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Impact of Implementation of the Core Elements of Outpatient Antibiotic Stewardship within Veterans Health Administration Emergency Department and Primary Care Clinics on Antibiotic Prescribing and Patient Outcomes

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Abbreviated Running Title: Core Elements in Outpatient Clinics

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Summary: A multi-centered intervention based on the *Core Elements of Antibiotic Stewardship* was conducted to improve outpatient acute respiratory tract infection management. The intervention was associated with reduced antibiotic prescribing and reductions in hospitalization.

ABSTRACT

Background: The *Core Elements of Outpatient Antibiotic Stewardship* provide a framework to improve antibiotic use, but evidence supporting safety are limited. We report the impact of *Core Elements* implementation within Veterans Health Administration sites.

Methods: A quasi-experimental controlled study assessed the effects of an intervention targeting antibiotic prescription for uncomplicated acute respiratory tract infections (ARI). Outcomes included per-visit antibiotic prescribing, treatment appropriateness, potential benefits and complications of reduced antibiotic treatment, and change in ARI diagnoses over a 3-year pre-implementation and 1-year post implementation period. Logistic regression adjusted for covariates [OR (95% CI)] and a difference-in-differences analysis compared outcomes between intervention and control sites.

Results: From 2014-2019, there were 16,712 and 51,275 patient-visits in 10 intervention and 40 control sites, respectively. Antibiotic prescribing rates pre-post implementation in intervention sites were 59.7% and 41.5%, respectively; in control sites they were 73.5% and 67.2%, respectively [difference-in-differences p<0.001]. The intervention site pre-post implementation odds ratio to receive appropriate therapy increased [1.67 (1.31, 2.14)] which remained unchanged within control sites [1.04 (0.91, 1.19)]. There was no difference in ARI-related return visits post-implementation [(-1.3% vs. -2.0%; difference-in-differences *p*=0.76] but all-cause hospitalization was lower within intervention sites [(-0.5% vs. -0.2%); difference-in-differences *p*=0.02]. The odds ratio to diagnose upper respiratory tract infection not otherwise specified compared to other non-ARI diagnosis increased post-implementation for intervention [1.27(1.21,1.34)] but not control [0.97(0.94,1.01)] sites.

Conclusions: Implementation of the *Core Elements* was associated with reduced antibiotic prescribing for uncomplicated ARIs and a reduction in hospitalizations. ARI diagnostic coding changes were observed.

Introduction

Most antibiotic prescriptions are written in the outpatient setting.[1] Estimates of unnecessary antibiotic prescribing indicate that at least 30-50% of outpatient antibiotic prescriptions are unnecessary.[1-3] Acute respiratory tract infections (ARI) are the largest diagnostic category for which unnecessary antibiotics are prescribed.[2] Even when antibiotics are indicated, guideline-recommended therapy is prescribed half of the time.[4]

Several interventions have improved outpatient antibiotic prescribing. Actions that focus on clinician behavior[5] like audit-feedback with peer comparison[6], accountable justification[6], academic detailing[7], public commitment posters[8], and clinician communication training[9,10] have been effective at reducing inappropriate use. To improve outpatient prescribing, the Centers for Disease Control and Prevention (CDC) released the *Core Elements of Outpatient Antibiotic Stewardship* [11] The *Core Elements* — commitment, action for policy and practice, tracking and reporting, education and expertise — provide a framework to healthcare systems to improve outpatient antibiotic prescribing.

The impact, effectiveness, and safety of implementing the *Core Elements* as a whole have not been assessed.

The study purpose was to describe *Core Elements* implementation in a multi-centered cohort of Veterans Health Administration (VHA) emergency departments (ED) and primary care clinics (PC), determine the impact of implementation on appropriate antibiotic prescribing for ARIs, and assess implementation impact on patient outcomes.

Methods

Four EDs and six PCs (e.g. sites) located in four VHA Medical Centers (VAMC) were recruited to participate by engaging the facility's inpatient antimicrobial stewards. Each site met these requirements: ability to gain commitment from the Chief of Staff to implement a clinician-focused intervention, ability to recruit a champion for each site, and availability of on-site VHA pharmacy services. Sites included four academically-affiliated EDs, three academically-affiliated PCs, and three non-academic PCs. Clinicians (*n* ~ 170) who diagnosed ≥15 uncomplicated ARI visits in the year preceding implementation (62.3% of uncomplicated ARI visits) were targeted for intervention.

<u>Intervention</u>

Targeted ARIs included acute sinusitis, pharyngitis, bronchitis, and upper respiratory tract infection not otherwise specified (URI-NOS).[12-15] Identification of diagnoses were based on International Classification of Diagnoses, 10th revision Clinical Modification (ICD-10) codes or 9th revision equivalent **(Appendix A)**. For patient-visits with multiple diagnoses, the ARI diagnosis was attributed to the visit based upon a tiered hierarchy of indications for antibiotic therapy.[2] Patients with pre-existing conditions (i.e. chronic pulmonary disease, immunosuppression, chronic sinusitis) or a previous ARI diagnosis within 30 days indicating a potentially complicated case were excluded; thus, the intervention and analysis were limited to uncomplicated ARI patient-visits **(Appendix A)**.

