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A Multifaceted Intervention Improves Prescribing for Acute Respiratory Infection for Adults and Children in Emergency Department and Urgent Care Settings

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Abstract

Background: Antibiotics are commonly prescribed during emergency department (ED) and urgent care center (UCC) visits for viral acute respiratory infection (ARI). We evaluate the comparative effectiveness of an antibiotic stewardship intervention adapted for acute care ambulatory settings (adapted intervention) to a stewardship intervention that additionally incorporates behavioral nudges (enhanced intervention) in reducing inappropriate prescriptions.

Methods: Pragmatic, cluster randomized clinical trial conducted in three academic health systems comprising five adult and pediatric EDs and four UCCs. Randomization of the nine sites

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Author Contributions: LM, KY, DM, RDM, JD, and AS conceived the study, designed the trial, and obtained research funding. LM, KY, RDM and KFD supervised the conduct of the trial and data collection. LM, KY, RDM, RJF, DM and SG undertook recruitment of participating centers and providers and managed the data, including quality control. DM, RJF and JD provided statistical advice on study design and analyzed the data. KY and LM drafted the manuscript, and all authors contributed substantially to its revision. KY takes responsibility for the paper as a whole.

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was stratified by health system; all providers at each site either received the adapted or enhanced intervention. The main outcome was the proportion of antibiotic inappropriate ARI diagnosis visits that received an outpatient antibiotic prescription by individual providers. We estimated a hierarchical mixed effects logistic regression model comparing visits during the influenza season for 2016–2017 (baseline) and 2017–2018 (intervention).

Results: There were 44,820 ARI visits among 292 providers across all nine cluster sites. Antibiotic prescribing for ARI visits dropped from 6.2% (95% CI: 4.5 – 7.9%) to 2.4% (95% CI:1.3 – 3.4%) during the study period. We found a significant reduction in inappropriate prescribing after adjusting for health-system and provider-level effects from 2.2% (95% CI: 1.0 – 3.4%) to 1.5% (95% CI: 0.7 – 2.3%) with an odds ratio of 0.67 (95% CI: 0.54 – 0.82). Difference-in-differences between the two interventions was not significantly different.

Conclusion: Implementation of antibiotic stewardship for ARI is feasible and effective in the ED and UCC settings. More intensive behavioral nudging methods were not more effective in high-performance settings.

INTRODUCTION

Inappropriate use of antibiotics exposes patients to the risk of opportunistic infections and other adverse drug events. It also is an accelerant to the natural selection of antibiotic-resistant bacteria, which kill an estimated 23,000 Americans every year.[1] Encouraging judicious prescribing of antibiotics in emergency departments (EDs) and urgent care centers (UCCs) is necessary in addressing the crisis of emerging antibiotic resistance. Each year 10 million antibiotic prescriptions are written from EDs alone;[2] approximately 5 million of these prescriptions are inappropriate.[3,4] Given strong evidence, well-established guidelines, and national calls to address antibiotic resistance, strategies are needed to reduce inappropriate antibiotic use in ED and UCC settings.

Despite emergency departments and urgent care centers being recognized as important sites for antibiotic stewardship, these programs have had limited success in these settings. Providers in ED and UCC settings are faced with challenges to rational decision-making in their day to day practice such as frequent interruptions,[5] the need to see high volumes of patients per hour,[6] boarding and overcrowding,[7] the need to make rapid decisions with limited diagnostic data,[8] frequent handoffs between providers, and concerns with patient satisfaction scores.[9] Emergency department and UCC providers understand the problem of antibiotic resistance, but this has not led to practice change.[10,11]

Considerable evidence from economic theory and research in other clinical areas suggests that adding a package of feedback, nudges, and peer comparisons could dramatically improve prescribing outcomes. Our investigative team previously showed that relatively simple interventions, grounded in behavioral economics and decision science, that leverage accountability and social norms, can reduce unnecessary antibiotic prescribing for ARI in primary care practices.[12,13] Peer comparisons dramatically improve prescribing outcomes in outpatient clinics and doctor's offices, and are sustained for at least 12 months after interventions end.[14] Interventions inspired by these "nudges" tailored to the acute ambulatory care workflow have potential to overcome barriers and promote stewardship for ARIs in emergency departments and urgent care settings.

METHODS

This study compared two interventions. The adapted intervention consisted of education for patients and providers using materials from CDC's Get Smart (currently called Be Antibiotics Aware) campaign adapted for the acute care setting, led by a physician champion at each site. The adapted intervention was compared with the enhanced intervention, which was an intensive intervention that incorporated the adapted Get Smart campaign, in addition to individualized audit and feedback, peer comparisons, and nudges. Our hypothesis was that both interventions would reduce inappropriate antibiotic prescribing for antibiotic nonresponsive ARIs by individual providers in EDs and UCCs, but that the enhanced intervention would be more effective.

Study design, setting, and population

Study Design: This study was a pragmatic cluster randomized clinical trial of providers at nine ED and UCCs across three academic medical centers in two states. The clinical trial was registered on Clinicaltrials.gov, NCT03022929. The study was approved by the Institutional Review Boards of the University of California (UC) Davis, Harbor-University of California Los Angeles (UCLA) Medical Center, Children's Hospital Colorado (CHCO) and the University of Southern California.

Setting: Our study included five EDs (UC Davis adult and pediatric ED, Harbor-UCLA adult and pediatric ED, and three CHCO pediatric EDs), and four UCCs (Harbor-UCLA adult UCC and three CHCO pediatric UCCs). We block randomized sites by medical system in a two-arm design to receive one of two interventions.

University of California-Davis (1 site): Quaternary care center level I Emergency Department with approximately 65,000 adult and 20,000 pediatric visits per year seeing a mix of urban and rural populations.

Harbor-UCLA Medical Center (2 sites): Level I trauma center and pediatric critical care center with 65,000 adult ED visits, 24,000 pediatric ED visits, and 11,000 adult urgent care center visits.

Children's Hospital Colorado (6 sites): CHCO is comprised of an urban, pediatric tertiary-care ED that is the region's only Pediatric Trauma Center, with 2 satellite EDs and 3 satellite UCCs. Across all ED and UCC sites, CHCO receives 170,000 pediatric visits each year.

