Antibiotic prescribing quality in patients presenting to primary care with respiratory tract infections in Antwerp: clinical trial versus routine data

Genné Tom, Hendrickx Axel, Mulders Victor; Universiteit Antwerpen

Promotor: Coenen Samuel, Universiteit Antwerpen

Co-promotor: Domen Julie, Universiteit Antwerpen

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Abstract

Achtergrond: Antibioticaresistentie neemt wereldwijd toe. Huisartsen zijn verantwoordelijk voor ongeveer 80% van de antibiotica voorschriften. De meeste antibiotica worden voorgeschreven voor luchtweginfecties. Extra inspanningen zijn nodig om onjuist antibioticagebruik te verminderen. Dit is een studie naar de huidige kwaliteit van antibioticavoorschriften bij patiënten in Antwerpen die zich presenteren met respiratoire infecties in de eerste lijn.

Methode: Tijdens PRUDENCE, een randomised controlled trial (RCT) naar het effect van sneltesten op antibiotica voorschrijfgedrag in de eerste lijn, werden in tien huisartspraktijken in Vlaanderen gegevens verzameld van patiënten die zich presenteerden met klachten van luchtweginfecties. Patiëntgegevens werden gedocumenteerd, diagnose en antibioticavoorschriften werden geregistreerd. Kwaliteit van antibioticavoorschriften werd beoordeeld aan de hand ziekte van specifieke kwaliteitsindicatoren (APQIs) voor eerste keus antibiotica en quinolone voorschriften voor vier indicaties. Voorschrijfgedrag in de studie werd vergeleken met gegevens van de Antibiotica Barometer in provincie Antwerpen.

Resultaten: In PRUDENCE werden 121 patiënten geïncludeerd. De percentages voor de APQI eerste keuze antibiotica voor de studiedata waren 29%, 0%, 67% en 80% voor tonsillitis en groep A streptokokken (GAS), bovenste luchtweginfectie, acute bronchitis en pneumonie respectievelijk. Barometer gegevens voor Antwerpse praktijken gaven percentages van 7%, 1%, 71% en 82% voor deze indicaties. Voor acute tonsilitis of GAS, bovenste luchtweginfectie en acute bronchitis werden in PRUDENCE geen quinolones voorgeschreven. Barometergegevens laten een voorschrijfpercentage van respectievelijk 0,4%, 0,6% en 4% zien. Voor longontsteking werden meer quinolones voorgeschreven, 10% in de barometer tegenover 8% in PRUDENCE.

Conclusie: Kwaliteitsindicatoren voor antibioticavoorschrijfgedrag bij patiënten die zich presenteren met luchtweginfecties in de eerstelijnszorg in Antwerpen, worden doorgaans niet gehaald. Vooral bij tonsillitis of GAS en bovenste luchtweginfecties is de kwaliteit van het voorschrijven onvoldoende. Breedspectrum antibiotica worden te frequent voorgeschreven. Quinolonen worden te vaak voorgeschreven voor longontsteking. Grote verschillen in voorschrijfgedrag tussen praktijken in dezelfde regio bestaan.

Introduction

Globally, antimicrobial resistance (AMR) rates are rising, this is a major public health concern (1). Each year, approximately 25 000 people in the EU die due to infections caused by resistant bacteria (2). There has been a worrying decline in the research and development of new antibiotic drugs, resulting in a scarcity of new available molecules in recent decades (3, 4). Most antibiotics are prescribed in primary care, especially for community-acquired respiratory infections (5, 6). Using antibiotics too often and prescribing them for the wrong disease increases AMR. To combat the rising problem of AMR, interventions to limit inappropriate antibiotic prescribing in primary care are needed (7).

There is evidence suggesting the implementation of point-of-care diagnostic tests (POCTs) in primary care could limit inappropriate antibiotic prescribing. For this master's thesis, we conducted a review of the existing evidence on the use of C-reactive protein (CRP), influenza antigen and group A streptococcal (GAS) antigen POCTs for managing respiratory tract infections (RTI) in primary care and the effect of their implementation on antibiotic prescribing behaviour. The detailed literature review with research question, search strategy, results and conclusions has been added as an appendix to this text (Appendix 1). Based on the review of existing evidence, we came to the following three conclusions regarding CRP, influenza, and GAS POCTs:

1. There is moderate to high-quality evidence indicating that the use of CRP-POCT in primary care can effectively reduce antibiotic prescribing for RTIs and that this reduction does not impact clinical recovery, symptom resolution, or hospital admissions (8-10). To extrapolate these results regarding elderly patients with comorbidities and immune deficiencies, more research is necessary (8, 11).

2. There is a considerable body of research on the utilization of POCT influenza tests in emergency department and hospital settings (12). Regarding the use of POCT for influenza in primary care and its effect on antibiotic prescribing behaviour, the available evidence is limited. However, some evidence suggests that employing POCT for influenza may result in a net reduction in antibiotic prescriptions (13-16).

3. There is some evidence that shows a reduction in antibiotic prescriptions when GAS POCT is implemented when addressing patients presenting with sore throat in primary care settings (17, 18). Belgian and Dutch primary care guidelines however still advocate against the usage of strep tests in primary care (19, 20). This is primarily because of the lack of clinical relevance of GAS POCTs in general (21). Different sources also show a significant number of antibiotic prescriptions even after a negative strep test, suggesting that clinical assessment of disease severity remains the most important factor influencing decision making in general practitioners (GPs) (20, 25).

In summary, easy access to and familiarity with POCTs can help primary care physicians enhance the accuracy of diagnosing RTI and limit inappropriate antibiotic prescriptions (8, 21-23). This is especially the case for CRP POCT (8). However, more high-quality research is needed on the effect of GAS and influenza POCTs on prescribing behavior in ambulatory care. Further research should focus on gathering data from children, elderly and patients with comorbidities (8). There is limited evidence of cost-effectiveness of POCT implementation in primary care (24).

PRUDENCE

PRUDENCE (Platform Randomised controlled trial of point of care Diagnostics for Enhancing the quality of aNtibiotic prescribing for Community-acquired acute respiratory tract infection in ambulatory care in Europe), being a pragmatic, platform based RCT is set to gather valid data, from a sizable sample size to make a precise estimate of the effect of POCT on antibiotic prescribing quality. PRUDENCE is carried out by VALUE-Dx (Value of diagnostics to combat antimicrobial resistance by optimizing antibiotic use) which is a project run by a collaboration between in-vitro diagnostic companies and non-industry organisations. Their goal is to combat growing antimicrobial resistance and improve patient outcomes (25). The aim of PRUDENCE is to investigate whether the availability of POCTs for community-acquired RTI presenting with symptoms such as sore throat and cough in general practice can lead to more appropriate antibiotic prescribing behaviour, without compromising patient safety. Over the course of almost 3 years, patients presenting to their GP with acute cough and/or acute sore throat aged 1 and above where antibiotic treatment was considered or decided on at any point during the consultation were included in 13 countries, including Belgium. Four different POCTs were selected to be used in this study: CRP, Influenza antigen, GAS antigen and Coronavirus disease (COVID-19) POCT. The COVID-19 POCT was added to the trial because of the COVID-19 pandemic during the trial period (26). Being part of PRUDENCE, we helped enrol the trial in our practices and recruit patients for the study (27).

Appropriateness of antibiotic prescribing

To combat the rising threat of AMR, limiting the number of inappropriate prescriptions in primary care is essential (28). Introducing evidence-based guidelines can effectively improve prescribing quality by assisting GPs in selecting the appropriate medications, dosage, and duration of treatment (29, 30).

In Belgium, the Belgian Antibiotic Policy Coordination Committee (BAPCOC) was founded in 1999 to promote antibiotic appropriateness country wide. BAPCOC has taken measures to promote rational use of antibiotics in human and animal medicine for over 20 years now (31). One of the most impactful initiatives by far is the publication of the Belgian Guideline for Anti Infectious therapy in ambulatory care, with the first edition being published in 2006. This was the first evidence-based guideline for antibiotic use in primary care and was urgently needed knowing that almost 95% of antibiotics at that time were prescribed in primary care and only hospitals used guidelines for rational use of antibiotics. These initiatives helped reducing antibiotic prescriptions with 33% from 1999-2000 to 2009-2010 (32). This guideline has seen continuous updates and improvements over the years, the latest version has been published online in November 2022 (33).

Despite the implementation of evidence-based guidelines and other initiatives on both national and global scale, recent evidence shows that more efforts need to be made to combat AMR (30). Adriaenssens et. al., for instance, found a decrease in antibiotic appropriateness in outpatients between 2004 and 2009 in Europe (34). A worrying trend towards the use of broad-spectrum antibiotics was observed. Belgium specifically is also underperforming on a European scale, as made clear by the Belgian Health Care Knowledge Centre (KCE) report from 2019 discussing antibiotic prescribing in ambulatory care. They found Belgium to be third highest on the list in Europe of overall volume of antibiotics. Only Greece and France were doing worse (35).

In face of this problem, the council of the European Union published a recommendation on stepping up EU actions to combat AMR in a “One Health approach”. One of the core goals of this report is reducing the total consumption of antibiotics in Defined Daily Dose (DDD). A reduction of 20% in the EU compared to the baseline year 2019 as soon as the year of 2030, in the community and hospital sectors combined is envisaged (30). The 2022 annual surveillance report of the European Centre for Disease Prevention and Control (ECDC) on antimicrobial consumption in the EU, showed a general decline in antibiotic consumption between 2013 and 2022. Following a remarkable decline in 2020 and 2021, antibiotic consumption throughout the EU experienced a resurgence in 2022, with consumption rates in both community and hospital sectors approaching levels seen in 2019. The 2022 data also showed a further trend towards the use of broad-spectrum antibiotics and antibiotics that need to be reserved for specific indications (7). Extra efforts need to be made to further reduce antibiotic consumption to achieve the EU 2030 target (36).

The European Surveillance of Antibiotic Consumption (ESAC) published a set of evidence-based disease-specific antibiotic prescribing quality indicators (APQI) based on the work of Adriaenssens et al. (37). These disease specific APQIs take indications into account and thus allow for an evaluation of antibiotic prescribing quality in the context of the disease for which antibiotics are prescribed. These APQIs could be used to assess the quality of antibiotic prescribing on the level of countries, regions or singular practices, creating homogenous data that allows for comparisons and follow up trough time. This could help pinpoint areas of improvement, guide interventions and improve guidelines (34, 38).