As antibiotics are sometimes prescribed shortly before physical visit documentation or once test results are available, antibiotics were attributed to a visit if filled within 2 days prior or 3 days after the visit.[16] To capture prescriptions filled at non-VA pharmacies, a natural language processing program was applied to extract antibiotic prescriptions from visit note text utilizing the same time-frame.[16]

Appropriate therapy was calculated for all uncomplicated ARI. Appropriate therapy for acute bronchitis or URI-NOS was defined as no antibiotic prescribed, whereas for sinusitis it was defined as prescription for an aminopenicillin (±clavulanate)—or in case of penicillin allergy, doxycycline or a respiratory fluoroquinolone—in patients-visits with an antibiotic prescribed.[13,14] Appropriate therapy for pharyngitis was determined based on (a) no antibiotic for cases with a negative Group A rapid antigen detection test or throat culture (or test not performed), (b) penicillin or amoxicillin for cases with a positive test, or (c) cephalexin or clindamycin for cases with a positive test and penicillin allergy.[15] Macrolides were not considered appropriate due to concerns about antibiotic resistance.

We leveraged a pre-existing VHA-ARI graphical interface (i.e. dashboard) to generate and distribute site- and clinician-specific audit-feedback reports with peer comparison.[17] This intervention served as a prototype for implementation within intervention sites.

Interviews were conducted with clinicians from intervention sites to inform the implementation approach. We provided a general description of potential intervention components and sought their opinion on barriers to appropriate antibiotic prescribing and preferences for clinician-focused interventions. The findings, published in a separate manuscript, indicated that implementation strategies should address clinicians' perceptions of their own and peers' antibiotic prescribing practices and enhance their patient communication skills.[18]

Implementation

Implementation was based on the *Core Elements of Outpatient Antibiotic Stewardship*.[5] For the commitment *Core Element*, site champions were recruited to promote and participate in delivery of intervention activities. Letters of commitment were obtained from champions and facility administration, and a kick-off presentation projected commitment to clinicians and staff. Key actions for the policy and practice *Core Element* included clinician-level academic detailing and audit-feedback. Detailing consists of non-commercial, peer-to-peer communication using reinforcement techniques to facilitate change in prescribing practices.[19] A detailing visit accompanied the dissemination of initial audit-feedback reports provided by site champions or surrogates. Follow-up detailing was offered to clinicians that did not improve antibiotic prescribing over time. The Tracking and reporting *Core Element* consisted of audit-feedback reports with the clinician's antibiotic prescribing rate in aggregate and by individual ARI diagnosis, the proportion of ARI diagnoses coded as acute sinusitis, and the proportion of sinusitis and pharyngitis cases treated with appropriate therapy. Graphs illustrated the clinician's ARI management relative to the top 20% of clinicians from their setting (ED or PC) within their VAMC. **(Appendix B)** Audit-feedback reports were distributed in person or e-mail by site champions or surrogates at kick-off and at 2-3-month intervals for 12 months. For the education and expertise *Core Element*, clinicians were encouraged to access vignettes on effective communication strategies for managing ARIs through a multimedia platform, and sites were provided patient educational materials for distribution during visits. Site champions received training on detailing for ARIs and how to generate audit-feedback reports. A common protocol was used to facilitate implementation. **(Appendix B)**

Outcomes

The primary outcome included prescribing an antibiotic for a coded ARI visit pre/post-implementation. Secondary outcomes included ARI appropriate therapy, potential complications of antibiotic under-prescribing (ARI return visits, hospitalizations, infectious complications), and over-prescribing (adverse medication events [ADE], *Clostridioides difficile* infection [CDI]) pre-post implementation. ARI return visits were defined as a physical visit to the participating VAMC with an ARI diagnostic code assigned within 30 days post-visit. Infectious complications (inpatient and outpatient) were identified by assignment of a new diagnostic code for likely related infections (i.e., pneumonia, meningitis, facial cellulitis) within 30 days post-visit **(Appendix A)**. CDI was defined by identification of a positive CDI laboratory test collected within 90 days post-visit for patients without a positive test within 14 days preceding the initial visit. ADE were identified by diagnostic codes consistent with potential

adverse antibiotic effects for visits occurring within 14 days post-visit for patients without a similar diagnostic code within 6 months preceding the index visit **(Appendix A)**.