Study Population: Sites were staffed by general emergency physicians, pediatric emergency physicians, advanced care practitioners, internists, and pediatricians. These providers treat a diverse patient population including the underserved (e.g. minorities, rural, elderly, those with poor access to care). All prescribing providers from the UC Davis and Harbor-UCLA adult and pediatric EDs, the Harbor-UCLA adult urgent care clinic, and

CHCO pediatric EDs and urgent care centers were approached for consent to participate after sites were randomized to study arm.

Study Protocol

Inclusion Criteria: Any licensed clinician at a participating site was eligible to participate as long as he or she was not a resident physician – fellows were eligible if they were practicing as attending physicians at a participating site.

Each study site has an electronic health record (EHR) system in place and its own physical space (as opposed to multiple clinics sharing the same space, such as the floor of a hospital, where interactions between providers assigned to different intervention groups would be more likely).

Eligible ED and UCC visits included those with diagnoses (primary and secondary) from the *International Classification of Diseases, Tenth Revision* (ICD-10-CM) codes consistent with antibiotic-nonresponsive ARI diagnoses with consideration of secondary diagnostic codes as modifiers (see Exclusion Criteria). The conditions targeted for reducing antibiotic prescribing were: nonsuppurative otitis media, H65*; acute nasopharyngitis, J00*; laryngitis, J041*; supraglottitis, J043*; croup, J050*; influenza, J09*/ J10*/ J11*; viral pneumonia, J12*; viral bronchitis J203*/ J204*/ J205*/ J206*/ J207*/ J208*; unspecified bronchitis, J209*; bronchiolitis J21*; lower RTI unspecified, J22*; vasomotor and allergic rhinitis, J30*; chronic nasopharyngitis, J31*; bronchitis NOS J42*; and asthma, J45*. This consensus definition was developed *a priori* by clinician investigators (LM, KY, RM, RF) and is publicly available as the MITIGATE toolkit hosted online by the Society for Academic Emergency Medicine.[15] The parameters for outcome definition were intended to be congruent with existing Healthcare Effectiveness Data and Information Set and National Quality Forum quality metrics on acute bronchitis, but broadened to include all other antibiotic-nonresponsive ARIs as well as pediatric and geriatric populations.

A patient visit was eligible for inclusion in the outcome denominator if: 1) the patient was evaluated by a participating provider at an enrolled practice site, and 2) the visit occurred during the baseline or intervention period. If multiple participating providers were involved in a patient's care, the visit was attributed to the supervising provider (e.g., attending physician rather than resident) and the prescription was also attributed to the discharging provider. We excluded patient encounters of residents with prescribing privileges practicing independently.

Exclusion Criteria: Visits were excluded from the primary analysis if patients had either a non-ARI bacterial infection diagnosis or an antibiotic-appropriate ARI diagnosis that co-occurred with their qualifying diagnosis at the visit. The sets of exclusionary diagnoses which were used to calculate the outcomes are listed in the public MITIGATE toolkit.

Enrollment Procedures: Provider enrollment was documented in writing at the time of consent for the enhanced intervention and opt-out verbal consent was obtained for providers at the adapted intervention sites. Interventions were initiated after all clinicians at a site had been enrolled or declined to participate.

Interventions: We adapted proven antibiotic stewardship approaches to the acute care ambulatory site level setting for our intervention. We first obtained stakeholder and provider feedback to inform adaptation of outpatient stewardship methods and achieve the greatest public health impact on antibiotic use in ED and UCC settings.[16]

Adapted Intervention.: The adapted intervention incorporated strategies from CDC's *Core Elements for Outpatient Antibiotic Stewardship*, including provider and patient education, a physician champion and departmental feedback,[17] using implementation tools found to be feasible in the acute care setting and accepted by local providers. We used existing CDC Get Smart materials appropriate to the ED and UCC settings (as determined with stakeholder input[16]) and adapted brochures and other campaign messages for acute care providers (see Table 1). The physician champion led the educational component.

Enhanced Intervention.: The enhanced intervention used all of the elements of the adapted intervention, and also included peer comparison feedback and locally-tailored public-facing demonstration of commitment to judicious antibiotic prescribing (Table 1). Peer comparison was proposed as an email-based intervention. Peer comparison was distinct from traditional audit-and-feedback interventions, in that individuals were compared to top-performing peers —a strategy shown to sustain performance in prior studies.[14]

Timeline: The comparative effectiveness of the enhanced intervention versus the adapted intervention was evaluated using a multicenter cluster randomized trial. The study interventions ran from July 2017 to February 2018 at UC Davis and Harbor-UCLA and from November 2017 to February 2018 at CHCO with a 12-month baseline period used for statistical analysis.

Randomization: The study used a cluster-randomized design at the site level to avoid contamination that might occur if individual providers within a site are randomized to different interventions (CONSORT diagram, Figure 1, CONSORT checklist, eTable 2). Clinicians who practiced at multiple sites were assigned to the intervention of the clinic for which they spend at least 80% of their time. True random integer sequences were generated using the random.org integer sequence generator for each of CHCO (n = 6), UC Davis (n= 1) and Harbor-UCLA (n=2) strata. Random.org uses atmospheric noise to generate random numbers, which can be better than the pseudo-random number algorithms typically used in computer programs. The greatest one-half of integers in the sequence were allocated to the enhanced intervention; this was independently pre-specified by a study methodologist (JD) prior to randomization. Each site had an ex ante 50% chance of being randomly assigned to the treatment condition.

Pre-implementation assessment: Across all participating sites, providers completed a baseline survey to assess provider characteristics and provider attitudes toward practice guidelines, clinical decision support, electronic health records, and practice environment. Three to six stakeholders at each site (departmental leadership, nursing staff, and providers) participated in pre-intervention interviews and a clinical walkthrough with study personnel. Interviews were audio recorded and transcribed at two sites (Harbor-UCLA and UC Davis) and comprehensive notes collected at CHCO for qualitative analysis of barriers and facilitators. Coupled with semi-structured stakeholder interviews and clinical environment walkthroughs, qualitative analysis using those surveys and interviews was conducted to triangulate adaptation of the stewardship intervention to local context.[18] This mixed methods approach was used to understand how to adapt outpatient antibiotic stewardship intervention components based on site-specific needs.[19]

Project managers at each location collaborated with clinical and operations staff to adapt each of the intervention components to ensure they were consistent with local workflows, policies, and standards. A plan was developed for implementing and monitoring each of the components. Standard operating procedures were refined and shared with staff. Clinician enrollment procedures for electronic and in-person enrollment were developed with clinical champions and departmental leads. Risk analysis was conducted with the monitoring plan to ensure that interventions were delivered with fidelity to the original design and deviations were recorded.

