Swiss Learning Health System

Improving guidance for antibiotic prescribing in Swiss ambulatory care: optimizing the use of C-reactive protein testing for respiratory tract infections

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Key Messages

The Challenge

Antibiotic consumption is a major modifiable driver of antibiotic resistance (ABR), a serious threat to public health globally. Primary care accounts for most antibiotic prescriptions, and 30-50% of these prescriptions are considered unnecessary. Acute respiratory tract infections (RTIs) are the most common reasons for patient encounters and inappropriate antibiotic prescribing in primary care, linked to the development of drug-resistant bacteria at the individual, community, and national levels. The unnecessary and inappropriate antibiotic use increases the incidence of adverse events, re-consultations, and complications and consequently increases healthcare costs. It has been estimated that if no effective actions are taken, by 2050 ABR could become the leading cause of death, surpassing cancer. C-reactive protein (CRP) point-of-care test(-ing) (POCT) is increasingly being promoted to reduce diagnostic uncertainty and enhance antibiotic stewardship. CRP-POCT's use in limiting ABR could be better established through best-practice guidelines. CRP-POCT can enable clinicians to discern inflammation due to bacterial from non-bacterial infections and identify the patients who can benefit the most from antibiotics. This, however, can be a challenge due to the following:

- data on antibiotic consumption (for RTIs) from Swiss primary care are limited, which makes it challenging to identify the strategies that are best to reduce prescribing;
- documentation of the use of CRP-POCT to reduce unnecessary antibiotic prescribing for RTIs in Swiss primary care is limited;
- clinical guidance on the use of CRP-POCT to reduce unnecessary antibiotic prescribing for RTIs in primary care is lacking;
- advice for physicians on how to deal with patients' pressure and the decision of not prescribing antibiotics, in the current clinical guidelines, is lacking.

Options to address the challenge

1. Strengthening clinical guidelines by integrating CRP-POCT into the clinical pathway to support diagnostic decisions and guide antibiotic prescribing for RTIs.
2. Strengthening the integration of CRP-POCT by incorporating guidance on interpreting CRP concentration levels to support diagnostic decisions and guide antibiotic prescribing for RTIs.
3. Strengthening physicians prescribing decisions by incorporating advice on how to deal with patients' pressure and the decision of not prescribing antibiotics to reinforce physicians' confidence and enhance the reduction in antibiotic prescribing.

Implementation Considerations

Potential windows of opportunity to consider include:

- integrating CRP-POCT as a target topic in local and national strategies already in place to enhance antibiotic stewardship;
- integrating the use of CRP-POCT and CRP cut-off guidance as part of the clinical examination in the clinical pathway of relevant local and national guidelines, e.g., StAR (Strategy on Antibiotic Resistance)-SSI (Society of Infectious diseases) guidelines, EMR, INFECT by ANRESIS;

- involving both GPs and specialists in the development and update of prescribing guidance with the target topic, e.g., a collaboration between the Swiss Society of General Internal Medicine (SGAIM) and the SSI;
- developing prescribing guidelines for GPs by GPs, which integrate the target topic, e.g., through SGAIM;
- adding the topic of patient-physician communication and shared-decision making as part of the national public information campaigns and in flyers for patients;
- adding the topic of how to deal with decisions of non-prescribing and patients' pressure or expectation to receive antibiotics in the clinical pathway, e.g., decision aids of rapid access;
- distinction between outpatient data on national surveillance, especially for primary care, to enable feedback for physicians and on the performance of strategies.

Potential barriers to implementation that should be considered include:

- high practice volume features such as time pressure and time constraints, increased workload and increased working time;
- a lack of involvement of general practitioners (GPs) in the development of prescribing clinical guidelines;
- a lack of a system that allows rapid access to information and guidance, and a lack of a back-up support system for doctors;
- a lack of a systematic approach supporting the development of clearer guidelines that regularly and timely integrate the up-to-date body of evidence;
- the limited evidence on intermediate CRP values to differentiate all types of RTIs, especially a lack of a strategy to deal with results from intermediate CRP values;
- a lack of data on antibiotic consumption exclusive to primary care could interfere with the proper quantification of antibiotic use and, thus, with the monitoring and achievement of implemented strategies.

Executive Summary

The Issue

There remains substantial variation in antibiotic consumption within and across healthcare systems, despite having established strong commitments to tackle ABR globally [1-3].

The outpatient setting, especially primary care, is where most of the antibiotics used in humans are prescribed, and half of these prescriptions are unnecessary. Acute RTIs are the most common reason for patient encounters in primary care and inappropriate antibiotic prescribing, which is linked to the development of drug-resistant bacteria at the individual, community, and national levels.

The excessive and inappropriate use of antibiotics have progressively turned antimicrobial resistance (AMR) and its consequences into "one of the most serious global threats to public health globally, while the pipeline of new antibiotics is drying out. The rise in resistance of antibiotics considered critical is of particular concern. The inappropriate use of antibiotics increases the incidence of adverse events, re-consultations, complications and healthcare costs. Furthermore, by 2050 infections with resistant pathogens could become the leading cause of death, surpassing cancer, if no effective actions are taken to limit ABR.

Diagnostic tests have the potential to dramatically reduce the unnecessary and inappropriate use of antibiotics if used effectively. Their value in tackling infectious diseases and limiting ABR could be better established through their integration in best-practice clinical guidelines. CRP-POCT is increasingly being promoted to reduce diagnostic uncertainty and enhance antibiotic stewardship since it can enable clinicians to discern bacterial infections from viral disorders. This creates situations where antibiotics are prescribed based on diagnosis, helping clinicians identify the patients who benefit the most from antibiotics. However, prescribing practices and diagnostic certainty can be influenced by doctor-patient behavioural factors. Considering these factors is key to achieving a sustainable change in the use of antibiotics.

Current strategies aiming to tackle infectious disease and limit ABR need to optimize the use of CRP-POCT [4], a clinical resource readily available and of widespread use in the Swiss ambulatory care setting, especially in primary care. At the same time, these strategies cannot underestimate the contribution of behaviour change to reducing antibiotics' unnecessary and inappropriate use. In this regard, multifaceted approaches have been shown to lower ABR and are recommended to address behaviour change.

One of the priorities of the Federal Council in the policy agenda "Health2020" is to raise awareness about the importance and appropriate use of antibiotics, and to monitor, control and eliminate ABR [5]. POCT has been acknowledged as a "key solution to the problem of antibiotic abuse and overprescribing" [6] after the launch of the Swiss Strategy StAR, which aims to ensure that antibiotics remain effective in the long term and to curb the development of ABR [7]. National surveillance of antibiotic consumption is another objective of the StAR and the Centre for Antibiotic Resistance (ANRESIS) strategies, both matching the "Health2020" agenda to enhance antibiotic stewardship [7-10]. All strategies sharing the goal of tackling ABR could contribute to optimising the use of CRP-POCT for RTIs, the most common clinical indication treated with antibiotics in primary care.

Reducing unnecessary antibiotic prescribing in Swiss primary care as a challenge

Reducing unnecessary antibiotic prescribing in Swiss primary care is a challenge for several reasons. Data on antibiotic consumption for RTIs from Swiss primary care are limited, which limits the quantification of antibiotic prescribing and consequently limits the identification and design of interventions that are best to tackle ABR. Although CRP-POCT is available and of widespread use in Swiss ambulatory care facilities, especially in primary care, there is limited documentation of its use as a diagnostic tool to reduce unnecessary antibiotic prescribing. Similarly, there is a lack of clinical guidance on using CRP-POCT and the interpretation of CRP levels in some of the most relevant national clinical guidelines. Moreover, guidelines and other sources providing information for the management and treatment of RTIs need to consider the behavioural factors influencing prescribing decisions, and provide advice on dealing with patients' pressure and deciding not to prescribe antibiotics.

Three recommendations for action

In view of the existing evidence, the widespread adoption of CRP-POCT internationally as a stewardship intervention to tackle ABR, and the availability and widespread use of CRP-POCT in Swiss ambulatory care, three actions have been identified to address the challenge of reducing unnecessary antibiotic prescribing. The recommendations are informed by evidence-based reviews and both high-profile randomized controlled trials (RCTs) and clinical guidelines. In particular, a meta-analysis of RCTs provides the most up-to-date evidence on the clinical effectiveness of CRP-POCT in reducing antibiotic prescribing for RTIs in outpatient care.

The first recommendation describes the evidence on the clinical effectiveness of CRP-POCT and its integration in the clinical pathway to support diagnostic decisions and guide prescribing.

The second recommendation for action describes using CRP values to guide diagnostic and prescribing decisions based on evidence of the clinical effectiveness of CRP-POCT and its integration into clinical guidelines. Systematic reviews and individual RCTs provide examples of the CRP cut-off values incorporated as part of CRP-POCT interventions to help physicians interpret results. High-profile guidelines show the CRP cut-off values adopted from scientific evidence to fit the local setting.

The third recommendation, also based on evidence-based research from systematic reviews and particularly from high-profile RCTs, describes the evidence on the use of negotiation-communication skills and internet-based training to address behaviour change and enhance and sustain the effect of longer-term CRP-POCT. Looking at the elements of CRP-POCT interventions provided in high-profile RCTs, potential components that can be adopted and adapted to the local context could be identified and contextualised.

Implementation Considerations

Potential windows of opportunity include the integration of CRP-POCT as a target topic in local and national strategies already in place to enhance antibiotic stewardship, e.g., StAR, Smarter Medicine, INFECT interface by ANRESIS. A high-level opportunity would be integrating the use of CRP-POCT as part of the clinical examination in the clinical pathway of relevant local and national guidelines, e.g., SSI guidelines which have a commitment with StAR. Furthermore, involving both GPs and specialists in developing and updating prescribing guidance that integrates the target topic, e.g., by collaboration between SSI and SGAIM.

