for distinguishing those patients who require antibiotic therapy.

Christensen et al. reported the mean CRP value in a group of patients (aged 15 to 40 years) presenting with signs of acute tonsillitis and meeting at least one of the four Centor criteria [6]. In contrast to the finding of Calvino et al., mean CRP levels were found to be significantly higher in patients with GAS isolated compared to those without GAS (44 mg/L [95% CI: 38–60], 15 mg/L [95% CI: 10–19], respectively) (Table 13).

Determining an optimal CRP threshold and the diagnostic accuracy at a specified threshold

A 1999 prospective observational study by Gulich et al. reported that CRP POCT can improve diagnostic accuracy in differentiating bacterial from non-bacterial pharyngitis in primary care [5]. The study population comprised patients presenting with symptoms of sore throat; the prevalence of bacterial pharyngitis was 23.6% [5]. An optimal threshold value of 35 mg/L was determined by ROC analysis to differentiate between bacterial and non-bacterial pharyngitis (AUC 0.85). At this cut-point, sensitivity and specificity were reported to be 0.78 (95% CI: 0.61–0.90) and 0.82 (95% CI: 0.73–0.88), respec-

tively (Table 14, Appendix 1 Table A9). This was an improvement from clinical diagnosis only (sensitivity 0.61 [95% CI: 0.45–0.75], specificity 0.73, [95% CI: 0.65–0.81]) (Appendix 1 Figure A1. Using clinical assessment and CRP measurement, 81% of patients presenting with symptoms of sore throat (n=161) were correctly diagnosed compared with 70% of patients diagnosed without information on CRP measurement (n=179). The distinction between bacterial and non-bacterial pharyngitis may not be as useful in terms of current antibiotic prescribing guidelines where antibiotic treatment is only recommended in those with GAS pharyngitis.

Determining an optimal CRP threshold and the diagnostic accuracy at a specified threshold in combination with a clinical prediction rule

In a subsequent 2002 study, Gulich et al. derived and validated a two-step clinical prediction rule combining clinical examination in patients presenting with a sore throat, with selective CRP POCT in patients at intermediate risk to aid in the diagnosis of GAS pharyngitis [7]. The study reported a prevalence of throat swabs positive for GAS of 28.7% (95% CI: 20.4–37.0) and 27.5% (95% CI: 22.2–37) for the derivation (n=116) and validation phases (n=265), respectively (Table 14). A 'strepto-score' was calculated based on clinical presentation and an algorithm used to triage patients as low, intermediate or high probability of GAS streptococcal infection. CRP POCT was only considered necessary in patients with an intermediate strepto-score (four or five points out of a possible eight). The NycoCard™ CRP device was used to measure CRP and a threshold of ≥35mg/L was used as per the 1999 study. The sensitivity and specificity of the algorithm in the derivation phase were 0.88 (95% CI: 0.58–0.99) and 0.95 (0.81-1.0) and in the validation phase were 0.74 (95% CI 0.53–0.89) and 0.95 (95% CI: 0.88–1.0), respectively, for the diagnosis of GAS infection compared with the diagnostic reference standard (Table 14, Appendix 1 Table A9). In the validation part of the study, 80 patients (30%) required a CRP POCT (148 (56%) had a low score and 37 (14%) had a high score and did not require a CRP POCT). The results suggest that use of CRP POCT (at a threshold of 35 mg/L) as part of a two-step clinical prediction rule may be useful in identifying patients with ambiguous clinical findings who would benefit from antibiotic treatment.

Christensen et al. aimed to determine if the addition of CRP levels to a diagnostic regime incorporating the Centor score and/or rapid antigen detection test (RADT) could increase diagnostic accuracy in the detection of GAS. The study was limited to patients aged 15 to 40 years presenting with a sore throat and who met one or more of the Centor criteria [6]. Microbiological analysis of throat swabs was used as the reference standard. CRP levels were measured using standard laboratory testing. The prevalence of GAS was 26%. The Youden index (sensitivity + specificity -1) was used to determine the best cut-off value (6 mg/L) to distinguish between GAS and non-GAS acute tonsillitis. At the threshold of 6 mg/L, sensitivity was high (90%), but specificity was found to be only 45% (Table 14). The discriminative power of the test was good with an AUC of 0.77 (0.66–0.87). The specificity of the test improved substantially (from 45% to 70%) when CRP measurement was used only in patients with a Centor score of 2 to 4; however, this was at the expense of decreased sensitivity (from 90% to 83%) (Table 14, Appendix 1 Table A9). Use of CRP testing only in patients with a Centor score of 2 to 4 resulted in a minimal change in the AUC (0.76 (95% CI: 0.65–0.88)). The sensitivity, specificity and AUC were higher for the RADT than CRP in the differentiation between GAS and non-GAS acute tonsillitis. The authors concluded that CRP testing at a cut-off of 6 mg/L was not useful in the diagnosis of GAS infection either alone or in combination with the RADT and should only be used when RADT is not available.

Table 13: CRP levels in patients with pharyngitis or tonsillitis

Author (year)	Prevalence	Mean CRP values (mg/L)
Calvino 2014 (n=149)	Bacterial pharyngitis: 80.4% GAS: 55.7%	**GAS (56.1%)**: 34.4 (95% CI: 25.6–43.3) **Non-GAS (43.9%)**: 29.9 (95% CI: 19.7–40.2) GBS (5.4%): 19.1 (95% CI: 0–41.0) GCS (8.8%): 56.3 (95% CI: 25.7–86.9) GGS (3.4%): 31.6 (95% CI:0–65.3) Other *Streptococcus* (6.7%): 9.2 (95% CI:4.4–14.0) No bacteria (19.5%): 27.9 (95% CI: 11.0–44.9)
Christensen 2014 (n=100)	BacterialTonsillitis: 52% GAS: 26%	**GAS (26%)**: 44 (95% CI: 38–60) **non-GAS (74%)**: 15 (95% CI:10–19)

Abbreviations: CRP – C-reactive protein; PPV – Positive predictive value; NPV – Negative predictive value; AUC – Area under the curve; CI – confidence interval; GAS – group A *Streptococcus*; GBS – group B *Streptococcus*; GCS – group C *Streptococcus*; GGS – group G *Streptococcus*.

Table 14: Diagnostic test accuracy of CRP in identifying patients with acute pharyngitis or tonsillitis in primary care settings who require antibiotic therapy

Author (number of patients, prevalence)	CRP Cut-point (mg/L)	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	AUC (95% CI)
Gulich 1999 *(N=161, bacterial pharyngitis: 23.6%)*	≥ 35ml/L*	0.78 (0.61–0.90)	0.82 (0.73–0.88)	0.57 (0.42–0.70)	0.92 (0.85–0.96)	0.85
Gulich 2002 *(Phase1: n=116, GAS:28.7%* *phase 2: n=265, GAS: 27.5%)*	≥ 35ml/L*	**Derivation Streptoscore**:** 0.88 (0.58–0.99) **Validation Strepto score:** 0.74 (0.53–0.89)	**Derivation Streptoscore**:** 0.95(0.81–1.0) **Validation Strepto score**: 0.95 (0.88–1.00)	**Validation Strepto score****: 0.86 (0.65–0.95	**Validation Strepto score****: 0.91 (0.81–0.96)	
Christensen 2014 (*n=100, bacterial tonsillitis 52%, GAS 26%)*	6mg/L	**Centor score 1–4:*** 0.90 **Centor score 2–4*** 0.83	**Centor score 1–4:*** 0.45 **Centor score 2–4*** 0.70			**Centor score 1–4:*** 0.77 (0.66–0.87) **Centor score 2–4:*** 0.76 (0.65–0.88)

Abbreviations: CRP – C-reactive protein; PPV – Positive predictive value; NPV – Negative predictive value; AUC – Area under the curve; CI – confidence interval; GAS – group A *Streptococcus*; GBS – group B *Streptococcus*; GCS – group C *Streptococcus*; GGS – group G *Streptococcus*.

*The Centor criteria (tonsillar exudate, tender anterior cervical lymphadenopathy or lymphadenitis history of fever (over 38°C), and/or absence of cough) are an algorithm to estimate the probability of group A β haemolytic *Streptococcus* (GABHS) as the origin of sore throat. Each of the Centor criteria score 1 point (maximum score of 4).
**The clinical strepto-score (throat mucosa, uvula, tonsils, soft palate) was based on clinical examination. Each criterion was scored 0 to 2 points (total score 0 to 8 points).

LRTI and Pneumonia

Nine studies included in the analysis investigated the diagnostic value of CRP measurement in patients presenting with signs and symptoms of LRTI including pneumonia in primary care (Appendix 1) (Table A7).

[D1005] – What is the optimal CRP threshold value in this context? Overlaps with:

[D1006] – Do CRP levels reliably rule in or rule out pneumonia?

CRP levels in pneumonia patients

Two studies presented the mean CRP level in patients with radiologically confirmed pneumonia, one in a paediatric population and the other in an adult population. Heiskanen-Kosma et al. studied the ability of CRP to distinguish bacterial from viral pneumonia in paediatric patients with radiologically confirmed pneumonia (n=193). Patients were divided into four groups according to the aetiology of infection (pneumococcal, mycoplasmal or chlamydial, viral or unknown aetiological groups) as determined by laboratory analysis of sera. CRP values as measured using standard laboratory testing were similar between the groups and there was no significant association with the aetiology of pneumonia (range 24.9 to 31.8 mg/L), (Table 15). Lagerstrom et al. analysed serum CRP concentrations using a laboratory-based NycoCard™ reader in adult patients with radiologically confirmed CAP [9]. The median CRP was reported to be 65 (5-150) mg/L. CRP levels exceeded 5 mg/L, 20mg/L, 50mg/L and 100mg/L in 93%, 79%, 59% and 31% of patients, respectively, suggesting that at a cut-point of 100 mg/L only a third of pneumonia cases would be identified (Table 15). It was noted that patients with CRP <20 mg/L had been ill for longer prior to CRP measurement (median 8.5 days [range 1-14] versus 6 days [range 1-28] for all patients).

Three studies presented the difference in the mean CRP value in patients with pneumonia and those without pneumonia. Hopstaken et al. assessed the diagnostic test accuracy of CRP in patients presenting with signs and symptoms of LRTI. Median CRP levels as measured using standard laboratory testing were higher in the pneumonia (145 mg/L (36-213)) than the non-pneumonia group (17 mg/L (2-216)). Substantial overlap was evident in measured CRP levels in patients with and without pneumonia. Three studies from the GRACE consortium reported average CRP levels within a sample of patients presenting to primary care physicians with acute cough [11, 14, 15]. Standard laboratory measurement was used in two studies while the third used a number of CRP POCT in the laboratory. The results may have been drawn from the same study data and are very similar for the studies by Van Vugt 2013 and Minnaard 2015. Teepe 2016 differed from the other two studies as it identified a subset of patients with bacterial pneumonia (Table 15). Overall, in adults, there was greater consistency in the mean CRP levels reported in patients without pneumonia than in those with pneumonia (Table 15).

Table 15: CRP levels in patients presenting with symptoms of LRTI in primary care

Author Year	Mean CRP values (mg/L)
Mean CRP levels in patients with radiologically confirmed CAP	
Heiskanen-Kosma 2000	Pneumococcal aetiology: 26.8 mg/L (20.1–33.5 mg/L) Mycoplasmal or chlamydial aetiology: 31.8 mg/L (20.5–33.1 mg/L) Viral aetiology: 26.1 mg/L (19.1–33.1 mg/L) Unknown aetiology: 24.9 mg/L (18.8–31.0 mg/L)
Lagerström 2006	65 (5–150)*

	CRP: > 100mg/L: 31% < 50mg/L: 41% < 20mg/L: 21% >5mg/L: 93%
Mean CRP levels in pneumonia and non-pneumonia patients	
Hopstaken 2009	Pneumonia : 145 mg/L (36–213)* No pneumonia: 17 mg/L(2–216)*
Minnaard 2015** Van Vugt 2013** Teepe 2016**	Pneumonia: 62 mg/L (SD 81) No pneumonia: 19 mg/L (SD 28) Pneumonia: 69 mg/L (SD 83) No pneumonia: 19 mg/L (SD 35) LRTI bacterial infection: 34 mg/L (SD 53) Bacterial pneumonia: 97 mg/L (SD 98) All patients: (19 mg/L (SD 35)

Abbreviations: CRP – C-reactive protein; CAP – community acquired pneumonia; SD – standard deviation.

*Data presented as median (range).

**These studies are presented together as they were both part of the GRACE consortium study and it would appear that the study population used in the Minnaard study was a subset of the cohort used by Van Vugt and Teepe.

Determining the optimal threshold and diagnostic accuracy of CRP measurement at specified cut-points

Five studies evaluated the use of CRP testing alone in the diagnosis of pneumonia at a cut-point of >20 mg/L (Table 16, Table 17, Table 18, Appendix 1 Table A9, Table A10). Holm et al. studied CRP levels (as measured using standard laboratory testing) as a predictor of pneumonia in adults diagnosed with community-acquired pneumonia (CAP) by their GP [151]. A cut-point of 20 mg/L was chosen by the authors from the literature, on the basis that a relatively low value is required to achieve acceptable sensitivity in predicting pneumonia in primary care. They reported that at a cut-off of 20 mg/L, CRP was found to have better sensitivity than a GP's clinical diagnosis alone in the identification of pneumonia patients (0.73 versus 0.60) while other measures of diagnostic test accuracy (specificity, PPV, NPV) were comparable. However, the authors concluded that the sensitivity and specificity of CRP in predicting pneumonia was too low (Table 16).

Lagerstrom et al. measured CRP levels in a laboratory using a POCT device in patients with respiratory symptoms and clinically suspected CAP (n=177) recruited into a previous study [9]. They reported CRP results at a threshold of 20 mg/L and 50 mg/L, but it was unclear why these thresholds were selected. At a cut-point of 20 mg/L, sensitivity and specificity were 0.79 and 0.65, respectively (Table 16). The improved specificity of the test at a cut-point of 50 mg/L (0.84) compromised test sensitivity (0.59). As 41% of pneumonia patients had CRP levels <50 mg/L and 21% had CRP levels <20 mg/L, the authors concluded that CRP testing is not sufficiently sensitive to rule out pneumonia in primary care.

Minnaard et al. aimed to compare the diagnostic test accuracy of CRP POCT devices versus laboratory standard CRP tests, and to determine if differences in test accuracy affect the ability of tests to predict pneumonia in adults [154]. Cut-points of 20 mg/L and 100 mg/L were selected from the literature and guidelines as they were the most commonly used thresholds for distinguishing pneumonia from non-pneumonia. At a cut-off of 20 mg/L, sensitivity was low for a rule-out test and was comparable across all CRP tests, ranging from 48.0% to 61.4% (Table 17). At a cut-point of 100 mg/L specificity was high and ranged from 97.7 to 99.0%, indicating that at this threshold the test was sufficiently

specific to rule in pneumonia (Table 18). The authors concluded that all five POCT devices used in the study performed as well as the laboratory analyser in detecting pneumonia.

Hopstaken et al. aimed to assess the diagnostic value of CRP for pneumonia in primary care patients with LRTI. CRP measurement was undertaken using standard laboratory testing. ROC curves were constructing summarising the diagnostic test accuracy of CRP in differentiating pneumonia from acute bronchitis across a range of CRP thresholds (10 mg/L, 20 mg/L and 100 mg/L) [12]. In contrast to the studies by Holm et al, Lagerstrom et al. and Minnaard et al., at a cut-point of 20 mg/L the test demonstrated 100% sensitivity in identifying pneumonia patients which was therefore determined by the authors to be the optimal cut-off value to rule out pneumonia in a primary care setting (Table 16).

Unlike the other studies (which were published between 2006 and 2015), an earlier study by Melbye et al. published in 1988 did not investigate CRP at a threshold of 20 mg/L. Instead, they investigated the diagnostic value of CRP measuring using standard laboratory testing at cut-points of >11 mg/L and >50 mg/L in differentiating pneumonia from non-pneumonia in patients aged 15 years and older treated with antibiotics by a GP for clinically suspected pneumonia [10]. The authors did not state their reasons for selecting these thresholds, but found at a threshold of 11 mg/L, sensitivity and specificity were 0.82 and 0.60, respectively (Table 16). Increasing the CRP threshold to 50 mg/L resulted in improved specificity (0.96), but at the expense of lower sensitivity (0.74). The authors concluded that further studies must be done to establish the most practical cut-off level in the diagnosis of pneumonia.

Table 16: Diagnostic test accuracy of CRP at pre-specified cut-points in patients presenting with symptoms of LRTI in primary care

Author Year	Sensitivity	Specificity	PPV	NPV	Likelihood ratios	AUC	DOR (95% CI)
Holm 2007	CRP ≥20 mg/L: 0.73	CRP ≥20 mg/L: 0.65	CRP ≥20 mg/L: 0.24	CRP ≥20 mg/L: 0.94			CRP ≥20 mg/L: 5.02 (2.59–9.88)
Hopstaken 2009	CRP 10 mg/L: 100, CRP 20 mg/L: 100, CRP 100 mg/L: 81.8	CRP 10 mg/L: 36.1, CRP 20 mg/L: 50.6, CRP 100 mg/L: 84.3	CRP 10 mg/L: 17.2, CRP 20 mg/L: 21.2, CRP 100 mg/L: 40.9	CRP 10 mg/L: 100, CRP 20 mg/L: 100, CRP 100 mg/L: 97.2		AUC 0.90	
Lagerstrom 2006	CRP 20 mg/L: 0.79 CRP 50mg/L: 0.59	CRP 20 mg/L: 0.65 CRP 50 mg/L: 0.84	CRP 20 mg/L: 66.33% CRP 50 mg/L: 76.19	CRP 20 mg/L: 78.48% CRP 50 mg/L: 70.18	CRP 20 mg/L: LR+ = 2.28 LR- = 0.32 CRP 50 mg/L: LR+ = 3.71		

					LR- = 0.49		
Melbye 1988	CRP > 11 mg/L: 82%, CRP > 50 mg/L: 74%	CRP > 11 mg/L 60%, CRP > 50 mg/L: 96%		CRP > 11 mg/L: 0.28, CRP > 50 mg/L: 0.8	CRP > 11 mg/L: 2.1, CRP > 50 mg/L: 37		
Minnaard 2015	Tables 17/18	Tables 17/18	Tables 17/18	Tables 17/18			

Abbreviations: CRP – C-reactive protein; PPV - Positive predictive value; NPV – Negative predictive value; AUC – Area under the curve; CI – confidence interval; LR+ – Positive likelihood ratio; LR- – Negative likelihood ratio; AUC – Area under the curve; DOR – Diagnostic odds ratio; SD – Standard deviation.

Table 17: Single test accuracy measures at CRP cut-point of 20 mg/L in patients presenting with acute cough in primary care [11]

CRP test	Sensitivity (95% CI)	Specificity (95% CI)	PPV % (95% CI)	NPV % (95% CI)
Laboratory analyser	61.4 (53.2 – 69.1)	76.0 (74.3 – 77.5)	11.8 (9.6 – 14.3)	97.4 (96.6 – 98.0)
Afinion	55.0 (45.2 – 64.4)	73.0 (63.6 – 80.7)	9.6 (7.8 – 11.9)	96.9 (96.0 – 97.6)
NycoCard™ Reader II	54.0 (44.3 – 63.4)	75.0 (65.7 – 82.5)	10.1 (8.2 – 12.5)	96.9 (96.1 – 97.6)
Eurolyser Smart	48.0 (38.5 – 57.7)	79.0 (70.0 – 85.8)	10.7 (8.5 – 13.3)	96.7 (95.8 – 97.3)
QuikRead go®	52.0 (42.3 – 61.5)	72.0 (62.5 – 79.9)	8.8 (7.1 – 11.0)	96.6 (95.7 – 97.3)
QuikRead® 101	49.0 (39.4 – 58.7)	74.0 (64.6 – 81.6)	9.0 (7.1 – 11.2)	96.5 (95.6 – 97.2)

Abbreviations: CI – confidence interval; PPV – Positive predictive value; NPV – Negative predictive value.

Table 18: Single test accuracy measures at CRP cut-point of 100 mg/L in patients presenting with acute cough in primary care [11]

CRP test	Sensitivity (95% CI)	Specificity (95% CI)	PPV % (95% CI)	NPV % (95% CI)
Laboratory analyser	24.3 (17.9 – 27.8)	97.7 (97.0 – 98.2)	35.4 (26.6 – 45.4)	96.1 (95.3 – 96.8)
Afinion	20.0 (13.3 – 28.9)	99.0 (94.6 – 99.9)	51.1 (38.2 – 63.8)	95.9 (95.1 – 96.6)
NycoCard™ Reader II	20.0 (13.3 – 28.9)	98.0 (93.0 – 99.4)	34.3 (24.9 – 45.1)	95.9 (95.1 – 96.6)
Eurolyser Smart	19.0 (12.5 – 27.8)	99.0 (94.6 – 99.9)	49.8 (36.9 – 62.8)	95.9 (95.1 – 96.6)
QuikRead go®	20.0 (13.3 – 28.9)	99.0 (94.6 – 99.9)	51.1 (38.2 – 63.8)	95.9 (95.1 – 96.6)
QuikRead® 101	19.0 (12.5 – 27.8)	99.0 (94.6 – 99.9)	49.8 (36.9 – 62.8)	(95.1 – 96.6)

Abbreviations: CI – confidence interval; PPV – Positive predictive value; NPV – Negative predictive value.

Determining the optimal threshold in combination with signs and symptoms

In daily practice, the interpretation of a CRP value is made in addition to clinical judgement based on presenting signs and symptoms.

Holm et al. investigated the diagnostic test accuracy of CRP measurement in combination with a GP's diagnosis of pneumonia. Holm et al. found the combination of a GP's clinical diagnosis and CRP measurement at a threshold of ≥20 mg/L was less sensitive (0.49 versus 0.60), but more specific (0.84 versus 0.68) than a GP diagnosis alone (Table 19).

Four studies investigated the use of CRP testing in combination with a clinical prediction rule to differentiate between pneumonia and other LRTI in general practice (Table 19). Three used standard laboratory testing while one reported CRP levels as measured using different CRP POCT devices in a laboratory. Hopstaken et al. described the diagnostic value of performing and recording extensive standardised medical history and clinical examination in combination with CRP measurement. ROC curves were constructed and the respective AUC were calculated to determine the overall diagnostic power of CRP at different cut-off values (10 mg/L, 20 mg/L, and 50 mg/L). In combination with signs and symptoms, CRP of 20 mg/L was selected as the optimal CRP threshold. The 'symptoms and signs + CRP cut-off value of 20' prediction model was significantly better at predicting the probability of pneumonia than the 'symptoms and signs' only model (P<0.001) [155]. Use of the clinical decision rule allowed a group of patients at low risk of pneumonia to be identified. The combined predictive value of patients not having pneumonia was 97% (95% CI: 92–99%). If the prediction rule was applied to patients who received antibiotic treatment, 41% of prescriptions could have been avoided, with a 2.5% risk of patients with pneumonia being missed. The authors noted further validation of the prediction rule to identify low-risk patients was required.

Van Vugt et al. aimed to quantify the diagnostic accuracy of CRP in addition to signs and symptoms for the prediction of pneumonia [14].Adults presenting with acute cough (n=2,820) were grouped into pneumonia (n=140) or no pneumonia based on chest radiographs (prevalence CAP = 5%). The diagnostic accuracy of CRP at clinically relevant thresholds (>20 mg/L, >30mg/L, >50mg/L, >100 mg/L) was investigated for the prediction of pneumonia in adults presenting with acute cough in addition to 14 preselected diagnostic criteria based on history taking and physical examination [14].The optimal cut-off level was assessed using the AUC. A simplified diagnostic risk classification system using six different signs and symptoms was subsequently developed by rounding all regression coefficients in the model. Addition of CRP at the optimal cut-off of >30 mg/L significantly increased the AUC (from 0.70 (0.65-0.75) to 0.77 (0.73-0.81); p<0.05), and improved the diagnostic classification (net reclassification improvement 28% (95% CI: 17–30%) (Table 19). The signs and symptoms model was useful in correctly identifying patients with low (score of 0, probability <2.5%) or high (score ≥3, probability >20%) risk of pneumonia in 26% of the patients. In 74% of patients where doubt remained (estimated risk 2.5%-20%), measurement of CRP helped to correctly exclude pneumonia. Of the 1,987 patients without pneumonia who were classified as intermediate risk, the addition of CRP >30 mg/L meant 957 were reclassified correctly to low risk and 64 were incorrectly classified as high risk. Of the 105 patients with pneumonia classified as intermediate risk, the addition of CRP reclassified 27 incorrectly to low risk and 22 to high risk. Thirty nine percent (54/140) of all patients with radiographic pneumonia had a CRP <20 mg/L. These patients tended to be older (p=0.01), more often had positive signs and symptoms of the diagnostic model and more often used steroids (inhaled or oral). However, despite increased diagnostic accuracy with the addition of CRP measurement to clinical signs and symptoms, a substantial group of patients were classified as intermediate risk, for which clinical decision-making remains challenging.

Minnaard et al. applied the same symptoms and signs model as Van Vugt with and without CRP to their nested case control population. Minnaard's study population was also drawn from the GRACE study and may be a subset of the cohort used in the Van Vugt study (Table 19). As with the Van Vugt study, use of the signs and symptoms model without CRP testing had an AUC of 0.70 (95% CI: 0.65–0.75) and this increased to 0.79 following the addition of CRP testing. Each of the five POC tests (Afinion™, NycoCard™ Reader II, Smart Eurolyser, QuikRead go® and QuikRead® 101) had a similar diagnostic accuracy to the laboratory CRP analyser (AUC 0.79 to 0.80 compared with 0.79 with laboratory CRP analyser).

A third study from the GRACE consortium used the same cohort of patients as Van Vugt and Minnaard (n = 3,104), but they used the presence of prespecified bacteria in respiratory samples (either sputum sample or nasopharyngeal swabs) to identify patients with a bacterial LRTI (n = 539, 17%) and a combination of chest radiograph and the presence of prespecified bacteria in respiratory samples to determine if patients had bacterial pneumonia (n=38, 1%) [15]. CRP was added dichotomously at a threshold of 30 mg/L to other diagnostic criteria that had been shown to be independent predictors of bacterial LRTI (discoloured sputum) or bacterial pneumonia (comorbidity, temperature ≥ 38^{o}C, crackles on lung auscultation). The addition of CRP to the other diagnostic criteria increased the AUC for bacterial LRTI from 0.56 (95% CI: 0.54 -0.59) to 0.62 (95% CI:0.59 – 0.65) and for bacterial pneumonia from 0.68 (95% CI: 0.58 – 0.77) to 0.79 (95% CI: 0.71 – 0.87). The authors concluded that although CRP added diagnostic value to their signs and symptoms models it had limited clinical utility in predicting a bacterial cause of LRTI.

Table 19: Diagnostic test accuracy of CRP in combination with signs and symptoms in patients presenting with symptoms of LRTI in primary care

Author Year	Sensitivity	Specificity	PPV	NPV	Likelihood ratios	AUC (95% CI)	DOR (95% CI)
Holm 2007	Clinical pneumonia + CRP ≥20 mg/L: 0.49	Clinical pneumonia + CRP ≥20 mg/L: 0.84	Clinical pneumonia + CRP ≥20 mg/L: 0.32	Clinical pneumonia + CRP ≥20 mg/L: 0.91			Clinical pneumonia + CRP ≥20 mg/L: 4.97 (2.60–9.52)
Hopstaken 2003						CRP 10 mg/L: 0.77 CRP 20 mg/L: 0.8 CRP 50 mg/L: 0.87	CRP 10 mg/L: 11.7 (1.55–88.61) CRP 20 mg/L: 8.48 (2.45–29.39) CRP 50 mg/L: 17.62 (5.77–53.85)
Teepe 2016*			For LRTI bacterial infection: Signs and Symptoms (discol-oured sputum) + CRP >30 mg/L: 0.371 (95% CI: 0.312 – 0.433) For bacterial pneu-monia: Signs and Symptoms (Comor-bidity, temperature ≥ 38oC, crackles on lung auscultation) + CRP >30 mg/L: 0.25 (95% CI: 0.006 – 0.806)	For LRTI bacterial infection: Signs and Symptoms (discol-oured sputum) + CRP >30 mg/L: 0.875 (95% CI: 0.854 – 0.893) For bacterial pneu-monia: Signs and Symptoms (Comor-bidity, temperature ≥ 38oC, crackles on lung auscultation) + CRP >30 mg/L: 0.997 (95% CI: 0.993 – 0.999)		For LRTI bacterial infection: Signs and Symptoms (discol-oured sputum) + CRP >30 mg/L: 0.62(95% CI: 0.59 – 0.65 For bacterial pneu-monia: Signs and Symptoms (Comor-bidity, temperature ≥ 38oC, crackles on lung auscultation) + CRP >30 mg/L: 0.79 (95% CI: 0.71 – 0.87	

Author Year	Sensitivity	Specificity	PPV	NPV	Likelihood ratios	AUC (95% CI)	DOR (95% CI)
VanVugt 2013*	Low risk:** 22% High risk:** 29%	Low risk:** 43% High risk:** 97%	High risk:** 31%	Low risk:** 98%	Low risk:** Positive likelihood ratio 0.4, Negative likelihood ratio: 1.8 Intermediate risk:** Positive likelihood ratio 1.2 Negative likelihood ratio 0.9 High risk:** Positive likelihood ratio 8.6 Negative likelihood ratio 0.7	CRP >30 mg/L: 0.77 (0.73–0.81)	CRP >20 mg/L: 3.5 (2.4–5) CRP >30 mg/L: 3.8 (3.7–5.5) CRP >50 mg/L: 4.8 (3.2–7.1) CRP >100 mg/L: 6.0 (3.6–10)
Minnaard 2015*						Signs and symptoms model: 0.70 (95% CI: 0.65–0.75) Signs and symptoms model + CRP: 0.79	

***** These studies are presented together as they were part of the GRACE study and it would appear that the study population used in the Minnaard study was a subset of the cohort used by Van Vugt and Teepe.

** Probability of pneumonia based on signs and symptoms (breathlessness, absence of runny nose, diminished vesicular breathing, crackles, tachycardia, temperature (>37.8°C)) in addition to CRP measurement.

[D1002] – How does the test compare to other optional tests in terms of accuracy measures?

This systematic review of diagnostic accuracy is limited to CRP testing for the specified indications, and as such a comprehensive analysis of the performance of alternative tests was beyond the scope of this study. This section is therefore restricted to descriptions of test accuracy of alternate tests identified in clinical guidelines (A0024) (A0025) and in the studies included in this systematic review (Table 11).

Sinusitis

Hansen et al. evaluated the diagnostic value of erythrocyte sedimentation rate (ESR) for acute maxillary sinusitis. ESR and CRP concentration were found to be better diagnostic criteria than other symptoms and signs related to this condition, and both analyses can be performed in general practice. The combination of these two variables had a sensitivity of 0.82 and specificity of 0.57, and were said to be better than clinical examination only as a basis for deciding to give antibiotics. However, the study did not seek to determine which of the two infection markers had greater diagnostic value. Ebell et al. found that CRP and ESR were the strongest individual predictors of acute bacterial rhinosinusitis compared to other signs and symptoms associated with the condition as determined by univariate logistic regression analysis. The odds ratio for CRP was higher than for ESR, suggesting that CRP may have greater predictive value at determining which patients have acute sinusitis. However, this study did not set out to ascertain which of the infection markers was a better predictor; the aim was to develop a clinical decision rule.

A 2016 systematic review of imaging and laboratory tests used in the diagnosis of acute rhinosinusitis identified a single study that evaluated the accuracy of a test strip comparable to those ordinarily used in the diagnosis of urinary tract infection [147]. It is suggested that such test strips offer an inexpensive, simple alternative to other diagnostic tests such as CT scans and antral puncture which are considered to be undesirable for use in primary care due to the associated expense and impracticality, respectively [156]. The researchers found that leucocyte esterase and nitrite were highly specific, while pH and protein were highly sensitive. A score that assigned points (0 to 3) to each of these tests successfully identified patients at low (0%), moderate (33%) and high (100%) risk of acute rhinosinusitis. However, the study was considered to be at high risk of bias as it used imaging rather than antral puncture as the reference standard and the thresholds for classifying patients into risk groups were established post-hoc [147]. Three studies identified in the systematic review evaluated the presence of leucocytes in nasal washings, with LR+ ranging from 3.06 to 4.92, and LR- from 0.08 to 0.74. Rhinoscopy for pus in the nasal cavity or throat and white blood cell count both lacked sufficient accuracy for the diagnosis of acute rhinosinusitis [147].

Pharyngitis or Tonsilitis

To enhance the appropriate prescribing of antibiotics, clinical prediction rules have been developed to distinguish streptococcal pharyngitis from pharyngitis by other causes. Rapid antigen detection tests (RADT), which use a pharyngeal swab and yield results in five to seven minutes, have also been developed to detect GAS.

Identified clinical practice guidelines for pharyngitis advocate the use of the four-point Centor score (oral temperature ≥38.3°C, tonsillar exudate, absence of cough, and swollen cervical lymph nodes), the McIsaac score or FeverPAIN score to stratify patients based on their probability of GAS. The guidelines recommend limiting antibiotic treatment (deferred or immediate) or antibiotic treatment conditional on further testing (that is, a positive rapid antigen detection test [RADT]) to those with higher scores (Centor score 3-4; McIsaac score ≥2; FeverPAIN ≥2) (A0025). A combination of CRP measurement and clinical examination based on the Centor score was used in three out of four studies retrieved evaluating CRP testing in pharyngitis patients [6, 7, 153, 157]. As a decision rule for considering antibiotic prescribing (score ≥3) in adults presenting to primary care with pharyngitis, the Centor score is reported to have a reasonable specificity (0.82, 95% CI: 0.72–0.88) and a post-test probability of 12% to 40% based on a prior prevalence of GAS of 5% to 20% [158]. In a systematic review of RADTs, the heterogeneity between studies was moderate but immunochromatographic RADTs were noted to be very sensitive (range 86% to 91%) and highly specific (range 93% to 97%) for the detection of GAS pharyngitis in adults, but the evidence was inconsistent in children. For enzyme-linked immunoassay RADTs, only a few studies were identified in the review; in adults the results were inconsistent, while they were shown to have high sensitivity and specificity in children (0.86 and 0.92). Specificity is decreased because of the poor capability of the test to differentiate between acute tonsillitis secondary to GAS and tonsillar infection of other origin in GAS carriers [159]. The clinical sensitivity of the RADT is noted to be influenced by the quality of the tonsillar swab, physician experience and the GAS inoculum [6].

Use of other infection markers, such as procalcitonin, white blood cell count and absolute neutrophil count to detect GAS acute tonsillitis, have also been investigated. In addition to CRP POCT, the study by Christensen et al. aimed to determine if the addition of infection markers such as procalcitonin, white blood cell count, and the absolute neutrophil count could increase diagnostic accuracy when used alongside the Centor score and RADT. CRP testing was more sensitive (90%), but less specific (45%), than procalcitonin (sensitivity 72%; specificity 58%), white blood cell count (sensitivity 69%; specificity 73%), or absolute neutrophil count (sensitivity 66%; specificity 87%). However, the sensitivities and specificities were higher using the RADT than any of the infection markers. The authors concluded that CRP, procalcitonin, white blood cell count and absolute neutrophil count should not be performed in patients with acute tonsillitis, as they do not contribute significantly to an increase in the sensitivity or specificity of the RADT.