Implementation phase: The adapted and enhanced interventions used the stewardship components as described in Table 1 with two exceptions. Based upon stakeholder and provider feedback, two components of the behaviorally-enhanced intervention were modified during the MITIGATE Trial.

Public commitment: The Centers for Disease Control and Prevention has made available commitment letters to be posted in waiting room or patient care areas. Physician commitment is an evidence-based strategy for antibiotic stewardship in primary care settings. Posters were signed by clinicians to remind both patients and providers of the site's commitment to appropriately prescribe antibiotics. Given the unique challenges of emergency departments and urgent care centers, who are faced with rapid patient turnover, crowding and multiple providers with potentially different levels of training working in shift-based formats, these posters (with or without signatures and/or headshots) were placed in areas that were visible to both patients and clinicians, such as triage areas, provider stations, screening rooms, or fast track exam rooms. Additional physician and advanced care practitioner commitment modes such as signing a commitment log and wearing visible flair (campaign-branded badge reels, buttons) were strategies developed with stakeholder input, allowing for variation of mode of public commitment across sites.

Peer comparison: A monthly mail merge provided individualized audit and feedback reports for peer comparison. These were sent by the local clinical champion at each site. Every provider in the enhanced group was notified if they were a "Top Performer" or "not a Top Performer." Percentiles were computed within each site. Emails included the number and proportion of inappropriate antibiotic prescriptions written for non-antibiotic-appropriate ARI cases and the proportion written by Top Performers. Providers in the lowest decile were sent "Top Performer" letters, all others were sent "Not a Top Performer" letter templates (further detail available in the MITIGATE toolkit[15]).

Visit inclusion and exclusion criteria were based on the same diagnostic codes described in the toolkit. If the provider had more than 20 qualifying ARI encounters in the past 30 days, all these encounters were included in the calculation. Otherwise, the most recent 20 qualifying ARI encounters were included if they occurred in the past 5 months. If fewer than 20 occurred in the past 5 months, only encounters in the past 5 months were included.

Post-implementation assessment: Consented providers at each site completed a survey at the conclusion of the intervention period. Providers were asked about attitudes toward antibiotic use and stewardship programs, knowledge of appropriate antibiotic use after the intervention. Additionally, they were asked about the stewardship intervention, their opinions of the program, specific components of the program, barriers and benefits of the intervention.

Key outcomes and measurements

The primary outcome was defined as the provider-level antibiotic prescribing rate for ARI diagnoses, defined as patient visits with antibiotic-nonresponsive diagnoses without concomitant diagnostic codes to support antibiotic prescribing (see public MITIGATE toolkit for complete list).[15] Only systemic antibiotic prescriptions were included; we excluded topical, otic and ophthalmic preparations, and any medications given in the ED (study protocol, eDocument 1).

Data analysis

Two analytic approaches were performed by a blinded assessor to measure the impact of the MITIGATE trial, which was a cluster randomized comparative effectiveness trial. We used a repeated cross-sectional design in which clustered site and its clinicians were followed up over time with regard to their patient visits, an approach employed in similar pragmatic trials of antibiotic stewardship interventions.[13,20] We analyzed the data using an interrupted time series approach while accounting for provider and site level random and fixed effects using previously published methods.[20]

For inferential analyses of our primary hypotheses of difference-in-differences effectiveness of the enhanced versus adapted interventions, we estimated a hierarchical mixed effects logistic regression model for visits that occurred during the influenza season (from November through February) for 2016–2017 (baseline) and 2017–2018 (intervention). Temporal trends were modeled as a linear spline with a knot on the first date the messages were sent for each site. We controlled for organization (Harbor-UCLA, UC Davis, CHCO), secular temporal trends, and provider fixed effects. This approach, applied in similar primary care and pediatric studies,[20] models prescribing as an interrupted time series, adjusts for trends in antibiotic prescribing in each group with interaction terms representing the difference-in-differences in prescribing trajectories between groups as well as across both groups before and after the intervention.

For CHCO and UC Davis we used data from the institutional electronic data warehouses and the Patient-Centered Outcomes Research Institute Patient-centered Clinical Data Research Network (PCORnet).[21,22] For Harbor-UCLA, we extracted data directly from the EHR (Cerner, Kansas City, MO). All analyses were conducted in Stata 14.0 (StataCorp, College Station, TX).

RESULTS

We demonstrated fidelity, or the degree to which the intervention elements were executed as planned, in adapting the stewardship intervention into acute care ambulatory settings, completing 100% of planned interviews, 52.4% of pre-implementation surveys, 99% collection of public commitment signatures, and 92.6% willingness to display public commitment “flair” (defined as acceptance of Get Smart-branded badge reels and pins as monitoring of flair display was not conducted). All cluster sites participated as allocated, and all providers consented to participate (baseline and intervention period participant numbers varied due to individuals joining or leaving the sites). There were no significant differences between baseline monthly prescribing rates between providers allocated to the enhanced group and those allocated to the adapted groups (Table 2), suggesting randomization successfully distributed interventions across the sample. All nine participating cluster sites and all consenting providers were included in the analysis based upon their assigned intervention arm. No providers at UC Davis or Harbor-UCLA practiced at more than one site, but the site allocation threshold for providers at CHCO sites was lowered from >80% of their time to >50% due to clinical scheduling needs. The trial was ended after all planned data was collected. Demographics of individual providers, or any trainee data, were not collected per IRB stipulations. The unadjusted prescribing rates at the provider level for the combined intervention effects during flu seasons are shown in Table 3.

Over the entire study period, there was an average of 84 visits per provider for antibiotic-inappropriate acute ARI diagnoses. The unadjusted baseline antibiotic prescribing rate for antibiotic-inappropriate ARIs during flu season of 2016–2017 was 4.3% across all sites. Grouped by academic center, all sites at CHCO had a significantly lower baseline prescribing rate (2.1%) than either those at Harbor-UCLA (7.4%) or at UC Davis (5.6%).

Intervention Effectiveness.