Especial consideration could be given to developing prescribing guidelines for GPs by GPs, e.g., by the lead of SGAIM, which could integrate the target topic. In particular, integrating CRP cut-off guidance in the clinical pathway of guidelines could further enhance prescribing decisions. Adding the issue of how to deal with decisions on non-prescribing and patients' pressure in the clinical pathway, e.g., through decision aids that allow rapid access to information to reinforce physicians' confidence and enhance the decisions of not prescribing.

Adding the topic of patient-physician communication and shared-decision making as part of the national public information campaigns and adding these topics in patient flyers could enhance behaviour change. Distinction between outpatient data on the national surveillance, especially for primary care, could enable feedback for physicians on antibiotic prescribing performance, for example.

Current and new strategies that aim to tackle ABR in Switzerland could face several barriers to implementing the proposed action recommendations. These barriers include the features of a high practice volume, i.e. time pressure and time constraints, increased workload and working time. These are perhaps the most important potential barriers to using evidence-based decisions in primary care. Therefore, complementary barriers are a lack of a system or format that allows rapid access to guidance and information on the topic and a lack of a back-up support system when the latter fails. Another potential barrier is a lack of a systematic approach that allows and supports the development of clearer guidelines for doctors, which can regularly and timely integrate the relevant, up-to-date body of evidence. The limited evidence on intermediate CRP values to differentiate all types of RTIs could be problematic, especially a lack of a strategy to deal with results from intermediate CRP values.

Table of technical definitions

Antimicrobial resistance (AMR): “the resistance of a microorganism to an antimicrobial medicine to which it was originally sensitive” – the WHO, 2012 [11].

Antibiotic resistance (ABR): “occurs when bacteria change in response to the use of antibiotics used to treat bacterial infections (such as urinary tract infections, pneumonia, bloodstream infections) making them ineffective” – the WHO, 2012 [11].

Outpatient care setting comprises services provided on an ambulatory basis including, but not limited to, primary and specialised care.

Point of care testing (POCT): aims to provide accessible results that are obtained far more rapidly than testing from traditional laboratories helping clinicians to clear diagnostic uncertainty and to enable rapid decision-making for the management and treatment of disease.

Antibiotics stewardship: a systematic and sustainable effort to measure and improve how antibiotics are prescribed by clinicians and used by patients. Improving antibiotic prescribing and use is critical to effectively treat infections, protect patients from harms caused by unnecessary antibiotic use, and combat antibiotic resistance [12].

1. Background and Context

Antibiotics are the most common antimicrobial medicine used in humans to prevent and treat bacterial infections. ABR is a natural process that develops over time. When bacteria in the body are exposed for the first time to an antibiotic, those bacteria more vulnerable to the antibiotic will die off [11]. The surviving bacteria will reproduce, passing their resistant features to succeeding generations. When the same antibiotic is again introduced into the body, fewer bacteria will die off, and a higher number of new bacteria resistant to that antibiotic will remain. Every new antibiotic can develop a cycle of resistance, and the body eventually produces bacteria that are resistant to multiple types of antibiotics. This cycle repeats every time an antibiotic is introduced in the body and only stops until another antibiotic kills the bacteria.

Antimicrobial resistance – a global challenge for public health and healthcare systems

> "The public will demand [the drug and] … then will begin an era … of abuses. The microbes are educated to resist penicillin, and a host of penicillin-fast organisms is bred out, which can be passed to other individuals and perhaps from there to others until they reach someone who gets septicaemia or pneumonia, which penicillin cannot save. In such a case, the thoughtless person playing with penicillin treatment is morally responsible for the death of the man who finally succumbs to infection with the penicillin-resistant organism. I hope the evil can be averted." –
>
> *Alexander Fleming*[1] *during his Nobel Prize speech in 1945* [13].

Fleming himself predicted how the misuse of penicillin could lead to the selection and spread of mutant-resistant bacteria [14]. Antibiotics revolutionised modern medicine, but the belief that infectious diseases would become a problem of the past led to their widespread use, very often without solid evidence of their benefits [15,16]. The world regularly responded to new infections or a problem of resistant bacteria with the development of new and 'better' drugs. Already, the early 1990s were characterised by a high number of antibiotic-resistant bacteria and a drying-out pipeline in the discovery of new drugs marking the beginning of the end of the golden age of antibiotics [17,18].

Today, eighty years after antibiotics became available, AMR and its consequences have escalated into "one of the most serious global threats to public health of the 21st century" – *the WHO, 2014* [3,19]. Globally, AMR is associated with 700,000 deaths yearly due to drug-resistant infections [2]. It is estimated that if AMR continues to rise, by 2050, 10 million people could die annually, costing society up to US$ 100 trillion (Figure 1). In Europe alone, 25,000 patients die yearly due to multi-drug resistant infections costing society about €1.5 billion yearly. In OECD countries, including Switzerland, it is estimated that by 2050 a cumulative loss due to AMR could reach US$ 2.9 trillion compared to a world with no AMR [20,21].

If no effective actions are taken, AMR could become the leading cause of death, surpassing cancer [2] (Figure 2). Already a large proportion of existing bacteria are antibiotic-resistant [22-26] and there is a lack of antimicrobials that could compensate for the loss of

[1] Alexander Fleming was a Scottish researcher who discovered penicillin in 1928.

effectiveness of existing antimicrobials [27]. The ultimate fear is *a 'post-antibiotic'* era in which no antimicrobials will be able to combat simple infections [3], as first raised in 1992 [28].

Figure 1. Geographical distribution of deaths attributable to antimicrobial resistance every year by 2050. Source: *O'Neill, 2014, for the Review on Antimicrobial Resistance* [2].

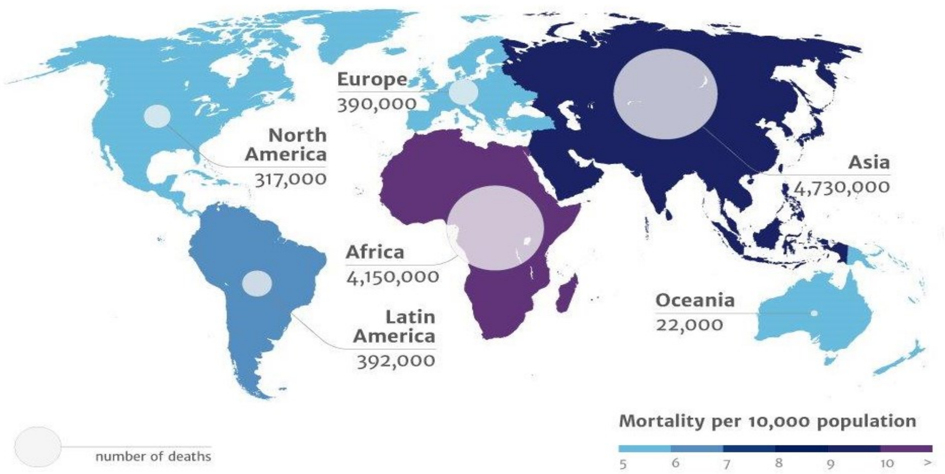
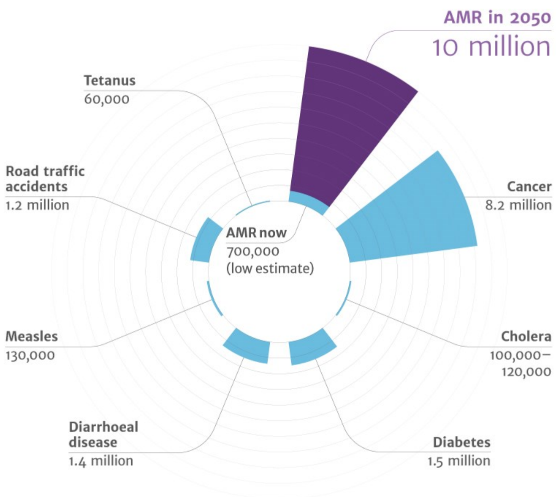


Figure 2. Deaths attributable to antimicrobial resistance every year compared to other major causes of death by 2050. Source: O'N*eill, 2014, for the Review on Antimicrobial Resistance* [2]. Notes. AMR, Antimicrobial Resistance.



Antimicrobial resistance is directly associated with antibiotic use

Antibiotic consumption is a major modifiable driver of AMR. Available evidence demonstrates that the extent of antibiotic consumption is directly and consistently associated with the development of drug-resistant bacteria [29,30]. Research data also shows rising rates of AMR at the individual (patient) level and increased resistance at the community, regional and national levels [29,31,32]. The inappropriate use of antibiotics, including overuse, underuse, or misuse, can highly compromise their effectiveness and contribute to the development and spread of ABR [11].

Box 1. Definitions of antibiotic consumption.

Overuse occurs when antibiotics are taken or prescribed when not needed or when taken without medical justification. This can result in partial bacterial resistance to a drug that offers no benefit when there is proof that antibiotics do not help, e.g., simple or viral infections.

Underuse occurs when antibiotics that are necessary to treat disease are not taken or prescribed at all or are taken or prescribed in the wrong, lower, or weaker than required dose. This can result in longer illness episodes and an increased risk of disease transmission, symptoms, and death.

Misuse occurs when antibiotics are not taken as prescribed, generally when a person feels recovered from an illness before completing the treatment and not finishing a full course. Resistance to antibiotics can last for months once bacteria develop resistance.

Inappropriate use of antibiotics occurs when all the above play a role: when antibiotics are taken when not needed; if the type, dose, route and length of therapy is not the correct choice, if used to treat non-bacterial infections, or if there is poor adherence to treatment guidelines.

Source: adapted from *the WHO, 2012* [1][18].