LRTI including pneumonia

Diagnosis of pneumonia in primary care is usually based on clinical findings, but may sometimes be supported by microbiological analysis of sputum samples. However, sputum culture may grow bacteria without any clinical relevance and therefore findings from microbiological analysis cannot be used as definitive evidence of the causative agent of infection [151]. As it is not feasible to obtain chest radiographs in all patients with LRTI in primary care, clinicians typically rely on signs and symptoms and simple additional tests, when available. The diagnostic value of history and findings on clinical examination for pneumonia in primary care were evaluated in the study by Van Vugt et al. included in this systematic review. The AUC for previously published models of signs and symptoms for pneumonia varied between 0.55 (95% CI: 0.50–0.61) and 0.68 (95% CI: 0.66–0.76). All models showed poor calibration for pneumonia, with a Hosmer-Lemeshow of $p<0.001$, indicating poor fit. The authors de-

veloped a simplified diagnostic model based on symptoms and signs (absence of runny nose; presence of breathlessness, crackles and diminished breath sounds on auscultation; tachycardia [>100/min]; and fever [≥37.8°C]) which had an AUC of 0.70 (95% CI: 0.65–0.75) and good calibration for pneumonia (Hosmer-Lemeshow of p=0.50). The diagnostic value of procalcitonin in addition to signs and symptoms was also evaluated but was found to provide limited additional value (increased AUC to 0.71 [0.67 to 0.76] in this cohort of primary care patients presenting with LRTI) [14] Teepe et al. investigated the diagnostic utility of adding CRP or procalcitonin to a signs and symptoms diagnostic model for bacterial LRTI and separately for bacterial pneumonia. Although they found that CRP added diagnostic value to their model, procalcitonin did not [15].

[D1003] – What is the reference standard for acute RTIs and how likely is it to classify the target condition correctly?

The reference standard varies depending on the clinical indication for which CRP testing is being used. As outlined in (A0002), RTIs comprise a collection of specific diagnoses which can be broadly classified as URTIs and LRTIs. The reference standards for these conditions differ (A0024) and (A0025). This section is limited to those RTIs for which studies were identified in this systematic review of diagnostic test accuracy.

Sinusitis

The identified reference standard for the diagnosis of acute maxillary sinusitis is computed tomography (CT) and/or sinus aspiration [4]. Practice guidelines generally do not recommend the use of imaging because: the accuracy of radiography is thought to be poor; ultrasound and radiography are not widely available in the primary care setting; and CT is expensive and results in potentially harmful radiation exposure. Although a CT scan is highly sensitive for the detection of fluid in the sinuses, this fluid may also be caused by a viral infection, so the test lacks specificity, and is therefore suboptimal as a reference standard [3, 147]. For example, in one study mucosal swelling or increased fluid in the maxillary sinuses was reported in 70% of patients on CT; however only 53% had purulence or mucopurulence on puncture, indicating that CT alone is not sufficient for the diagnosis of acute maxillary sinusitis [4]. Antral puncture can detect purulent secretions which are associated with bacterial infection. Bacterial culture of these secretions is the most specific test for the diagnosis of acute maxillary sinusitis. However, as bacteria may not grow in vitro, even if present in the sinus, the test cannot be considered 100% sensitive as a reference standard [3]. While antral puncture plus/minus bacterial culture is suggested as the preferred reference standard test, it is not widely used due to the discomfort associated with the test and the lack of expertise in performing antral puncture in the primary care setting [147]. ROC curves constructed for the three different reference standards for acute sinusitis, abnormal finding on a CT scan, the presence of purulent or mucopurulent fluid from an antral puncture of the maxillary sinus, and positive bacterial culture of antral fluid yielded AUC of 0.75, 0.77 and 0.72, respectively [3].

Pharyngitis or tonsillitis

Microbiological culture of throat swabs remains the gold standard to diagnose tonsillar bacterial infection. The accuracy of throat swab cultures was noted to be 90% by Gulich et al., as reported in a pre-

vious study [5]. Microbiological culture has several limitations which limit its routine use in primary care, most notably its relative expense and that it cannot inform therapeutic decisions during the first consultation given a turnaround time of 48 to 72 hours [6]. The majority of clinical guidelines recommend limiting the use of antibiotics to pharyngitis/tonsillitis caused by streptococcal infections and/or GAS in particular. Microbiological culture of throat swabs may determine GAS carrier status; however, the cause of infection may be attributable to other pathogens. Furthermore, in vitro culture conditions may not facilitate growth of the bacterial sample, even if present in the respiratory tract.

LRTI including pneumonia

No gold standard for LRTI requiring antibiotics exists. Community acquired pneumonia is an anatomical diagnosis based on radiographic and clinical criteria. It includes infections due to bacterial, fungal and viral aetiologies with the severity of the condition varying depending on host and virulence factors. It is not considered necessary to distinguish between bacterial and viral pneumonia given that all relevant guidelines advocate identification of patients with pneumonia and treatment with antibiotics regardless of bacterial or viral aetiology [14]. Conventional radiography is the reference standard for defining pneumonia in international guidelines and medical literature. However, interpretation of chest radiographs is subject to inter-observer variation [10, 151]. It is noted that interpretation of minor pathological changes may not be reliable [9, 10], with studies acknowledging that use of chest radiography as a reference standard has the potential to lead to misclassification [11]. A 2015 meta-analysis of the diagnostic test accuracy of different imaging options for community-acquired pneumonia reported a pooled sensitivity of 0.77 (0.73 to 0.80) and specificity of 0.91 (0.87 to 0.94) for chest X-ray using hospital discharge diagnosis as the reference standard [160, 161]. One study, used a combination of chest radiograph and the presence of pre-specified bacteria from a respiratory sample (sputum or nasopharyngeal swab) to identify patients with bacterial pneumonia [15].

Chest radiography is not recommended for routine use in primary care for economic and logistical reasons [12, 151]. Good practice also recommends that patient exposure to potentially harmful ionising radiation should be avoided where possible. In general practice, the decision to initiate antibiotic treatment therefore relies on clinical assessment, although its predictive value is noted to be poor. For example, the study by Holm et al. noted that the PPV of a GP's clinical diagnosis of radiographic pneumonia was only 0.23 [151]. Accurate diagnostic markers are therefore needed to inform clinical decision-making during the first consultation.

5.10 Discussion

CRP POCT was carried out in primary care by the intended user in only four studies. As noted in B0001, POCT refers to testing at or near the site of the patient encounter with the result being available within minutes to inform decision-making. In the context of this DTA review, the question addressed is whether the availability of a CRP level could improve DTA compared with the reference diagnostic standard being used for that condition. How CRP is measured is therefore not an issue, so studies that measured CRP levels using CRP POCT devices in the laboratory (that is, operated by laboratory-trained personnel) or standard laboratory CRP measurement were considered as eligible for inclusion. The relative accuracy and precision of CRP POCT compared with these techniques is considered in SR3 (analytical performance) The evidence base for the diagnostic test accuracy of

CRP testing in primary care is characterised by a high level of heterogeneity in patient populations, diagnostic criteria, CRP cut-points, how the performance of the test was reported and the absence of a universal reference standard for the diagnosis of RTIs requiring antibiotic treatment. Meta-analysis of the data was therefore not appropriate and a narrative review is presented. Planned subgroup analysis (children, older adults (≥65 years of age), patients attending out-of-hours (OOH) services and those in long-term care (LTC) facilities) were not possible due to limited data. However, the results of this systematic review do provide important insights into the performance of CRP as a test to help identify patients who will benefit from antibiotic treatment and to aid decision-making for a number of conditions.

As outlined in the study PICOS, the study was limited to patients presenting to primary care with symptoms of acute RTI. This criterion was strictly applied, so studies that included patients presenting to other treatment settings such as hospital emergency departments, urgent care centres and outpatient clinics were excluded unless the data specific to primary care could be extracted. The applicability of data from these settings to primary care was considered limited due to differences in staffing, access to diagnostic services and the spectrum of presenting patients. This restriction may not be relevant to all countries, where certain outpatient clinics and urgent care centres may be considered part of the primary care system. While some studies highlighted the similarity between patients presenting to primary care clinics and those who self-refer to urgent care clinics and emergency departments, these studies were still excluded as concerns remained around potential differences in staffing and access and diagnostics services. However, this meant that certain CRP POC devices such as FebriDx® were not included in this systematic review as the available studies did not meet our inclusion criteria for setting [162, 163]. FebriDx® combines CRP at a cut-point of 20 mg/L with a viral biomarker.

The diagnostic test accuracy of CRP in sinusitis

Two studies reporting the usefulness of CRP testing in diagnosing acute sinusitis provided limited evidence of benefit. Both studies examined a range of thresholds and chose a relatively low CRP threshold (10 mg/L and 17 mg/L) that was suitable for ruling out a diagnosis of acute bacterial sinusitis. A clinical decision rule incorporating signs, symptoms and CRP at a cut-point of ≥17 mg/L allowed half of patients to be identified as low risk for acute bacterial sinusitis, allowing clinicians treat them symptomatically without prescribing antibiotics, with the authors noting that prospective validation of the tool through further research was required. However, considering many current clinical guidelines do not generally recommend the use of antibiotics in acute sinusitis, the utility of CRP testing on its own or as part of a clinical prediction rule is unclear [98]. A 2016 systematic review of test accuracy in the diagnosis of acute rhinosinusitis in primary care identified four studies that assessed the performance of CRP testing [147]. While this review was not limited to a GP setting, it did include one of the studies reported here [4]. Pooled analysis of all four studies reported sensitivities of 73%, 39% and 22% at thresholds of 10mg/L, 20-25mg/L and 40-49mg/L. The corresponding specificity estimates were 60%, 87% and 91%, respectively. The review concluded that there was “no clearly preferred single threshold for defining an abnormal (CRP) test”, and suggested the use of two thresholds to define low (<10mg/L), medium (10-30mg/L) and high (>30mg/L) risk groups. In the context of current antibiotic prescribing guidelines, CRP testing has limited additional benefit to clinical decision-making for the diagnosis of sinusitis.

The diagnostic test accuracy of CRP in pharyngitis or tonsillitis

Among patients with acute pharyngitis, many clinical guidelines recommend that only those infections caused by streptococcal infections and particularly group A beta-haemolytic *Streptococcus* (GAS) should be treated with antibiotics [164]. Patients with other viral or bacterial infections generally do not benefit from antibiotics. GAS pharyngitis is usually self-limiting, but may rarely be associated with serious complications which can be prevented with antibiotic treatment. For this reason, the majority of the evidence retrieved on the diagnostic test accuracy of CRP in identifying patients with acute pharyngitis/tonsillitis who require antibiotic therapy specifically relates to the identification of those patients with GAS pharyngitis. Two studies presented the mean levels of CRP in patients with acute pharyngitis or tonsillitis, with contrasting results [6, 153]. The inclusion criteria differs substantially between these studies with patients in the Calvino study presenting with all four Centor criteria, while in the Christensen study none of the included patients had a Centor score of four. The studies also differed in the proportion of patients in the non-GAS group with no bacteria or other non-GAS bacteria. It is unclear if other types of bacterial infection would be expected to cause a similar rise in CRP levels; in the Calvino study group C streptococcal infection caused the highest rise in CRP values (mean CRP 56.3mg/L group C versus 34.4 mg/L group A). In addition, as the reference standard was a throat swab, some of the patients who were positive for GAS may have been carriers who also had viral/other bacterial pharyngitis and this proportion may have differed between studies.

Two studies sought to determine the optimal threshold for CRP testing in patients presenting with sore throats [5, 6, 157]. The cut-point chosen differed substantially (6 mg/L versus 35 mg/L). The studies differed in their aim in that the Guilich study sought to use CRP to distinguish between bacterial and non-bacterial pharyngitis, while the study by Christensen et al. wanted to distinguish between GAS and non-GAS pharyngitis.

Guilich et al. reported that at a threshold of 35 mg/L, CRP is better at ruling in than ruling out bacterial pharyngitis and improves both the sensitivity and specificity of GP clinical diagnosis alone. They subsequently went on to use this threshold as part of a two-step clinical algorithm whereby about 30% of patients presenting with sore throat required a CRP measurement after clinical assessment. The specificity of the algorithm was higher than the sensitivity (Table 14). As not treating patients with GAS pharyngitis is generally not a major safety concern in most countries, the lower sensitivity but higher specificity may be an acceptable trade-off. However, the score developed in this study needs validation. Christensen et al., at a threshold of 6 mg/L, reported that CRP in combination with the Centor score may be useful in ruling out GAS pharyngitis, but only if RADT is not available. Given the mean value and 95% CI for those with non-GAS infection was 15 mg/L (95% CI: 10–19) in this study, the cut-point of 6 mg/L may have been too low to adequately distinguish between patients with acute pharyngitis caused by GAS and non-GAS infection. The low specificity of this cut-point means that many false positives may be treated unnecessarily with antibiotics.

Overall, CRP at a cut-point of 6 mg/L CRP is unlikely to be useful in guiding antibiotic prescribing either on its own or in combination with the Centor score as it is better at ruling out GAS pharyngitis, but would lead to unnecessary antibiotic prescribing.

A cut-point of 35 mg/L may be useful for determining bacterial pharyngitis and one study suggests it could be useful for determining GAS pharyngitis as part of a clinical prediction rule, but further validation studies would be required. Notably, patients with evidence of GAS infection according to microbi-

ological analysis of pharyngotonsillar swabs had a mean CRP concentration of 34.4 mg/L (95% CI: 25.6–43.3) in the study by Calvino et al. suggesting that at a threshold of 35 mg/L as proposed by Gulich et al. some patients presenting with GAS infection may not be identified.

In conclusion, the identification of GAS infection, CRP testing appears to be most useful when used in combination with a clinical signs and symptoms. However, it should be noted that other alternatives exist, such as RADT, while may have better diagnostic test accuracy for GAS pharyngitis.

The diagnostic test accuracy of CRP in LRTI / pneumonia

Current clinical guidelines recommend antibiotic treatment for pneumonia, but not for other lower respiratory tract infections as these are generally considered to be self-limiting with limited clinical benefit from antibiotic treatment [42].

There was limited data on the levels of CRP in paediatric patients. One study included in this review included paediatric patients with pneumonia and reported mean levels between 24 and 32 mg/L, they reported infants <12 months had very low CRP levels (mean 14 mg/L, unmeasurable in 65% of infants <12 months) and therefore more studies are needed to establish the diagnostic accuracy of CRP in children presenting with LRTIs. In adults, there was greater consistency in CRP levels in those patients without pneumonia (mean CRP 17 to 19 mg/L), than those with those with pneumonia (mean CRP 62 to 145 mg/L). CRP concentration was shown to be low (<20 mg/L) in a proportion of adults with pneumonia (Van Vugt 39%, Lagerstrom 21%) [9, 14].

Five studies reported on the diagnostic accuracy of CRP at a specified threshold for diagnosing pneumonia. Four studies reported on a cut-point of 20 mg/L, three of which reported a sensitivity between 0.48 and 0.79, which was considered by the authors to be too low to reliably rule out pneumonia [9, 11, 151]. In contrast, the fourth study by Hopstaken reported a sensitivity of 100% at a cut-point of 20 mg/L. Melbye reported a sensitivity of 0.82 at a cut-point of 11 mg/L, suggesting that 18% of pneumonia patients could be missed at this lower CRP level. At a threshold of 50 mg/L (n=2) and 100 mg/L (n=2) specificity was between 0.84 and 0.99, and may be suitable for ruling in a diagnosis of pneumonia [9-12].

Five studies investigated the diagnostic accuracy of CRP in combination with signs and symptoms for determining pneumonia in patients presenting with LRTIs. One study, Holm et al., found the addition of CRP at a cut-point of 20 mg/L increased the specificity of clinical judgement, but reduced the sensitivity, suggesting it would have limited use in primary care unless the GP was trying to rule in a diagnosis of pneumonia. Three other studies [13-15] used CRP in combination with a clinical prediction rule to classify patients as being at low, intermediate or high risk of pneumonia. In these studies, addition of CRP testing to the prediction rule increased its discriminative power. In Teepe the addition of CRP increased the diagnostic value of their prediction rule, but the authors concluded that it was insufficient to exclude a bacterial pneumonia. In the Hopstaken paper, use of the rule would have saved 41% of prescriptions for antibiotics with a 2.5% risk of missing a case of pneumonia. In the Van Vugt study, CRP was only useful in the intermediate risk category where there was clinical uncertainty, and allowed for the reclassification of around half of this group into high- or low-risk categories.

A number of identified studies reported mean CRP levels in pneumonia patients. While not a measure of DTA, it provides useful context for decision-making. Low CRP values do not preclude a diagnosis

of pneumonia as evident from studies of adults [9] and children [150] with radiologically confirmed pneumonia. This was also evident in the substantial overlap in measured CRP levels between pneumonia and non-pneumonia patients in one large prospective study by the GRACE consortium.[14] Overall, the results suggest that low values of CRP cannot exclude a diagnosis of pneumonia, and should only be used to supplement clinical decision-making. Based on the findings of the assessment, integrating signs and symptoms with CRP testing is likely to be the most useful application of CRP POCT. However, given the potential for CRP levels to remain below those expected to be indicative of pneumonia, particularly in relation to paediatric patients, the results should be interpreted with caution. The addition of CRP to clinical decision rules may improve antibiotic prescribing decisions in general practice. However, despite increased diagnostic accuracy with the addition of CRP measurement to clinical signs and symptoms, using the clinical decision rules in the available literature, a substantial group of patients remain classified as intermediate risk, for which clinical decision-making remains challenging.

A key finding of the review is therefore that the sensitivity and specificity of CRP was generally poor. It would be possible to pick a cut-point such that either the sensitivity or specificity was high, but not both. If a cut-point is chosen that ensures high sensitivity then the test may be better for ruling out, whereas setting it for high specificity is better for ruling in. The findings suggest that different cut-points might be suitable depending on the type of acute RTI with which the patient presents. However, the use of different cut-points could cause confusion, while the use of a universal cut-point would entail different rates of misdiagnosis across RTI types. Taken at face value, based on the diagnostic test accuracy, CRP POCT is not a very good test for distinguishing between viral and bacterial RTIs. However, that finding is contradicted by the significant impact on antibiotic prescribing observed in the clinical effectiveness trials. It may therefore be that the accuracy of the test is of lesser importance, and what is more critical is that it facilitates a discussion between the clinician and the patient and perhaps a more conservative treatment approach to managing acute RTIs.

5.11 Research questions – Systematic review 3 (analytical performance)

Element ID	Research question
Diagnostic core model	
D1001	How does the analytical performance of CRP POCT compare with standard laboratory CRP testing?
D1007	How does analytical performance vary in different settings?
D1008	What is known about the intra- and inter-observer variation in test interpretation?

5.12 Study selection

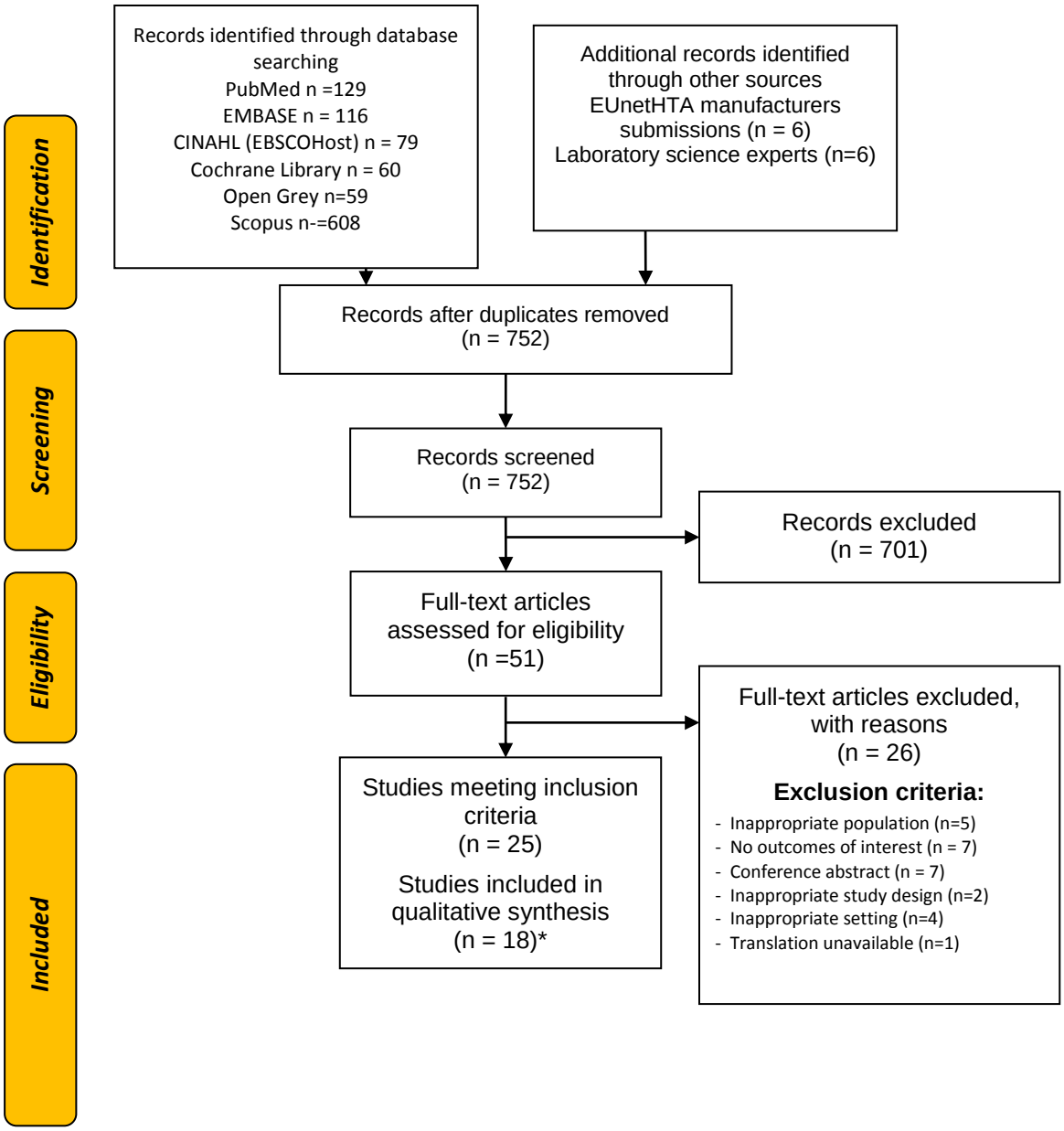


Figure 14: Flow chart systematic review 3 (analytical performance)

*Seven studies meeting inclusion criteria were subsequently excluded for reasons outlined in section 5.4 “Included studies”.

A total of 746 studies were identified from database searching. Submission files received from manufacturers were also consulted to identify relevant studies for this review; six articles were identified as being potentially relevant, however, all six had already been identified through the systematic search. After consultation with laboratory experts, six additional studies were identified from the Scandinavian evaluation of laboratory equipment for point of care testing (SKUP) [20-23, 165, 166] resulting in 752

studies to be screened. After title and abstract screening, 51 potentially relevant articles were identified for full-text review. Following the exclusion of 26 studies for reasons listed in Figure 14, 25 studies remained that were relevant for inclusion in this review. At the full-text stage the most common reasons for exclusion were inappropriate population and no relevant outcomes. These studies often included a specific irrelevant disease group as the population of interest or did not report on accuracy, precision or ease of use of the device. Four studies were excluded as they were performed in the emergency department. One study was in Korean and no appropriate translation could be identified [167]. No relevant systematic review was retrieved from any database during the search.

5.13 Results

Included studies – study characteristics

The systematic review of analytical performance of CRP POCT devices retrieved a total of 25 studies [16-23, 168-177]. While five of these studies relating to the NycoCard™ device were identified as meeting the inclusion and exclusion criteria, on review it was evident that there had been substantive updates to the device (from a semi-quantitative to a quantitative device) since their publication, so that the results could not be considered relevant to the currently marketed version of the device. These studies were therefore excluded from this review [178-182]. In addition, of the six studies undertaken as part of an external validation assessment by the Scandinavian evaluation of laboratory equipment for point of care testing (SKUP), two studies were identified as being updates due to substantive changes in the POCT device, so the decision was taken not to include the two original studies in the review. This review is therefore limited to 18 studies [16-23, 168-177]. The literature was identified from eight countries with all but one study (n=1 Japan) conducted in Europe. Study details are summarised in Table 20 below. A detailed summary of the included studies is provided in Appendix 1 (Table A8).

In all studies the analytical performance of CRP POCT was compared with standard CRP measurement by trained laboratory staff using laboratory-grade analyser equipment. Three approaches to how the comparison was undertaken were identified:

Approach A: fresh whole capillary or whole blood samples were obtained as appropriate and tested at the point of care by those who would ordinarily use the device at the point of care with a second venous sample from the patient sent to the laboratory for standard testing. In most studies a healthcare professional performed the test at the point of care, but in some Scandinavian studies, biomedical scientists in the primary care centres performed the test at the point of care.

Approach B: venous samples submitted from patients in primary care or hospital inpatients were tested in the hospital laboratory by a trained laboratory technician using both a POCT device and a laboratory analyser. The venous samples included fresh whole blood (with anticoagulant) or serum samples and frozen samples from laboratory library stores.

Approach C was taken by an external quality assurance (EQA) study in Norway. Blood samples of known CRP concentration were distributed to primary care centres. POCT was then undertaken by healthcare professionals and staff to assess the performance of the device when operated by the intended user.

Approach A only was adopted in two studies [176, 177], approach B only in ten studies [16, 18, 168-175] and approach C only in one study [17]. Both approaches A and B were adopted in four studies, thereby allowing different aspects of analytical performance to be assessed within the same study [20-23]. Finally, in one study Approach A was used for one device and approach B was used to assess another device [19].

Blood samples used for CRP testing were obtained from patients attending primary care (n=5) [16, 19, 174, 176, 177] and samples submitted to the hospital laboratory (n=3) [168, 169, 175]. In five studies [18, 170-173] CRP testing was undertaken on frozen samples from laboratory library stores. There were four external quality assessment studies by SKUP that used both hospital and primary care blood samples. Finally, the external quality assessment study by Bukve et al. used prepared laboratory and hospital samples [17].

One study limited the inclusion criteria to patients presenting to primary care with symptoms of suspected RTI [174]. The remaining studies did not have specific inclusion criteria, but instead included patients with a range of medical conditions for which a CRP blood test was clinically indicated. Details of the patient population (presenting symptoms, age, gender) were not generally reported for those studies using laboratory library samples.

Length of time between testing samples at the point-of-care and transportation of a patient blood sample to the laboratory for standardised laboratory measurement was unclear across the literature. Longer time delays may have led to sample degradation, but it is unclear the effect this would have on the CRP levels. Furthermore, in most studies it was unclear for what length of time laboratory library samples had been stored before CRP levels were tested.

There were five studies that compared the performance of more than one CRP POCT device (range 2-8) [16-19, 170]. These studies were mostly conducted in a laboratory to eliminate or reduce the risk of operator bias. One study tested one device at the point of care and then transferred a venous sample to the laboratory to be tested on a different POCT device by laboratory technicians [19]. A total of two semi-quantitative (Actim®, Cleartest®) [16, 172] and eleven quantitative POCT devices were assessed. Results for the NycoCard™ and NycoCard™ Reader II device have been presented separately, as have results for the QuikRead® 101 and QuikRead go® devices.

In two of the included studies (Brouwer et al. and Bukve et al.), graphs were provided with relevant bias data, the data points were extracted from these graphs using two software packages (https://automeris.io/WebPlotDigitizer/ and https://datathief.org/).

Table 20: Main characteristics of studies included (all studies included in the effectiveness domain)

Author and year or study name	Study type	Number of samples (setting tested)	Intervention (s)	Main endpoints
Bains (2017)	Analytical Performance	44 (Lab)	iChroma™	Accuracy (bias, correlation)
Brouwer (2015)	Analytical Performance	100 (Lab)	Actim®*; Cleartest®*, Afinion™, QuikRead go®, Eurolyser Smart, iChroma™, Microsemi, AQT90 Flex	Accuracy (agreement, bias, correlation) Precision (CV) Ease of use
Bukve (2016)	Analytical Performance	3 (Lab) 22 (POC)	ABX Micros 200, Afinion™, iChroma™, NycoCard™, QuikRead go®	Accuracy (bias)
Ciftci (2014)	Analytical Performance	96 (Lab)	iChroma™	Accuracy (bias
Clouth (2009)	Analytical Performance	200 (Lab)	NycoCard™, ABX Micros CRP	Accuracy (agreement, bias) Precision (CV) Ease of use
De Graff (2016)	Analytical Performance	43 (Lab))	Spinit®	Accuracy (correlation) Precision (CV)
Evrard (2005)	Analytical Performance	100 (Lab)	Actim®*	Accuracy (agreement) Ease of use
Ivaska (2015)	Analytical Performance	48 (Lab)	Afinion	Accuracy (bias, correlation)
Matheeussen (2018)	Analytical Performance	2,922 (POC)	QuikRead® 101	Accuracy (agreement, bias, correlation) Precision (CV)
Minnaard (2013)	Analytical Performance	8 (Lab)	Afinion™, NycoCard™ Reader II, Eurolyser Smart,QuikRead go®, QuikRead® 101	Accuracy (bias) Precision (CV) Ease of use
Monteny (2006)	Analytical Performance	59 (Lab and POC)	NycoCard™, QuikRead®	Accuracy (agreement, bias, correlation)
Nomura (2014)	Analytical Performance	244 (Lab)	Microsemi	Accuracy (correlation)
Seamark (2003)	Analytical Performance	234 (POC)	QuikRead®	Accuracy (bias, correlation) Precision (CV) Ease of use

Author and year or study name	Study type	Number of samples (setting tested)	Intervention (s)	Main endpoints
SKUP (2001)	Analytical Performance	40 (Lab) 40 (POC)	QuikRead® 101	Accuracy (agreement, bias, correlation) Precision (CV) Ease of use
SKUP (2002)	Analytical Performance	160 (Lab and POC)	ABX Micros CRP	Accuracy (agreement, bias, correlation) Precision (CV) Ease of use
SKUP (2011)	Analytical performance	114 (Lab) 80 (POC)	iChroma™	Accuracy (agreement, bias, correlation) Precision (CV) Ease of use
SKUP (2013)	Analytical Performance	100 (Lab) 86 (POC)	Smart Eurolyser	Accuracy (agreement, bias, correlation) Precision (CV) Ease of use
Verbakel (2013)	Analytical Performance	135 (POC)	Afinion	Accuracy (agreement, bias) Ease of use

Notes: * Semi-quantitative tests. All other quantitative.

Abbreviations: CV – co-efficient of variation; POC – point of care; Lab – laboratory.

5.14 Quality rating

Details of the quality of the evidence included in this systematic review are included in Appendix 1, Figures A5 and A6.

An important potential source of bias is the source of funding of the studies. One study was sponsored by the manufacturer [176] and in a further two studies, the equipment and training was funded by the manufacturer [171, 177]. Research in one of the studies was undertaken by company employees [175]. Four studies were recipients of educational grants [19, 173, 174, 177].

[D1001] – How does the analytical performance of CRP POCT compare with standard laboratory CRP testing?

- How does the accuracy of CRP POCT devices compare with standard laboratory-based CRP testing?
- How precise are the CRP POCT devices?

Accuracy

Data in relation to three main indicators of accuracy were presented in the literature for quantitative CRP POCT devices: correlation, agreement and bias. These terms were used interchangeably in the literature. The following is a brief explanation of how these terms are used in this assessment.

Correlation: This was presented as a linear regression which quantifies the strength of the relationship [183]. Correlation was reported as a Spearman's, Pearson's or intra-class correlation coefficient with the r value indicating the strength of relationship (range: -1 to +1) and the r^2 value (range: 0-1) explaining the proportion of variance that the two variables have in common [183].

Agreement: Regression analysis was used to indicate the level of agreement between the laboratory standard method and the POCT method. For quantitative devices, this was reported using a Passing Bablok regression analysis (n=4 studies) [16, 19, 174, 177] or a Deming regression (n=1). The Passing Bablok regression analysis overcomes some of the limits of correlation analysis related to data distribution and presents a constant or proportional difference between two methods. If the slope of the regression line includes 1.00, there is no proportional difference between the device and the laboratory reference method. For semi-quantitative devices, the agreement between the CRP POCT device and the reference test was reported as a Cohen's Kappa value (range 0-1), with values closer to 1 indicated high levels of agreement between the methods.

Bias: This was reported in five studies as a mean difference or percentage difference in CRP values calculated from a Bland-Altman plot [16, 18, 19, 174]. The Bland-Altman method describes the agreement between two quantitative measurements and establishes limits of agreement using the mean and standard deviation. Bland-Altman recommends that 95% of the data points for the mean difference between the two methods should lie within two standard deviations. It gives an indication of how much the POCT measurements deviate from the reference measurements and the direction of this bias. In other studies, a mean difference or percentage mean difference was presented but it was not clear if Bland-Altman methodology had been used [17, 20-23, 168, 169, 173, 176, 177].

Accuracy of semi-quantitative devices

The accuracy of two semi-quantitative devices compared with standard CRP laboratory measurement was reported in two studies, both of which were undertaken by trained laboratory staff in the laboratory (Table 21). In the study by Brouwer et al., two independent observers read the test-strip results and these values were compared with the CRP level as measured by standard laboratory testing using four CRP concentration categories (CRP <10 mg/L, 10-40 mg/L, 40-80 mg/L and >80 mg/L); results were reported as Cohen's Kappa values reflecting the level of agreement between the measurements. Both semi-quantitative devices performed poorly when read after five minutes (the optimal time as indicated by the manufacturer) with Kappa values ≤0.63 and ≤0.61 for Actim® and Cleartest®, respectively. The percentage discrepancy between CRP POCT and standard testing measurement ranged between 27% and 35% for the Actim® strips and 29% and 33% for Cleartest®. The tests were re-read at 15 minutes to evaluate if test accuracy varied according to the time at which they were read. The accuracy of both tests was found to decline, with Kappa values of ≤0.46 and ≤0.25 reported for the Actim® and Cleartest® devices, respectively. Separately, the accuracy of the Actim® device was also reported by Evrard et al. who reported an overall Kappa value of 0.93 when tested using samples from four CRP concentration categories (<10, 10-40, 40-80, >80mg/L).

Table 21: Agreement of the semi-quantitative POCT tests with the reference standard

Device	Agreement (κ)	Discrepancy (%)	Agreement (κ)	Discrepancy (%)
	After 5 minutes		After 15 minutes	
Actim®[172]	0.93			
Actim®[16]				
Observer 1	0.53	35	0.46	39
Observer 2	0.63	27	0.39	44
Inter-observer agreement	0.81	14	0.83	12
Intra-observer agreement	5 minutes vs. 15 minutes			
Observer 1	0.64			
Observer 2	0.60			
Cleartest®[16]				
Observer 1	0.61	29	0.17	60
Observer 2	0.56	33	0.25	56
Inter-observer agreement	0.55	33	0.74	16
Intra-observer agreement	5 minutes vs. 15 minutes			
Observer 1	0.40			
Observer 2	0.20			

Abbreviations: K - Cohen's Kappa

Accuracy of quantitative devices

A summary of the accuracy results for the quantitative CRP POCT are presented in Table 22. Results obtained under idealised laboratory conditions and at the point of care (primary care setting) are presented separately. Seventeen studies evaluated quantitative devices, twelve of which evaluated the accuracy of 10 different POCT devices in the laboratory; eight studies evaluated the accuracy of seven POCT devices in the primary care setting. As noted in Section 5.3, all studies compared the CRP result obtained on the POCT device with that obtained using standard CRP measurement by trained laboratory staff using laboratory-grade analyser equipment. The comparator equipment differed between studies. (Appendix 1 (Table A8).) Three main indicators of accuracy were reported: correlation, agreement and bias; studies varied in the number of accuracy indicators they reported (range: 1 to 3).

In Table 22 the correlation coefficients (r or R) and the coefficient of determination (r^2 or R^2) all exceed 0.9, indicating excellent correlation between the devices and the reference laboratory measurement irrespective of whether the device was tested in the laboratory or at the point of care. No correlation data were available for the NycoCard™ Reader II.

Agreement with a laboratory reference standard was reported in four studies as the result of Passing-Bablok regression analysis for seven devices tested in the laboratory setting [16, 19, 170, 174]. In a comparative study of six quantitative devices, Brouwer et al. noted that the AQT90 Flex and Smart

Eurolyser exhibited the best agreement (1.03 [95% CI: 1.00–1.06]; 1.00 [95% CI: 0.96–1.04], respectively). Values close to the reference standard were reported for the Afinion™, Microsemi and QuikRead go® devices, but their 95% CI did not include the value 1.00 (0.87, 95% CI: 0.84–0.91, 1.16, 95% CI: 1.14–1.18 and 0.85, 95% CI: 0.83–0.87 respectively), indicating that the devices systematically under- or overestimated the CRP level (Table 22). A lower level of agreement was noted for the iChroma™ device (0.79 [95% CI: 0.76–0.82]) [16]. Results from studies by Matheeussen et al. and Monteny et al. reported a systematic underestimation of CRP levels by the QuikRead® 101 device (0.94 [95% CI: 0.93–0.95])[174], (0.83 [95% CI: 0.81–0.85]) [19], respectively).

