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Impact of selective reporting of antibiotic susceptibility test results in urinary tract infections in the outpatient setting: a protocol for a pragmatic, prospective quasi-experimental trial

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ABSTRACT

Introduction Antibiotic resistance is a serious and increasing worldwide threat to global public health. One of antibiotic stewardship programmes' objectives are to reduce inappropriate broad-spectrum antibiotics' prescription. Selective reporting of antibiotic susceptibility test (AST) results, which consists of reporting to prescribers only few (n=5-6) antibiotics, preferring first-line and narrow-spectrum agents, is one possible strategy advised in recommendations. However, selective reporting of AST has never been evaluated using an experimental design.

Methods and analysis This study is a pragmatic, prospective, multicentre, controlled (selective reporting vs usual complete reporting of AST), before-after (year 2019 vs 2017) study. Selective reporting of AST is scheduled to be implemented from September 2018 in the ATOUTBIO group of 21 laboratories for all *Escherichia coli* identified in urine cultures in adult outpatients, and to be compared with the usual complete AST performed in the EVOLAB group of 20 laboratories. The main objective is to assess the impact of selective reporting of AST for *E. coli*-positive urine cultures in the outpatient setting on the prescription of broad-spectrum antibiotics frequently used for urinary tract infections (amoxicillin-clavulanate, third-generation cephalosporins and fluoroquinolones). The primary end point is the after (2019)–before (2017) difference in prescription rates for the previously mentioned antibiotics/classes that will be compared between the two laboratory groups, using linear regression models. Secondary objectives are to evaluate the feasibility of selective reporting of AST implementation by French laboratories and their acceptability by organising focus groups and individual semi-structured interviews with general practitioners and laboratory professionals.

Ethics and dissemination This protocol was approved by French national ethics committees (*Comité d'expertise pour les recherches, les études et les évaluations dans le domaine de la santé (TPS 29064)* and *Commission Nationale de l'Informatique et des Libertés (Décision DR-2018–141)*). Findings of this study will be widely disseminated through conference presentations, reports, factsheets and academic publications and generalisation will be further discussed.

Trial registration number NTC03612297.

Strengths and limitations of this study

- This study is the first interventional prospective controlled study to evaluate the effectiveness of selective reporting of antibiotic susceptibility test (AST) results to reduce the prescription of broad-spectrum antibiotics.
- This study is conducted in the French outpatient setting, accounting for 90% of all antibiotics used in humans, and targets urinary tract infections caused by *Escherichia coli* (the most frequent causal agent).
- This study includes a feasibility evaluation for laboratories by collecting prospectively in a database all material/informatics, financial and human laboratory resources needed to implement selective reporting of AST.
- This study includes an acceptability evaluation by organising focus groups and individual semi-structured interviews to collect general practitioners' and laboratory professionals' perceptions on selective reporting of AST.
- The main limitation of this study is the non-randomised design. To limit the selection bias due to the lack of randomisation, we selected two laboratory groups that are comparable in terms of urine cultures activity and epidemiology, and an adjustment for potential observed differences is planned in the analyses.

INTRODUCTION

Antibiotic resistance (ABR) is a serious and increasing worldwide threat to global public health.[1] It has been estimated that multidrug-resistant bacteria affect 158 000

French persons annually, of whom 12 500 die from these infections.[2]

In France, the increase of multidrug resistance among Enterobacteriaceae is the most alarming: the prevalence of *Escherichia coli* resistant to third-generation cephalosporins and to fluoroquinolones has dramatically increased in the last decade and has reached now 11% and 17%, respectively.[3]

More than 90% of antibiotics used in humans in France are prescribed to outpatients (70% by general practitioners (GPs)) and urinary tract infections (UTIs) account for a considerable proportion of these prescriptions (15% of all outpatient prescriptions, about 10 million of prescriptions each year) with *E. coli* being the pathogen most frequently (70%–95%) isolated in community-acquired UTIs.[4 5]

Antibiotic stewardship programmes aim both at limiting antibiotic therapy to proven or strongly suspected non-self-limiting bacterial infections, and at reducing broad-spectrum antibiotics use, such as amoxicillin-clavulanate, cephalosporins and fluoroquinolones. So, two goals are pursued: to avoid unnecessary antibiotic use and to limit inappropriate antibiotic prescribing.

