



Rapid antigen test use for the management of group A streptococcal pharyngitis in community pharmacies

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Abstract

Despite group A streptococci being an infrequent cause of pharyngitis in adult outpatients, sore throat remains a common indication for antibiotic prescription. This prospective multicentre non-randomised study describes a community pharmacy-based antimicrobial stewardship intervention consisting in the implementation of rapid antigen testing (RAT) for the management of adults with sore throat. Trained pharmacists triaged patients presenting with symptoms of pharyngitis using the modified Centor score. Those at risk for streptococcal infection were tested with RAT. Patients with a positive RAT were invited to consult a physician, whereas others were offered a symptomatic treatment. All patients received educational leaflets and were asked to fill in a follow-up form 7 days later. Ninety-eight pharmacies in one French region participated, and 559 patients were included over 6 months. RAT was proposed in 367 (65.7%) cases, and it was positive in 28 (8.3%). The follow-up form was returned by 140 (38.5%) participants. Of these, 10/10 patients with positive RAT further consulted a physician and were prescribed an antibiotic treatment, whereas 96.5% (110/114) of patients with negative results and not having any other reason to seek for doctor's advice did not consult. All participants found the intervention useful. Pharmacists spent 6–15 min to perform the intervention, and 98.6% (73/74) of pharmacists giving a feedback declared to be ready to implement this intervention in daily practice, if endorsed and reimbursed. Our results suggest that a pharmacy-based programme for the management of sore throat is feasible and could increase adherence to guidelines.

Keywords *Streptococcus pyogenes* · Pharyngitis · Point-of-care testing · Antibiotics · Community pharmacy · Antibiotic stewardship

Introduction

Up to 80–90% of antibiotics are prescribed in the outpatient setting [1], but around half of these prescriptions are either un-

necessary or inappropriate [2], underlying the need for antibiotic stewardship (ABS) programmes in the outpatient setting [3–5].

A significant number of infections treated in the community are self-limiting conditions at low risk of complications,

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where the potential benefits of antibiotic treatment need to be carefully weighed against the risk of side effects, bacterial resistance and increased costs [6]. Sore throat is a common indication for antibiotic prescription and a good target for ABS for many reasons. First of all, in adult patients, 85–95% of cases are of viral origin [7] and do not require an antibacterial treatment, which should be reserved for pharyngitis due to *Streptococcus pyogenes* (group A streptococci; GAS) [8, 9]. Moreover, the effectiveness of the antibiotic treatment in terms of symptom relief and prevention of suppurative and non-suppurative complications is modest, particularly in high-income countries with low prevalence of rheumatic heart disease [10]. Despite this evidence, some large and well-conducted studies showed that more than 60% of pharyngitis are treated with antibiotics [11, 12] and sore throat remains among the commonest cause of self-medication with antimicrobials [13].

Several guidelines in many countries [8, 9, 14, 15] suggested to carefully select patients who will most benefit from an antibiotic treatment, combining in adults the use of clinical scores (mainly Centor score [16] and modified Centor score (McIsaac score) [17]) with rapid antigen tests (RATs) for the detection of GAS. In most guidelines, adult patients with a clinical score suggesting a moderate to high pre-test probability of GAS pharyngitis should undergo a RAT, and an antibiotic treatment should be prescribed only in positive cases [8, 9, 14]. Adult patients with scores < 2 have a risk of GAS infection < 10% and can be safely managed with symptomatic treatment, avoiding RAT. On the other hand, patients with scores > 2 could have a GAS pharyngitis, but also in this subgroup, viral infections cannot be reliably distinguished only on the basis of clinical findings. As much as 50% of patients with the highest scores (≥ 4) still have a viral infection. RATs can therefore reliably and quickly identify the true GAS pharyngitis, reducing diagnostic uncertainty and facilitating medical decision-making [8, 16, 17].

These point-of-care tests are performed on a pharyngeal swab, and detect reliably and rapidly the presence of GAS in the pharynx (sensitivity > 85%, specificity > 95% depending on the test [18]).

In France, a study showed that RATs were not widely used by general practitioners (GPs), even if they are provided free of charge by health insurance. The time needed to perform the test was one of the main declared barriers to RAT use [19]. Another study showed that only 60.1% among 1126 participating French GPs used RATs in paediatric patients with pharyngitis. GPs not using RATs prescribed antibiotics in 50.2% of cases, compared to 30.5% of prescriptions among GPs who performed RATs [20].