Consequences of inappropriate antibiotic consumption

Antibiotics commonly cause unwanted effects such as diarrhoea, vomiting, and rash. When used inappropriately, however, their effectiveness can be highly compromised, reducing the chance of curing the infection and increasing the likelihood of developing drug-resistant bacteria [29]. This increases the incidence of adverse events ranging from mild gastrointestinal distress to life-threatening infections, more frequent re-consultations, and risk of complications, subsequently raising healthcare costs [29,30,33-35].

Trends in antibiotic consumption

Evidence shows that countries with higher antibiotic consumption have higher rates of ABR [31,36,37]. In 2018, the European Surveillance for Antibiotic Consumption Network (ESAC-Net) showed that Southern and Northern Europe had the highest and lowest, respectively, average total rates of antibiotic consumption in the community and hospital sectors [38]. The Netherlands and Greece had the lowest and highest rates, respectively. The ECDC estimates that 30-50% of all antibiotics prescribed in Europe are unnecessary.

According to the Federal Office of Public Health (FOPH) and ANRESIS, Switzerland holds an intermediate position in the rates of ABR and antibiotic consumption in the hospital and outpatient care sectors relative to its population [10,39,40]. The rates are lower than France, Italy, and Great Britain but higher than the Netherlands or the Scandinavian countries. In 2017, antibiotic consumption in Switzerland was lower than in many ESAC-Net countries [40]. There are important differences between cantons, however, with the Italian- and French-speaking cantons consuming up to three times more than the German-speaking cantons.

Factors influencing (unnecessary) antibiotic prescribing

Decision-making surrounding antibiotic prescribing is a complex phenomenon shaped by an interaction between patient, physician and other non-pharmacological factors [41].

Diagnostic uncertainty is an important driver of antibiotic prescribing. The overlapping clinical features of bacterial and viral infections are important factors affecting the physicians' ability to identify the patients who would benefit the most from antibiotics. With ambiguous symptoms, physicians may feel it is a safer choice to prescribe antibiotics, especially if they fear a diagnostic error and if it is suspected that a condition would respond to antibiotics [42]. For difficult diagnoses, physicians may perceive that the risk of undertreatment is greater than the risk of unnecessary antibiotics [43]. Point of care test(-ing) (POCT) increase diagnostic certainty, making physicians feel more confident in their decision not to prescribe antibiotics [44-46]. C-reactive protein (CRP) can be used to communicate the results to patients and the unnecessary use of antibiotics [47].

Evidence-based clinical guidelines are proven to address ABR as they aim to standardise the quality of care, including prescribing decisions [47-49]. Physicians have identified that a lack of suitable guidance for treating disease and antibiotic use can influence their prescribing decisions [50-52]. Research shows, however, that factors such as physicians' experience, professional autonomy and influence of others may override the 'book of rules' [53-55]. This makes beliefs and habits key drivers in changing antibiotic prescribing using clinical guidelines.

Physicians have identified patient expectations and demand to receive antibiotics as one of the major drivers influencing their prescribing decision [57,58]. Studies show a direct association between physician perception of patient expectation of antibiotics and increased rates of unnecessary prescriptions [59-62] but increased patient satisfaction as physicians try to maintain a good relationship with their patients [60].

Box 2. Average total rates of antibiotic consumption in the community and hospital sectors.

ESAC-Net	**Community and hospital sectors combined, 2018**
ESAC-Net EU/EEA countries, overall	20.1 DDDs per 1 000 inhabitants per day
ESAC-Net: the Netherlands	9.7 DDDs per 1 000 inhabitants per day
ESAC-Net: Greece	34.0 DDDs per 1 000 inhabitants per day
Healthcare setting	**Switzerland* vs ESACT-Net countries, 2017**
Outpatient sector, overall	10.7 vs 21.8 DDD per 1,000 inhabitants per day
ESAC, range: Netherlands - Cyprus	10.1 to 33.6 DDD per 1,000 inhabitants per day
Hospital sector, overall	1.3† vs 2.0 DDD per 1,000 inhabitants per day
ESAC, range: Netherlands - Malta	0.9 to 3.1 DDD per 1,000 inhabitants per day

*FOPH/ANRESIS; †2016 data; Community = outpatient; EU/EEA, European Union/The European Economic Area; DDDs, defined daily doses; ESAC-Net, the European Surveillance for Antibiotic Consumption Network; FOPH, Federal Office of Public Health; ANRESIS, the Swiss Centre for Antibiotic Resistance. Source: [10,38,39,56].

Factors in the practice environment may also lead to unnecessary prescribing. High-volume practice, increased workload, time constraints (e.g., due to length of consultations), and risk of patient loss to follow-up can cause physicians' anxiety and concern about missing a diagnosis that truly needs antibiotics. Physicians may prescribe 'just in case' if they have 'no time' to provide adequate explanations to their patients, to avoid the risk of disease deterioration, or if they feel exposed to legal action if a patient's condition deteriorates [63-67].

Systematic reviews and other studies show that interventions that reduce clinician uncertainty regarding social and clinical outcomes and provide strategies to meet patients' needs within a consultation are most likely to reduce antibiotic prescribing [68].

2. The Challenge

How best to reduce unnecessary (and inappropriate) antibiotic prescribing for RTIs in Swiss ambulatory primary care is challenged by several contributing factors:

1. the outpatient care setting, especially primary care, is a major driver of ABR since most antibiotics are inappropriately prescribed for RTIs, which are the most common reason for patient encounters in primary care
2. limited data on antibiotic consumption (for RTIs) from Swiss primary care
3. limited documentation on the use of CRP-POCT to reduce unnecessary antibiotic prescribing for RTIs in Swiss primary care
4. lack of guidance on the use of CRP-POCT to reduce unnecessary antibiotic prescribing for RTIs in primary care

These factors are explained in more detail in the following sections.

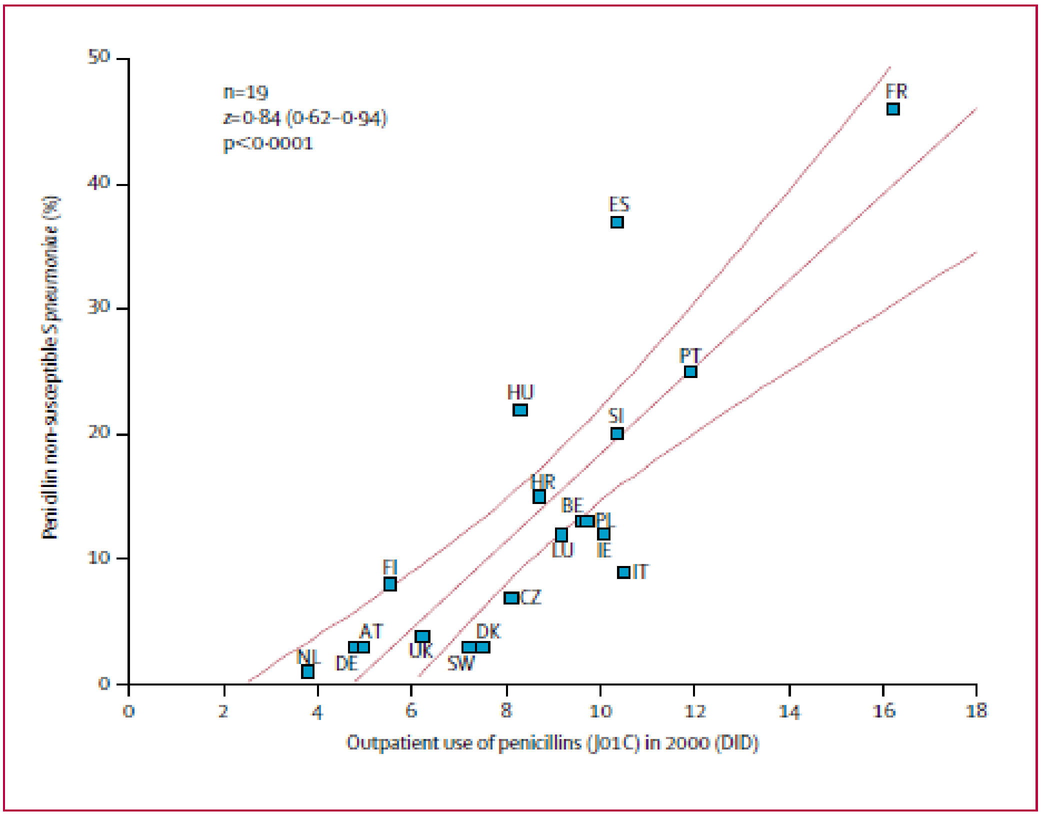
Primary care and inappropriate antibiotic prescribing – a major driver of ABR

The outpatient setting, especially primary care, is where the vast majority of the antibiotics used in humans are prescribed and in which GPs are the main prescribers of antibiotics [29,31,40,69,70]. In primary care, a large proportion of prescriptions are issued to treat conditions for which antibiotics have little or no benefit. Of all antibiotics, 80-90% are prescribed in primary care, and 50% of these antibiotics are unnecessary [40,71-73].

Strong evidence demonstrates, based on different types of resistance and prescribing data from 19 countries, that as prescribing of a specific antibiotic increased in primary care, resistance to that antibiotic in the community was likely to increase, too (Figure 3) [31,36]. Countries with higher rates of antibiotic use also had higher rates of ABR [31,74].

Evidence also shows that the rates of antibiotic prescribing in primary care are significantly and directly associated with the rates of ABR at the individual, community, and national levels [29,31]. Since the use of antibiotics at the population level in a given area is directly associated with the rates of ABR in that area, antibiotic consumption at the community level may influence the rates of ABR in hospital care [75].

Figure 3. Correlation between the use of penicillin in primary care in 19 European countries: penicillin use and prevalence of penicillin non-susceptible *S pneumoniae*.