Several studies have shown that half of antibiotic prescriptions for UTIs in primary care are either unnecessary or inappropriate, and that GPs prescribe more antibiotics than necessary.[6 7] Broad-spectrum antibiotics (in particular amoxicillin-clavulanate, cephalosporins and fluoroquinolones) are frequently inappropriately prescribed in UTIs, whereas first-line and narrow-spectrum antibiotics (eg, amoxicillin, nitrofurantoin, fosfomycin, etc) would have been sufficient to treat the infection.[8]

One strategy recommended by French national authorities[9 10] and by international recommendations[11 12] to limit the inappropriate overprescription of broad-spectrum antibiotics is the use of selective reporting for antibiotic susceptibility test (AST) results. Selective reporting means that AST are reported back to the practitioner only for few (n=5–6) antibiotics, those that should be used first-line according to guidelines. However, the laboratory is still testing all the 20–25 antibiotics reported in the usual complete AST, and susceptibility results not mentioned in the selective reporting of AST are available at the practitioners' request to the microbiologist. Data usually used to determine which antibiotics to report for urine samples are the isolated microorganism, the patient's age and gender and the list of antibiotics recommended in national guidelines. For example, in a wild-type *E. coli* isolated in urine in an adult woman, the only antibiotics to report could be amoxicillin, trimethoprim/sulfamethoxazole, nitrofurantoin, fosfomycin and pivmecillinam.[5 13–15]

To date however, even if recommended by the French authorities, selective reporting of AST is still limited to rare local initiatives.[16]

Two randomised controlled case-vignette surveys conducted among junior medical doctors and GPs in France revealed that selective reporting of AST could improve the appropriateness of antibiotic treatment for UTIs and decrease prescriptions of broad-spectrum antibiotics, while being well accepted by most physicians.[13 14] However, these two surveys used fictitious clinical vignettes and no study has yet been conducted in the 'real life' French health context to evaluate the impact of selective reporting of AST on antibiotic prescribing.

METHODS AND ANALYSIS

Study objectives

The main objective of this study is to assess the impact of selective reporting of AST for *E. coli*-positive urine cultures in adult outpatients on the prescription of broad-spectrum antibiotics frequently used in UTIs (amoxicillin-clavulanate, third-generation cephalosporins and fluoroquinolones). These antibiotics/classes have been indeed flagged since 2013 as 'critical' antibiotics (ie, antibiotics with a high risk of selection of bacterial resistance) by the French Medicines Agency,[8] in line with the recent AWaRe categorisation introduced by WHO in its Essential Medicines List.[17] The corresponding end points are prescription rates of amoxicillin-clavulanate, third-generation cephalosporins, fluoroquinolones and all three antibiotics/classes for suspected UTIs.

Secondary objectives are to evaluate the feasibility of the selective reporting of AST implementation by French laboratories and their acceptability by GPs and laboratory professionals (microbiologists, technicians and secretaries) in order to generalise AST if proved to be effective.

Study design and setting

This study is a pragmatic, prospective, multicentre, controlled (selective reporting vs usual complete reporting of AST), before-after study.

Selective reporting of AST is scheduled to be implemented, from 1 September 2018, in the ATOUTBIO group of 21 laboratories for all *E. coli* identified in urine cultures of adults, and to be compared with the complete reporting of AST performed in the EVOLAB group of 20 laboratories. ATOUTBIO and EVOLAB are the two main laboratory networks located in Lorraine (north-eastern France region with a population of 2 346 000 according to the 2014 census), and each of them is set up on approximatively one-third of the regional territory.

The target study population is adults, with an *E. coli*-positive urine culture on which an AST is realised, (according to national recommendations[15 18]), who are prescribed an antibiotic by primary care physicians (GPs and other specialties) located in the geographic areas served by all the 41 laboratories studied (in the intervention ATOUTBIO group or the control EVOLAB group).