The use of RATs is a very attractive ABS intervention, since they can be used directly at the site of patient care, they need a short training to be correctly performed and they can allow a prompt targeting of antimicrobial treatment, reducing

inappropriate antibiotic use. Furthermore potentially transmissible agents, as GAS, can be rapidly identified and treated, reducing their spreading [21].

Frequently, community pharmacists are the first health care professional visited by patients with sore throat and through the use of RATs they might be able to correctly select patients needing only symptomatic treatment versus those requiring to consult a physician for antibiotic prescription.

The aim of this prospective multicentre study was to test the feasibility, benefit and acceptance of a community pharmacy-based ABS intervention based on RAT use in adult patients with sore throat.

Material and methods

Setting, participants and study protocol

This was a prospective multicentre non-randomised feasibility study conducted in community pharmacies in one French region (Lorraine, 2.3 million inhabitants). Community pharmacies (named pharmacies thereafter) in France are facilities designated to dispense drugs, as well as para medical products and devices. Each pharmacy is managed by at least one community pharmacist, who can autonomously provide over-the-counter products, but not prescription drugs (as are all antibiotics in France). According to the national register, 742 pharmacies were recorded in Lorraine at the end of 2014.

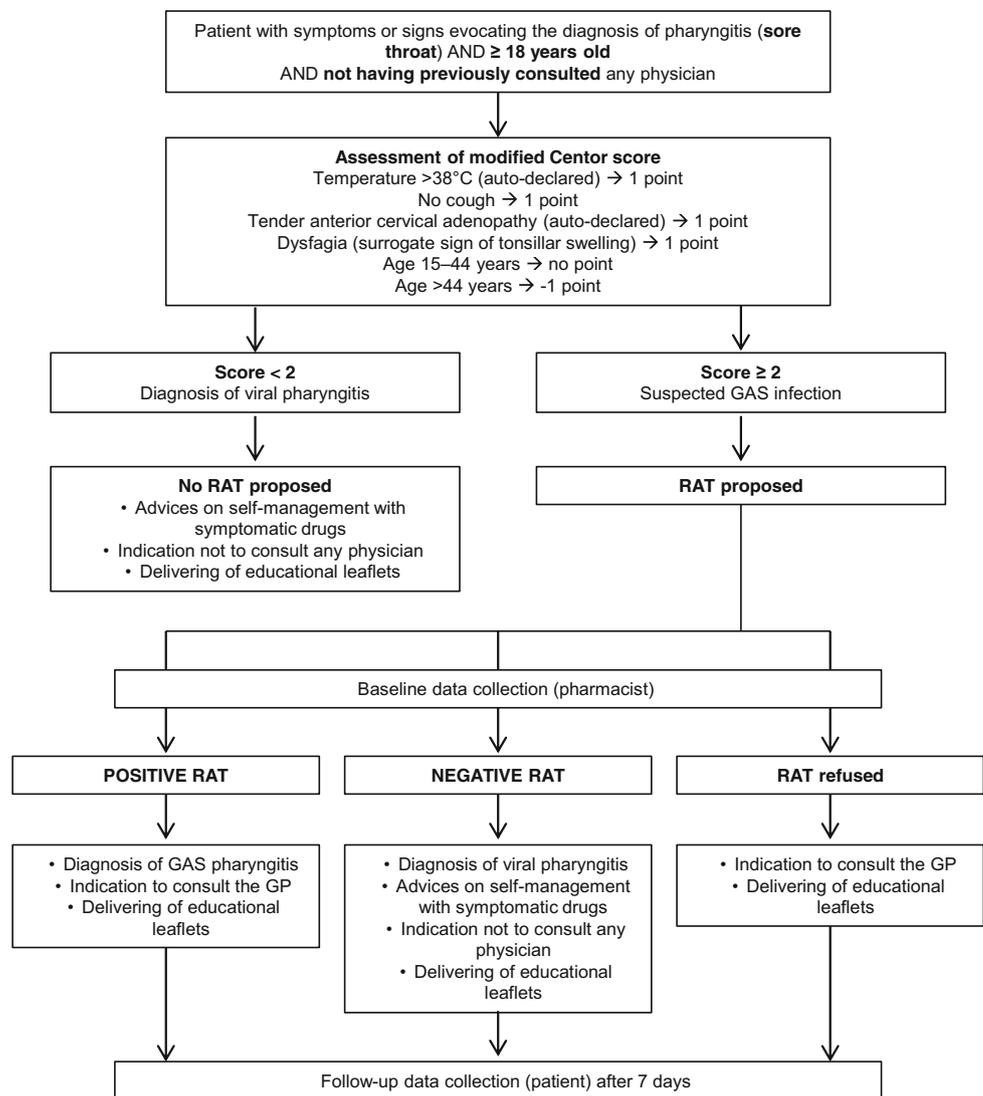
An invitation to participate to the study was sent to all pharmacies in April 2015 (departments of Moselle, Meuse and North of Meurthe-et-Moselle) or September 2015 (South of Meurthe-et-Moselle and Vosges). A pharmacy was further considered eligible if the pharmacist was able to take part in a training session and if the pharmacy disposed of a confidentiality area to allow a proper patient clinical assessment. In case of pharmacies with more than one pharmacist, only one was invited to take part in the study.

