eTable 2: CONSORT 2010 checklist when reporting a cluster randomised trial

Section/Topic	Item No	Standard Checklist item	Extension for cluster designs	Page No *
Title and abstract				
	1a	Identification as a randomised trial in the title	Identification as a cluster randomised trial in the title	N/A
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)[1,2]		1
Introduction				
Background and objectives	2a	Scientific background and explanation of rationale	Rationale for using a cluster design	4
	2b	Specific objectives or hypotheses	Whether objectives pertain to the the cluster level, the individual participant level or both	2
Methods				
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	Definition of cluster and description of how the design features apply to the clusters	4
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons		6
Participants	4a	Eligibility criteria for participants	Eligibility criteria for clusters	2-3
	4b	Settings and locations where the data were collected		2-3
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	Whether interventions pertain to the cluster level, the individual participant level or both	3-4
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	Whether outcome measures pertain to the cluster level, the individual participant level or both	3, 6
	6b	Any changes to trial outcomes after the trial commenced, with		N/A

		reasons		
Sample size	7a	How sample size was determined	Method of calculation, number of clusters(s) (and whether equal or unequal cluster sizes are assumed), cluster size, a coefficient of intracluster correlation (ICC or *k*), and an indication of its uncertainty	Online supplement appendix S1
	7b	When applicable, explanation of any interim analyses and stopping guidelines		N/A
Randomisation:				
Sequence generation	8a	Method used to generate the random allocation sequence		4
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	Details of stratification or matching if used	4
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	Specification that allocation was based on clusters rather than individuals and whether allocation concealment (if any) was at the cluster level, the individual participant level or both	4
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	Replace by 10a, 10b and 10c	
	10a		Who generated the random allocation sequence, who enrolled clusters, and who assigned clusters to interventions	4
	10b		Mechanism by which individual participants were included in clusters for the purposes of the trial (such as complete enumeration, random sampling)	4
	10c		From whom consent was sought (representatives of the cluster, or individual cluster members, or both), and whether consent was sought before or after randomisation	3

Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how		6
	11b	If relevant, description of the similarity of interventions		3-4
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	How clustering was taken into account	6
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses		N/A
Results				
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	For each group, the numbers of clusters that were randomly assigned, received intended treatment, and were analysed for the primary outcome	Figure 1, 6
	13b	For each group, losses and exclusions after randomisation, together with reasons	For each group, losses and exclusions for both clusters and individual cluster members	6
Recruitment	14a	Dates defining the periods of recruitment and follow-up		4
	14b	Why the trial ended or was stopped		6
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	Baseline characteristics for the individual and cluster levels as applicable for each group	Table 2, 6
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	For each group, number of clusters included in each analysis	6
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	Results at the individual or cluster level as applicable and a coefficient of intracluster correlation (ICC or k) for each primary outcome	7-8, 10

	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended		7-8
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory		11
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms[3])		11
Discussion				
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses		11-12
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	Generalisability to clusters and/or individual participants (as relevant)	11
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence		9-10
Other information				
Registration	23	Registration number and name of trial registry		2
Protocol	24	Where the full trial protocol can be accessed, if available		Online supplement appendix S1
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders		Funding statement

** Note: page numbers optional depending on journal requirements*

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1 Hopewell S, Clarke M, Moher D, Wager E, Middleton P, Altman DG, et al. CONSORT for reporting randomised trials in journal and conference abstracts. *Lancet* 2008, 371:281-283

2 Hopewell S, Clarke M, Moher D, Wager E, Middleton P, Altman DG at al (2008) CONSORT for reporting randomized controlled trials in journal and conference abstracts: explanation and elaboration. *PLoS Med* 5(1): e20

3 Ioannidis JP, Evans SJ, Gotzsche PC, O'Neill RT, Altman DG, Schulz K, Moher D. Better reporting of harms in randomized trials: an extension of the CONSORT statement. *Ann Intern Med* 2004; 141(10):781-788.

Table S2. Timeline for Study Events

Site	Date	Event
All	10/4/2016	CDC ED stewardship kickoff
	11/28/2016	Randomization Results
UC Davis		Baseline data
	12/17-1/18	Stakeholder interviews
	12/19/2016	California Medical Association Foundation's Alliance Working for Antibiotic Resistance Education (AWARE)
	2/17-4/17	Study talks and info sessions
	4/3/2017	Materials distributed
	4/4/2017	Pre-Intervention Provider Survey
	7/13/2017	Mail Merge Announcement sent to all consented providers
	7/13/2017	Mail Merge Feedback report #1
	9/5/2017	Mail Merge Feedback report #2
	10/10/2017	Mail Merge Feedback report #3
	11/9/2017	Mail Merge Feedback report #4
	12/11/2017	Mail Merge Feedback report #5
	1/19/2018	Mail Merge Feedback report #6
	2/20/2018	Post-Intervention Provider Survey
Harbor		Baseline data
	11/3/2016	Grand rounds
	2/22/2017	Grand rounds
	2/17-3/17	Stakeholder interviews
	3/17-4/17	Information sessions (ED, Nurse, UCC, NP)
	4/2/2017	Pre-Intervention Provider Survey
	4/13/2017	HUCLA ED and UCC materials distributed
	7/24/2017	Mail Merge Announcement sent to all consented providers
	8/1/2017	Mail Merge Feedback report #1
	8/14/2017	Mail Merge Feedback report #2
	9/19/2017	Mail Merge Feedback report #3
	11/4/2017	Mail Merge Feedback report #4
	11/13/2017	Mail Merge Feedback report #5
	12/27/2017	Mail Merge Feedback report #6
	1/19/2018	Mail Merge Feedback report #7
	2/12/2018	Mail Merge Feedback report #8
	3/1/2018	Post-Intervention Provider Survey
CHCO		Baseline data
	4/17 -9/17	Stakeholder interviews
	4/9/2017	Materials distributed
	6/22/2017	Study talks and info sessions
	9/14/2017	Study talks and info sessions
	11/11/2017	Pre-Intervention Provider Survey
	11/8/2017	Mail Merge Announcement sent to all consented providers
	12/1/2017	Mail Merge Feedback report #1
	1/4/2018	Mail Merge Feedback report #2
	2/2/2018	Mail Merge Feedback report #3
	2/27/2018	Mail Merge Feedback report #4
	3/6/2018	Mail Merge Feedback report #5
	2/23/2018	Post-Intervention Provider Survey

APPENDIX S1: STUDY PROTOCOL

A Multifaceted Intervention to Improve Prescribing for Acute Respiratory Infection for Adults and Children in Emergency Department and Urgent Care Settings (MITIGATE TRIAL)

Principal Investigator:

Larissa May, MD, MSPH, MSHS, Associate Professor, University of California-Davis

Supported by:

Centers for Disease Control and Prevention

Under OADS BAA 2016-N-17812

Version 1
Date: November 7, 2016

TABLE OF CONTENTS

Study Title

A Multifaceted Intervention to Improve Prescribing for Acute Respiratory Infection for Adults and Children in Emergency Department and Urgent Care Settings (MITIGATE TRIAL)

EXECUTIVE SUMMARY: Inappropriate antibiotic use is a major public health concern. Excessive exposure to antibiotics results in emergence and spread of drug-resistant bacteria, potentially avoidable adverse drug reactions, and increased healthcare utilization and cost. As antibiotic prescribing in emergency departments and urgent care centers remains unchecked, national professional organizations including the Infectious Diseases Society of America (IDSA) and the Society for Healthcare Epidemiology (SHEA), and an Executive Order from the President of the United States, recommend expansion of antimicrobial stewardship to these ambulatory care settings. The goal of antimicrobial stewardship is to effectively promote judicious antibiotic use in all healthcare settings, yet stewardship programs have not achieved their potential in terms of either reach or effectiveness. Reach has been limited mostly to inpatient settings; at the same time, recent critical experiments in behavioral science suggest that the effectiveness of existing stewardship programs could be greatly augmented through inclusion of specific implementation strategies such as behavioral nudges, benchmarked audit and feedback, and peer-to-peer comparisons.