Three studies assessed agreement with the reference standard when tested at the point of care using Passing Bablok regression analysis (Table 22) [19, 171, 177]. Good agreement was noted for the Afinion™ (1.02, 95% CI: 1.01–1.08) [177] and NycoCard™ (0.95, 95% CI: 0.9–1.0) devices [19, 177]. Using Deming regression, the spinit® device was noted to overestimate CRP values by 12% [171].

Thirteen studies reported the accuracy of CRP POCT devices compared with the laboratory standard on the basis of their bias calculated as a mean difference or percentage difference in CRP level. Six of these studies were set in the laboratory [16, 18, 19, 23, 168, 170, 173, 174], seven were set in the POC [17, 19-21, 23, 176, 177], with two studies reporting bias from the laboratory and the POC (Table 22) [19, 23].

Two studies provided the majority of the data for the laboratory setting as they compared multiple devices [16, 18]. Minnaard et al. compared five quantitative CRP devices (Afinion™, NycoCard™ Reader II, Smart Eurolyser, QuikRead go® and QuikRead® 101) [18]. The study took place under idealised laboratory conditions and compared the accuracy of the devices using low concentration (<20mg/L), intermediary (20-100mg/L) and high concentration (100mg/L) CRP samples, the results of which are summarised in Table 22. For all devices, the mean difference was less than 2mg/L at low concentrations (<20 mg/L), with QuikRead go® (0.2mg/L, 95% CI: -1.2–1.5) and the NycoCard™ Reader II (0.3 mg/L, 95% CI: -4.4–5.0) being the most accurate. At the intermediary concentration (20-100 mg/L) the Afinion™ was the most accurate device (-0.3mg/L, 95% CI: -6.4–5.8) with all the other devices reporting a mean difference between 2.3 mg/L (QuikRead go®) and 7.8 mg/L (Smart Eurolyser). The largest mean difference values were reported with the high concentration (>100 mg/L) CRP sample, ranging between 0.9mg/L (95% CI: -53.2–55.0) (Smart Eurolyser) and 14.7mg/L (95% CI: -21.1–50.5) (Afinion). The authors concluded that the Afinion™, NycoCard™ Reader II, QuikRead go® and QuikRead® 101 showed better agreement than the Smart Eurolyser device and that for all of the POC devices tested the agreement between the POC test and the laboratory standard decreased at higher CRP concentrations resulting in wider confidence intervals around the mean differences at CRP concentrations greater than100 mg/L.

Brouwer et al. reported on six quantitative devices (QuikRead go®, Smart Eurolyser, Afinion™, iChroma™, Microsemi and AQT90 Flex), with all bar the iChroma™ (-12.3 mg/L) reporting a mean difference between ±3.7mg/L (Afinion) and ±9.2 mg/L (QuikRead go®) (Table 22) [16]. Additional studies for the Afinion™, NycoCard™ and QuikRead® 101 devices in the laboratory reported mean differences <±2.5 mg/L [170, 173, 174]. Additional studies for the iChroma™ device reported mean differences of -8.1mg/L [168] and -7 mg/L [169]. A SKUP analysis reported on the % bias for the iChroma™ device in the laboratory setting as 0.4%, however, the device over predicted at low concentrations by

6.6% and under predicted at high concentrations by 6.2%, clearly showing that presenting the bias at different concentrations of CRP provides a more useful overview of the devices performance [22].

One external quality assurance scheme (EQAS) for CRP POCT reported the accuracy of multiple devices (Afinion™, NycoCard™, QuikRead go®, QuikRead® 101, iChroma™ and ABX Micros) in the primary care setting in Norway [17]. The EQAS scheme evaluated instrument performance at two different CRP concentration levels using certified reference material. Each participant received two EQA samples which comprised whole blood with human recombinant CRP added to a known concentration (25.0mg/L and 63.9mg/L). The Afinion™ and the QuikRead® 101 were found to have low bias (<±2%) at both concentrations (Table 22). Comparable results were found for the QuikRead go®, NycoCard™ and iChroma™ devices with estimates of bias at 25 mg/L between ±7% and ±10% and estimates of bias at 63.9 mg/L between ±9% and ±15%. The QuikRead go® (12.0%, 95% CI: 11.0; 13.0) and NycoCard™ (14.9%, 95% CI: 10.1; 20.0) performed particularly poorly when the higher concentration sample was tested. The ABX Micros had bias of -6.2% at the lower concentration and lower bias at the higher concentration level (25.0 mg/L -6.2%, at 63.9 mg/L 0.0%). Consistent with the Bukve study, Verbakel et al. reported low levels of bias (≤ 2%) for the Afinion™ device when tested in the primary care setting [17, 177]. Inconsistent data were found for a number of these devices in other studies. In contrast to the Bukve study, the NycoCard™ device was found to have low levels of bias (<2%), even at high concentrations (>70 mg/L) [19]. A SKUP study from 2002, in contrast to the Bukve study, reported poor levels of accuracy for the ABX Micros device in four primary care centres [17, 21]. The SKUP study reported the POC results to be around 40% lower (n= 4 primary care practices) than the hospital reference method. Testing was repeated in two of these practices after six months of use with improvements in accuracy seen (from approx. 28% lower to 14% lower than the reference method) in these centres, suggesting that with practice operators made fewer mistakes.

In two of the SKUP reports and a study by Monteny et al., accuracy data is reported in the laboratory and at the point of care [19, 20, 23]. A 2001 SKUP study reported data on the QuikRead® device when tested at the point of care in three general practices using whole blood and in the laboratory setting using plasma. In the laboratory, the study found good consistency between the laboratory reference method and the QuikRead device (Regression equation y=0.98x +0.32, Table 22). However, in the POC setting the device consistently underestimated the CRP levels compared with the hospital reference method; this underestimation was greater at higher CRP concentrations (<75 mg/L approx.-10%, >75 mg/L up to -20%). The authors suggested the discrepancy was due to the use of whole blood at the point of care with no correction for haematocrit. Subsequent to this feedback, the company responded that the device would be recalibrated (3% at the lower end of the concentration range and 13% at the higher end) to correct these systematic differences. The data from this 2001 SKUP report are therefore less likely to be relevant.

In the SKUP analysis for the Smart Eurolyser, data were reported as a percentage bias at different concentrations (Table 22) [23]. The bias in the laboratory ranged from -4.4% (-7.4; -1.4) to 9.6% (5.6; 13.5). When tested at two POC centres the bias was a maximum of -17.0% (-24.0;-9.6) at low CRP concentrations. The overall bias across the range of CRP concentrations at the two POC centres was -9.8% and -10.3%, respectively. This indicates a clear difference when using CRP POCT devices in the laboratory and at the point of care. SKUP pre-defines an acceptable level of bias as of +/- 1 mg/L or <26% from the comparison method. In total, 98% of the results for the Smart Eurolyser fulfilled this

goal for accuracy with venous EDTA samples in the hospital evaluation and with capillary samples at both primary health care centres.

Monteny et al. also reported the Bland Altman mean difference based on CRP concentration in the laboratory and POC setting [19]. However in this study different devices were used, with NycoCard™ being used at the POC and QuikRead® being used in the laboratory setting. The overall mean difference for the QuikRead® 101 was -6.1mg/L; at concentrations below 70mg/L the mean difference was -0.4mg/L, but this increased to -26.4mg/L at higher concentrations (>70mg/L). This is in contrast with the Minnaard study that reported a bias of 3.2 mg/L at concentrations over 100 mg/L. Monteny also reported on the NycoCard™ device at the POC and overall the NycoCard™ device was more accurate than the QuikRead® 101 device (overall mean difference of 0.6 mg/L; 1.4 mg/L at lower CRP concentrations and -1.9 mg/L at higher concentrations). The authors concluded that the NycoCard™ device was more suitable for use in primary care.

In addition to accuracy results reported in Table 22, Bukve et al. reported on an external quality assurance scheme (EQAS) for CRP POCT in Norway which comprised 19 rounds of EQAS (twice a year for nine years), with a mean of 2,134 participating GP offices or nursing homes in each round [17]. Participants' performance was considered good if the reported CRP measurement from their POCT equipment was within +/- 8% of the target interval, poor if the result exceeded the target value by +/- 15% and acceptable for results between these limits. The percentage of participants exhibiting good performance in each survey varied from 78% to 81%; good performance increased over time with participation in further rounds of EQA. The authors also examined what factors were associated with good performance compared with acceptable/poor performance and found that participants were more likely to achieve a good performance if they had taken part in more than one EQAS round, had a trained laboratory scientist performing the test, performing the test more than ten times per week, performing internal quality control at least once per week and the type of instrument used. In the logistic regression analysis, the authors reported QuikRead® 101 as the reference values and found QuikRead go® had an OR of 0.87 (95% CI: 0.76–0.98), Afinion™ OR 0.70 (95% CI: 0.65–0.77), iChroma™ OR 0.36 (95% CI: 0.31–0.42), ABX Micros CRP OR 0.34 (95% CI: 0.29–0.42) and NycoCard™ CRP/NycoCard™ CRP with Reader II OR 0.32 (95% CI: 0.31–0.42). This suggests that those who had good participant performance were more likely to be using QuikRead® 101, QuikRead go® or Afinion™. However, the authors also noted that changing the instrument did not seem to have a significant effect on results. Overall, GP offices tended to perform better than nursing homes, emergency primary healthcare centres and occupational healthcare centres, but the authors noted this may be related to how often the test is performed in these settings.

Table 22: Accuracy of the quantitative POCT tests compared with a reference standard when tested in the laboratory or at the point of care

	Laboratory				Point of Care			
Device	**Number of studies (n)**	**Agreement (Slope of Passing-Bablok Regression [95% CI])**	**Bias: Mean difference from Bland Altman Plot (CI 95%) or % Bias**	**Correlation* (95% CI)**	**Number of studies (n)**	**Agreement: Slope of Passing-Bablok Regression (95% CI)**	**Bias: Mean difference from Bland Altman Plot (CI 95%) or % Bias**	**Correlation* (95% CI)**
Afinion™	n=3 [16, 18, 173]	0.8 (0.84-0.91) [16]	**<20mg/L:** -1.1 mg/L (-3.2; 1.0) **20-100mg/L:** -0.3mg/L (-6.4;5.8) **>100mg/L:** 14.7mg/L (-21.1;50.5) [18] -3.7mg/L [16] to 2.3mg/L (-5.5;10.1) [173]	SCC r^2: 0.982 (0.973-0.988) [16] ICC: 0.994 (0.990-0.997) [173]	n=2 [17, 177]	1.02 (1.01-1.08) [177]	1.3% (-15.4;12.8) [177] **25mg/L**: 1.7% (1.0;2.5) **63.9mg/L**: 2.0% (1.0;3.0) [17]	NR
NycoCard	n=1 [170]	Equivalency of both tests shown by Passing- Ba-blok [170]	No systematic differences between tests shown with Bland Altman [170]	SCC R: 0.9838 [170]	n=2 [17, 19]	0.95 (0.9 – 1.0) [19]	**0-70mg/**L:1.4mg/L (2SD:11) **>70mg/L**:-1.9mg/L (2SD:35.4) **Overall**: 0.6mg/L (2SD: 19.7)[19] **25.0mg/L**: 7.8% (3.0;13.0) **63.9mg/L**: 14.9% (10.1;20.0) [17]	PCC r: 0.99 [19]
NycoCard™ Reader II	n=1 [18]	NR	**<20mg/L:** 0.3mg/L (-4.4;5.0) **20-100mg/L:** 3.0mg/L (-6.2;12.2) **>100mg/L: -**10.7mg/L (-30.4;9.1) [18]	NR	n=0	NR	NR	NR

QuikRead go®	n=2 [16, 18]	0.85 (0.83-0.87) [16]	**<20mg/L:** 0.2mg/L (-1.2;1.5) **20-100mg/L:** 2.3mg/L (-3.6;8.3) **>100mg/L:** -8.9mg/L(-21.4;3.5)[18] -9.2 mg/L [16]	SCC r^2: 0.996 (0.994-0.997) [16]	n=1 [17]	NR	**25.0mg/L**: 8.0% (7.1;8.9) **63.9mg/L**: 12.0% (11.0;13.0) [17]	NR
QuikRead® 101	n=4 [18-20, 174]	0.83 (0.81-0.85)[19] to 0.94 (0.93-0.95) [174] Regression slope: 0.98 [20]	**<20mg/L:** -1.4mg/L (-3.2;0.4) **20-100mg/L:** -6.5mg/L (-15.6;2.7) **>100mg:** 3.2mg/L(-8.4;14.8) [18] **0-70mg/**L:-0.4mg/L (2SD:11.8) **>70mg/L**:-26.4mg/L (2SD: 44) **Overall**: -6.1mg/L (2SD 31.3)[19] 0.4mg/L (18.8;19.5) [174]	PCC r: 0.99[19] SCC r:0.976 (0.973-0.979) [174] R^2: 0.977 [20]	n=3 [17, 20, 176]	NR	**25.0mg/L**: 1.7% (0.8;2.6) **63.9mg/L**: -0.6% (-1.6;0.5) [17] -1mg (+/-10mg/L) [176] **<75mg/L**: -10% **>75 mg/L**: -20% Stated as approximate results [20]	PCC r: 0.996 [176]
Smart Euro-lyser	n=3 [16, 18, 23]	1.00 (0.96;1.04) [16]	**<20mg/L:** 1.9mg/L(-10.2;14.1) **20-80mg/L:** 7.8 mg/L (-27.7;43.3) **>100mg/L:** 0.9mg/L (-53.2;55.0) [18] **Low** (1.8-27,4 mg/L): -4.4% (-7.4;-1.4) **Medium** (27.5-41.1 mg/L) 5.5% (2.9;8.2) **High** (41,7-280 mg/L): 9.6% (5.6;13.5) [23] -3.9 mg/L [16]	SCC r^2: 0.970 (0.954-0.980) [16]	n=1 [23]	NR	Primary Health Centre 1: **Low** (0.3-13.5mg/L): -11.2% (-14.7;-7.8) **High** (14.3-148mg/L): -8.6%(-12.9;-4.3) **Overall:** -9.8% (-12.5;-6.9) Primary Health Centre 2: **Low** (**0.3-9.0mg/L): -**17.0% (-24.0;-9.6) **High** (**9.7-109mg/L):** -4.8% (-9.9;0.3) **Overall:** -10.3%(-15.1;-5.6) [23]	NR

iChroma™	n=4 [16, 22, 168, 169]	0.79 (0.76;0.82) [16] Linear Regression = 0.74 [168]	**Low** (0.0-13.5mg/L): 6.6% (2.8;10.4) **Medium** (13.5-56.4mg/L): 3.3% (1.0;7.6) **High** (56.6-264.6mg/L): -6.2% (-10.2;2.2) **Overall:** 0.4%(-2.2;2.9)[22] -8.1mg/L [168] -7mg/L (-139.1;125.1) [169] -12.3 mg/L [16]	r^2 = 0.905[168] SCC r^2: 0.967 (0.953-0.976) [16]	n=1 [17]	NR	**25.0mg/**L:-9.7%(-11.6;-7.7) **63.9mg/L**:-9.1%(-8.18;-0.2) [17]	NR
Microsemi	n=2 [16, 175]	1.116 (1.14;1.18) [16]	5.1 mg/L [16]	r=0.989[175] SCC r^2: 0.997 (0.9969-0.998) [16]	n=0	NR	NR	NR
spinit®	n=0		NR	NR	n=1 [171]	Deming re-gression value =1.12 [171]	NR	R=0.98 [171]
AQT90 Flex	n=1 [16]	1.03 (1.00;1.06) [16]	5.8 mg/L [16]	SCC r^2: 0.992 (0.995-0.998) [16]	n=0	NR	NR	NR
ABX Micros 200	n=2 [21, 170]	Regression slope 0.84 to 1.15 [21]	NR	SCC R:0.9934 R: 0.98 – 0.99 [21]	n=2 [17, 21]	NR	**25.0mg/L**: -6.2%(-10.0;-2.1) **63.9mg/**L: 0.0%(-1.0;1.0) [17] **Primary care centres (n=4):** **Overall: 40%** **Primary care centres in-volved initially and at 6 months (n=2):** **10-135mg/L**: -27.6% After 6 months use this de-creased to -14.7%. [21]	R^2: 0.81 to 0.98 for 4 practices [21]

Note: Correlation values reported included: Spearman (SCC) Pearson (PCC)* & Intra-class correlation coefficient (ICC)

Precision

The precision of eleven CRP POCT devices was evaluated in ten studies (Table 23). Precision was most often expressed as the level of imprecision and reported as a coefficient of variation (CV). Imprecision was reported as “within-day variation”, whereby the same samples are tested multiple times on the same device on the same day and a “between-day variation” where the same sample was tested on the same device on multiple days. Studies also compared the precision of the devices at different CRP concentrations (low, medium, high). The number of samples used; the range of CRP concentrations defined as low, medium and high; and the number of measurements taken varied greatly between studies. A number of studies noted that there is no agreed international standard in relation to the maximum acceptable level of imprecision. The studies by SKUP and Brouwer stated a priori that the maximum acceptable imprecision they considered was a CV of ≤10%. Minnaard et al. considered a value of ≤15% sufficient.

Of the ten studies reporting precision data for devices when tested under idealised laboratory conditions, two studies by Brouwer et al. [16] and Minnaard et al. [18] which compared the analytical performance of eight and five CRP POCT devices, respectively, provided the majority of the data. Brouwer et al. [16] tested within-day variation using two samples with CRP concentrations ranging from 57mg/L to 120mg/L. Minnaard et al. [18] used a low concentration sample (18-25mg/L) and high concentration sample (95-136mg/L) and tested both within-day and between-day precision.

Overall acceptable levels of precision (CV <10%) were reported for the Afinion™, QuikRead go®, QuikRead® 101, Microsemi, AQT90 Flex and ABX Micros devices when tested in in the laboratory setting. In studies that compared the precision of the devices at a number of CRP concentration ranges, precision was noted to be concentration dependent with greater levels of imprecision reported at the extremes of the concentration range (Table 23).

High levels of imprecision (CV >10%) were reported in studies for the iChroma™, NycoCard™ II Reader devices. Inconsistent data were obtained for the Smart Eurolyser device with acceptable (within-day CV <10%) precision reported by Brouwer et al. and poor levels of precision (maximum CV = 19.4% [within-day] and 30.5% [between-day]) reported by Minnaard et al. (Table 23).

Fewer studies reported data in relation to the precision of the devices when tested at the point of care with data available for only five quantitative devices (ABX Micros 200, iChroma™, QuikRead® 101, Smart Eurolyser & spinit®). Six studies reported within-day precision of devices when tested at the point of care [22, 23, 176], four of which were SKUP reports. Acceptable levels of precision (CV <10%) were reported for two (QuikRead® system and spinit®) of the five CRP POCT devices assessed. Inconsistent levels of precision were reported for the iChroma™, Smart Eurolyser and ABX Micros devices with CV values of greater than 10% reported in at least one primary care practice or at one of the specific concentration ranges assessed. High levels of imprecision were recorded with the ABX micros device (CV ≥24.6%) at CRP concentrations under 25mg/L; however, at CRP concentrations over 25mg/L the CV value was less than 3.2% (Table 23).

Table 23: Summary range of the within-day and between-day imprecision values of the quantitative POCT devices

	Laboratory			Point-of--Care		
Device	**Studies (n)**	**Within-Day CV (%)**	**Between-Day CV (%)**	**Studies (n)**	**Within-Day CV (%)**	**Between-Day CV (%)**
Afinion™	2	2.6[b][16] - 7.4[a][18]	4.6[a] - 7.3[b][18]	0	NR	NR
Ny-coCard™	1	1.876[170]	NR	0	NR	NR
Ny-coCard™ Reader II	1	9.8[b] to 13.3[a][18]	6.0[b] to 16.9[a][18]	0	NR	NR
QuikRead go®	2	1.1[b] to 2.6[a][18]	4.0[b] to 8.3[a][18]	0	NR	NR
QuikRead® 101	3	5.4[a] to 5.7[b][18] **8-25mg/L**: 6.1 (5.0-7.8) **25-100mg/L**: 2.4 (2.1-2.9) **>100 mg/L**: 1.7 (1.4-2.3) **Overall**: 2.5 (2.1-2.8)[20] 3.4%[174]	6.3[b] - 9.3[a][18]	2	Inter-assay: **21mg/L**: 8.7 **63mg/L**: 4.5 Intra-assay: **25mg/L:** 6.4 **70mg/L**:3.6[176] 3.4 - 6.0[20]	2.5 (1.9 - 3.6) - 2.6 (2.1 - 3.7) [20]
Smart Eurolyser	3	2.8[a][16] to19.4[a][18]	18.0[b] to 30.5[a][18]	1	Overall CV: 8 (6.8-9.7) 7.4 - 12.1[23]	21.0 – 25.7 with control material[23]
iChroma™	2	3.3[22] - 18.7[a][16]	NR	1	5.7 - 15.0[22]	16.1 – 24.1 with control material[22]
Microsemi	1	1.3[b] - 3.0[a][16]	NR	0	NR	NR
spinit®	0	NR	NR	1[171][172][174][174][175][175][175][176][177][178][178][178][179][179][179][180][180][181][181][181][182][182][184][185][185][185][186][186][187][188][189][189][187	6.9[171]	NR

				][187][188][188][188][188][188][188][189][189][190][191][190][190][190][190][190][176][174](174)(174)(174)(173)(173)		
AQT90 Flex	1	3.5[a] - 7.6[b][16]	NR	0	NR	NR
ABX Micros	2[21, 170]	0.9160[170] **<2mg/L**: 57.7 **2-25mg/L**: 3.9 **25-75mg/L**: 5.3 **75-100mg/L**: 1.4 [21]	NR	1	Initial Results: **<2mg/L**: 53.4-103.6 **2-25mg/L**: 24.6-38.4 **25-75mg/L**: 0.1-3.1 **>75mg/L**: 0.7 Six month results: 1.4 - 5.0[21]	NR

Notes: [a,b] Two studies reporting on precision measured imprecision at two different CRP concentrations. [a] represents the lower concentration range (16 -37 mg/L in Minnaard et al. and 57 to 82 mg/L in Brouwer et al.) and [b] represents the higher concentration range (82 to 160 g/L in Minnaard et al. and 77 to 120 mg/L in Brouwer et al.).

[D1008] – What is known about the intra- and inter-observer variation in test interpretation?

This outcome overlaps with D1001. Data on this outcome are limited to one study which evaluated two semi-quantitative tests (Actim® and Cleartest®) [16]. As illustrated in Table 21, there was evidence of inter-observer variation for both devices. Inter-observer agreement values after five minutes were 0.81 and 0.55 for Actim® and Cleartest®, respectively. When tests were re-read at 15 minutes, the inter-observer agreement values were 0.83 and 0.74 for Actim® and Cleartest®, respectively.

In terms of intra-observer variation, as noted, tests were read at five minutes and re-read by the same two observers at 15 minutes. For the Actim® device, the intra-observer agreement for observers one and two were 0.64 and 0.60, respectively. For the Cleartest® device, these values were 0.40 and 0.20, respectively. Although the test was read twice by the same observer, the ten-minute time lapse between the readings may account for the low intra-observer agreement as the test is known to be time critical, with five minutes being the optimal time to read the test.

[D1007] – How does the analytical performance vary in different settings?

This assessment element overlaps with D1001. While data comparing the accuracy of the POCT versus a laboratory standard in laboratory and primary care settings are available for eight devic-

es, due to differences in the choice of comparator, it is only appropriate to evaluate the impact of setting if the device was tested in both settings (laboratory by trained laboratory personnel and in primary care by the intended users) within the same study. Data to inform this question are derived from the external quality assurance reports by SKUP on the Smart Eurolyser, iChroma™, ABX Micros and QuikRead® 101 devices (Table 24).

In terms of accuracy, SKUP set an allowable level of bias of +/- 1 mg/L or <26% from the comparison method. A total of 98% of the results for the Smart Eurolyser fulfilled this goal for accuracy with venous EDTA samples in the hospital evaluation and with capillary samples at both primary health care centres. In the laboratory setting the Smart Eurolyser exhibited a negative bias at low concentrations <30 mg/L and a positive bias at higher concentrations (all <10%) while at the POC a negative bias was seen at low and high concentrations but it was more pronounced at lower concentrations (at low concentration bias 11.2% and 17.0%) in two primary care centres (Table 24). In terms of precision, the Smart Eurolyser fulfilled the quality goals for imprecision in the laboratory setting and in primary care at CRP concentrations above 3.2 mg/L. However the mean CV was higher in the primary care setting (8%, 95% CI: 6.8–9.7) compared with the laboratory setting (4.9%, 95% CI: 4.3–5.7). The internal control material was used to assess reproducibility and was measured each day of the evaluation. In the laboratory setting an acceptable CV was reported (CV <10%), but at the point of care the CV was between 21% and 25.7% at different concentrations in the two centres, suggesting poor reproducibility with the control material in the primary care setting. It was unclear if this poor reproducibility was due to operator error or had to do with the control material. Overall, the Smart Eurolyser had acceptable performance (except for the control material) but the performance of the device was consistently better in the laboratory setting (Table 24).

The iChroma™device was tested by SKUP in 2011. Accuracy was not accessed at the point of care as the blood taken for comparison to the laboratory method did not reach the laboratory within the day of sampling. Precision was reported in both settings with acceptable within-day repeatability reported in the laboratory for both capillary and venous blood samples. The internal quality control material was measured each day of the evaluation and used to measure between-day variation, this was also found to be acceptable in the laboratory setting (<10%). Precision measured in forty samples from two primary care health centres resulted in a CV of 5.7% in one centre and 15.0% in the other. The between-day variation measured using the quality control material resulted in unacceptable imprecision of 16% and 20% in the two primary health care centres. It was suggested that the colourless control material may not be ideal for use in the primary care setting.

The QuikRead® device was analysed by SKUP in 2001 in the laboratory using plasma samples and in three general practices using whole blood. Although the agreement was acceptable in the laboratory setting, when used at the POC, the device consistently underestimated the CRP levels compared with the reference method (<75 mg/L approx. -10%, >75 mg/L up to -20%). The authors suggested the discrepancy was due to the use of whole blood at the point of care with no correction for haematocrit. Subsequent to this feedback, the company responded that the device would be recalibrated (3% at the lower end of the concentration range and 13% at the higher end) to correct these systematic differences. The data therefore may not be relevant to the current QuikRead® technology. In terms of precision, overall precision was considered acceptable with

CV <10% in the laboratory and in two out of three general practices. One practice had a higher variation of 3% to 12%. The highest CV was with samples with CRP concentrations of <25 mg/L [20].

SKUP reported that the ABX Micros had acceptable levels of bias in the laboratory setting (< ± 15%), but unacceptable high levels of bias when first measured in the primary care setting (around 28% lower than reference method). Accuracy improved after six months of use to -14%, suggesting that, with practice, operators made fewer mistakes. The device had acceptable precision in the laboratory setting at CRP concentrations above 2 mg/L and at concentrations above 25 mg/L in the primary care setting. The overall precision in the primary care setting improved after six months of practice particularly, in the CRP 2-25 mg/L concentration range category. Imprecision reduced from 24% to 5% in one primary care site and from 37.8% to 2.7% in the other.

Table 24: Accuracy and precision of the quantitative POCT tests compared with a reference standard when tested both in the laboratory and at the point-of-care

	Laboratory		**Point-of-care**	
Device	**Measures of accuracy**	**Measures of precision**	**Measures of accuracy**	**Measures of precision**
QuikRead® 101 [20]	Regression equation: 0.98x +0.32 R^2: 0.977	Within day CV %: **8-25mg/L**: 6.1 (5.0-7.8) **25-100mg/L**: 2.4 (2.1-2.9) **>100 mg/L**: 1.7 (1.4-2.3) 20 **Overall**: 2.5 (2.1-2.8) Between day CV %: **62.9 mg/L**: 3.4% (2.3-6.4)	**<75mg/L**: -10% **>75 mg/L**: -20% Stated as approximate results	Within day CV %: Practice A: **8-25 mg/L**: 7.7 **25-100 mg/L**:1.3 **>100 mg/L:** 0.6 **Overall**:3.4 Practice B: **8-25 mg/L**: 5.9 **25-100 mg/L**:2.0 **>100 mg/L:** - **Overall**:2.8 Practice C:: **8-25 mg/L**: 11.5 **25-100 mg/L**:8.3 **>100 mg/L:** 3.0 **Overall**:6.0 Between day CV %: Practice A: **58.7 mg/L**: 2.5 (1.9-3.6) Practice B: **58.5 mg/L**: 2.6 (2.1-3.7)
Smart Eurolyser [23]	**Low** (1.8-27,4 mg/L): -4.4% (-7.4;-1.4) **Medium** (27.5-41.1 mg/L) 5.5% (2.9;8.2) **High** (41,7-280 mg/L):	Within day CV %: **Low**(1.8-27.4): 6.7% (5.4-8.9) **Medium**(27.5-	Primary Health Centre 1: **Low** (0.3-13.5mg/L): -11.2% (-14.7;-7.8) **High** (14.3-	Within day CV %: Primary Health Centre 1: **Low**(0.3-13.5mg/L): 8.3% (6.1;12.8)

	9.6% (5.6;13.5)	41.1): 4.1%(3.4-5.4) **High**(41.7-281): 3.3% (2.7-4.4) **Overall**: 4.9 (4.3-5.7). Between day CV%: **Low**(9.7mg/L): 7.9% **High**(75.5mg/L): 3.7%	148mg/L): -8.6%(-12.9;-4.3) **Overall:** -9.8% (-12.5;-6.9) Primary Health Centre 2: **Low** (**0.3-9.0mg/L): -** 17.0% (-24.0;-9.6) **High** (**9.7-109mg/L):** -4.8% (-9.9;0.3) **Overall:** -10.3%(-15.1;-5.6)	**High** (14.3-148mg/L): 6.7% (6.0-9,6) **Overall**: -9.8% (-12.5;-6.9) Primary Health Centre 2: **Low**(0.3-9.0mg/L): 15.4% (11.3;24.3) **High**(9.7-109mg/L): 8.6% (6.5-12.9) **Overall**:-12.1% (9.7;16.2) **Overall**: 8.0% (6.8;9.7) Between day CV%: Primary Care centre 1 **Low**(9.7mg/L): 23.1% **High**(74.5mg/L): 25.7% Primary Care Centre 2: **Low**(11.3mg/L): 25.4% **High**(79.1mg/L): 21.0%
iChroma™[22]	**Low** (0.0-13.5mg/L): 6.6% (2.8;10.4) **Medium** (13.5-56.4mg/L): 3.3% (1.0;7.6) **High** (56.6-264.6mg/L): -6.2% (-10.2;2.2) **Overall:** 0.4%(-2.2;2.9)[22]	Capillary samples within day CV %: **Low**: 4.5(3.5-6.6) **Medium**: 3.7 (3.0-4.8) **High**:4.9 (4.0-6.4) **All**: 4.3 (3.8-5.1) Venous samples within day CV%: **Low**: 4.8 (3.7-4.8) **Medium**: 2.9 (2.4-3.9) **High:** 4.3 (3.6-5.7) **All**: 3.9 (3.5-4.7)	NR	Within day CV %: 5.7 - 15.0 Between day CV%: Primary care centre 1: 24.1% Primary care centre 2:16.1%
ABX Micros 200 [21]	NR	Within day CV %: **<2mg/L**: 57.7 **2-25mg/L**: 3.9 **25-75mg/L**: 5.3 **75-100mg/L**: 1.4	**10-135mg/L**: -27.6% After 6 months use this decreased to -14.7% R^2: 0.81 to 0.98 for 4 practices	Within day CV %: Initial Results: **<2mg/L**: 53.4-103.6 **2-25mg/L**: 24.6-38.4 **25-75mg/L**: 0.1-3.1 **>75mg/L**: 0.7 Six month results: 1.4 - 5.0

Ease of Use

The ease of use of the C-reactive protein POCT devices was presented in some form in ten [16, 18, 20-23, 170, 172, 176, 177] of the 18 studies. Often this was a note in the discussion without reference to the use of a validated tool to objectively measure the ease of use. In a number of the studies the operator was a trained laboratory technician rather than a healthcare professional and therefore may have a different view on ease of use of equipment. Of the ten studies included in this section, only seven used a questionnaire or other tool to obtain the information [16, 18, 20-23, 177]. The information presented below is summarised in Table 25.

Ease of use recorded by laboratory personnel

Brouwer et al. compared six quantitative POCT devices (QuikRead go®, Smart Eurolyser, Afinion™, iChroma™, Microsemi) and two semi-quantitative methods to measure CRP. The authors carried out a practical evaluation of all of the POC devices in the laboratory setting evaluating the: minimum amount of material required, analytical range, pre-analytical handling of the samples and estimated pre-analytical time, if haematocrit (Ht) correction was required, size and weight of the analyser and the possibility of also measuring other analytes [16]. Details on pre-analytical handling time can be found in Table 25, other details on size, weight and analytical range of the devices can be found in Section 3, Table 7. The authors concluded that the Afinion™ device required the least pre-analytical handling. The Afinion™ and the Smart Eurolyser required less than a minute pre-analytical handling while the QuikRead go®, the iChroma™, the Actim® and Clearest® semi-quantitative strips required two to three minutes of pre-analytical handling. These six devices all use capillary blood samples. AQT90 Flex required no additional pre-analytical handling, but required a venous blood sample which is a disadvantage given the intended use of the equipment in the primary care setting. The Microsemi also required little pre-analytical handling but the size and weight of the device was noted as a possible issue. It was reported that a clear disadvantage of the semi-quantitative strips was the requirement that they be read after five minutes and that the results were time sensitive, which may be restrictive in a busy clinical environment. The upper CRP cut point used by the strips was 80 mg/L; this is not consistent with the cut point of 100 mg/L identified in a number of national and European guidelines. The authors concluded that when combining analytical performance and practical evaluation, the Afinion™ and the Smart Eurolyser were the preferred analysers for CRP POCT.

The practicality of a requirement to read the Actim® strip at exactly five minutes was also questioned by Evrand and colleagues, who assessed the performance of this device in the laboratory setting [172].

In the study by Clouth et al. [170], the authors used two point-of-care devices, the NycoCard™ and the Micros CRP. No questionnaire or survey was used, rather the authors provided a narrative account that both tests were rapid and easy to perform and required no specialist training. They also noted that both are useful for use in POCT in a range of settings including general practice.

Ease of use recorded by primary care personnel

Minnaard et al. compared five quantitative devices (Afinion™, NycoCard™ Reader II, Smart Eurolyser, QuikRead go® and QuikRead® 101) using a standardised questionnaire published by Geersing et al. to assess user friendliness [18, 184]. The questionnaire was completed by 20 GPs and GP assistants who were unfamiliar with point-of-care testing. Two main items were reported for user friendliness: the time required for analysis (including warm-up time of the device, pre-analytical handling, analysis time, blank measurement and time needed for calibration and/or internal quality control measurements) and susceptibility to flaws (blood application on test kit flaws, buffer application flaws, test kit placement in analyser flaws and loss of material flaws). Table 25 reports the pre-analytical handling time as reported by Minnaard et al. as well as the total time for assay with and without a warm-up period. For most devices the warm-up period is less than a minute and therefore adds little to the overall time; however, for the Afinion™ device it adds an additional four minutes to the assay time, which brings the total time to 8 minutes and 15 seconds. The warm-up time would not be a factor in every consultation and if not taken into account the total time required varies between 3 minutes and 20 seconds (QuikRead® 101) and 6 minutes and 50 seconds (NycoCard™ Reader II). In terms of susceptibility to flaws, Minnaard reported that the Afinion™ and the Smart Eurolyser were the least susceptible to flaws based on the opinion of 20 GPs and GP assistants. The Afinion™ was least susceptible to flaws in blood application, buffer application, placement in analyser and loss of material. The NycoCard™ Reader II scored poorly in each category, while QuikRead go® and QuikRead® 101 were moderate in overall liability to flaws. The Afinion™ and the Smart Eurolyser required the fewest separate actions minimising the chance of mistakes. The conclusion from this study was that four devices (not the Smart Eurolyser) showed adequate analytical performance and agreement and that Afinion™ and the Smart Eurolyser were the easiest to operate [18].