Pharmacists interested in participating were included if they attended a 2-h teaching session, including an overview on upper respiratory tract infections, the presentation of the study protocol and a theoretical and practical training on RAT use. This teaching session was led by trained GPs and pharmacists. Afterwards, the participants received the study material, containing the study protocol with explanatory guidance, the data collection forms (Online Resource 1), information leaflets for patients and RATs. Streptatest® (Dectrapharm, Strasbourg, France) is the RAT currently used in France for GAS, and it has a sensibility of 92–97%, according to the French Health Products Safety Agency [22]. The study was endorsed by the Regional Health Agency (Agence Régionale de Santé, ARS) and by ANTIBIOLOR, the Lorraine Regional Network of antibiotic therapy.

The study protocol (Fig. 1) was developed by a multidisciplinary team including one pharmacist and one physician from the Regional Health Agency, one hospital pharmacist, two community pharmacists, one infectious diseases specialist and two GPs. Adult patients (≥ 18 years old), presenting to a pharmacy for sore throat and not having previously consulted any physician, were considered eligible for the study. Participating pharmacies were asked to enrol all consecutive eligible patients over a 6-month period. As a first step, the pharmacist assessed the risk of GAS pharyngitis based on the modified Centor score [17]. French community pharmacists are not allowed to perform a physical examination; therefore, the presence of dysphagia (complicating odynophagia) was considered as a marker of tonsillar swelling and the presence of cervical lymphadenopathy was self-reported by

patients. According to French guideline [14], patients with a score < 2 were considered at low risk of bacterial pharyngitis, so they received advices on self-management with symptomatic drugs and were invited not to consult any physician. If the score was ≥ 2 , the RAT was proposed and the pharmacist filled in the baseline data collection form, including information on patient's age and gender, acceptance of RAT, results or eventual reasons for refusal (Online Resource 1). Patients with positive RAT or refusing the test were advised to consult their GP, whereas those with negative RAT were encouraged not to consult and were offered symptomatic drugs and counselling for self-management. Patients with a severe presentation or atypical features were referred to GPs or an emergency service for further assessment. Every patient was routinely told to consult a GP if symptoms worsen or persist after 72 h. All

Fig. 1 Study protocol



GAS: Group A streptococci
 RAT: rapid antigen test for GAS
 GP: general practitioner

patients with a score ≥ 2 received also a follow-up data collection form in a stamped envelope (Online Resource 1), with the indication to complete and send it back after 7 days. It contained anonymous information on adherence to pharmacist's recommendations, reasons for eventual non adherence, antibiotic prescription and satisfaction with the use of RAT. All participants also received educational material on responsible antibiotic use (Online Resource 2).

At the end of the study, the pharmacists were invited to fill in an online questionnaire to assess their feedback on the protocol, the feasibility of the intervention and their level of satisfaction.

Anonymity was guaranteed both to patients and pharmacists, since only the postcode was required. Both baseline and follow-up collection forms contained a barcode, which allowed tracing every participant while preserving anonymity. Pharmacies received 250 euros in total in reimbursement of their time devoted to the study. All patients gave an oral informed consent and did not pay any additional expense compared with usual practice.

Data analysis

Variables were presented as numbers and percentages, and 95% confidence intervals were reported, when appropriate. In order to detect an eventual selection bias, the distribution of each subpopulation in the sample (based on gender, age and department of origin) was compared with that of the same subpopulation in Lorraine. Similarly, the characteristics of participants providing the follow-up form at day 7 were compared to those of participants not providing it. The statistical significance was set at 5% ($p < 0.05$). The analyses were performed using Excel VBA (Microsoft® Inc., Redmond, WA, USA).