Analysis

A quasi-experimental design with non-equivalent control group was utilized to assess effects of implementation.[20] The pre-implementation period included all uncomplicated ARI patient-visits that occurred between October 2014 through at least September 2017. The intervention was implemented in three pilot sites in September 2017, and seven additional sites in January of 2018. A 12-month post-implementation observation period for each site ended between October 2018 and February 2019 depending upon the intervention initiation date of the site **(Figure 1)**.

A difference-in-differences analysis controlled for potential external trends in the observational pre-post implementation design. Control sites were selected and matched with intervention sites 4:1 partially based on the Euclidean distance between standardized ARI visit counts and pre-implementation antibiotic prescription proportions. Additional selection criteria for control sites included: geographic region; setting (ED, PC); and number of times the site's VAMC accessed the VHA national Academic Detailing Service (ADS) ARI dashboard. This dashboard was distinctly separate from the dashboard used in our study, and the frequency of its use served as a proxy for the degree of participation in the VHA national ADS ARI campaign.[21] We intentionally selected sites from VAMCs without evidence of extensive participation in the ADS ARI campaign which ran concurrently with our study.

Mixed effect logistic regression models were fitted for primary and secondary outcomes of all uncomplicated ARI patient-visits. Models included a random intercept for VAMC to account for clustering of observations within facility. Fixed effects included calendar month and year, patient age and temperature, setting [ED versus (vs.) PC], pre vs. post implementation time, intervention vs. control site, and the interaction between pre vs. post implementation time by intervention vs. control site. To control for baseline differences in outcomes, models also adjusted for the site-level average event rate before implementation. Odds ratios (OR) with 95% confidence intervals (CI) of pre/post-implementation outcomes were estimated within intervention and control sites separately and a ratio of odds ratios (ROR) with 95% CI reported the estimated intervention effect.

To assess whether clinicians changed diagnostic coding practices associated with the intervention (i.e. diagnostic shifting), mixed effect multinomial logistic regression models that controlled

for calendar year and month were fitted. Changes in diagnoses for each ARI relative to URI-NOS and relative to non-ARI diagnoses pre/post-implementation were estimated.

The intervention was conducted as an operations activity; however, the analysis activities constitute research based on VHA Policy Handbook guideline 1058.05. The research activities were approved by the institutional review boards of each VAMC.

Results

There were 16,712 and 51,275 uncomplicated ARI patient-visits in intervention and control sites over the study time-period, respectively. Most patients were male, in their 50s, and afebrile (T<100.4 F) at presentation. Compared to control sites, patients seen in intervention sites were older, more likely male, seen by a physician, and treated in PC. The absolute number of qualifying coded ARI patient-visits decreased similarly across intervention and control sites post-implementation **(Table 1)**.

The absolute difference in coded uncomplicated ARI patient-visits with antibiotics prescribed was -18.2% lower post-implementation within intervention sites compared to -6.3% lower within control sites [ROR 0.6 (0.48,0.75), *p* value <0.001] **(Figure 2)**. All but one site exhibited a significant reduction in antibiotic prescribing **(Figure 3)**. Antibiotic prescribing within intervention sites declined post-implementation for acute bronchitis, URI-NOS, and sinusitis, but not for pharyngitis, whereas antibiotic prescribing within control sites for all diagnoses remained unchanged **(Table 2)**. The absolute reduction in prescribing within intervention sites was most pronounced for bronchitis [intervention (-21.7%) vs. control (5.9%) sites] [ROR 0.39 (0.27,0.55); *p* value <0.001], but a reduction in prescribing was also observed for sinusitis [intervention (-7.7%) vs. control (-1.7%)] [ROR 0.54 (0.32, 0.92), *p* value 0.02]. The proportion of visits with appropriate therapy increased from 53.8% pre-implementation to 69.1% [OR 1.67 (1.31, 2.14)] post-implementation within the intervention sites. Within control sites the proportion receiving appropriate therapy was unchanged [pre-implementation (41.2%) vs. post-implementation (46.6%), [1.04 (0.91, 1.19); ROR 1.6(1.26,2.04), *p* value<0.001]].

Analysis of outcomes identified a potential benefit associated with the intervention and did not identify harms. **(Table 3)** The proportion of coded ARI return visits decreased from baseline post-implementation in both intervention [-14.8%] and control [-20.4%] sites; however, ARI return visits between study arms were not different [ROR 1.03(0.79,1.34)]. Overall, return visits for ADE were infrequent (<2%) and not different between intervention and control sites [ROR 0.93 (0.58,1.5)]. Random chart review of 125 ADE within intervention sites indicated that 60% were possibly or probably

associated to antibiotic exposure.[22] The most common ADE-related diagnostic codes identified were gastrointestinal [38.9%] and dermatologic [24.6%]. Similarly, infectious complications were uncommon [≤0.5%] and were not different between intervention and control sites [ROR 0.88 (0.38,2.0)]. The predominant infectious complication was pneumonia, which was identified in all but one case. Only two cases of new onset CDI were identified. Notably, 30-day all-cause hospitalization was lower within intervention [-0.5%] compared to control [-0.2%] sites [ROR 0.64 (0.43,0.94), *p*-value 0.02]. The proportion of admissions with a pneumonia diagnosis was lower post-implementation (3.5% vs. 2.1%) within intervention sites compared to control sites (5.0% vs. 5.2%). In summary, implementation was associated with improvements in antibiotic utilization and potential improvement in clinical outcomes.

