ORIGINAL ARTICLE

Evaluation of Postprescription Review and Feedback as a Method of Promoting Rational Antimicrobial Use: A Multicenter Intervention

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OBJECTIVE. To evaluate the impact of postprescription review of broad-spectrum antimicrobial (study-ABX) agents on rates of antimicrobial use.

DESIGN. Quasi-experimental before-after study.

SETTING. Five academic medical centers.

PATIENTS. Adults receiving at least 48 hours of study-ABX.

METHODS. The baseline, intervention, and follow-up periods were 6 months each in 2 units at each of 5 sites. Adults receiving at least 48 hours of study-ABX entered the cohort as case-patients. During the intervention, infectious-diseases physicians reviewed the cases after 48 hours of study-ABX. The provider was contacted with alternative recommendations if antimicrobial use was considered to be unjustified on the basis of predetermined criteria. Acceptance rates were assessed 48 hours later. The primary outcome measure was days of study-ABX per 1,000 study-patient-days in the baseline and intervention periods.

RESULTS. There were 1,265 patients in the baseline period and 1,163 patients in the intervention period. Study-ABX use decreased significantly during the intervention period at 2 sites: from 574.4 to 533.8 study-ABX days/1,000 patient-days (incidence rate ratio [IRR], 0.93; 95% confidence interval [CI], 0.88–0.97; $P = .002$) at hospital B and from 615.6 to 514.4 study-ABX days/1,000 patient-days (IRR, 0.83; 95% CI, 0.79–0.88; $P < .001$) at hospital D. Both had established antimicrobial stewardship programs (ASP). Study-ABX use increased at 2 sites and stayed the same at 1 site. At all institutions combined, 390 of 1,429 (27.3%) study-ABX courses were assessed as unjustified; recommendations to modify or stop therapy were accepted for 260 (66.7%) of these courses.

CONCLUSIONS. Postprescription review of study-ABX decreased antimicrobial utilization in some of the study hospitals and may be more effective when performed as part of an established ASP.

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Antimicrobial use in acute care settings is common and is estimated to account for at least 20% of hospital pharmacy budgets.[1] Recent single-center studies have shown that one-third of antimicrobial use is inappropriate or suboptimal.[2-5] Investigators have not identified the optimal method of improving antimicrobial use in the acute care hospital. The 2 most common approaches are requiring clinicians to obtain permission before prescribing an antimicrobial, known as preprescription approval, and review of antimicrobial use 48–72 hours after initiation, when additional clinical data are available, coupled with feedback as to whether treatment should be modified or stopped (postprescription review).[1] Several studies have shown the effectiveness of both approaches; however, studies have not assessed these approaches across more than one institution.[4-7]

The objectives of this investigation were to implement postprescription review at 5 academic medical centers and to assess its effect on antimicrobial use. We hypothesized that direct feedback by infectious-diseases physicians regarding all broad-spectrum antimicrobial agents over a 6-month time

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period would lead to a high level of acceptance of recommendations and reduce days of broad-spectrum antimicrobial therapy.

METHODS

Setting

Five tertiary care academic hospitals participated in this study: Johns Hopkins Medical Institutions (Baltimore), Hunter Holmes McGuire Veteran Affairs Medical Center (Richmond, VA), Memorial Sloan Kettering Cancer Center (New York), Northwestern University Feinberg School of Medicine (Chicago), and the University of Iowa Hospitals and Clinics (Iowa City). All institutions were members of the Centers for Disease Control and Prevention (CDC) Prevention Epicenters Program at the time the study was performed. The institutional-review boards of the CDC and all participating centers approved the study.

Study Design

The study included a 6-month retrospective baseline period, a 6-month intervention period, and a 6-month follow-up period. The baseline data collection period was either the same 6 calendar months in a year before the year in which the intervention occurred (4 sites; hospitals A, D, and E provided data from the previous calendar year, and hospital B provided data from 3 years earlier) or the 6 months immediately before the intervention period (hospital C). The intervention period began on or about September 1, 2003, or 1–3 months thereafter and at each site lasted for 6 months or until 200 patients were reviewed. The follow-up period was the 6 months immediately after the intervention period. One site was unable to provide data for the follow-up period because the intervention was continued due to hospital policy.

