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Impact of a checklist used by pharmacists on hospital antimicrobial use: a patient-level interrupted time series study

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SUMMARY

Background: Antimicrobial misuse leading to drug resistance is a growing concern for clinicians. Improving antimicrobial stewardship programmes through development of new tools could be part of the solution.
Aim: To evaluate antimicrobial use in hospitalized patients after implementation of an antimicrobial checklist for ward-based clinical pharmacists.
Methods: A checklist based on quality indicators of optimal antimicrobial use was implemented to standardize hospital pharmacists' assessments of antimicrobial therapy. Antimicrobial use metrics from adults hospitalized during the control and intervention periods were assessed in an interrupted time series analysis of individual patient data. The primary endpoint was days of therapy (DOT) for all antimicrobials per 1000 days present for included patients. Secondary endpoints were the DOT of extended-spectrum antimicrobials (DOT-ES), length of therapy of all antimicrobials (LOT) and the number of pharmacist interventions.
Findings: One-thousand six-hundred and nineteen patients were included: 800 and 819 in the pre- and post-checklist implementation periods, respectively. As indicated by the point estimates and their 95% confidence intervals (CIs), there were no changes in trend for DOT, DOT-ES or LOT. A change in level was not found for the DOT, while a change of -118 DOT-ES [-209,-28] and -51 LOT [-97,-4] was documented. Furthermore, pharmacists' interventions regarding antimicrobials increased by 18.7% (14.0, 23.5) and progress notes by 32.3% (27.8, 36.8).

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Conclusion: An antimicrobial checklist used by ward-based clinical pharmacists did not decrease DOT for all antimicrobials, but decreased DOT-ES and LOT upon its implementation.

Introduction

According to the World Health Organization (WHO), the misuse of antimicrobials promotes treatment resistance and is deemed one of the highest threats to global health [1,2]. Antimicrobial resistance is also associated with increased duration of hospitalization, healthcare-associated costs and mortality [2]. Antimicrobial stewardship programmes (ASPs) play a major role in preventing misuse of antimicrobials and its consequences and, according to the 2016 Infectious Diseases Society of America (IDSA) ASP guidelines, pharmacists' participation in these programmes is essential [3]. While many have described the ASP pharmacist's role in the literature, less is known about the contribution of the ward-based pharmacist on antimicrobial stewardship activities [4]. A prospective, quasi-experimental study previously showed that ward-based clinical pharmacists trained to comply with an antimicrobial stewardship care bundle improved appropriate antimicrobial use [5]. While the ward-based pharmacist could enhance appropriate antimicrobial use, there is limited evidence regarding tools that can facilitate and standardize their antimicrobial evaluation. Safety checklists have been used in numerous healthcare settings such as surgery and intensive-care units where they were found to decrease costs, morbidity and mortality [6–8]. However, few antimicrobial therapy checklists have been evaluated and previous reports of their impact involved physicians, not pharmacists [9,10]. In this context, a checklist was developed by ASP pharmacists from our hospital centre based on predetermined antimicrobial use quality indicators (QIs) (see Supplementary material) [11]. Its aim was to help the ward pharmacist comprehensively assess a patient's antimicrobial therapy and communicate any ensuing recommendations. The main objective of this study was to evaluate the effect of this checklist designed to assist ward-based pharmacists in achieving optimal antimicrobial use.

Methods

Study design and setting

A quasi-experimental study was conducted consisting of an interrupted time series (ITS) of two 16-week periods (pre-intervention: August 2016 to December 2016 and post-intervention: January 2017 to May 2017) conducted on the three sites of an 873-bed tertiary-care teaching hospital in Montréal, Canada. The studied intervention was the implementation of an antimicrobial checklist which was developed based on quality indicators of appropriate antibiotic use in hospitalized adults, as identified by van den Bosch *et al.* [11]. The checklist was approved by a panel of pharmacists and physicians of the institution. Two versions of the checklist were available: a treatment initiation and a follow-up antimicrobial evaluation checklist. The first included indicators such as adequacy of blood cultures timing, appropriateness of antimicrobial choice according to guidelines, clinical setting, patient's allergies or resistance risk factors, adequate antimicrobial dosing for weight, renal or hepatic function, treatment duration and potential drug interactions. The follow-up checklist included similar items as well as assessment of drug dosing and pharmacokinetic modelling, if applicable, potential for de-escalation of antimicrobial spectrum or change of route of administration and evaluation of side effect. Each checklist had a specific section where the pharmacist could state his recommendations to the medical team. This tool was meant to be used as part of the routine Monday to Friday clinical activities of the ward-based pharmacist. The checklist was designed to be directly included in the patient's medical chart after the initial evaluation and after each follow-up of the ward-based pharmacist. Over the two-week interval preceding the start of the post-intervention period, all pharmacists were trained in using the checklist. During the post-intervention period, pharmacists received weekly reminders to use the checklist for all patients receiving antimicrobial therapy.