The unadjusted monthly inappropriate prescribing rate for each of the three academic centers is shown in Figure 2 on a log scale to allow better visualization of high performing sites. Note that the vertical event lines do not represent the first intervention components occurring at each site — some providers engaged in activities such as interviews and surveys several weeks to months prior (eTable 1). However, no intervention activities were part of the 2016–2017 flu season. After adjusting for provider, seasonal, and institutional fixed effects, there was a significant year-over-year reduction from baseline to intervention period (odds ratio of 0.67 [0.54–0.82]), with an absolute effect size of 0.7% (0.2 – 1.2%).

This decrease was evident across both the enhanced and adapted groups in Figure 2, with the exception of the CHCO sites (light grey dashed lines), which had low prescribing rates throughout. Of note, the only adult UCC included in the study was randomized to the adapted intervention (noted as HAR – Adapted on Figure 2). After accounting for the provider- and organization effects as well as changes and temporal trends impacting all providers, reductions in prescribing between the two interventions favored the enhanced intervention, with an effect size of 1.9% (−0.7 – 4.6%), but this difference-in-differences was not significant (p=0.06). The distribution of both baseline rates and changes were significantly skewed (p<0.001), with the top quartile of providers (high prescribers) accounting for more than 75% of the reduction.

Summary of Survey Responses: As the survey data was exploratory by design, we are not reporting tests of significance for the qualitative data. For the pre-implementation survey, 52.5% (159/303) providers responded (83% attendings and fellows, 17% nurse practitioners and physician assistants). For the post-implementation survey, 39.9% (120/301) providers responded (83.3% attendings and fellows, 16.7% nurse practitioners and physician assistants). The overall contribution to responses by site was 24% UC Davis, 35% Harbor-UCLA, and 42% CHCO.

Self-Reported Prescribing.

Providers generally reported low prescribing rates for themselves except for disease where antibiotics are sometimes indicated (acute sinusitis and acute otitis media). They perceived their colleagues to prescribe more frequently than themselves for acute bronchitis (Figure 3).

Attitudes before and after interventions.

Participants were asked about public health and antibiotic resistance concerns (Figure 4). Both before and after the intervention, almost all participants agreed or strongly endorsed statements that cited (a) resistance as a public health problem; and (b) the assertion that inappropriate antibiotic use contributes to resistance. Sentiments about patient education were more evenly distributed with about half agreeing that education was sufficient both before and after the intervention.

There was also conflicting sentiments regarding acute care antibiotic stewardship programs as a result of the program. More people strongly agreed or agreed that acute care antibiotic stewardship is important after the intervention (Figure 4), but there was more neutral or negative sentiments when responding to a *negative* question “Do you believe that ED and urgent care based antibiotic stewardship programs would interfere with your usual approach to clinical decision-making in treatment of infectious diseases?”

DISCUSSION

The *Core Elements of Outpatient Antibiotic Stewardship* have never been evaluated for effectiveness when implemented as a bundle. This study is the first to do so and shows effectiveness in ED and UC settings. Overall, inappropriate antibiotic prescribing rates during our cluster randomized trial decreased by approximately 33% in our population of academic ED and UCC providers, who treated both children and adults, though the absolute change was a modest 0.7% (0.2 – 1.2%). We did not find any significant difference-in-differences between reductions in unnecessary antibiotic prescribing between our two intervention methods: the stewardship intervention adapted for the acute care ambulatory setting (adapted intervention), and the more resource-intensive intervention that included personalized provider-level feedback (enhanced intervention). Nonetheless, we were able to demonstrate the effectiveness of behavioral and educational interventions in reducing inappropriate antibiotic prescribing in the ED and UCC settings, two settings in great need of antibiotic stewardship program implementation.

Our success in reducing inappropriate antibiotic prescribing even with a relatively low intensity intervention is surprising as standard approaches emphasizing the education of patients and providers have previously demonstrated limited success in outpatient settings. We anticipated that a "one size fits all" approach was not feasible for ED- and urgent care-based implementations, and stewardship strategies should be tailored to these settings. One possible explanation for the success was our use of a specialized implementation science approach, which tailored the antibiotic stewardship program to the local context of each emergency department and urgent care center, and iteratively refined the intervention based upon engagement with local champions and stakeholders.

While a systematic review of audit and feedback on clinician behavior has demonstrated a positive effect,[23] a more recent antibiotic stewardship study that promoted guidelines through quarterly feedback to primary care physicians in Switzerland did not find significant improvement.[24] However, our study differed in that it incorporated social motivation in a positive reinforcement mode (top performer/ not top performer), more frequent monthly email notification, and more robust implementation science methods to adapt the intervention to the local setting. We used an automated mail merge that allowed for more efficient and monthly reporting of feedback, which may have had a more regular and repeated impact on provider performance.

Behavioral nudges, based on insights from economics and psychology, have the advantage of being designed to improve care decisions without limiting the choices available to physicians,[25] a primary reason for failure of other interventions.[26,27,28] They are also scalable and do not require much extra time to improve quality of care.[29] However, despite optimism that efficiency gains of behavioral economics strategies in other settings could be translated to ED and UCC settings, we were not able to show significant impact of the enhanced intervention over the adapted intervention.

The low baseline inappropriate prescribing rate may have limited our ability to detect a difference-in-differences since there was a limit for improvement that could be observed. Post-hoc power analysis revealed we underestimated the intra-provider correlation, or interclass correlation (ICC) (estimated 0.10, observed 0.27), leading to lower power (0.23) to detect a small difference, which we had originally estimated at 5–10% (which was also too large for our unexpectedly low baseline rates) (eDocument 1). The higher-than-expected ICC is likely due to the heterogenous study settings, such that behavior of providers within each site (and the site-based interventions) is more alike than between providers across sites. A lack of difference-in-differences between interventions may also be explained by insights from behavioral science that suggest clinicians may be most motivated to reduce their inappropriate prescribing when they believe it occurs at a very low rate, especially by peers in their own practice setting. Studies show that eliminating risk is more desirable than lowering it from a higher baseline risk in the same measure.[30] Knowing that by changing your prescribing habits you have eliminated the chance your actions will lead to your patient acquiring a *Clostridium difficile* infection or other negative outcome may be a compelling motivator. This suggests a second interpretation of our null difference-in-differences—to the extent all participating clinicians correctly perceived themselves as low rate prescribers, study participants in both treatments may have been motivated to "get to zero." And while "getting to zero" may be a worthy conceptual goal, health systems under pay-for-performance reimbursement programs, like the Public Hospital Redesign and Incentives in Medi-Cal (PRIME) project, are expected to show year-over-year improvements in quality measures like inappropriate antibiotic prescribing for acute bronchitis, and overperformance may allow recovery of unearned funds for other underperforming project metrics.