Identification of Study Patients

Each site identified 2 wards that admitted adult medicine or surgery patients; 4 sites identified a medicine ward and a surgery ward, and 1 site identified 2 combined medicine and surgery wards. Patients aged 18 years or older on these wards were eligible for entry into the study if they received specific antimicrobial agents for at least 48 hours. The antimicrobial agents of interest, referred to as study antimicrobials, were fluoroquinolones, β-lactam/β-lactamase inhibitor combinations, third- and fourth-generation cephalosporins, carbapenems, and vancomycin. Patients were entered into the cohort on the day that treatment with the broad-spectrum agents was started, if they met the eligibility criteria. During the intervention period, all case patients were followed prospectively, and if they were still receiving the study antimicrobials at 48 hours, the case was referred to the site investigator for the evaluation described below. If the 48-hour time point fell on a weekend or holiday, the case was reviewed on the next business day. Patients could receive more than 1 review if they subsequently started receiving a new agent of interest that was not recommended as part of the study intervention. Patients who were eligible to receive an intervention but did not were included in the intervention cohort.

Evaluation and Classification of Antimicrobial Use during the Intervention Period

Medical records of case patients were reviewed to determine whether usage of the antimicrobial agents of interest was indicated. A standardized data collection form was used to classify reasons for justified or unjustified antimicrobial use both before and after the prescriber was contacted. Unjustified antimicrobial use was divided into two categories: cases in which antimicrobial therapy had to be changed and cases in which it had to be stopped. Examples of the former included having an organism that was not susceptible to the current regimen, existence of a more appropriate regimen based on clinical and/or microbiologic data, unnecessary intravenous therapy, and therapy with agents with overlapping spectra of activity. Examples of the latter included a lack of further need for antimicrobial therapy, given a lack of evidence for infection, and inappropriate surgical prophylaxis.

If, after initial review of medical records, antimicrobial use was deemed unjustified, an infectious-diseases physician investigator contacted the healthcare provider (usually a resident caring for the patient) to discuss the case. If the healthcare provider did not have additional information to justify the use of the agent, the investigator recommended either stopping use of the agent or modifying therapy. The primary team decided whether to make the change. Investigators recorded their recommendations, and research assistants reviewed the patient's pharmacy records from the subsequent 48 hours to determine whether the clinicians had implemented the recommendations. Before initiation of the interventions, all study investigators participated in an educational teleconference during which mock cases of justified and unjustified antimicrobial use were adjudicated, to ensure that the investigators' identification of cases and antimicrobial recommendations were consistent. In addition, new issues regarding case adjudication were discussed and resolved in weekly conference calls during the study.

Status of Antimicrobial Stewardship during the Study Periods

The intervention was overlaid on whatever stewardship activities were present in the study institutions. Two of the study institutions, hospitals B and D, had established (more than 2 years old) antimicrobial stewardship programs with dedicated physician and pharmacist time. One institution, hospital C, had a new program with dedicated physician and pharmacist time, and 2 institutions did not have programs. None of the programs was performing comprehensive post-

TABLE 1. Rate of Study and Total Antimicrobial (ABX) Use and Incidence Rate Ratios (IRR) in Each Study Period

	Hospital A	Hospital B[a]	Hospital C	Hospital D	Hospital E
ABX-days/1,000 patient-days					
Study ABX					
Baseline	419.56	574.37	509.03	615.59	519.85
Intervention	469.62	533.84	497.28	512.62	596.07
Follow-up	446.33	...	476.67	602.72	642.47
Total ABX					
Baseline	395.63	548.02	474.07	522.25	473.46
Intervention	443.30	484.01	460.80	421.42	560.87
Follow-up	397.36	...	425.20	500.57	605.77
IRR (95% CI)					
Study ABX					
Intervention vs baseline	1.12 (1.05–1.19)	0.93 (0.88–0.98)	0.98 (0.91–1.04)	0.83 (0.79–0.88)	1.14 (1.08–1.22)
Intervention vs follow-up	0.95 (0.89–1.01)	...	0.96 (0.90–1.02)	1.18 (1.12–1.24)	1.08 (1.01–1.15)
Total ABX					
Intervention vs baseline	1.12 (1.06–1.18)	0.88 (0.85–0.92)	0.97 (0.92–1.03)	0.81 (0.77–0.84)	1.18 (1.13–1.25)
Intervention vs follow-up	0.90 (0.85–0.95)	...	0.92 (0.87–0.97)	1.19 (1.14–1.24)	1.08 (1.03–1.13)

NOTE. CI, confidence interval.