Participants were identified from daily pharmacy parenteral preparation log sheets and enrolled prospectively. Eligibility criteria were confirmed retrospectively from the patient's medical file. Patients eligible for analysis were adults (18 years and older) who had received at least 24 h of parenteral antimicrobial therapy from Monday to Friday while on the following units offering clinical pharmacy services: emergency department (ED), intensive care unit (ICU), internal medicine, hepatology, transplantation, haematology, coronary care unit, cardiology and burns centre. Antimicrobial therapies of interest were antibiotics, antivirals and antifungal agents. Patients receiving parenteral antimicrobials solely for prophylaxis or for a non-infectious indication were excluded. The pre- and post-intervention phases were mutually exclusive such that enrolled patients who were still hospitalized two weeks after the end of each recruitment period were excluded retrospectively.

The primary endpoint was a change in days of therapy (DOT) per 1000 days present. DOT represents the total number of days of each specific antimicrobial received. Every antimicrobial received enterally or parenterally for an infectious indication was included in this calculation. Days present (DP) were defined as the total number of days that patients enrolled in the study were hospitalized in any unit of our hospital. Secondary endpoints included DOT for extended-spectrum antimicrobials (DOT-ES), length of therapy (LOT), length of stay (LOS) and 30-day mortality. The number of pharmacists' chart entries and interventions regarding antimicrobial therapy was also evaluated.

Demographic characteristics (age, sex, body mass index, medical or surgical hospitalization), comorbidities (immunosuppression, diabetes, chronic obstructive pulmonary disease and chronic kidney disease (CKD)), number of pharmacists' entries in medical files and pharmacists' interventions were collected from patients' electronic medical records (EMRs), whereas duration of antimicrobial therapy was obtained from

the medication administration record. The following factors likely to influence antimicrobial use were also collected in the EMRs: infection type (by system), multi-drug-resistant bacteria carrier status, use of an antimicrobial in the last three months, infectious diseases (IDs) physician consultation and ICU hospitalization. Because data abstraction was carried out manually, all data collectors were trained to maximize its consistency and then performed random data collection audits. The protocol was reviewed and accepted by the Scientific Evaluation and Research Ethics Committee of our institution.

Statistical analysis

The metrics of antimicrobial use, DOT, DOT-ES, and LOT were assessed using linear regression of the ITS model using the individual patient data normalized for 1000 days present (bilateral alpha <0.05) [12]. It was hypothesized that the intervention would have an immediate impact on antimicrobial use (level) and could further decrease upon implementing the antimicrobial checklist (trend). To allow for individually adjusted regression analyses, predictors were determined a priori for the outcomes and potential confounders, i.e. variables associated with pharmacists' use of the checklist intervention and the DOT, DOT-ES, and LOT outcomes. Selection of variables to include in adjusted models was guided by results of univariate analyses and further informed by clinical insights. Crude and covariate-adjusted analyses performed by using Stata version 12.1 (College Station, TX: StataCorp LP) are reported here. Autocorrelation was assessed with the Breusch–Godfrey test. Before and after comparisons of categorical variables were performed by using Chi-squared or when appropriate, Fisher's exact test, whereas those for continuous variables were evaluated with Student's *t*-test. All results are presented as point estimates with their 95% confidence intervals (95% CIs).