Our finding of high performance in these three academic settings is not inconsistent with the evidence. High performance settings have inappropriate prescribing rates far lower than 10%, despite reported national averages of 50%.4 The CDC National Hospital Ambulatory Medical Survey (NHAMCS) indicates that 54% of ED patients diagnosed with a URI received an antibiotic. However, only 3% of patients with URIs were seen by resident physicians, suggesting that the vast majority of ED care for these conditions occurs in community EDs. Unfortunately, evidence from pediatric asthma research suggests resource overutilization, lack of guideline adherence, and inappropriate antibiotic use is more common in community, as opposed to academic, EDs.[31] These differences in care occur in spite of the fact that academic settings tend to be in urban areas, serve patients with a higher rate of comorbidities with less access to care, and are more likely to be underserved and medically and socially vulnerable.2,[32] Perhaps the perception that privately insured patients can "take their business elsewhere" and will be more satisfied if they receive antibiotics (despite evidence to the contrary[33]), incentivizes community-based providers to prescribe inappropriately.

More recent data from NHAMCS suggest that while rates of antibiotic prescribing for URI have dropped significantly in pediatric patients, they remain stable (and unacceptably high) in adults.2 While most of our sites being pediatric settings explains most of our baseline high performance, it is worth looking more closely at the adult site performance. The adapted site at Harbor-UCLA was an adult UCC, and the Harbor-UCLA and UC Davis EDs saw both children and adults. While all were performing below nationally reported rates, as Figure 2 demonstrates, a relatively low-intensity stewardship intervention motivated clinicians to reduce inappropriate prescribing even further. When comparing the rate reporting in Table 3 and Figure 2, the apparent discrepancy is because there is one observation per month per provider in the table, which makes it so that the rates of high and low volume providers contribute equally. In Figure 2, plotted lines are smoothed mean daily rates for all patients in each site and arm and do not aggregate provider-level rates. The highest volume providers in each site-arm contribute the most to each line, and it is bringing down these outlier providers that leads to the more dramatic improvements seen in Figure 2. Further subgroup analyses to better understand the heterogeneity of treatment effects were not pre-planned, and would be exploratory in nature.

The detection of a robust effect size is encouragement to seek out low-performing community sites as interventions that produce small absolute effects (e.g., a 5-percentage point reduction) in a high performing ED may have larger absolute effect if carried out in a low performing ED. Moreover, in a high rate inappropriate prescribing environment, one treatment approach may well outperform the other. However, there are challenges to scale and spread of rigorous implementation science methods. While such methods have been shown to enable research teams to operationalize and deliver research-developed interventions in the context of research studies, the artificial circumstances and low external validity of these studies (e.g., use of research funds for additional staff and services, highly specialized mixed methods research expertise, additional technical assistance provided by research teams to local sites and staff, carefully selected sites) reduce generalizability and the likelihood of reproducibility outside of research contexts. Therefore, study of these interventions in community acute care ambulatory settings and improved accessibility of implementation science approaches are critical to have the greatest impact on stewardship.

LIMITATIONS

As this was a comparative effectiveness study without a contemporaneous control, we cannot definitively say that the interventions themselves fulfilled a causal role in reducing inappropriate antibiotic prescribing, though the natural trends in Figure 2 suggest they did. Moreover, we did not have a safety endpoint such that we could measure an unintended harm of return visits for pneumonia or other illness progression, though recent empirical evidence suggests this is unlikely.[12,13] There is also limited generalizability since all sites were affiliated with academic health centers located in only two states. Moreover, the study is limited by the use of consensus-defined ICD-10 diagnosis code sets to define included and excluded visits. It is possible that as providers became aware their behavior was being watched, they altered their diagnosis coding behavior to justify their antibiotic prescribing behavior (e.g., coding a visit as pneumonia or an exacerbation of chronic bronchitis rather than an upper respiratory infection). A corollary to that awareness by providers is the potential for a Hawthorne Effect at all sites, whereby all sites improved performance not because of effect of either intervention, but simply because they knew their performance was under scrutiny. Not all of the outcome effect can be attributed to this package of interventions, as we did identify other antibiotic stewardship initiatives that were ongoing in some of the departments (UC Davis had an skin and soft tissue infection antibiotic stewardship program in the ED that predated this study, and Harbor-UCLA had pediatric ED case-based antibiotic stewardship rounds during the spring and summer of 2017 between the baseline and intervention study periods).

There may also have been limited ability to detect a difference-in-differences between the two interventions due to contamination of the CHCO sites due to provider overlap between sites. In total, at CHCO, 83 (50.9%) providers worked at both sites assigned to the adapted and enhanced intervention. Of these providers, 52 were assigned to the adapted intervention, and 31 to the enhanced intervention. Only 38 (45.8%) of the 83 overlapping providers worked at least 80% of their shifts at sites within their allocated treatment arm. A total of 25 (48.1%) of the 52 assigned to the adapted intervention arm spent at least 80% of their time at sites randomized to the adapted arm. For the enhanced arm, 13 (41.9%) of 31 providers spent least 80% within their assigned sites. Coupled with the low baseline rate of antibiotic prescribing, we may have lacked sufficient power to demonstrate a difference-in-differences.

Lastly, improvement may not have been possible to reach zero because responses may cluster around a "floor" rate of inappropriate prescribing if unmeasured factors at a small number of visits are not identified as exclusions (including the possibility of trainees prescribing antibiotics in lower acuity patients prior to the attending of record finalizing the visit record). Alternatively, interventions may reach a certain "ceiling" in the type of visits at which they can affect prescribing. In the first case, a low but positive rate of inappropriate prescribing reflects a "logical zero", beyond which no lower score is possible.[34] In the second case, overcoming residual inappropriate prescribing is impossible. Yet, these concerns are theoretical. That we did find a robust effect size is a strong justification for addressing prescribing with either intervention in acute care settings that have a low inappropriate prescribing rate.