[a] Hospital B lacks follow-up data because the intervention was continued as hospital policy.

prescription review during the baseline study period on the study units, although all institutions except hospital A performed some postprescription review and feedback for some antimicrobial agents in the hospital. All hospitals had preprescription approval for some antimicrobial agents (range, 2–18 agents), with infectious-diseases fellows or pharmacists assessing requests in most institutions. Hospitals B and D required preprescription approval for the highest number of agents (10 and 18, respectively).

Outcome Measures

The primary outcome measure of the study was days of therapy with the study antimicrobials per 1,000 study-patient-days in the baseline and intervention periods. A day of therapy was defined as any day on which a patient received 1 or more doses of an antimicrobial. Patients with renal dysfunction who were treated with vancomycin were considered to have had a day of vancomycin therapy if they had therapeutic levels even without receiving a dose on that day. Study-patient-days included the day on which therapy with the agent of interest was started through the last day of therapy or until discharge. Days of therapy after discharge were not included. Other study outcomes included comparisons of total antimicrobial use in the baseline and intervention periods and comparisons of study and total antimicrobial use in the follow-up and intervention periods. All outcomes related to rates of antimicrobial use are stratified by institution; a combined rate is not presented because of the differences seen between institutions. Other measures evaluated included the intervention rate, defined as the number of courses of therapy in which a modification was recommended divided by the total number of courses reviewed, and the acceptance rate, defined as the number of recommendations accepted divided by the total number of recommendations made.

Collection of Other Study Variables

The All Patient Refined Diagnosis Related Groups (APR-DRG) complexity level (0 [least complex]–4 [most complex]) was calculated for all patients who entered the study cohort, to estimate their severity of illness. Data regarding all antimicrobials (excluding antifungal agents) received in addition to the study antimicrobials were recorded for all patients once they entered the cohort.

Statistical Analysis

Statistical analyses were performed with STATA software (ver 9; StataCorp). Rates of antimicrobial use during different periods were compared using crude incidence rate ratios (IRR). All statistical tests were 2-tailed; $P \leq .05$ was considered significant.

RESULTS

Study Population

In the baseline period, 1,265 patients were enrolled; 1,163 patients were enrolled in the intervention period and 975 in the follow-up period. One institution, hospital B, did not contribute patients to the follow-up period. At institutions without combined medical/surgical units, more medical patients than surgical patients were evaluated in each period (baseline, 582 vs 320; intervention, 547 vs 310; follow-up, 587 vs 384). All sites had median APR-DRG complexity levels of 2 or 3. There were small differences in mean age and