Source: *Goossens et al*., *for the ESAC project group, 2005* [20]. **Notes.** Outpatient use of penicillins = amount of penicillins prescribed in primary care by defined daily dosage (DDD) per 1000 inhabitants daily (DID). DDD: assumed average maintenance dose per day for the drug's *main* indication in adults as recommended by the WHO. AT, Austria; BE, Belgium; HR, Croatia; CZ, Czech Republic; DK, Denmark; FI, Finland; FR, France; DE, Germany; HU, Hungary; IE, Ireland; IT, Italy; LU, Luxembourg; NL, The Netherlands; PL, Poland; PT, Portugal; SI, Slovenia; ES, Spain; UK (England).

Respiratory tract infections – the most common condition for inappropriate antibiotic prescribing in primary care

Every year most people would develop an acute RTI, making it the most frequent acute condition for patient visits to their primary care physician. Most patients with acute RTIs receive an antibiotic prescription for systemic use after a visit to their primary care physician [31,76-78]. In most healthy individuals, however, RTIs are predominantly of viral aetiology and self-limiting. They resolve without the need for antibiotics since an individual's immune system is strong enough to fight a simple infection.

Evidence from systematic reviews and other studies show that antibiotics are minimally effective or have no benefit in treating most patients suffering from RTIs. These infections include the common cold, sore throat, acute sinusitis, rhinosinusitis, pharyngitis, acute bronchitis and otitis media [79-85]. With a few exceptions (e.g., pharyngitis and otitis media also caused by bacteria, and COPD) [86] antibiotics for RTIs are often inappropriate [30,85,87-90], especially for upper RTIs (URTIs) [91,92]. Clinical practice guidelines thus advise against routine treatment of antibiotics for uncomplicated RTIs [93].

Limited data on antibiotic consumption (for RTIs) from Swiss primary care

Monitoring antibiotic use in outpatient care is one of the targets of the national surveillance strategy by the StAR-FOPH and ANRESIS to enhance antibiotic stewardship [7-10]. The strategies aim to match the objectives of the Swiss policy agenda "Health2020"[2] [5] and the WHO global action plan [44]. Surveillance feeds from datasets of pharmacies and self-dispensing physicians or only pharmacies. Current data, however, do not distinguish between outpatient services, which encompass services provided on an ambulatory basis, including but not limited to primary and specialised care. Moreover, Swiss primary care comprises about 45% of the outpatient care setting [94]. Research shows substantial variation in antibiotic prescribing between primary and specialised care and other outpatient services [95].

Observational studies have provided some insights into the practical prescribing of antibiotics exclusive to Swiss primary care. These have shown that RTIs are the most common clinical conditions for antibiotic prescribing [96-100]. The rates of antibiotic prescribing vary highly by season, show heightened peaks in winter [100], range from 22-32% for RTIs [97-99], and are suggested to be lower than outpatient settings in other countries (rates: 15%-83%) [79,101,102]. High-prescribing GPs in the French and German regions appear to prescribe non-recommended antibiotics across all conditions at rates that surpass (31.5%–88.7%) the maximum (20%) recommended by the ESAC project, however [103]. A substantial overuse of macrolides and quinolones for several conditions, including RTIs [99] and broad-spectrum (macrolides and beta-lactams) antibiotics for RTIs, surpasses the recommended maximum. Antibiotic use is lower in German-speaking than in Italian- and French-speaking areas [100,101].

These overall trends in antibiotic use from primary care are similar to those reported by outpatient national surveillance (Box 1) [10]. However, the proportions in which antibiotics are used in primary care may differ greatly from outpatient care surveillance. Inappropriate use of critical or non-recommended antibiotics is present in both sources.

Limited documentation on the use of CRP-POCT to reduce (inappropriate) antibiotic prescribing for RTIs in Swiss primary care

Research shows that uncertainty about RTI diagnosis can lead to inappropriate antibiotic prescribing, overuse of resources and complications [104,105]. CRP enables clinicians to discern bacterial infections from viral disorders and helps them identify the patients most benefit from antibiotic therapy [106].

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[2] One of the health priorities of the Swiss federal government in the policy agenda "Health2020" is to raise awareness about the importance and appropriate use of antibiotics, and to monitor, control and eliminate ABR.

CRP-POCT is one of the top interventions targeted at clinicians to reduce antibiotic prescribing, and it is increasingly being promoted to enhance antibiotic stewardship [107]. Its robustness and accuracy have been demonstrated by diagnostic studies [108]. Several studies report reduced antibiotic prescribing when using it [109,110], and it is guideline-recommended with a prior assessment of the clinical presentation [109,111-113].

In ambulatory care facilities throughout Switzerland, particularly in the primary care setting, CRP-POCT is widely implemented and readily available to diagnose disease routinely [98-100,114]. Evidence from RCTs in Swiss (GP) ambulatory care on the effectiveness of CRP-POCT to reduce (unnecessary) antibiotic prescribing for RTIs is not available, however [115].

Observational research indicates the overall use of CRP-POCT and its potential use in prescribing decisions for RTIs in the Swiss primary care setting. Prevalence and survey studies show that between 35% [114] and 47% [99] of the patients consulting their GP for RTIs have a CRP-POCT performed. Lower CRP values have been used to diagnose RTIs, such as the common cold or not a "serious" infection in adult patients [114]. An uncontrolled observational study in adult patients with acute cough showed that CRP, as part of a clinical assessment, together with an assessment of symptoms duration and white blood cell count, were significant predictors of antibiotic prescribing [98]. Higher use of any POCT, including CRP-POCT, was associated with fewer antibiotic prescriptions for all antibiotic classes mostly used for RTIs, in another study [100]. Also, a positive CRP-POCT result was strongly associated with antibiotic prescribing, especially with CRP ≥50 mg/L. In a recent study using a bottom-up approach based on daily practice experience, Swiss GPs recommend not using CRP-POCT as a stand-alone routine intervention [116].

Lack of guidance on the use of CRP-POCT to reduce (inappropriate) antibiotic prescribing for RTIs in primary care

As part of the Swiss national strategy against AMR in humans (StAR-M) [7], a Swiss public information campaign commissioned by the FOPH was launched in 2015 to develop uniform national prescribing guidelines for the use of antibiotics [117] in collaboration with the Swiss Society of Infectious diseases (SSI) [118,119]. The INFECT strategy, a subproject from ANRESIS, links the SSI guidelines to a graphical tool that displays information on resistance among pathogens [9].

Currently, the SSI guidelines lack guidance on the use of CRP-POCT and the interpretation of CRP levels for the management of RTIs. Similarly, advice for clinicians on how to deal with the decision of not prescribing antibiotics and patients' demand for antibiotics is not considered.

Box 3. C-reactive protein – a biomarker of systematic inflammation.

CRP is a cytokine-induced acute-phase protein released by the liver in response to tissue injury and systematic inflammation due to general and non-specific infections. CRP can indicate pathological changes related to the disease's extent, activity and severity based on its serum or plasma concentration levels. The levels are represented as cut-off values, and their interpretation depends on the presentation of the disease. The generally considered cut-offs for inflammatory disease or bacterial infection are:

- CRP <10 mg/L for ≤99% of healthy people
- CRP <20 mg/L for healthy adults with RTIs
- CRP <5 mg/L for healthy children with RTIs, depending on symptoms and clinical assessment

CRP as POCT is performed on a finger-prick capillary blood sample. Its measuring range (e.g., 5-200 mg/L) depends on the type of assay, and its results are generally available within (2-5) minutes of sampling, thus available to the physician during the patient consultation.

Source: [120].

Box 4. Diagnostic point of care test(-ing) to reduce (inappropriate) prescribing.

Over the past thirty years, technology has brought some pathology testing closer to the patient, mainly due to healthcare changes and, in particular, the need for less fragmented but more patient-centred care. POCT aims to clear diagnostic uncertainty and enable rapid decision-making for the management and treatment of disease.

Despite having established strong commitments to tackle ABR, there remains substantial variation in antibiotic consumption within and across healthcare systems [1-3]. Several strategies led by WHO and calling for global action to fight ABR have highlighted the need to develop or effectively use existing diagnostic testing to enhance antibiotic stewardship, particularly to improve antibiotic prescribing [21,44,45,121].

In Switzerland, POCT was promptly raised in the Swiss news in 2018 as a “key solution to the problem of antibiotic abuse and overprescribing” [6] after the launch of a campaign with the slogan “antibiotics: use wisely, take precisely” (“Antibiotika: Nutze sie richtig, es ist wichtig”) [122]. The campaign is part of the national strategy StAR supported by the FOPH and aims to ensure that antibiotics remain effective in the long term and to curb the development of ABR [7]. It was suggested that establishing whether or not patients need antibiotics could lead to a dramatic drop in the inappropriate use of antibiotics.

ABR, Antibiotic Resistance; POCT, point of care test(-ing), StAR, Swiss Strategy on Antibiotic Resistance.

3. Recommendations for improving antibiotic prescribing in Swiss primary care

The various causes leading to ABR call for policy interventions at different levels of society. Unnecessary antibiotic prescribing, however, is primarily related to medical practice and potentially to diagnostic uncertainty, and as such, it is addressed within the frame of this policy brief.

CRP-POCT can help to change the way antibiotics are prescribed for RTIs. Three options to address inappropriate prescribing for RTIs in Swiss ambulatory care are proposed:

1. Strengthening clinical guidelines by integrating CRP-POCT into the clinical pathway to support diagnostic decisions and guide antibiotic prescribing for RTIs.
2. Strengthening the integration of CRP-POCT by incorporating guidance on the interpretation of CRP concentration levels to support diagnostic decisions and guide antibiotic prescribing for RTIs.
3. Strengthening physicians prescribing decisions by incorporating advice on how to deal with patients' pressure and the decision of not prescribing antibiotics.