Verbakel et al. [177] evaluated the ease of use of the Afinion™ device by asking ten participating physicians who performed the CRP POCT to fill out a questionnaire, consisting of a five-point Likert scale to rate seven items (device start-up, handling of the capillary, filling of the capillary, placing the capillary in the cartridge, placing the test cartridge in the test device, duration of analysis and display of results). Median scores of 4 to 5 were obtained for each item evaluated, indicating that GPs found it very user friendly.

Seamark et al. [176] evaluated the QuikRead® device. The study was funded by an educational grant by the supplier of the QuikRead® system. Although no formal questionnaire or instrument was used to evaluate ease of use, the authors state that the QuikRead® system was quick and simple to use in a routine phlebotomy clinic and that the capillary blood method was acceptable to patients. They also commented on the time taken for the assay as being six and eight minutes in a real-life situation and that there were no device failures during the testing period.

SKUP (Scandinavian Evaluations of Laboratory Equipment for Primary Health Care) evaluations

SKUP carried out evaluations on four point-of-care devices (iChroma™, QuikRead® 101, Smart Eurolyser and ABX Micros systems) [20-23]. In each case, a questionnaire was used that asked the end user (either biomedical scientists or GPs) to evaluate the device based on a list of criteria within four domains: (i) the information provided by the user manual, (ii) the time factors in the

measurement and preparation of the test, (iii) the rating for the performance of the internal and external quality control and (iv) the rating of the operation facilities and how easy the system was to handle. Each area was graded as satisfactory, intermediate, or unsatisfactory.

The smart Eurolyser was evaluated in the primary care setting by two nurses and two biomedical scientists. The manual provided with the device, time factors and the operation of the device were rated as satisfactory by the four evaluators. However, all evaluators reported having difficulties with the control material, and although acceptable precision (CV <10%) was reported in the hospital laboratory evaluation, high levels of imprecision (CV >20%) were reported in the two primary health care centres. There were also three technical errors (out of 86 samples measured in duplicate) with the device reported during the evaluation.

For the iChroma™, two evaluators rated the user friendliness of the device. According to both of the evaluators the instrument is best suited for users with laboratory experience. The preparation of instrument and sample as well as the number of steps involved were rated as intermediate, suggesting that these steps were not as straightforward as they could be. No invalid tests were reported during the testing.

For the QuikRead® 101 device, three evaluators rated the device, one GP and two biomedical scientists in primary care centres. The overall assessment of the QuikRead® instrument was that it was relatively easy to operate, but requires training. Some of the evaluators commented that there may be problems with putting the lid on the cuvettes. The analysis time of two to four minutes was acceptable to biomedical scientists but the GP commented it may be too long.

The ABX micros system was assessed in primary care by a GP, a nurse and two biomedical scientists. The questionnaire for this assessment asked about the manufacturer's training, the manual, the instrument and ability to operate the instrument. The device received an above average rating for connections, reagent storage, waste disposal and operation of the device. The device scored well overall, scoring 3.8 out of 4.0. Maintenance of the device was set as one to two minutes per day and five to ten minutes per week. The authors stated that the ABX required a very long training time as pre-analytical errors probably contributed to bias and uncertainty in their analysis.

Table 25: Summary of the ease of use evidence for CRP POCT devices

Analyser	Pre-analytical handling time and (total time)[16] *	Pre-analytical handling time and (total time with warm up, without warm up)[18]	Overall handling time[176]	Overall Liability to flaws[18]	SKUP evaluation	Practical aspect of test[16]
Semi quantitative tests						

Analyser	Pre-analytical handling time and (total time)[16] *	Pre-analytical handling time and (total time with warm up, without warm up)[18]	Overall handling time[176]	Overall Liability to flaws[18]	SKUP evaluation	Practical aspect of test[16]
Actim®	2.5 min (7.5 min)					Relatively complex pre-analytical handling, cut off at 80 mg/L.
Cleartest®	2.5 min (7.5 min)					Relatively complex pre-analytical handling, cut of at 80 mg/L.
Quantitative tests						
QuikRead go®	2.5 min (4 min)	30 sec (4.83 min, 4 min)		Moderate		Relatively complex pre-analytical handling, issues with cap on cuvette.
Smart Eurolyser	45 sec (5.25 min)	50 sec (5.25 min, 5.17 min)		Small	Satisfactory in terms of the manual, time factors and the operation of the device. Unsatisfactory for the control materials.	No Ht correction, integrated capillary not always easy to fill with blood
Afinion	30 sec (4.25 min)	35 sec (8.25 min, 4.25 min)		Small		Not portable when on. Relatively often error codes due to small sample volume and sample drying out.
iChroma	2 min (5 min)				Better suited to users with laboratory experience as the preparation of the device and the number of steps involved rated as intermediate	Relatively complex pre-analytical handling. No Ht correction

Analyser	Pre-analytical handling time and (total time)[16] *	Pre-analytical handling time and (total time with warm up, without warm up)[18]	Overall handling time[176]	Overall Liability to flaws[18]	SKUP evaluation	Practical aspect of test[16]
Microsemi	30 sec (4.5 min)					CRP measurement only possible in combination with haematology parameters. Size of analyser may be issue as large and heavy.
AQT90 Flex	30 sec (13.5 min)					Needs venous blood sampling. Size of analyser may be issue as large and heavy.
NycoCard™ Reader II		3.33 min (7.25 min, 6.83 min)		Large		
QuikRead® 101		1.83 min (3.83 min, 3.33 min)	6 to 8 minutes in primary care setting	Moderate	Overall operation was satisfactory, but training was required. May be issue with cuvette lids. Biomedical scientists found timing acceptable but the GP thought it may be too long.	
ABX Micros					Score 3.8/4. However, may be issues with pre-analytical handling.	

Note: * The minutes and seconds listed by Brouwer et al. were recalculated into minutes.

5.15 Discussion

A total of 18 studies evaluated the analytical performance of two semi-quantitative POCT devices and 11 quantitative POCT devices. The literature regarding the analytical performance of quantitative and semi-quantitative point of care tests varied widely in terms of the study design, reported

results and the quality of evidence presented. Analytical performance was presented as a measure of accuracy and/or precision. Ten studies also include information on the ease of use of the device. There were three methodologies used in the included studies, with methods differing in the origin of the blood sample, the operator performing the test or the setting for the test (laboratory or primary care). All studies compared the CRP levels obtained when using a POCT device with those obtained using a standard laboratory technique; the most common methods of reporting accuracy were agreement from a Passing Bablok regression, correlation from a Pearson or Spearman correlation coefficient or a mean difference from Bland-Altman plots. The most common method of reporting precision was a coefficient of variation based on measuring samples a number of times in one day (within-day CV) or measuring samples a number of times over a number of days (between-day CV).

Analytical performance refers to the ability of a laboratory assay to conform to predefined technical specifications [185]. Studies noted that there are few international guidelines that specify analytical quality requirements for CRP POCT devices. Two of the studies identified in this systematic review reported on acceptable levels of accuracy from three Scandinavian quality improvement schemes [17, 23]. Accuracy criteria used by the Norwegian EQAS scheme were noted to be as follows: good if the CRP value was +/- 8% of the target value; poor if it exceeded +/- 15%; and adequate if it was between these two values [17]. The 2013 SKUP report [23] outlined the analytical performance requirements specified by a number of bodies including the National Danish Committee for General Practice Laboratory Testing. These criteria are based on consultation with GPs in Denmark who have highlighted that they want to be able to detect a CRP decrease from 40 mg/L to 20 mg/L and to be able to detect the difference between 35 mg/L and 50 mg/L. The Danish analytical quality goals for CRP POCT in primary care (CRP >15mg/L) are: bias ≤+/- 10% and imprecision (CV) ≤10%. In Sweden, the Equalis Expert group has recommended that a maximum deviation for a single result measured in whole blood should be within +/- 15% of hospital laboratory method (as measured by five agreeing hospitals) for CRP POCT used in primary care centres. SKUP themselves consider a deviation of +/- 1 mg/L or ≤+/- 26% (depending on the concentration range) acceptable for bias and a CV <10% for precision. Other studies specified criteria for accuracy as (r^2 > 0.95 and 95% confidence interval (CI) of the slope and intercept including 1.0 and 0.0, respectively). Correlation by itself is not generally recommended as a method for assessing comparability between methods and good correlation does not necessarily mean good agreement between methods particularly when two methods are being used to measure the same analyte [183]. These differences in the assessment of analytical performance as well as differences in the study methodology, makes direct comparison of the study data difficult.

The relevance of accuracy and precision of these devices in clinical decision-making can be seen by using the NICE guidelines for pneumonia as an example. These provide a recommendation that CRP POCT should be considered for patients with symptoms of LRTI in primary care if a diagnosis is unclear after clinical assessment, and that antibiotics should be prescribed based on the test result, that is, CRP <20 mg/L (no antibiotic required), a CRP ≥100 mg/L (immediate antibiotic prescription), and a CRP of 20–99 mg/L (consider a delayed antibiotic prescription These are broad concentration categories and it could be argued that we are only interested to know if the analytical performance using CRP POCT is sufficient to ensure that the categorisation of pa-

tient samples is consistent with what can be achieved with laboratory-grade testing. Therefore while some of the devices have poorer performance in the lower (<2 mg/L) or upper (>100 mg/L) CRP concentrations, this may not be clinically relevant for use of these devices for patients presenting with RTIs.

There were very few studies (n=2) that evaluated semi-quantitative devices, the agreement between the reference test and the POCT was found to be moderate to good with Kappa values of 0.53 to 0.93 for the Actim® test [16, 172] and moderate for the Cleartest® (Kappa values 0.56 to 0.61) [16]. The interobserver variation was lower for the Actim® test than the Cleartest® (Table 21). There was also evidence from one study that the test was time dependant and that accuracy decreased between reading the results at the optimal 5 minutes compared to 15 minutes [16]. The time-critical nature of these semi-quantitative tests may not be ideal in a busy clinic environment where it may be difficult to read a test at exactly five minutes. Both of the semi-quantitative tests were found to have complex pre-analytical handling and were difficult to interpret [16]. The main advantage of the strips was said to be the cost as no analyser was needed and the main disadvantages were the difficult pre-analytical handling, the accuracy, the time-critical nature of the strips and that the results are not automatically entered into the patient record. In addition, the semi-quantitative test included here (Actim® and Cleartest®) have an upper limit of 80mg/L and are therefore of limited use in terms of a number of current guidelines for managing LRTIs where a cut-point of 100 mg/L is recommended for antibiotic prescribing.

In the laboratory setting, the majority of the evidence suggested acceptable performance for all eleven quantitative devices. In comparison to a standard laboratory technique, the accuracy data showed that most devices had acceptable levels of accuracy except at the higher end of CRP concentration levels (CRP >100 mg/L). Although precision was also acceptable for most devices, CV values greater than 10% were reported in the laboratory setting in at least one study for the Smart Eurolyser, the NycoCard™ Reader II and the iChroma™devices. This suggests that under idealised circumstances most of the devices are accurate and precise.

When used at the point of care (that is, the primary care setting) the data available for accuracy and precision were far more variable. In terms of accuracy, the Afinion™ (n=2) and the iChroma™(n=1) devices both reported levels of bias <10%. Bias was variable or not available for the other devices. Very little data were available on precision in the primary care setting. Acceptable precision was reported for the QuikRead® 101 and the spinit® devices, while the Smart Eurolyser and the iChroma™ devices had inconsistent results. The lack of data at the point of care and the variable results makes it difficult to draw conclusions about the suitability of many of these devices for the primary care setting.

All data on the difference in analytical performance of the devices in the laboratory setting compared to the primary care setting came from four SKUP reports (D1007) [20-23]. Four devices were analysed. The Smart Eurolyser had acceptable accuracy and precision in the laboratory and at the POC, but it had better performance in the laboratory. The other devices (ABX Micros, iChroma™ and QuikRead®) had acceptable levels of precision and accuracy in the laboratory but unacceptable levels of either precision or accuracy in at least one primary care centre. Based on the SKUP data, it appears that all four devices had acceptable analytical performance in the laboratory setting, but performance was more variable and poorer at the point of care. This may

have been caused by the type of material used in the analysis (whole blood versus plasma), the method of blood extraction (capillary versus venous sample) or related to the skill, experience or training of the operator (non-laboratory trained personnel versus trained laboratory technician) or the level of training received by the operator. There was evidence that analytical performance varied between primary care sites and improved over time, suggesting that thorough and ongoing training is necessary when using CRP POCT devices in the primary care setting. The difference in analytical performance was larger for some devices than others.

Four of the studies provided a direct comparison of multiple devices either in the laboratory or point-of-care setting [16-19]. Minnaard et al. and Brouwer et al. compared multiple devices in the laboratory setting (Appendix 1, Table A8). The Afinion™ device was consistently found to be a preferred device based on analytical performance and ease of use both in the laboratory [16, 18] and at the point-of-care [17], Consistent evidence of acceptable analytical performance was also found for the QuikRead go®, and QuikRead® 101 devices both in the laboratory [16, 18] and at the POC [17] and for the NycoCard™ device [18, 19]. Evidence for the Smart Eurolyser device were conflicting with findings of unacceptably high imprecision [18] and that it was a preferred analyser [16]. The iChroma™ device was reported by Brouwer et al. to be the poorest in terms of accuracy and precision in the laboratory setting, while Bukve et al. reported the accuracy of the iChroma™ to be similar to the NycoCard™, but poorer than the Afinion™ or QuikRead® systems [16, 17].

Devices with less pre-analytical handling and that are designed in a way that they are less susceptible to flaws tend to be easier to use. Complex pre-analytical handling might introduce variation if the test is not performed on a regular basis, can lead to spills of biological materials, test errors and use of more than one set of consumables if the test fails [16]. The overall time taken for the test to be performed was an important factor, with times ranging from just over three minutes (QuikRead®) to over 13 mins (AQT90 Flex), but it is unclear from the literature what time period would be considered acceptable in the primary care setting. Two studies comparing multiple devices and reporting on ease of use found the Afinion™ and the Smart Eurolyser to be the easiest to use [16, 18].

On the basis of these findings, it would appear that most of the devices could be used in the primary care setting, but training would need to be put in place to ensure healthcare personnel who are likely to use the devices in practice are thoroughly trained. In addition, an external quality assurance scheme would need to be established to ensure adequate levels of accuracy and precision are being maintained over time. Bukve et al. presented the results of the Norwegian EQAS scheme from 2006 to 2015 and reported that: participating in the EQAS scheme more than once, performing internal quality control at least weekly, the type of instrument used, having laboratory-qualified personnel performing the tests and performing more than ten C-reactive protein tests per week were associated with good test performance. Core to a quality assurance scheme is the use of predefined levels for accuracy and precision so that those using CRP POCT in primary care can be assured that test results have an acceptable level of analytical performance.

One of the limitations of any study of this type is selecting a suitable reference test. All included studies used an established laboratory method in a hospital setting as their reference standard, and although some studies reported details of the accuracy and precision of the device used, many provided no information beyond the name of the instrument. SKUP reports used the aver-

age of more than one reference standard, which should provide a more reliable reference standard assuming the two methods are in agreement. In addition, the devices can be updated and improved and therefore some of the data included in this review may refer to the analytical performance of a device that has since been improved by the manufacturer on the basis of user feedback.

6 SAFETY (SAF)

6.1 Research questions

Element ID	Research question
Safety	
C0008	**How safe is the use of CRP POCT in guiding antibiotic prescribing in comparison with standard care?** Does the use of CRP POCT to guide antibiotic prescribing impact mortality in those presenting with symptoms of an acute RTI compared with standard care? How does CRP POCT to guide antibiotic prescribing affect the duration and severity of symptoms associated with an acute RTI compared with standard care? Does the use of C-reactive protein POCT to guide antibiotic prescribing impact reconsultation or hospitalisation rates in those presenting with symptoms of an acute RTI compared with standard care?
C0005	What are the susceptible patient groups that are more likely to be harmed through the use of CRP POCT to guide antibiotic prescribing for acute RTIs?
C0007	As the skin will be broken to remove a small amount blood, is there a risk of harm to staff from blood-borne contamination?
B0010	What kind of data/records and/or registry is needed to monitor the use of the technology and the comparator?

6.2 Results

Included studies

Effectiveness and safety of using CRP POCT to guide antibiotic prescribing in patients with acute respiratory infections in primary care settings

For the assessment of safety, all 12 studies identified for inclusion in systematic review 1 were considered. The main characteristics of individual studies as well as the risk of bias and the QoE of the studies retrieved can be found in the clinical effectiveness domain.

Patient safety

[C0008] – How safe is the use of CRP POCT in guiding antibiotic prescribing in comparison with standard care? This AE overlaps with D0011.

Does the use of CRP POCT to guide antibiotic prescribing impact mortality in those presenting with symptoms of an acute RTI compared with standard care?

None of the included RCTs or observational studies reported the death of a patient. Five of the included RCTs specifically stated that there were no deaths during the study period (n=7,165

patients, CRP test group n=3,696, usual care group n= 2,469) [127, 129, 130, 132, 135]. It is therefore unlikely that the use of CRP POCT will have any beneficial or detrimental effect on mortality. However, it should be noted that the follow-up period for these studies was short (max of 28 days) and most of the observational studies had no follow-up beyond the initial consultation.

Adverse drug reactions (ADR), including number of patients reconsulting or hospitalised due to ADR

This AE overlaps with D0011. There were no studies that reported specifically on reconsultations or hospitalisations due to an antibiotic-related ADR. Most papers that did report on hospitalisations or reconsultations did not state the reason for the hospitalisation. It is therefore conceivable that a number of the hospitalisations and reconsultations presented in the next section could have been due to ADRs, although it is noted that with the exception of anaphylactic reactions, antibiotics are generally not associated with serious ADRs.

Number of patients in need of hospitalisation

In the RCTs, five studies reported on hospitalisations during the follow-up period [127, 129, 130, 132, 135]. Three studies of these reported either no serious adverse events (defined as death or hospitalisation) [127, 129, 130] or patient recovery to some extent during the two-week follow-up period [127]. Two studies by Do et al. [132] and Little et al. [135] reported 14/1,775 and 30/4,264 hospitalisations, respectively. In the study by Do et al. there was no significant difference between the CRP POCT group and the control group (RR 0.73, 95% CI: 0.25–2.09), but in the case of the study by Little et al. there were significantly more hospitalisations in the CRP POCT group than the control group (RR 2.52, 95% CI: 1.13–5.65). However, the authors state that after controlling for all potential confounders this difference was no longer significant (OR 2.91, 95% CI: 0.96–8.85, p = 0.060). The reasons for hospitalisation were available for 15/30 patients and included cardiac problems (n=2), respiratory problems (n=8), generally unwell or pyrexia (n=2), gastrointestinal symptoms (n=2) and sinusitis (n=1). It is unclear whether these reasons are directly related to the RTI the patients presented with and the prescribing or non-prescribing of an antibiotic, or if the hospitalisations were due to unrelated problems.

[C0005] – What are the susceptible patient groups that are more likely to be harmed through the use of CRP POCT to guide antibiotic prescribing for acute RTIs?

No studies were retrieved in the systematic reviews that reported on patient groups that were more susceptible to harm from the use of CRP POCT.

[C0007] – As the skin will be broken to remove a small amount blood, is there a risk of harm to staff from blood-borne contamination?

No studies were retrieved in the systematic reviews that reported on harms to staff (or patients) from blood-borne contamination.

[B0010] – What kind of data/records and/or registry is needed to monitor the use of the technology and the comparator?

No studies were retrieved in the systematic reviews that reported on specific data records or registries that should be used to monitor use of CRP POCT.

6.3 Discussion

The reduction in antibiotic prescribing observed in Section 5 (Effectiveness domain) arising from the use of CRP POCT to inform antibiotic prescribing appears not to lead to an increase in mortality. For the majority of studies (five out of seven) there was no hospitalisations reported; two studies reported hospitalisations within the study period, but it was unclear if the events were directly related to the RTI or not. In the study by Do et al. there were a similar number of hospitalisations in both the CRP POCT group and in the usual care group, suggesting that CRP POCT had no influence on hospitalisations. The study by Little et al., on the other hand, had significantly more hospitalisations in the CRP POCT group than in the usual care arm. The authors investigated this finding further and state that after controlling for confounders the difference is no longer significant, but more studies are needed that specifically look at the effect of using CRP POCT on hospitalisation rates and to determine the main reasons for hospitalisation and if these are related to the under- or over-prescribing of antibiotics following a CRP POCT.

Our study shows similar results to other published systematic reviews in the area in terms of safety [24, 48, 139, 142], which concluded that use of CRP POCT to inform antibiotic prescribing in primary care for acute RTIs leads to a significant reduction in antibiotic prescribing without compromising patient safety.

It is noted, that the outcomes reported in the trials may not capture all safety concerns. While serious adverse events that result in substantial morbidity or mortality are rare, antibiotic-related adverse events are common and may impact short-term health-related quality of life. However, it is also recognised that changes in the incidence of rare serious suppurative complications of RTIs (e.g., peritonsillar abscess, empyema, and intracranial abscess) arising from a failure to provide timely antibiotic treatment cannot be evaluated precisely in clinical trials. These data are provided by large long term cohort studies which suggest that substantial reductions in antibiotic prescribing can be safely achieved, although caution may be required in subgroups at higher risk of pneumonia. (A0006)

7 CONCLUSION

Based on a systematic review of the clinical effectiveness and safety of CRP POCT in patients presenting with acute RTIs in primary care, we are moderately certain that its use leads to a significant reduction in the prescribing of antibiotics compared with usual care. Although some studies showed no significant difference, when combined, the pooled estimates suggest CRP POCT does have a significant effect on prescribing. We included both RCTs and observational studies in our review to ensure the review reflected the findings from a range of study types and not just clinical trials where GPs might be more motivated to follow the suggested algorithms and limit their antibiotic prescribing. This reduction in prescribing is achieved without compromising patient safety, with no evidence of an increase in hospitalisations or patient mortality. These findings are based on short-term data. It is not clear if the behavioural change is sustained over time or if the conditions in the trials (that is, ongoing use of CRP POCT to inform decision making) can be maintained. Further research is required to validate the efficacy and safety of CRP POCT in specific sub-populations such as children and in older adults (>65 years) and in different primary care settings (out-of-hours clinics and long-term care facilities) where the spectrum of patients presenting may differ. Given the very limited data regarding the effectiveness of CRP POCT by prescription type (immediate versus deferred), further research on this outcome would be useful, including data on the relative rates of redemption of these prescriptions. Further research is also required to investigate the impact of CRP POCT on patient referral for other diagnostic testing and to determine its long-term effectiveness to change prescribing behaviour.

Results from the systematic review of diagnostic test accuracy suggest that there is limited evidence for the use of CRP testing in acute sinusitis. Even if a suitable threshold could be established it is unclear based on current clinical guidelines what the aim of the test would be. In pharyngitis it is unclear if there is a difference in the mean CRP value of GAS compared with non-GAS infections. A cut-point of 35 mg/L CRP may be useful in discriminating bacterial from non-bacterial pharyngitis. One study suggests that at this threshold, CRP may be useful as part of a two-step clinical prediction rule in patients presenting with sore throats, for whom diagnosis is still inconclusive after clinical examination; however, this score system required further validation. In contrast, at a threshold of 6 mg/L, the use of CRP in combination with a clinical prediction rule to rule out GAS could lead to unnecessary prescribing of antibiotics. Patients with pneumonia may present with low levels of CRP, therefore use of CRP levels in isolation may lead to cases of pneumonia being missed. At a CRP cut-point of 20 mg/L, three out of four studies found the sensitivity to be <0.75, and considered it too low to use as a rule-out threshold for pneumonia, while most studies found a CRP cut-point of 50 or 100 mg/L to be sufficiently specific to use as a rule-in threshold for the diagnosis of pneumonia and prescribing of antibiotics. Two studies found that at a cut-point of 20 or 30 mg/L, the addition of CRP to a clinical prediction rule improved its performance compared with a rule based on signs and symptoms only. While the value of CRP testing in addition to clinical signs and symptoms for the diagnosis of pneumonia in primary care is unclear, it appears most useful in identifying a group of low-risk patients who do not require antibiotics or to aid primary care physicians in the management of patients for whom there is still diagnostic uncertainty (that is, those considered at intermediate risk) after the review of signs and symptoms. Further research is, however, required to validate clinical algorithms that incorporate CRP POCT for specific RTIs.

Limited data were identified to support the analytical performance of two semi-quantitative CRP POCT devices in primary care, both of which were found to have complicated pre-analytical handling and were difficult to interpret. The analytical performance of most of the CE marked quantitative CRP POCT devices evaluated in this assessment are acceptable under the ideal conditions found in a laboratory. Performance may be poorer at extreme levels, but this is unlikely to impact decision-making in primary care where the decision to prescribe or not prescribe an antibiotic applies to all values above or below a threshold. There is evidence of greater variability in performance when carried out by non-laboratory trained healthcare staff in primary care, with the variation most likely due to operator error. Devices that are easier to use may be associated with improved performance. To minimise risk of operator error contributing to poor analytical performance, adequate training is necessary to ensure devices are used correctly and appropriately along with the use of a quality assurance programme to ensure that test performance is maintained over time. Further research that directly compares the performance of different CRP POCT devices in their intended setting (primary care) is required as well as research on their ease of use in this setting (preferably collected using a validated survey) to inform decisions around preferred device(s).

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APPENDIX 1: METHODS AND DESCRIPTION OF THE EVIDENCE USED

DOCUMENTATION OF THE SEARCH STRATEGIES

Search strategy for systematic review 1

Medline OVID – Date of search 19/04/2018

51 34 and 50
50 or/35-49
49 exp Ciprofloxacin/
48 ciprofloxacin*.tw,nm.
47 quinolone*.tw,nm.
46 exp Quinolones/
45 tetracycline*.tw,nm.
44 exp Tetracyclines/
43 amoxacillin*.tw,nm.
42 (amoxicillin* or amoxycillin*).tw,nm.
41 exp Amoxicillin/
40 macrolide*.tw,nm.
39 exp Macrolides/
38 penicillin*.tw.
37 exp Penicillins/
36 antibiotic*.tw.
35 exp Anti-Bacterial Agents/
34 18 and 33
33 or/19-22
22 (c reactive protein or c-reactive protein or C-reactive protein).tw,nm.
21 c-reactive protein/
20 (("point of care" or "point-of-care" or "near patient" or poc or rapid or bedside) adj5 (test* or analys* or immunoassay* or technique* or immunofluorescence or "fluorescent antibody")).tw.
19 Point-of-Care Systems/
18 or/1-17
17 ((acute or exacerbation*) adj3 (copd or coad or chronic obstructive pulmonary disease or chronic obstructive airway* disease or chronic obstructive lung disease)).tw.
16 Pulmonary Disease, Chronic Obstructive/
15 croup.tw.
14 (severe acute respiratory syndrome or sars).tw.
13 (influenza* or flu or ili).tw.
12 ((acute or viral or bacter*) adj2 rhinit*).tw.
11 (common cold* or coryza).tw.
10 (sinusit* or rhinosinusit* or nasosinusit*).tw.
9 (nasopharyngit* or rhinopharyngit*).tw.
8 (pharyngit* or laryngit* or tonsillit* or sore throat* or cough*).tw.
7 (bronchit* or bronchiolit*).tw.
6 (otitis media or aom).tw.
5 exp otitis media/

4 (pneumon* or bronchopneumon* or pleuropneumon*).tw.
3 (ari or urti or lrti).tw.
2 (respiratory* adj3 (inflam* or infect*)).tw.
1 exp Respiratory tract infections/

EMBASE Date of search: 19/04/2018

#35#30 NOT #34
#34#31 NOT #33
#33#31 AND #32
#32'human'/de
#31'animal'/de OR 'animal experiment'/de OR 'nonhuman'/de
#30#20 AND #24 AND #28
#29#25 OR #26 OR #27 OR #27
#28penicillin*:ab,ti OR macrolide*:ab,ti OR amoxicillin*:ab,ti OR amoxycillin*:ab,ti OR tetracycline*:ab,ti OR quinolone*:ab,ti OR ciprofloxacin*:ab,ti
#27'quinolone derivative'/exp OR 'ciprofloxacin'
#26antibiotic*:ab,ti
#25'antibiotic agent'/exp
#24#21 OR #22 OR #23
#23('c reactive protein':ab,ti OR 'c-reactive protein':ab,ti OR 'c reactive') AND protein:ab,ti
#22'c reactive protein'/de
#21(('point of care' OR 'point-of-care' OR 'near patient' OR poc OR rapid OR bedside) NEAR/5 (test* OR analys* OR immunoassay* OR technique* OR immunofluores* OR 'fluorescent antibody' OR 'florescent antibodies')):ab,ti
#20#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19
#19(((acute OR exacerbation*) NEAR/3 (copd OR coad OR 'chronic obstructive pulmonary disease' OR 'chronic obstructive airways disease' OR 'chronic obstructive lung disease')):ab,ti) OR aecb:ab,ti
#18'chronic obstructive lung disease'/de
#17croup:ab,ti
#16'severe acute respiratory syndrome':ab,ti OR sars:ab,ti
#15influenza*:ab,ti OR flu:ab,ti OR ili:ab,ti
#14((acute OR viral OR bacter*) NEAR/2 rhinit*):ab,ti
#13'common cold':ab,ti OR 'common colds':ab,ti OR coryza:ab,ti
#12rhinosinusit*:ab,ti OR nasosinusit*:ab,ti
#11nasopharyngit*:ab,ti OR rhinopharyngit*:ab,ti
#10'sore throat'/de
#9phary AND ngit*:ab,ti OR laryngit*:ab,ti OR tonsillit*:ab,ti OR 'sore throat':ab,ti OR 'sore throats':ab,ti OR cough
#8bronchit*:ab,ti OR bronchiolit*:ab,ti
#7'otitis media':ab,ti OR aom:ab,ti
#6'otitis media'/de OR 'acute otitis media'/exp
#5pneumon*:ab,ti OR bronchopneumon*:ab,ti OR pleuropneumon*:ab,ti
#4ari:ab,ti OR urti:ab,ti OR lrti:ab,ti
#3(respiratory NEAR/2 (infect* OR inflam*)):ab,ti
#2'respiratory tract inflammation'/exp

#1'respiratory tract infection'/exp

CINAHL via EBSCOHOST

S29 S18 AND S23 AND S28

S28 S24 or S25 OR S26 OR S27

S27 TI (penicillin* or macrolide* or amoxicillin* or amoxycillin* or amoxacillin* or tetracyclin* or quinolon* or ciprofloxacin*) OR AB (penicillin* or macrolide* or amoxicillin* or amoxycillin* or amoxacillin* or tetracyclin* or quinolon* or ciprofloxacin*)

S26 (MH "Antiinfective Agents, Quinolone+")

S25 TI antibiotic* OR AB antibiotic*

S24 (MH "Antibiotics+")

S23 S19 or S20 or S21 or S22

S22 TI ("c reactive protein" or c-reactive protein or C-reactive protein) OR AB ("c reactive protein" or c-reactive protein or C-reactive protein)

S21 (MH "C-Reactive Protein")

S20 TI (("point of care" or point-of-care or poc or "near patient" or rapid or bedside*) N5 (test* or analys* or immunoass* or technique*or immunofluores* or "fluorescent antibody")) OR AB (("point of care" or point-of-care or poc or "near patient" or rapid or bedside*) N5 (test* or analys* or immunoass* or technique* or immunofluores* or "fluorescent antibody"))

S19 (MH "Point-of-Care Testing")

S18 S1 or S2 or S3 or S4 or S5 or S6 or S7 or S8 or S9 or S10 or S11 or S12 or S13 or S14 or S15 or S16 or S17

S17 TI ((acute or exacerbation) N3 (copd or coad or chronic obstructive pulmonary disease or chronic obstructive airway* disease or chronic obstructive lung disease)) OR AB ((acute or exacerbation) N3 (copd or coad or chronic obstructive pulmonary disease or chronic obstructive airway* disease or chronic obstructive lung disease))

S16 (MH "Pulmonary Disease, Chronic Obstructive+")

S15 TI croup OR AB croup

S14 TI (severe acute respiratory syndrome or sars) OR AB (severe acute respiratory syndrome or sars)

S13 TI (influenza* or flu or ili) OR AB (influenza* or flu or ili)

S12 TI ((acute or viral or bacter*) N2 rhinit*) OR AB ((acute or viral or bacter*) N2 rhinit*)

S11 TI (common cold* or coryza) OR AB (common cold* or coryza)

S10 TI (sinusit* or rhinosinusit* or nasosinusit*) OR AB (sinusit* or rhinosinusit* or nasosinusit*)

S9 TI (nasopharyngit* or rhinopharyngit*) OR AB (nasopharyngit* or rhinopharyngit*)

S8 TI (pharyngit* or laryngit* or tonsillit* or sore throat* or cough*) OR AB (pharyngit* or laryngit* or tonsillit* or sore throat* or cough*)

S7 TI (otitis media or aom) OR AB (otitis media or aom)

S6 (MH "Otitis Media+")

S5 TI (bronchit* or bronchiolit*) OR AB (bronchit* or bronchiolit*)

S4 TI (pneumon* or bronchopneumon* or pleuropneumon*) OR AB (pneumon* or bronchopneumon* or pleuropneumon)

S3 TI (ari OR arti OR urti OR lrti) OR AB (ari OR arti OR urti OR lrti)

S2 TI (respiratory N3 (inflam* or infect*)) OR AB (respiratory N3 (inflam* or infect*))

S1 (MH "Respiratory Tract Infections+")

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#1 (respiratory* near/3 (inflam* or infect*))

#2 Respiratory Tract Infections
#3 (ari or urti or lrti)
#4 (pneumon* or bronchopneumon* or pleuropneumon*)
#5 Otitis media
#6 (otitis media or aom)
#7 (bronchit* or bronchiolit*)
#8 (pharyngit* or laryngit* or tonsillit* or sore throat* or cough*)
#9 (nasopharyngit* or rhinopharyngit*)
#10 (sinusit* or rhinosinusit* or nasosinusit*)
#11 (common cold* or coryza)
#12 ((acute or viral or bacter*) near/2 rhinit*)
#13 (influenza* or flu or ili)
#14 (severe acute respiratory syndrome or sars)
#15 croup
#16 Chronic Obstructive Pulmonary disease
#17 ((acute or exacerbation*) near/3 (copd or coad or chronic obstructive pulmonary disease or chronic obstructive airway* disease or chronic obstructive lung disease))
#18 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17
#19 Point-of-Care Systems
#20 (("point of care" or "point-of-care" or "near patient" or poc or rapid or bedside) near/5 (test* or analys* or immunoassay* or technique*or immunofluorescence or "fluorescent antibody"))
#21 C-Reactive Protein
#22 (c reactive protein or c-reactive protein or C-reactive protein)
#23 #19 or #20 or #21 or #22
#24 Anti-Bacterial Agents
#25 antibiotic*
#26 Penicillins
#27 penicillin*
#28 Macrolides
#29 macrolide*
#30 Amoxicillin
#31 (amoxicillin* or amoxycillin*)
#32 amoxacillin*
#33 Tetracyclines
#34 tetracycline*
#35 Quinolones
#36 quinolone*
#37 ciprofloxacin*
#38 ciprofloxacin
#39 #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37 or #38
#40 #18 and #23 and #39