In this proposed acute care project, we will compare a package consisting of education for providers using existing materials from CDC's GetSmart for Antibiotics campaign adapted for the acute care setting and led by a physician champion at each site (the adapted intervention), to a more intensive intervention that incorporates adapted GetSmart materials enhanced with individualized audit and feedback, peer comparisons, and behavioral nudges (the enhanced intervention). The comparative effectiveness of the enhanced intervention will be evaluated in a multicenter randomized trial nested within a quasi-experimental study of stewardship in emergency and urgent care settings. Our hypothesis is that both interventions will reduce inappropriate antibiotic prescribing for antibiotic nonresponsive acute respiratory infections (ARIs) in emergency departments and urgent care centers, but that the enhanced intervention will be more effective. We will use an interrupted time series study design to measure the impact of our interventions against the baseline period of usual care as well as against seasonally-adjusted historical controls. The randomized design for the two types of acute care stewardship interventions will allow measurement of the difference-in-differences in antibiotic prescribing rates for antibiotic non-responsive respiratory infections including acute bronchitis, acute bronchiolitis, viral pharyngitis, influenza, and nonspecific URI. Translation of proven behavioral techniques is a new and innovative approach to improving prescribing decisions. This project will expand stewardship to a new setting using innovative and effective approaches including the adaptation of behavioral techniques for ED and urgent care settings. We will also further establish our research group as a network for developing novel tools, measuring outcomes for antimicrobial stewardship, and disseminating research findings through acute care setting-specific toolkits.

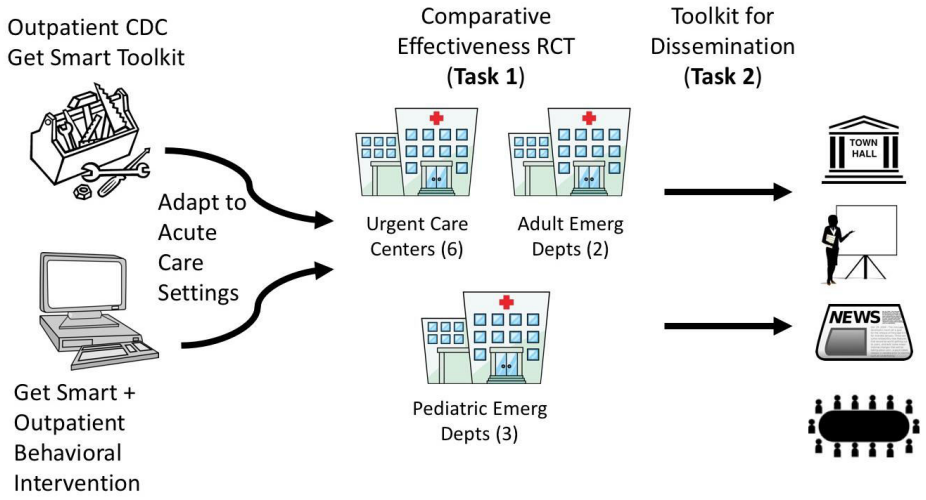
Objectives

1. Evaluate the effect of an adapted intervention consisting of education and practice feedback vs. an enhanced antimicrobial stewardship intervention with the addition of behavioral nudges on reducing inappropriate prescribing for ARI in the adult and pediatric emergency department and urgent care settings.

2. Create a dissemination toolkit for best practices for implementing these interventions to reduce inappropriate prescribing for ARI specific to emergency department and urgent care settings.

Design and Outcomes

We focus on "supply-side" interventions that target providers to change prescribing behavior, an approach well matched to the goal of encouraging uptake of effective evidence-based treatments in healthcare. Nudges, a behavioral science theory focused on positive reinforcement and suggestions have the advantage of being designed to improve care decisions, without limiting the choices available to physicians,[1] a primary reason for failure of other interventions.[16,17,2] They are also scalable and do not require much extra time to improve quality of care.[3] We propose to extend proven approaches to the outpatient setting by obtaining stakeholder feedback to adapt current methods and achieve the greatest public health impact on antimicrobial use in ED and urgent care settings consistent with CDC core elements for outpatient antimicrobial stewardship: ***commitment, action, monitoring, reporting and education***, using implementation tools found to be feasible in the ED and accepted by ED providers. ***A toolkit from this setting specific intervention will inform dissemination efforts***.



Interventions and Duration

Task 1. **Objective**: Evaluate the effect of an adapted vs adapted antimicrobial stewardship intervention (described below) on reducing inappropriate prescribing for ARI in ED and urgent care settings.

Study Design: We will compare an adapted Get Smart stewardship package consisting of an educational intervention led by a physician champion to an enhanced package that also includes a behavioral intervention that uses individualized audit and feedback, peer comparison, and public commitment nudging ***in addition to education*** to reduce antibiotic prescribing for antibiotic nonresponsive ARIs in a diverse population of adults and children presenting to emergency departments and urgent care centers (Table 1). Both packages will implemented after obtaining stakeholder input that will allow individualization for variation across sites. The comparative effectiveness of the two approaches will be evaluated in a pragmatic multicenter cluster randomized trial (with randomization at the practice level). We will use an interrupted time series study design to measure the impact of our interventions against a baseline period of usual care as well as against seasonally-adjusted historical controls. We have chosen a cluster trial nested in a quasi-experimental study design to ensure all providers and patients will be able to benefit from stewardship interventions. We will use a difference-in-differences analysis to estimate the additive benefit of the enhanced intervention, which is the pre- to post-intervention difference of the adapted intervention and pre- to post-intervention difference of the enhanced intervention. Provider randomization will be stratified by site/setting to the two arms.

Participant Selection*:* Sites are staffed by general emergency physicians, pediatric emergency physicians, advanced care practitioners, internists, and pediatricians treating a diverse patient population including the underserved (e.g. minorities, rural, elderly, poor access to care). Providers from the UC Davis and Harbor-UCLA adult and pediatric EDs, the Harbor-UCLA adult urgent care clinic, and Children's Hospital Colorado pediatric EDs and 4 urgent care centers will be approached for consent to participate. We will enroll approximately 381 providers and extract retrospective baseline data. We will randomize providers in a two-arm design to receive one of two interventions (Table 2). Patients with antibiotic-nonresponsive diagnoses include nonspecific upper respiratory infections, acute bronchitis, and influenza without concomitant diagnostic codes to support antibiotic prescribing (e.g. pneumonia). Outcomes for emergency department and urgent care visits will include antibiotic selection for visits with International Classification of Diseases, Tenth Revision [ICD-10-CM] codes consistent with antibiotic-nonresponsive ARI diagnoses[4,5] including J02.9, J06.9,

J06, J11, J20, H65. We will exclude visits with diagnosis codes for general acute pharyngitis or acute rhino-sinusitis because guidelines permit antibiotic prescription when certain criteria are met, and clear diagnostic coding definitions are lacking to identify this antibiotic-appropriate subset. Visits in which another diagnosis typically requiring antibiotics are made will also be excluded (attached in separate appendix). A visit for an antibiotic-nonresponsive ARI will be eligible for outcome inclusion if (1) the provider and site are enrolled in the study, (3) the visit occurs during the intervention period or is a seasonal historical control We will exclude visits with comorbidities that are guideline exclusions.

Study Procedures: As part of the adaptations of stewardship interventions for acute ambulatory care settings, we will use GetSmart materials appropriate to the emergency department and urgent care settings and select and adapt brochures and other campaign messages for acute care providers (Table 1). For the enhanced package, we will perform similar adaptations to behavioral interventions that have been proven successful in the outpatient setting (Table 1).