Results

A total of 2000 patients were screened and 1619 were included; there were 800 in the pre-intervention and 819 in the

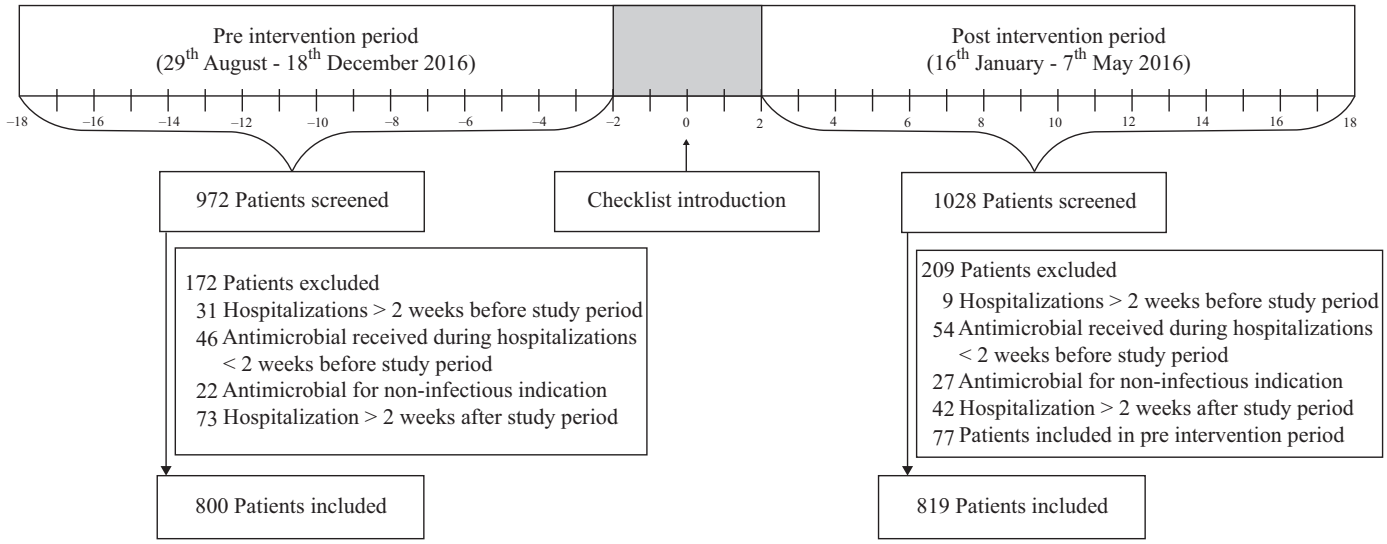

Figure 1. Flow diagram illustrating the timeline of pre- and post-intervention periods, with patient exclusion justifications.

Table I
Patient characteristics

Variable	Pre-intervention ($N = 800$)	Post-intervention ($N = 819$)	Difference (95% CI)
Medical hospitalization	660 (82.5)	646 (78.9)	3.6 (−0.2, 7.5)
Male	460 (57.5)	473 (57.8)	−0.3 (−5.1, 4.6)
Age	61.3 (17.6)	62.0 (17.4)	−0.6 (−2.3, 1.1)
Diabetes	252 (31.5)	241 (29.4)	2.1 (−2.4, 6.6)
CKD	168 (21.0)	136 (16.6)	4.4 (0.6, 8.2)
COPD	155 (19.4)	155 (18.9)	0.5 (−3.4, 4.3)
Immunosuppression	268 (33.5)	269 (32.8)	0.7 (−3.9, 5.2)
ESBL	23 (2.9)	14 (1.7)	1.2 (−0.3, 2.6)
CPE	30 (3.8)	8 (1.0)	2.8 (1.3, 4.2)
VRE	49 (6.1)	30 (3.7)	2.5 (0.4, 4.6)
MRSA	41 (5.1)	36 (4.4)	0.7 (−1.3, 2.8)

Data are number and percentage or mean and standard deviation.
CI, confidence interval; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CPE, carbepenemase-producing Enterobacteriaceae; ESBL, extended spectrum beta-lactamase; MRSA, meticillin-resistant *Staphylococcus aureus*; VRE, vancomycin-resistant Enterococci.

Table II
Most frequent infection type

System	Pre-intervention ($N = 800$) number (%)	Post-intervention ($N = 819$) number (%)	Difference (95% CI)
Pulmonary	286 (35.8)	330 (40.3)	−4.5 (−9.3 to 0.2)
Skin and soft tissus	200 (25.0)	175 (21.4)	3.6 (−0.5 to 7.7)
Urinary	143 (17.8)	144 (17.6)	0.3 (−3.4 to 4.0)
Blood	137 (17.1)	113 (13.8)	3.3 (−0.2 to 6.9)
Abdominal	123 (15.4)	137 (16.7)	−1.3 (−4.9 to 2.3)
Unknown origin	54 (6.8)	66 (8.1)	−1.3 (−3.9 to 1.2)
CDI	47 (5.9)	39 (4.8)	1.1 (−1.1 to 3.3)
ENT	31 (3.9)	41 (5.0)	−1.1 (−3.1 to 0.9)
Influenza	11 (1.4)	48 (5.9)	−4.5 (−6.3 to −2.7)
Bone	22 (2.8)	27 (3.3)	−0.6 (−2.2 to 1.1)
Febrile neutropenia	18 (2.3)	12 (1.5)	0.8 (−0.5 to 2.1)
CNS	12 (1.5)	23 (2.8)	−1.3 (−2.7 to 0.1)