A recent Belgian initiative called the “Antibiotic Barometer” uses these APQIs, that were validated by the Flemish Institute for Quality of Care (VIKZ) (39), to stimulate GPs to critically approach their own prescribing habits. The barometer is an automatic audit and feedback system which uses codified data on antibiotic prescription linked to specific diagnoses from the International Classification of Primary Care (ICPC) extracted the electronic medical file (EMD) kept by GPs. Starting from December 2023 all GPs were able to consult feedback reports comparing their antibiotic prescribing habits to those of practices in the same region, province and primary care zones (40). Gaining insight in prescribing habits could lead to more appropriate prescribing.

Research questions

PRUDENCE

The aim of PRUDENCE is to investigate whether the availability of POCTs for community-acquired RTI presenting with symptoms such as sore throat and cough in general practice can lead to more appropriate antibiotic prescribing behaviour, without compromising patient safety (27). The corresponding research question (RQ) is presented in a PICO format in table 1 (41):

PICO of the PRUDENCE trial

Population (P)	Patients aged 1 year and above with RTI presenting to primary care where the GP has considered OR decided to prescribe antibiotics
Intervention (I)	Point-of-care diagnostic tests (CRP testing, influenza and streptococcal antigen tests, COVID-19)
Control (C)	Usual care (care in accordance with primary care guidelines)
Outcome (O)	Reduction in antibiotic prescriptions

Table 1: Structure of the research question in PRUDENCE presented in the form of a PICO.

For the answers to this RQ, we will have to wait for the publications by the research group based on the complete European data.

Appropriateness of antibiotic prescribing

We had access to relevant data on GP consultations for RTI and antibiotic prescriptions from Flemish general practices participating in PRUDENCE. Using disease specific APQIs, we wanted to investigate whether or not antibiotic prescribing for selected ICPC codes differed between the population recruited in PRUDENCE and the most recent data in the Antibiotic Barometer for Antwerp. The corresponding RQ and presented in a PICO format in table 2 (41).

What is the quality of antibiotic prescribing in patients presenting with RTI to primary care in Antwerp?

PICO of this thesis

Population (P)	Patients presenting with RTI to primary care in the province of Antwerp
Intervention (I)	Patients in routine care i.e. Antibiotic Barometer data in the province of Antwerp
Control (C)	Patients included in PRUDENCE
Outcome (O)	Adherence to primary care guidelines i.e. BAPCOC for disease specific APQI

Table 2: Structure of the research question in our thesis presented in the form of a PICO.

Methods

PRUDENCE

Ten GP practices in Flanders participated in the PRUDENCE trial. We contributed by including patients ourselves in the practices we were working at the time.

Patients who presented to their GP with symptoms of upper respiratory tract infection (URTI) (sore throat) or with symptoms of lower respiratory tract infection (LRTI) (cough) were considered eligible for inclusion. Inclusion was possible whenever the GP considered prescribing antibiotics or had already decided to prescribe antibiotics. Other inclusion and exclusion criteria are listed below. An online platform, SLIM, was used to capture registration data of the participants. A separate platform, Research Online, was used to register patient and consultation data. First, baseline data were entered into Research Online (table 3), after which the patient was randomised to a specific POCT or usual care. Available POCT in the PRUDENCE study were CRP-POCT, GAS POCT or influenza POCT. The GP also had the option to use a COVID-19 POCT in case COVID-19 status was unknown. COVID-19 positive patients were not excluded from participating in the trial, the COVID-19 status of the participant was used within the algorithm to determine the possible randomisation arms. After randomisation more data was gathered on further management as shown in the table below (table 4). A flow diagram of the inclusion and randomisation procedure for PRUDENCE is added as an appendix (appendix 2). During influenza epidemic season an additional study arm with influenza POCT randomisation was added, this has not been displayed in this flowchart.

Inclusion criteria

Every male or female patient aged one or above was eligible for inclusion when presenting with symptoms of LRTI (since < 28 days) of which cough was the predominant symptom or with symptoms of URTI (since < 14 days) of which throat ache was the predominant symptom. Patients or guardians of the patient had to give informed consent verbally and subsequently this informed consent was registered during consultation in the online database (SLIM) or signed on paper.

Exclusion criteria

Patients with solely rhinosinusitis or otitis symptoms were not eligible for inclusion. Patients who were immunocompromised or of which the physician decided admission to the hospital was necessary were neither eligible. Other exclusion criteria were not speaking the local language, being terminally ill, having a severe psychiatric illness or being ineligible by judgement of recruiting physician.

After inclusion, the patient was asked to keep track of symptoms, therapy adherence and use of other medications (and most important antibiotics) via an online diary or on paper. After 14 days and after 28 days a study employee contacted the patients to follow up on these topics.

Data category	Input options online platform
Age	Numerical
Comorbidities	Yes / no and if so, which
COVID-19 vaccinations	Yes / no and if so, how many doses
Smoking	Yes / no
Symptoms	Choice from a list of RTI symptoms
Duration of symptoms	Number of days
Severity of symptoms	Mild/moderate/severe
Suspected pathogen	Bacterial / viral / not sure yet
Probability of antibiotic prescription	Low / medium / high

Table 3: Baseline data gathered before randomisation and entered in Research Online platform. The first column displays different categories, the second column displays possible answers.

Data category	Input options online platform
POCT result (if applicable)	Which test and result
Diagnosis of choice (only one)	• Acute pharyngitis (GAS) • Acute pharyngitis (other) • Acute tonsillitis (GAS) • Acute tonsillitis (other) • Laryngitis/laryngotracheitis • Peritonsillar abscess • Influenza • Bronchiolitis • Acute bronchitis • Community-acquired pneumonia • Wheezing • Exacerbation of chronic pulmonary disease • COVID-19 • other (specify)
Antibiotic prescription	Yes / no. Which antibiotic? Immediate/delayed?
Other prescriptions	Which?
Additional tests	Additional diagnostic/laboratory tests requested

Table 4: Additional data gathered after randomisation and entered in Research Online platform. The first column displays different categories, the second column displays possible answers.

General practitioners prescribing antibiotics were asked to register what class of antibiotic was used. The trial differentiated between narrow spectrum penicillin, broad spectrum penicillin, amoxicillin/clavulanate, tetracyclines, macrolides, quinolones and cephalosporins. Other types of antibiotics could also be registered using free text input (table 5). They were also asked to report whether the prescription was immediate or delayed.

Antibiotic Subclass	Corresponding molecule
Narrow spectrum penicillin	Pheneticillin
Broad spectrum penicillin	Amoxicillin
Amoxicillin/clavulanate	Amoxicillin/clavulanate
Cephalosporins	Cefadroxil, cefalexin
Tetracyclines	Doxycycline, minocycline,
Macrolides	Erythromycin, clarithromycin, azithromycin
Quinolones	Moxifloxacin, ciprofloxacin, levofloxacin
Other	Specify (free text)

Table 5: The different antibiotic subclasses as used in PRUDENCE and their corresponding molecules. The antibiotic subclass chosen had to be entered into the Research Online platform by participating GPs.

Appropriateness of antibiotic prescribing

Disease Specific Antibiotic Prescribing Quality Indicators (APQI)

Adriaenssens and colleagues developed seven disease specific APQIs to better evaluate antibiotic prescribing behaviour and evaluate the quality of antibiotic prescribing in ambulatory care (37). In this thesis we assessed quality of prescribing of four indications listed below in table 6.

Antibiotic Prescribing Quality Indicator (APQI)			**Acceptable use**	
ICPC Code	**Indication**	**Age group**	**% first choice antibiotic (lower limit)**	**% quinolone prescriptions (upper limit)**
R72 + R76	GAS infection + Acute tonsillitis	> 1 year	80%	5%
R74	Acute upper airway infections	> 1 year	80%	5%
R78	Acute bronchitis	18 - 75 year	80%	5%
R81	Pneumonia	18 - 65 year	80%	5%

Table 6: The four different diseases of which APQIs are validated and are applicable to PRUDENCE and their limits of acceptable use.

Every disease specific APQI consists of 3 separate indicators:

1. Percentage of antibiotic prescriptions per ICPC code per age group.
2. Percentage of antibiotic prescriptions that is considered the first-choice antibiotic per ICPC code per age group.
3. Percentage of prescriptions that are quinolone antibiotics per ICPC code per age group.

To assess quality of prescribing for the selected indications, we used the second and third indicator (point 2 and 3).

Adriaenssens and colleagues also report limits of acceptable use as displayed in table 6. Regarding percentage of first choice antibiotic, this limit indicates that at least 80% of prescriptions for a certain indication should be in line with current guidelines. Regarding percentage of quinolone prescription, this limit indicates that a maximum of 5% of patients with a certain diagnosis should be treated with a quinolone.

Calculating APQIs using PRUDENCE trial data

In PRUDENCE extensive data was collected including data on diagnosis and antibiotic prescribing. We were granted access to demographic, disease specific (signs and symptoms), diagnostic, prescription and comorbidity data from patients included during the clinical trial in the ten participating GP practices in Flanders. We used this data to calculate disease specific APQIs.

In the PRUDENCE trial, diagnosis was coded as one possibility out of a list of several diagnoses as presented in table 7. To make calculation of APQIs possible, we first translated the diagnoses as recorded in PRUDENCE into ICPC codes (table 7).

PRUDENCE diagnoses	ICPC code
• Acute upper airway infection/common cold • Acute/viral pharyngitis	R74
• Acute GAS pharyngitis • Acute tonsillitis • Acute GAS tonsillitis • Peritonsillar abscess	R72 + R76
• Acute bronchitis • Bronchiolitis	R78
• Community-acquired pneumonia • Atypical pneumonia	R81

Table 7: The diagnoses included in PRUDENCE and their corresponding International Classification of Primary Care (ICPC) code.

Using the Antibiotic Barometer information sheet and BAPCOC, the appropriate molecule and regimen of administration was selected per diagnosis (table 8). See Appendix 3 for an overview of relevant BAPCOC recommendations.

Indications	First choice antibiotic
Acute tonsilitis/GAS	Pheneticillin
Acute upper airway infection	Pheneticillin
Acute bronchitis	Amoxicillin, amoxicillin/clavulanic acid
Pneumonia	Amoxicillin, amoxicillin/clavulanic acid

Table 8: Indications and their corresponding first choice antibiotic according to the Antibiotic barometer.

Doing this we have created a data set on which APQIs can be calculated. We will plot these results against limits of acceptable use as determined by Adriaenssens et.al. (37).