CONCLUSIONS

Antibiotic stewardship programs using behavioral approaches can be feasibly developed and implemented in the ED and UCC settings. Overall performance improvements are still needed in systems with both high-and low-performers as institutions strive towards optimum quality in antibiotic prescribing for their acute ambulatory care patients. Our study demonstrates that getting to zero inappropriate antibiotic use for acute respiratory infections is a potentially achievable goal, and for those institutions with average or high inappropriate prescribing rates, antibiotic overuse can potentially be cut by a third with attention to the problem.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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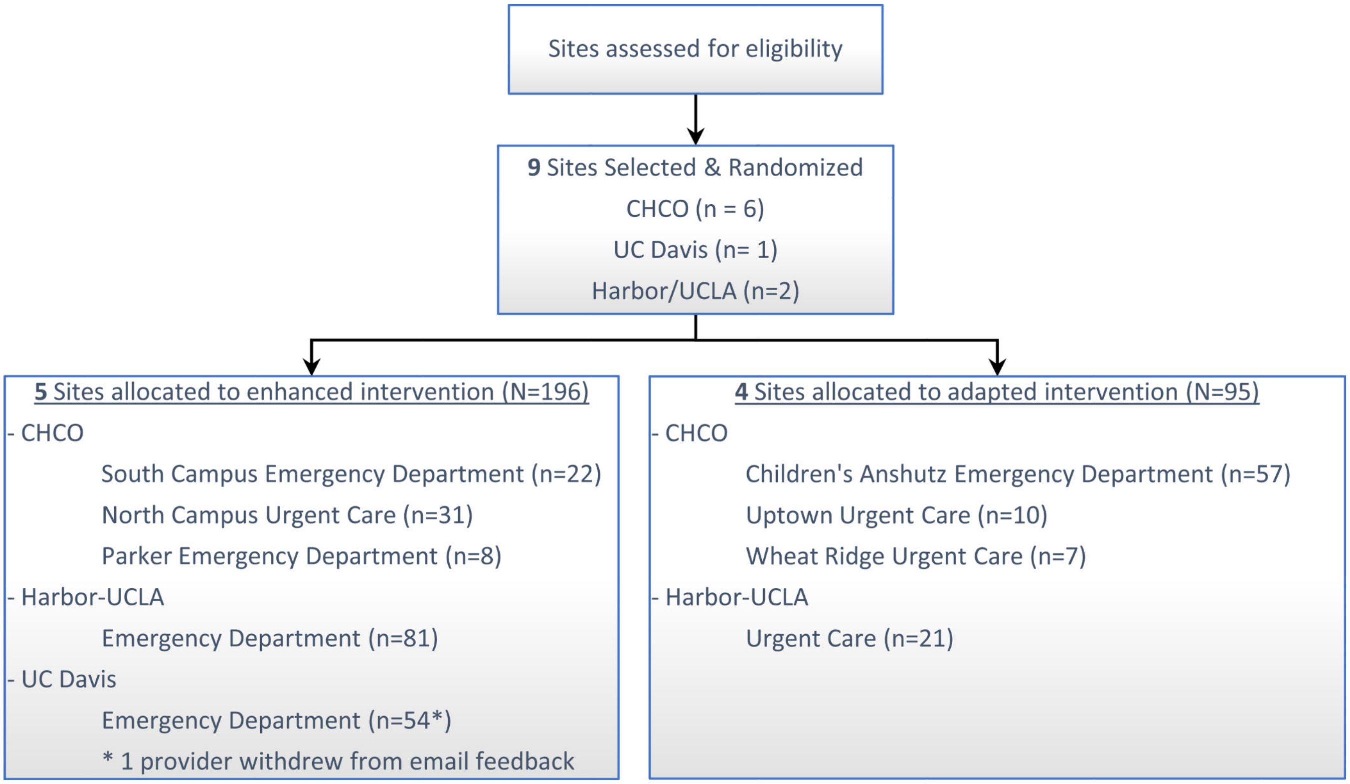