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 GetSmart posters in waiting rooms, discharge handouts	X	X
Provider Commitment-Enhanced Patient Education	Personalized Posters in exam rooms including modified GetSmart content directed at patients, enhanced with E-BIFEP clinicians' photos and signed public commitment to antibiotic stewardship [20].	**	X
Physician champion	Designated physician at each site who will lead provider education and be an advocate for antimicrobial 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-comparisons in personalized Audit and Feedback	Personalized monthly performance ranking with each physician receiving designation of being a "top performer" (top decile) or "not a top performer" for appropriate antibiotic Rx for ARI delivered by email[20]*		X

*Peer comparison will be distinct from traditional audit-and-feedback interventions in its comparison with top-performing peers instead of average-performing peers and its delivery of positive reinforcement to top performers—a strategy shown elsewhere to sustain performance. Norms will be computed within each clinical institution.
**Because exam rooms are shared across enrolled providers and patients from both experimental arms, those in the adapted arm will be exposed to commitment posters despite having not been offered to make the commitment or be pictured on posters.

Special attention will be made to adapting materials in the care of pediatric patients due to potential differences in pediatric caregiver demand for antibiotics compared to that of adult patients. Prior work in outpatient pediatric settings evaluating a 1-hour on-site provider education session followed by 1 year of personalized, quarterly audit and feedback of prescribing for ARIs found that adherence to prescribing guidelines for antibiotic prescribing for viral infections was not affected compared to usual practice although prescribing for bacterial infections was improved (see Appendix).[6] Therefore, pre-intervention surveys and stakeholder discussions will be used to guide nudging strategies specifically geared towards caregiver demand. Two to three providers at each site will participate in a pre-intervention interview and work flow review with study personnel. Interviews will be audio recorded and comprehensive notes collected for later coding. This qualitative data collection, using semi structured interviews with managers and providers, paired with organizational observations will allow for the adaptation of the current tool kit, development of the adaptations, understanding how to individualize procedures based on site specific variations (Miles and Huberman, 1994). Based on these interviews, specific questions will be developed to individualize intervention procedures.

We will comply with Institutional Review Board policy to obtain informed consent for provider participation, with a waiver for patient data. Risks to subject confidentiality will be mitigated by all PHI information being kept at the individual sites with secure locked cabinets and/or on password-protected computer files, de-identified prior to analysis. All study personnel will be trained by site investigators and certified by site IRBs.

During the preparatory phase of the trial, project managers at each location will work with clinical and operations staff to localize each of the intervention procedures to ensure they are consistent with local workflows, policies, and standards. A plan will be developed for implementing and monitoring each of the personal engagement points. Standard operating procedures will be refined and shared with staff. Clinician enrollment procedures for electronic and in-person enrollment will be developed with clinical champions and departmental leads. Risk analysis will be conducted with the monitoring plan to ensure that interventions are delivered with fidelity to

the original design and deviations are recorded (e.g. lapse in feedback to Departmental Lead after management turnover). Senior residents with prescribing privileges will be integrated into the interventions.

Table 2. Potential Intervention Logistics (7 Month Period from November to May)

Site	Adapted		Enhanced		Personal Engagement Points	
	Clinicians	ARI Visits*	Clinicians	ARI Visits*	# Clinical Champions	#Department Leads
Harbor Adult ED	104	637			1	1
Harbor Pediatric ED	8**	1189		1190	1	1
Harbor Adult Urgent Care		2	14	517	1	1
CHCO ED	79	3,061	80	3,099	1	1
CHCO Satellite ED and Urgent Cares (5)	79***	8,141	80	8,244	5	1
UC Davis Adult ED	96	261			1	1
UC Davis Pediatric ED	10**	549			1	1

* Based upon 7 m baseline (retrospective data), 7 m intervention is expected to have similar numbers
** These are unique providers to the Harbor and UC-Davis Pediatric EDs, many work in both Adult and Pediatric EDs
*** The same group of providers work in the CHCO ED and Urgent Cares
Larger patient volume seen at CHCO accounted for by low acuity pediatric UC visits and sole regional pediatric provider

Sample Size and Population

For the initial interviews/surveys we will recruit 2-3 providers at each site to complete the interviews and work flow review.

We will recruit physicians and advanced practice providers (nurse practitioners and physician assistants) from three different regions affiliated with three healthcare organizations who see acute respiratory infection patients. These will include three emergency departments (UC Davis adult and pediatric ED, Harbor-UCLA adult and pediatric ED, Children's Hospital of Colorado ED), and 7 urgent care centers (Harbor-UCLA adult urgent care and six CHOC pediatric urgent care sites). Approximately 381 eligible providers seeing acute respiratory patients will be recruited for this study.

We will randomize practices (blocking on geographical region) to the enhanced or standard intervention to avoid contamination between individual clinicians within the same practice.

1. STUDY OBJECTIVES

The primary study outcome is the likelihood an antibiotic is prescribed in an antibiotic-nonresponsive ARI visit. This information will be obtained from electronic health record data. Since primary clinical outcome data collection will leverage the data infrastructure all sites have implemented for the Patient Centered Outcomes Research Institute Clinical Data Research Network (PCORnet), data from all patients in electronic medical records will be included; there will not be a reduction in subject numbers from sampling. The primary outcome for Task 2 will be creation of the dissemination toolkit. We will assess provider and stakeholder attitudes and experience as well as assess the implementation experience by adapting previous surveys for Task 2. [16]

2. BACKGROUND AND RATIONALE

2.1 Background on Condition, Disease, or Other Primary Study Focus

2.2 Background: According to the Centers for Disease Control and Prevention, antibiotic-resistant bacteria cause two million illnesses and approximately 23,000 deaths each year in the United States. A recent White House Executive Order, in addition to IDSA/SHEA practice guidelines, recommend expanding antimicrobial stewardship to ambulatory care settings, including emergency departments (ED) and urgent care (UC) centers, where antibiotic prescribing is highly unregulated. Each year 10 million antibiotic prescriptions are written from the emergency department; unnecessary antibiotics are frequently prescribed for known viral infections, including 75% of adults with acute bronchitis and 45% of children with viral URI. Given the rising number of ED visits in the U.S., strategies are desperately needed to reduce inappropriate antibiotic use, associated adverse events, and development of local resistance in acute care outpatient settings.

2.3 A “one size fits all” approach is not feasible for ED- and urgent care-based implementations. Stewardship strategies need to be adapted to these settings. Providers in these settings are faced with unique challenges to rational decision-making such as frequent interruptions, high-volume care, the need for rapid decisions with limited information, variation in staff over different shifts, and concerns with immediate patient satisfaction. While acute-care providers understand the problem of antibiotic resistance, practice change is difficult.

2.4 Current approaches emphasizing the education of patients and providers are not that effective in outpatient settings. Despite consensus on guidelines and national campaigns devoted to education and performance measurement, inappropriate prescribing rates for acute respiratory infections remain at an unacceptable 50% in the United States. Considerable evidence from economic theory

and empirical study in other clinical areas suggests that adding a package of feedback, nudges, and peer comparisons could dramatically improve prescribing outcomes. Our investigative team has already shown 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 settings. In complex healthcare delivery environments such as emergency departments and urgent care centers, providers often rely on heuristics ("rules of thumb") in situations where deliberative decision-making is constrained. Use of behavioral economics can improve clinical decision-making by engineering choices in a way to help providers make better decisions. Interventions inspired by these behavioral "nudges" tailored to the ED workflow have potential to overcome barriers and promote stewardship for ARIs in emergency departments and urgent cares.

2.5 Study Overview: We focus on "supply-side" interventions that target providers to change prescribing behavior, an approach well matched to the goal of encouraging uptake of effective evidence-based treatments in healthcare. Nudges have the advantage of being designed to improve care decisions, without limiting the choices available to physicians, a primary reason for failure of other interventions.[16,17] They are also scalable and do not require much extra time to improve quality of care. We propose to extend proven approaches in the outpatient setting to achieve the greatest public health impact on antimicrobial use in ED and urgent care settings consistent with CDC core elements for outpatient antimicrobial stewardship: commitment, action, monitoring, reporting and education, using methods acceptable to ED providers. We will use a community-based approach to adaptation by obtaining stakeholder input into the use of behavioral nudges and other adaptations needed to the Get Smart stewardship plan for use in ERs and urgent care settings in multiple locations and age groups. A toolkit from this setting specific intervention will inform dissemination efforts.