Comparing trial data and routine data from Antibiotic Barometer using APQIs

The Antibiotic Barometer feedback reports offer insight in antibiotic prescribing for four indications using the same APQIs that are extractible from the EMD kept by GP practices. Reports are published every three months (39). The use of APQIs allowed for a direct comparison between our calculated APQIs from trial data and routine data on antibiotic prescribing as presented by the Antibiotic Barometer (37).

Besides feedback on antibiotic prescribing for specific indications from your own GP practice, aggregated data is also given for your region, province, and primary care zone (artificial zones of collaboration between first line healthcare providers). Data for PRUDENCE was collected in ten GP practices in Flanders. Eight practices are located in Antwerp, two in Flemish Brabant. All practices are

located in urban areas. Therefore, we decided to only use data from the province of Antwerp for our analysis, because we estimated this would offer the most comparable groups.

Regarding acute upper airway infections and acute / viral pharyngitis and GAS infections / tonsillitis, barometer data contains all consultations from patients aged 1 year and above. These are the same inclusion criteria that we used for including patients in PRUDENCE. Barometer data on acute bronchitis and pneumonia however only contain consultations from patients aged 18 – 75 and 18 – 65 respectively. We therefore only included patients falling in these age categories in our comparison.

For our analysis, we conducted a descriptive analysis of this data by comparing these results with routine care data from the Antibiotic Barometer for Antwerp. We presented this data by plotting these percentages against the limits of acceptable use as determined by Adriaenssens et.al. (37) in bar charts using Excel.

Results

PRUDENCE

Demographics

In Belgium, 121 patients were included, of whom 83 were women and 38 were men. The ages ranged from 3 years to 80 years.

Diagnoses and prescribing

Of 121 inclusions these, 43 patients were immediately prescribed antibiotics and 14 patients received a delayed prescription. Overall, a total of 57 (47%) patients were prescribed an antibiotic.

Diagnosis	ICPC code	Number of inclusions n	Antibiotic prescriptions n (%)
Tonsillitis/GAS	R72 + R76	58	42 (72%)
Pharyngitis/viral upper airway infection	R74	22	2 (9%)
Bronchitis	R78	12	3 (25%)
Pneumonia	R81	12	10 (83%)
Influenza		10	0
Covid		3	0
Other		4	0 (0%)
Laryngitis		1	0 (0%)
Bronchiolitis		1	0 (0%)
Erythema infectiosum		1	0 (0%)
No diagnosis		1	0 (0%)
Total		121	57 (47%)

Table 9: Results of data gathered during PRUDENCE in 10 GP practices in Flanders. ICPC: International Classification of Primary Care.

Tonsilitis or GAS and pharyngitis or upper respiratory tract infections were the most common diagnoses. One person in the tonsillitis and GAS group was diagnosed with peritonsillar abscess which is also coded R76 in ICPC. All results are displayed in table 9.

Of the patients with tonsilitis or GAS 42 out of 58 (72%) were prescribed an antibiotic. Nineteen (45%) patients were given a broad-spectrum penicillin. Only 12 patients (29%) received a narrow

spectrum penicillin. Seven (17%) patients received a cephalosporine, 3 (7%) a macrolide and 1 (2%) patient was treated with a tetracycline.

Of the patients with pharyngitis or viral upper airway infection 2 out of 22 (9%) were treated with antibiotics. One of them was prescribed a cephalosporin and one a broad-spectrum penicillin.

For the group of people with pneumonia, a total of 10 patients (83%) were prescribed antibiotics. The most prescribed antibiotic within this group was a broad-spectrum penicillin antibiotic, 8 patients received this. Additionally, a macrolide was prescribed once, and in one case, a quinolone was prescribed.

In the group of people with bronchitis, 3 patients (25%) got an antibiotic, 2 of them got broad-spectrum penicillin and 1 got a macrolide.

		Tonsillitis / GAS R72 R76 n (%)	**Pharyngitis / Viral URTI R74** n (%)	**Bronchitis R78** n (%)	**Pneumonia R81** n (%)
Type of prescribed antibiotic (% of total antibiotics prescribed)	Narrow spectrum penicillin	12 (29%)	0 (0%)	0 (0%)	0 (0%)
	Broad spectrum penicillin	19 (45%)	1 (50%)	2 (66.7%)	8 (80%)
	Macrolides	3 (7%)	0 (0%)	1 (33.3%)	1 (10%)
	Cephalosporine	7 (17%)	1 (50%)	0 (0%)	0 (0%)
	Quinolones	0 (0%)	0 (0%)	0 (0%)	1 (10%)
	Tetracycline	1 (2%)	0 (0%)	0 (0%)	0 (0%)
	Total antibiotic prescriptions	42 (100%)	2 (100%)	3 (100%)	10 (100%)

Table 10: Antibiotic subclass prescribed for each specific diagnosis with ICPC code during PRUDENCE. ICPC: International Classification of Primary Care.

Appropriateness of antibiotic prescribing: Comparing with antibiotic barometer

Percentage first choice antibiotics

Calculating the selected disease specific APQI for percentage of first choice antibiotic for the PRUDENCE data set, we came to the following results displayed in table 11.

		PRUDENCE		Antibiotic Barometer	
ICPC code	**Indications**	**Calculated APQI for first choice antibiotic (%)**	**Calculated APQI for quinolone prescriptions (%)**	**APQI for first choice antibiotic (%)**	**APQI for quinolone prescriptions (%)**
		[>80%]	[<5%]	[>80%]	[<5%]
R72 + R76	Acute tonsilitis	29%	0%	7%	0,4%
R74	Acute upper airway infection	0%	0%	1%	0,6%
R78	Acute bronchitis	67%	0%	71%	4%
R81	Acute pneumonia	80%	8%	82%	10%

Table 11: Antibiotic prescribing quality indicators (APQI) calculated with data from the PRUDENCE trial. ICPC: International Classification of Primary Care; []: limits of acceptable use

We plotted data on percentage of first-choice antibiotics for specific diagnosis from our data set against the most recent data from the Antibiotic Barometer for the province of Antwerp. We also included the lower limit of acceptable use according to the disease specific APQI (Figure 1).

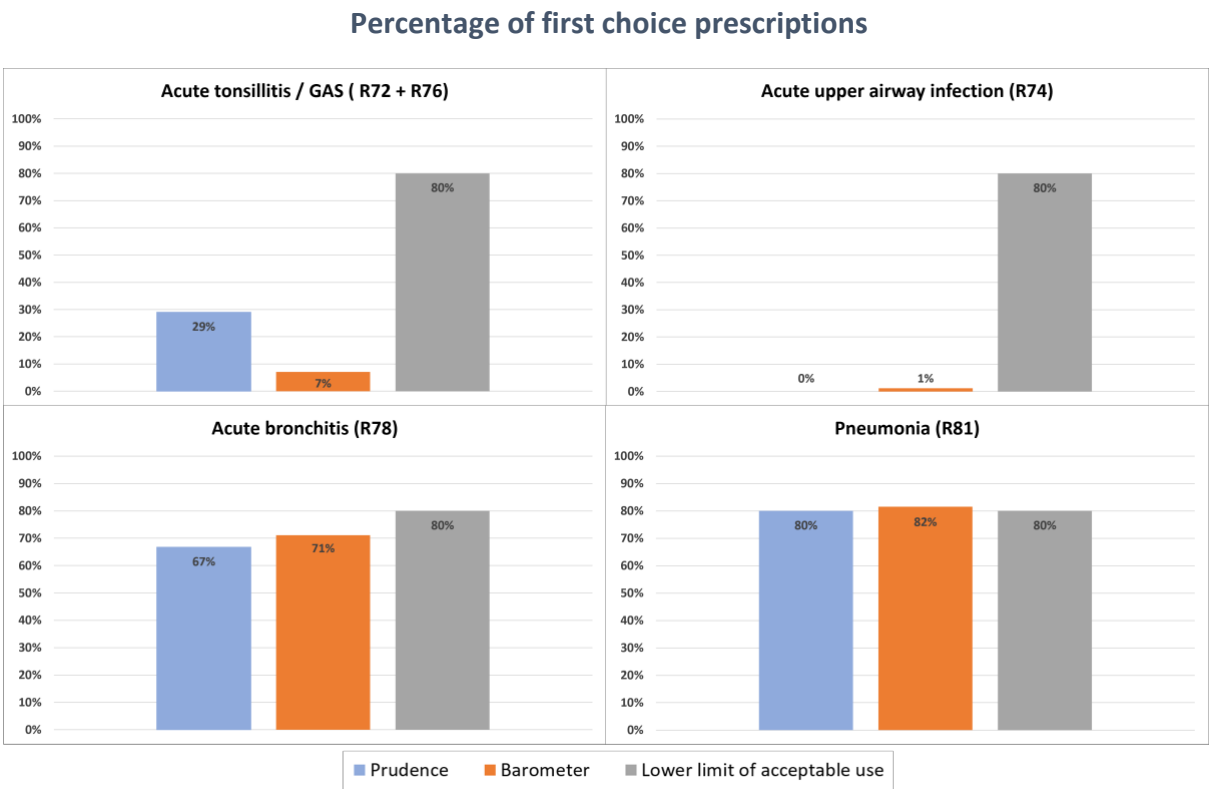


Figure 1: Percentage of first-choice antibiotic prescriptions in PRUDENCE and Antibiotic Barometer. Lower limit of acceptable use as defined by the disease specific antibiotic prescribing quality indicators (APQI)

For acute tonsilitis or GAS, PRUDENCE showed that 29% of antibiotic prescriptions were narrow spectrum penicillin and thus in accordance with primary care guidelines versus 7% in the Antibiotic Barometer. Regarding acute upper airway infection, 0% were prescribed first choice products in PRUDENCE versus 1% in the Antibiotic Barometer. For acute bronchitis the PRUDENCE trial scored 67% versus 71% in the Antibiotic Barometer. For pneumonia, PRUDENCE and the Antibiotic Barometer report percentages of first choice antibiotics being prescribed of 80% and 82% respectively.

Percentage of quinolone prescriptions

Calculating the selected disease specific APQI for percentage of quinolone prescriptions for the PRUDENCE data set, we came results displayed in table 11:

Here we plotted the amount of quinolone prescriptions for a certain diagnosis against each other (figure 2). The APQIs recommend that less than 5% of patients consulting for one of the included indications get a prescription for quinolones.