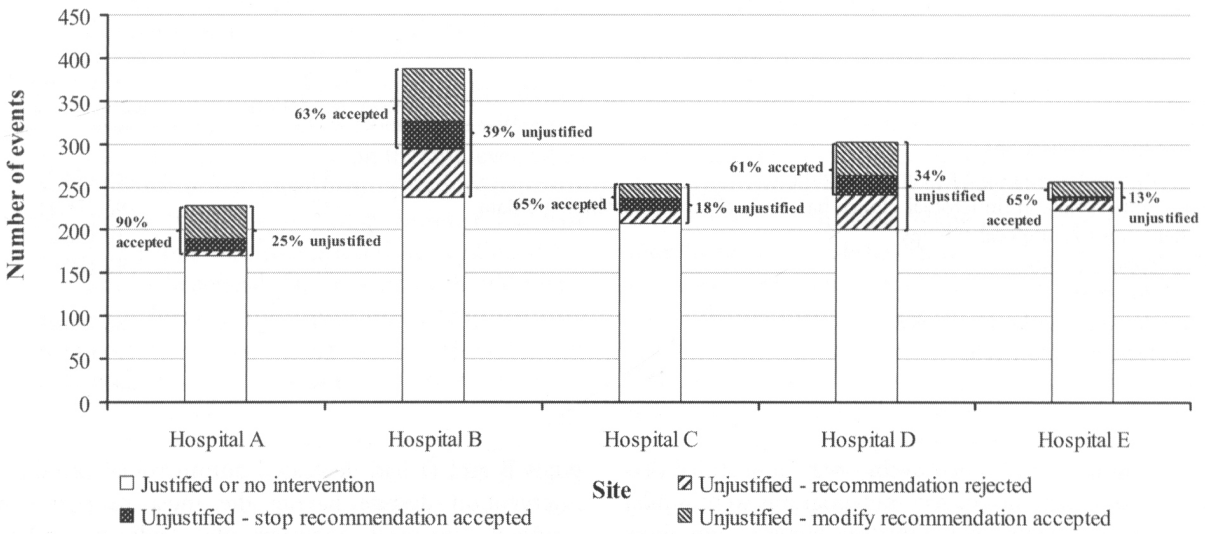

FIGURE 1. Acceptance of recommendations regarding unjustified study antimicrobial use in 5 teaching hospitals.

median APR-DRG complexity level among the sites but not within the sites from period to period (data not shown).

Study and Total Antimicrobial Use

The effect of postprescription review and feedback on study antimicrobial use differed across institutions (Table 1). Study antimicrobial use decreased significantly in 2 institutions, hospitals B and D. Use of study drugs decreased from 574.4 study-antimicrobial-days/1,000 patient-days in the baseline period to 533.8 study-antimicrobial-days/1,000 patient-days in the intervention period (IRR, 0.93; 95% confidence interval [CI], 0.88–0.97; $P = .002$) at hospital B and from 615.6 study-antimicrobial-days/1,000 patient-days in the baseline period to 512.6 study-antimicrobial-days/1,000 patient-days in the intervention period (IRR, 0.83; 95% CI, 0.79–0.88; $P < .001$) at hospital D. Use of study antimicrobials at hospital C decreased from 509.0 study-antimicrobial-days/1,000 patient-days at baseline to 497.3 study-antimicrobial-days/1,000 patient days during the intervention (IRR, 0.99; 95% CI, 0.93–1.06; $P = .38$). In contrast, use of study antimicrobials increased significantly during the intervention period at hospitals A and E: from 419.6 study-antimicrobial-days/1,000 patient-days in the baseline period to 469.6 study-antimicrobial-days/1,000 patient-days during the intervention period (IRR, 1.11; 95% CI, 1.05–1.19; $P < .001$) at hospital A and from 519.8 study-antimicrobial-days/1,000 patient-days in the baseline period to 596.1 study-antimicrobial-days/1,000 patient-days in the intervention period (IRR, 1.15; 95% CI, 1.08–1.22; $P < .001$) at hospital E. Similar trends were seen for total antimicrobial use across the institutions. Use of study antimicrobial agents did not decrease significantly during the follow-up period in the 4 hospitals that submitted follow-up data.

Unjustified Antimicrobial Use and Rates of Acceptance of Recommendations

During the intervention period, 1,429 courses of antimicrobials in 1,163 patients were evaluated at all institutions; of these, 533 were believed, on the basis of medical-record review, to be potentially unjustified and thus eligible for intervention. This evaluation led to 480 conversations with healthcare teams, and recommendations to stop or alter antimicrobial therapy were made for 390 of the 1,429 courses (27.3%). Recommendations were accepted in 260 of these 390 episodes (66.7%). For 53 of the 533 potentially unjustified courses (9.9%), potential interventions did not occur because the team could not be reached or the investigator did not place a call. The percentage of study antimicrobial courses that were considered unjustified varied by institution, ranging from 13% to 39% (Figure 1). The percentage of recommendations that were accepted at 48 hours was similar at 4 institutions, but 1 site had a higher acceptance rate (hospital A, 89.7%).

The most common reasons for unjustified antimicrobial use were unnecessarily continuing therapy in the absence of evidence of infection (109 courses of therapy) and continuation of therapy with broad-spectrum agents after new clinical and/or microbiological data suggested that the spectrum could be narrowed (122 courses; Table 2). Acceptance rates were higher when the recommendation involved modifying therapy (75.8%) than when the recommendation involved stopping therapy (53.5%). At all sites, there were both more recommendations involving modifying study antimicrobials and more acceptances of these recommendations.