CDI, *Clostridium difficile* infection; CI, confidence interval; CNS, central nervous system; ENT, ear, nose and throat.

post-intervention periods. Figure 1 presents the study dates and flow of patients. Most patients were male (57.8 vs 57.5%) and hospitalized for medical reasons (78.9% vs 82.5%) (Table I). They also had several comorbidities as nearly one-third were diabetic (29.4% vs 31.5%) or immunocompromised (32.8% vs 33.5%) and almost one in five had CKD. Although resistant bacteria were generally rare at baseline (around 5% or less), there were more patients with carbapenem-resistant Enterobacteriaceae (CRE) (difference 2.8%; 95% CI: 1.3, 4.2) and vancomycin-resistant Enterococcus (VRE) (difference 2.5%; 95% CI: 0.4, 4.6) in the pre-intervention period. A high proportion of patients were admitted to the ED (76.2 vs 77.1%), the ICU (27.1% vs 25.9%) and the internal medicine units (18.3 vs 20.1%). Patients in the pre-intervention period stayed 1.8 days longer in the ICU than those in the post-intervention period. As shown in Table II, the most frequent infection

Table III
Most frequent antimicrobial, all treatments combined

Antimicrobial[e]	Pre-intervention ($N = 800$) Number (%)	Post intervention ($N = 819$) Number (%)	Difference (95% CI)
Penicillin[*]	537 (67.1)	580 (70.8)	−3.7 (−8.2, 0.8)
Piperacillin-tazobactam	501 (62.6)	549 (67.0)	−4.4 (−9.0, 0.2)
Cephalosporins	239 (29.9)	226 (27.6)	2.3 (−2.1, 6.7)
First generation[‡]	128 (16.0)	110 (13.4)	2.6 (−0.9, 6.0)
Third generation[§]	129 (16.1)	125 (15.3)	0.9 (−2.7, 4.4)
Carbapenem[‖]	212 (26.5)	186 (22.7)	3.8 (−0.4, 8.0)
Fluoroquinolones[¶]	263 (32.9)	262 (32.0)	0.9 (−3.7, 5.5)
Aminoglycoside[a]	28 (3.5)	14 (1.7)	1.8 (0.2, 3.3)
Vancomycin IV	247 (30.9)	234 (28.6)	2.3 (−2.1, 6.8)
Macrolides[b]	80 (10.0)	112 (13.7)	−3.7 (−6.8, −0.5)
Clindamycin	42 (5.3)	56 (6.8)	−1.6 (−3.9, 0.7)
Metronidazole	75 (9.4)	80 (9.8)	−0.4 (−3.3, 2.5)
Trimethoprim–sulfamethoxazole	28 (3.5)	24 (2.9)	0.6 (−1.1, 2.3)
Vancomycin PO	42 (5.3)	42 (5.1)	0.1 (−2.0, 2.3)
Caspofungin	47 (5.9)	31 (3.8)	2.1 (<0.1, 4.2)
Imidazoles[c]	43 (5.4)	37 (4.5)	0.9 (−1.3, 3.0)
Oseltamivir	12 (1.5)	51 (6.2)	−4.7 (−6.6, −2.9)
Nuclosides and nucloetides[d]	33 (4.1)	38 (4.6)	−0.5 (−2.5, 1.5)

CI, confidence interval; IV, intravenous; PO, per os.
[*] Amoxicillin, ampicillin, amoxicillin–clavulanate, cloxacillin, penicilline G, piperacillin–tazobactam.
[‡] Cefadroxil, cefazolin.
[§] Cefotaxim, ceftazidime, ceftriaxone.
[‖] Ertapenem, meropenem.
[¶] Ciprofloxacine, levofloxacine, moxifloxacine.
[a] Amikacin, gentamicin, tobramycin.
[b] Azithromycin, clarithromycin.
[c] Fluconazole, itraconazole, posaconazole, voriconazole.
[d] Acyclovir, valacyclovir.
[e] Data for the following antimicrobials are not shown because frequency is <2% in both periods: doxycyclin, linezolid.