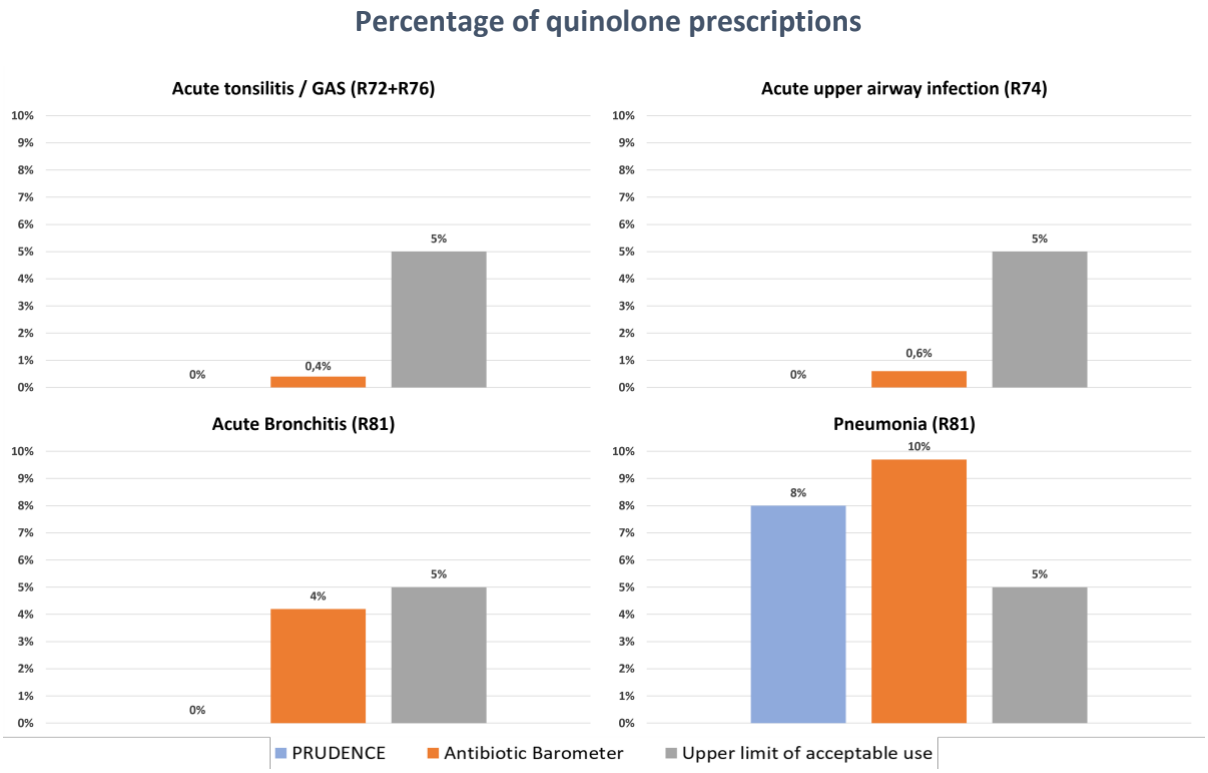


Figure 2: Percentage of quinolone antibiotic prescriptions in PRUDENCE and Antibiotic Barometer. Upper limit of acceptable use as defined by the disease specific antibiotic prescribing quality indicators (APQI)

For acute tonsilitis or GAS, acute upper airway infection and acute bronchitis no quinolones were prescribed in PRUDENCE. Antibiotic Barometer data shows a prescription rate of 0,4%; 0,6% and 4% respectively. For pneumonia, more quinolones were prescribed, with PRUDENCE results showing 8% and the Antibiotic Barometer showing 10% of patients with pneumonia being prescribed a quinolone.

Discussion

PRUDENCE

Recruitment for PRUDENCE was concluded in January 2024 after almost 3 years. PRUDENCE enrolled 2240 patients from primary care. They have now entered the phase of data cleaning and will subsequently start statistical analysis. The final dataset will be analysed by the team of statisticians in Oxford (UK) and Basel (Switzerland). Before the first results will be published, we cannot offer any early insights on the primary endpoints of the trial, of which one is the effect of POCTs on antibiotic prescribing. However, considering existing evidence, we dare prudently say that POCTs in primary care could attribute to more appropriate antibiotic prescribing in primary care and might become an effective tool in the fight against antibiotic resistance (8, 22) (appendix 1 for more context).

Appropriateness of antibiotic prescribing

Being part of PRUDENCE, we were granted access to data from ten GP practices in Flanders. Herein we saw an opportunity to compare antibiotic prescribing behaviour in the trial with routine data as presented in the Antibiotic Barometer using disease specific APQIs for RTI and doing so assess the quality of prescribing between trial data and routine data. We decided not the use the first APQI since this indicator assesses the total amount of antibiotics prescribed for a certain diagnosis. The population in PRUDENCE was subject to selection bias, because only patients were included where the GP was already considering to or had decided to prescribe an antibiotic. The two other APQIs still offer insight in antibiotic prescription quality and allow for comparison between trial and routine data.

Our results showed that apart from pneumonia, none of the APQIs for percentage of first choice antibiotics met the lower limit of acceptable use of 80%. Especially Tonsilitis/GAS and upper airway infection score low on this indicator (29% and 0% respectively). One reason for the low use of small spectrum penicillin, which is the first-choice treatment for these indications, in favour of the more commonly used broad spectrum penicillin (amoxicillin), is the unavailability of a small spectrum penicillin on the Belgian market. After the discontinuation of Penicillin V in 2019, no small spectrum penicillin was available for several years. These molecules however are still the first-choice antibiotic in the treatment of GAS throat infections. In spite of several recommendations pointing out the importance of the availability of small spectrum antibiotics, it was only in March of 2022 that a small spectrum penicillin was commercialised again in the form of pheneticillin. It then took another 2 months until this molecule was reimbursed, making it finally a practical choice for GPs. It should also be noted that despite reimbursement of this antibiotic, the public price of a package of pheneticillin is still almost 3 times as expensive as a package of amoxicillin (€15 versus €5,2). The prolonged unavailability and higher costs of the first-choice antibiotic could partially explain their underuse. Small spectrum antibiotics are important in limiting AMR. Initiatives should aim to encourage their use in primary care settings for certain indications such as GAS throat infections (42). The results for bronchitis and pneumonia are more favourable but still disappointing. This could be explained because amoxicillin is considered the first-choice treatment for these indications.

Regarding quinolone prescriptions, in the trial data no quinolone was prescribed for acute tonsillitis or GAS, acute upper airway infection or acute bronchitis. One quinolone prescription was prescribed for pneumonia, resulting in 8% of patients with pneumonia being treated with a quinolone. The APQI

sets the upper limit of acceptable use at 5% for this indication (34). This is also the upper limit as suggested by Belgian national action plan for 2020- 2024 (43).

When interpreting these results, we should consider our very small sample size. To get to the acceptable range of 5% quinolone prescriptions you only need one prescription per 20 pneumonia diagnoses. Considering the relative rarity of pneumonia diagnoses in primary care, it makes sense that a lot of practices will prescribe well over the maximal rate proposed by the APQI.

Monitoring and limiting quinolone prescribing has become very important in the face of growing antimicrobial resistance. It should be very clear that the use of quinolones needs to be reserved for specific indications (44). Some of these indications are *N. gonorrhoeae* infections, urinary tract infections, *P. aeruginosa* infections, typhoid and paratyphoid fever, shigella spp. and campylobacter spp. infections (45). Additionally, due to its broad spectrum of action quinolones are correlated to higher risk of a *C. difficile* infection in hospitalized patients and in community (46). Belgium has taken several measures to limit quinolone prescriptions including a recent change in reimbursement criteria. Since 01/05/2018 quinolones are no longer reimbursed for airway infections, unless in case of exceptional or very urgent cases (47). Quinolone prescriptions for throat ache or bronchitis should therefore be considered absolutely inappropriate. Seeing no prescriptions for these indications in the trial data could mean GPs are generally aware of the place of quinolones for these indications.

Appropriateness of antibiotic prescribing: trial data versus routine data

Regarding tonsilitis and GAS infection, our data showed that only 29% of antibiotic prescriptions consisted of the first-choice product. Barometer data for Antwerp shows an incredibly low 7%. Data presented by the Dutch Society for General practitioners (Nederlandse Huisartsen Genootschap i.e. NHG) showed 54% of prescriptions to be first choice products for treating tonsillitis. The top 10% performers in Antwerp only managed to achieve 48% on average. This data resulted to two conclusions. Firstly, GPs generally tend to overprescribe broad spectrum antibiotics for throat ache while small spectrum penicillin should be preferred for reasons previously discussed. Secondly, huge differences between practices most likely exist.

PRUDENCE data showing relatively good results could be explained by GPs participating in the trial being generally more up to date with recent prescribing guidelines. Participating GPs also had access to GAS POCT results (for patients in the intervention group). This could have influenced prescribing because a confirmed GAS infection could have led to more appropriate prescribing considering small spectrum penicillin is the recommended treatment for GAS infections. We were however blind to both POCT allocation and results, therefore we could not correct for this potential bias. This blinding is a strength when analysing the effects of POCT use on antibiotic prescribing, the primary outcome measure of PRUDENCE, but an important limitation when interpreting results from our study.

Regarding upper airway infections, our data showed 0% of prescriptions being first choice. Antibiotic Barometer data for Antwerp again is very low with 1%. These low results could be explained by the same arguments discussed above. We should however point out that prescribing rates for upper airway infections tend to be much lower. In our data only 9% of patients with upper airway infection were treated with antibiotics. Barometer data shows 20% of patients were treated with antibiotics in Antwerp. This is in line with data from The Netherlands, were 19% of patients with upper airway infection got antibiotic treatment (21).

Regarding bronchitis, in PRUDENCE 67% of prescriptions belonged to the recommended antibiotics. Antibiotic Barometer shows 71% of prescriptions being considered first choice. Looking at the average of the top 10% best performing practices 100% of first choice antibiotics were prescribed.

Regarding pneumonia, the proportion of prescriptions belonging to the first-choice molecules proposed by the guideline should again be above 80% (37, 43). In the trial data this number was 80%. The Antibiotic Barometer for Antwerp shows that 82% of prescriptions were considered first choice. The average of the top 10% best performing practices recorded in the Antibiotic Barometer was again 100%.

Both acute bronchitis and pneumonia are scoring much higher for the proportions of used first choice antibiotics in comparison to acute tonsilitis, GAS and upper airway infection. Reasons for this could be that amoxicillin is in this case the first-choice antibiotic according to BAPCOC guidelines for lower respiratory tract infections and that GPs are generally more acquainted with this recommendation.