Data availability

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Results

Study population

The intervention was implemented for 6 months, from April 2015 in the departments of Moselle, Meuse and North of Meurthe-et-Moselle and from September 2015 in South of Meurthe-et-Moselle and Vosges. One-hundred sixty-one pharmacies participated in the training session (21.7% of the pharmacies in Lorraine), and 98 (56.5%) actively took part in the intervention, enrolling 6 patients on average. A total of 584 patients were eligible. For 7 patients, data were missing, leaving 559 subjects included in the study; for 18 patients, only the

follow-up form at day 7 was available without baseline data (Fig. 2). The demographic characteristics are shown in Table 1.

Workflow and feedback results

On the basis of the modified Centor score, GAS pharyngitis was suspected in 367 (65.7%) patients. Three of them were further excluded since data were missing, leaving 364 participants. Among these, 336 underwent the RAT, while 28 refused the test. The median age of patients undergoing the RAT was 27.8 years, and 64.3% were female. Twenty-eight tests were positive, representing 8.3% of subjects being tested and 5.0% of the total population (28/559) (Fig. 2).

The follow-up form was sent back by 140/364 (38.5%) patients and allowed to estimate the adherence to pharmacists' recommendations, the consequences of the intervention in terms of antibiotic prescription and patients' satisfaction with the protocol. All (10/10) evaluable patients with positive RAT followed the pharmacist's advice and consulted a physician, being prescribed an antibiotic in all cases. Almost all (96.5%, 110/114) patients with negative RAT, and not having any other reason to seek doctor's advice (including persistence or worsening of symptoms), effectively did not consult and did not have any antibiotic prescribed.

All (138/138) evaluable patients undergoing the test declared to be satisfied with the use of RAT, and 99.3% (136/137) would accept the test again in the future. Moreover, 99.4% (157/158) judged positively the educational leaflets. Results are further detailed in Table 2.

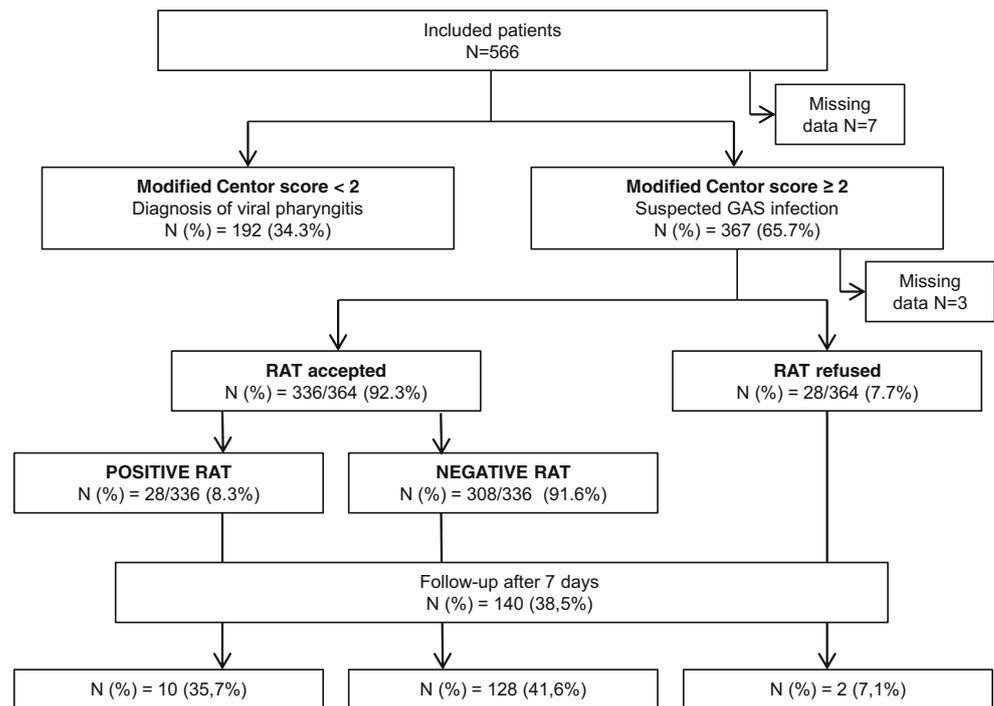
Among the 28 patients declining the RAT, the commonest causes for refusal were lack of time to perform the test (24/28, 85.7%) and low perceived benefit (3/28, 10.7%).