Analysis of changes in ARI diagnosis pre-post implementation indicated a reduction acute bronchitis diagnosis compared to URI-NOS within intervention sites **(Table 4)**. Similarly, reductions in the diagnosis of acute bronchitis and sinusitis, but also an increase in the diagnosis of URI-NOS relative to all other non-ARI diagnoses were observed **(Table 4)**. Other ARI diagnosis relative to URI-NOS was unchanged within the control sites, while the diagnoses of acute bronchitis and URI-NOS decreased relative to all non-ARI diagnoses. Finally, the OR of an ARI patient-visit classified as uncomplicated was lower post-implementation in the intervention sites [OR 0.83 (0.73, 0.95)] but was unchanged in the control sites [OR 1.11 (1.01, 1.21)] [ROR 0.75 (0.66, 0.86), *p*-value <0.001].

Discussion

We implemented the *Core Elements of Outpatient Antibiotic Stewardship* across multiple practice settings to improve ARI management. Antibiotic treatment was reduced compared to baseline within intervention sites and compared to control sites. Reduced prescribing was greatest for visits coded as bronchitis; however, lesser reductions in prescribing were also observed for other targeted ARIs. Appropriate therapy for uncomplicated ARI improved within intervention sites post-implementation; but was unchanged within control sites.

Core Elements implementation was safe and associated with potential clinical benefit. While ARI-related return visit rates were not different between study arms, all- cause hospitalizations declined within intervention sites relative to control sites. Possible explanations for reduction in hospitalization include unmeasured differences in patient co-morbidity or differences in practice, enhanced application of respiratory tract-related diagnostic and treatment criteria, or unexplained effects of reduced antibiotic therapy. Differences in antibiotic harms due to ADE or CDI were not observed and are unlikely to explain the differences in hospitalization rates.

Study strengths include the integrated electronic health record (EHR) that captured outpatient and inpatient clinician-level diagnoses, treatment, and outcomes data. While the VHA provided an ideal environment for measuring outcomes, many healthcare systems have EHRs that could leverage similar interventional approaches to implement the *Core Elements*. A common protocol provided guidance to site champions on approaches to *Core Element* implementation and facilitated adaptation of the intervention within sites. Finally, the study analysis included a pre-implementation internal control and an external cohort control—which increases causal inference. Our team collaborated with the VHA ADS to implement a national ARI campaign launched in October 2017. The campaign utilized similar ARI diagnostic definitions, treatment recommendations, and antibiotic use measurements. VAMC participation in the ARI Campaign is voluntary; while many facilities participate, others do not. As control sites were selected in part based on how frequently they accessed national VHA ARI Campaign resources, we could not exclude the possibility that control sites were exposed to similar interventions or were less interested in improving ARI management than intervention sites.

Limitations include the small number of audited ARI cases, labor intensiveness of detailing, use of administrative codes to assign diagnoses, and difficulty in identifying suitable control sites. The audit-feedback intervention and analysis excluded potentially complicated ARI cases, which accounted for approximately half of all ARI patient-visits. Audit-feedback reports distributed outside of the ARI season were based on limited numbers of observations, and sites had to adapt the frequency of feedback to 3-month intervals during summer to deliver useful feedback to clinicians. Some clinical outcomes were infrequently observed which may have limited our ability to detect differences for these endpoints. A post-implementation survey indicated that while site champions were comfortable delivering the intervention, they found it challenging to find time to perform these tasks, particularly detailing. As targeted diagnoses were based upon administrative codes the intervention effect was contingent upon accurate diagnostic coding by clinicians. Finally, intervention sites were selected based on their interest in improving outpatient stewardship and their antibiotic prescribing rates were already decreasing prior to implementation more than control sites. It is possible that pre-implementation activities lead to a Hawthorne effect resulting in improved prescribing. While regression modelling adjusted for differences between study arms in estimating intervention effect, it is possible that unmeasured differences in site characteristics contributed to the findings.