In the trial data, one patient was treated with a quinolone. This means that 8% of patients with pneumonia were treated with quinolones. Compared to barometer data for Antwerp, we find similar results with quinolone prescriptions in 10% of pneumonia diagnoses. The APQI accepts an upper limit of acceptable use of 5% for this indication (37, 43). As previously states a lot of practices will prescribe well over the maximal rate proposed by the APQI considering the relatively uncommon nature of pneumonia.

Antibiotic Barometer data on quinolone prescriptions for tonsilitis or GAS, upper airway infections and bronchitis showed 0,4%, 0,6% and 4% of patients with these diagnoses respectively were treated with quinolones in Antwerp. These prescribing rates were lower than the upper limit of acceptable use of 5% (37, 43). Even though APQI results for percentage of first choice antibiotics being prescribed for tonsilitis or GAS and acute upper airway infection were poor in routine data, we did not see the same poor results regarding quinolone usage. Here routine data supported the idea that GPs are aware of the absence of indications for quinolones in treating tonsilitis or GAS, upper airway infections and bronchitis. The average of the top 10% best performing practices regarding quinolone prescriptions for bronchitis was 0%, showing improvement is possible for a lot of GP practices in Antwerp.

Our assessment of appropriateness of antibiotic prescribing using trial and routine care data, comes with some important limitations. Extrapolating results to general practice in Antwerp is difficult. The trial data was collected in 10 practices in and around Antwerp, this sample may not represent all general practices. Data was collected by a combination of GPs in participating practices. Prescribing behaviour can differ, even amongst GPs working under the same roof. This same limitation was applicable for Antibiotic Barometer data, where data collection also happens on a practice level. The trial data consisted of a small sample size, this limited precision of our results. The sample size of the Antibiotic Barometer should be much larger, but we did not have insight in this sample's composition nor size. Having had no insight into sample sizes for the APQIs, this limited interpretations on result precision. Without insight in what practices make up the APQI for, in this case, Antwerp, no valid claims could be made regarding prescribing behaviour in the province.

As investigators we were blind to POCT allocation and results in PRUDENCE. This made us blind for any difference in prescribing behaviour that might have been explained by the introduction of POCTs. We tried to avoid this pitfall by using percentage of prescriptions that were considered first choice and quinolone prescribing rate as measures of prescribing quality, because it was unlikely that these results would have been influenced by the introduction POCTs.

Belgian GPs were not forced to use the Antibiotic Barometer, they were however required to subscribe to the barometer starting from 2023 if they wanted to receive funding for IT support. This gave participating physicians financial incentives. Such financial incentives were also present in PRUDENCE, participating GPs were offered a compensation for each patient included in the trial.

An important fact that should be taken into consideration is that the Antibiotic Barometer calculates its APQIs on a prescription basis and did not look at dispensed medication. It was estimated that in developed countries the adherence rate for short term treatment is 70-80% (48). A European study from 2013 found that only 44% of patients completed their antibiotic treatment as prescribed (49). Given this fact, it is possible that the total amount of prescribed antibiotics did not correspond with the actual quantity of antibiotics that was taken. In the PRUDENCE trial, we tried to take this into account by providing follow up regarding actual antibiotic use by means of diaries and telephone calls. This was a study on quality of prescriptions, which makes assessing prescriptions a logical choice. When assessing antibiotic use, using defined daily doses (DDD) for measuring drug utilisation might provide a more correct estimation.

When analysing quality if antibiotic prescriptions for RTI in Antwerp, we found that prescription rates for tonsillitis and GAS are high. The NHG reported prescription rates of 51% for tonsilitis and 53% for GAS in 2012 (21). Antibiotic Barometer data for December 2023 showed 65% antibiotic prescriptions for tonsilitis and GAS in the province of Antwerp. In our data set, 42 out of 58 (72%) patients with tonsilitis or GAS were prescribed an antibiotic. The upper limit of acceptable use for antibiotic prescriptions for patients older than 1 year with tonsillitis or GAS is 20% (37). Guidelines generally advocate against the use of antibiotics in treating sore throat. Evidence showed that antibiotic treatment only marginally influences disease course by shortening disease duration by only half a day. The place of antibiotics to prevent complications was at most unclear, with even bacterial throat infections generally having a mild disease course and healing spontaneously (50). We did however wanted to report this data, because it supported the consensus that antibiotic prescriptions for sore throat were still too high. A Dutch study even concluded that half of antibiotic prescriptions for sore throat were inappropriate (51). Recent Antibiotic Barometer data supported the idea that this overprescribing is still a problem to this day.

One important factor that has to be considered is that based on symptoms and clinical signs, it is next to impossible to distinguish between a bacterial and a viral cause of throat ache. Without insight into randomization and POCT results of the trial data, it was impossible to say how many patients had confirmed GAS infection and how many were diagnosed on clinical grounds. It is important to note that Belgian and Dutch primary care guidelines still advocate against the usage of strep tests in primary care due to a lack of clinical relevance (19, 20). Antibiotics should only be considered for severely ill patients and patients with higher risks of severe disease course or complications (52). Without access to GAS POCT, treatment for throat ache is mostly based on clinical presentation (21). Different clinical decision-making tools to help diagnose and treat throat infections have been

proposed. One such tool were the Centor rules. This clinical decision-making tool calculates a score based on age, presence of exudate or swelling of tonsils, presence of cervical lymphadenopathy, elevated temperature and absence of cough. This score correlates with a probability of GAS infections and was meant to help physicians to decide whether or not diagnostic tests or treatment was appropriate (53, 54). Even though differentiating between GAS infection and other causes of sore throat was not very clinically relevant, these were the clinical signs and patient characteristics that generally dictate decision making when dealing with patients presenting with throat ache (21). It could have been interesting to analyse if these clinical findings influenced GP's decision making in our data set, but a superficial look at the results failed to expose any statistically significant differences regarding these signs in patients presenting to their GPs with throat ache who received antibiotic treatment versus those who did not. There were, however, some potentially clinically relevant differences. Patients who received antibiotics exhibited more cervical lymphadenopathy, fever and had generally higher symptom severity scores. A deep dive into these results would take us too far from our initial RQ. Understanding what primarily dictates clinical decision making when prescribing antibiotics is however very important when trying to combat inappropriate antibiotic prescribing.

Another important factor influencing GP's prescribing behavior are expectations from both patient and GP are very important in prescribing behavior. Studies showed that GP's tend to overestimate the wish for antibiotic prescriptions in their patients. Assessing the patients' expectations is therefore very important (55, 56).

Having looked at data of the Antibiotic Barometer, big local differences in prescribing became apparent, even in the small region of Flanders. For instance, antibiotic prescribing rate for the province of Antwerp was 65% regarding tonsillitis or GAS. The average antibiotic prescribing rate for of the top 10% best performing practices in Antwerp however was way lower at 15%. These results should be interpreted carefully because of the limitations that come with using Antibiotic Barometer data as benchmark for prescribing quality in the community. It is well established that a lot of regional variation exists in antibiotic prescribing behaviour (38, 57). This data does however support the hypothesis that big differences in antibiotic prescribing behaviour could exist between practices, even in the same part of a country, or between individual GPs. It was too soon to estimate the effect of the introduction of the barometer on this discrepancy. But offering individual practices insight in their own prescribing behaviour compared to other practices, might bring antibiotic prescribing more in line. Future research should aim to pinpoint factors influencing prescribing behaviour, especially in outliers.

The introduction of APQIs allows for the assessment of prescribing per indication, pinpointing potential areas of improvement. Getting feedback in a timely manner (every three months), allows for tracking of progress on a practice level. The use of APQI also allows for comparative studies between regions or even countries, which is a key factor in combating antibiotic resistance trough a "One Health approach" on European scale. Vellinga et. al. recorded over 6000 RTI consultations in general practices in 13 European countries in 2020 and 2022, calculating the same APQIs. They found that APQIs regarding prescribing rates for bronchitis and tonsillitis are generally not met. They also found that in a lot of countries, GPs still prescribe antibiotics that are not recommended by guidelines such as macrolides and amoxicillin clavulanic acid. Belgium even showed the highest rates of broad-spectrum penicillin being used out of all participating countries. These results should be interpreted carefully, because they are based on limited samples from participating GPs and should

therefore not be considered benchmarks for the entire country. Lastly, antibiotic prescribing behaviour varied widely between countries (38). These findings supported the findings from analysing our data set and early Antibiotic Barometer data.

The assessment of prescribing behaviour trough disease specific APQIs and receiving feedback in a timely manner, are advantages of the Antibiotic Barometer. These advantages stand in contrast to the National Council for Quality Promotion (Nationale Raad voor KwaliteitsPromotie(NRKP)) indicators being used in the feedback system by RIZIV. The three NRKP indicators do not take indications into account. The first indicator indicates the maximum percentage of patients with a prescription for an antibiotic compared to the total number of patients with a prescription for a pharmaceutical specialty. The second indicator indicates the minimum percentage amoxicillin alone compared to the total number of prescriptions containing amoxicillin (whether combined with clavulanic acid or not). The third indicator indicates the maximum percentage second line antibiotics compared to the total number of antibiotics. They are presented only once yearly and take into account results from five years previous. This creates a substantial lag, restricting GPs to change their behaviour before being checked. General practitioners not meeting the criteria, will be contacted to justify their prescribing behaviour. Depending on the situation, proportional measures such as raising awareness, issuing warnings, or conducting control investigations could be undertaken (40, 58). We are concerned that being subjected to strict inspection this way does not provide the right motivation to GPs to change their behaviour. We think that this strategy risks leading GPs into finding ways to not be picked up by the indicators by for instance writing more inappropriate prescriptions rather than limiting inappropriate antibiotic prescriptions. Thus, leading to more inappropriate prescribing rather than limiting it.

Conclusion

When assessing the quality of antibiotic prescribing in patients presenting with RTI to primary care in Antwerp using disease specific APQIs we found that quality indicators are usually not met. The quality of prescribing regarding tonsilitis or GAS and upper airway infections was especially unfeasible. Broad spectrum antibiotics were prescribed too often over the first-choice antibiotic in RTI. Quinolones are overprescribed for pneumonia and should be preserved for strict indications. These should be considered primary targets for policy makers. Data from routine care as presented in the Antibiotic Barometer showed a lot of regional variation in quality of prescribing. These variations should be taken into account when trying to enhance antibiotic prescribing behaviour.