Table IV
Changes in levels and trends after implementation of an antimicrobial checklist on metrics of antimicrobial use

Endpoints	Pre-intervention level	95% CI	Pre-intervention trend	95% CI	Change in level	95% CI	Change in trend	95% CI
DOT								
Unadjusted model*	1135	1054, 1216	0.15	−0.03, 0.33	−87	−206, 31	−0.14	−0.39, 0.10
Adjusted model†	967	861, 1074	0.18	−0.0003, 0.36	−92	−209, 24	−0.17	−0.41, 0.07
DOT-ES								
Unadjusted model	842	778, 906	0.07	−0.09, 0.23	−118	−209, −28	0.01	−0.19, 0.22
Adjusted model‡	766	688, 844	0.09	−0.07, 0.24	−124	−214, −35	0.01	−0.19, 0.22
LOT								
Unadjusted model	775	743, 808	0.05	−0.03, 0.12	−51	−99, −4	−0.01	−0.10, 0.09
Adjusted model§	704	662, 746	0.05	−0.02, 0.12	−51	−97,−4	−0.01	−0.11, 0.09

CI, confidence interval; DOT, days of therapy; DOT-ES, days of therapy of extended spectrum antimicrobial; LOT, length of therapy.
* Time unit = 1 day.
† Medical patients, age, meticillin-resistant *Staphylococcus aureus*, immunosuppression.
‡ Medical patients, age, meticillin-resistant *S. aureus*.
§ Medical patients, age, chronic renal disease, chronic obstructive pulmonary disease.

types were similarly distributed between periods, except for influenza infections, which were more prevalent in the post-intervention period (difference 4.5%; 95% CI: 2.7, 6.3). The number of infection types per patient was the same for both periods (1.4 ± (standard deviation (SD)) 0.7)) as was the number of infectious episodes per patient (1.5 ± 0.7). No difference was found in the proportion of patients with an infectious disease physician consultation. Antimicrobials used are listed in Table III. Over 90% of patients received extended-spectrum antimicrobials. There were no noteworthy differences in antimicrobials used between study time periods except for the expected higher prevalence of oseltamivir use in post-intervention (difference 4.7%; 95% CI: 2.9, 6.6). Patients in each period spent a similar number of days within a unit with clinical pharmacy services (9.6 vs 10.5 days). The antimicrobial checklist was used by the pharmacists in 50.3% (412/819) of the eligible patients. On average 1.3 (±0.7) checklists per patient were filled.

In the unadjusted analyses, there was no significant change in levels or trends for the DOT (level: -87 DOT per 1000 DP), 95% CI: -206, -31, trend: -0.14 DOT per 1000 DP, 95% CI: -0.39, 0.10) (Table IV, Figure 2). The use of extended-spectrum antimicrobials was reduced by 118 DOT-ES per 1000 DP (95% CI: -209, -28) after the introduction of the checklist (Table IV, Figure 2). There was also an immediate decrease of 51 LOT per 1000 DP (95% CI: -99, -4]) in the post intervention period (Table IV, Figure 2). However, there was no change in the trends of those endpoints (DOT-ES and LOT) over time during the period of checklist use (0.01 DOT-ES per 1000 DP, 95% CI: -0.19, 0.22, -0.01 LOT per 1000 DP, 95% CI: -0.10, 0.09). All models were also adjusted for a medical (as opposed to surgical-type) hospitalization, age and meticillin-resistant *Staphylococcus aureus*. Models for DOT-ES and LOT were additionally adjusted for comorbidities (see Table IV). Results of adjusted analyses were consistent with the above crude findings (Table IV). The Breusch–Godfrey test showed no significant autocorrelation in the ITS analysis. There were no between-period differences in the mean LOS (14.7 days, difference: -0.05%, 95% CI: -1.47, 1.36) or the 30-day mortality (88 deaths (post-checklist) vs 66 (pre-checklist), difference: 2.5%, 95% CI: -0.4, 5.3). Pharmacists' interventions on antimicrobial therapy increased from 275 to 435 after implementing the checklist (difference 18.7%; 95% CI: 14.0, 23.5) while the documentation of their antimicrobial stewardship activities in the form of progress notes in the EMRs increased from 192 to 461 (difference 32.3%; 95% CI: 27.8, 36.8).