Several studies have described improved antibiotic prescribing after implementation of clinician-directed audit-feedback or detailing.[7-8,19,23-25] While audit-feedback with peer comparison of antibiotic

prescribing data without diagnoses can be implemented broadly, the absolute reduction in antibiotic use per clinician is modest.[26,27] Diagnosis-based clinician-level feedback gives important context on how and when clinician's prescribe antibiotics. Respiratory diagnoses are attractive targets for improved antibiotic utilization given the volume of visits and frequency that antibiotics are prescribed for these conditions, but actions based upon administrative coding are susceptible to diagnostic shifting. [28,29] We demonstrated that coding practices for ARI changed post-implementation within intervention sites with reductions in coding of bronchitis and sinusitis but also large increases in the coding for URI-NOS. Smaller changes for bronchitis and URI-NOS diagnoses also declined within the control sites. Diagnostic shifting in response to audit-feedback may be due to appropriate improvements in diagnosis and coding, or deliberate attempts to avoid detection of audited practice. For example, a clinician could correct historical mis-coding practices by correctly coding J44.1 for chronic obstructive pulmonary disease (COPD) with (acute) exacerbation as opposed to J20.9 for acute bronchitis incorrectly in patients with COPD. Likewise, a clinician could intentionally not code J20.9 for acute bronchitis but code R0.05 for "cough" instead, thus avoiding detection of an audited case. We are unsure if the increased diagnosis of URI-NOS relative to other diagnoses within intervention sites was due to improved diagnostic accuracy or an increased willingness to code conditions without antibiotics prescribed as viral. Future interventions utilizing administrative coding data should include broader definitions of organ-system and/or symptoms-based ICD-10 codes in some measures of antibiotic prescribing so that intervention can be summative and targeted. Diagnostic shifting studies should identify individual clinician diagnostic patterns that significantly deviate from peers and quantify the extent of diagnostic shifting attributed to the intervention. Additional areas for study include the feedback delivery method (electronic vs. in person), the contribution of detailing in addition to audit-feedback on antibiotic appropriateness, and development of metrics that capture the unintended consequences of antibiotic excess and omission. Finally, studies that measure the sustained impact of *Core Elements* implementation are needed.

In conclusion, implementation of the *Core Elements of Outpatient Antibiotic Stewardship* associated with safe reductions in antibiotic prescribing for uncomplicated ARIs across varied outpatient settings in the VHA. Healthcare systems interested in improving outpatient antibiotic prescribing should embrace the *Core Elements* framework and consider implementation of similar interventions.

Potential conflicts of interest

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Notes

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Tables and Figure Legends

Table 1. Comparison of Baseline Patient, Clinician, and Site Characteristics within Intervention and Control Sites.

Variable	Pre-Implementation Patient-Visits Intervention Sites *N*=13,439	Pre-Implementation Patient-Visits Control Sites *N*=40,517	Post-Implementation Patient-Visits Intervention Sites N=3,273	Post-Implementation Patient-Visits control sites N=10,758
Patient Characteristic				
Age (Median, IQR)	56 (41, 66)	54 (39, 65)	56 (40, 66)	54 (39,66)
Sex, n (%)				
Female	2,116 (16)	7,322 (18)	572 (17)	2,068 (19)
Male	11,320 (84)	33,195 (82)	2,701 (83)	8,690 (81)
Temperature, n (%)				
No fever (Temperature < 100.4°F)	13,108 (98)	39,498 (97)	3,188 (97)	10,542 (98)
Fever (Temperature 100.4° - <102°F)	254 (2)	737 (2)	68 (2)	174 (2)
High fever (Temperature >102° F)	77 (<1)	282 (<1)	17 (<1%)	42 (<1)
Clinician Characteristics, n (%)				
Clinician Type[A]				
Physician	9,020 (67)	24,479 (60)	2,218(68)	6,369 (59)
Advanced Practice	4,188 (31)	13,406 (33)	1,011 (31)	3,793 (35)
Other	231 (2)	2,632 (6)	44 (1)	596 (6)
ARI visits/Quarter[B] (Mean, SD)				
Emergency Department Clinicians	10 (8.5)	12.7(10.4)	7.7 (7.6)	9.9 (8.7)
Primary Care Clinicians	6.4 (2.8)	6.4 (4.5)	4.8 (2.1)	5.1 (5.3)
Site Characteristics, n (%)				
Site type[C]				
Emergency Department	7,818 (58)	27,760 (69)	1,997 (61)	7,047 (66)
Primary Care	5,621 (42)	12,686 (31)	1,276 (39)	3,711 (34)

Legend:
[A] There were 10,712 patient-visits without a clinician-type identified.
[B] The number of uncomplicated ARI visits per quarter for clinicians with ≥15 visits in the year preceding the intervention.
[C] There were 71 patient-visits without a site-location identified.
Percentages rounded and may not reflect a total of 100 percent.

Abbreviations: IQR-interquartile range, F-Fahrenheit, Advanced Practice - nurse practitioner or physician assistant

Table 2. Antibiotic Prescribing Outcomes for Intervention and Control Sites.