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Appendices

Appendix 1: Literature review

Axel Hendrickx
Tom Genné
Victor Mulders

PRUDENCE: literature review

Introduction

Using antibiotics too often and prescribing them for the wrong indications increases antibiotic resistance. This leads to reduced effectiveness of antibiotics. Globally, antibiotic resistance rates are rising, this is a major public health problem of the 21st century that requires further research and needs to be addressed as soon as possible (1). Point-of-care diagnostic tests could help primary care physicians distinguish between those patients who would and those who would not benefit from antibiotic treatment. This could lead to more appropriate antibiotic prescriptions. Most antibiotics are prescribed in primary care, especially for community-acquired respiratory infections. (2, 3) To combat the rising problem of antibiotic resistance, interventions to limit inappropriate antibiotic prescribing in primary care are needed. (4).

The aim of PRUDENCE is to investigate whether the availability of point-of-care diagnostic tests for assessing patients with community-acquired respiratory infections presenting with symptoms such as sore throat and cough in general practice can lead to more appropriate antibiotic prescribing behaviour, without compromising patient safety.

Methods

We have formulated the research question using the PICO format as described in table 1. We used the following databases to conduct our search: PubMed, Cochrane and CEBAM. In these databases we used a structured search query (table 2).

Table 1: research question using the PICO format

Population (P)	Patients aged 1 year and above with respiratory infections in primary care settings
Intervention (I)	Point-of-care diagnostic tests (CRP testing, influenza and streptococcal antigen tests)
Control (C)	Usual care (care in accordance with primary care guidelines)
Outcome (O)	Reduction in antibiotic prescriptions

Table 2: search query used to search selected databases

	"Respiratory tract infections" OR "lower respiratory tract infections" OR "upper respiratory tract infections" OR "respiratory infection" OR "respiratory infections" OR "respiratory illness" OR "respiratory diseases"
AND	"Point-of-care testing" OR "rapid diagnostic tests" OR "CRP testing" OR "influenza testing" OR "streptococcal testing" OR "o"
AND	"Primary care" OR "general practice" OR "family practice" OR "primary health care"
AND	"Antibiotic prescribing" OR "antimicrobial prescribing" OR "antibiotic prescription" OR "antimicrobial prescription" OR "antibiotic resistance" OR "antimicrobial resistance" OR "reducing antibiotic prescribing" OR "reducing antimicrobial prescribing"

Search limitations

We limited our search to studies published within the last 5 years (2017-2023), articles published in English or Dutch, articles with full text available.
After applying the search limitations, the results were screened on title and abstract by three researchers (A.H., T.G. and V.M.). Subsequently inclusion and exclusion criteria listed below were checked.

Inclusion criteria:

- Studies conducted in primary care settings in Europe.
- Participants with respiratory infections.
- Intervention involving point-of-care diagnostic tests, specifically rapid CRP testing, influenza, and streptococcal antigen tests.

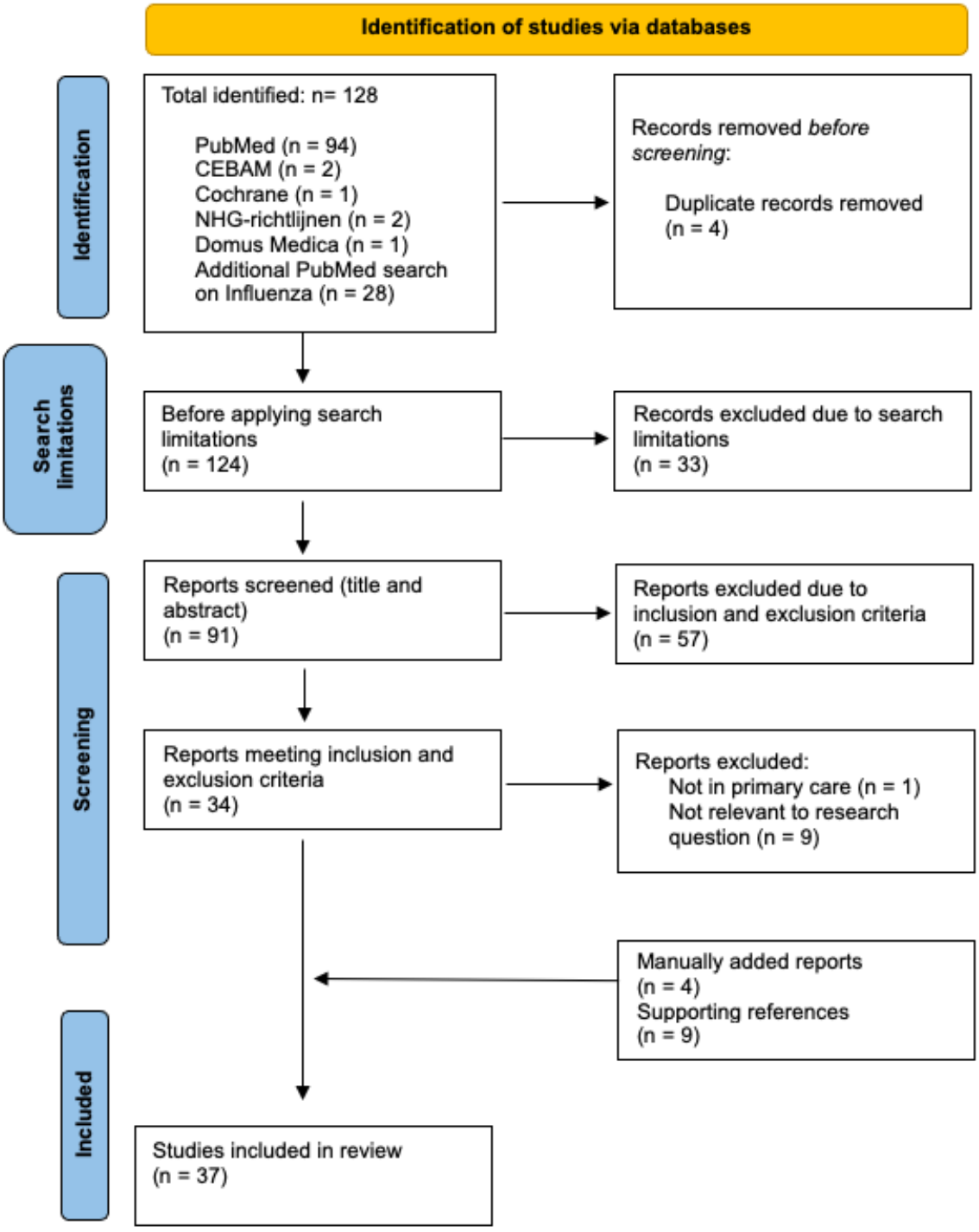
Exclusion criteria:

- Studies conducted in non-primary care settings or outside of Europe.
- Participants without respiratory infections.
- Interventions not involving point-of-care diagnostic tests for respiratory infections.

Our initial search yielded a lack of reports on the effects of point-of-care influenza tests on antibiotic prescribing in patients with respiratory tract infections in primary care. Therefore, an additional PubMed search was conducted using keywords "influenza", "point-of-care tests" and "antibiotic". These publications were screened using the same inclusion and exclusion criteria. We did however expand the search to include studies older than 5 years. Later three more studies were manually added to the review to be able to paint a full picture of existing evidence.

In addition to the search in PubMed, Cochrane and CEBAM we manually added local primary care guidelines from the Netherlands and Belgium (NHG, Domus Medica). To clarify some aspects in our text we added other relevant references. Figure 1 shows the integral process of the search strategy step by step.

Figure 1: detailed flow chart showing search strategy



Results

In our search it became clear that by far most research has been done with C-reactive protein (CRP) point-of-care tests (POCTs). This is not very surprising since CRP is a general marker of inflammation and can be put to use for a broad range of symptoms. Rather than strep and influenza POCTs which are only useful in a very specific cluster of symptoms.
Hereunder, we provided an overview of existing evidence on the use of three different POCTs (CRP, strep and influenza) in primary care and their impact on antibiotic prescribing behaviour. We divided the review in three separate sections to give a clear overview of existing evidence per test.

C-reactive protein point-of-care test

CRP, a biomarker of systematic inflammation, is a broadly used laboratory test commonly requested in primary care. The availability of CRP-POCTs allows healthcare professionals to distinguish bacterial infections from other inflammatory conditions and assists them in identifying the patients who would benefit most from antibiotic treatment (5, 6). According to a study performed by Danish general practitioners (GPs), CRP-POCT has been shown to be the most important factor that influences decisions by GPs to prescribe an antibiotic. Patient's general condition, crackles at auscultation and fever have also been found to be important factors in decision making, but only secondary to CRP levels (7).

As CRP-POCTs become more accessible and accurate (8), their implementation has been suggested to be an effective measure in the fight against inappropriate antibiotic prescriptions and the concurrent rise in antibiotic resistance.

Boere et al. studied in a cluster of randomized controlled trials (RCTs) the effect of CRP-POCT on antibiotic prescribing for lower respiratory tract infections in nursing homes. A total of 242 patients from 11 nursing home organisations were included in this study. They found that patients in the intervention group had 4.04 higher odds of not being prescribed an antibiotic compared to the control group which had no CRP testing. For suspected lower respiratory tract infection safely reduced antibiotic prescribing compared with usual care in nursing home residents. These findings suggest that implementing CRP-POCT in nursing homes might contribute to reduced antibiotic use in this setting and help to combat antibiotic resistance (9). Further research by Boere et al. found CRP-POCT to be a cost-effective tool for reducing antibiotic prescribing for patients with suspected lower respiratory tract infections, including acute exacerbations of chronic obstructive pulmonary disease (10).

An important systematic review on the use of POCTs to guide antibiotic prescriptions reviewed twelve trials (10,218 participants in total, 2335 of which were children). The researchers found that the use of CRP-POCT reduced the number of patients given an antibiotic prescription. Importantly this reduction is achieved without affecting recovery rates. Additionally, the results showed no increased mortality within 28 days of follow-up in the test group compared to control group who did not receive a CRP-tests. Therefore, the reduction in antibiotic use was deemed safe (11).

Martínez-González et al. found similar results in their systematic review and meta-analysis of thirteen included RCTs (12). The study assessed antibiotic prescription rate as primary outcome measure. Secondary outcomes were resolution of symptoms, visit duration and follow up, re-consultation and intention to re-consult, referral to secondary care, admission to hospital and mortality, ordering of investigations and patient satisfaction/enablement. The meta-analysis demonstrated significantly lower antibiotic prescribing in the CRP-POCT group compared with the usual care group at the index consultation. In this study several interesting subgroup analyses were performed. The most interesting ones for our literature study are described below.