Search strategy for systematic review 2

Embase search: Date of search: 17/05/18

No.	Query	Results
40.	#33 NOT #39	2,602
39.	#34 NOT #36	5,840,761
38.	#33 NOT #37	462
37.	#35 NOT #36	17,556,070
36.	#34 AND #35	1,732,020
35	'human'/de	19,288,090
34.	'animal'/de OR 'animal experiment'/de OR 'nonhuman'/de	7,572,781
33.	#32 AND [embase]/lim NOT ([embase]/lim AND [medline]/lim)	2,621
32.	#27 AND #31	6,193
31.	#28 OR #30	7,371,204
30.	'diagnostic accuracy' OR 'diagnostic test accuracy' OR 'dta'	292,693
29.	#27 AND #28	6,193
28.	sensitiv* OR detect* OR accura* OR specific* OR reliab*	7,366,875
27.	#20 AND #24	19,694
26.	#25 AND #24 AND #20	14,685
25.	sensitiv* OR detect* OR accura* OR specific* OR reliab* OR positive OR negative OR diagnos*	12,746,185
24.	#21 OR #22 OR #23	174,668
23.	crp:ab,ti	77,014
22.	('c reactive protein':ab,ti OR 'c-reactive protein':ab,ti OR 'c reactive') AND protein:ab,ti	86,282
21.	'c reactive protein'/de	142,108
20.	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19	1,098,229
19.	(((acute OR exacerbation*) NEAR/3 (copd OR coad OR 'chronic obstructive pulmonary disease' OR 'chronic obstructive airways disease' OR 'chronic obstructive lung disease')):ab,ti) OR aecb:ab,ti	11,916
18.	'chronic obstructive lung disease'/de	108,899
17.	croup:ab,ti	1,729
16.	'severe acute respiratory syndrome':ab,ti OR sars:ab,ti	9,484
15.	influenza*:ab,ti OR flu:ab,ti OR ili:ab,ti	134,361
14.	((acute OR viral OR bacter*) NEAR/2 rhinit*):ab,ti	361
13.	'common cold':ab,ti OR 'common colds':ab,ti OR coryza:ab,ti OR coryza:ab,ti	5,105
12.	rhinosinusit*:ab,ti OR nasosinusit*:ab,ti	9,318
11.	nasopharyngit*:ab,ti OR rhinopharyngit*:ab,ti	2,216
10.	'sore throat'/de	13,685
9.	pharyngit*:ab,ti OR laryngit*:ab,ti OR tonsillit*:ab,ti OR 'sore throat':ab,ti OR 'sore throats':ab,ti OR cough*	137,640
8.	bronchit*:ab,ti OR bronchiolit*:ab,ti	41,697
7.	'otitis media':ab,ti OR aom:ab,ti	26,302
6.	'otitis media'/de OR 'acute otitis media'/exp	26,423
5.	pneumon*:ab,ti OR bronchopneumon*:ab,ti OR pleuropneumon*:ab,ti	234,837

4.	ari:ab,ti OR urti:ab,ti OR lrti:ab,ti	6,126
3.	(respiratory NEAR/2 (infect* OR inflam*)):ab,ti	59,010
2.	'respiratory tract inflammation'/exp	485,474
1.	'respiratory tract infection'/exp	409,603

Cochrane library: Date of search: 17/05/18

ID	Search	Hits
1.	MeSH descriptor: [Pulmonary Disease, Chronic Obstructive] this term only	3395
2.	(copd or coad or "chronic obstructive pulmonary disease" or "chronic obstructive airway disease" or "chronic obstructive airways disease" or "chronic obstructive lung disease"):ti,ab,kw (Word variations have been searched)	14023
3.	#1 or #2	14211
4.	"severe acute respiratory syndrome" or sars	141
5.	croup	210
6.	influenza* or flu or ili	2283
7.	common cold* or coryza	2160
8.	sinusit* or rhinosinusit* or nasosinusit*	3035
9.	nasopharyngit* or rhinopharyngit*	2942
10.	pharyngit* or laryngit* or tonsillit* or sore throat* or cough*	13359
11.	bronchit* or bronchiolit*	4962
12.	otitis media or aom	2708
13.	MeSH descriptor: [Otitis Media] this term only	714
14.	pneumon* or bronchopneumon* or pleuropneumon*	15364
15.	ari or urti or lrti	6655
16.	MeSH descriptor: [Respiratory Tract Infections] explode all trees	11801
17.	#3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16	57737
18.	MeSH descriptor: [C-Reactive Protein] this term only	4259
19.	"c reactive protein" or "c-reactive protein" or "C-reactive protein" or CRP	14874
20.	#18 or #19	14874
21.	"Diagnostic test accuracy" or "diagnostic accuracy" or dta	10166
22.	MeSH descriptor: [Sensitivity and Specificity] this term only	12095
23.	predict* or diagnose* or diagnosi* or diagnosti* or accura*	237612
24.	#21 or #22 or #23	240077
25.	#24 and #20 and #17	680

CINAHL (via EBSCOhost): Date of search: 17/5/18

No.	Query	Results
S28	s27 and s22 and s19	611
S27	s23 or s24 or s26	1,077,841
S26	(MH "Sensitivity and Specificity")	70,314
S25	"predict* or diagnose* or diagnosi* or diagnosti* or accura*"	0
S24	predict* or diagnose* or diagnosi* or diagnosti* or accura*"	1,056,784

S23	"Diagnostic test accuracy" or "diagnostic accuracy" or dta"	8,815
S22	s20 or s21	18,378
S21	TI (“c reactive protein” or c-reactive protein or C-reactive protein) OR AB (“c reactive protein” or c-reactive protein or C-reactive protein)	12,993
S20	(MH “C-Reactive Protein”)	12,758
S19	S1 or S2 or S3 or S4 or S5 or S6 or S7 or S8 or S9 or S10 or S11 or S12 or S13 or S14 or S15 or S16 or S17	115,467
S18	TI ((acute or exacerbation) N3 (copd or coad or chronic obstructive pulmonary disease or chronic obstructive airway* disease or chronic obstructive lung disease)) OR AB ((acute or exacerbation) N3 (copd or coad or chronic obstructive pulmonary disease or chronic obstructive airway* disease or chronic obstructive lung disease))	1,980
S17	(MH “Pulmonary Disease, Chronic Obstructive+”)	15,507
S16	TI croup OR AB croup	384
S15	TI (severe acute respiratory syndrome or sars) OR AB (severe acute respiratory syndrome or sars)	1,412
S14	TI (severe acute respiratory syndrome or sars) OR AB (severe acute respiratory syndrome or sars)	2,550
S13	TI (influenza* or flu or ili) OR AB (influenza* or flu or ili)	21,505
S12	TI ((acute or viral or bacter*) N2 rhinit*) OR AB ((acute or viral or bacter*) N2 rhinit*)	50
S11	TI (common cold* or coryza) OR AB (common cold* or coryza)	997
S10	TI (sinusit* or rhinosinusit* or nasosinusit*) OR AB (sinusit* or rhinosinusit* or nasosinusit*)	3,663
S9	TI (nasopharyngit* or rhinopharyngit*) OR AB (nasopharyngit* or rhinopharyngit*)	220
S8	TI (pharyngit* or laryngit* or tonsillit* or sore throat* or cough*) OR AB (pharyngit* or laryngit* or tonsillit* or sore throat* or cough*)	11,162
S7	TI (otitis media or aom) OR AB (otitis media or aom)	3,582
S6	(MH “Otitis Media+”)	4,416
S5	TI (bronchit* or bronchiolit*) OR AB (bronchit* or bronchiolit*)	3,781
S4	TI (pneumon* or bronchopneumon* or pleuropneumon*) OR AB (pneumon* or bronchopneumon* or pleuropneumon)	25,341
S3	TI (ari or arti or urti or lrti) OR AB (ari or arti or urti or lrti)	1,310
S2	TI (respiratory N3 (inflam* or infect*)) OR AB (respiratory N3 (inflam* or infect*))	8,504
S1	(MH “Respiratory Tract Infections+”	62,810

Search strategy for systematic review 3

Embase: **Date of search: 14/06/2018**

No. Query

#23 AND ‘HUMAN’

#22 #10 AND #14 AND #21

#21 #15 OR #16 OR #17 OR #18 OR #19 OR #20

#20 ‘bedside’

#19 ‘near patient’

#18 ‘point of care system’

#17 ‘point of care testing’

#16 POC

#15 POCT

#14 #11 OR #12 OR #13

#13 ‘CRP’

#12 ‘c-reactive protein’

#11 ‘c reactive protein’

#10 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9

#9 ‘Quality control’

#8 ‘User friendliness’

#7 ‘Ease of use’

#6 Variability

#5 ‘coefficient of variation’

#4 Agreement

#3 Accuracy

#2 Precision

#1 ‘analytical performance’

EBSCO Host (Cinhal): Date of search: 14/06/2018

No. Query
#22 #10 AND #14 AND #21
#21 #15 OR #16 OR #17 OR #18 OR #19 OR #20

#20 'bedside'
#19 'near patient'
#18 'point of care system'
#17 'point of care testing'
#16 POC
#15 POCT
#14 #11 OR #12 OR #13
#13 'CRP'
#12 'c-reactive protein'
#11 'c reactive protein'
#10 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9
#9 'Quality control'
#8 'User friendliness'
#7 'Ease of use'
#6 Variability
#5 'coefficient of variation'
#4 Agreement
#3 Accuracy
#2 Precision
#1 'analytical performance'

PubMed: **Date of search: 14/06/2018**

No. Query
#22 #10 AND #14 AND #21
#21 #15 OR #16 OR #17 OR #18 OR #19 OR #20
#20 'bedside'
#19 'near patient'
#18 'point of care system'
#17 'point of care testing'
#16 POC
#15 POCT
#14 #11 OR #12 OR #13
#13 'CRP'
#12 'c-reactive protein'
#11 'c reactive protein'
#10 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9
#9 'Quality control'
#8 'User friendliness'
#7 'Ease of use'
#6 Variability
#5 'coefficient of variation'
#4 Agreement
#3 Accuracy
#2 Precision
#1 'analytical performance'

Cochrane Library: Date of search: 14/06/2018

No. Query

#22 #10 AND #14 AND #21

#21 #15 OR #16 OR #17 OR #18 OR #19 OR #20

#20 ‘bedside’

#19 ‘near patient’

#18 ‘point of care system’

#17 ‘point of care testing’

#16 POC

#15 POCT

#14 #11 OR #12 OR #13

#13 ‘CRP’

#12 ‘c-reactive protein’

#11 ‘c reactive protein’

#10 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9

#9 ‘Quality control’

#8 ‘User friendliness’

#7 ‘Ease of use’

#6 Variability

#5 ‘coefficient of variation’

#4 Agreement

#3 Accuracy

#2 Precision

#1 ‘analytical performance’

Table A1: Studies excluded at full-text review for systematic review 1

Reason for exclusion*		Study reference
1	Inappropriate patient group	De La Flor[186], Lemiengre 2018[187], Llor 2013[188], André 2005[189], Takemura 2005,[190] Van den Bruel 2016[50], Takemura 2005[191], Diar 2012[192], Verbakel 2016[193]
2.	Not set in primary care	Chauhan 2013[194], Gotta 2017[195], Fagan 2001[143], Gonzales 2011[144]
3.	Not CRP POCT	Atlas 2005[196], Christakis 2001[197], Llor 2017[198], Llor 2011[199], Hopstaken 2003[13]
4.	No relevant comparator	Lindstrom 2015[200], Muszyńska 2007[201], Neumark 2010[202], André 2004[203], Salwan 2015[204], Haldrup 2017[205], Schuijta 2018[206], Engstrom[207], Boonman De Winter 2016[208], Steurer 2011[209], Minnaard 2016[46], Yebyo 2016[210], Streit 2015[211], Hoffmann 2013[212], Davidson 2017[213]
5.	Inappropriate study design	Clinical laboratory news 2017[214], Schwartz 2017[215], Bjerrum 2010[216], Oppong 2013[217], Cals 2011[218]
6.	Study protocol	Altiner 2012[219]
7.	Conference abstract	Keitel 2016[220], Andreeva 2012 [221], Moreno 2014[222], Harmans 2015[223], Demir 2014[224], Herman 2015[225]
8.	Not original study	The Netherlands Organisation for Health Research and Development 2005[226], Andre 2008[227], Aabenhus 2016[228]
9.	Duplicate	Cals 2009[123], Diederichersen 2001[125], Strykowski 2015[126], Bjerrum 2005[122]
10.	Cannot extract outcome data	Llor 2013[229], Rebnord 2016[230], Bjerrum 2011[231], Rebnord 2017[232], Hughes 2016[53], Llor 2014,[233] Bjerrum 2006[234]

*****Studies may have been excluded for more than one reason. For studies with more than one reason for exclusion, the first reason identified is listed.

Table A2: Studies excluded at full-text review for systematic review 2

Reason for exclusion*		**Study reference**
1.	Not set in primary care	Almirall 2014[235], Chen 2006 [236], Elsammak 2006[237], Flanders 2004[238], Gan 2017[239], Garcia Vazquez[240], Higdon 2017[241], Hu 2010[242], Isaacman 2002[243], Kang 2009[244], Kaur 2013[245], Kerttula 1987[246], McCarthy 1978[247], Melbye 1992[248], Peng 2013[249], Poyrazoğlu 2003[250], Prat 2003[251], Principi 1986[252], Requejo 2003[253], Stolz 2006[254], Shapiro 2018[163], Self 2017
2.	Study irretrievable	Babu 1989[255], Hu 2003[256], Khomerki 1966[257], Udovicki 1980[258]
3.	Study outcomes not relevant	Broekhuizen 2012[259]

	to current systematic review	
4.	Inappropriate study design	Schaaf 2006[260], Searle-Barnes 2017[261], Tomas 2015[262]
5	Abstract only	Rautakorpi 2008[263]
6.	Duplicate	Hopstaken 2004[264]
7.	Inappropriate patient population	Bielsa 2014[265]
8.	Data irretrievable	Young 2003

*Studies may have been excluded for more than one reason. For studies with more than one reason for exclusion,only one reason is listed.

Table A3: Studies excluded at full-text review for systematic review 3

Reason for exclusion*		**Study reference**
1.	Inappropriate patient group	Davis and Bigelow 2001[266], Grisales et al 2016[267],Inaba et al 2015[268],Inaba et al 2016 [269]
2.	No outcome of interest	Albersen et al 2013[270], Albersen et al 2014[271], Bustinduy et al 2017[272], Demir et al 2014[224], Hopstaken et al 2012[273], Kotani et al 2014[274], Shapiro et al 2018[163]
3.	Inappropriate study design	Minnaard et al 2015[11], Rogers and Bayston 1991[275]
4.	Inappropriate setting	Esposito et al 2005[276],Fernandes et al 2016 [277], Hernandez-Bou et al 2017[278], Papaevangelou et al 2006[279]
5.	Conference abstract	Hofmans et al 2015[280], Kratochvila and Budina 2013[281], Minnaard et al 2015[282], Ono et al 2010[283], Scwanzar et al 2013[284], Van Aelst et a 2015al[285],Van Aelst et al 2015b [286], Venkatesh et al 2017[287]
6.	No sufficient translation	Rim et al 2016[167]

DESCRIPTION OF THE EVIDENCE USED

Table A4: Acute respiratory tract infections (RTIs) – definition and symptoms of conditions, burden of disease and natural course in the individual patient [288, 289]

Type of RTI	Definition	Symptoms and burden of disease	Natural course of illness
Upper Respiratory Tract Infections			
Common cold	The **common cold** is a viral infectious disease of the upper respiratory tract that is marked by inflammation of the mucous membranes of the nose, throat, eyes, and eustachian tubes and by a watery then purulent discharge and is caused by any of several viruses (such as a rhinovirus or an adenovirus). The condition is associated with more than 200 virus subtypes. The condition is rarely characterised by a discrete set of specific symptoms, with the illness varying according to individual and causative pathogen. Occasionally, there is spread to the lower respiratory tract.	Symptoms include: blocked or runny nose; sore throat; headaches; muscle aches; coughs; sneezing; a raised temperature; pressure in ears and face; loss of taste and smell; malaise. Most of the population experience at least one episode per year; these are usually self-limiting illnesses and resolve within a few days.	One and a half weeks[93]
Acute sore throat/pharyngitis	**Pharyngitis** is inflammation of the pharynx, also known as a sore throat, and can be caused by viral or bacterial illnesses.	Symptoms include: swollen tonsils; enlarged and tender lymph nodes (glands) in the neck; a painful, tender feeling at the back of the throat; discomfort when swallowing. 82% of cases resolve in 7 days, and pain is only reduced by 16 hours[290].	One week[93]
Acute tonsillitis	**Tonsillitis** is inflammation of the tonsils. The main symptom is a sore throat, and it can be caused by viral or bacterial illnesses – although most cases are viral. The viruses that cause tonsillitis include the flu virus, parainfluenza virus (which also causes laryngitis and croup), adenovirus, enterovirus and rhinovirus. Bacterial tonsillitis may be caused by a number of different bacteria, but is usually caused by group A streptococcus bacteria.	Symptoms include: red and swollen tonsils; pain when swallowing; high temperature (fever) over 38°C (100.4°F); coughing; headache; tiredness; pain in ears or neck; white pus-filled spots on the tonsils; and swollen lymph nodes (glands) in the neck. Illness comes on suddenly and gets worse during the first 3 days. Most cases are viral and resolve within a few days.	One week[93]

Type of RTI	Definition	Symptoms and burden of disease	Natural course of illness
Acute laryngitis	**Laryngitis** refers to inflammation of the larynx. This can lead to oedema of the true vocal folds, resulting in hoarseness. Laryngitis can be acute or chronic, infectious or non-infectious. Accompanying signs of infectious laryngitis include pain on swallowing foods or liquids, cough, fever, and respiratory distress. The most common variant is acute viral laryngitis, which is self-limiting and usually related to an upper respiratory infection such as the common cold. Bacterial laryngitis often caused by *Haemophilus influenza*, and can be life threatening. Other causes can include tuberculosis (TB), diphtheria, syphilis, and fungi.	Symptoms include: hoarse (croaky) voice; sometimes losing the ability to speak; sore throat, cough, difficulty swallowing, and fever. Most patients make a full recovery within three weeks without developing complications.	One to two weeks
Acute otitis media	**Acute otitis media** (AOM) is defined as an infection of the middle-ear space and is a common complication of viral respiratory illnesses. It is associated with rapid onset of signs and symptoms (<48 hours) of inflammation, such as otalgia, fever, irritability, anorexia, vomiting, and otorrhoea. Otoscopic findings include a yellow–red exudate behind the tympanic membrane (TM).	Symptoms include: severe earache (caused by the pressure of mucous on the eardrum); a high temperature (fever) of 38°C (100.4°F) or above; flu-like symptoms in children, such as vomiting and lethargy (a lack of energy); slight deafness. Most common in young children, with more than 75% of episodes occurring in children under 10 years of age. AOM resolves in 60% of cases in 24 hours without antibiotics[290] .	Four days[93]
Acute rhinosinusitis	**Acute sinusitis** (also commonly known as acute rhinosinusitis) is defined as symptomatic inflammation of the mucosal lining of the nasal cavity and paranasal sinuses for less than 4 weeks. This swelling of the sinuses is usually caused by either a viral or a bacterial infection.	Symptoms include: pain, swelling and tenderness around cheeks, eyes or forehead; a blocked nose; reduced sense of smell; green or yellow mucous from the nose; a sinus headache; a high temperature of 38C or above; toothache and/or bad breath. Most infections resolve in 14 days without treatment and antibiotics only offer marginal benefit after 7 days.[290]	Two and a half weeks[93]

Type of RTI	Definition	Symptoms and burden of disease	Natural course of illness
Lower Respiratory Tract Infections			
Acute bronchitis/cough	An acute illness, occurring in a patient without chronic lung disease, with symptoms including cough, which may or may not be productive and associated with other symptoms or clinical signs that suggest LRTI (sputum production, dyspnoea, wheeze or chest discomfort /pain) and no alternative explanation (e.g. sinusitis or asthma).	Symptoms include: Cough with sputum production, dyspnoea, wheeze or chest discomfort/pain.	Three weeks[93]
Influenza	An acute illness, usually with fever, together with the presence of one or more of headache, myalgia, cough or sore throat.	The illness can be categorised into uncomplicated or complicated influenza.[291] **Uncomplicated influenza**: Influenza presenting with fever, coryza, generalised symptoms (headache, malaise, myalgia, arthralgia) and sometimes gastrointestinal symptoms, but without any features of complicated influenza. Symptoms peak after two to three days and most patients begin to feel much better within five to eight days. **Complicated influenza**: Influenza requiring hospital admission and/or with symptoms and signs of lower respiratory tract infection (hypoxaemia, dyspnoea, lung infiltrate), central nervous system involvement and/or a significant exacerbation of an underlying medical condition. Immunocompromised patients and young children can experience prolonged durations of infection and/or greater viral burden, compared to other groups. Elderly patients may also develop pneumonia. While pregnant women are more likely to have complications if they become ill with influenza.	One week (if uncomplicated)

Community-acquired pneumonia (CAP)	Suspected CAP An acute illness with cough and at least one of new focal chest signs, fever >4 days or dyspnoea/tachypnoea, and without other obvious cause. Definite CAP As above, but supported by chest radiograph findings of lung shadowing that is likely to be new. In the elderly, the presence of chest radiograph shadowing accompanied by acute clinical illness (unspecified) without other obvious cause.	Symptoms include: cough (dry or with thick mucous that is yellow, green, brownish or blood-stained); difficulty breathing; tachycardia; fever; feeling generally unwell; sweating and shivering; loss of appetite; chest pain. Every year between 0.5% and 1% of adults in the UK will have community-acquired pneumonia. It is diagnosed in 5–12% of adults who present to GPs with symptoms of lower respiratory tract infection, and 22–42% of these are admitted to hospital, where the mortality rate is between 5% and 14%. Between 1.2% and 10% of adults admitted to hospital with community-acquired pneumonia are managed in an intensive care unit, and for these patients the risk of dying is more than 30%. More than half of pneumonia-related deaths occur in people older than 84 years.[42]	After starting treatment for community-acquired pneumonia, the symptoms of patients should steadily improve, although the rate of improvement will vary with the severity of the pneumonia, and most people can expect that by: • 1 week: fever should have resolved; • 4 weeks: chest pain and sputum production should have substantially reduced; • 6 weeks: cough and breathlessness should have substantially reduced; • 3 months: most symptoms should have resolved but fatigue may still be present; • 6 months: most people will feel back to normal.[42]
Acute exacerbation of COPD (AECOPD)	An event in the natural course of the disease (COPD) characterised by a worsening of the patient's baseline dyspnoea, cough and/or sputum beyond day-to-day variability sufficient to warrant a change in management. If chest radiograph shadowing, consistent with infection, is present the patient is considered to have CAP.[58]	On the day of onset, symptoms can increase sharply with symptoms of dyspnoea (64%), increased sputum volume (26%), sputum purulence (42%), colds (35%), wheeze (35%), sore throat (12%) and cough (20%).[87]	Recovery of Peak Expiratory Flow (PEF) was achieved in only 75.2% of exacerbations within 35 days, and 7.1% of exacerbations had still not returned to baseline after 91 days.[87]

Definitions extracted from: the 2011 European Respiratory Society (ERS) in collaboration with The European Society for Clinical Microbiology and Infectious Disease (ESCMID) Guidelines for the management of adult lower respiratory tract infections, the 2017 Public Health England Antibiotic Guidance for primary care on the management and treatment of common infections, 2017 Public Health England guidance on use of antiviral agents for the treatment and prophylaxis of seasonal influenza HSE Health A-Z and other resources (NHS choices, HSE A-Z and BMJ best practice guidance).

Guidelines for diagnosis and management

Table A5: Overview of guidelines

Name of society/organisation issuing guidance	Date of issue	Country/ies to which applicable	Summary of recommendation	Level of evidence (A,B,C)/ class of recommendation (I, IIa, IIb, III)
Upper Respiratory Tract Infections				
Common cold				
[93]	2008	UK	A no antibiotic prescribing strategy or a delayed antibiotic prescribing strategy should be agreed for patients with the common cold. Offer all patients advice about the usual natural history of the illness and average total illness length of one and a half weeks. Advice about managing symptoms including fever (particularly analgesics and antipyretics).	
Acute sore throat/ pharyngitis /tonsillitis				
European Society for Clinical Microbiology and Infectious Diseases (ESCMID) guideline for acute sore throats[292]	2012	Europe	The Centor clinical scoring system can help to identify those patients who have a higher likelihood of group A streptococcal infection. However, its utility in children appears lower than in adults because of the different clinical presentation of sore throat in the first years of life. Throat culture is not necessary for routine diagnosis of acute sore throat to detect group A *Streptococci*. If rapid antigen testing (RAT) is performed, throat culture is not necessary after a negative RAT for the diagnosis of group A streptococci in both children and adults. In patients with high likelihood of streptococcal infections (e.g. 3–4 Centor criteria) physicians can consider the use of RATs. In patients with lower likelihood of streptococcal infections (e.g. 0–2 Centor criteria) there is no need to routinely use RATs. It is not necessary to routinely use biomarkers in the assessment of acute sore throat. Clinical scoring systems and rapid tests can be helpful in targeting antibiotic use.	A-3 C-3 B-2 B-3 C-3 B-2

Name of society/organisation issuing guidance	Date of issue	Country/ies to which applicable	Summary of recommendation	Level of evidence (A,B,C)/ class of recommendation (I, IIa, IIb, III)
			Either ibuprofen or paracetamol are recommended for relief of acute sore throat symptoms. Use of corticosteroids in conjunction with antibiotic therapy is not routinely recommended for treatment of sore throat. It can however be considered in adult patients with more severe presentations, e.g. 3–4 Centor criteria. Zinc gluconate is not recommended for use in sore throat. There is inconsistent evidence of herbal treatments and acupuncture as treatments for sore throat. Sore throat should not be treated with antibiotics to prevent the development of rheumatic fever and acute glomerulonephritis in low-risk patients (e.g. patients with no previous history of rheumatic fever. The prevention of suppurative complications is not a specific indication for antibiotic therapy in sore throat. Clinicians do not need to treat most cases of acute sore throat to prevent quinsy, acute otitis media, cervical lymphadenitis, mastoiditis and acute sinusitis. Antibiotics should not be used in patients with less severe presentation of sore throat, e.g. 0–2 Centor criteria, to relieve symptoms. In patients with more severe presentations, e.g. 3–4 Centor criteria, physicians should consider discussion of the likely benefits with patients. Modest benefits of antibiotics, which have been observed in group A *b-haemolytic Streptococcus*-positive patients and patients with 3–4 Centor criteria, have to be weighed against side effects, the effect of antibiotics on the microbiota, increased antibacterial resistance, medicalization and costs. If antibiotics are indicated, penicillin V, twice or three times daily for 10 days, is recommended. There is not enough evidence that indicates shorter treatment length.	A-1 A-1 B-2 C-1 to C-3 A-1 A-1 A-3 A-1 A-1 A-1
Finnish Medical Society Duodecim, the Finnish Association for Central Practice, the Finnish Otolaryngological Society, Infectious Diseases Society of Finland and the Clinical Microbiologists Society: Current care guide-	2012	Finland	Sore throat (pharyngitis) is typically a viral infection. Patients should be informed that pharyngitis is usually a mild, self-healing disease. Throat swab is recommended for adults with two or more symptoms: fever over 38°C, swollen submandibular lymph nodes, tonsillar exudate and no cough. Children under 15 years of age with any of these symptoms should be tested. If antibiotic is indicated, penicillin is the preferred choice, whereas first generation cephalosporins are recommended for those with penicillin allergy. Antibiotics can be started for	

Name of society/organisation issuing guidance	Date of issue	Country/ies to which applicable	Summary of recommendation	Level of evidence (A,B,C)/ class of recommendation (I, IIa, IIb, III)
lines for sore throat			patients with high fever before culture results are available. Adequate pain medication is important. **http://www.kaypahoito.fi/web/english/guidelineabstracts/guideline?id=ccs00095**	
Diagnostics and non-surgical management of tonsillitis (2016)[107]	2016	Germany	**Diagnosis** To estimate the probability of tonsillitis caused by β-haemolytic Streptococci, a diagnostic scoring system according to Centor or McIsaac is suggested. If therapy is considered, a positive score of ≥3 should lead to pharyngeal swab or rapid test or culture in order to identify β-haemolytic streptococci. Routinely performed blood tests for acute tonsillitis are not indicated. After acute streptococcal tonsillitis, there is no need to repeat a pharyngeal swab or any other routine blood tests, urine examinations or cardiological diagnostics such as ECG. The determination of the antistreptolysin O-titer (ASLO titer) and other antistreptococcal antibody titers do not have any value in relation to acute tonsillitis with or without pharyngitis and should not be performed. **Management** First-line therapy of β-hemolytic streptococci consists of oral penicillin. Instead of phenoxymethylpenicillin–potassium (penicillin V potassium), also phenoxymethlpenicillin–benzathine with a clearly longer half-life can be used. Oral intake for 7 days of one of both the drugs is recommended. Alternative treatment with oral cephalosporins (e.g. cefadroxil, cefalexin) is indicated only in cases of penicillin failure, frequent recurrences, and whenever a more reliable eradication of β-hemolytic streptococci is desirable. In cases of allergy or incompatibility of penicillin, cephalosporins or macrolides (e.g. Erythromycin-estolate) are valuable alternatives.	
German Society of General Practice and Family Medicine guidelines for the management of sore throat [106]	2011	Germany	**Management** Routine antibiotic treatment of sore throat for the prevention of complications is currently not indicated. The effect of antibiotics on symptoms and duration of disease is, at best, moderate. It is more pronounced in patients with typical clinical symptoms and signs of pharyngitis caused by group A *Streptococc*i (GAS) and slightly more pronounced again in cases of additional positive throat swab for GAS. An algorithm for decision-making is proposed. Rapid testing for strep-	

Name of society/organisation issuing guidance	Date of issue	Country/ies to which applicable	Summary of recommendation	Level of evidence (A,B,C)/ class of recommendation (I, IIa, IIb, III)
			tococcal antigen or a culture for GAS is only recommended if the result is likely to influence therapeutic decision-making. Patients with more severe illness and signs of GAS pharyngitis can be given antibiotic therapy for symptomatic relief.	
HAS guidelines for acute naso-pharyngitis and strep throat in children and adults	2017	France	No antibiotics in adults with: an acute nasopharyngitis; an acute strep throat with a McIsaac score < 2 or with a McIsaac score ≥ 2 and a negative rapid diagnostic test (RDT). In case of acute strep throat with a McIsaac score ≥ 2 and a positive RDT: amoxicillin, 2g per day for 6 days. https://www.has-sante.fr/portail/upload/docs/application/pdf/2017-05/dir82/memo_sheet_-_acute_nasopharyngitis_and_acute_strep_throat_in_adults.pdf No antibiotics in a child with: an acute nasopharyngitis; under the age of 3 years with an acute strep throat ≥3 years with an acute strep throat with a negative RDT. In a child ≥3 years with an acute strep throat and a positive RDT amoxicillin, 50mg/kg/days for 6 days. https://www.has-sante.fr/portail/upload/docs/application/pdf/2017-05/dir82/memo_sheet_-_acute_nasopharyngitis_and_acute_strep_throat_in_children.pdf	
ISKRA guidelines on sore throat: diagnostic and therapeutic approach [104]	2009	Croatia	For streptococcal sore throat diagnostics, the Working Group recommends evaluation of clinical presentation according to Centor criteria and for patients with Centor score 0-1, antibiotic therapy is not recommended nor bacteriological testing, while for patients with Centor score 2-4 bacteriological testing is recommended (rapid test or culture) as well as antibiotic therapy in case of positive result. The drug of choice for the treatment of streptococcal tonsillopharyngitis is oral penicillin taken for ten days (penicillin V) or in case of poor patient compliance benzathine penicillin G can be administered parenterally in a single dose. Other antibiotics (macrolides, clindamycin, cephalosporins, co-amoxiclav) are adminis-	

Name of society/organisation issuing guidance	Date of issue	Country/ies to which applicable	Summary of recommendation	Level of evidence (A,B,C)/ class of recommendation (I, IIa, IIb, III)
			tered only in case of hypersensitivity to penicillin or in recurrent infections. Tonsillectomy is a widely accepted surgical procedure that decreases the number of sore throats in children and should be performed only if indications for this procedure are established. Absolute indications include five or more streptococcal infections per year, tonsillitis complications, permanent respiratory tract obstruction, obstructive sleep apnoea syndrome and suspected tonsillar malignancy. Relative indications include chronic tonsillitis and occlusion disturbances.	
National Institute of Health Guidelines: Management of acute pharyngitis in Children	2012	Italy	None of the available scoring systems are sufficiently accurate to identify group A β-hemolytic *Streptococci* (GABHS) pharyngitis in settings with low prevalence for rheumatic disease. RADT should be performed by trained personnel in every child with a history and signs/symptoms suggestive of GABHS pharyngitis. RADT is not recommended in children with a McIsaac score of 0 or 1 with ≥2 signs/symptoms suggestive of viral infection. Backup culture in children with negative RADT result is not recommended. Culture test with antibiotic susceptibility assay should be performed exclusively for epidemiologic purposes. Streptococcal antibody titers are of no value in diagnosing acute pharyngitis. Antibiotic therapy is recommended in microbiologically documented GABHS pharyngitis. Because penicillin V is not available in Italy, amoxicillin (50 mg/kg/d in 2–3 doses orally) for 10 days is the first choice of treatment. In noncompliant cases, benzathine penicillin may be administered. Although not routinely recommended due to the high cost and wide spectrum of activity, a 5-day course with a second-generation cephalosporin may be used in noncompliant cases. Macrolides should be limited to children with demonstrated type I hypersensitivity to penicillin. Ibuprofen or paracetamol is recommended for relief of pain or fever associated with discomfort. Because the carrier state is not associated with increased risk of suppurative complications and risk of GABHS transmission to contacts is minimal, the carrier state should never be investigated and treated.	
NICE: Sore throat (acute): antimicrobial prescribing(2018)[93, 164]	2018	UK	Use FeverPAIN or Centor criteria to identify people who are more likely to benefit from an antibiotic **People who are unlikely to benefit from an antibiotic (FeverPAIN score of 0 or 1, or Centor score of 0, 1 or 2)** : Do not offer an antibiotic prescription.	