Approximately one-third of the courses of the 3 most commonly used antimicrobials—fluoroquinolones, β-lactam/β-

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TABLE 2. Reasons for Recommending Modifying or Stopping Antimicrobial Therapy and Acceptance Rates

Reason	All hospitals	
	No. of recommendations	No. of recommendations accepted (%)
Reasons for modifications		
Organism not susceptible to current regimen	33	26 (78.8)
More appropriate antimicrobial choice based on clinical/microbiologic data	122	93 (76.2)
Patient can tolerate oral therapy	19	10 (52.6)
Overlapping agents	57	46 (80.7)
Reasons for stops		
Antimicrobials no longer needed	109	66 (60.9)
Inappropriate prophylaxis	50	19 (38.0)
Total	390	260 (66.7)

lactamase inhibitors, and vancomycin—were unjustified (Table 3). Rates of acceptance of recommendations were similar for all study agents—β-lactam/β-lactamase inhibitors (63.3%), third- or fourth-generation cephalosporins (65.5%), fluoroquinolones (66.9%), and vancomycin (72.7%).

DISCUSSION

This investigation demonstrates that postprescription review and feedback can reduce broad-spectrum and total antimicrobial use, although its efficacy varies by institution. It is of interest that the 2 sites in our investigation that had established antimicrobial stewardship programs, in which the institution endorsed a program and invested resources, including money for pharmacists' and physicians' salaries, decreased antimicrobial use significantly during the intervention periods, whereas the institutions without such resources did not. This finding suggests that at least at academic centers, such as those included in this study, institutional support and endorsement may facilitate the success of postprescription review and feedback programs that target reduced antimicrobial use. Although the acceptance rates for recommendations at these 2 institutions were not higher than those at the other institutions, the numbers of cases identified for intervention were higher, and this more frequent contact with the providers may have contributed to the reduction in antimicrobial use by encouraging regular evaluation. Of note is that hospitals B and D had decreased antimicrobial use during the intervention despite having the most restrictive preprescription approval requirements, indicating that preprescription approval alone may not optimize antimicrobial use.

The finding that decreased antimicrobial use did not reach statistical significance during the intervention period at hospital C, which had a new stewardship program, might support the common belief that changing overall antimicrobial use in a hospital is likely to take several months as more prescribers "buy into" the process. Hospitals A and E experienced increases in antimicrobial use during the intervention period. As the baseline period for these sites was a year earlier and antimicrobial use has trended upward in academic centers over the past decade,[8] this finding likely reflects the natural course of antimicrobial use at these sites rather than suggesting that the intervention led to increased antimicrobial consumption.

In addition, the absence of a significant decrease in antimicrobial use may also relate to the fact that the majority of recommendations made and accepted in the study were to modify rather than to stop therapy. While these recommendations may improve patient care, they may not result in overall decreased antimicrobial use, because the duration of therapy may not be reduced. Thus, one must consider carefully what outcomes to measure and how to measure them

TABLE 3. Unjustified Use and Acceptance of Recommendations by Antimicrobial Classification

Antimicrobial class	No. of courses of treatment[a]	No. of unjustified episodes (%)	No. of recommendations accepted (%)
β-lactam/β-lactamase inhibitor	430	150 (34.9)	95 (63.3)
Carbapenem	40	7 (17.5)	5 (71.4)
Third- or fourth-generation cephalosporin	151	29 (19.2)	19 (65.5)
Fluoroquinolone	447	127 (28.4)	85 (66.9)
Vancomycin	218	77 (35.3)	56 (72.7)
Total	1,286	390 (30.3)	260 (66.7)

[a] Excludes 53 courses in which no call was made or the team could not be reached and 90 courses in which no change was recommended by the investigator after discussion with the team.

when demonstrating a stewardship program's value to an institution and when assessing the efficacy of different stewardship approaches.

The apparent reluctance to stop rather than modify therapy reflects the discomfort that some prescribers have with stopping therapy if a patient has improved on therapy, even when an infectious etiology is not identified.[9] This problem may be compounded by the perception that antimicrobials are rarely harmful and thus that they should be continued because they might be beneficial. Future studies should investigate methods for helping prescribers understand the risks of unnecessary antimicrobial treatment and should assess whether changing prescribers' perceptions decreases unjustified use of antimicrobials.