Outcomes: The primary study outcome for Task 1 is the likelihood an antibiotic is prescribed by a clinician in an antibiotic-nonresponsive ARI visit. This information will be obtained from electronic health record data. Since primary clinical outcome data collection will leverage the data infrastructure all sites have implemented for the Patient Centered Outcomes Research Institute Clinical Data Research Network (PCORnet), data from all patients in electronic medical records will be included; there will not be a reduction in subject numbers from sampling. Data not available from PCORnet (e.g., specialty and level of training of prescribing providers will be obtained from the electronic health record of each institution. The primary outcome for Task 2 will be creation of the dissemination toolkit that provides a systematic method for implementing the stewardship program and individualizing to each site. We will assess provider and stakeholder attitudes and experience by adapting previous surveys for Task 2. [16] (see Appendix for examples)

Evaluation: Antibiotic prescribing for ARI by providers randomized to the adapted vs. enhanced interventions compared to baseline prescribing rate and seasonally-matched historical controls using interrupted time series and cluster randomized design. To ensure generalizability we will:

1. Conduct a difference-in-differences analysis to estimate pre- to post-intervention differences of the two interventions.
2. Compare observed changes in prescribing rates in our intervention sites to matched comparison sites using data from non-participating sites in the PCORnet Patient-centered SCAlable National Network for Effectiveness Research (pSCANNER) Clinical Data Research Network

Statistical Analysis Plan: Our primary analysis will be difference in interrupted time series employed in similar pragmatic trials of antibiotic stewardship interventions. We will estimate a piecewise hierarchical mixed effects logistic regression model with a knot at month 0 (intervention start) and provider fixed effects. This approach adjusts for trends in antibiotic prescribing in each group with interaction terms representing difference in prescribing trajectories between groups. To assess robustness to seasonality, we will also include a sensitivity analysis using a simpler, difference-in-difference mixed effects model without time series effects but comparing the intervention period to the prior year. This will be less sensitive to small differences in effect size between groups than the time series approach, but affords a priori power analysis and a conservative bound on power (see below). Our secondary analysis may measure each intervention in comparison to unexposed providers at other facilities in the pSCANNER distributed data set (e.g. USC Verdugo Hills Hospital Emergency Department, Los Angeles County USC Hospital, Children's Hospital of Los Angeles). Providers in this comparison group will be selected by matching provider demographics, specialty, and baseline prescribing rates.

Sample size and population: Using interrupted time series methods, rigorous studies of the effect size of outpatient and ED educational stewardship interventions for ARI ranged from 0.48 to 1.02.[7,8,9] We expect 190 providers per arm; stewardship studies cited above with lower sample sizes (81 per arm) were able to detect significant differences between groups as low as 6.7 percentage points. We have selected analysis models shown to have high sensitivity to small effect sizes in simulation studies[10]; a lower bound can be computed analytically - both the interrupted time series and seasonally matched differencing models will be more sensitive to detect effects than a group difference. [11] For a two-group comparison, Table 3 shows randomized power calculations using two-sided z-test with 0.05 significance. We estimate a 7-month study period average cell size of 70 patients for each of 381 physicians randomized to two arms across all participating sites (Table 3). Differences between groups smaller than 5 percentage points are unlikely to be considered to be clinically significant. Thus we have confidence that we will have the statistical power to detect effects sufficiently large to merit investment in further dissemination.

Table 3. Power Calculation for Comparative Effectiveness Study

Clusters (per arm)	Cell Size	ICC*	Baseline Effect+	Power	Difference
190 providers	70 patients	0.10	10-60%	83-100%	5-10%

*ICC: intra-class correlation. Conservatively estimated at 0.10 for provider prescribing measures (was reported as 0.05 in prior stewardship RCT).[Meeker 2016] +Baseline Effect. For clinical outcome, difference in differences of education vs behavioral intervention impact on reductions inappropriate antibiotic prescribing reported a baseline effect of an educational intervention of -11.0%, with a difference-in-differences ranging from -5.2 to -7.0% comparing behavioral interventions to education.[Meeker 2016]

Task 2. Objective: Create a dissemination toolkit for best practices for implementing these interventions to reduce inappropriate prescribing for ARI specific to the ED and UC settings.

Design: We will use survey methods with Likert Scale and open-ended question format to assess pre and post-intervention provider knowledge and attitudes about antimicrobial antibiotic use and to obtain stakeholder and physician champion feedback on feasibility of the intervention, including facilitators and barriers to intervention use, and use these results to develop a resource toolkit and a dissemination and implementation strategy for sharing the information.

Procedures: *Participant survey*: Providers at each site will complete the survey prior to implementation of the intervention and at the conclusion of the intervention period. Providers will be asked about attitudes toward antibiotic use and stewardship programs, knowledge of appropriate antibiotic use and education before and after the intervention. Additionally, at the end of the intervention period they will be asked about the stewardship intervention, their opinions of the program, specific components of the program, barriers and benefits of the intervention. *Champion and stakeholder survey*: A small group of 2-3 providers, nurses, and support staff from each site will complete a baseline workflow assessment. Responses will be used as covariates in implementation assessment and shared with practice champions prior to adopting the interventions to help inform and guide local implementation. Examples of survey materials and an implementation guide are provided in the Appendix and will be based on prior survey work in this area.[10, 16, 20, 21] All surveys will be finalized through collaboration with CDC staff and expert consultants. Stakeholders will include site PIs, local healthcare system and department leaders, and CDC. Stakeholders will also be engaged at the study outset to help define objectives and to target and modify the intervention packages to the local setting for Task 1.

Procedures: Any modifications to the implementation strategy and their outcomes will be recorded for use in the toolkit. At the conclusion of the study, providers will have the opportunity to review their data on the use of intervention strategies with a member of the research team. Additionally, aggregate outcome results for patients they served will be shared at the close of the study both for provider information as well as to gather information about the program for use in developing the toolkit. Expertise in behavioral economics and implementation science will allow us to develop context-specific resources that health care systems can apply to EDs and urgent cares that will enhance implementation of CDC's goals to clinical environments not traditionally thought feasible for

stewardship. We will develop the toolkit in collaboration with stakeholders using an iterative process that involves development of tool kit components, review by key stakeholder partners and further adaptation and review.

Outcome: In consultation with CDC and project stakeholders, we will summarize and disseminate study results using community-friendly language. The toolkit will be disseminated through the Get Smart Campaign, the Society for Healthcare Epidemiology of America and an existing partnership between CDC and the Society for Academic Emergency Medicine led by Dr. May since 2013, engaging emergency providers to reduce inappropriate antibiotics. We will leverage existing stewardship partnerships with health departments (e.g. Illinois DPH, Los Angeles County DHS) and the pSCANNER Network.

3. STUDY DESIGN

Study Design: We will compare an adapted package consisting of an educational intervention (Get Smart) led by a physician champion to an enhanced behavioral intervention that uses individualized audit and feedback, peer comparison, and public commitment nudging ***in addition to education*** to reduce antibiotic prescribing for antibiotic nonresponsive ARIs in a diverse population of adults and children presenting to emergency departments and urgent care centers (Table 1). The comparative effectiveness of the two approaches will be evaluated in a pragmatic multicenter cluster randomized trial (with randomization at the provider level). We will use an interrupted time series study design to measure the impact of our interventions against a baseline period of usual care as well as against seasonally-adjusted historical controls. We have chosen a cluster trial nested in a quasi-experimental study design to ensure all providers and patients will be able to benefit from stewardship interventions. We will use a difference-in-differences analysis to estimate the additive benefit of the enhanced intervention, which is the pre- to post-intervention difference of the adapted intervention and pre- to post-intervention difference of the enhanced intervention. Provider randomization will be stratified by site/setting to the two arms.