	Intervention Sites			Control Sites				
Outcome	**Pre-Implementation *n* (%)** [A]	**Post-Implementation *n* (%)** [A]	**Odds Ratio[B] (± 95%CI)**	**Pre-Implementation *n* (%)** [A]	**Post-Implementation *n* (%)** [A]	**Odds Ratio [B] (± 95%CI)**	**Ratio of ORs (± 95%CI) [C]**	**P Value**
All ARI	8,017 (59.7)	1,357 (41.5)	0.57 (0.45, 0.70)	29,794 (73.5)	7,226 (67.2)	0.94 (0.81, 1.08)	0.6 (0.48,0.75)	<0.001
Bronchitis	3,082 (84.4)	366 (62.6)	0.32(0.22, 0.46)	11,136 (86.2)	2,638 (80.3)	0.81 (0.62, 1.08)	0.39 (0.27,0.55)	<0.001
Pharyngitis	1,231 (65.3)	249 (52.5)	0.81(0.62, 1.09)	4,324 (73.6)	1,070 (64.8)	0.99 (0.81, 1.21)	0.82 (0.6,1.12)	0.21
Sinusitis	2,264 (89.8)	467 (82.1)	0.56(0.36, 0.90)	7,607 (91.1)	1,912 (89.4)	1.04 (0.71, 1.53)	0.54 (0.32,0.92)	0.02
URI-NOS	1,440 (26.8)	275 (16.7)	0.66(0.44, 0.99)	6,727 (50.3)	1,606 (43.6)	0.94 (0.76, 1.16)	0.71 (0.47,1.06)	0.09

Legend:

[A] The outcomes expressed, *n* (%), are counts and percentages of patient-visits with a specific ARI diagnosis type and with an antibiotic prescribed over total visits with the specified diagnosis type during the pre and post implementation periods. Uncomplicated ARI patient visits within intervention sites pre-implementation *n*= 13,439; post-implementation *n*= 3,273. Uncomplicated ARI patient visits within control sites pre-implementation *n*= 40,517; post-implementation *n*= 10,758.

[B] Odds Ratios (ORs) are the odds of each prescribing outcome pre-implementation and post-implementation within the time-period in either intervention or control sites.

[C] Ratio of Odds Ratios (ROR) is the interaction OR between site group (control vs intervention sites) and intervention indicator (pre and post intervention) or the interaction effect.

Abbreviations: ARI- uncomplicated Acute Respiratory Infection, URI-NOS- viral upper respiratory tract infections, (±95CI)-95% Confidence Intervals

Table 3. Clinical Outcomes for Intervention and Control Sites.

Outcome[A]	Intervention Sites			Control Sites				
	Pre-Implementation *n* (%)	**Post-Implementation *n* (%)**	**Odds Ratio (± 95%CI)**	**Pre-Implementation *n* (%)**	**Post-Implementation *n* (%)**	**Odds Ratio (± 95%CI)**	**Ratio of ORs (± 95%CI)[B]**	**P Value**
ARI-Related Return Visit	1,042 (9.05)	271 (7.71)	1.09 (0.84,1.42)	7,310 (9.75)	1,114 (7.72)	1.06 (0.89,1.27)	1.03 (0.79,1.34)	0.84
Adverse Events	154 (1.07)	28 (0.8)	0.94 (0.60,1.49)	1,286 (1.71)	145 (1.26)	1.01 (0.76,1.36)	0.93 (0.58,1.5)	0.77
Infectious Complication	85 (0.59)	16 (0.46)	0.91 (0.40,2.07)	415 (0.55)	62 (0.54)	1.03 (0.61,1.75)	0.88 (0.38,2.04)	0.77
Hospitalization	307 (2.13)	58 (1.65)	0.70 (0.50,0.99)	1,451 (1.93)	205 (1.78)	1.10 (0.81,1.50)	0.64(0.43,0.94)	0.02
CDI Event	1 (0.01)	1 (0.03)	NA[C]	4 (0.01)	1 (0.01)	NA[C]	NA[C]	NA[C]

Legend:

[A]30-day outcomes for ARI-related return visits, infectious complications, and hospitalization, 14-day outcomes for adverse medication events, and 90-day outcomes for CDI events. The outcomes expressed, n (%), are counts and percentages of patient-visits with the specific clinical outcome over total uncomplicated ARI visits. Uncomplicated ARI patient visits within intervention sites pre-implementation *n*= 13,439; post-implementation *n*= 3,273. Uncomplicated ARI patient visits within control sites pre-implementation *n*= 40,517; post-implementation *n*= 10,758.

[B] Ratio of Odds Ratios (ROR) is the interaction OR between site group (control vs intervention sites) and intervention indicator (pre and post intervention) or the interaction effect.

[C] Insufficient observations resulting in model non-convergence.

Abbreviations: ARI – uncomplicated Acute Respiratory Infection, CDI- *Clostridioides difficile* infection

Table 4. Diagnostic Shifts for Individual ARI Diagnoses in Intervention and Control Sites Post-Implementation.