Name of society/organisation issuing guidance	Date of issue	Country/ies to which applicable	Summary of recommendation	Level of evidence (A,B,C)/ class of recommendation (I, IIa, IIb, III)
			People who may be more likely to benefit from an antibiotic (FeverPAIN score of 2 or 3): Consider no antibiotic prescription or a back-up antibiotic prescription taking account of: evidence that antibiotics make little difference to how long symptoms last (on average, they shorten symptoms by about 16 hours); evidence that most people feel better after 1 week, with or without antibiotics; the unlikely event of complications if antibiotics are withheld; possible adverse effects, particularly diarrhoea and nausea. When a back-up antibiotic prescription is given, give advice about: an antibiotic not being needed immediately; using the back-up prescription if symptoms do not start to improve within 3 to 5 days or if they worsen rapidly or significantly at any time; seeking medical help if symptoms worsen rapidly or significantly or the person becomes systemically very unwell. **People who are most likely to benefit from an antibiotic (FeverPAIN score of 4 or 5, or Centor score of 3 or 4):** Consider an immediate antibiotic prescription or a back-up antibiotic prescription with advice taking account of: the unlikely event of complications if antibiotics are withheld; possible adverse effects, particularly diarrhoea and nausea. **People who are systemically very unwell, have symptoms and signs of a more serious illness or condition, or are at high-risk of complications:** Offer an immediate antibiotic prescription with advice or further appropriate investigation and management. Refer people to hospital if they have acute sore throat associated with any of the following: a severe systemic infection; severe suppurative complications (such as quinsy [peri-tonsillar abscess] or cellulitis, parapharyngeal abscess or retropharyngeal abscess or Lemierre syndrome). Give advice about seeking medical help if symptoms worsen rapidly or significantly, do not start to improve after 1 week, or the person becomes systemically very unwell. Self-help: All people with acute sore throat: Consider paracetamol for pain or fever, or if preferred and suitable, ibuprofen; advise about the adequate intake of fluids; explain that some adults may wish to try medicated lozenges containing either a local anaesthetic, a non-steroidal anti-inflammatory drug (NSAID) or	

Name of society/organisation issuing guidance	Date of issue	Country/ies to which applicable	Summary of recommendation	Level of evidence (A,B,C)/ class of recommendation (I, IIa, IIb, III)
			an antiseptic. However, they may only help to reduce pain by a small amount; be aware that no evidence was found on non-medicated lozenges, mouthwashes, or local anaesthetic mouth spray used on its own. Reassess at any time if symptoms worsen rapidly or significantly, taking account of: other possible diagnoses; any symptoms or signs suggesting a more serious illness or condition; previous antibiotic use, which may lead to resistant organisms. First line antibiotic treatment: phenoxymethylpenicillin (dose age-dependent) two or four times a day for 5 to 10 days. .	
Acute otitis media (AOM)				
Finnish Medical Society Duodecim, the Finnish association of otorhinolaryngology and head and neck surgery, the Finnish Paediatric Society, the Finnish Otolaryngological Society and the Finnish Association for General Practice: Current care guideline for acute otitis media	2017	Finland	The diagnosis of acute otitis media is based on the presence of middle-ear effusion, signs of inflammation of the tympanic membrane, and signs and symptoms of an acute infection. Effective treatment of ear pain is crucial in the management of the disease. Antibiotic treatment for 5–7 days with amoxicillin or amoxicillin/clavulanate is recommended as a rule, because antibiotics shorten the time to resolution of illness, and no individually applicable criteria to guide antibiotic use are available. The follow-up of children with acute otitis media should be tailored individually. http://www.kaypahoito.fi/web/english/guidelineabstracts/guideline?id=ccs00071	
NICE Otitis media (acute: antimicrobial prescribing) [93] https://www.nice.org.uk/guidance/ng91/evidence/evidence-review-pdf-4787286589	2018	UK	Patients should be given advice that: acute otitis media is a self-limiting infection that mainly affects children; acute otitis media can be caused by viruses and bacteria, and it is difficult to distinguish between these (both are often present at the same time); symptoms last for about 3 days, but can last for up to 1 week; most children and young people get better within 3 days without antibiotics. Offer regular pain-relief at right dose, time; use maximum dose for severe pain. **Consider no antibiotic prescription or a back-up antibiotic prescription**, taking account of: evidence that antibiotics make little difference to symptoms (no improvement in pain at 24 hours, and after that the number of children im-	

Name of society/organisation issuing guidance	Date of issue	Country/ies to which applicable	Summary of recommendation	Level of evidence (A,B,C)/ class of recommendation (I, IIa, IIb, III)
			proving is similar to the number with adverse effects); evidence that antibiotics make little difference to the development of common complications (such as short-term hearing loss [measured by tympanometry], perforated eardrum or recurrent infection); evidence that acute complications such as mastoiditis are rare with or without antibiotics; possible adverse effects of antibiotics, particularly diarrhoea and nausea. **Children and young people who may be more likely to benefit from antibiotics** (those of any age with otorrhoea or those under 2 years with infection in both ears): Consider no antibiotic or a back-up antibiotic prescription with advice to commence the back-up prescription (if provided) or to seek medical help if symptoms worsen rapidly or significantly, do not start to improve after 3 days, or if becomes systemically very unwell) **Children and young people who are systemically very unwell, have symptoms and signs of a more serious illness or condition, or are at high-risk of complications**: Offer an immediate antibiotic prescription with advice or further appropriate investigation and management. Refer children and young people to hospital if they have acute otitis media associated with: a severe systemic infection; acute complications, including mastoiditis, meningitis, intracranial abscess, sinus thrombosis or facial nerve paralysis. First choice antibiotic (<18 years): Amoxicillin 3 times daily for 5 to 7 days. Antibiotic compared with placebo (children): Pain reduction at 2-3 days RR: 0.7, 95%CI: 0.58-0.86; NNT=24 [95%CI: 15-70])), at 4-7 days (RR 076 [0.63-0.91], NNT= 16 [95% CI: 10-44]. Abnormal tympanometry: RR 0.82, 95% CI 0.74 to 0.90; NNT 12 [95% CI 8 to 21]; Tympanic membrane perforation: RR 0.37, 95% CI 0.18 to 0.76; NNT 33 [95% CI 20 to 100] NNT to prevent mastoiditis = 4,831	

Name of society/organisation issuing guidance	Date of issue	Country/ies to which applicable	Summary of recommendation	Level of evidence (A,B,C)/ class of recommendation (I, IIa, IIb, III)
			NNH (vomiting, diarrhoea, rash) =13 (95%CI: 5-19).	
HAS guidelines for purulent acute otitis media in children (> 3 months) and adults	2017	France	Adults: In a case of purulent acute otitis media confirmed by visualisation of the tympanic membranes: amoxicillin: 3 g/day for 5 days. If conjunctivitis-otitis syndrome (*Haemophilus influenzae*): amoxicillin-clavulanic acid, 3 g/day, for 5 days. https://www.has-sante.fr/portail/upload/docs/application/pdf/2017-05/dir82/memo_sheet_-_purulent_acute_otitis_media_in_adults.pdf Children: In case of congestive or seromucinous acute otitis media: no antibiotics If purulent acute otitis media: Children <2 years: amoxicillin 80-90mg/kg/day for 8-10 days. If conjunctivitis-otitis syndrome (*Haemophilus influenzae*): amoxicillin-clavulanic acid, 80mg/kg/day, for 8-10 days https://www.has-sante.fr/portail/upload/docs/application/pdf/2017-05/dir82/memo_sheet_-_purulent_acute_otitis_media_in_adults.pdf Children >2 years with mild symptoms: no antibiotics Children > 2 years with severe symptoms: 80-90mg/kg/day for 5days. If conjunctivitis-otitis syndrome (*Haemophilus influenzae*): amoxicillin-clavulanic acid, 80mg/kg/day, for 8-10 days https://www.has-sante.fr/portail/upload/docs/application/pdf/2017-05/dir82/memo_sheet_-_purulent_acute_otitis_media_in_children_over_3_months.pdf	
Acute rhinosinusitis				
Current Care Guidelines/Finnish Medical Society Duodecim: Current care guidelines for sinusitis	2018	Finland	Patients with common cold have often symptoms similar to sinusitis. Mild or moderate symptoms often resolve in time, but symptomatic treatment (e.g. analgesics, decongestants) may be used. If the patient has severe pain (unilateral), purulent excretion in nose and/or pharynx, pain radiating to teeth or fever, bacterial sinusitis should be suspected. Diagnosis is based on clinical findings. Symptomatic treatment is recommended for patients with mild or moderate symptoms. Those with purulent excretion may benefit from antibiotics. First line treatment for	

Name of society/organisation issuing guidance	Date of issue	Country/ies to which applicable	Summary of recommendation	Level of evidence (A,B,C)/ class of recommendation (I, IIa, IIb, III)
			patients with chronic or recurrent sinusitis is conservative. http://www.kaypahoito.fi/web/english/guidelineabstracts/guideline?id=ccs00022	
HAS guidelines for sinusitis	2016	France	In case of maxillary sinusitis: • acute purulent, uncomplicated with suspected bacterial infection with at least 2 of the following 3 criteria: persistent or increased infraorbital sinus pain despite a prescribed symptomatic treatment for at least 48 hours; unilateral nature of pain and/or its increase when the head is tilted forward, and/or its pulsating nature and/or its peak in late afternoon and at night; increased rhinorrhoea and continued purulence. These signs are all the more significant because they are unilateral; amoxicillin, 3 g/day, for 7 days. • unilateral maxillary sinusitis associated with an obvious dental infection of the upper dental arch: amoxicillin clavulanic acid, 3 g/day, for 7 days. In case of frontal, ethmoid, sphenoid sinusitis: amoxicillin-clavulanic acid, 3 g/day, for 7 days.	
AWMF Association of Scientific Medical Societies	2017	Germany	***Not in English***	
NHG Dutch College of General Practitioners	2014	Netherlands	***Not in English***	
NICE sinusitis (acute) (2017)[98]	2017	UK	***People presenting with symptoms for around 10 days or less*** Do not offer an antibiotic prescription. Give advice about: • the usual course of acute sinusitis (2 to 3 weeks) • an antibiotic not being needed • managing symptoms, including fever, with self-care (see the recommendations on self-care) • seeking medical help if symptoms worsen rapidly or significantly, do not improve after 3 weeks, or they become systemically very	

Name of society/organisation issuing guidance	Date of issue	Country/ies to which applicable	Summary of recommendation	Level of evidence (A,B,C)/ class of recommendation (I, IIa, IIb, III)
			unwell. Reassess if symptoms worsen rapidly or significantly, taking account of: • alternative diagnoses such as a dental infection • any symptoms or signs suggesting a more serious illness or condition. ***People presenting with symptoms for around 10 days or more with no improvement*** Consider prescribing a high-dose nasal corticosteroid[1] for 14 days for adults and children aged 12 years and over, being aware that nasal corticosteroids: • may improve symptoms but are not likely to affect how long they last • could cause systemic effects, particularly in people already taking another corticosteroid • may be difficult for people to use correctly. Consider no antibiotic prescription or a back-up antibiotic prescription (see the recommendations on choice of antibiotic), taking account of: • evidence that antibiotics make little difference to how long symptoms last, or the proportion of people with improved symptoms • withholding antibiotics is unlikely to lead to complications • possible adverse effects, particularly diarrhoea and nausea • factors that might make a bacterial cause more likely (see symptoms and signs). When a back-up antibiotic prescription is given, give verbal and written advice about: • managing symptoms, including fever, with self-care (see the recommendations on self-care) • an antibiotic not being needed immediately • using the back-up prescription if symptoms do not improve within 7 days	

Name of society/organisation issuing guidance	Date of issue	Country/ies to which applicable	Summary of recommendation	Level of evidence (A,B,C)/ class of recommendation (I, IIa, IIb, III)
			or if they worsen rapidly or significantly at any time • seeking medical help if symptoms worsen rapidly or significantly despite taking the antibiotic, or the antibiotic has been stopped because it was not tolerated. ***People presenting at any time who are systemically very unwell, have symptoms and signs of a more serious illness or condition, or are at high risk of complications*** Offer an immediate antibiotic prescription (see the recommendations on choice of antibiotic) or further appropriate investigation and management in line with the NICE guideline on respiratory tract infections (self-limiting): prescribing antibiotics. Refer people to hospital if they have symptoms and signs of acute sinusitis associated with any of the following: • a severe systemic infection (see the NICE guideline on sepsis) • intraorbital or periorbital complications, including periorbital oedema or cellulitis, a displaced eyeball, double vision, ophthalmoplegia, or newly reduced visual acuity • intracranial complications, including swelling over the frontal bone, symptoms or signs of meningitis, severe frontal headache, or focal neurological signs.	
Lower Respiratory Tract Infections				
Acute bronchitis/cough				
The Dutch College of General Practitioners (NHG) guideline for acute cough (2011)[111]	2011	Netherlands	The guideline covers the diagnosis, treatment, and education of patients with cough, pneumonia, bronchiolitis, croup, whooping cough, and Q-fever. Acute cough is defined as cough lasting less than 3 weeks at presentation. It is important to distinguish an uncomplicated respiratory tract infection from a complicated respiratory tract infection that requires antibiotic treatment. In most cases, cough is caused by an uncomplicated respiratory tract infection (viral or bacteri-	

Name of society/organisation issuing guidance	Date of issue	Country/ies to which applicable	Summary of recommendation	Level of evidence (A,B,C)/ class of recommendation (I, IIa, IIb, III)
			al) A patient with an uncomplicated respiratory tract infection has no risk factors for complications (age > 3 months and < 75 years, no relevant comorbidity), is not very ill, doesn't have signs of a complicated respiratory tract infection and has a fever < 7 days. The symptoms (cough) can last up to 4 weeks. There is no effective therapy. There are two groups of patients with a complicated respiratory tract infection. **1** Patients with a pneumonia (severely ill [tachypnea, tachycardia, hypotension or confusion] OR moderately ill and one-sided auscultatory findings, CRP > 100 mg/l [a CRP of 20-100 mg/l doesn't exclude a pneumonia, [management depends on presentation and risk-factors], infiltrate on chest X-ray or sick > 7 days with fever and a cough). These patients are prescribed an antibiotic. **2** Patients with other risk factors for complications (age < 3 months or > 75 years and/or relevant comorbidity [in children cardiac and pulmonary disease not being asthma, in adults congestive heart failure, severe chronic obstructive pulmonary disease, diabetes mellitus, neurological disorders, severe renal failure, compromised immunity]). In these patients, the decision to prescribe antibiotics is based on the presentation, supported, if necessary, by measurement of CRP. The measurement of C-reactive protein can help differentiate between pneumonia and mild respiratory tract infection in moderately ill adults with general and/ or local symptoms. This recommendation does not apply to children. Specific management recommendations are made for croup, bronchiolitis and whooping cough. In cases of moderate croup, a single dose of corticosteroid (e.g. dexamethasone, 0.15 mg/kg, oral or intramuscular, or 2 mg of nebulized budesonide) should be given. Mild croup is self-limiting; children with severe croup should be referred to a paediatrician. Children with bronchiolitis and dyspnoea should be monitored regularly during the first few days. Use of medication has not proven to be effective. In whooping cough antibiotics might be useful in preventing secondary cases only Additional investigations should be performed if there is suspicion of whooping cough in a patient from a family with unvaccinated or incomplete vaccinated children younger than 1 year or with a pregnant woman of more than 34 weeks gestation. The increasing resistance to doxycycline and macrolide antibiotics makes amox-	

Name of society/organisation issuing guidance	Date of issue	Country/ies to which applicable	Summary of recommendation	Level of evidence (A,B,C)/ class of recommendation (I, IIa, IIb, III)
			icillin (for 5 days) the drug of first choice for pneumonia, with doxycycline as second choice. Doxycycline remains the first-choice drug if there is an increased risk of pneumonia caused by Coxiella burnetii (Q-fever) or Legionella. Because of lack of evidence on the effectiveness of noscapine and codeine and their known side effects these drugs are not recommended.	
NICE diagnosis and management of pneumonia in adults (2014)[42]	2014	UK	For people presenting with **symptoms of lower respiratory tract infection** in primary care, consider a point of care C-reactive protein test if after clinical assessment a **diagnosis of pneumonia has not been made** and it is not clear whether antibiotics should be prescribed. Use the results of the C-reactive protein test to guide antibiotic prescribing in people **without a clinical diagnosis of pneumonia** as follows: **1** Do not routinely offer antibiotic therapy if the C-reactive protein concentration is less than 20 mg/litre. **2** Consider a delayed antibiotic prescription (a prescription for use at a later date if symptoms worsen) if the C-reactive protein concentration is between 20 mg/litre and 100 mg/litre. **3** Offer antibiotic therapy if the C-reactive protein concentration is greater than 100 mg/litre.	
ESCMID/ERS guidelines for adult LRTI (2011)[58]	2011	Europe	Elderly LRTI patients with relevant co-morbidity should be followed-up 2 days after the first visit. All patients with LRTI should be advised to return to the doctor if the symptoms take longer than 3 weeks to disappear. Antibiotic treatment should also be considered for patients with LRTI and serious co-morbidity such as: **1** selected exacerbations of COPD (see section 'acute exacerbation of COPD'); **2** cardiac failure; **3** insulin-dependent diabetes mellitus; or **4** a serious neurological disorder (stroke, etc.). Cough suppressants, expectorants, mucolytics, antihistamines, inhaled corticosteroids and bronchodilators should not be prescribed in acute LRTI in primary	C3 A1

Name of society/organisation issuing guidance	Date of issue	Country/ies to which applicable	Summary of recommendation	Level of evidence (A,B,C)/ class of recommendation (I, IIa, IIb, III)
			care.	
Finnish Medical Society Duodecim, the Finnish Respiratory Society, Infectious Diseases Society of Finland and the Finnish Association for General Practice: Current care guidelines for acute lower respiratory tract infection in adults	2015	Finland	**Adults:** Pneumonia is recognised in patients suffering from acute cough or deteriorated general condition. Patients with acute cough without pneumonia-related symptoms or clinical findings do not benefit from antimicrobial treatment. Those with suspected or confirmed pneumonia are treated with antibiotics, amoxicillin being the first choice. Most patients with pneumonia can be treated at home. Those with severe symptoms are referred to hospital. Patients are always encouraged to contact his/her physician if the symptoms worsen or do not ameliorate within 2–3 days. Patients aged 50 years or older and smokers are controlled by thoracic radiography in 6–8 weeks. http://www.kaypahoito.fi/web/english/guidelineabstracts/guideline?id=ccs00108	
Finnish Medical Society Duodecim, the Finnish Society of Pediatrics and the Finnish Society of General Medicine: Current care guidelines for lower respiratory tract infections in children	2014	Finland	**Children:** All respiratory viruses are capable of causing lower respiratory tract infections. Active testing of influenza viruses during influenza epidemics is recommended. Antitussive medications are ineffective and should not be used. Croup presenting with inspiratory stridor is recommended to be treated with oral corticosteroids and inhaled racemic adrenalin. Corticosteroids and inhaled racemic adrenalin are ineffective for the treatment of bronchiolitis. Inhaled salbutamol administered by a spacer (with a mask) is recommended for wheezy bronchitis. Amoxicillin is recommended for treating pneumonia at home and intravenous penicillin in hospital (combined with macrolide if mycoplasma is suspected). Pertussis is treated with azithromycin or clarithromycin.	
Community acquired pneumonia				
ESCMID/ERS guidelines for adult LRTI (2011)[58]	2011	Europe	To differentiate between pneumonia and other respiratory tract infections: A patient should be suspected of having pneumonia when one of the following signs and symptoms are present: new focal chest signs, dyspnoea, tachypnoea, pulse rate >100 or fever >4 days. In patients with a suspected pneumonia a test for serum-level of C-reactive protein (CRP) can be done. A level of CRP <20mg/L at presentation, with symptoms for >24 h, makes the presence of pneumonia	B-1

Name of society/organisation issuing guidance	Date of issue	Country/ies to which applicable	Summary of recommendation	Level of evidence (A,B,C)/ class of recommendation (I, IIa, IIb, III)
			highly unlikely; a level of >100 mg/L makes pneumonia likely. In case of persisting doubt after CRP testing, a chest X-ray should be considered to confirm or reject the diagnosis.	
			Should the primary care physician test for a possible microbiological aetiology of LRTI? Microbiological tests such as cultures and gram stains are not recommended	B-1
			Biomarkers to assess the presence of a bacterial pathogen are not recommended in primary care	A-1
			Patients with an elevated risk of complications should be monitored carefully and referral should be considered. In patients over 65 years of age the following characteristics are associated with a complicated course: presence of COPD, diabetes or heart failure, previous hospitalization in the past year, taking oral glucosteroids, antibiotic use in the previous month, general malaise, absence of upper respiratory symptoms, confusion/diminished consciousness, pulse >100, temperature >38, respiratory rate >30, blood pressure <90/60, and when the primary care physician diagnoses pneumonia.	A-3
			In patients under 65 the working group thinks that diabetes, a diagnosis of pneumonia and possibly also asthma are risk factors for complications. For all age groups, serious conditions such as active malignant disease, liver and renal disease and other disorders that are relatively rare in primary care but affect immunocompetence, do also increase risk of complications.	C-3
			Cough suppressants, expectorants, mucolytics, antihistamines, inhaled corticosteroids and bronchodilators should not be prescribed in acute LRTI in primary care.	A-1
			Antibiotic treatment should be prescribed in patients with suspected or definite pneumonia.	C-1
			Antibiotic treatment should be considered for patients with LRTI and serious comorbidity such as: selected exacerbations of COPD; (see below) 2 cardiac failure; 3 insulin-dependent diabetes mellitus; 4 a serious neurological disorder (stroke etc.) .	C-3

Name of society/organisation issuing guidance	Date of issue	Country/ies to which applicable	Summary of recommendation	Level of evidence (A,B,C)/ class of recommendation (I, IIa, IIb, III)
			An antibiotic should be given in exacerbations of COPD in patients with all three of the following symptoms: increased dyspnoea, sputum volume and sputum purulence. In addition, antibiotics should be considered for exacerbations in patients with severe COPD.	C-1
			Amoxicillin or tetracycline should be used as the antibiotic of first choice based on least chance of harm and wide experience in clinical practice. In the case of hypersensitivity, a tetracycline or macrolide such as azithromycin, clarithromycin, erythromycin or roxithromycin is a good alternative in countries with low pneumococcal macrolide resistance. National/local resistance rates should be considered when choosing a particular antibiotic. When there are clinically relevant bacterial resistance rates against all first choice agents, treatment with levofloxacin or moxifloxacin may be considered.	C-1
			The empirical use of antiviral treatment in patients suspected of having influenza is usually not recommended.	B-1
			Only in high-risk patients who have typical influenza symptoms (fever, muscle ache, general malaise and respiratory tract infection), for <2 days and during a known influenza epidemic, can antiviral treatment be considered	A-1
			A patient should be advised to return if the symptoms take longer than 3 weeks to disappear'. 'Clinical effect of antibiotic treatment should be expected within 3 days and patients should be instructed to contact their doctor if this effect is not noticeable. Seriously ill patients, meaning those with suspected pneumonia and elderly with relevant co-morbidity, should be followed-up 2 days after the first visit'. 'All patients or persons in their environment should be advised to contact their doctor again if fever exceeds 4 days, dyspnoea gets worse, patients stop drinking or consciousness is decreasing.	C-3
			In the following categories of patients, referral to hospital should be considered. 1 Severely ill patients with suspected pneumonia (the following signs and symptoms are especially relevant here: tachypnoea, tachycardia, hypotension and confusion). 2 Patients with pneumonia who fail to respond to antibiotic treatment. 3 Elderly patients with pneumonia and elevated risk of complications, notably those with relevant co-morbidity (diabetes, heart failure, moderate and	C-3

Name of society/organisation issuing guidance	Date of issue	Country/ies to which applicable	Summary of recommendation	Level of evidence (A,B,C)/ class of recommendation (I, IIa, IIb, III)
			severe COPD, liver disease, renal disease or malignant disease). 4 Patients suspected of pulmonary embolism. 5 Patients suspected of malignant disease of the lung.	
NICE diagnosis and management of pneumonia in adults (2014)[42]	2014	UK	**Management** When a clinical diagnosis of community-acquired pneumonia is made in primary care, determine whether patients are at low, intermediate or high risk of death using the CRB65 score. The CRB65 score assesses the mortality risk, and guides place of care and use of antibiotics. Each CRB65 parameter scores one: **C**onfusion (AMT<8 or new disorientation in person, place or time); **R**espiratory rate >30/min; **B**P systolic <90, or diastolic <60; age >**65**. Use clinical judgement in conjunction with the CRB65 score to inform decisions about whether patients need hospital assessment as follows: Stratify patients presenting with community-acquired pneumonia into those with low-, moderate- or high-severity disease. The grade of severity will usually correspond to the risk of death. **Score 0:** low risk, consider home-based care; **1-2:** intermediate risk, consider hospital assessment; **3-4:** high risk, urgent hospital admission. **Treatment** Put in place processes to allow diagnosis (including X-rays) and treatment of community-acquired pneumonia within 4 hours of presentation to hospital. Offer antibiotic therapy as soon as possible after diagnosis, and certainly within 4 hours to all patients with community-acquired pneumonia who are admitted to hospital. **Low-severity CAP:** Offer a 5-day course of a single antibiotic to patients with low-severity community-acquired pneumonia. Consider amoxicillin in preference to a macrolide or a tetracycline for patients with low-severity community-acquired pneumonia. Consider a macrolide or a tetracycline for patients who are allergic to penicillin.	

Name of society/organisation issuing guidance	Date of issue	Country/ies to which applicable	Summary of recommendation	Level of evidence (A,B,C)/ class of recommendation (I, IIa, IIb, III)
			Consider extending the course of the antibiotic for longer than 5 days as a possible management strategy for patients with low-severity community-acquired pneumonia whose symptoms do not improve as expected after 3 days. Explain to patients with low-severity community-acquired pneumonia treated in the community, and when appropriate their families or carers, that they should seek further medical advice if their symptoms do not begin to improve within 3 days of starting the antibiotic, or earlier if their symptoms are worsening. Do not routinely offer patients with low-severity community-acquired pneumonia: a fluoroquinolone or dual antibiotic therapy. **Moderate and high severity CAP:** Consider a 7- to 10-day course of antibiotic therapy for patients with moderate or high-severity community-acquired pneumonia. Consider dual antibiotic therapy with amoxicillin and a macrolide for patients with moderate-severity community-acquired pneumonia. Consider dual antibiotic therapy with a beta-lactamase stable beta-lactam and a macrolide for patients with high-severity community-acquired pneumonia. **Give safety-net advice** and likely duration of different symptoms, e.g. cough present for up to 6 weeks. Hospital-acquired infections can be caused by highly resistant pathogens that need treatment with extended-spectrum antibiotics (for example, extended-spectrum penicillins, third-generation cephalosporins, aminoglycosides, car-bapenems, linezolid, vancomycin, or teicoplanin), as recommended by British Society of Antimicrobial Chemotherapy guidance.	

Name of society/organisation issuing guidance	Date of issue	Country/ies to which applicable	Summary of recommendation	Level of evidence (A,B,C)/ class of recommendation (I, IIa, IIb, III)
Influenza				
ESCMID/ERS guidelines for adult LRTI (2011)[58]	2011	Europe	The empirical use of antiviral treatment in patients suspected of having influenza is usually not recommended. Only in high-risk patients who have typical influenza symptoms (fever, muscle ache, general malaise and respiratory tract infection), for <2 days and during a known influenza epidemic, can antiviral treatment can be considered.	B-1 A-1
National Institutes for Health (Italy) guidelines for the management of influenza in children [294]	2002	Italy	**Management** Rapid diagnostic tests are not recommended due to insufficient sensitivity and specificity. Etiological treatment with neuraminidase inhibitors or other antiviral agents is not recommended. Symptomatic treatment should be based on acetaminophen or ibuprofen. Antibiotics are not recommended unless fever persists for more than 7 days and signs of lower respiratory tract infection are present. Admission to hospital should be limited to cases with pre-existing risk conditions, young infants with bronchiolitis, cases with respiratory distress and oxygen desaturation, or cases where home management is difficult due to social reasons.	
Public Health England (2017) **Management and treatment of common infections (Antibiotic guidance for primary care: For consultation and local adaptation)** With reference to: **NICE influenza prophylaxis (2008)[73] and treatment (2009)[295]**	2017 2008/ 9	England UK	**At risk:** pregnant (including up to two weeks post-partum); children under six months; adults 65 years or older; chronic respiratory disease (including COPD and asthma); significant cardiovascular disease (not hypertension); severe immunosuppression; diabetes mellitus; chronic neurological, renal or liver disease; morbid obesity (BMI>40). **Annual vaccination is essential for all those "at risk" of influenza.** Antivirals are not recommended for healthy adults. **Treat "at risk" patients** with five days oseltamivir 75mg BD, when influenza is circulating in the community, and ideally within 48 hours of onset (36 hours for zanamivir treatment in children), or in a care home where influenza is likely. See PHE Influenza guidance for the treatment of patients under 13 years of age. **At risk:** In severe immunosuppression, or oseltamivir resistance, use zanamivir 10mg BD (two inhalations by diskhaler for up to 10 days) and seek advice.	

Abbreviations:

Evidence tables of individual studies included for clinical effectiveness and safety

Table A6: Characteristics of included studies for effectiveness and safety of using C reactive protein POCT to guide antibiotic prescribing in patients with acute RTIs in primary care settings (Systematic Review 1)

Author (Year)	Country	Study design	Number of participants	Length of follow-up	Gender	Inclusion criteria	Exclusion criteria	Funding source	Non responders/ loss to follow-up	Device type
Randomised controlled trials (cluster and individually randomised)										
Andreeva 2014	Russia	RCT cluster	179	2 weeks	72% female in CRP arm and 74% female in Usual care group.	Adult patients (≥18 years). Patients with acute cough/LRTI (including acute bronchitis, pneumonia, and infectious exacerbations of COPD or asthma) were included. An illness of less than 28 days duration, first consultation for the illness episode, being seen in a physician's office, and written consent to participate.	Exclusion criteria were an inability to fill out study documentation, being previously included in the study, immunocompromised status (HIV patients, immunosuppressive treatment), and ongoing treatment with oral corticosteroids.	None stated but authors declared no competing interests	99 out of 101 in CRP group completed follow-up. 77 out of 78 in usual group completed follow-up. 20 patients excluded from analysis as 2 GPs not completing forms	Afinion™ test system (Axis Shield)
Cals 2009	Netherlands	RCT cluster	431 patients, 40 GPs from 20 practices	28 days	CRP group 59% female; no CRP test arm 64% female.	Patients were eligible if they had a suspected lower respiratory tract infection with a cough lasting less than four weeks together with one focal and one systemic symptom	(from protocol) Immediate hospitalisation, previous hospitalisation within last 6 weeks, previous participation in the study, current or within past 2 weeks antibiotic use, insufficient understanding of	Netherlands Organisation for Health Research and Development (grant 945-04010)	90% completed	NycoCard™ II reader

							Dutch language			
Cals 2010	Nether-lands	RCT	258	28 days	CRP group 68.2% female, control group 70.1% female.	Adult (≥18+ years) presenting with current episode of 1) LRTI or 2) rhinosinusitis. 1) For LRTI, cough duration <4 weeks with at least 1 focal sign and 1 systemic sign or symptom. 2) For rhinosinusitis, duration <4 weeks with at least 2 symptoms or signs.	1. Immediate requirement of admission to a hospital, 2. No understanding of the Dutch language, 3. Previous participation in the study, 4. Antibiotic use or hospitalisation in the past 2 weeks, 5. Immunocompromised status.	Orion Diagnostica. Cals supported by grant of the Netherlands Organization for Health Research and Development.	100% for antibiotic follow-up data. 91% (CRP arm) and 97% (control arm) for patient reported outcomes.	QuikRead® CRP analyser (Orion Diagnostica)
Diederichsen 2000	Denmark	RCT	812	7 days	57% female	Patients: Children and adults. Patients who consulted their GP during normal working hours because of respiratory infections, and who belonged to the National Health Insurance Group 1, were eligible for participation. Practices: All GP's in single handed practices in the County of Fenen	Patients: Patients who had previously been seen by a GP as a result of the infection in question, patients who had a *Streptococcus* test carried out, and patients known to have chronic inflammatory disease were excluded Practices: GP's already using the CRP test	NR	792 (98%) follow-up	NycoCard™ reader
Do 2016	Vietnam	RCT	2,037	14 days	60% (of 2036) female	Children and adults aged 1-65 years with at least one focal and one systemic symptom lasting for less than 2 weeks for a non-severe acute respiratory tract infection.	Patients with severe acute respiratory tract infection were excluded. Patients were also excluded if already taking anti-	Wellcome Trust, UK, and Global Antibiotic Resistance Partnership, USA. Alere Technologies provided rea-	Out of 1019 in usual care arm (139 missed 14 day follow-up). Out of 1017 in the CRP POCT arm(123	NycoCard™ analyser used with NycoCard™ II reader (Alere

							biotics, convulsions, confusion, chronic disease e.g. Liver disease, cancer. No access to a telephone, not able to come for follow-up visit.	gents	missed 14 days follow-up)	Technologies)
Little 2013	European (Belgium, Spain, Wales, Poland, UK and Netherlands)	RCT cluster	4,264 patients 372 GPs in 228 practices	4 weeks	CRP arm 64% female; no CRP arm 64% female	Practices needed to recruit more than 10 patients in baseline audit. Patients Adults (≥18 years). First consultation for acute cough of up to 28 days' duration or what the clinician believed to be an acute lower-respiratory-tract infection, despite cough not being the most prominent symptom; and diagnosis judged by the physician to be an acute upper-respiratory-tract infection (e.g., sore throat, otitis media, sinusitis, influenza, and coryzal illness)	Exclusion criteria were a working diagnosis of a non-infective disorder (e.g., pulmonary embolus, heart failure, oesophageal reflux, or allergy); use of antibiotics in the previous month; inability to provide informed consent (e.g., because of dementia, psychosis, or severe depression); pregnancy; and immunological deficiencies.	European Commission Framework 6 Programme and the National Institute for Health Research and the Research Foundation Flanders.	For primary outcome 100% follow-up. For patient diaries more than 95% follow-up. 18 GPs excluded as not enough patients recruited.	QuikRead® CRP kits
Melbye 1995	Norway	RCT	239	21 days	63% female	Adults (≥18 years). Patients presenting with suspected pneumonia, bronchitis or asthma during normal office hours were included as well as those who presented the symptoms cough or shortness of breath, chest pain on deep inspiration or cough	Patients with sore throat, blocked nose or pain in ears or sinuses were excluded. Patients with angina or myocardial infarction like chest pain	Nycomed Pharma funded study. Melbye had scholarship from Norwegian Research council	For antibiotic prescribing 100% follow-up over 3 weeks. For symptoms 98/108 (91%) in CRP arm and 121/131 (92%) in usual care arm	NycoCard™ Reader (Axis Shield)

Non randomised studies										
Bjerrum 2004	Denmark	Observational study	367 GPs	none	CRP arm 56% (55 to 57) female, No CRP arm 59% (57 to 60) female	All ages, adults and children presenting with acute sinusitis, acute tonsillitis or acute otitis	not reported	Grant from The Health Insurance Foundation of Denmark	No follow-up period	Not reported
Jakobsen 2010	Norway, Sweden and Wales	Observational study	803	none	CRP arm males = 37%, No CRP use arm males = 34%, no access to CRP arm males = 38%	Adults (≥18 years). Consecutive patients presenting for consultation with first episode of acute cough. Duration of episode less than 28 days since onset of symptoms.	Anyone who is immunocompromised	Funded through the GRACE study by the 6th Framework Program of the European Commission	no follow-up period	NycoCard™ CRP Single Test (Axis-Shield) and QuikRead® CRP (Orion Diagnostica)
Kavanagh 2011	Ireland	Pilot non randomised study	120	28 days	Not reported	Adults (≥18 years). Participants presented with acute cough and/or sore throat with duration ≤1 month. Informed consent.	Not reported	Research Bursary funded by MSD	CRP arm 3/60 (5%) missing patient questionnaire, 1 patient completed questionnaire but refused CRP test. Usual care arm 3/60 (5%) missing patient questionnaire and 1 doctors questionnaire.	Quik-Read CRP kit (Orion Diagnostica)

Llor(a) 2012	Spain	Non-randomised before–after study	Patients: 3,356 in full intervention group. 280 GPs	None	Not stated	Patient presenting with LRTI	None stated	European Commission: DG SANCO under the Frame Program 6	No follow-up but 14 physicians didn't complete the intervention	NycoCard™ CRP apparatus (Axis-Shield)
Llor(b) 2012	Spain	Non-randomised before–after study	Patients: 560 in full intervention group. GPs 175	None	2008 (pre) 36.1% men. 2009 (post) 34.2% men.	Patients presenting with acute rhinosinusitis	Not reported	European Commission: DG SANCO under the Frame Program 6	No follow-up, but 14 physicians did not complete intervention.	NycoCard™ CRP apparatus (Axis-Shield)

Table A7: Characteristics of included studies for diagnostic test accuracy of C reactive protein POCT to guide antibiotic prescribing in patients with acute RTIs in primary care settings (Systematic Review 2)

Author year	Country and setting	Population	Reference test	CRP test	Other diagnostic /prognostic tests /clinical prediction rule	Groups (size)	CRP cut-off used (mg/L)
Sinusitis							
Ebell 2017	General practice in Denmark	Adult patients aged 18-65 with suspected acute rhinosinusitis	Acute rhinosinusitis: • Abnormal CT finding OR • Abnormal CT finding + + purulent antral puncture fluid Acute bacterial rhinosinusitis: • Abnormal CT finding +purulent antral puncture fluid + positive bacterial culture of antral fluid	Blood test	None	Acute rhinosinusitis (n=91) Not acute rhinosinusitis (n=84)	>15
Hansen 1995	General practice in Denmark	Patients 18-65 years suspected of having acute maxillary sinusitis	CT + aspiration + laboratory culture	NycoCard™ CRP whole blood	Erythrocyte sedimentation rate	Acute maxillary sinusitis (n= 89) Not acute maxillary sinusitis (n=79)	10
Pharyngitis/tonsillitis							
Christensen 2014	General practice in Denmark	Acute tonsillitis patients aged 15-40 years with a Centor score of 1-4	Laboratory culture	Laboratory test		GAS (n=29) Non-GAS (n=71)	6
Calvino 2014	Primary care in Spain	Adults >18 years old with acute pharyngitis and the presence of the	Microbiologic culture confirmed with posterior serogrouping	QuikRead®/Go® devices	None	GAS (n=83) GBS (n=8)	None

		4 Centor criteria				GCS (n=13) GGS (n=5) Other *Streptococcus* (n=10) No bacteria (n=29)	
Gulich **2002**	General practice in Germany	Patients aged ≥16 with newly developed sore throat	Microbiological culture of throat swabs	NycoCard™ CRP Whole Blood test	Clinical score of 4 parameters (throat mucosa, uvula, soft palate, tonsils), 2 points per criterion: High=6-8 Ambiguous=4-5 Low=0-3 . CRP test only in patients in ambiguous category	GAS (n=73) non-GAS (n=192)	≥35
Gulich **1999**	General practice in Southern Germany	Patients 16-75 years presenting with sore throat	Microbiological culture of a throat swab. GPs clinical diagnosis	NycoCard™ CRP Whole Blood test	Routine physical exam	Bacterial pharyngitis (n=38) Non-bacterial pharyngitis (n=123)	≥35
Pneumonia							
Heiskanen-Kosma **2000**	Primary care in Finland	Children with radiologically confirmed pneumonia	EIA and immune complex assays (bacterial) Routine complement fixation (viral and mycoplasma)	Immunoturbidometric method (LKB 8600 Reaction rate analyser)	None	Pneumococcal (n=57) Mycoplasmal /chlamydial (n=43) Viral (n=29) Unknown (n=64)	None
Holm **2007**	Primary care in Denmark	Adults diagnosed with community-acquired LRTI	Chest radiography + laboratory culture	Laboratory test	None	Pneumonia (n=48) Non-Pneumonia (n=316)	20
Hopstaken **2003**	GP surgeries in southern part of	Adults presenting with LRTI	Chest radiograph	Laboratory test	Signs and symptoms	Pneumonia (n=32) Non-Pneumonia (n=211)	10 20 50

	The Nether-lands						
Hopstaken 2009	General practice in The Nether-lands	Patients presenting with signs and symp-toms of LRTI	Chest radiograph (lat-eral and postero-anterior) + laboratory tests	Laboratory test	None	Pneumonia (n=11) No pneumonia (n=84)	10 50 100
Lagerström 2006	Primary care in Sweden	Adults with radiological-ly confirmed CAP	Chest X-ray	Laboratory based Ny-coCard™ reader	None	Pneumonia (n=82) Non-pneumonia (n=95)	None
Melbye 1988	General practices in Nor-way	Patients aged ≥15 years treated with antibiotics for clinically suspected pneumonia	Chest X-ray (postero-anterior and lateral projections)	Laboratory blood test	None	Pneumonia (n=11) Non-pneumonia (n=58)	> 11 > 50
Minnaard 2015	Primary care in 12 Euro-pean countries	Adult out-patients pre-senting with acute cough	Chest radiograph + Laboratory culture	Afinion™ Nyco-Card Reader II Eurolyser Smart 700|340 QuikRead go® QuikRead® 101	Signs and symp-toms	Pneumonia (n=100) No pnuemonia (n=100)	20 100
Teepe 2016	GPs in 16 prima-ry care research networks in 12 Europe-an coun-tries (GRACE consorti-	At least 18 years of age presenting for the first time with the main symptom of acute or deteriorating cough (duration ≤ 28 days) or any clinical presentation considered by the GP to be caused by LRTI	Bacterial LRTI: The presence of prespecified bacteria in respiratory samples. Bacterial pneunomia: Chest radiography within 7 days of presentation in combination with the presence of prespecified bacteria from sputum or nasopharyngeal swab	Laboratory test	LRTI bacterial infection (CRP at 30 mg/l reported in combination with discoloured sputum) Bacterial pneumonia (CRP at 30 mg/L reported in combination with comorbidity, temperature greater	All Patients (n=3,104) LRTI bacterial infection (n=539) Radiologically confirmed pneumonia (n=141) Bacterial pneumonia (n=38)	> 20 > 30 >100

	um)				or equal to 38 degrees centrigrade and crackles on lung ausculation)		
Van Vugt 2013	Primary care centres in 12 Europe-an coun-tries (GRACE consorti-um)	Adults presenting with acute cough	Chest radiograph	Laboratory test	Signs and symp-toms	No pneumonia: CRP level ≤20 (n=2039; 76.1%) 21-30 (n=214, 8%) 31-50 (n=230; 8.6%) 51-100: (n=135; 5%) >100 (n=62; 2.3%). Pneumonia: CRP level ≤20 (n=55; 39.3%) 21-30 (n=11, 7.9%) 31-50 (n=16; 11.4%) 51-100: (n=24; 17.1%) >100 (n=34; 24.3%). Diagnostic risk group*: Low: (n=1,556; 55.2%) Intermediate: (n=1132 40.1%) High: (n= 132; 4.7%)	> 30

Abbreviations: CAP – community acquired pneumonia CRP – C reactive protein; CT – computed tomography; GAS - group A *Streptococcus*; GBS - group B *Streptococcus*; GCS - group C *Streptococcus*; GGS - group G *Streptococcus*; GP – General Practitioner; LRTI – Lower respiratory tract infection;.