Participant Selection*:* Sites are staffed by general and pediatric emergency physicians, advanced care practitioners, internists, and pediatricians treating a diverse patient population including the underserved (e.g. minorities, rural, elderly, poor access to care). Providers from the UC Davis and Harbor-UCLA adult and pediatric EDs, the Harbor-UCLA adult urgent care clinic, and Children's Hospital Colorado pediatric EDs and 4 urgent care centers will be approached for consent to participate. We will enroll approximately 381 providers and extract retrospective baseline data. We will randomize providers in a two-arm design to receive one of two interventions (Table 2). Antibiotic-nonresponsive diagnoses include nonspecific upper respiratory infections, acute bronchitis, and influenza without concomitant diagnostic codes to support antibiotic prescribing (e.g. pneumonia). Outcomes for emergency department and urgent care visits will include antibiotic selection for visits with International Classification of Diseases, Tenth Revision [ICD-10-CM] codes consistent with antibiotic-nonresponsive ARI diagnoses[12,13] including but not limited to J02.9, J06.9, J06, J11, J20, H65 (see ICD10 list). We will exclude visits with diagnosis codes for general acute pharyngitis or acute rhino-sinusitis

because guidelines permit antibiotic prescription when certain criteria are met, and clear diagnostic coding definitions are lacking to identify this antibiotic-appropriate subset. A visit for an antibiotic-nonresponsive ARI will be eligible for outcome inclusion if (1) the provider and site are enrolled in the study, (3) the visit occurs during the 6-month intervention period or is a seasonal historical control, and (4) the patient has no visit for ARI within the prior 30 days. We will exclude visits with comorbidities that are guideline exclusions.

Study Procedures: As part of the adaptations of stewardship interventions for acute ambulatory care settings, we will use GetSmart materials appropriate to the emergency department and urgent care settings and select and adapt brochures and other campaign messages for acute care providers. For the enhanced package, we will perform similar adaptations to behavioral interventions that have been proven successful in the outpatient setting (Table 1).

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 GetSmart posters in waiting rooms, discharge handouts	X	X
Provider Commitment-Enhanced Patient Education	Personalized Posters in exam rooms including modified GetSmart content directed at patients, enhanced with E-BIFEP clinicians' photos and signed public commitment to antibiotic stewardship [20].	**	X
Physician champion	Designated physician at each site who will lead provider education and be an advocate for antimicrobial 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-comparisons in personalized Audit and	Personalized monthly performance ranking with each physician receiving designation of being a "top performer" (top decile) or "not a top performer" for appropriate antibiotic Rx for ARI		X

Feedback	delivered by email[20]*		

*Peer comparison will be distinct from traditional audit-and-feedback interventions in its comparison with top-performing peers instead of average-performing peers and its delivery of positive reinforcement to top performers—a strategy shown elsewhere to sustain performance. Norms will be computed within each clinical institution.

Special attention will be made to adapting materials in the care of pediatric patients due to potential differences in pediatric caregiver demand for antibiotics compared to that of adult patients. Prior work in outpatient pediatric settings evaluating a 1-hour on-site provider education session followed by 1 year of personalized, quarterly audit and feedback of prescribing for ARIs found that adherence to prescribing guidelines for antibiotic prescribing for viral infections was not affected compared to usual practice although prescribing for bacterial infections was improved (see Appendix).[14] Therefore, pre-intervention surveys and stakeholder discussions will be used to guide nudging strategies specifically geared towards caregiver demand. We will comply with Institutional Review Board policy to obtain informed consent for provider participation, with a waiver for patient data. Risks to subject confidentiality will be mitigated by all confidential information being kept on password-protected computer files, de-identified prior to analysis. All study personnel will be trained by site investigators and certified by site IRBs.

During the preparatory phase of the trial, project managers at each location will work with clinical and operations staff to localize each of the intervention procedures to ensure they are consistent with local workflows, policies, and standards. A plan will be developed for implementing and monitoring each of the personal engagement points. Standard operating procedures will be refined and shared with staff. Clinician enrollment procedures for electronic and in-person enrollment will be developed with clinical champions and departmental leads. Risk analysis will be conducted with the monitoring plan to ensure that interventions are delivered with fidelity to the original design and deviations are recorded (e.g. lapse in feedback to Departmental Lead after management turnover). Senior residents with prescribing privileges will be integrated into the interventions.

4. SELECTION AND ENROLLMENT OF PARTICIPANTS

4.1 Inclusion Criteria

The subjects involved in this trial are clinicians who will be recruited from multiple clinical sites in Sacramento, Los Angeles, and Colorado. The target group of physicians (and the patients that they treat) is fully inclusive and representative. Clinicians will be eligible if they treat adult and/or pediatric patients with acute respiratory infections. All consenting clinicians at these practices will be offered enrollment.

Each study clinic has an electronic health record (EHR) system in place and has its own physical building (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). Clinicians must meet the following inclusion criteria to participate in this study: 1) treat adult or pediatric patients with acute respiratory infections and practice at one of the study clinics.

A patient visit is eligible for inclusion in the outcome denominator if: 1) the provider and practice site were enrolled in the study, and 2) the visit occurred during the baseline or intervention period. If multiple participating providers were involved in a patient's care, the visit will be attributed to the more senior provider (eg, attending physician rather than senior resident).

4.2 Exclusion Criteria

Visits will be excluded from the primary analysis when: 1) patients have certain medical co-morbidities that make ARI guidelines less likely to apply, 2) patients have concomitant visit diagnoses indicating a non-ARI possible bacterial infection, 3) patients have concomitant visit diagnoses indicating potentially antibiotic appropriate ARI diagnoses or other ARI diagnoses suggestive of a bacterial infection. Visits for which a provider records another condition that is not an ARI for which antibiotics might be indicated will also be excluded from the analysis. The sets of diagnoses which will be used to calculate the outcomes are listed in Appendix E: Code Set Definitions.

4.3 Study Enrollment Procedures

All clinicians with pediatric and/lr adult patients in participating practices will be contacted by email and in-person meetings.
Enrollment and consent will be conducted using an online survey administration application and/or in person.
The email includes a description of the broad goals of the study, a general description of the intervention, and a link to the electronic consent form and baseline survey (under separate IRB).
The email will describe the interventions to which a clinician's site was assigned, including changes they would observe in their EHR (for Accountable Justifications and Suggested Alternatives interventions) and examples of the kinds of emails they would receive (Peer Comparison) listed in the Appendix : Sample Peer Comparison Email Text.

5. STUDY INTERVENTIONS

5.1 Interventions, Administration, and Duration

The intervention period will be 7-months in length for all participants, with a follow-up period to measure persistence of effects after interventions end. The pre-intervention baseline period will be 12 months in length.

5.2 Handling of Study Interventions

The following interventions will be compared: **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 GetSmart posters in waiting rooms, discharge handouts	X	X
Provider Commitment-Enhanced Patient Education	Personalized Posters in exam rooms including modified GetSmart content directed at patients, enhanced with E-BIFEP clinicians' photos and signed public commitment to antibiotic stewardship [20].	**	X
Physician champion	Designated physician at each site who will lead provider education and be an advocate for antimicrobial 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-comparisons in personalized Audit and Feedback	Personalized monthly performance ranking with each physician receiving designation of being a "top performer" (top decile) or "not a top performer" for appropriate antibiotic Rx for ARI delivered by email[20]*		X

*Peer comparison will be distinct from traditional audit-and-feedback interventions in its comparison with top-performing peers instead of average-performing peers and its delivery of positive reinforcement to top performers—a strategy shown elsewhere to sustain performance. Norms will be computed within each clinical institution.

Peer Comparison (PC) is an email-based intervention. Clinicians will be ranked from highest to lowest inappropriate prescribing rate within each region using EHR data. Clinicians with the lowest inappropriate prescribing rates (the top-performing 10th percentile) will be informed that they are a "Top Performer" in a congratulatory email. The remaining clinicians will be told that they are "Not a Top Performer" by email. Emails will include the number and proportion of inappropriate antibiotic prescriptions written for a month for non-antibiotic-appropriate ARI cases and the proportion written by Top Performers.

5.3 Adherence Assessment

In order to ensure that the study interventions are being reliably delivered we will create testing scripts that cover logical and coding variation in EHR-based interventions. Study staff will conduct site visits regularly during the intervention to ensure that tests do not fail. For example, staff will verify that intervention materials are being used and posted and if not, we will assess the barriers to implementation and facilitate their uptake.
Throughout the course of the study, we will also be monitoring "diagnostic drift" that may result in provider shifting diagnosis to avoid guideline conflicts that might trigger alerts or poor performance reports.