Pharmacists' feedback

Seventy-four (75.5%) participating pharmacists completed the end of study questionnaire (Table 2). Concerning the protocol, 95.4% (62/65) of them judged the time spent during the training session sufficient to deal with the study, even if after the beginning of the study 83.1% (54/65) further consulted the explanatory material, and 6.2% (4/65) needed to re-contact the investigators for clarification. All pharmacists found the RAT easy to use, 75.7% (56/74) did not encounter any difficulty realising the pharyngeal swab and 97.3% (72/74) estimated that the result was sufficient to guide clinical management. Seventy-six percent (56/74) declared that the average time to realise the entire protocol was 6–15 min, and 91.6% considered this duration convenient (Fig. 3).

Overall, 71.6% (53/74) of the respondents thought that the participation in the protocol was an opportunity for professional development and 98.6% (73/74) of them would welcome the routine introduction of RAT in their daily practice, if endorsed and financed by the Health Authorities.

Fig. 2 Flow chart and included patients



GAS: Group A streptococci
RAT: rapid antigen test for GAS

Table 1 Characteristics of the 559 patients included in the study

Characteristic	Number (%)
Gender	
Female	348 (61.5%)
Male	218 (38.5)
Age (years)	
< 20	32 (5.7%)
20–29	133 (23.5%)
30–39	156 (27.6%)
40–49	108 (19.1%)
50–59	62 (11.0%)
60–69	52 (9.2%)
70–79	22 (3.9%)
≥ 80	1 (0.2%)
Department	
Meurthe-et-Moselle	266 (47.0%)
Meuse	86 (15.2%)
Moselle	123 (21.7%)
Vosges	90 (15.9%)
Missing data	1 (0.2%)
Area of origin	
Urban	306 (54.1%)
Rural	93 (16.4%)
Mixed	165 (29.1%)
Missing data	2 (0.4%)

Analysis of the selection bias

The 98 participating pharmacies were geographically distributed on 73 (27.5%) postal codes in the region (Online Resource 3). Comparing the study population with the general population in Lorraine, at enrolment, urban areas were slightly but significantly underrepresented (54.1% of pharmacies in the study population versus 60.4% in Lorraine, $p < 0.001$), while Meurthe-et-Moselle and Meuse Department were overrepresented (Online Resource 4), as well as female (61.5 vs 51.2%, $p < 0.001$) and 30–59-year-old participants (57.6 vs 40.3%, $p < 0.001$).

Concerning follow-up data, comparing participants sending the follow-up form and those who did not send it, only Meuse was overrepresented, whereas patients with both positive and negative RAT, male and female and younger subjects were equally represented.

Discussion

Main findings

This study showed that the implementation of an intervention promoting the use of a clinical score associated with targeted RAT use by community pharmacists in adult patients

Table 2 Results of the questionnaire: patients' feedback at day 7 ($N = 140$) and community pharmacists' feedback at the end of the study ($N = 74$)

Outcome	Number (%)	[95% confidence interval]
Patients who underwent RAT: follow-up data at day 7	N	
Patients consulting a physician after a positive RAT	10/10 (100%)	na
Patients being prescribed an antibiotic after a positive RAT	10/10 (100%)	na
Patients not consulting a physician after a negative RAT ¹	110/114 (96.5%)	[93.2–99.9%]
Patients who underwent the RAT and declared to be satisfied with the intervention	138/138 (100%)	na
Patients who underwent the RAT and would accept the intervention again in the future	136/137 ² (99.3%)	[97.8–100%]
Patients judging the educational leaflets beneficial	157/158 ³ (99.4%)	[98.1–100%]
Participating community pharmacists: feedback at the end of the study	N	
Pharmacists considering the training session sufficient to manage the protocol	62/65 ⁴ (95.4%)	[90.3–100%]
Pharmacists consulting at least sometimes the explanatory material during the study	54/65 ⁴ (83.1%)	[70.0–90.2%]
Pharmacists needing to consult the investigators for further explanation during the study	4/65 ⁴ (6.2%)	[0.3–12.0%]
Pharmacists considering the protocol sufficient to guide the patient management	72/74 (97.3%)	[93.6–100%]
Pharmacists considering the study material easy to read	72/74 (97.3%)	[93.6–100%]
Pharmacists considering the use of RAT sufficiently convenient	74/74 (100%)	na
Pharmacists not encountering particular difficulties performing the pharyngeal swab	56/74 (75.7%)	[65.9–85.5%]
Pharmacists not encountering particular difficulties to use the RAT kit	73/74 (98.6%)	[96.0–100%]
Pharmacists considering as convenient the time needed to fill in the data collection form	73/74 (98.6%)	[96.0–100%]
Pharmacists considering as convenient the time needed to complete the protocol	65/71 ⁵ (91.5%)	[85.1–98.0%]
Pharmacists declaring to have delivered the educational leaflets to all enrolled patients	60/74 (81.1%)	[72.2–90.0%]
Pharmacists declaring to have delivered an oral educational message on responsible antibiotic use to all patients with negative RAT	72/74 (97.3%)	[93.6–100%]
Pharmacists thinking that the educational inputs delivered had an effective impact on the patients	68/74 (91.9%)	[85.7–98.1%]
Pharmacists feeling that patients appreciated their action	74/74 (100%)	na
Pharmacists thinking that the participation to the programme was an opportunity for professional development	53/74 (71.6%)	[61.3–81.9%]
Pharmacists welcoming the routine implementation of the intervention in their daily activity, if it is endorsed and reimbursed	73/74 (98.6%)	[96.0–100%]