These recommendations were identified by evidence-based research. Recommendations one and two are informed by a comprehensive systematic review and a meta-analysis of randomised controlled trials (RCTs) [115]. The review expands and complements previous evaluations with similar scope, including a Cochrane review, and represents by far the most up-to-date body of evidence on the clinical effectiveness of CRP-POCT in reducing antibiotic prescribing for RTIs in the outpatient setting including primary care. Recommendation three is based on two high-profile RCTs [123,124] included in the same review [115]. The intervention in one of these RCTs was developed in a consensus process with the GRACE consortium[3], had previously been tested, and was found acceptable and applicable by GPs from five European countries, including Belgium, England, the Netherlands, Poland, and Spain [125].

The recommendations are considered feasible and could contribute to reducing (unnecessary) antibiotic prescribing in the ambulatory setting, especially in primary care. Multifaceted interventions are more likely to improve overall antibiotic consumption, reduce the rates of antibiotic prescribing and increase the use of recommended antibiotics [126,127].

A detailed description of the recommendations Is presented in the following sections, and considerations for implementation are presented in Chapter 4 of this brief.

[3] GRACE: a network of excellence focusing on the Genomics to Combat Resistance against Antibiotics in Community-acquired LRTI in Europe; formed by investigators from basic laboratory sciences, clinical medicine, and health economics; and promotes research and good practice in the field of community-acquired LRTIs.

Recommendation 1: Strengthening clinical guidelines by integrating CRP-POCT in the clinical pathway to support diagnostic decisions and guide antibiotic prescribing for RTIs

Clinicians could find proper support and be better guided in their prescribing decisions by following a clinical pathway that integrates CRP-POCT in the process of diagnosis, management, and treatment of RTIs.

The primary source for informing this recommendation is the most up-to-date meta-analysis evaluating the clinical effectiveness of CRP-POCT compared with Usual Care to reduce antibiotic prescribing for RTIs in the outpatient setting, including primary care [115].

It has been recommended that existing diagnostic tests be used more effectively to stop unnecessary and inappropriate antibiotic use, revitalise antibiotics and reduce healthcare costs [4]. It has also been recommended that the value of such tests could be better established through best-practice guidelines that aim to mitigate ABR.

CRP-POCT, in addition to clinical examination, is effective in reducing the overall rates of antibiotic prescribing for RTIs at the index consultations compared to usual care

The meta-analysis incorporated evidence of moderate- to high-quality from thirteen RCTs carried out mostly in high-income countries, predominantly in GP practices from the northern European setting, and mainly in the Netherlands [123,124,128-147] (Appendix, Table 1). In the included studies, the CRP-POCT intervention emphasised the value of performing a clinical examination prior to CRP-POCT.

The analysis showed lower rates of antibiotic prescribing in the CRP-POCT group compared to usual care at the index (initial) consultation. It demonstrated that compared to usual care, CRP-POCT adjunct to the clinical examination significantly reduced immediate (i.e. at index consultation) antibiotic prescribing for RTIs. Moreover, clinical recovery, resolution of symptoms, and hospital admissions were not significantly different between the CRP-POCT group and the group receiving usual care.

The meta-analysis also found significantly higher re-consultation rates within 30 days of the initial consultations in the CRP-POCT group compared with the group receiving usual care. However, an analysis of the combined effects of benefits and harms (NNTnet[4]) [148] revealed that the overall benefits of CRP-POCT (reducing antibiotic prescribing) outweigh the potential harms (increased re-consultations). Exposure to CRP-POCT compared to usual care resulted in an absolute risk reduction of 13.2% in antibiotic prescribing (NNTB=8) and an absolute risk increase of 3.8% in re-consultations (NNTH=27). For every 11 (NNTnet) patients getting usual care and CRP-POCT, one patient would experience the net benefit of treatment without antibiotics.

Meta-analyses also showed no significant differences between the CRP-POCT and usual care groups in the rates of referrals to secondary care, ordering of further investigations, patient satisfaction, and patient enablement. Only one study reported on mortality and found no deaths in either group.

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[4] The NNTnet metric takes into account the outcome of benefit and any outcome resulting in potential harm based on 1) NNTB: the average no. of patients needed to treat* (=to perform CRP-POCT) to see the benefit in one additional patient; 2) NNTH: the average no. of patients needed to treat* for harm in one additional patient.

CRP-POCT is effective in reducing antibiotic prescribing for upper and lower RTIs

The meta-analysis also demonstrated a significant reduction in antibiotic prescribing for URTI (32.3% vs 49.4%) and LRTIs (37.1% vs 55.2%) at index consultations in the CRP-POCT group compared to usual care.

CRP-POCT is (most) effective in reducing antibiotic prescribing in the GP setting

The meta-analysis also demonstrated that CRP-POCT effectively reduces antibiotic prescribing in the GP setting at index consultations. There were significantly lower antibiotic prescriptions in the CRP group of patients attending GP practices than in patients attending other outpatient services compared to usual care.

Delayed prescribing for intermediate CRP levels

As intermediate CRP levels may be more difficult to interpret, two high-profile RCTs recommended delayed[5] prescribing as an option when CRP values were intermediate (20–100 mg/L) and if illness severity did not require immediate antibiotics [123,124]. The individual estimates and the inclusion of these RCTs in the meta-analysis showed a significant reduction in antibiotic prescribing at the index consultation. Another systematic review also showed reduced antibiotic use with delayed prescribing [81].

Examples of adopting recommendations one and two

Research shows that GPs not only seem generally positive about using CRP-POCT but have also expressed the need for a proper indication (cut-offs) to interpret CRP levels and safely use POCT [149]. Research also shows that GPs comply with professional guidelines in up to 70% of their management decisions [150].

Early evidence on the clinical effectiveness of CRP-POCT in reducing antibiotic prescribing for RTIs [113,124,151,152] led to the integration of CRP-POCT in European guidelines for the diagnosis and management of RTIs and pneumonia in primary care adult patients [109,112]. In addition, delayed prescribing was also adopted in these guidelines.

The NICE[6] clinical guideline on pneumonia is a high-profile example of adopting this evidence to guide antibiotic prescribing decisions in practice [109]. It has been recommended that the most appropriate context in which CRP-POCT should be considered is when a patient presents RTI symptoms and the clinical assessment and evaluation of risk factors are unclear on whether the patient would benefit from antibiotics. For example, CRP-POCT is recommended for patients with suspected pneumonia to rule out CAP in patients with lower RTIs and in moderately ill adults with general or localized RTIs symptoms in whom pneumonia has not been diagnosed, but there is uncertainty if these patients would benefit from taking antibiotics [109]. Table 1 presents the CRP-POCT criteria adopted and adapted from the evidence to two clinical practice guidelines.

In children with RTIs, two studies propose CRP-based prescribing criteria [129,136]; please see Table 2.

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[5] Delayed prescribing: a prescription for use at a 20 later date if symptoms worsen [109].

[6] NICE: National Institute for Health and Care Excellence.

Table 1. CRP criteria for managing RTIs in adults with a prior clinical examination.

<table>
<tr><th colspan="2">Evidence from high-profile studies included in the meta-analysis</th><th colspan="2">Evidence implementation of CRP-POCT in high profile guidelines</th></tr>
<tr><th>GRACE for LRTI and URTI [115,124]</th><th>IMPACT3T for LRTI [115,123,141]</th><th>NICE for Pneumonia [109]</th><th>ERS for RTIs [112]</th></tr>
<tr><td>CRP <20 mg/L:
• self-limiting LRTI
• withhold antibiotics</td><td>CRP <20 mg/L:
• withhold antibiotics in most patients with low values (<75% of patients with LRTI in primary care)
• pneumonia extremely unlikely</td><td>CRP <20 mg/L:
• self-limiting RTI
• do not routinely offer antibiotics
• pneumonia unlikely
• give education</td><td>CRP <20 mg/L:
• self-limiting RTI with symptoms of >24 h
• pneumonia highly unlikely</td></tr>
<tr><td>CRP 21–50 mg/L:
• most patients have self-limiting LRTI
• assessment of signs, symptoms, risk factors and CRP is important
• withhold antibiotics in most cases</td><td>CRP 21–99 mg/L = Delayed antibiotics at the discretion of physicians:
• patients should be carefully assessed based on the combination of medical history, physical examination, and CRP value

CRP 20–50 mg/L:
• pneumonia very unlikely</td><td rowspan="2">CRP 20–100 mg/L:
• consider a Delayed antibiotic prescription
• clinical presentation is decisive
• prescribe antibiotics only in patients with a high risk of complications*

CRP 21–50 mg/L: GRACE criteria

CRP 51–99 mg/L: GRACE criteria</td><td></td></tr>
<tr><td>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</td><td>CRP 21–99 mg/L = Delayed antibiotics at the discretion of physicians:
• patients should be carefully assessed based on the combination of medical history, physical examination, and CRP value
CRP 50–100:
• clear infection, most likely acute bronchitis, possibly pneumonia: combine with clinical findings
• CRP is very important</td><td></td></tr>
<tr><td>CRP >100 mg/L:
• severe infection; prescribe antibiotics</td><td>CRP >100:
• immediate antibiotics
• severe infection
• pneumonia more likely</td><td>CRP >100 mg/L:
• severe infection
• high risk of pneumonia
• offer antibiotic therapy</td><td>CRP >100 mg/L:
• one of the following signs and symptoms: new focal chest signs, dyspnoea, tachypnoea, pulse rate >100, fever >4 days; perform CRP test
• symptoms lasting >24 hrs
• pneumonia highly likely
• if persisting doubt, a chest X-ray should be considered</td></tr>
</table>

Source: *Little et al 2013* [115,124], *Cals et al 2009* [115,123,141], *NICE guideline* [109], *Woodhead et al, 2011* [112]. **Notes.** URTI: Upper RTIs; LRTI: Lower RTIs; GRACE: the Genomics to Combat Resistance against Antibiotics in Community-acquired LRTI in Europe: Spain, England, Wales, Poland, Belgium, The Netherlands; IMPACT3T: Improving Management of Patients with Acute cough by C-Reactive Protein Point of Care Testing and Communication Training: the Netherlands; NICE: National Institute for Health and Care Excellence: UK; ERS: European Respiratory Society.