6. STUDY PROCEDURES

6.1 Schedule of Evaluations

Assessment	Screening: Baseline prescribing (Month -12 to Month 0)	Baseline, Enrollment, Randomization: (Day 1)	Intervention start (Month 1)	Continuously Measured or monitored	Intervention end:	Follow-up period:
Clinician-level Assessments						
Informed Consent Form		X				
Demographics		X				

Assessment	Screening: Baseline prescribing (Month -12 to Month 0)	Baseline, Enrollment, Randomization: (Day 1)	Intervention start (Month 1)	Continuously Measured or monitored	Intervention end:	Follow-up period:
Inclusion/Exclusion Criteria	X	X				
Provider Attitudes Survey		X			X	
Visit-level assessments						
ICD-10 codes	X	X	X	X	X	X

6.2 Description of Evaluations

6.2.1 Screening Evaluation

Consenting Procedure

With the assistance of each site's principal investigator, we will send providers at participating sites an introductory email that includes a description of the broad goals of the study, a general description of the intervention, and a link to the electronic consent form and baseline survey. The consent document will indicate that participation is voluntary and that decisions to participate (or not) will have no bearing on any provider's status at his or her clinic. Providers who provide consent to participate will be asked to complete an online survey and brief educational session prior to the intervention phase, permit de-identified patient records pertaining to patients who saw them for ARIs to be included in the study database, and complete a 15 minute post-intervention survey. We will send up to 6 follow up emails to providers who do not respond, and study personnel will contact them in person when feasible.

6.2.2 Enrollment, Baseline, and/or Randomization

Enrollment

Enrollment date will be documented on the online consent form at the time of consent. Interventions will be initiated after all clinicians in a practice have been enrolled or declined to participate.

Baseline Assessments

- Baseline prescribing rates
- Baseline survey to assess provider characteristics and provider attitudes toward practice guidelines, clinical decision support, electronic health records, and practice environment (see IRB#).

Randomization

We will implement a cluster-randomized design at the site level to avoid contamination that might occur if individual providers in close proximity are randomized to different interventions. Providers who practice at multiple clinics will be assigned to the intervention of the clinic for which they spend at least 80% of their time. Geographically distinct individual clinics will be the unit of randomization. We will conduct a block randomization of clinics by region.[15]

7. STATISTICAL CONSIDERATIONS

7.1 General Design Issues

Hypotheses

Our primary hypothesis is that practices randomized to receive behavioral economic interventions will have decreases over time in antibiotic prescribing rates for non-antibiotic appropriate ARIs, compared to contemporaneous antibiotic prescribing rates and a general educational intervention for non-antibiotic appropriate ARIs among control practices. This hypothesis will be evaluated in an intent-to-treat difference-in-differences framework using a mixed-effects logistic regression model. Fixed effects will include the effects of interventions over time (i.e., interactions between randomization assignment and time), using a period 12-months prior to the intervention baseline period. Providers and randomization unit (clinic) will be modeled as random effects.

Design

We will conduct a between-group factorial cluster randomized trial of ambulatory clinic visits in a multi-regional sample of clinics. Clustering (by clinic) helps us prevent treatment contamination between individual clinicians within the same clinic. The factorial design will allow us to study the effects of multiple antibiotic policies as often happens in the real-world, where State and Federal public health as well as clinic organization quality improvement interventions may be happening at the same time. Using this factorial design, three interventions will be tested for their ability to alter inappropriate physician prescribing behavior:

Outcome measures

The primary outcome measure is the rate of antibiotic prescribing for non-antibiotic-appropriate acute respiratory infections.

The ICD-10 codes for primary outcomes are defined in detail in this protocol document. These outcomes are computable clinical quality measures from the electronic health record. These are widely used in medicine to evaluate quality improvement and reliability and validity are generally supported.[16] As a secondary outcome, effects on potentially appropriate acute respiratory infection diagnosis will be evaluated with respect to diagnostic drift.

A visit is eligible for inclusion in the outcome denominator if: 1) the provider and practice site were enrolled in the study, 2) the visit occurred during the 7- month intervention period or pre-intervention period, and 4) the patient did not have a visit with any ARI diagnosis in the prior 30 days. Visits are excluded from the primary analysis when: 1) patients have certain medical co-morbidities that make ARI guidelines less likely to apply, 2) patients had concomitant visit diagnoses indicating a non-ARI possible bacterial infection, or 3) patients had concomitant visit diagnoses indicating potentially antibiotic appropriate ARI diagnoses or other ARI diagnoses suggestive of a bacterial infection. Visits for which a provider recorded another condition that was not an ARI for which antibiotics might be indicated were also excluded from the analysis.

Risk Analysis: The two proposed interventions aim to guide appropriate treatment of ARI in accordance with established evidence, and the results of this investigation have the potential to benefit society and future persons who have ARI. One concern when conducting implementation research in healthcare settings is sustainment of practices once the research is completed. We have broad buy-in from hospital and health system leadership to ensure sustainment of practices, and possibly scale and spread through the larger health systems. Strategies have been developed and will continue to be refined with local stakeholders and the hospital leadership. After project completion, all materials will be provided to each site for ongoing training of existing and new staff with the goal for continuation of stewardship activities. Strong stakeholder champions already identified and site PIs themselves will be available to provide ongoing coaching at each clinical site. If the project yields positive results, methods of scaling up training through each health system could be developed and offered in the form of the implementation toolkit. Providers will also have the opportunity to review their data on the use of intervention strategies with a research team member. We have experience with similar mechanisms for audit and feedback to improve quality of care in our departments with near 100% provider participation. We will hold kickoff conferences at each site to train recruited stakeholders (hospital administrators, ED and UC providers) and study personnel. We anticipate study design improvements to fit local priorities and enrich clinical relevance to providers. The study team will hold biweekly calls to address potential challenges and provide progress updates at each site to ensure uptake.

7.2 Sample Size and Randomization

Using interrupted time series methods, rigorous studies the effect size of outpatient and ED educational stewardship interventions for ARI ranged from 0.48 to 1.02.[xv,xvi,xvii] We expect 190 providers per arm; stewardship studies cited above with lower sample sizes (81 per arm) were able to detect significant differences between groups as low as 6.7 percentage points. We have selected analysis models shown to have high sensitivity to small effect sizes in simulation studies[xviii]; a lower bound can be computed analytically - both the interrupted time series and seasonally matched differencing models will be more sensitive to detect effects than a group difference. [xix] For a two-group comparison, Table 3 shows randomized power calculations using two-sided z-test with 0.05 significance. We estimate a 7-month study period average cell size of 70 patients for each of 381 physicians randomized to two arms across all

participating sites (Table 3). Differences between groups smaller than 5 percentage points are unlikely to be considered to be clinically significant. Thus we have confidence that we will have the statistical power to detect effects sufficiently large to merit investment in further dissemination.

Table 3. Power Calculation for Comparative Effectiveness Study

Clusters (per arm)	Cell Size	ICC*	Baseline Effect+	Power	Difference
190 providers	70 patients	0.10	10-60%	83-100%	5-10%

*ICC: intra-class correlation. Conservatively estimated at 0.10 for provider prescribing measures (was reported as 0.05 in prior stewardship RCT).[Meeker 2016] +Baseline Effect. For clinical outcome, difference in differences of education vs behavioral intervention impact on reductions inappropriate antibiotic prescribing reported a baseline effect of an educational intervention of -11.0%, with a difference-in-differences ranging from -5.2 to -7.0% comparing behavioral interventions to education.[Meeker 2016]

7.2.1 Treatment Assignment Procedures

Randomization of study sites

We have chosen a randomized design at the practice site level to avoid contamination that might occur if individual providers in close proximity are randomized to different interventions. Providers who practice at multiple clinics are assigned to the intervention of the clinic for which they spend at least 80% of their time.