The 'before' period is the year preceding the implementation of selective reporting of AST in the ATOUTBIO group (ie, the 2017 year) and the 'after' period is the year following this implementation (ie, the 2019 year).

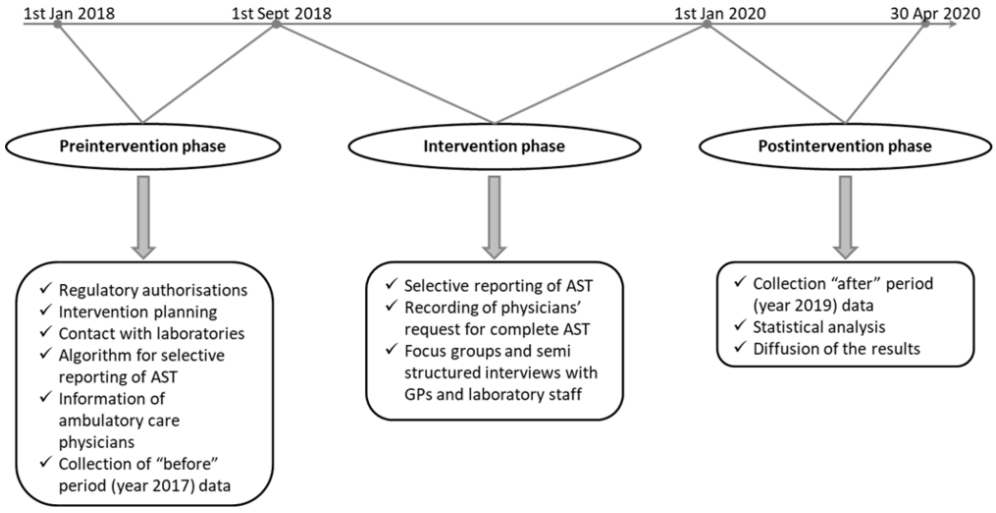

Figure 1 Phases of the study and timeline. AST, antibiotic susceptibility test results; GP, general practitioner.

The feasibility of the intervention for laboratories is evaluated by collecting prospectively in a database all material/informatics, financial and human laboratory resources used in 2018 and 2019 for the implementation of selective reporting of AST.

The acceptability of the intervention is assessed by organising focus groups and individual semi-structured interviews with a randomised sample of GPs and laboratory professionals to collect their perceptions on selective reporting of AST 1 year after its implementation (September 2019). The monthly number of complete reporting of AST requested by physicians is also calculated as an indicator of prescribers' acceptability.

In this study, we comply with existing methodology guidance for stewardship studies.[19] The phases of the study are summarised in figure 1.

Study organisation

This study is promoted and coordinated by Nancy University Teaching Hospital. A scientific committee is in charge of supervising all scientific aspects and organisational issues occurring during the study period. This committee is multidisciplinary, comprising four microbiologists, two infectious diseases physicians, one GP, one epidemiologist and public health specialist, one sociologist and one pharmacist. The committee will meet regularly: at least one meeting before the study starts to define the protocol, at least two meetings per year during the study period to solve organisational issues and at least one meeting after the end of the study period to present and discuss the results.

Patient and public involvement

The development of the research questions is based on previous pilot studies describing the impact of selective reporting of AST on the appropriateness of antibiotic treatment in fictitious situations and perceptions of GPs. The patients and public have not been involved in the design and will not be involved in recruitment or conduct of the study. The results will be disseminated to participants (primary care physicians and patients) through media and information in the waiting rooms of participating laboratories.

Description of the intervention: selective reporting of AST

As French guidelines for UTIs' treatment[5] differ by gender (see online supplementary appendix A), two algorithms (tables 1 and 2) have been developed and pilot-tested by three GPs, one microbiologist and two infectious diseases physicians. During the development of algorithms, two possible risks associated with selective reporting of AST have been taken into account. First, physicians may face problems prescribing an antibiotic for patients with multiple allergies or contraindications; indeed, for each possible clinical situation, at least two different classes of antibiotics are reported on the selective report and the sentence 'the complete AST is available at the prescriber' request is specifically mentioned on the report. Second, as the clinical diagnosis is unknown to the microbiologist and then, in order to avoid the increased use of antibiotics reported on the selective report but not appropriate to the clinical context (eg, nitrofurantoin in pyelonephritis as previously reported in other studies[13 14]), antibiotics that should not be used in pyelonephritis or prostatitis are specifically flagged on the report. In addition, to try to reduce unnecessary antibiotic use, the statement 'when a urine culture is positive, only clinical symptoms can differentiate between asymptomatic bacteriuria and a UTI; therefore, an antibiotic treatment is not needed for all positive urine cultures' is also mentioned on the report.