RAT rapid antigen test, *na* not applicable

¹ Excluding those having any other reason to seek doctor's advice (i.e. atypical or severe presentation, persisting symptoms)

² Missing data from 1 patient

³ Including 18 patients with follow-up data at day 7, but without baseline data

⁴ Missing data from 9 community pharmacists, since the question was not present in a first version of the end of study questionnaire

⁵ Missing data from 4 community pharmacists

presenting with sore throat is a feasible and potentially beneficial ABS intervention. It allowed to identify patients with GAS pharyngitis, directing them to GPs for antibiotic treatment; to manage patients with negative test results avoiding antibiotics and medical consultation; and to deliver educational material, which was perceived to be useful by patients. The level of acceptance of RAT and the compliance with instructions received were both very high among patients. Furthermore, most pharmacists declared to be satisfied with the intervention and gave overall a positive feedback on feasibility in terms of practicality, rapidity and applicability in real life.

Main results in light of previous literature

In our study, only 5.0% (28/556) of adult patients presenting to the pharmacists with sore throat had a positive RAT. This finding is in line with the literature [7] and confirms that GAS is an infrequent cause of sore throat in adults, justifying efforts to rationalise antibiotic use. Based on literature findings, RAT-guided therapy for pharyngitis is encouraged in several countries, such as France and the USA [9, 14]. In a RCT by Worrall et al., RAT-guided therapy allowed a reduction of 20% in antibiotic prescription compared to usual practice and 17% compared to score use only [23]; similarly, in another RCT,

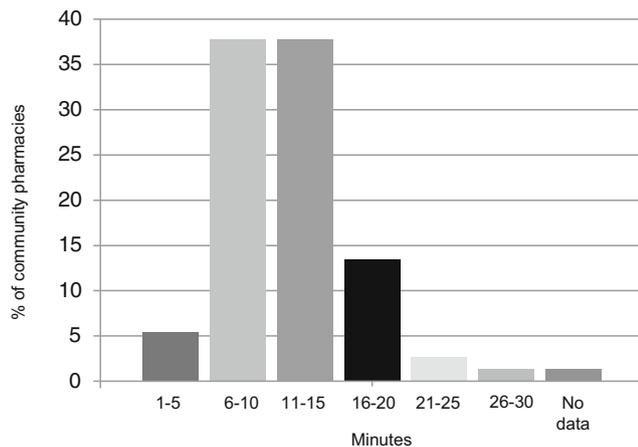


Fig. 3 Time dedicated in average by each community pharmacy to complete the protocol (74 respondents)

Llor et al. showed a reduction of inappropriate prescriptions from 60 to 27% in the RAT-guided arm [24]. Moreover, the use of RAT has proven to be cost-effective [25].

In this study, the involvement of community pharmacists in the management of sore throat, combining the use of clinical score and RAT, with educational sessions and material, has proven to be feasible and beneficial. The follow-up data showed that all patients with a positive RAT got an antibiotic prescription and 96.5% of those having a negative RAT did not consult a physician and therefore did not receive antibiotics, in accordance with the French guidelines. This finding is encouraging, since adherence to guidelines for sore throat is frequently poor, the use of RAT inconsistent (even in countries where it is recommended) and physicians often prescribe antibiotics even in the case of a negative RAT [11, 19, 26, 27].