Table 2. CRP criteria for managing RTIs in Children with a prior clinical examination.

- CRP ≤ 20 mg/L = no antibiotics for patients aged 6–65 years
- CRP < 5 mg/L = low level = ruling out antibiotics
- CRP ≤ 10 mg/L = no antibiotics for patients aged 1–5 years
- CRP > 20 to <50 mg/L = no specific recommendation; clinicians are advised to use their clinical discretion
- CRP ≥ 50 mg/L = should generally receive antibiotics; hospital referral should be considered

Recommendation 2: Strengthening the integration of CRP-POCT by incorporating guidance on the interpretation of CRP concentration levels to support diagnostic decisions and guide antibiotic prescribing for RTIs

Complementing the use of CRP-POCT in the clinical pathway with sufficient guidance on the interpretation of CRP values could support clinicians' decisions on whether or not to prescribe antibiotics for RTIs.

This option is linked to recommendation one, and the primary source for informing this recommendation is the same meta-analysis [115]. The meta-analysis also examines the use of CRP levels reported in the literature to guide diagnostic and prescribing decisions for the comparative clinical effectiveness of CRP-POCT with Usual Care.

Research shows that physicians not only seem generally positive about using CRP-POCT but have expressed the need for a proper indication (e.g., cut-offs) to interpret CRP levels [149]. Meta-analyses and diagnostic studies show that CRP has improved the discrimination and risk classification of patients with RTIs, especially when CRP values are intermediate and more difficult to interpret [108,153]. For example, community-acquired pneumonia (CAP) has a worse prognosis than other RTIs and requires antibiotic therapy [109,111]. Low CRP levels indicate no need for antibiotics for acute LRTIs, and if symptoms last >24hrs and CRP is <20 mg/L, CAP is considered unlikely. Typical signs and symptoms and CRP >30 mg/L are considered a risk for CAP. CRP >100 mg/L indicates, however, a high likelihood of CAP.

While the optimal CRP-POCT threshold to rule in or out the need for antibiotics would depend on the specific clinical presentation and symptoms, antibiotic prescribing could be optimized in patients with low CRP values without compromising patients' recovery.

CRP values in the studies included in the meta-analysis

Several RCTs included in the meta-analysis [115] provided the CRP levels used to guide antibiotic prescribing. In the studies, CRP concentration levels below 20 mg/L were considered safe to rule out serious RTIs in adults and/or to withhold antibiotics. CRP levels of 5-10 mg/L were used to rule out antibiotics in children. In two high-profile RCTs, a group of collaborators used a consensus process to develop interpretative and antibiotic prescribing criteria based on CRP levels [123,124]. Besides the lower and upper CRP cut-off criteria, these RCTs recommended physicians use delayed prescribing when CRP levels are intermediate. Table 1 presents the CRP-POCT criteria from studies included in the meta-analysis used to generate practice guidance.

CRP-POCT plus guidance on the interpretation of CRP values is effective in reducing antibiotic prescribing

The meta-analysis showed that applying CRP cut-off guidance to withhold antibiotics in addition to clinical examination significantly reduced antibiotic prescribing at index consultations in the CRP-POCT group compared to the group receiving usual care [115]. Reported reductions were 37.6% vs 54.4%, respectively.

CRP-POCT plus CRP cut-off guidance for adults and children is effective in reducing antibiotic prescribing

While there is increasing evidence on the use of CRP cut-off values to guide antibiotic prescribing for adults with RTIs, considerably little research from RCTs has assessed the clinical effectiveness of CRP cut-off guidance for children with RTIs [113,115,154].

The meta-analysis showed significantly lower antibiotic prescribing at index consultations in adults (≥18 years) but not in children in the CRP-POCT group compared to usual care [115]. Reductions were 39.8% vs. 56.0% for adults, and 34.3% vs. 41.8% for children. When CRP cut-off guidance was applied to withhold antibiotics, however, CRP-POCT significantly reduced antibiotic prescribing in adults and children in the CRP-POCT group compared to usual care. Reductions were 38.8% vs. 54.4% for adults, and 31.9% vs. 43.5% for children.

Recommendation 3. Strengthening physicians prescribing decisions by incorporating advice on how to deal with patients' pressure and the decision of not prescribing antibiotics

Optimizing antibiotic prescribing can create tension in the relationship between GPs and patients, particularly in the communication between patients and their doctors after a clinical decision has been made. Potential tensions can differ in how physicians perceive them and take them into account in the decision-making process and in the use of support and resources that are available for them to strengthen their decisions. Physicians have expressed the need for mechanisms to support their decisions not to prescribe antibiotics [155] and skills training to use POCT safely [148].

CRP-POCT plus guidance for interpreting CRP values plus negotiation-communication skills training further enhances the reduction in antibiotic prescribing

A systematic review [115] identified two RCTs in which one of four intervention arms consisted of CRP-POCT with or without the added effect of communication skills training (CST). The results suggest that the combined intervention (CRP-POCT plus CST) positively affects patient behaviour, self-awareness, and management of RTIs. CST also showed a sustainable effect over 12 months [138].

In one of the RCTs, the effect of CST could not be disassociated from CRP-POCT [123]. Including the RCT with the combined intervention in the meta-analysis further enhanced the overall effect already gained by CRP-POCT in reducing antibiotic prescribing at index consultations compared with usual care. The other RCT reported a separate CST intervention arm, for which data were not considered in the systematic review and were not aggregated in the meta-analysis [124]. CST reduced antibiotic prescribing at index consultations when individually compared to CRP-POCT or usual care. In this RCT, the combined intervention (CRP-POCT plus CST) further enhanced the overall effect already gained by CRP-POCT in reducing antibiotic prescribing [124]. The combined intervention showed no significant rates of re-consultation.

The interventions in one of the RCTs included internet-based training on how to target testing and negotiate with the patient about management decisions [124,125,155]. The intervention was developed in a consensus process with the GRACE consortium, had previously been tested, and was found acceptable and applicable by GPs from five European countries, including Belgium, England, the Netherlands, Poland, and Spain [125]. The components and modules integrated into the intervention are presented in Table 3.

With adequate communication and negotiation skills, clinicians could provide efficient explanations about the pros, cons, and course of antibiotics, which may lead to decisions to non-prescribing antibiotics that are better accepted by patients [156].

Educational interventions have also been shown to strengthen physician'' communication skills, are perceived positively, and influence prescribing behaviour by improving GP'' confidence in not prescribing antibiotics [157]. Moreover, when interventions target the entire team in the practices, there is less conflict and more consistency of messages among physicians supporting the overall antibiotic stewardship. Studies have also reported that supportive practice-level policies help to improve prudent antibiotic prescribing among physicians [158].

Table 3. Content of the GRACE-Intro Web-Based Training component.

Module 1: general introduction for three intervention arms (Communication, CRP-POCT, and Combined groups)

Background to the problem of ABR and its relation to antibiotic over-prescribing regarding healthcare, patients, RTIs and clinicians, the medicalization of self-limiting illness, which encourages re-consultations, and the concerns and difficulties in determining how patients with RTIs may benefit from antibiotic treatment. It also explains how GP training in communication skills and/or GPs' use of CRP-POCT could assist in their consultation.

Module 2: training in communication skills with the use of a patient booklet for two communication intervention arms (Communication and Combined groups)

Aim: improving GPs' understanding of patients' concerns, perceived needs, and expectations to facilitate GPs in using specific patient-centred communication skills in their consultations and to support them in making informed management decisions.

The three key elements of an effective consultation are to gather information, exchange information, agree to management, and check information on patient understanding and concordance, providing patients with information about the disease course.

- Clinicians were provided with examples of questions to ask patients in the consultation.
- Introduction of a patient booklet.
- Video clips showing examples of consultations between GPs and patients, with clinicians using communication skills and discussing the patient booklet.

Module 3: training in using CRP-POCT for two CRP intervention arms (CRP-POCT and Combined groups)

Aim: to inform GPs about how CRP-POCT can assist them in both differentiating self-limiting from more serious infections and making antibiotic prescribing decisions.

Introduction to the CRP test as a method to assist in diagnosing RTIs: differentiating between self-limiting and serious LRTIs.

- Training in how to use the test, including instructional videos.
- Explanation of how to interpret specific CRP values and results, and GPs were provided with interpretative and antibiotic prescribing criteria.
- Instructions on how to use the test the consultations.

Sourc e: adapted from *Anthierens et al., 2012, Little et al., 2013, Anthierens et al., 2015* [124,125,155]. **Notes.** Combined groups: CRP-POCT + CST; GRACE: the Genomics to Combat Resistance against Antibiotics in Community-acquired LRTI in Europe.

4. Implementation Considerations

An analysis by the WHO in 2015 about the world situation in response to the crisis of ABR revealed that even countries with solid healthcare systems needed to make more progress [44]. Switzerland has taken major steps towards fighting and containing ABR to match the WHO Global Action Plan on Antimicrobial Resistance by establishing various measures to monitor and contain AMR.

Potential opportunities and facilitators for implementation

As recommended, existing diagnostic tests could and should be used more effectively to stop unnecessary and inappropriate antibiotic use, and their value could be better established through best-practice guidelines to mitigate ABR [4].