Data collected

Data collected for each AST performed on *E. coli*-positive urine cultures in 2017 (before period) and 2019 (after period) in all laboratories of the two groups are: patient's gender and age, living residence (community/nursing home), study group (intervention (ATOUTBIO)/control (EVOLAB)), antibiotic(s) dispensed by a community pharmacy during the 15 days following the AST (yes/

Table 1 Algorithm for selective reporting of AST for urine cultures positive for *Escherichia coli* in adult women

	Situation 1	*Situation 2*	*Situation 3*	*Situation 4*
Resistance profile	**AMX S**	**AMX R/I and (AMC S or TMP-SMX S)**	**AMX I/R and AMC I/R and TMP-SMX I/R and 3GCs S**	**3GCs R**
Antibiotics reported on AST	AMX Pivmecillinam* Nitrofurantoin* Fosfomycin* TMP-SMX	AMX Pivmecillinam* Nitrofurantoin* Fosfomycin* TMP-SMX AMC	AMX Pivmecillinam* Nitrofurantoin* Fosfomycin* TMP-SMX AMC Cefixime Ciprofloxacin Levofloxacin Ofloxacin	All antibiotics usually reported on a complete AST
Antibiotics occasionally reported on AST	FQ reported only if R/I	FQ reported only if R/I	–	–
Antibiotics not reported on AST	FQ not reported if S, 3GCs, AMC	FQ not reported if S, 3GCs	–	–

Complete AST is available at the prescriber's request.
When a urine culture is positive, only clinical symptoms can differentiate between asymptomatic bacteriuria and a urinary tract infection; therefore, an antibiotic treatment is not needed for all positive urine cultures.
For more information regarding national guidelines: https://antibioclic.com.
*Do not use for pyelonephritis (lack of diffusion in renal parenchyma).
AMX, amoxicillin; AMC, amoxicillin-clavulanate; AST, antibiotic susceptibility test; FQ, fluoroquinolones; I, intermediate; R, resistant; S, susceptible; TMP-SMX, cotrimoxazole; 3CGs, third-generation cephalosporins.

no, molecule(s), dosage, type of package and quantity) and the prescriber's specialty. During the 'after period', we also collect the number of medical consultations and hospitalisations during the 30 days following the AST, in order to look for any unintended consequences. All these data stem from the French health insurance database Système National des Données de Santé (SNDS)[20] that contains individualised, anonymous and linkable data. Prospectively recorded for all beneficiaries of healthcare in France, the SNDS covers almost the entire French population (67 million inhabitants). Data recorded include especially all medical expenditure reimbursements (all antibiotics are reimbursed in France) and information from hospital stays. The SNDS database is one of the largest databases in the world that has been extensively used to guide public health policies in France.[21 22] A probabilistic data linkage method[23] is applied within the anonymous SNDS database to identify patients for which urine cultures positive for *E. coli* and with an AST were processed in 2017 and 2019 in the two groups of laboratories.