Pharmacists are frequently the first professional consulted for sore throat, and their involvement could both speed the diagnosis, reducing transmission, and decrease the number of medical consultations for self-limiting infections [28]. There is a known link between medical consultation, re-consultation and antibiotic prescription on one hand, and between antibiotic prescription, and reinforcement of the patients' expectations for antibiotics on the other hand [29, 30]. In this community pharmacy-based intervention, these chain of events was averted, since patients with a viral infection were advised not to consult a doctor, after some time spent with the pharmacist. Pharmacists also delivered educational material, to increase patients' understanding and awareness on antibiotic resistance and responsible antibiotic use, which is known to be poor [31]; almost all (99.4%) patients found this information beneficial. This less paternalistic and more empowering approach may encourage patients to better manage self-limiting infections, reducing the perceived need for antibiotics [32, 33]. The high acceptance of the RAT, the adherence to indications and the overall satisfaction suggest a favourable perception of this approach by patients, at least in

this study. This is in line with some evidence showing that patient's satisfaction is related to receiving reassurance and pain relief, more than to antibiotic prescription [34].

Pharmacists involved in the study gave a positive feedback regarding feasibility. Overall, 98.6% of involved pharmacists declared they would be pleased to introduce RAT in their daily practice, if this intervention is endorsed and reimbursed. They usually needed 6–15 min to complete the whole procedure, and they judged this duration suitable and the test sufficient to guide them for patient management. This is in contrast with the perception of French GPs, who identified lack of time as the most important barrier to RAT implementation in their daily practice [19]. To the best of our knowledge, this was the first evaluation of the amount of time practically required to perform RAT for GAS in community pharmacies and we think that this information could help guide further implementation of the intervention. Recently, two other interventional studies conducted in the UK and in the USA showed that the implementation of RAT for sore throat in community pharmacies can be also feasible and beneficial, supporting the generalisability of this strategy [28, 35].

The French authorities recognised in August 2016 the possibility to perform RAT in community pharmacy [36]. This decree is however not yet connected with a system of reimbursement.

Strengths and limitations

Our study reported some original findings and have some strengths. It was a multicentre study including a relevant percentage of pharmacies in Lorraine. The intervention was implemented after a training session and participating pharmacists had the occasion to consult some explanatory material or to contact the investigators in case of doubt. This should have assured a good performance of the test, since the proficiency of the operator can influence the reliability of RAT [37]. The data collection 7 days after the RAT gave an insight of the effect of the intervention in terms of antibiotic prescription and test acceptance. The feedback data from involved pharmacists are original and highlight some important practical points, which will inform the future implementation of the intervention.

As previously detailed, a certain degree of selection bias at enrolment was unavoidable, due to the non-randomised nature of the study; our analysis suggests however that this bias might be limited. Moreover, each pharmacist enrolled only a few participants on average. However, the main outcomes (particularly patients' consultation rate after the RAT, and findings on patients' and pharmacists' feedbacks) showed highly consistent results.

The participation was voluntary both for pharmacists and patients, and the enrolment was limited to only one region. This might limit the generalisability of results, particularly to other

countries, even though this multicentre study involving 98 pharmacies is larger than other studies previously published [35].

Finally, the pharmacists applied the modified Centor score on the basis of patients' self-reported symptoms, without physical examination. This approach is more practical, reduces time spent in the procedure and is adapted to French legislation (not allowing pharmacists to perform clinical examination), but it needs further validation. Our study included only adults' patients, and it would be interesting to extend the investigation to children.

Conclusions

The implementation of a community pharmacy-based ABS intervention with clinical score and RAT use for the management of sore throat is feasible and is perceived favourably both by patients and pharmacists. This kind of intervention could increase the adherence to guidelines, limit antibiotic overuse and encourage self-management of self-limiting infections. Further investigations are needed, to fully understand the overall impact. A randomised selection of participating pharmacies and patients, with a control arm and a detailed evaluation of outcomes in terms of safety, antibiotic consumption and costs is required.

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Compliance with ethical standards

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

An oral informed consent was obtained from all participants included in the study.

A declaration to the CNIL (Commission Nationale de l'Informatique et des Libertés, the French National Agency regulating data protection) was made.

Conflicts of interest The authors declare that they have no conflict of interest.

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