The present framework of the Swiss healthcare system is favourable for implementing evidence on CRP-POCT presented in previous chapters. A window of potential opportunities for the performance of the proposed recommendations is described below.

At the national level

The importance of the prudent use of antibiotics and the threat posed by ABR to public health is well acknowledged and advocated by the Swiss government. This acceptance is evident by the several strategies that have already been implemented at the national level towards containing ABR, including StAR, ANRESIS, and Smarter Medicine (the Swiss Choosing Wisely), for example [7,159-161]. The FOPH supports these strategies, the action plans that have been implemented in partnership with individuals and stakeholders from all relevant (medical and academic) sectors. The recommendations proposed in this brief are well-matched with the activities related to the appropriate use of antibiotics in these strategies [162]. A wide engagement of political support could accompany the recommendations presented in this brief.

Increasing evidence on the effectiveness of CRP-POCT continues to be published in favour of its wide-scale adoption for reducing (unnecessary and inappropriate) antibiotic prescribing [115]. This is after the initial [113,163] and more recent [154,164] evaluations of its clinical and cost-effectiveness. Swiss clinical practice guidelines are based on existing international guidelines, which get adapted to the local context and needs by a group of experts following a review process in which relevant issues are identified for consideration of change, adaptation or addition [165]. High-profile European clinical guidelines have already adopted the evidence on CRP-POCT with the interpretation of CRP levels [109], which further supports its potential consideration for adoption, adaptation and contextualisation for the Swiss setting.

In particular, a high-level opportunity is the potential inclusion of the topic of CRP-POCT in the human subproject of the StAR strategy commissioned by the FOPH. An essential objective of StAR is the development of guidelines to help standardise and reduce the consumption of antibiotics. Antibiotic prescribing is one of the three areas for applying these guidelines, and the SSI commissioned by the FOPH leads the development and update of guidelines relevant to this brief's topic. A most valuable strength in developing such guidelines would be the collaboration of the Swiss Society of General Internal Medicine (SGAIM) as a member of the guidelines committee, allowing the involvement of GPs too. The development of prescribing guidelines for GPs by GPs is also a potential opportunity that SGAIM could lead. For example, the German College of General Practitioners and Family Physicians (DEGAM) develops its own guidelines [166].

Moreover, the StAR initiative encourages GPs to follow these guidelines in their decisions for managing and treating patients with infections that may require antibiotics. It also states that physicians' adherence to these guidelines should be promoted and monitored to have an impact on the outpatient setting. Clinical guidelines are an essential part of quality medical practice, and their value consists of optimising the quality of patient care. As such, the integration of CRP-POCT with guidance on the interpretation of CRP levels could be a valuable strength to the care and treatment pathway of the SSI and other clinical guidelines that aim at the diagnosis, management, and treatment of RTIs in primary care.

Including the topic in the INFECT interface [9] would not only facilitate its acceptance at prescriber and national levels, but it could serve as an additional high-level opportunity to achieve quality medical practice. Currently, the interface allows users to access general information about treatment for the clinical indications considered in the SSI guidelines. The interface could provide information that is rapid and easily accessible on the topic in the respective guidelines, most needed when GPs' decision-making is at risk due to time constraints, patients' pressure or demand. This could reach a higher number of prescribers, helping thus to standardize practice guidance and to improve antibiotic consumption further.

Once the topic is integrated into the above-mentioned sources, surveillance on antibiotic consumption exclusive to the primary care setting could be integrated [10,167] to quantify antibiotic prescribing appropriateness better. In turn, this could enable a feedback approach to reach the goals of adopting current and new strategies to optimize antibiotic prescribing.

At prescriber level

The human resources and infrastructure available in Swiss primary care allow the use of CRP-POCT whenever it is necessary since it is readily implemented and widely available in outpatient care throughout Switzerland. It is also the most used rapid POCT in primary care with a turn-around time of results within five minutes [98,100,114], and it is cheaper than other tests. Capillary blood is used for the test, and only a small sample is needed, providing easy and rapid access to perform it, which makes it more acceptable to patients. CRP-POCT is also easier to apply than other tests. Moreover, GPs are already trained in the use, function, and purpose of CRP-POCT, and when appropriately used, it can increase diagnostic confidence.

GPs could be powerful supporters of the topic and adherence to guidelines. Including a network of GPs as partners in adopting the topic could be a key enabler of structural decisions in primary care. GPs' best practice interest is quality of care so that they can be the best advocates of quality and monitoring compliance with practice guidelines among their colleagues. Well-informed healthcare providers are more likely to embrace a medical approach to dealing with antibiotics that are supported by evidence, experts in the field, and their leading peers. This could increase GPs' confidence, uniformity in the adoption of the topic, and improvement in adherence to topic guidelines, achieving further reductions in (unnecessary) antibiotic prescribing.

In particular, recommendation three as part of the guidelines' strategy, e.g., as a decision aid in the clinical pathway, could reinforce GPs' confidence. This could serve as a reminder of rapid access in times of patient pressure or demand, lack of resources or increased practice volume, and time constraints. Research has shown that GPs comply with professional guidelines in up to 70% of their management decisions [150].

Physicians are generally positive about the use of CRP-POCT and have expressed that they need proper indication to interpret POCT cut-off values and skills training to use POCT safely [149]. Incorporating the topic of negotiation, shared decision-making, and communication skills as part of the routine training for all new and regular in-house GPs could be an easier way to ensure that GPs improve communication with patients. It would also increase their confidence when in doubt or when they feel under pressure to prescribe antibiotics.

National and local conferences for GPs provide an opportunity for an update of medical education, and communication skills are part of the teaching profiles for medical students.

At patient level

Including the topic of patient-physician communication and shared-decision making as part of the public information campaign on ABR led by StAR could be an opportunity to enable the population to modify their perception and attitudes towards a decision of no antibiotic prescribing. An additional opportunity could be the use of patients' flyers in GP practices addressing how POCTs are used to support a doctor's decision and the importance of a prior clinical examination before considering POCT.

Potential barriers to implementation

In line with the opportunities and facilitators described in previous sections, some barriers to implementation merit consideration.

Very importantly, a lack of clearer guidelines for doctors that integrate relevant up-to-date evidence could limit the scope and adoption of strategies that aim to reduce (unnecessary) antibiotic prescribing, leading to less effective results [7,118,159]. Especially a lack of involvement of GPs in developing prescribing guidelines could be a major limitation.

A lack of evidence-based guidance with support for interpreting CRP values, especially a lack of strategy to deal with intermediate CRP concentration values, could limit and compromise doctors' decision-making. It is well acknowledged that CRP-POCT does not allow clear discrimination for all types of RTI when CRP values range as intermediate, as these could be very broad [108,115].

Addressing both time pressure concerning medical decision-making and time constraints in negotiating not prescribing antibiotics is pivotal in the acceptance and adherence to guidelines. In particular, time pressure is one of the most important potential barriers to using evidence-based decisions in primary care [168]. Not having enough time to consult all patient needs and the potential for illness deterioration (especial concern from GPs) and for establishing proper patient-physician communication to deal with patient's expectations (for antibiotics) could lead to the unnecessary administration of antibiotics. A high practice volume with increased workload and decreased resources could also increase time pressure and affect adherence to evidence-based recommendations. Consequently, a lack of rapid access to information on the topic and a lack of a backup support system for GPs could further compromise implementation and increase the withdrawal of commitment.

If the recommendations are adopted, feedback on this performance will be needed. A lack of data on antibiotic consumption exclusive to primary care and a lack of distinction between outpatient services could be a barrier to properly quantifying the appropriateness of antibiotic prescribing. Consequently, this could interfere with the potential for feedback on the monitoring and achievements of implemented strategies.

5. Summary

This policy brief summarises the issues for the need to reduce unnecessary antibiotic prescribing for RTIs in ambulatory (primary) care by optimizing the use of CRP-POCT and its integration into clinical practice guidelines. It integrates a summary of the current evidence from a meta-analysis of RCTs on the clinical effectiveness of CRP-POCT to reduce antibiotic prescribing for RTIs. Based on this, and both high-profile RCTs and guidelines, it considers the steps that can be taken to address the continuing issue of unnecessary antibiotic prescribing, which can be a challenge due to the following main factors:

- data on antibiotic consumption (for RTIs) from Swiss primary care are limited
- documentation of the use of CRP-POCT to reduce unnecessary antibiotic prescribing for RTIs in Swiss primary care is limited
- guidance on the use of CRP-POCT to reduce unnecessary antibiotic prescribing for RTIs in primary care is lacking
- advice for physicians on how to deal with patients' pressure and the decision of not prescribing antibiotics is lacking

The most up-to-date meta-analysis demonstrates that CRP-POCT can significantly and safely reduce antibiotic prescribing at the index consultations for RTIs in outpatient care compared with usual care. When CRP cut-off guidance was applied, CRP-POCT significantly reduced antibiotic prescribing in children and enhanced the overall effect in adults. Although there was an increase in the re-consultation rates, the meta-analysis demonstrates that the benefits of CRP-POCT in reducing antibiotic prescribing outweigh the potential harms. One high-profile RCT included in the meta-analysis showed that the immediate effect was sustained at 12 months. Two high-profile RCTs included in the meta-analysis showed that the multifaceted intervention consisting of CRP-POCT plus the added effect of negotiation-communication skills further enhanced the effect already gained by CRP-POCT in reducing antibiotic prescribing. This and evidence from economic evaluations and individual RCTs have led to the wide-scale adoption of CRP-POCT in many countries, especially Europe. Several international clinical guidelines have integrated CRP-POCT as part of the clinical assessment for managing and treating RTIs.