Sample size

Based on national published data,[24 25] the prescription rate of broad-spectrum antibiotics frequently used in UTIs is estimated to be at around 70% in French outpatients. A sample of 300 urine cultures positive for *E. coli*

Table 2 Algorithm for selective reporting of AST for urine cultures positive for *Escherichia coli* in adult men

	Situation 1	*Situation 2*	*Situation 3*	*Situation 4*
Resistance profile	**FQ S TMP-SMX S and 3GCs S**	**FQ S TMP-SMX S and 3GCs R**	**FQ R and/or TMP-SMX R and 3GCs S**	**FQ R TMP-SMX R and 3GCs R**
Antibiotics reported on AST	Ciprofloxacin Levofloxacin Ofloxacin TMP-SMX	Ciprofloxacin Levofloxacin Ofloxacin TMP-SMX Cefotaxime Ceftriaxone	Ciprofloxacin Levofloxacin Ofloxacin TMP-SMX Cefotaxime Ceftriaxone	All antibiotics usually reported on a complete AST

Complete AST is available at the prescriber's request.
When a urine culture is positive, only clinical symptoms can differentiate between asymptomatic bacteriuria and a UTI; therefore, an antibiotic treatment is not needed for all positive urine cultures.
For more information regarding national guidelines: https://antibioclic.com.
AMC, nitrofurantoin, fosfomycin, pivmecillinam and cefixime should not be used in male UTIs (lack of diffusion in prostate).
AMX, amoxicillin; AMC, amoxicillin-clavulanate; AST, antibiotic susceptibility test; FQ, fluoroquinolones; I, intermediate; R, resistant; S, susceptible; TMP- SMX, cotrimoxazole; 3CGs, third-generation cephalosporins; UTI, urinary tract infection.

and with an AST per group would be sufficient to detect a 10% decrease difference in the prescription rate between groups after intervention, with a 90% power, a 5% α risk and an inflation factor at 3 (due to the cluster design). Our network of laboratories will definitely be sufficient to detect such a difference as >16 000 AST on *E. coli* urine cultures are performed each year by both EVOLAB and ATOUTBIO groups.

Statistical analyses

The statistical analysis plan includes the following procedures:

i. A comparison of laboratory activities between the two groups (ATOUTBIO and EVOLAB) in 2017 and 2019: number of AST in urine cultures, *E. coli* prevalence in urine cultures, antibiotic resistance profiles of *E. coli* isolated from urine cultures.
ii. A comparison of age and sex ratio of patients with *E. coli*-positive urine cultures (with AST) between the two groups in 2017 and 2019.
iii. The calculation, for each laboratory group, of the prescription rates in suspected UTIs of amoxicillin-clavulanate, third-generation cephalosporins, fluoroquinolones and all these three antibiotics/classes combined in 2017 and 2019, as follows: number of prescriptions of antibiotic/class y for *E. coli*-positive urine cultures with AST during the year n/number of prescriptions of all antibiotics for *E. coli*-positive urine cultures with AST during the year n.
iv. A comparison of the after (2019)–before (2017) difference of the prescription rates for the above-mentioned antibiotics/classes between the two groups, using linear regression models adjusted for variables that might differ between groups (laboratory activities, sex ratio, age). As a sensitivity analysis, a time-series analysis is planned using interventional autoregressive integrated moving average models to compare the evolution of monthly prescription rates between 2017 and 2019 in each group.

A p value of <0.05 for two-sided tests is considered significant. All analyses are performed with SAS V.9.4 (SAS Institute, Cary, North Carolina, USA).

DISCUSSION

Optimising the use of antibiotics in the French outpatient setting is a priority and selective reporting of AST may be an effective antibiotic stewardship intervention. Our research hypothesis is that the implementation of selective reporting of AST in urine samples will lead to a decrease in the prescription of broad-spectrum antibiotics by encouraging prescribers to use in priority first-line and narrow-spectrum antibiotics. Very few studies have been conducted so far to evaluate the impact of selective reporting of AST on antibiotic prescribing.

Two observational, retrospective, before-after studies performed in North America hospital setting showed that mentioning rifampicin and ciprofloxacin on the AST report led to an increase of these drugs' prescriptions.[26 27] Another observational retrospective study performed in the USA on 73 hospitalised patients showed that selective reporting of AST could reduce the prescriptions of broad-spectrum antibiotics and promote de-escalation practices without any adverse event on patients' outcome.[28] In the primary care settings, two other observational, retrospective, before-after studies performed in the UK showed that modifying the antibiotics listed on the AST report significantly influenced the GPs' antibiotic prescriptions, in favour of drugs that were reported.[29 30]

To date, no interventional prospective controlled trial has been conducted to evaluate the effectiveness of selective reporting of AST, as compared with usual complete reporting, to reduce the prescription of broad-spectrum antibiotics and our present study would be the first to do so, to the best of our knowledge; indeed, all previous encouraging results were provided by observational retrospective studies where the risks of selection and confusion bias may not be excluded.