The effect of the intervention was not sustained during the follow-up period, when the prescribers were no longer contacted by the investigators. There are at least 2 possible reasons for this observation. First, investigators interacted with numerous prescribers about numerous patients with unique, complex medical problems. Second, in academic settings, prescribers are often housestaff and fellows who rotate on many services, making education about appropriate antimicrobial choices challenging. Thus, the intervention probably did not create a cadre of educated prescribers who could continue to improve antimicrobial use in the absence of an active intervention. Rather, the results of our study suggest that at least in academic settings, ongoing postprescription review and follow-up are needed to continuously improve antimicrobial prescribing.

The percentage of unjustified antimicrobial use seen in this investigation was similar to those reported in other studies.[2-5] However, the proportion of courses that were unjustified varied significantly by institution, despite the fact that investigators used a specific set of criteria to judge whether antimicrobial use was justified or unjustified and despite the fact that all of the investigators were trained to assess whether antimicrobial use was justified. This finding may have important implications for efforts to compare antimicrobial use and appropriateness of antimicrobial use among multiple institutions or across a country. In particular, we must first determine whether definitions of "justified" or "appropriate" antimicrobial use can be applied reproducibly on a large scale.

This study has several important limitations. First, undetected changes in patient populations between the baseline, intervention, and follow-up periods could have affected antimicrobial use. Although we were unable to collect patient-level data during the 3 study periods to assess changes in comorbidities and illness severity more accurately, the percentages of patients at each institution who were in different APR-DRG complexity levels were similar during each time period, as were the median complexity scores, suggesting that the severity of illness of patients at each institution remained stable over the study period.

Second, antimicrobial use is seasonal and increases in the winter with the increased incidence of respiratory viruses.[10] We attempted to mitigate this effect by including a surgical unit at each of the 4 sites that had separate medical and surgical units, because we believed that the impact of respiratory viruses on antimicrobial use would be lower in these units than in medical units. In addition, we obtained baseline data from similar months in preceding years at 4 of the 5 sites. Of note is that the follow-up periods did not include months in which substantial respiratory virus activity would be expected; however, study antimicrobial use did not decrease during these periods.

Third, some patients who were eligible to receive the intervention did not because the investigator was not available to call the clinicians or the investigator could not reach any of the treating clinicians. Missed opportunities for interventions may have decreased our ability to detect a significant effect of postprescription review and feedback at some sites. However, even the most established antimicrobial stewardship programs cannot intervene every time an intervention is warranted. Thus, this weakness reflects what is possible under nonstudy circumstances.

Fourth, the study was performed in 2003–2004, and antimicrobial prescribing may have improved since that time, making postprescription review and feedback less necessary in 2011. However, recent studies have not found that prescribing has improved significantly in the intervening years.[3,5] Moreover, the Centers for Medicare and Medicaid Services and the Joint Commission have not required hospitals to implement antimicrobial stewardship quality measures and to report their results publicly as a means to improve antimicrobial use.

To date, the majority of investigations assessing the utility of antimicrobial stewardship interventions have been performed at single institutions, thus limiting their generalizability to other institutions or settings. Our investigation represents the first attempt to assess the utility of postprescription review and feedback implemented with a standardized approach across several academic medical centers. Our results suggest that postprescription review and feedback can be an effective approach to reduce unjustified antimicrobial use, although the robustness of the existing antimicrobial stewardship infrastructure at an institution may enhance the effectiveness of a broad postprescription review and feedback program in reducing overall antimicrobial use. The lack of reduction of antimicrobial use at 3 of the 5 institutions involved in the study should not be viewed as evidence that antimicrobial stewardship programs are not valuable; unjustified use was detected and intervened on, with acceptance of the majority of recommendations, at all of these sites. However, it may suggest that very broad interventions—for example, assessment and intervention on multiple broad-spectrum agents with multiple potential indications—may not be the best target for stewardship programs that are just getting started if their goal is to show a reduction in anti-

microbial use. Further investigation is required to determine whether more-focused interventions, such as initiatives to decrease antimicrobial use and duration of therapy for patients on specific agents or with specific infections, such as community-acquired pneumonia or urinary-tract infections, may be more likely to reduce antimicrobial use across institutions reproducibly.

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