* Risk of radiologically confirmed pneumonia based on prediction model using signs and symptoms only. Risks defined a priori: low = <2.5%; intermediate = 2.5-20%; high = >20%.

Table A8: Characteristics of included studies for analytical performance of CRP POCT devices (Systematic Review 3)

Author (Year)	Study Type & Country	Test setting(s) and operator(s)	Sample source(s) (n)	Population / Inclusion criteria	POCT device	Comparator device	Blood sample type(s)	Funding source
Bains (2017)[168]	UK – AP	Laboratory – Lab technician	Hospital Samples (n=44)	NR	iChroma	Architect ci8200	Venous	NR
Brouwer (2014)[16]	Netherlands – AP	Laboratory – Lab technicians	Primary Care Samples (n=100)	Adults aged >18 years. GP's patients, CRP concentrations from 5 to 200 mg/L	QuikRead® 101	Synchron	Venous	None – analysers were provided for free
					Smart Eurolyser		Venous	
					Afinion		Venous	
					iChroma		Venous	
					Microsemi		Venous	
					AQT Flex 90		Venous	
					Actim®		Venous	
					Cleartest®		Venous	
Bukve (2016)[17]	Norway – EQA	Primary Care – GP & Nurses	Laboratory Samples (n=3) Primary Care Samples (n=2134) Hospital samples (n=22)	Healthy volunteers, blood stored in K2-EDTA and spiked with recombinant CRP (range 8-92 mg/L)	ABX Micros 200	Cobas 600	Venous	None
					Afinion			
					iChroma			
					NycoCard			
					QuikRead go®			
					QuikRead® 101			
Ciftci (2014)[169]	Turkey – AP	Laboratory – Lab technicians	Hospital Blood Sample (n=96)	NR	iChroma	Immage 800	Venous	None

Author (Year)	Study Type & Country	Test setting(s) and operator(s)	Sample source(s) (n)	Population / Inclusion criteria	POCT device	Comparator device	Blood sample type(s)	Funding source
Clouth (2009)[170]	Germany – AP	Laboratory – Not stated	Hospital Blood Samples (n=200)	NR	NycoCard Micros CRP	Tina Quant	Venous	NR
De Graaf (2017)[171]	Netherlands – AP	Primary Care – GP	NR (n=100)	NR	spinit®	Roche Cobas 8000	EDTA anti coagulated whole blood	Device provided for free by manu-facturer
Evrard (2005)[172]	France – AP	Laboratory – Lab technicians	(n=43)	NR	Actim®	Modular P900	Venous	NR
Ivaska (2015)[173]	Finland – AP	Laboratory – Lab technicians	Clinical blood sam-ples (n=48)	NR	Afinion	Modular P	Serum from EDTA venous blood	Turku University Research grant
Matheeu-sen (2018)[174]	12 European Countries – AP	Laboratory – Lab technicians	Primary Care (n=2922)	Adults >18 years of age. Symptoms of LRTI, acute cough lasting less than 28 days, presenting to primary care	QuikRead® 101	Dimension Vista	Plasma from venous blood	EU funding Kits provided by manufacturers

Author (Year)	Study Type & Country	Test setting(s) and operator(s)	Sample source(s) (n)	Population / Inclusion criteria	POCT device	Comparator device	Blood sample type(s)	Funding source
Minnaard (2013)[18]	Netherlands – AP	Laboratory samples – Lab technicians	Hospital Samples	NR	Afinion	Olyumpus AU 2700	Venous	None
					NycoCard™ Reader II			
					Smart Eurolyser			
					QuikRead go®			
					QuikRead® 101			
Monteny (2006)[19]	Netherlands – AP	Primary care – GP	Primary Care (n=61)	Any child attending out-of-hours primary care service with a fever	NycoCard	Tina Quant	Capillary Venous	ZonMW – health research/ development funding Distributor provided equipment
					QuikRead® CRP			
Nomura (2014)[175]	Japan – AP	Unclear	Hospital Samples (n=244)	NR	Microsemi	Hitachi 7600	Venous	Authors employed by Horiba – manufacturers of Microsemi
Semark (2003)[176]	UK – AP	Primary Care – Practice Nurse	Primary Care (n=124)	NR	QuikRead® 101	Vitros 950 dry slide	Venous & Capillary	Grant from Bio-Stat Ltd – supply QuikRead system

Author (Year)	Study Type & Country	Test setting(s) and operator(s)	Sample source(s) (n)	Population / Inclusion criteria	POCT device	Comparator device	Blood sample type(s)	Funding source
SKUP (2001)[20]	Denmark – EQA	Hospital Laboratory – Lab Technicians & Primary Care Centres	Primary Care (n=40) Hospital samples (n=40)	Each hospital chose 40 samples with concentration of CRP in required range. Each GP selected 40 patients	QuikRead® 101	Bayon, Cobas Integra, Hitachi	Venous	SKUP
SKUP (2002)[21]	Denmark – EQA	Hospital Laboratory – Lab Technicians & General Practice	Primary Care (n=160)	160 patients general practice and laboratory samples	ABX Micros	Vitros 250, Axon, Cobas Integra 700, Vitros 950	Venous	SKUP
SKUP (2011)[22]	Denmark – EQA	Hospital Laboratory – Lab Technicians & Primary Care Centres	Hospital (n=109) venous (n=114) capillary Primary Care (n=80)	109 venous and 114 capillary bloods from same patients in hospital laboratory, 80 capillary blood in primary care	Smart Eurolyser	Cobas Integra 800	Capillary and Venous	SKUP
SKUP (2013)[23]	Denmark – EQA	Hospital Laboratory – Lab Technicians & Primary Care Centres	Hospital (n=100) Primary Care (n=86)	100 venous whole blood EDTA patient samples in a hospital laboratory and capillary samples from 86 patients in two primary health care centres	iChroma	Cobas Integra	Capillary and Venous	SKUP
Verbakel (2014) [177]	Belgium – AP	GP carried out the test in primary care	Primary care (n=35 adults)	(Adults aged 18-65 years attending a general practice surgery	Afinion	Cobas c702	Capillary	Fund for Scientific Research (FWO) devices were provided by the manufacturer

Abbreviations: AP – analytical performance; EQA – external quality assurance; GP – general practitioner; NR – not reported.

Table A9: Systematic review 2 (diagnostic test accuracy) - likelihood ratios from included studies

Author Year	CRP Threshold (mg/L) + Clinical Criteria	Likelihood Ratios	
		LR (+)	LR (-)
Sinusitis			
Hansen 1995	10	1.83	0.45
	25	2.36	0.62
	50	3.3	0.74
Pharyngitis or tonsillitis			
Christensen 2014	6 + Centor Score 1-4*	1.64	0.22
	6 + Centor Score 2-4*	2.77	0.24
Gulich 2002	35 + derivation strepto-score**	17.6	0.13
	35 + validation strepto-score**	14.8	0.27
Gulich 1999	35 + clinical assessment	4.33	0.27
Pneumonia			
Holm 2007	20	2.09	0.42
	20 + clinical pneumonia	3.06	0.61
Hopstaken 2009	10	1.56	0
	20	2.02	0
	100	5.21	0.22
Lagerstrom 2006	20	2.26	0.32
	50	3.69	0.49
Melbye 1988	11	2.05	0.3
	50	18.5	0.27
Minnaard 2015	Table A10	Table A10	Table A10
Van Vugt 2013	30 + low probability of pneumonia***	0.39	1.81
	30 + high probability of pneumonia***	9.67	0.73

Abbreviations: LR (+) – positive likelihood ratio; LR (-) – negative likelihood ratio.

Notes: [a] These likelihood ratios were calculated using an online calculator based on the sensitivity and specificity data reported in the paper (http://getthediagnosis.org/calculator.htm)

*The Centor criteria (tonsillar exudate, tender anterior cervical lymphadenopathy or lymphadenitisk, history of fever (over 38°C), and/or absence of cough) are an algorithm to estimate the probability of group A β-haemolytic *Streptococcus* (GABHS) as the origin of sore throat. Each of the Centor criteria score 1 point (maximum score of 4).

**The clinical strepto-score (throat mucosa, uvula, tonsils, soft palate) was based on clinical examination. Each criterion was scored 0-2 points (total score 0-8 points).

*** Probability of pneumonia based on signs and symptoms (breathlessness, absence of runny nose, diminished vesicular breathing, crackles, tachycardia, temperature (>37.8°C)).

Table A10: Systematic review 2 (diagnostic test accuracy) likelihood ratios from Minnaard et al 2015

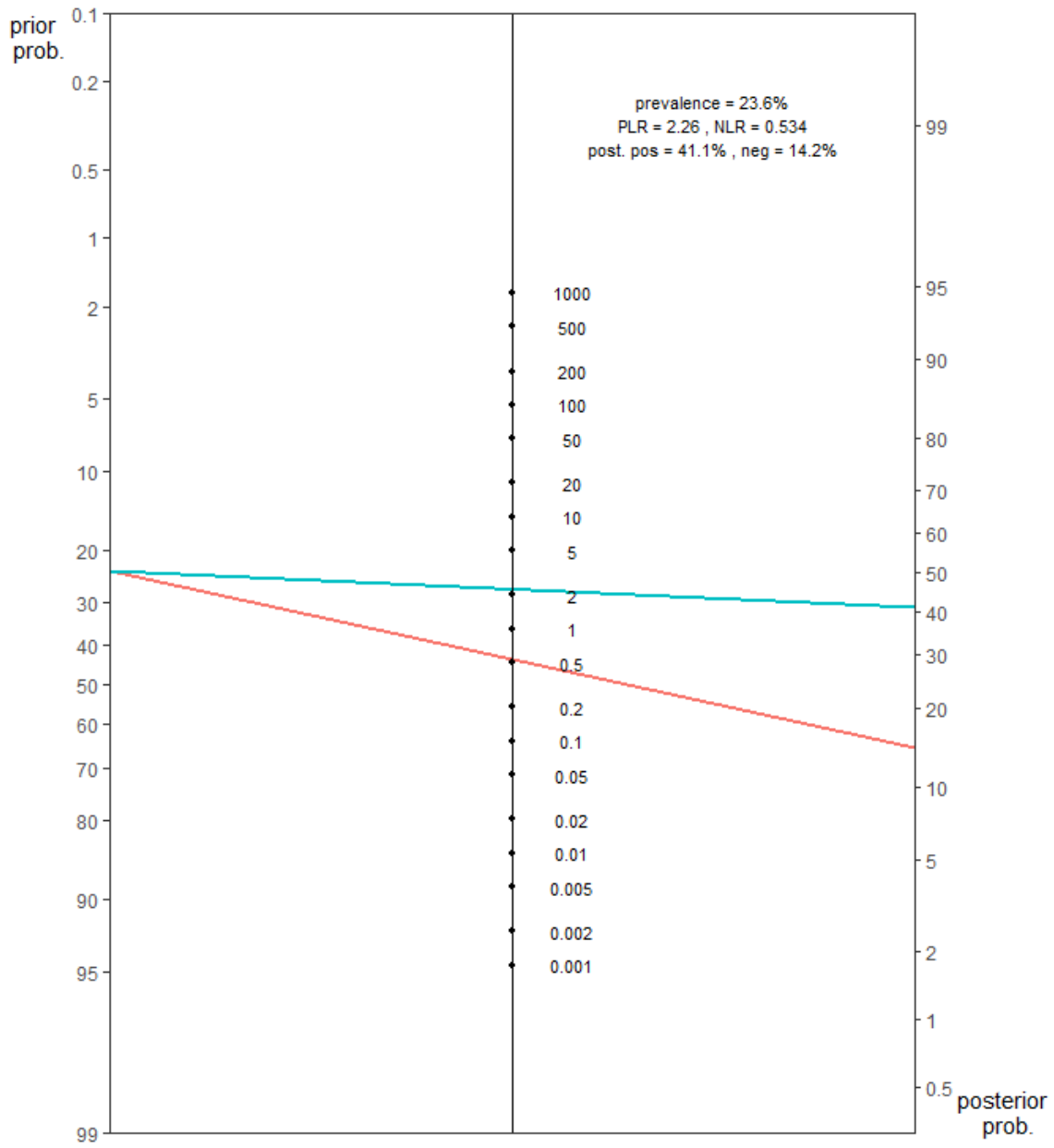
Author Year	CRP test	CRP Threshold (mg/L)	Likelihood Ratios	
			LR (+)	LR (-)
Minnaard **2015**	Laboratory analyser	20	2.56	0.51
		100	10.57	0.77
	Afinion	20	2.04	0.62
		100	20	0.81
	NycoCard™ Reader II	20	2.16	0.61
		100	10	0.82
	Eurolyser Smart	20	2.29	0.66
		100	19	0.82
	QuikRead go®	20	1.86	0.67
		100	20	0.81
	QuikRead® 101	20	1.88	0.69
		100	19	0.82

Abbreviations: LR (+) – positive likelihood ratio; LR (-) – negative likelihood ratio.

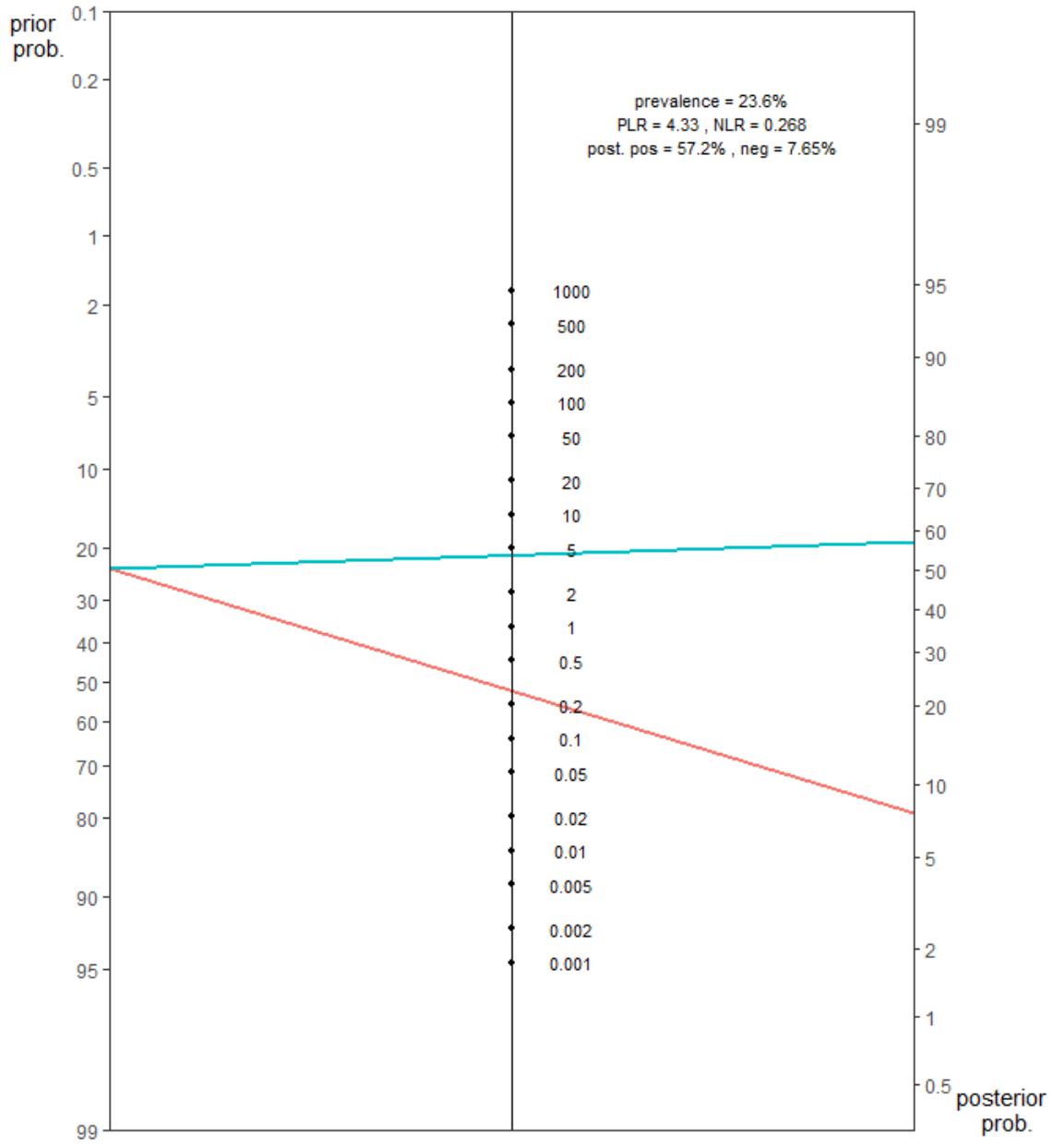
Notes: [a] These likelihood ratios were calculated using an online calculator based on the sensitivity and specificity data reported in the paper (http://getthediagnosis.org/calculator.htm)

Figure A1: Systematic Review 2 (Diagnostic test accuracy) examples of Nomograms

a. Nomogram for clinical diagnosis without CRP (Gulich et al. 1999)



b. Nomogram for diagnosis with CRP (Gulich et al. 1999)



List of ongoing and planned studies

The following sites were searched in January 2019: ClinicalTrials.gov and International Clinical Trials Registry Platform (ICTRP). Feedback was also obtained from a manufacturer during the factual accuracy check confirmed One planned or ongoing studies in relation to the use of CRP POCT to inform antibiotic prescribing in primary care was identified (Table A11). Feedback was also obtained from the trial sponsor to confirm the details of the trial protocol.

Table A11: List of planned and ongoing studies with CRP POCT

Study Identifier	Estimated start date	Study type	Number of patients	Intervention	Comparator	Patient population	Endpoints
NCT02018198 'DIStinguish Respiratory Underlying Pathogen associaTed host response in Upper Respiratory Infection: An Evaluation of FebriDx® POC Test'(FebriDx® DISRUPT URI Trial)'	04/2019	Prospective observational study	1,225	FebriDx®	Expert clinical reviewers' evaluation in conjunction with the results of clinical standardised microbiologic and laboratory testing Clinical Reference Algorithm)	Patients (one year and older) presenting with reported fever and acute respiratory symptoms to primary care and urgent care outpatient offices and emergency departments	The primary analysis will determine performance characteristics of FebriDx® test by assessing negative and positive agreement of FebriDx® results in determining the presence of a bacterial associated systemic host immune response or viral associated systemic host immune response compared with a Clinical Reference Algorithm (comparator method) that is supervised by clinical experts.

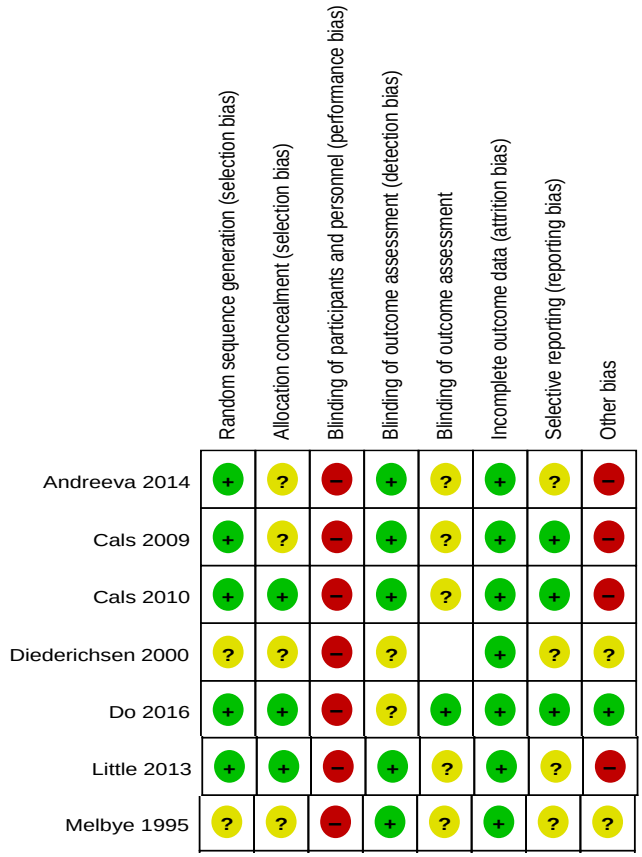
Source: www.clinicaltrials.gov and RPS Diagnostics

Risk of bias tables

Figure A2 shows an overview of the risk of bias of the RCTs included in systematic review 1 (effectiveness and safety). Most of the RCTs had adequate randomisation procedures [127, 129, 130, 132, 135]. In two studies it was unclear how the randomisation was done as no details were provided in the paper [131, 138]. It was often unclear from the description of the randomisation process if steps had been taken to ensure allocation concealment in the studies. All the RCTs had a high risk of performance bias as it was not possible to blind clinicians as to which group a patient was in as they had to know the CRP level when it was available in order for it to influence their management of a patient. It would also be difficult to blind patients to which group they were in as a placebo (sham) procedure would need to be carried out instead of the CRP measurement. For the primary outcome of antibiotic prescribing, most of the outcome data were gathered from electronic databases or from forms filled out by the clinician and were judged to be at low risk of bias. Symptom duration and patient satisfaction were often recorded in patient diaries or by interview and it was often unclear how the data were

extracted and if it was open to bias. For the primary outcome of antibiotic prescribing at index consultation, the data were complete and at low risk of attrition bias. For other outcomes, where data was collected up to 28 days later, the follow-up was good for most of the studies. When a protocol was available it was usually clear that there was no or low risk of reporting bias; however, a few older studies had no available protocol [131, 138]. Other sources of bias included the cluster randomised controlled design [127, 129, 135], stopping the study early [138], and the method used to recruit patients [131].

Figure A2: Risk of bias of included RCTs in systematic review 1 (clinical effectiveness and safety)



Key

Low risk of bias High risk of bias Unclear risk of bias

Table A12 shows an overview of the risk of bias of included non-randomised studies in systematic review 1. All of the studies scored either a four or a five out of a possible seven, or in the case of Kavanagh et al. [134], five out of a possible nine (as this study included a follow-up period). All of the studies scored a star for the representativeness of the cohort that underwent the CRP POCT. All bar the study by Jakobson et al. [133] also scored a star for selection of the control group. In the study by Jakobson et al., the CRP POCT group included patients from Norway and Sweden, with Wales in the UK used as the control group as CRP POCT was not available in Wales at the time. The authors justified

this choice stating that the countries have similar characteristics. However as these countries have very different health systems and the presenting characteristics of the patients were different between the intervention and control groups, the suitability of the control group is questionable. For most studies it was unclear if antibiotics had been prescribed to any of the patients before the start of the study. Only the study by Jakcobsen et al. stated that patients were only included if it was their first visit for the current RTI episode, suggesting that the outcome had not been present before the start of the study. For assessment of the outcome; in four out of five of the studies the antibiotic information was recorded by the clinician at the time of consultation which means these studies do not score a star based on the Newcastle Ottawa scale, as a point is only scored for this domain if the assessment of the outcome is done independently and blinded or by record linkage. However, as the clinician must know the outcome of the CRP POCT for it to influence antibiotic prescribing, it seems unlikely that this would be a source of bias in this type of study. Also, it seems unlikely that there would be inherent bias in the clinician recording the antibiotic prescribing either in the medical records or on a form.

Table A12: Quality rating of included non-randomised studies (systematic review 1 – effectiveness and safety)

Study, Year	Selection				Comparability		Outcome			Overall quality score (Max. =9)
	Representativeness of exposed cohort?	Selection of the non-exposed cohort?	Ascertainment of exposure?	Demonstration that outcome of interest was not present at start of study?	Study controls for age/sex?	Study controls for at least 3 additional risk factors?	Assessment of outcome?	Was follow-up long enough for outcome to occur?	Adequacy of follow-up of cohorts?	
Bjerrum 2004	*	*	*	X	*	X	X	N/A	N/A	4 out of 7
Jakobsen 2010	*	X	*	*	*	X	*	N/A	N/A	5 out of 7
Kavanagh 2011	*	*	*	X	X	X	X	*	*	5 out of 9
Llor 2012(b)	*	*	*	X	*	*	X	N/A	N/A	5 out of 7
Llor 2012(a)	*	*	*	X	*	*	X	N/A	N/A	5 out of 7

Figure A3: Risk of bias of included studies in systematic review 2 (diagnostic test accuracy)

Study	RISK OF BIAS				APPLICABILITY CONCERNS		
	PATIENT SELEC-TION	INDEX TEST	REFER-ENCE STAND-ARD	FLOW AND TIMING	PATIENT SELEC-TION	INDEX TEST	REFER-ENCE STAND-ARD
Calvino 2014	Low	Low	Low	Low	Low	Low	Low
Christen-sen 2014	Low	Unclear	Low	Low	Low	High	Low
Ebell 2017	Unclear	Unclear	Low	Low	Unclear	High	Low
Gulich 2002	Low	Low	Low	Low	Low	Low	Low
Gulich 1999	Low	Low	High	Low	Low	Low	High
Hansen 1995	Low	Low	Low	Low	Low	Low	Low
Heiskanen -Kosma 2000	Low	High	Low	Low	Low	High	Low
Holm 2007	Low	Unclear	Low	Low	Low	High	Low
Hopstak-en 2003	Low	Low	Low	High	Low	High	Low
Hopstak-en 2009	Low	Unclear	Low	Unclear	Low	High	Low
Lager-strom 2006	Low	Unclear	Low	Unclear	High	Unclear	Low
Melbye 1988	High	Unclear	Low	Low	High	High	Low
Minnaard 2015	Low	Unclear	Low	High	Low	High	High
Teepe 2016	Low	Low	Low	High	Low	High	Low
Van Vugt 2013	Low	Low	Low	High	Low	High	Low

A tabular presentation of the QUADAS-2 quality assessment of the 15 studies included in systematic review 2 is shown in Figure A3. All studies reported clearly defined selection criteria. The majority of studies included either all patients presenting with symptoms of RTI or consecutive patients, therefore risk of bias and concerns regarding applicability were generally low. Potential risk of bias or applicabil-ity concerns were identified regarding patient selection in five studies. Exclusion of patients living in

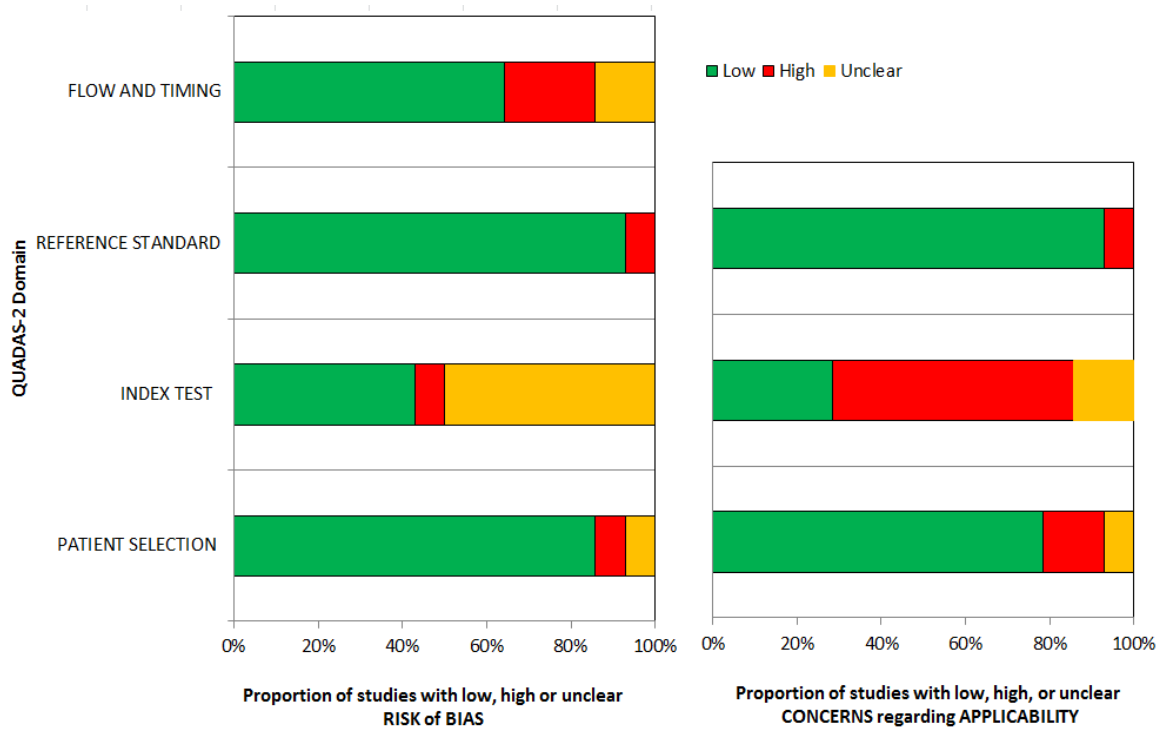
nursing homes by Lagerstrom et al. may reduce the applicability of the findings to the target population identified in our review question as this patient group is of particular interest due to high antibiotic prescribing rates in long term care facilities in Europe [149]. Melbye et al. included only patients treated with antibiotics by a general practitioner for a suspected pneumonia [10]. Failure to include patients not treated with antibiotics introduces a potential risk of bias. Furthermore, patients who were too ill to attend the outpatient clinic for analysis of CRP levels were excluded which could lead to underestimation of diagnostic test accuracy. Van Vugt et al. reports that not all consecutive eligible patients were recruited [14]. The authors state that sequential recruitment was impossible given the high volume of patients presenting with LRTI during the winter period, and the time required to recruit and assess each patient. Given the large sample size in this study, clinically important selection bias was considered to be unlikely. Ebell et al. state that a large proportion of eligible patients declined to participate and data on nonparticipants were not available, introducing potential selection bias[3].

In all included studies patients received both the index and reference standard tests. The risk of bias and applicability of a number of included studies was judged to be unclear in terms of the index test. Insufficient information was provided in the majority of cases in order to determine if the results of the reference standard were available prior to interpretation of the index test. In studies where a POC CRP test was used, it was assumed that interpretation of the index test result was carried out during the consultation, eliminating the potential for the reference standard to influence interpretation of the test. Gulich et al. defined evidence of bacterial pharyngitis as throat swabs growing bacteria caused by group A- and C-β-haemolytic *Streptococci* and *Haemophilus Influenzae* [5]. This has the potential to underestimate the prevalence of bacterial pharyngitis as infections may be attributable to other types of bacteria.

Variation in test technology or execution may affect estimates of diagnostic test accuracy. This systematic review aimed to evaluate the diagnostic test accuracy of CRP testing at the POC. An important limitation to the study conducted by Minnaard and colleagues was noted [11]. All tests were carried out in a laboratory setting by laboratory analysts, which may not be representative of the primary care setting where CRP POCTs are intended for use. A number of studies used laboratory-based CRP testing and the findings of these studies may not be directly transferable to the primary care setting [3, 6, 10, 12, 14, 150-152]. Studies for which CRP testing was carried out in a laboratory setting rated high in terms of concerns regarding the applicability of these findings to the primary care setting.

Four studies rated poorly in terms of patient flow and timing. Ideally, results of the index test and reference standard should be collected at the same time. The studies by Minnaard et al. and Teepe et al. reported that blood samples were taken on day one for analysis of CRP levels, however chest radiographs were obtained within seven days [11, 15]. Similarly, Hopstaken et al. reports that blood samples were taken for analysis of CRP levels on the day of presentation to the GP, while chest radiographs were not obtained until three days after inclusion in the study [152]. The time interval between the execution of the index test and reference standard has the potential to introduce bias as a result of misclassification due to changes in patient condition or the potential of the results of one test to influence the results of another. A graphical summary of the overall quality assessment for each of the QUADAS-2 domains is illustrated in Figure A4.