Individual ARI Diagnoses' Shifts[A]						
	Intervention Sites			**Control Sites**		
Diagnosis[B]	**Pre- Implementation *n* (%)**	**Post-Implementation *n* (%)**	**Odds Ratio (±95%CI)**	**Pre-Implementation *n* (%)**	**Post- Implementation *n* (%)**	**Odds Ratio (±95%CI)**
Sinusitis	4,472 (19.3)	1,081 (18.6)	0.81 (0.61, 1.07)	13,685 (18.5)	3,533 (18.5)	1.02 (0.84, 1.23)
Bronchitis	7,401 (31.9)	1,273 (21.9)	0.59 (0.43, 0.80)	29,524 (39.8)	7,126 (37.2)	1.00 (0.84, 1.19)
Pharyngitis	2,891 (12.4)	811 (14.0)	0.89 (0.67, 1.17)	8,509 (11.5)	2,418 (12.6)	1.05 (0.86, 1.28)
URI-NOS	8,471 (36.5)	2,641 (45.5)	Reference	22,459 (30.3)	6,076 (31.7)	Reference
Individual ARI Diagnoses' Shifts Relative to Non-ARI Diagnoses[C]						
	Intervention Sites			**Control Sites**		
Diagnosis[B]	**Pre- Implementation *n* (%)**	**Post-Implementation *n* (%)**	**Odds Ratio (±95%CI)**	**Pre-Implementation *n* (%)**	**Post- Implementation *n* (%)**	**Odds Ratio (±95%CI)**
Sinusitis	4,472 (0.4)	1,081 (0.4)	0.93 (0.89,0.98)	13,685 (0.5)	3,533 (0.4)	1.01 (0.97,1.07)
Bronchitis	7,401 (0.7)	1,273 (0.4)	0.73 (0.70,0.76)	29,952 (1.09)	7,126 (0.7)	0.92 (0.90,0.95)
Pharyngitis	2,891 (0.3)	811 (0.3)	1.08 (1.02,1.15)	8,509 (0.3)	2,418 (0.3)	0.98 (0.93,1.03)
URI-NOS	8,471 (0.8)	2,641 (0.9)	1.22 (1.18,1.27)	22,459 (0.8)	6,076 (0.6)	0.94 (0.91,0.97)
Non-ARI Diagnoses	1,023,123 (97.8)	298,989 (98.)	Reference	2,627,249 (97.3)	948,033 (98.0)	Reference

Table 4 Legend:

[A] Odds ratios represent the odds of the stated ARI diagnosis (uncomplicated and complicated cases) post-implementation over the odds of the specific ARI diagnosis (uncomplicated and complicated cases) pre-implementation as compared to URI-NOS within the intervention and control sites during the same time-frame.

[B] Wald tests were used to determine if shifts in ARI diagnoses differed in intervention sites versus non-intervention clinics during the same time-period. Portion titled "Individual ARI Diagnoses' Shifts," $p=0.005$; Portion titled "Individual ARI Diagnoses' Shifts Relative to Non-ARI Diagnoses," $p<0.001$.

[C] Odds ratios represent the odds of the stated ARI diagnosis (uncomplicated and complicated cases) post-implementation over the odds of the specific ARI diagnosis pre-implementation as compared to all non-ARI diagnoses (uncomplicated and complicated cases) within the intervention and control sites during the same time-frame. The analysis included all ARI visits (e.g. not restricted to uncomplicated ARI patient-visits)

Abbreviations: ARI – Acute Respiratory Infection, URI-NOS- viral upper respiratory tract infections

Figure 1 Title: Study Design Timeline Demonstrating Staggered Implementation Rollout Period in Control Sites, Pilot Intervention Sites, and Additional Intervention Sites.