However, despite the lack of high level of evidence about the impact of selective reporting of AST, 11 of 36 European countries routinely use selective reporting (Belgium, Croatia, Czech Republic, Denmark, Ireland, the Netherlands, Slovakia, Slovenia, Sweden, Turkey and the UK), according to a recent European Society of Clinical Microbiology and Infectious Diseases (ESCMID) survey.[16]

In France, selective reporting of AST is still limited to very rare local initiatives. Indeed, French microbiologists are reluctant to replace the complete usual AST (20–25 antibiotics reported) with the selective reporting one because this change implies an important material and informatic reorganisation in the laboratory, as well as a significant financial and time investment. Furthermore, they fear that prescribers will not accept easily this change and then will frequently ask microbiologists for a complete AST, resulting in significant extra work for laboratory staff. These barriers were also identified in the ESCMID survey.[16] Feasibility assessment of selective reporting of AST, as well as acceptability by laboratory professionals and GPs, as secondary objectives of this study, aim at exploring these potential barriers to implementation. Likewise, showing a likely lack of higher morbidity (consultations, hospitalisations) in the target population should reassure physicians, patients and institutions regarding the safety of such an intervention.

The main limitation of our study is the non-randomised design. The decision to implement selective reporting of AST is often the result of a long process because it requires, as previously mentioned, a significant time and resources' investment for the laboratory, with all financial consequences. In this context, asking laboratories to implement selective reporting of AST only for the need of a research study would have been very difficult. We therefore identified two laboratory groups which volunteered to participate in this study but only one of them was technically ready to introduce selective reporting of AST

(ATOUTBIO, intervention group). To limit the selection bias due to the lack of randomisation, we decided to select two laboratory groups that are comparable in terms of urine cultures' activity and epidemiology. The ATOUTBIO group indeed received 83 473 urine samples in 2016 and realised 18 977 (23%) AST, of which 12 679 (67%) were positive for *E. coli*; in the same period, the EVOLAB group received 82 584 urine samples, and realised 20 615 (25%) AST, of which 14 127 (68%) were positive for *E. coli*. Additionally, *E. coli* isolated from urine cultures had comparable resistance phenotypic profiles in both laboratory groups. Moreover, the planned statistical analysis includes a comparison of urine cultures' activity and epidemiology between both groups in 2017 (before period) and 2019 (after period), and an adjustment for potential observed differences in the main end points analyses.

Another limitation of our study is that we do not aim at evaluating the appropriateness of antibiotic prescriptions as we do not have access to clinical and laboratory data for each patient.

In summary, our study is the first interventional prospective controlled study conducted to evaluate in a 'real-life setting' the impact of selective reporting of AST on prescription of antibiotics in UTIs, its feasibility for French laboratories and its acceptability for laboratory professionals and main prescribers (GPs) in France. If selective reporting would indeed reduce the use of broad-spectrum antibiotics, this may significantly change the way AST is reported in France and encourage other countries to consider implementing such a strategy. Our results will also give us important information on how best to implement selective reporting of AST.

ETHICS AND DISSEMINATION

This study is conducted according to the principles of the Declaration of Helsinki. Findings of this study will be widely disseminated through conference presentations, reports, factsheets and academic publications and generalisation will be further discussed.

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Contributors CP (principal investigator), NT (methodologist), SF, PDM and AF-C significantly contributed to designing the study protocol. FB drafted the manuscript under NT supervision. CP, SF, PDM and AF-C critically reviewed the manuscript. All authors approved the final version of the manuscript.

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Competing interests None declared.

Patient consent Not required.

Ethics approval Comité d'expertise pour les recherches, les études et les évaluations dans le domaine de la santé (TPS 29064) and Commission Nationale de l'Informatique et des Libertés (Décision DR-2018-141).

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