Figure A4: Graphical overview of the overall quality rating of included studies in systematic review 2 (diagnostic test accuracy) for each of the key domains using the QUADAS-2 quality appraisal tool



Overall, studies included in systematic review 3 were of low or unclear risk of bias by QUADAS 2 (Figure A5 and A6). However, there were three clear areas where bias was of concern. It was not clear if operators were blinded to the results of the POCT or had prior information regarding the CRP concentration of the sample being tested. This could introduce bias, particularly in the laboratory setting where the same individual could be performing both the POCT and laboratory reference test. Another potential source of bias related to the lack of clarity around the length of time the samples were stored prior to their use or the time interval between performance of the POCT and reference tests. The absence of a clear explanation of the experimental design of these studies limits the interpretation of the results. Finally, in several of the studies, the population samples were not specific to patients presenting to primary care with symptoms of RTI with samples also taken from hospital inpatient and outpatient settings in addition to stored laboratory samples for which little if any detail of the patient population from which they were derived provided. Therefore the spectrum of patients was often not the same as those who would receive the test in practice. In many studies, principally those where multiple devices were compared with each other, frozen or EDTA-treated venous samples were taken from laboratory stores. The advantage of this approach is that the samples are of a known concentration allowing a range of CRP concentrations to be analysed. This method also eliminates bias that could be introduced due to heterogeneity of the operator at the point of care, which is important when comparing devices with each other. The disadvantage of the approach is that laboratory venous blood samples that have been frozen or treated with EDTA or heparin are not the same as capillary blood samples tested at the point of care, thereby introducing a potential source of bias. By controlling the sample and operator variables, these studies also create an artificial environment that does not reflect the intended use of these POCT devices, that is, in primary care by non-laboratory trained health care professionals.

An additional potential source of bias is the source of funding of the studies. One study was sponsored by the manufacturer [176] and in a further two studies, the equipment and training was funded by the manufacturer.[171, 177] Research in one of the studies was undertaken by company employees.[175] Four studies were recipients of educational grants.[19, 173, 174, 177]

Figure A5: QUADAS 2 – Risk of bias of included studies systematic review 3 (analytical performance)

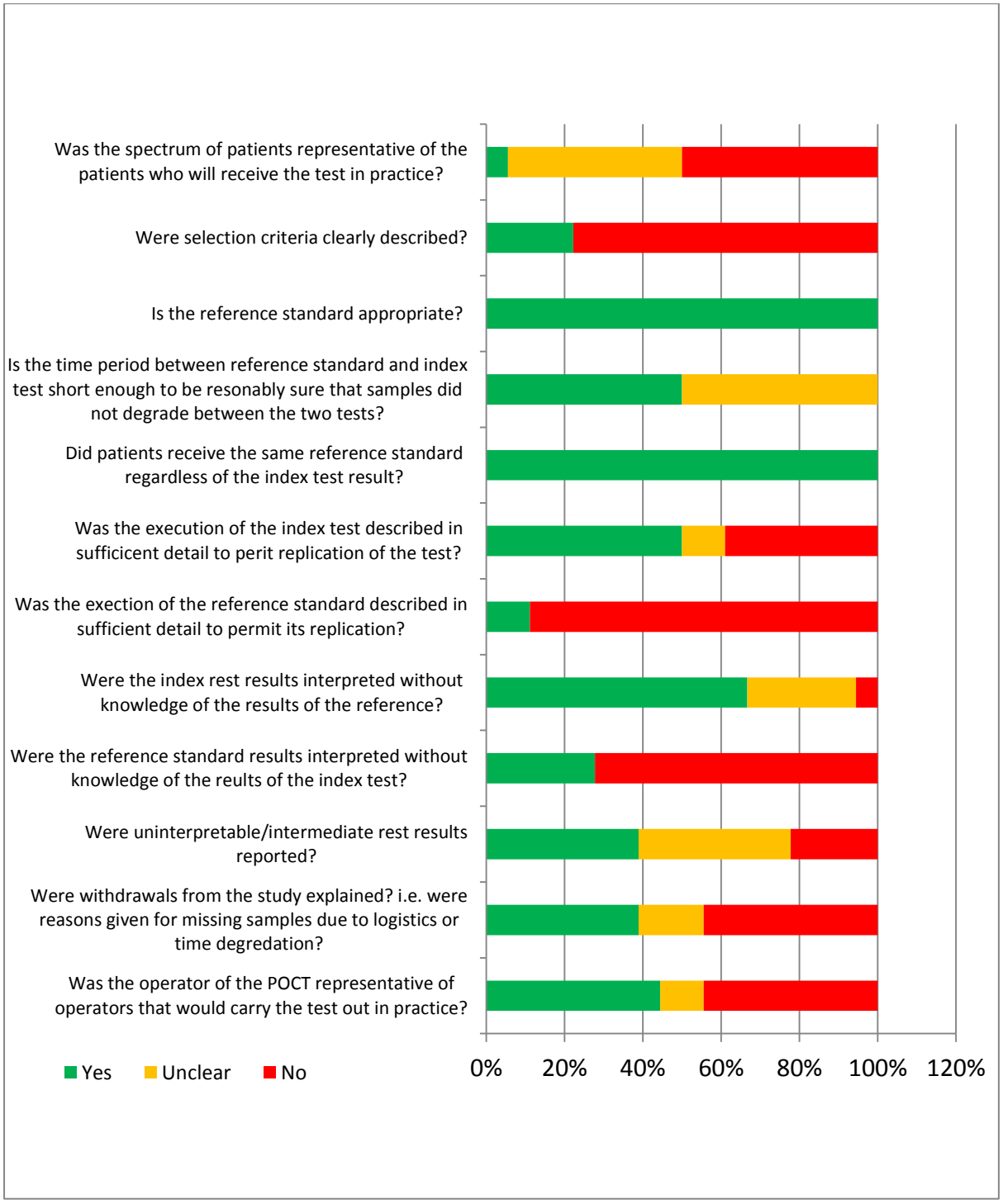


Figure A6: Risk of bias of included studies in systematic review 3 (analytical performance)

Author	Was the spectrum of patients' representative of the patients who will receive the test in practice?	Were selection criteria clearly described?	Is the reference standard appropriate?	Is the time period between reference standard and index suitable to ensure the sample did not degrade?	Did patients receive the same reference standard regardless of the index test result?	Was the execution of the index test described in sufficient detail to permit replication of the test?	Was the execution of the reference standard described in sufficient detail to permit its replication?	Were the index rest results interpreted without knowledge of the results of the reference?	Were the reference standard results interpreted without knowledge of the results of the index test?	Were interpretable or intermediate test results reported?	Were withdrawals from the study explained?	Was the operator of the POCT representative of operator in practice?
Bains	High	High	Low	Unclear	Low	Low	High	Unclear	Unclear	Low	Low	High
Brouwer	Unclear	High	Low	Low	Low	High	High	High	Unclear	Unclear	High	High
Bukve	High	High	Low	Low	Low	Unclear	High	Unclear	Low	Unclear	Unclear	Low
Ciftci	High	High	Low	Low	Low	High	High	Low	Low	Unclear	High	High
Clouth	High	High	Low	Low	Low	Low	High	Unclear	Low	Unclear	Unclear	High
De Graaf	Unclear	High	Low	Unclear	Low	High	High	Unclear	Unclear	High	High	Unclear
Evrard	High	High	Low	Unclear	Low	Low	Low	Low	Unclear	Low	Unclear	High

Ivaska	High	High	Low	Low	Low	Unclear	High	Low	Unclear	High	High	Low
Matheeussen	Low	Low	Low	Unclear	Low	High	High	Low	Low	Unclear	Low	High
Minnaard	High	High	Low	Unclear	Low	Low	High	Low	Low	High	High	High
Monteny	Unclear	High	Low	Unclear	Low	High	High	Low	Low	Unclear	Low	Low
Nomura	High	Low	Low	Unclear	Low	High	High	Unclear	Unclear	Unclear	Low	High
Seamark	Unclear	Low	Low	Unclear	Low	Low	High	Low	Unclear	High	High	Unclear
SKUP Smart Eurolyser	Unclear	High	Low	Low	Low	Low	High	Low	Unclear	Low	Low	Low
SKUP iChro-ma	Unclear	Low	Low	Unclear	Low	High	High	Low	Unclear	Low	Low	Low
SKUP ABX Micros	Unclear	High	Low	Low	Low	Low	High	Low	Unclear	Low	Low	Low
SKUP QuikRead® 101	Unclear	High	Low	Low	Low	Low	High	Low	Unclear	Low	Low	Low
Verbakel	High	High	Low	Low	Low	Low	High	Low	Unclear	Low	High	Low

Notes: * Two-part study involving initial testing of samples in laboratory and then at the point of care.

Applicability tables

Table A13: Summary table characterising the applicability of the body of studies – systematic review 1 (effectiveness and safety)

Domain	Description of applicability of evidence
Population	As mentioned in the PICO question, patients of all ages who present with symptoms of acute RTI in primary care were considered relevant to this systematic review. Subgroups of particular interest included: patients presenting with upper versus lower RTI, children, older adults (≥65 years of age), patients attending OOH services and those in LTC facilities. Most studies only included adults, while three included adults and children. No study reported data that could be extracted for a population restricted to older adults (>65 years). Subgroup analysis was performed for upper versus lower RTI for the outcome of antibiotic prescribing at index consultation. No further planned subgroup analysis was performed due to retrieval of insufficient data to facilitate analysis. Of the eleven studies retrieved in the systematic review, nine were carried out in EU countries, one in Russia and one in Vietnam. Therefore, the findings of this systematic review are believed to be transferable to the majority of European primary care settings given that the findings of the review are largely based on European data.
Intervention	The intervention of interest was any CE marked CRP POC quantitative or semi-quantitative test designed for use in the primary care setting. The identified studies included in this systematic review related to only three of the 15 CE marked devices (QuikRead® CRP kit/QuikRead® 101, Alere Afinion™ CRP, and NycoCard™ CRP for use with NycoCard™ II Readers). All three of these devices are quantitative devices. No data were retrieved in relation to the clinical effectiveness and safety of semi-quantitative CRP POC devices. Therefore, there is no evidence to suggest that the findings of the systematic review of clinical effectiveness and safety are applicable to semi-quantitative devices. A number of RCTs [129, 135, 137] included an educational component or communication skills training as part of the intervention arm alongside CRP POCT. This may have enhanced the effect of CRP POCT on antibiotic prescribing. However, removal of Little 2013 and Cals 2009 from the RCT meta-analysis resulted in only a minor change in the pooled RR and still suggests that CRP POCT leads to a significant reduction in antibiotic prescribing. In this way, the findings should be applicable to primary care settings in which healthcare workers carrying out CRP POCT have not received additional education or communication skills training beyond that necessary to conduct the test.
Comparators	The comparison of interest was standard care, which is the case of two of the trials (Little 2013 and Cals 2009) also included either an educational or communication component. For the majority of included studies, standard care comprised clinical assessment only with no access to CRP POCT. The usual care arms are therefore thought to be representative of a typical primary care setting prior to the introduction of CRP POCT. Some of the cluster RCTs [129, 135] identified in this systematic review included educational components or communication skills training as part of standard care which may not be representative of the current standard of care across Europe. However, as both intervention and control groups were exposed to the educational or communications component in these studies, it is likely that any observed effect is due to CRP POCT. Exposure of the usual care arm to education or communication skills training is therefore not thought to reduce the applicability of the evidence. A study by Jakobsen et al. used patients presenting to primary care settings in Wales as the usual care group, due to the fact that standard care in Scandinavian countries already involves the use of CRP POCT, therefore it was not possible to use a control population from the same region. Removal of this study from the meta-analysis led to a decrease in heterogeneity, but CRP POCT was still associated with a significant reduction in antibiotic prescribing at index consultation. Therefore, the lack of a suitable comparator in this study does not reduce the applicability of the evidence.

Domain	Description of applicability of evidence
Outcomes	While no deaths were reported in any of the studies identified, there was limited evidence retrieved in relation to safety outcomes. No evidence was retrieved to answer the following assessment elements: C0005, C0007, B0010. Therefore the results should be interpreted and applied to relevant healthcare settings in the context of the limited evidence base in relation to safety. Very few studies reported on the number of antibiotics prescribed as a delayed prescription, It may be that delayed prescriptions are common in cases where CRP levels are between 20 and 99 mg/L this could mean that our effect estimate is lower than would be seen in practice as a portion of delayed prescriptions may not be redeemed.
Setting	All studies included in the primary analysis were carried out in primary care settings with nine of the 11 included studies undertaken in European countries. They were therefore considered to be applicable to the settings in which CRP POCT will typically be used in Europe. The study by Do et al was carried out in Vietnam and may not be as applicable as the Vietnam healthcare system would differ to most European countries, However removal of this study decreased erogeneity but did not substantially change the overall pooled estimate.

Abbreviations: CRP POCT – C-reactive protein point-of-care testing; LTC – long-term care; RTI – respiratory tract infection.

Table A14: Summary table characterising the applicability of the body of studies retrieved for systematic review 2 (diagnostic test accuracy)

Domain	Description of applicability of evidence
Population	Patients of all ages who present with symptoms of acute RTI in primary care were considered relevant to this systematic review. Subgroups of particular interest included: children, older adults (≥65 years of age), patients attending out-of-hours (OOH) services and those in Long Term Care (LTC) facilities. If sufficient data were retrieved, it was intended that subgroup analysis would be carried out for the following subgroups: children versus adults; and older adults (≥65 years) versus younger adults (<65 years). The body of evidence retrieved did not contain sufficient information to facilitate analysis of the aforementioned subgroups. Only one study included children aged between 3 months to 15 years of age[150]. No study reported on the DTA of CRP POCT in older adults (>65 years). Therefore this systematic review cannot draw conclusions on the DTA of CRP POCT in these specific subgroups. All results should be interpreted in terms of the general population. Studies included in this systematic review contained evidence regarding the DTA of CRP POCT in relation to a number of types of RTI. Evidence was retrieved and evaluated with regard to the following RTI types: Pharyngitis and tonsillitis; sinusitis; and LRTI and pneumonia. The DTA of CRP POCT differed by RTI type, therefore, the findings of this review may be CRP POCT may be of limited applicability to patients presenting with signs and symptoms of other URTI in primary care.
Intervention	The intervention of interest was any CE marked C-reactive protein POC quantitative or semi-quantitative method designed for use in the primary care setting. No relevant studies were identified that used semi-quantitative CRP POCT devices. Therefore, this systematic review cannot draw conclusions on the applicability of semi-quantitative CRP POCT to the primary care setting.

Domain	Description of applicability of evidence
Comparators	A number of comparators were considered relevant in this systematic review given the absence of a universal reference standard for the diagnosis of RTI requiring antibiotics. The diagnostic standard used depended on the type of RTI under consideration. For studies investigating the DTA of CRP POCT in patients presenting with LRTI or pneumonia, the conclusive finding of an infiltrate on a chest radiograph was regarded as evidence of pneumonia. Chest radiography is not typically performed in the primary care setting. However, given the absence of a more appropriate comparator, chest radiography was considered to be a suitable comparator to identify patients with pneumonia. Culture of throat swab was used as the gold standard to diagnose tonsillar bacterial infection and is considered to be applicable to the primary care setting. Reference standards for acute sinusitis were abnormal finding on a CT scan, the presence of purulent or mucopurulent fluid from an antral puncture of the maxillary sinus, and, for acute bacterial sinusitis, positive bacterial culture of antral fluid. Antral puncture is the preferred reference standard test, but is not widely used in primary care due to the discomfort it causes and a lack of expertise in performing antral puncture in the primary care setting.
Outcomes	Outcomes of interest were measures of diagnostic test accuracy including; Sensitivity and specificity; PPV and NPV; likelihood ratio, AUC; and DOR. A variety of statistical measures were used to report on diagnostic test accuracy across the studies. Three studies reported measures of DTA of CRP POCT for the combination of signs and symptoms and CRP testing at a threshold of 20 mg/L, however the signs and symptoms included in the clinical examination were either inconsistent [14, 152] or not reported[8]. Some studies did not report typical measures of DTA, and reported only mean or median CRP concentrations (mg/L) in the patient groups. In such studies, the best available measures of DTA were extracted, however such measures are not typically considered informative in determining the DTA of an intervention. Meta-analysis of data was not possible due to considerable heterogeneity among studies therefore it is difficult to comment on the accuracy of CRP POCT for the body of evidence.
Setting	All studies were carried out in primary care settings in European countries and were considered to be reflective of the settings in which CRP POCT will typically be used. Eight of the included studies used standardised laboratory testing for CRP. In the context of this systematic review, the intended user is healthcare staff who are non-laboratory specialists working in the primary care setting. The inclusion of studies where CRP testing was carried out by laboratory specialists in a laboratory setting may reduce the applicability of the findings to the primary care setting due to the potential of variation in user's technique and the environment to impact the results of the CRP test, and thereby possibly lead to variation in clinical diagnoses. Therefore, the applicability of the findings of this review are dependent on the analytical performance of the CRP POCT as determined in the systematic review of analytical performance.

Abbreviations: AUC – area under the curve; CRP – C-reactive protein; DOR – Diagnostic odds ratio; DTA – diagnostic test accuracy; LTC – Long-term care; NPV – negative predictive value; OOH – out-of-hours; PICO – Population, Intervention, Comparator, Control; POCT – point-of-care testing; PPV – positive predictive value; RTI – respiratory tract infection.

Table A15: Summary table characterising the applicability of the body of studies retrieved for systematic review 3 (analytical performance)

Domain	Description of applicability of evidence
Population	As mentioned in the PICO question, patients of all ages who present with symptoms of acute RTI in primary care were considered relevant to this systematic review. This inclusion criteria was expanded to include blood samples from any setting as long as the CRP measurement was likely to be within a similar range to that found in patients with RTIs. Studies set in primary care did not specifically target patients suffering from RTI and often included any patient who required a blood sample to be taken and sent to the laboratory. One laboratory-based study did specify that samples used were obtained from patients suffering from RTI. The origin of the blood samples for other laboratory studies was either primary care or unspecified. The findings of the current systematic review are based on samples obtained from patients presenting with a variety of symptoms, rather than the target population only (patients presenting with symptoms of acute RTI in primary care). However, it is not believed that the origin of the sample would significantly impact measures of accuracy or precision, therefore the impact in terms of applicability is considered minimal.
Intervention	The intervention of interest was any CE marked C-reactive protein POC quantitative or semi-quantitative method designed for use in the primary care setting. Only two studies evaluated semi-quantitative CRP POCT. Due to this limited data for semi-quantitative CRP POCT this systematic review cannot draw conclusions on the applicability of these devices to the primary care setting. Ten quantitative devices were evaluated in seventeen studies. These studies provided substantial data on the quantitative CRP POCT however there was no standardised testing method used to evaluate the devices. Two laboratory based studies compared multiple devices reporting detailed results enabling a direct comparison of a number of quantitative CRP POC devices. However as they were carried out in a laboratory setting by trained technicians the applicability of the data to use in primary care settings is more limited.
Comparators	In each study the CRP result recorded by the POCT device was compared to a laboratory analyser. Laboratory analysers are currently utilised to measure the level of CRP in blood. Most of these analysers were based in a hospital and are a robust comparator against which the devices were evaluated. Many of the studies had limited information on the comparator, however the studies did state what the comparator was and in general there are no concerns regarding the applicability of the evidence in terms of the comparator given that in all studies the comparator used was representative of the current standard of care.

Domain	Description of applicability of evidence
Outcomes	The outcomes of interest for analytical performance of CRP POCT were the accuracy, precision and the ease of use. No standardised assay or universally agreed acceptable levels of accuracy and precision for CRP POCT devices exists. For accuracy the POC CRP level was compared to a hospital analyser and for precision samples were measured numerous times in a day (within day precision) or measured once a day over a number of days (between day precision). There were three indicators of the accuracy of POCT devices stated in the literature: agreement, bias and correlation. The agreement was predominantly reported as the slope of a Passing-Bablok regression comparing the POCT device to the reference standard. Bias was reported as the mean difference between the POCT device and the reference standard. The correlation between the reference standard and result of the POCT device was stated as a Spearman or Pearson correlation coefficient. All included studies presented one or more of these measures of accuracy. The applicability of the accuracy data depended on the setting and the method used for comparison with the reference standard. Precision was reported as a coefficient of variation (CV). The CV value was calculated by testing the same sample multiple times with the aim of obtaining the same result. There was no standardised assay for determining precision. Studies differed in the number of samples tested, the CRP concentration of the sample, the number of times the sample was measured and the time period the samples where tested for. These factors ensured that it was difficult to directly compare the reported precision. There is no universally acceptable level of precision, however, imprecision <10% was generally considered to be acceptable in the literature. The ease of use was reported in studies from the perspective of laboratory technicians and healthcare professionals. In some cases a standardised questionnaire was used and in others the author had made a comment on ease of use often without any justification around their statement. Many components of ease of use are subjective and are likely to be influenced by the users opinions and experience of POC testing and therefore, the reported ease of use may not be representative of the users who are likely to use the devices in practice.
Setting	All studies included in the primary analysis were carried out in primary care or laboratory settings. Seventeen studies were conducted in European countries and one in Japan. Studies that took place in an emergency department were omitted as the operators in emergency departments may not be representative of healthcare professionals in primary care. The inclusion criteria were expanded to include laboratory based studies as these studies present analytical performance of the devices in an ideal environment where operator error is less likely to be a factor. While studies conducted in primary care give us an insight into user variability, when the operators are likely to be similar as those who will use the devices in practice (Laboratory based studies n=8, Primary care based studies n=5). Four studies were part of an external quality assurance programme and tested devices in the laboratory and at the point-of-care. One study did not state the setting where the analysis took place. In the context of this systematic review, the intended user is healthcare staff who are non-laboratory specialists working in the primary care setting. The inclusion of studies where CRP testing was carried out by laboratory specialists in a laboratory setting may reduce the applicability of the findings to the primary care setting due to the potential of variation in user's technique and the environment to impact the results of the CRP test.

APPENDIX 2: REGULATORY AND REIMBURSEMENT STATUS

Table A16: Regulatory status

Model	Country	Institution issuing approval	Authorisation status yes/no/ ongoing	Verbatim wording of the (anticipated) indication(s)	Specified contra-indications	Date of approval (include expiry date for country of assessment)	Launched yes/no If no include date of launch	Approval number (if available)
Quantitative CRP analysers								
QuikRead go® CRP assay and **QuikRead go® instrument**	Valvira, Finland	CE mark	Yes	QuikRead go® CRP (Cat.No. 135171) The QuikRead go® CRP test is intended for quantitative determination of CRP (C-reactive protein) in whole blood, serum and plasma using the QuikRead go® instrument. For in vitro diagnostic use only.	Diagnostic and treatment decisions must always be made by the healthcare professional in the light of all clinical information on the patient, never on the QuikRead® test result only.	2010	Yes	
QuikRead go® CRP assay and **QuikRead go® instrument**	USA	FDA		QuikRead go® CRP (Cat.No. 145215) The QuikRead go® CRP test is an immunoturbidimetric assay for the in vitro quantitative determination of C-reactive protein (CRP) in K2-EDTA and lithium heparin whole blood, K2-EDTA and lithium heparin plasma and in serum samples. The test is carried out by means of the QuikRead go® instrument. Measurement of C-reactive protein aids in the evaluation of injury to body tissues, and infection and inflammatory disorders. The instrument and assay are for use by trained professionals in the clinical laboratory. For in vitro diagnostic use only. Not for point-of-care use.		2016	Yes	

Model	Country	Institution issuing approval	Authorisation status yes/no/ ongoing	Verbatim wording of the (anticipated) indication(s)	Specified contra-indications	Date of approval (include expiry date for country of assessment)	Launched yes/no If no include date of launch	Approval number (if available)
QuikRead go® CRP+Hb assay and **QuikRead go Instrument**	Valvira, Finland	CE mark		QuikRead go® CRP+Hb (Cat. No. 140068) The QuikRead go® CRP+Hb test is intended for quantitative determination of CRP (C-reactive protein) in whole blood, serum and plasma and for quantitative determination of haemoglobin (Hb) in whole blood using the QuikRead go® instrument. For in vitro diagnostic use only.		2012	Yes	
QuikRead® CRP assay and **QuikRead® 101 Instrument**	Valvira, Finland	CE mark		QuikRead® CRP (Cat. No. 67961) For quantitative determination of CRP (C-reactive protein) in whole blood, serum or plasma, using the QuikRead® 101 Instrument. For in vitro diagnostic use.		2003	Yes	
QuikRead® CRP assay and **QuikRead® 101 Instrument**	Valvira, Finland	CE mark		QuikRead® CRP with prefilled cuvettes (Cat. No. 134192) For quantitative determination of CRP (C-reactive protein) in whole blood, serum or plasma, using the QuikRead® 101 instrument. For in vitro diagnostic use.		2003	Yes	
NycoCard™ CRP assay and **NycoCard™ Reader II**	Norway	CE mark	Yes	NycoCard™ CRP is an *in vitro* diagnostic test for the quantitative determination of C-reactive protein (CRP) in human whole blood and in human serum and plasma. The measurement of CRP provides information for the detection and evaluation of infection, tissue injury, inflammatory disorders and associated diseases.	Not available		Yes	

Model	Country	Institution issuing approval	Authorisation status yes/no/ ongoing	Verbatim wording of the (anticipated) indication(s)	Specified contra-indications	Date of approval (include expiry date for country of assessment)	Launched yes/no If no include date of launch	Approval number (if available)
Alere Afinion ™ CRP assay and **Alere Afinion ™ AS100*** or **Alere Afinion ™ 2** Analyser**	Norway	CE mark	Yes	Alere Afinion™ CRP is an in vitro diagnostic test for the quantitative determination of C-reactive protein (CRP) in human whole blood and in human serum and plasma. The measurement of CRP provides information for the detection and evaluation of infection, tissue injury, inflammatory disorders and associated diseases.	Not available	May 2005	Yes	Not available
Eurolyser CRP assay and **Cube Analyser**	Austria	CE mark	Yes		Not available	10-03-2010	Yes	
Eurolyser CRP assay and **Cube S Analyser**	Austria	CE mark	Yes		Not available	10-03-2010	Yes	
Eurolyser CRP assay and **Eurolyser smart 700/340**	Austria	CE mark	Yes		Not available	04-05-2008	Yes	
Eurolyser CRP assay and **Eurolyser smart 700/546**	Austria	CE mark	Yes	The Eurolyser smart (single method automated reading technology 546 is intended to provide a precise, user-friendly measurement system for rapid, direct ascertainment of CRP /hsCRP concentrations from whole blood and serum, as a true point-of-care system.	Not available	10-03-2010	Yes	

Model	Country	Institution issuing approval	Authorisation status yes/no/ ongoing	Verbatim wording of the (anticipated) indication(s)	Specified contra-indications	Date of approval (include expiry date for country of assessment)	Launched yes/no If no include date of launch	Approval number (if available)
iChroma™ CRP test cartridge and **iChroma™ Reader**	UK	CE mark	Yes	Not available	Not available	04-11-2014 Expiry date: 02/11/2019	Yes	
iChroma™ CRP test cartridge and **iChroma™ Reader**	US	FDA	Yes	Not available	Not available	13-07-2007	Yes	
AQT90 Flex CRP assay and **AQT90 Flex™ analyser**	Denmark	CE mark	Yes	The AQT90 FLEX analyzer is an immunoassay instrument based on the quantitative determination of time-resolved fluorescence to estimate the concentrations of clinically relevant markers on whole-blood and plasma specimens to which a relevant anticoagulant has been added. It is intended for use in point-of-care and laboratory settings.		01-2008	Yes	
Microsemi™ CRP Reagent Unit		CE mark	Yes				Yes	
spinit® CRP disposable disc and **spinit® instrument**	Portugal	CE mark	Yes	spinit® is a fully automated Point-of-Care diagnostics solution designed to deliver quantitative measurement of blood parameters to physicians in minutes. spinit® CRP disposable disk is used with the spinit® instrument as a quantitative assay for the measurement of CRP concentration in whole blood (venous and capillary), serum and plasma samples.	Not available	06-2016	Yes	Not available

Model	Country	Institution issuing approval	Authorisation status yes/no/ ongoing	Verbatim wording of the (anticipated) indication(s)	Specified contra-indications	Date of approval (include expiry date for country of assessment)	Launched yes/no If no include date of launch	Approval number (if available)
				This type of assay is used for the detection and evaluation of infection, tissue injuries, inflammatory responses and associated diseases.				
CRP IS™ test kits and **Innovastar™ analyser**		CE mark	Yes			21-07-2016		
Semi-quantitative CRP tests								
Actim® CRP dip sticks	Finland	CE mark	Yes	The Actim® CRP test is a visually interpreted, semi quantitative immunochromatographic dipstick test, which is used for determination and monitoring of CRP concentrations in whole blood samples. The test is intended for professional use.	Not available	01-06-2015		
Clearetst® CRP strips								
FebriDx®	US	CE Mark	Yes	FebriDx® is a rapid immunoassay for the visual, qualitative, in vitro detection of elevated levels of both MxA and CRP directly from peripheral whole blood. The test measures a clinically significant immune response to a suspected invasive viral and/or bacterial infection in patients older than 1 years that present within 3 days of an acute onset fever (exhibited or reported) and within 7 days of new onset respiratory symptoms consistent with a community-acquired upper respiratory infection. The FebriDx® test aids in the	The following conditions could lead to erroneous results: ● Current immunosuppressive state or use of immunosuppressive drugs. ● Current use of oral anti-infective	October 2014 Approval; Updated registration July 2018	No launch yet. Anticipated European launch September 2018.	

Model	Country	Institution issuing approval	Authorisation status yes/no/ ongoing	Verbatim wording of the (anticipated) indication(s)	Specified contra-indications	Date of approval (include expiry date for country of assessment)	Launched yes/no If no include date of launch	Approval number (if available)
				clinical identification of patients with an underlying acute respiratory viral infection from either Influenza A/B, Adenovirus, Respiratory Syncytial Virus, Metapneumovirus, Parainfluenza Virus, Rhinovirus, Coronavirus, Cytomegalovirus, Herpes Simplex Virus, and Epstein-Barr Virus; and/or patients with a clinically significant immune response consistent with an underlying bacterial infection. The test is intended for professional use in an outpatient setting and should be used in conjunction with other clinical evidence including laboratory, radiographic, and epidemiological information. Negative results do not preclude respiratory infection (e.g. rhinovirus, coronavirus) and should not be used as the sole basis for diagnosis, treatment, or other clinical and patient management decisions. In addition to utilizing radiography and clinical presentation to aid in diagnosis, additional laboratory testing (e.g. bacterial and viral culture, immunofluorescence, and polymerase chain reaction [PCR]) may be used to confirm whether a specific respiratory pathogen exists.	drugs. ● Current use of interferon therapy (e.g. for multiple sclerosis, HIV, hepatitis B/C). ● Live viral immunization within the last 14 days. ● Major trauma, major surgical intervention, and severe burns within the preceding 14 days. ● Chronic fevers lasting more than 7 days.			

Sources: Dossier submissions from Orion, Abbott, Medix Biochemica and RPS Diagnostics, and available information from manufacturers' websites.

Table A17: Summary of (reimbursement) recommendations in European countries for CRP POCT

Country	Implementation of CRP POCT	Status of recommendation (positive/negative/ongoing/not-assessed/no detail available)	If positive, level of reimbursement*
Belgium	Yes [99]	No details available	No details available
Czech Republic [b]	Yes[52]	No details available	No details available
Denmark [b]	Yes[131]	Positive	about DKK 65-77 per test [b]
Estonia	Yes[52, 128]	No details available	No details available
Finland	Yes[296]	No details available	No details available
Germany [a, b]	Yes[52] (ambulatory care setting only) [a]	Positive, also under assessment appears to be ambulatory care setting only) [a]	€1.15 per test in general laboratory, €4.90 in special laboratory [a]
Hungary [a b]	Yes	Positive (reimbursed regardless of test product) [a]	No price available
Ireland	No	Not assessed	Not relevant
Italy [a]	Yes (inpatient & outpatient settings only) [a]	Positive (tests are performed and reimbursed in the NHS, but this may vary between regions. CRP POCT is not reimbursed by the NHS in primary care)	About €3.87/test [a]
Lithuania [a]	Yes (inpatient & outpatient settings only) [a]	Positive (inpatient and out-patient only)	No price available
Netherlands [a b]	Yes[52]	Positive (depending on the indication (e.g. pneumonia)) [a]	About €3.90/test [b]
Norway [a b]	Yes[52]	Positive (CRP tests are reimbursed; CRP POCT are the most widely used)	NOK 42/test [b]
Poland [a b]	Yes (primary care, ambulatory & hospital setting)[a]	Positive	No price available
Slovakia [b]	Yes	No details available	No details available
Slovenia [a]	Yes (emergency and primary care settings)	Positive (higher costs for CRP POCT than lab test) [a]	No details available
Spain	No details available	No details available	No details available
Sweden	Yes[52]	No details available	No details available
Switzerland [a b]	Yes[52]	Positive (regardless of setting; fixed price per test) [a]	CHF 10 [b]
United Kingdom [a]	Yes[42, 44]	Negative (non-mandatory recommendation in guideline)	No price available

Abbreviations: CHF – Swiss Franc; DKK – Danish Krone; NHS – National Health Service; NOK – Norwegian Krone.

Sources: a. Feedback from WP4 partners; b. Dossier submission from Orion on availability of QuikRead® (and price if available) in European countries.

APPENDIX 3: CHECKLIST FOR POTENTIAL ETHICAL, ORGANISATIONAL, PATIENT AND SOCIAL AND LEGAL ASPECTS

•	**Ethical**	
○	Does the introduction of the new technology and its potential use/non-use instead of the defined, existing comparator(s) give rise to any new ethical issues?	Yes
	As the skin will be broken to remove a small amount blood, there is a small risk of harm to patient or staff from blood borne contamination.	
○	Does comparing the new technology to the defined, existing comparators point to any differences that may be ethically relevant?	Yes
	As the skin will be broken to remove a small amount blood, there is a small risk of harm to patient or staff from blood borne contamination.	
•	**Organisational**	
○	Does the introduction of the new technology and its potential use/non-use instead of the defined, existing comparator(s) require organisational changes?	Yes
	Yes, it requires the use of a test and therefore the time taken to collect the blood sample and run the test would need to be incorporated into the care pathway. It is currently unclear who would administer the test (GP/practice nurse/ other staff member) and it may differ between practices based on the their availability. In either case, use of CRP POCT is likely to prolong the consultation period, even when the time take to run the test is short. The reimbursement for the cost of purchasing and administering the technology would need to be considered. Those involved in testing with require training in the use of the device and the interpretation of the findings. To ensure the accuracy and reliability of testing, all testing should be ISO-accreditable, including meeting requirements in relation to internal quality control, quality assurance and the recording of training and test results. Careful planning including of a quality management system is required to support implementation at a regional or national level.	
○	Does comparing the new technology to the defined, existing comparator(s) point to any differences that may be organisationally relevant?	Yes
	Introduction of CRP POCT may lead to changes in the patient care pathway depending on by whom the test is administered and who communicates the test results to the patient. Introduction of delayed prescriptions for patients with equivocal results may be considered which could represent a change in practice.	
•	**Social**	
○	Does the introduction of the new technology and its potential use/non-use instead of the defined, existing comparator(s) give rise to any new social issues?	Yes
	Yes, the introduction of CRP POCT could potentially lead to inequality of care for different patient groups (e.g. public and private patients) depending on how and for whom the test is reimbursed.	
○	Does comparing the new technology to the defined, existing comparator(s) point to any differences that may be socially relevant?	Yes
	Given wide variation between countries in prescribing guidelines, patient access and pathways, and cultures, availability of CRP POCT could be used to change the conversation between clinician and patient, rather than reduce diagnostic uncertainty and subsequent management. Clinicians may already have high clinical certainty of diagnosis, the value of the CRP POCT may be around patient education rather than just clinician behaviour change	
•	**Legal**	
○	Does the introduction of the new technology and its potential use/non-use instead of the defined, existing comparator(s) give rise to any legal issues?	No
○	Does comparing the new technology to the defined, existing comparator(s) point to any differences that may be legally relevant?	No

For the purpose of transparency, a separate document with comments on the 2nd draft assessment from external experts and the MAH/manufacturer(s) (fact check), as well as responses from authors, is available on the EUnetHTA website.