Figure 1.
CONSORT Diagram

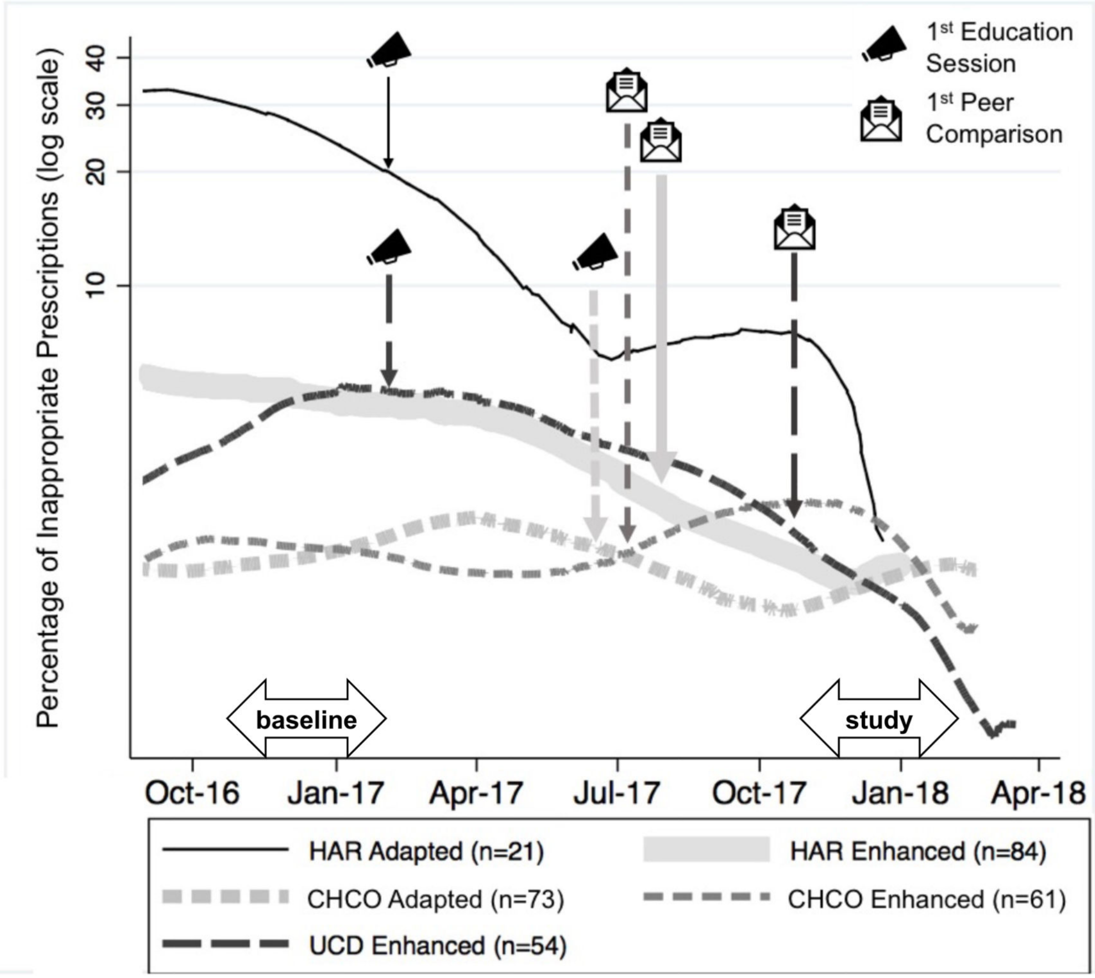

Figure 2.
Ungrouped antibiotic prescribing rate for antibiotic-inappropriate ARIs, averaged by provider, over time for the three academic centers. ARI = acute respiratory infection; CHCO = Children's Hospital Colorado; UCD = University of California–Davis.

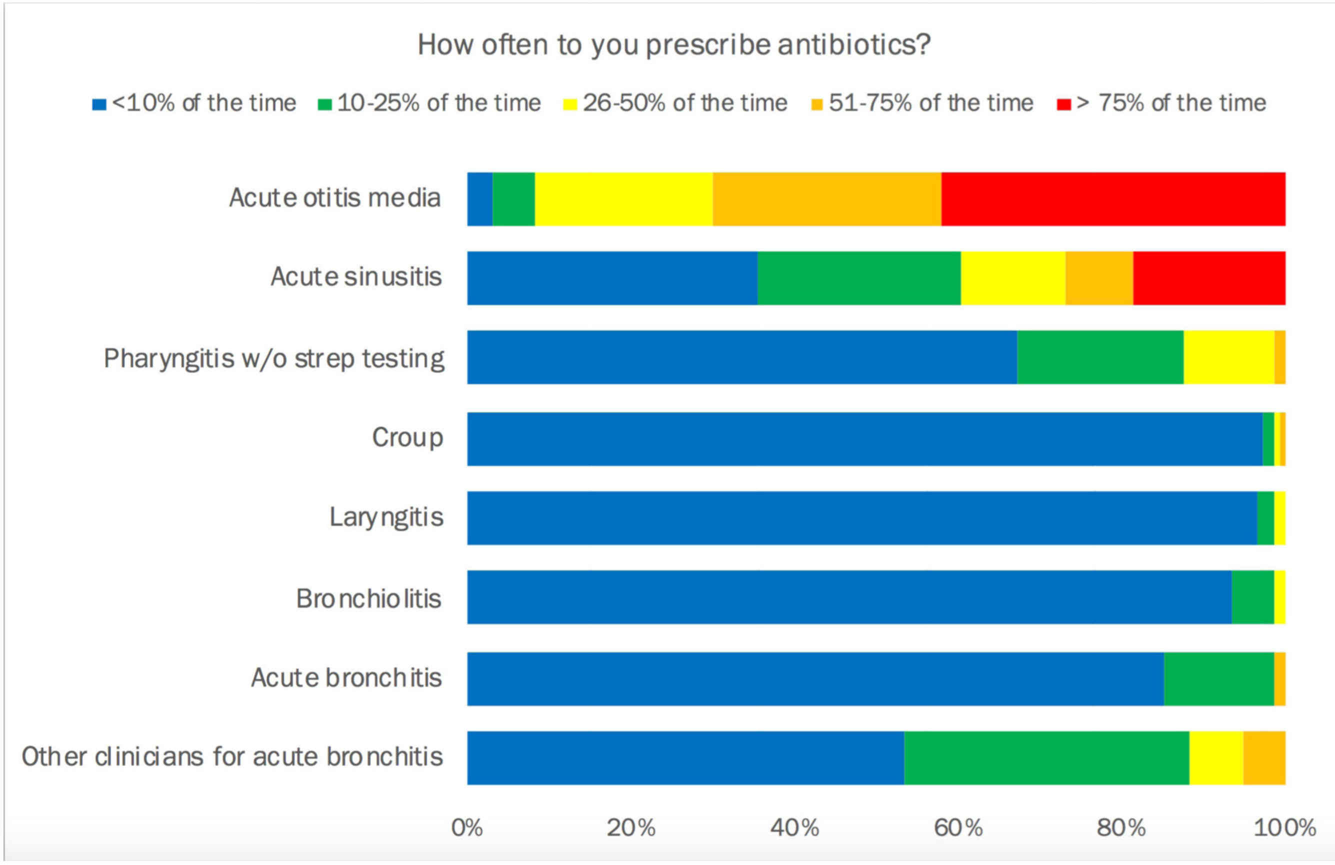

Figure 3.
Self-reported frequency of antibiotic prescribing by condition.