Less antibiotics were prescribed for both upper and lower respiratory tract infections in the CRP-POCT group. When analysing for age, adults in the CRP-POCT group got significantly fewer antibiotic prescriptions. The reduction seen in children however was not significant. Antibiotic prescribing rate during patient's follow-up was also analysed. This analysis of seven RCTs found no significant difference between CRP-POCT and usual care in the rates of antibiotic prescribing at any point during 28 days of follow-up.

Regarding the secondary outcomes there were not found any significant differences in clinical recovery and resolution of symptoms, the visit duration and follow up, referrals to secondary care and admission to hospital and mortality, patient satisfaction/enablement. Regarding medical imaging requests two studies showed no significant differences while another study showed less medical imaging requests in the test group. However, this difference was not significant between the CRP-POCT and usual care group from another study. In the CRP-POCT group there was a significant increase in re-consultation compared to the usual care.

When comparing exposure to usual care including CRP-POCT versus exposure to usual care alone, there was a significant reduction in antibiotic prescribing at index consultations, resulting in an absolute risk reduction of 13.2% (38.2% vs. 51.4%) with a number needed to treat to benefit (NNTB) of 8. However, there was also an increase in re-consultations, leading to an absolute risk increase of 3.8% (13.5% vs. 9.7%) with a number needed to treat to harm (NNTH) of 27. Taking into account both the reduction in antibiotic prescribing and the increase in re-consultations, the NNT net effect for usual care including CRP-POCT is 11. This means that for every 11 patients who receive usual care including CRP-POCT, one patient will experience a net benefit by receiving treatment without antibiotics.

Van der Velden et al. found a large variation between countries in antibiotic prescribing for respiratory tract infections in their prospective audit in 18 European countries. The proportion of patients who got antibiotics prescriptions ranged from 18% (Belgium and Denmark) to over 50% (Hungary and Ireland). The use of POC tests (CRP and strep) also varied wildly between countries. Important factors influencing antibiotic prescribing were illness severity, older age, presence of comorbidity, fever, and longer illness duration. Interestingly, in the full sample the researchers found no association between having performed a POC test and antibiotic prescribing. Subgroup analysis showed antibiotics were less often prescribed for patients with lower respiratory tract diagnoses when CRP-POCT testing was done. On the contrary, when a

strep A POC test was done, antibiotics were prescribed more often. The researchers also found antibiotic prescribing behavior to differ between countries. Although they warn that only a limited number of general practices participated in each country, therefore outcomes might not accurately represent primary care provided in the country. In face of this large variation in between countries, GPs expressed a high level of confidence in their antibiotic prescribing decisions. The authors conclude that POC testing may help combat inappropriate antibiotic prescribing on the condition that the implementation of POCTs can safely reverse decisions made on clinical grounds alone (13).

Anna Köchling et al. made a systematic review on reduction of antibiotic prescriptions for acute respiratory tract infections in ≥ 13-year-old patients in primary care. In this review the effectiveness of interventions in primary care was analyzed. The two most important interventions leading to significantly lower antibiotic prescription rates were communication skills training (CST) and POCT. The role of computerized clinical decision-making support systems (CDSS) was also investigated. Looking at the results, this review suggests that, in countries with relatively low prescription rates (Germany or the Netherlands), CST seems to be the key element for successful interventions. In contrast, interventions focusing on making a diagnosis in terms of POCT and CDSS showed relevant reductions in high-prescribing countries (e.g. Spain, USA, Russia) (14).

The literature on CRP-POCTs effectiveness in reducing antibiotic prescriptions is as good as unanimous. Systematic reviews and meta-analyses (12, 14) show a clear reduction of prescriptions in all test groups, these results are also supported by smaller studies and reviews (15-17). Two RCTs found no reduction in antibiotic use in children (respectively aged 1m-16y and 3m-12y) who consulted their GP for non-severe acute RTIs and received CRP-POCTs. The authors conclude that CRP-POCT testing without guidance is not an effective strategy to reduce antibiotic prescribing in this population (18, 19).

Group A Streptococcal antigen point-of-care test

First of all, it is important to clarify that the group A streptococcal antigen test, from now on referred to as strep test, only detects the Group A streptococci (GAS) through their antigen. This means other bacteria commonly causing throat infection are not detected with this test. This of course is a limitation since only in approximately 1/3th of cultured swabs taken in patients with sore throat GAS were detected (20). Other sources suggest an even lower prevalence of GAS in bacterial throat infections of 5-10% (21). Furthermore, the Dutch primary care guideline comes up with three reasons why testing for GAS is irrelevant. Firstly, serious complications of streptococcal infections like acute rheumatic fever, have become very rare in the Netherlands Secondly, other bacteria are probably equally important. And thirdly the effect of antibiotics solely given to reduce disease duration is unclear (20).

The guideline mentions three RCTs which evaluated the effect of strep tests on antibiotic prescriptions. Two of them were conducted in Europe: in Spain and England.

The trial held in Spain showed a clear difference in amount of antibiotics prescribed between the group with strep tests and the group without, respectively 48,3% and 64,1%. Notably, in the group with strep test availability an antibiotic was prescribed in 30% of cases even though strep test was negative (22).

The trial held in England randomised patients into three groups: a control group where a delayed antibiotic prescription was provided (patients got instructed to start antibiotic treatment 3 to 5 days after the consultation if symptoms persisted or worsened). Regarding the 2 treatment groups, antibiotic prescribing was determined either by a clinical score (FeverPAIN) alone or the combination of this clinical score and strep testing. The delayed prescription group reported antibiotic use in 46% of cases. The two other groups both had less antibiotic use reported but between them there was no significant difference. The clinical score group had a relative risk reduction of 29% compared to a relative risk reduction of 27% in the strep test group (23).

Cohen et al. reviewed a large portion of available data in 2020 and found interesting results: pooled data from five trials showed a significant reduction in antibiotic prescriptions in the rapid strep test groups, risk difference -25% (24).

We can cautiously conclude that there are indicators that strep tests might reduce antibiotic prescriptions. However, some research also found an increase in antibiotic prescriptions in strep test groups (13). There are other important considerations such as GAS not being the only causative agent of throat infections. Both Dutch and Belgian primary care guidelines discourage the use of strep test to reduce antibiotic prescriptions at the moment (20, 25). For sure more research has to be done to be able to make a clearer conclusion of the effect of strep tests on antibiotic prescriptions (20, 25). With PRUDENDE, we hope to aid in this process.

Influenza antigen point-of-care test

We already established that the majority of antibiotic prescriptions are made in primary care and are prescribed for acute respiratory tract infections, despite evidence suggesting that antibiotics are often unnecessary and ineffective for these conditions (3, 26, 27). One of the biggest challenges of primary care physicians is differentiating between patients who are more likely to benefit from antibiotics from those who are not. POCTs are suggested to give clinicians the tools to make more precise diagnoses, therefore combatting clinical uncertainty, which in turn is a big driving force for inappropriate antibiotic prescriptions (28, 29).

A lot of research exists on the use of POCT influenza tests in emergency department (and hospital) settings. Lee et al. found no effect of POCT use in ambulatory care on antibiotic prescriptions in their systematic review and meta-analysis from 2019 (RR 0.97, 95% CI 0.82–1.15). Most evidence came from pediatric emergency departments. The authors conclude that there is an evidence gap on the use of POCTs for influenza in both adults and children, particularly in primary care settings. Further research is required (30).
Research regarding the use of POCTs for influenza and the effect on antibiotic prescribing behavior in primary care is more sparce. Some evidence suggests that the use of POCTs for influenza can change antibiotic prescribing behavior.

A 2020 study conducted in England found that using POCT for influenza might improve correct antibiotic use. In this study, 312 people consulting their general practitioner with influenza like symptoms were tested for influenza using POCT. The researchers concluded that the patients receiving a positive POCT for influenza received significantly fewer antibiotic prescriptions than people with negative results (odds Ratio 0,4). Note that this study included patients with influenza like symptoms, and not only patients with coughing or throat ache as presenting symptom (31). In a smaller study from Greece from 2009, 197 patients with respiratory tract symptoms were tested for influenza during house call visits by GPs. The authors found that less antibiotics were prescribed for patients who tested positive for influenza (32).

Another study in a paediatric population (children aged < 6y) from Spain assessed antibiotic prescription rates and additional visit rates during flu-seasons 2016-2017 and 2017-2018. The researchers found that influenza-confirmed patients using POCT received fewer antibiotics in comparison to children presenting with fever as presenting complaint. Children with confirmed influenza diagnosis received antibiotics in 4,4% of cases in comparison to children without diagnosis who received antibiotics in 11,5% of cases in the season of 2016-2017. In the season of 2017-2018 children with confirmed diagnosis received antibiotics in 10,2% of cases in comparison to 17,2% of children without confirmed viral diagnosis. The latter result was statistically significant. Influenza-confirmed patients in both seasons showed significant lower additional visit rate (33). A second study from Poland in children younger than 5 years old with symptoms of febrile respiratory tract infection support the finding that POCT for influenza can reduce inappropriate use of antibiotics. 256 children were divided in two groups. 115 children were tested using an influenza POCT. 141 children were not tested and formed the control group. 16% of children in the control group were treated with an antibiotic, in comparison to 7% in the test group (34). No details on patient characteristics and disease

severity were reported. Also, no review of patient safety was included, therefore these results should be interpretated carefully.

Bruning et al. evaluated diagnostic performance and clinical feasibility of POCTs in primary care in the Netherlands. They compared test characteristics (sensitivity and specificity) of the POCT tests for influenza to PCR testing (which is considered the golden standard). GPs were interviewed to explore clinical feasibility of the use of these POCTs in the general practitioner's office. The availability of POCTs was deemed useful by both patients and GPs. GPs reported that the POCT is a helpful tool to convince patients about the viral origin of the disease and the ineffectiveness of antibiotics. Therefore, the authors conclude that the use of diagnostic POCTs for respiratory viruses has the potential to enhance the accuracy of diagnosing respiratory tract infections and positively impact the prescription of antibiotics by GPs. Nevertheless, prior to integration into primary healthcare, it is crucial to enhance the diagnostic accuracy of the POCTs and evaluate their impact on clinical decision-making more comprehensively. Also note that Bruning et al. did not investigate nor reported a reduction in (inappropriate) antibiotic prescriptions with the use of viral POCTs in primary care (35). Khalid et al. found in their 2021 study on the feasibility and impact of POCT for influenza (and other pathogens). The authors supported the idea that incorporating influenza POCT into general practice workflows is feasible and may help improve antimicrobial use. However, the authors conclude that further evidence from RCTs is needed to demonstrate the effect POCT use on antibiotic prescribing behavior in primary care settings (36).