Discussion

In this study, the use of an antimicrobial checklist by pharmacists had no effect on overall antimicrobial use, but was associated with immediate decreases in the use of extended-spectrum antimicrobials and in the length of overall antimicrobial therapy. Although the primary endpoint (a reduction in DOT level and trend) was not met, the implementation of the checklist had a positive impact on the amount of ward-based pharmacist interventions, with a 2.4-fold increase in pharmacists' documentation and a 1.6-fold increase in the proportion of patients with interventions on antimicrobial therapy.

Very few other studies have evaluated antimicrobial checklists. Van Daalen conducted a stepped wedge cluster randomized trial involving physicians and evaluating an antibiotic checklist based on a different set of quality indicators [10]. While their study showed an increase in appropriate antimicrobial use based on their predefined QIs, there was no significant change in antimicrobial use metrics (LOS and DOT) [10]. The authors found that higher adherence to the QIs of the checklist was significantly correlated with shorter LOS [10]. Evaluating the implementation of another checklist, but for physicians, Lee *et al.* showed that monthly teaching sessions and use of their structured electronic antimicrobial checklist reduced the defined daily dose (DDD) of moxifloxacin and the overall antimicrobial cost [9].

Our study has a number of methodological strengths. The ITS design met the quality criteria proposed in the literature, as evidenced by the facts that: (1) sources and methods of data collection were consistent and reliable; (2) all outcomes were objective endpoints; (3) follow-up of participants was complete; (4) the impact of the intervention was pre-specified; (5) data points were equally distributed before and after the intervention; and (6) appropriate time series techniques were used for the analysis [13,14]. Our study also has clinical strengths. Although they are intermediate goals, our chosen outcome measures — DOT, DOT-ES, and LOT — are major