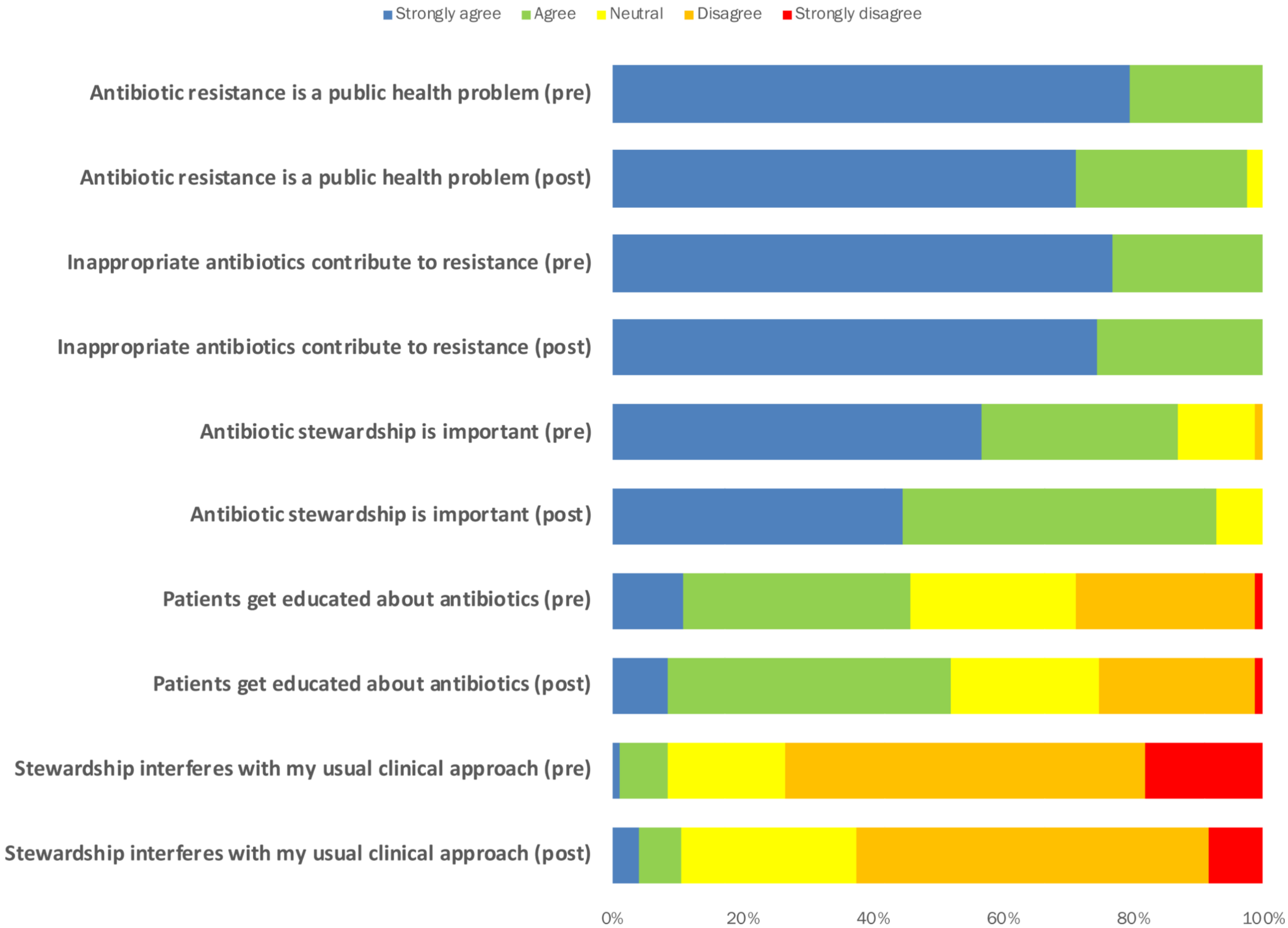

Figure 4.

Pre- and postintervention provider knowledge, attitudes, and beliefs regarding antibiotic stewardship

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Table 1.

Intervention Components by Intervention Package

Component	Definition	Adapted	Enhanced
Provider education	Educational presentations, electronic reminders of ARI guidelines, GetSmart brochures	X	X
Patient education	CDC Get Smart posters in waiting rooms, discharge handouts	X	X
Provider commitment-enhanced patient education	Personalized posters in exam rooms including modified Get Smart content directed at patients, enhanced with clinicians' photos and signed public commitment to antibiotic stewardship		X
Physician champion	Designated physician at each site who will lead provider education and be an advocate for antibiotic stewardship	X	X
Departmental feedback	Monthly aggregate of antibiotic prescribing practices for ARI from electronic health record data provided to departmental leadership	X	X
Peer-comparison	Personalized monthly performance ranking delivered by email with each physician receiving designation of being a "top performer" (top decile) or "not a top performer" for avoiding antibiotics for ARI.		X

Table 2.

Baseline Characteristics of Study Sites Randomized to Each Intervention

	Adapted Group at Baseline			Enhanced Group at Baseline		
Site	**No. Providers**	**Mean* Antibiotic Prescription Rate for Antibiotic-Nonresponsive ARIs* (95% CI)**	**Median* No. Antibiotic-Nonresponsive ARI Visits per provider per month (IQR)**	**No. Providers**	**Mean* Antibiotic Prescription Rate for Antibiotic-Nonresponsive ARIs (95% CI)**	**Median* No. Antibiotic-Nonresponsive ARI Visits per provider per month (IQR)**
UC Davis	No Adapted Group			52	5.6% (2.9–8.3)	6 (3–10)
CHCO	73	2.0% (0.9–3.1)	15 (8–23)	61	2.3% (1.2–3.4)	16 (10–24)
Harbor-UCLA	11	20.5% (3.6–37.5)	6.5 (3.5–14)	64	5.2% (1.8–8.5)	6 (2–12)
Total	84	4.4% (1.9–6.9)	14 (7–22)	177	4.3% (2.8–5.8)	9 (1–19)

*Mean-of-means and median of medians for monthly prescribing rates and visits, respectively. Up to 4 months per provider.

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Table 3.

Combined Intervention Unadjusted Provider-Level Antibiotic Prescribing Rates for Antibiotic-Nonresponsive ARIs During Flu Seasons (November 2016 – February 2017 and November 2017 – February 2018)

	CHCO	Harbor-UCLA	UC Davis	Total
Number of Providers (n)				
Pre-Interventions	134	75	52	261
Post-interventions	126	82	41	249
Median monthly visits antibiotic-nonresponsive ARIs per provider [Mdn, (IQR)] *				
Pre-Interventions	16 (8–23)	6 (2–12)	6 (3–10)	11 (5–20)
Post-interventions	19 (12–31)	4 (2–8)	7 (4–13)	13 (5–25)
Antibiotic prescription rate for antibiotic-nonresponsive ARIs during flu season *				
Pre-Interventions (95% CI)	2.1% (1.3% −2.9%)	7.4% (3.7%−11.2%)	5.6% (2.9%−8.3%)	4.3% (3.0% −5.6%)
Post-Interventions (95% CI)	1.6% (1.0% −2.2%)	2.3% (0.8%−3.7%)	1.4% (0.6%−2.0%)	1.8% (1.2% −2.4%)

* Mean of means and median of medians, up to 4 months per provider each season.

* Excludes visits for ARIs which also had a diagnosis for an antibiotic-susceptible condition.