In conclusion, some evidence exists that POCT for influenza could influence antibiotic prescribing behavior and reduce inappropriate antibiotic prescriptions in both children and adults. However, most evidence stems from research in emergency departments and hospital settings, conclusions from research in this setting cannot easily be transferred to primary care. Evidence from RCTs in primary care is especially sparce. More research is needed to determine whether influenza POCT might positively affect antibiotic prescription rates without compromising patient safety. Research on feasibility of the inclusion of POCTs shows that their implementation is accepted by both GPs and patients.

Discussion

CRP-POCT

To date, there is moderate to high-quality evidence indicating that the use of CRP-POCT in primary care can effectively reduce antibiotic prescribing for respiratory tract infections (RTIs). This reduction does not impact clinical recovery, symptom resolution, or hospital admissions (12, 14, 37). It is improbable that additional research will significantly alter this conclusion regarding the decrease in the number of antibiotic prescriptions, although the magnitude of the estimated effect may vary (37).

Group A streptococcal antigen POCT

GAS POCTs are valid tests in comparison to a strep culture, which is considered the gold standard for diagnosing strep infections. Belgian and Dutch primary care guidelines however still advocate against the usage of strep tests for a number of reasons, mainly because of the lack of clinical relevance of strep testing in general. This is because other bacteria can also cause throat infections, negative GAS tests could therefore lead to a false sense of safety (in case of peritonsillar abscess for instance). Moreover, serious complications of GAS infections like rheumatic fever, glomerulonephritis or scarlet fever have become so rare that diagnosing GAS infections in primary care to prevent this serious complication is no longer relevant. Different sources also show a significant number of antibiotic prescriptions even after a negative strep test, suggesting that clinical assessment of disease severity remains the most important factor influencing decision making in GPs (20, 25).

There is however some evidence that shows a reduction in antibiotic prescriptions when strep testing is implemented when adressing patients presenting with troatache in primary care settings. We do note some limitations regarding the trials included in this overview. Llor et al. randomised physicians into control an intervention groups with the intervention group having access to strep testing. Therefore, patients were granted access to a strep test depending on what physician they were visiting, leading to potential bias. Results could be influenced by changes in antibiotic prescribing behaviour in either the control or test group or by differences in preexisting behaviour of physicians (22). Little et al. included patients aged 3 and above presenting with sore throat and erythema/pus on throat inspection. Therefore, including patients where antibiotics were never even considered, this could influence results when assessing reductions in antibiotic prescriptions (23).

In PRUDENCE we try to prevent these pitfalls by randomising patients to treatment or control groups instead of physicians or practices. This allows us to more accurately assess the effect of POCTs on antibiotic prescribing behaviour. We also chose to only include patients where the caring physician considered antibiotic prescribing in some capacity. Potentially leading to a cleaner data set. With this we hope to provide additional insights in the potential role of GAS testing in combatting inappropriate antibiotic prescribing.

Influenza antigen POCT

There is a considerable body of research on the utilization of POCT influenza tests in emergency department and hospital settings (30). Regarding the use of POCT for influenza in primary care and its effect on antibiotic prescribing behaviour, the available evidence is

limited. However, some evidence suggests that employing POCT for influenza may influence antibiotic prescribing behaviour (31, 33). Generally, patients receiving a positive influenza test seem to receive less antibiotics, resulting in a possible net reduction in antibiotic prescriptions. This makes sense knowing that diagnostic uncertainty plays a big role in clinical decision making. Evidence supporting a viral origin of disease therefore logically leads to less antibiotic prescribing. Note that due to the non-randomised nature of these trails, they can only offer limited insight on the potential of influenza POCT implementation on reducing inappropriate antibiotic prescribing in general. Proving only that less antibiotics are prescribed after positive influenza POCTs compared to negative POCTs. These studies are further limited by small sample sizes and lack of reports on patient characteristics and patient safety. Trails like the prospective cohort study from Nitsch-Osuch et al., comparing test groups and control groups, are much more relevant regarding the research question at hand.

Both patients and GPs found incorporating influenza POCT into general practice workflows to be feasible (35, 36). More research is needed to determine whether influenza POCT might positively affect antibiotic prescription rates without compromising patient safety. Future research should especially focus on RCTs.

Conclusion

Most antibiotics are prescribed in primary care, excessive use of antibiotics is most common for respiratory tract infections. RTIs are frequently caused by viruses and are typically self-limiting. In the strife against antibiotic resistance, reducing inappropriate antibiotic prescriptions should be the goal. Easy access to and familiarity with POCTs can help primary care physicians enhance the accuracy of diagnosing respiratory tract infections and limit inappropriate antibiotic prescriptions. More research is needed, especially on the effect of strep and influenza POCTs on prescribing behavior.

With PRUDENCE being a pragmatic, platform based RCT we hope to gather qualitative data to be able to formulate a general conclusion on this topic. We aim to gain high quality and homogenous information from a sizable sample size.

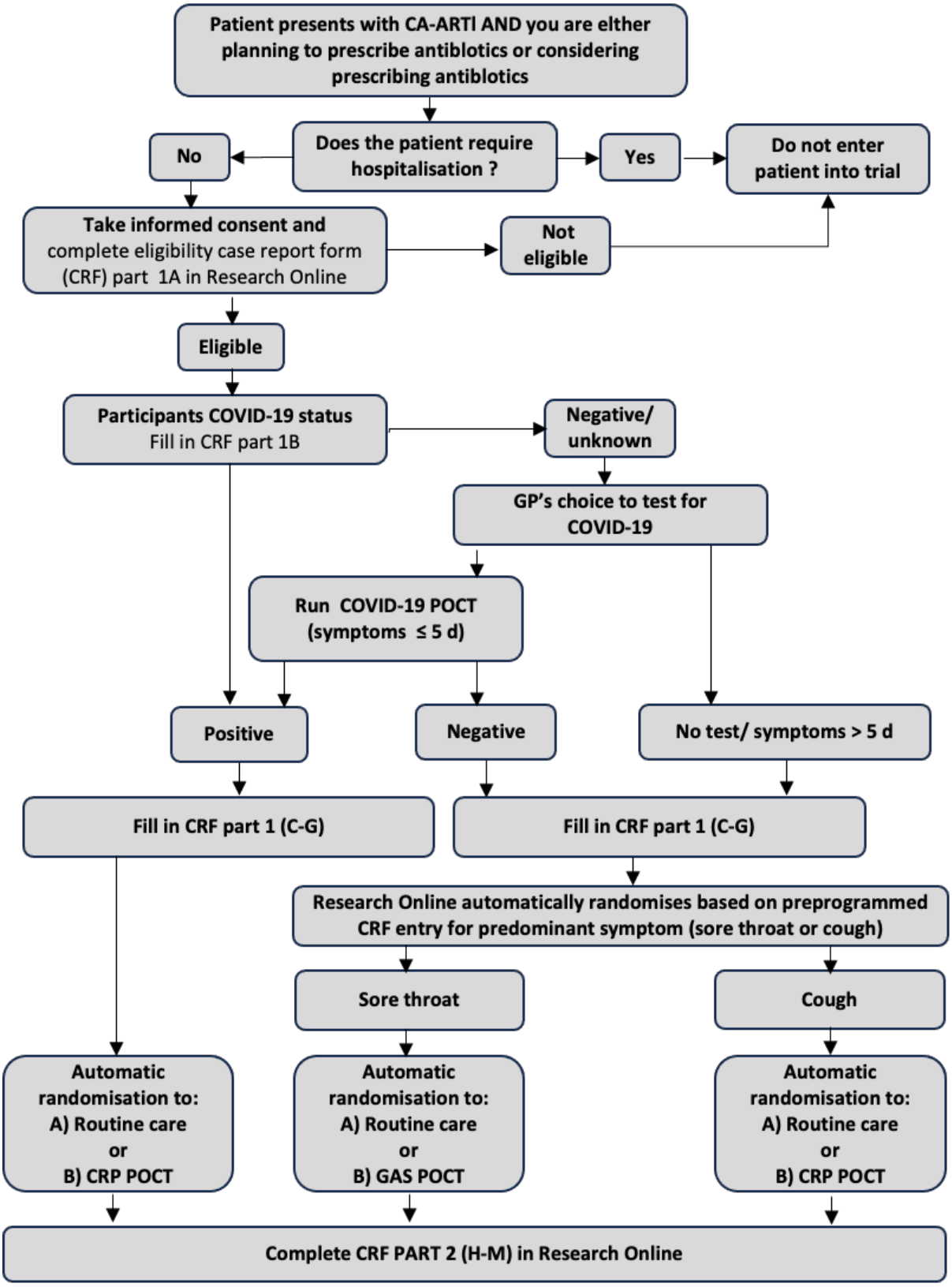
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Appendix 2: Flowchart of inclusion and randomisation during PRUDENCE



Appendix 3: BAPCOC guideline

Diagnosis	First choice antibiotic	Alternative first choice /	Alternative in case of IgE mediated penicillin allergy
Acute throat ache	Generally not indicated **Pheneticillin** • Adult and > 10 years old: 1500mg per day in 3 gifts • 2-10 years old: 750mg per day in 3 gifts • <2 years old: 375mg per day in 3 gifts	**Cefadroxil** • Adult: 2g per day in 2 gifts, 7 days • Child: 30 mg/kg per day in 2 gifts, 7 days **Cefalexin** • Adult: 2g per day in 2 gifts, 7 days	**Azithromycin** • Adult: 500mg per day, 3 days • Child: 10 mg/kg per day, 3 days
Acute bronchitis	Antibiotic usually not indicated. If indicated; see *lower respiratory tract infection*		
Lower respiratory tract infection	**Amoxicillin** • Child: 100 mg/kg/day in 3 gifts, 5 days • Adult: 3g per day in 3 gifts, 7 days No improvement within 48h* **Azithromycin** • Child: 10 mg/kg/day in 1 dose for 3 days • Adults: 500 mg 1 per day,	In case of comorbidity or aspiration: **Amoxicillin/ clavulanate** • Adult: 875mg 3 times per day 7 days	**Moxifloxacin** • 400mg per day, 7 days

		3 days
Acute exacerbation COPD	**Amoxicillin and Clavulanic acid**	• 875 mg 3 times per day, 5 days

* Note that the guideline recommends the following strategy to cover probable atypical pathogens: when re-evaluating the patient 48h after initial antibiotic treatment; a macrolide (azithromycin) can be associated to the treatment in case of limited improvement and when home treatment is acceptable. Re-evaluation after another 48h is indicated.