Geographically distinct individual clinics will be treated as the unit of randomization. These are clinics belonging to one of three larger clinical organizations covering a connected geographic area in either Northern California (University of California-Davis), Southern California (Harbor-UCLA) or Colorado (Children's Hospital Colorado). We will carry out a block randomization of clinics by clinic organization using simple randomization in each blocked region (using random sequences generated at http://Random.org Harbor-UCLA and UC Davis, three sites total, we will assign the enhanced intervention within each block to the upper half of the sequence). UC Davis has only one site and Harbor-UCLA has two sites. Allocation of the sequence will be concealed until after the interventions were assigned.

7.3 Interim analyses

No interim analysis will be conducted on primary or secondary outcomes. *Outcomes*

7.3.1 Primary outcome

The primary outcome is defined as the antibiotic prescribing rate for acute respiratory infection diagnoses changes in antibiotic prescribing rate for the following ICD-10 diagnoses: J00; J20 ,J40; J02.9, J06.9, J06, J11, J20, H65 (see Appendix for complete list)

7.3.2 Secondary outcomes

To study safety and diagnostic drift we will evaluate an expanded list of potentially appropriate and other diagnoses of interest. For potentially antibiotic appropriate acute respiratory infection diagnoses these are: Acute sinusitis J01; Acute sinusitis/rhinosinusitis; Acute pharyngitis; 462 Acute pharyngitis J02. Otitis media H65, H66

Data Analyses

We will use the following descriptive statistics to characterize the sample: Means and medians for continuous measures, frequencies for count data, standard deviations and interquartile ranges for variance.

For inferential analysis of our hypotheses, we will employ a mixed-effects hierarchical logistic regression model to estimate the adjusted marginal effect over time of each intervention on the primary outcome using. Fixed effects will include intervention assignment, time period dummy variables (the baseline prescribing rate for each clinician, the intervention and intervention months 0-7), and time period interacted with intervention assignment. Providers and randomization unit (clinic) will be included as random effects to isolate the effect of each individual intervention (basic and enhanced) on the primary outcome.

To assess diagnostic drift, we will use the same analytic model as for the primary outcome, but with the percentage of *all* ARIs that is coded as antibiotic-appropriate in each study arm as the dependent variable (a secondary outcome).

8. DATA COLLECTION AND QUALITY ASSURANCE

8.1 Data Collection Forms

Two types of data will be collected – de-identified data from electronic medical and billing records (provider, month of service, age under 18 yes/no, antibiotic selection and ICD10 diagnosis) and data from self-administered online surveys at the

beginning and end of the study. We will use PScanner PCORnet Patient-centered SCAlable National Network for Effectiveness Research (pSCANNER) Clinical Data Research Network. All sites participate in the PCORNet pSCANNER Clinical Data Research Network, with pre-coordinated data and streamlined governance to enable efficient data provisioning and analysis.

8.2 Data Management

Each of the participating sites will create an extract from their Electronic Medical or Billing Records of the Data Elements for all patients with an upper respiratory infection using a limited dataset. These records will be transferred to the coordinating center on a weekly basis.

8.3 Quality Assurance

Training

Staff will be trained on the permissible values present in Electronic Records, frequency of update, and expected volumes of data. In addition, verification of use and implementation of the tools and educational materials will be part of the QA program.

Metrics

Quality control metrics will be based on reports verifying visits with ARI ICD-10 Codes. All drugs prescribed at these visits will be categorized as "antibiotic" or "non-antibiotic". Incorrect categorizations will be corrected and outcome computations recomputed before each email is delivered. All case identification and data extraction will be done by automated queries, with ten percent of charts being manually reviewed from the electronic health record for validation.

9. PARTICIPANT RIGHTS AND CONFIDENTIALITY

9.1 Institutional Review Board (IRB) Review

The study protocol and the informed consent document for all clinic sites will be reviewed and approved by the Institutional Review Boards (IRB) at the University of California Davis. Individual site protocols will also be submitted for review and approval by the site local IRBs.

9.2 Informed Consent Forms

An electronically signed consent form will be obtained from each participating provider. The consent form will describe the purpose of the study, the procedures to be followed, the risks and benefits of participation, and compensation for participation.

9.3 Participant Confidentiality

Data will be recorded with SSL protected web sites to a data warehouse, and transferred over secure network protocol. Data will be kept in encrypted files on computers in locked offices.
Identified data will only be released to providers participating in the "behavioral intervention" arm of the study with individualized audit and feedback. As stored, data will be de-identified with MD5 hash to link a participant number (unique to physician) to a primary outcome. Study researchers will have password protected access to coded data only.
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10. PUBLICATION OF RESEARCH FINDINGS

Publication of results from our research will follow the NIH Public Access Policy, which requires that we submit to the National Library of Medicine's PubMed Central an electronic version of final, peer-reviewed manuscripts upon acceptance for publication, to be made publicly available no later than 12 months after the official date of publication.

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APPENDIX B: POST-IMPLEMENTATION SURVEY

Antimicrobial Stewardship Post-Intervention Provider Survey

Attitudes:

1. Antibiotic resistance is a public health problem facing the United States.
    a. Strongly Agree
    b. Agree
    c. Neutral
    d. Disagree
    e. Strongly Disagree

2. Inappropriate antibiotic use contributes to antimicrobial resistance.
    a. Strongly Agree
    b. Agree
    c. Neutral
    d. Disagree
    e. Strongly Disagree

3. Do you feel antibiotics are overused or underused in your emergency department or urgent care center with 1 being very underused and 10 being very overused?

	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	
Frequently underused											**Frequently overused**

4. For which conditions are antibiotics most frequently **over-prescribed** (either inappropriate use or overly broad spectrum use)? Check all that apply.
    a. Common cold
    b. Sinusitis
    c. Otitis media
    d. Pharyngitis

e. Influenza
f. Acute bronchitis
g. Bronchiolitis
h. Asthma
i. Skin and Soft Tissue
j. Gastrointestinal Infection
k. Urinary tract infection
l. NONE
m. Other

Comments:

5. For which conditions are antibiotics most frequently **under-prescribed** (either inappropriate use or overly narrow spectrum use)? Check all that apply.
    a. Common cold
    b. Sinusitis
    c. Otitis media
    d. Pharyngitis
    e. Influenza
    f. Acute bronchitis
    g. Bronchiolitis
    h. Asthma
    i. Skin and Soft Tissue
    j. Gastrointestinal Infection
    k. Urinary tract infection
    l. NONE
    m. Other

Comments:

6. Antibiotic Stewardship programs are important to optimize antibiotic use in the ED and urgent care.
    a. Strongly Agree
    b. Agree
    c. Neutral
    d. Disagree
    e. Strongly Disagree

7. ED and urgent care patients receive adequate education about the use and duration of antibiotic prescriptions prior to discharge.
    a. Strongly Agree
    b. Agree
    c. Neutral
    d. Disagree
    e. Strongly Disagree

8. What resources do you use to stay up-to-date on current approaches to antibiotic prescribing?
    a. Departmental lectures/CME
    b. Web-based resources (Up to Date or other)
    c. Smart phone App or pocket guide (EMRA, Sanford Guide)
    d. Other lectures
    e. Other, Please specify _____

ED/Urgent Care Stewardship Experience:

9. Did you take part in the ED or urgent care stewardship program for acute respiratory infections?
    a. Basic intervention (education materials)
    b. Enhanced intervention (individual audit and feedback, peer to peer comparisons)
    c. I don't know

10. Which components of our stewardship intervention did you receive?
    a. Educational presentations at Academic Forum or other venues
    b. Distribution of clinical practice guidelines in person
    c. Distribution of clinical practice guidelines electronically
    d. Emails from stewardship program
    e. Departmental feedback on overall prescribing
    f. Individualized audit and feedback on your practice patterns
    g. I don't know

11. Did you participate in the individual audit/feedback portion of the ED or urgent care stewardship program?
    a. Yes
    b. No
    c. I don't know

Please answer the following three questions if you participated in the audit and feedback portion of the program.