The present framework of the Swiss healthcare system is favourable for implementing evidence on CRP-POCT. The window of potential opportunities to reduce unnecessary antibiotic prescribing by optimising the use of CRP-POCT lies in integrating the topic into the existing local and national strategies to enhance antibiotic stewardship. The value of CRP-POCT in tackling infectious diseases and limiting ABR could be better established through their integration into best-practice guidelines.

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Appendix I

Table 1. Studies assessed in the meta-analysis: CRP-cut-off values applied to withhold or recommend antibiotic prescribing.

Study and country	**Study design and clinical setting**	**Patient population**	**Intervention and number randomised at baseline (N)**	**CRP-POCT turnaround time and manufacturer**	**CRP (cut-off) interpretation guidance algorithm**
Schot, 2018 [128] The Netherlands	Individual RCT general practices and OOH services	Children with suspected LRTI; 3 months to 12 years	GP CRP: N = 136 Usual Care: N = 165	≤4 min Afinion, Alere Technologies AS, Oslo, Norway	• CRP <10 mg/L = Pneumonia less likely, but should not be excluded if a child is ill, or when the duration of symptoms is <6 hours • CRP >100 mg/L = Pneumonia much more likely; however, such levels can also be caused by viral infections • CRP 10 to 100 mg/L = Likelihood of pneumonia increases with increasing CRP levels
Verbakel, 2016 [129-132] Belgium	Cluster RCT general practices	Children with an acute infection; 1 month to 16 years	GP CRP: N = 1730 infectious episodes in 2773 patients Usual Care: N = 1417 infectious episodes in 2773 patients	≤4 min Afinion AS100 Analyzer, Alere, USA	• CRP < 5 mg/L = Low level = ruling out antibiotics • CRP ≥ 5 mg/L = Elevated level
Van den Bruel, 2016 [133] United Kingdom (England)	Individual RCT OOH services	Children with an acute illness: 1 month to 16 years	Physicians CRP: N = 26 Usual Care: N = 28	3-4 min Afinion, Alere Technologies	• CRP < 20 mg/L = Serious infection is less likely • CRP > 80 mg/L = Serious infection is more likely
Rebnord, 2016 [134,135] Norway	Individual RCT OOH services and paediatric walk-in emergency	Children with fever or any respiratory symptoms: 0 to 6 years	NP CRP pre-tested: N = 138 Usual Care: N = 259	≤2 min QuikRead Go, Orion Diagnostica	n.r.
Do, 2016 [136] Vietnam	Individual RCT primary health-care centres	Children and adults with suspected non-severe acute RTI: 1 to 65 years	Physician CRP: N = 1017 Usual Care: N = 1019	≤3 min CRP single test kit NycoCard II Reader, Alere Technologies, Norway	General • CRP ≤ 20 mg/L = No antibiotics for patients aged 6–65 years Children • CRP ≤ 10 mg/L = No antibiotics for patients aged 1–5 years • CRP > 20 to <50 mg/L = No specific recommendation but clinicians were advised to use their clinical discretion

Study and country	Study design and clinical setting	Patient population	Intervention and number randomised at baseline (N)	CRP-POCT turnaround time and manufacturer	CRP (cut-off) interpretation guidance algorithm
					• CRP ≥ 50 mg/L = Should generally receive antibiotics and hospital referral should be considered Adults • CRP > 20 to <99 mg/L = No specific recommendation but clinicians were advised to use their clinical discretion • CRP ≥ 100 mg/L = Should generally receive antibiotics and hospital referral should be considered
Andreeva, 2014 [137] Russia	Cluster RCT GP practices	Adults with acute cough / LRTI: ≥18 years	GP CRP: N = 8 GP offices, 101 patients Usual Care: N = 9 GP offices, 78 patients	≤5 min Afinion test system, Axis-Shield, Norway	• CRP < 20 mg/L = Antibiotics usually not needed • CRP > 50 mg/L = Antibiotics could be indicated considering duration of illness
Little, 2013 [124,138,139] Spain, England, Wales, Poland, Belgium, The Netherlands	Individual RCT GP practices	Adults with acute cough: ≥18 years	GP CRP: N = 1062 Usual Care: N = 870	≤5 min QuikRead CRP kits, Orion Diagnostica, Espoo, Finland	• CRP ≤ 20 mg/L = Withhold antibiotics: self-limiting LRTI • CRP 21 to 50 mg/L = Withhold antibiotics for most cases: most patients have self-limiting LRTI; assess signs, symptoms, risk factors; CRP is important • CRP 51 to 99 mg/L = Withhold antibiotics in the majority of cases and consider Delayed antibiotics in the minority of cases: assessment of signs, symptoms, risk factors; CRP is crucial • CRP ≥ 100 mg/L = Prescribe antibiotics: severe infection
Gonzales, 2011 [142] United States	Individual RCT ED	Adults with a new cough: ≥ 18 years	NP CRP: N = 69 Usual Care: N = 62	1 min QuikRead CRP, Orion Corporation, Orion Diagnostica, Espoo, Finland	Low to Intermediate (<30%) probability of Pneumonia = abnormal signs OR abnormal chest examination: • CRP < 10 mg/L = Normal = No antibiotics and no chest x-ray • CRP 10 to 99 mg/L = Intermediate: Not helpful • CRP ≥ 100 mg/L = High: Perform chest x-ray: − normal x-ray = no antibiotics − abnormal x-ray = antibiotics High (>30%) probability of Pneumonia = abnormal signs WITH abnormal chest examination: • CRP < 100 mg/L = Perform chest x-ray: − normal x-ray = no antibiotics − abnormal x-ray = antibiotics • CRP ≥ 100 mg/L = Perform chest x-ray: − consider antibiotics regardless of chest x-ray results

Study and country	Study design and clinical setting	Patient population	Intervention and number randomised at baseline (N)	CRP-POCT turnaround time and manufacturer	CRP (cut-off) interpretation guidance algorithm
Cals, 2010 [143] The Netherlands	Individual RCT family practice centres	Adults with a current episode of LRTI or Rhinosinusitis: ≥ 18 years	NP CRP: N = 129 Usual Care: N = 129	≤3 min QuikRead CRP analysers, Orion Diagnostica, Espoo, Finland	• CRP < 20 mg/L = No antibiotics • CRP > 100 mg/L = Immediate antibiotics • CRP 20 to 99 mg/L = Delayed prescription at physicians' discretion
Cals, 2009 [123,140,141] The Netherlands	Cluster RCT GP practices	Adults with suspected LRTI: ≥ 18 years	1) GP CRP: N = 110 2) Usual Care: N = 120 3) ECST: N = 84 4) CRP + ECST; N = 117	≤3 min NycoCard II Reader, Axis-Shield, Norway	• CRP <20 mg/L = Withhold antibiotics in most patients with low values (<75% of patients with LRTI in primary care): pneumonia extremely unlikely • CRP 21 to 99 mg/L = Delayed antibiotics at discretion of physicians: patients should be carefully assessed based on the combination of medical history, physical examination, and CRP value: - CRP 20 to 50 mg/L = pneumonia very unlikely - CRP 50 to 100 = clear infection, most likely acute bronchitis, possibly pneumonia: combine with clinical findings; CRP is very important • CRP > 100 = Immediate antibiotics: severe infection, Pneumonia more likely
Takemura, 2005 [144] Japan	Individual RCT general/internal medicine clinic	Children and adults with a clinically relevant fever of >37.5˚C, and symptoms suspected of infection: 8 to 83	Advanced testing group: Physician CRP + WBC testing before initial consultation: N = 147 Usual Care: non-advanced: N = 154	CRP approx. 40–50 min; WBC 10 min CRP multichannel analyser, model TBA-30FR; Toshiba, Saitama City, Japan	• CRP ≤ 5 mg/L = Normal reference intervals
Diederichsen, 2000 [145,146] Denmark	Individual RCT GP practices	Children and adults with respiratory infections: 0 to 90 years	GP CRP: N = 414 Usual Care: N = 398	≤3 min NycoCard CRP Reader, Nycomed, Alere Technologies, Afinion, Norway	• CRP < 10 mg/L = Normal • CRP < 10 mg/L = Seldom the result of bacterial infection • CRP < 50 mg/L = Seldom the result of bacterial infection
Melbye, 1995 [147] Norway	Individual RCT GP practices	Adults with signs of pneumonia, bronchitis, and asthma: ≥18 years	GP CRP: N = 108 Usual Care: N = 131	≤3 min NycoCard CRP Reader, Nycomed, Alere Technologies, Afinion, Norway	Disease duration 0-24 hours • CRP < 50 mg/L = No change in clinical decision • CRP ≥ 50 mg/L = Antibiotics Disease duration 1-6 days • CRP < 11 mg/L = No antibiotic prescribing • CRP 11-49 mg/L = No change in clinical decision • CRP ≥ 50 mg/L = Antibiotics

Study and country	Study design and clinical setting	Patient population	Intervention and number randomised at baseline (N)	CRP-POCT turnaround time and manufacturer	CRP (cut-off) interpretation guidance algorithm
					Disease duration ≥7 days • CRP < 11 mg/L = No antibiotic prescribing • CRP 11-24 mg/L = No change in clinical decision • CRP ≥ 25 mg/L = Antibiotics

Source: compilation adapted from the most up-to-date meta-analysis on the topic: Martinez-Gonzalez et al [115].

Notes: OOH, Out-Of-Hours care services; ED, Emergency Department services; SD, standard deviation; CRP, C-Reactive Protein; ECST, Enhanced Communication Skills Training; GP, General Practice or General Practitioner; NP, nurse or Nurse Practitioner; RTI, Respiratory Tract Infection; URTI, Upper Respiratory Tract Infection; LRTI, Lower Respiratory Tract Infection; COPD, Chronic Obstructive Pulmonary Disease; EB, Evidence-Based; n.r., not reported.

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