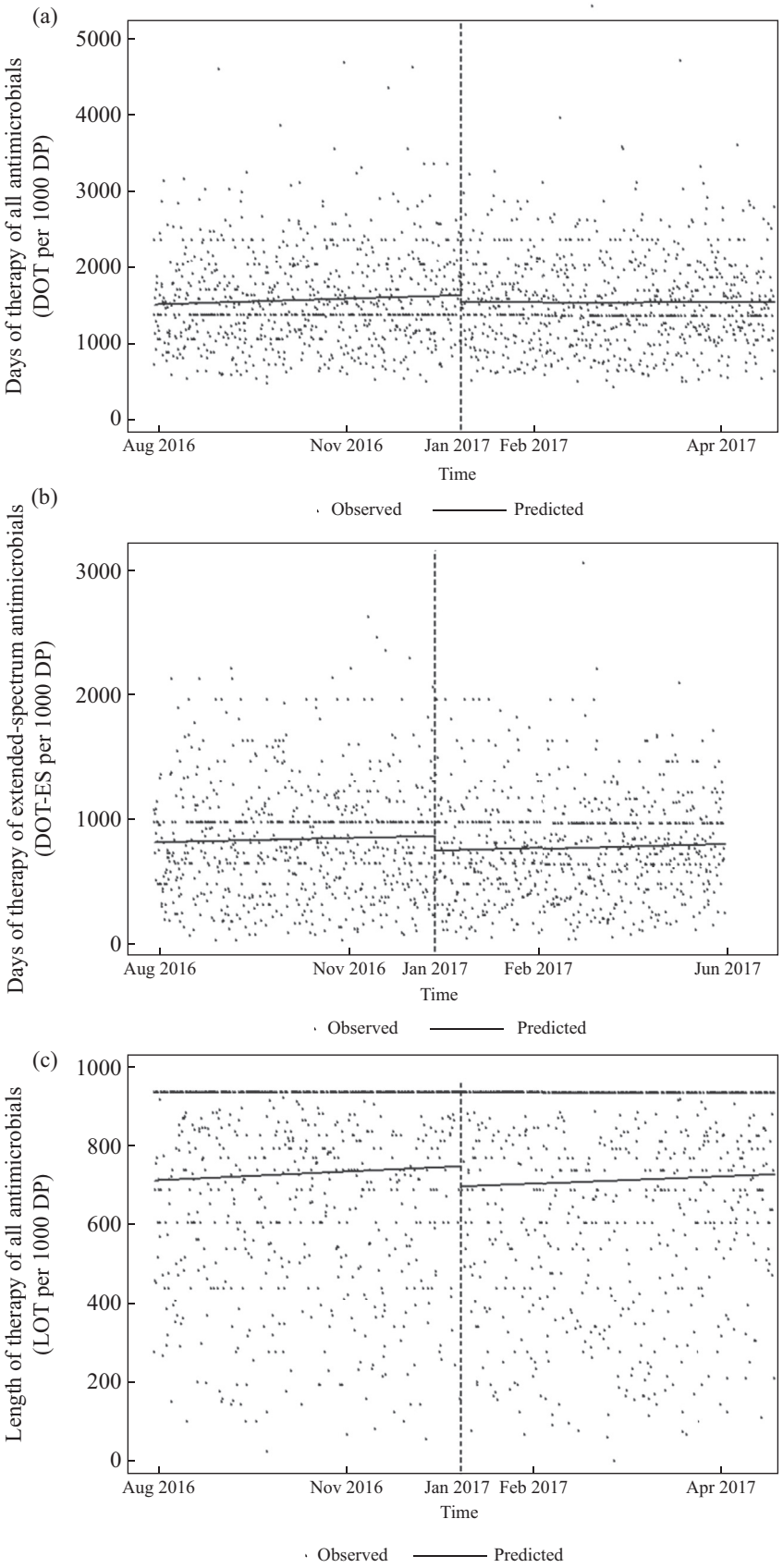

Figure 2. Pre- and post-intervention antimicrobial use metrics for each patient included: (a) days of therapy (DOT); (b) DOT of extended-spectrum antimicrobials (DOT-ES); and (c) length of therapy of all antimicrobials (LOT). Each data point represents the normalized data for 1000 days present for each included patient. Each line represents the trend of the period.

antimicrobial stewardship metrics [15]. While the DOT is the preferred metric to assess antimicrobial use according to the latest ASP guidelines, the DOT-ES and LOT allows a better overview of ASP interventions enabled by the checklist (de-escalation and shorter duration of treatment) than the DOT [3]. The eligibility criteria were inclusive and exclusions were minimal, thus contributing to external validity.

The study has limitations and specific potential biases. Because of time restrictions, it was not possible to adjust for seasonality. As the post-intervention period was during the winter, a season usually associated with higher antimicrobial use, this may have underestimated the effect of our checklist and masked a change in trends. Other antimicrobial interventions implemented during the study periods and their influence on antimicrobial prescribing are hard to mitigate during an ITS of this type. However, to our knowledge, apart from the studied checklist, no major change influencing antimicrobial prescribing practice was observed in our medical centre during the study period. Since ward-based clinical pharmacists were aware of the upcoming implementation of the checklist, they may have improved their assessment of antimicrobial therapy right before its deployment, decreasing the perceived effect of the checklist.

This ITS study is innovative in that, rather than relying on aggregated data, patient-level data were modelled. This allowed measuring predictors and potential confounders individually rather than at group level. The number of pharmacist interventions was found to predict the total number of checklists used over the post-intervention period, indicating that pharmacists' interventions might mediate the checklist effect. However, the date of pharmacist interventions was not recorded, nor was the confounder status measured according to time. Consequently, it was not possible to adjust for time-varying confounding, or time-dependent confounding affected by previous use of the checklist, which are limitations.

This quasi-experimental ITS study allowed evaluation of a hospital pharmacy quality-improvement tool using longitudinal, patient-level data. Implementing an antimicrobial checklist used by ward-based clinical pharmacists was associated with an immediate decrease in the use of extended-spectrum antimicrobials and the length of therapy of all antimicrobials. However, the impact of the checklist might be broader than the studied antimicrobial use endpoints as they were not designed to evaluate appropriateness of antimicrobial therapy, nor was this study designed to detect a potential decrease in infections caused by multi-resistant bacteria. These aspects should be evaluated in further studies. Quality improvement checklists are inexpensive tools, but several barriers can limit their uptake, as evidenced by an adherence rate of 50%. Proactive measures should be taken to address potential barriers to effectiveness of such checklists. This is a worthy goal as use of the antimicrobial checklist seemed to facilitate interventions in this study and might help standardize antimicrobial stewardship activities by the pharmacist.

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Conflict of interest statement
All authors report no conflicts of interest relevant to this article.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhin.2019.06.009.

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