12. Did you find it the audit and feedback portion of the program:
    a. Very useful
    b. Mostly useful
    c. Somewhat useful
    d. Marginally useful
    e. Not at all useful

13. How bothersome was the audit and feedback?
    a. Extremely intrusive
    b. Very intrusive
    c. Somewhat intrusive
    d. A little intrusive
    e. Not at all intrusive

14. How willing were you to change your practices based on the audit and feedback, with 1 being unwilling and 10 being very willing?

1 2 3 4 5 6 7 8 9 10
Unwilling Very willing

15. Do you believe that ED and urgent care based antibiotic stewardship programs would interfere with my usual approach to clinical decision-making in treatment of infectious diseases.
    a. Strongly agree
    b. Agree
    c. Neutral
    d. Disagree
    e. Strongly Disagree

    If yes, why:_____

16. In your opinion, what are the best strategies to decrease inappropriate use of antibiotics? Check all that apply.
    - ☐ Better education in pre-clinical training (medical/nursing school)
    - ☐ Better education in residency training
    - ☐ Availability of antibiotics prior to prescribing/ordering
    - ☐ Developing rigorous practice guidelines for empiric antibiotic treatment of common infections
    - ☐ Developing more order sets or decision support tools for the ED or urgent care
    - ☐ Other, Please specify _____

17. Based on your preference, please rank, in order (1 being the most preferable), the following methods to implement antimicrobial stewardship for the emergency department or urgent care?
    ___ Provider continuing education
    ___ Published institutional or local guidelines
    ___ Point-of-care clinical decision support via the electronic health record

___ Individual feedback clinicians
___ Other, Please specify _____

18. What barriers do you see in appropriate prescribing for acute respiratory infections?
    a. Lack of access to guidelines or information on prescribing
    b. Patient expectation
    c. Psychosocial barriers
    d. EHR
    e. Other, please specify

    Why?

19. What are your personal feelings about the emergency department or urgent care stewardship program/intervention?
    a. Very helpful
    b. Slightly helpful
    c. Neutral
    d. Wasn't helpful at all
    e. Other:_____

20. What additional resources would you like to see available as part of an ED or urgent care stewardship program and why?

21. Has taking part in the stewardship intervention changed or improved your clinical practices?
    a. Yes.
    Please explain _____

    b. No.
    Please explain _____

22. In what ways do you think we could better present the information to clinicians?
    Please explain _____

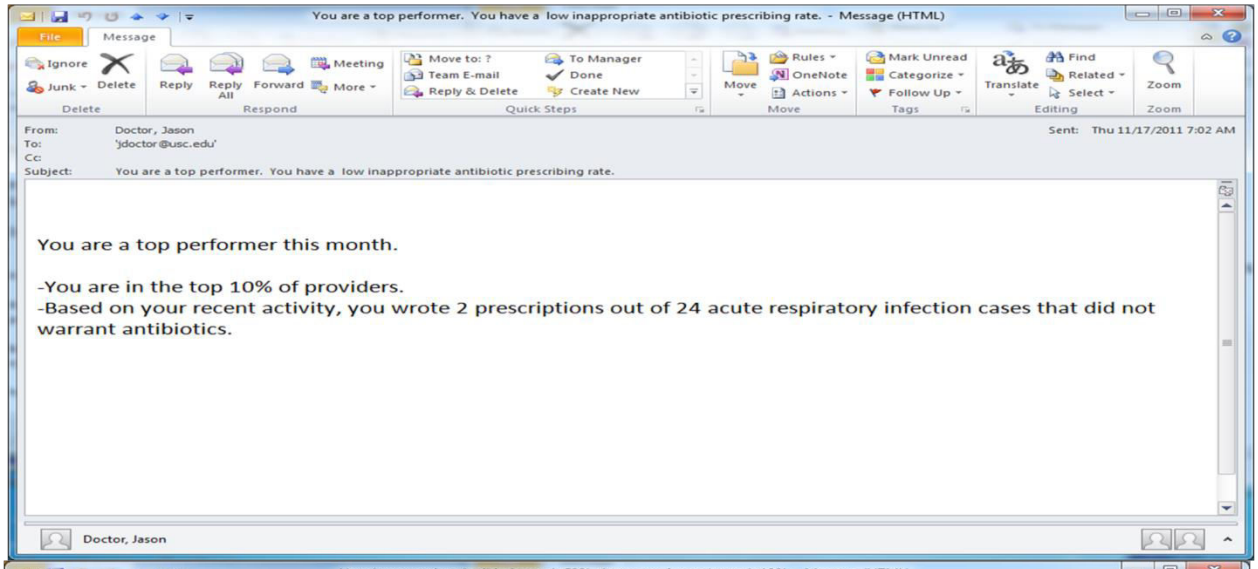
23. If you have any additional comments about ED-based antimicrobial stewardship, please provide them below:

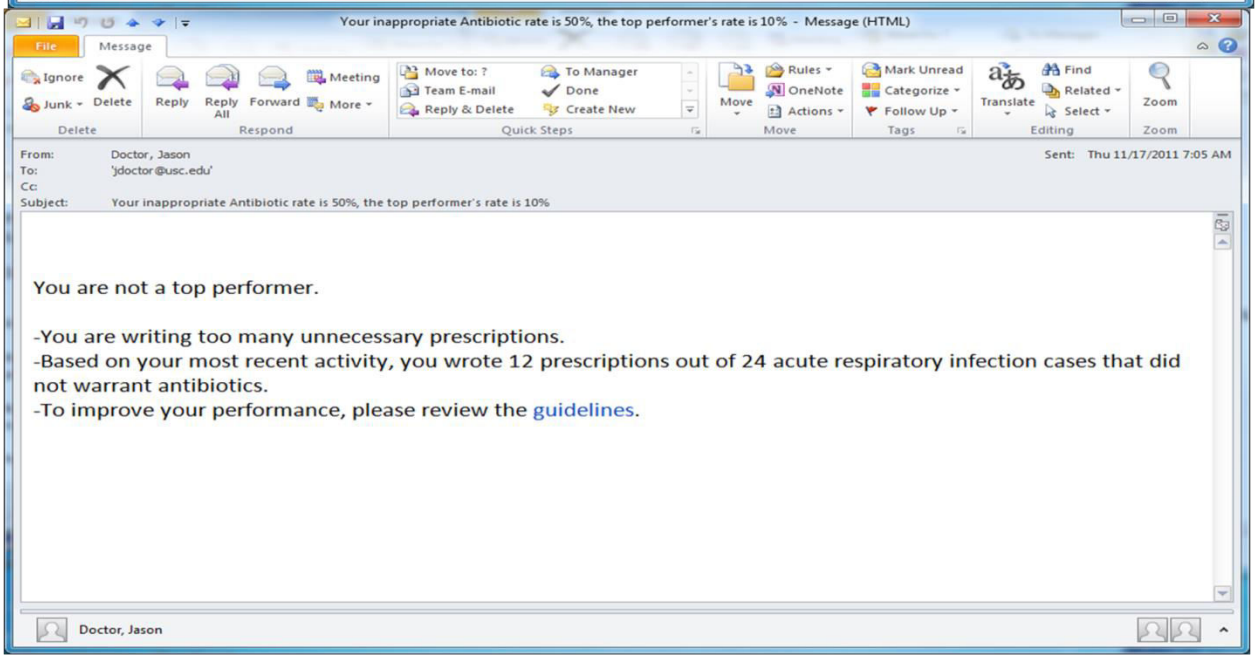
If you are interested sharing more information about your experience please contact us at: lsmay@ucdavis.edu

APPENDIX: DIAGNOSIS CODE SETS USED IN OUTCOME ASSESSMENTS

This is contained in an accompanying Microsoft Excel file

APPENDIX: SAMPLE PEER COMPARISON EMAILS TO PROVIDERS





APPENDIX: ORAL ANTIBIOTICS INCLUDED IN OUTCOME MEASUREMENTS

Cephalosporins	Other antimicrobials
Macrolides	Clindamycin
Penicillins	Linezolid
Quinolones	Telithromycin
Sulfonamides	Trimethoprim
Tetracyclines	

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