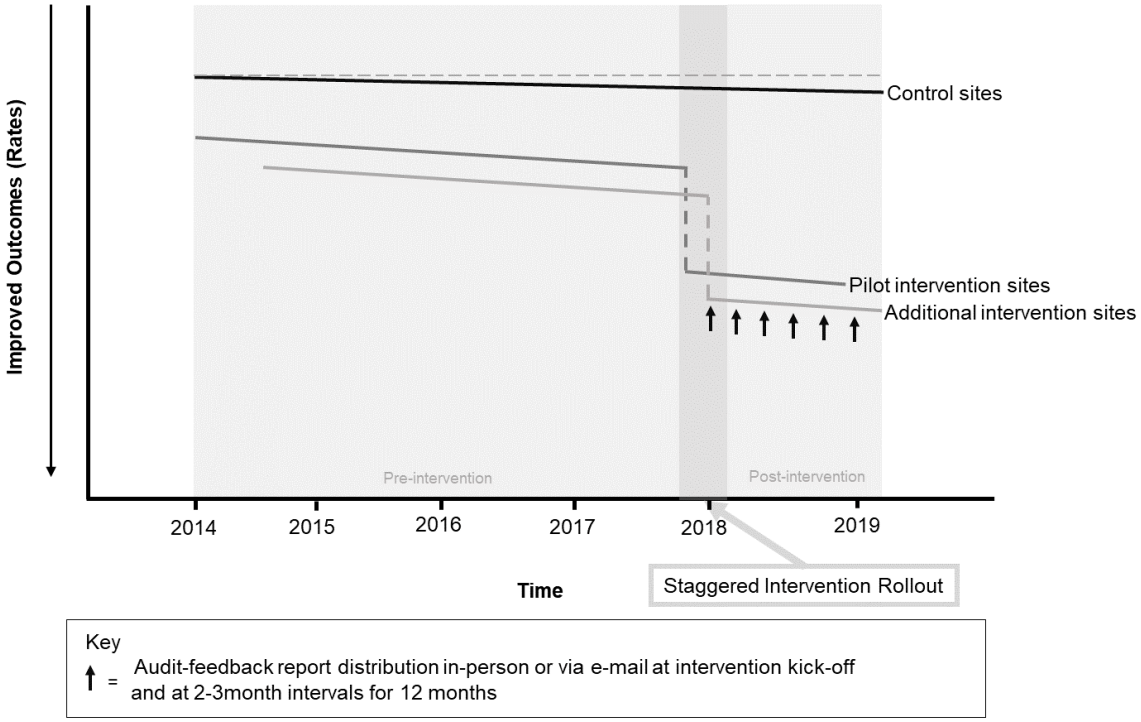

Figure 1 Legend: Conceptual model describing the baseline pre-intervention period, staggered intervention rollout across piloted and additional intervention sites, and the 12-month follow-up post-implementation period. Green arrows indicate the frequency of audit-feedback reports (at baseline and subsequently every 2-3 months).

Figure 2 Title: Antibiotic Prescribing Rate for Uncomplicated ARI in Intervention and Control Sites.

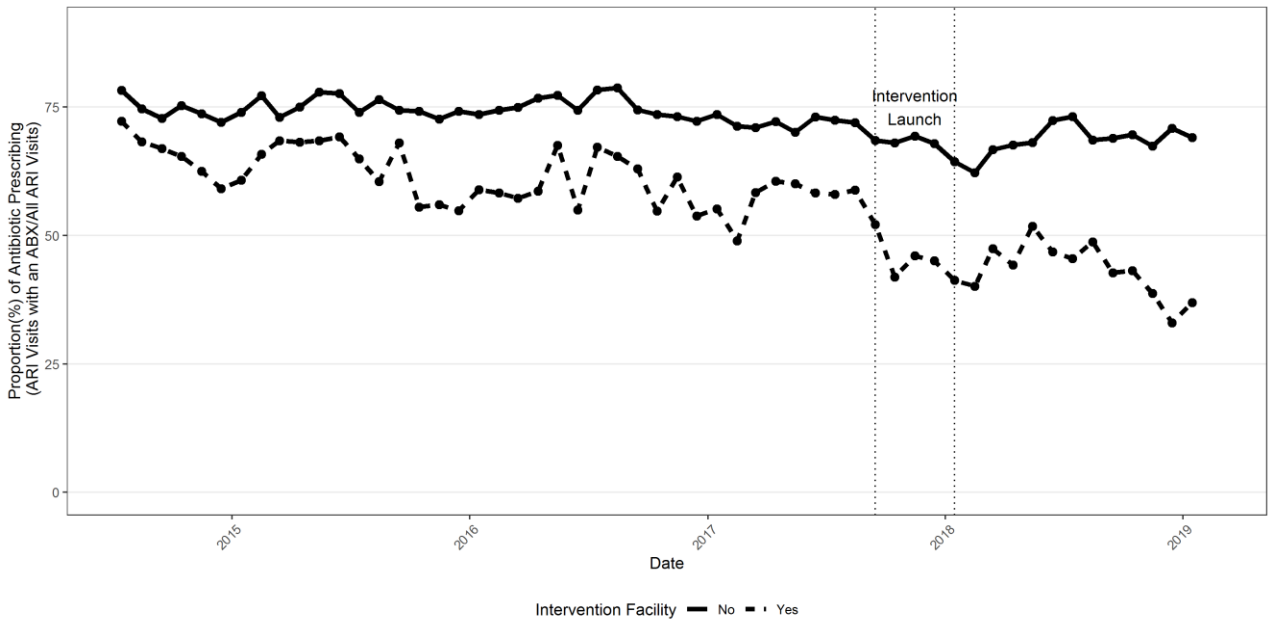

Figure 2 Legend: Monthly antibiotic prescribing rates for control sites (*solid line*) and intervention sites (*dashed line*) over time used in the comparison analyses. Implementation within intervention sites occurred between September 2017 and January 2018 (vertical dashed lines).

Figure 3 Title: Odds Ratio to Receive an Antibiotic for Uncomplicated ARI within Intervention Sites Post-Implementation compared to Pre-Implementation.

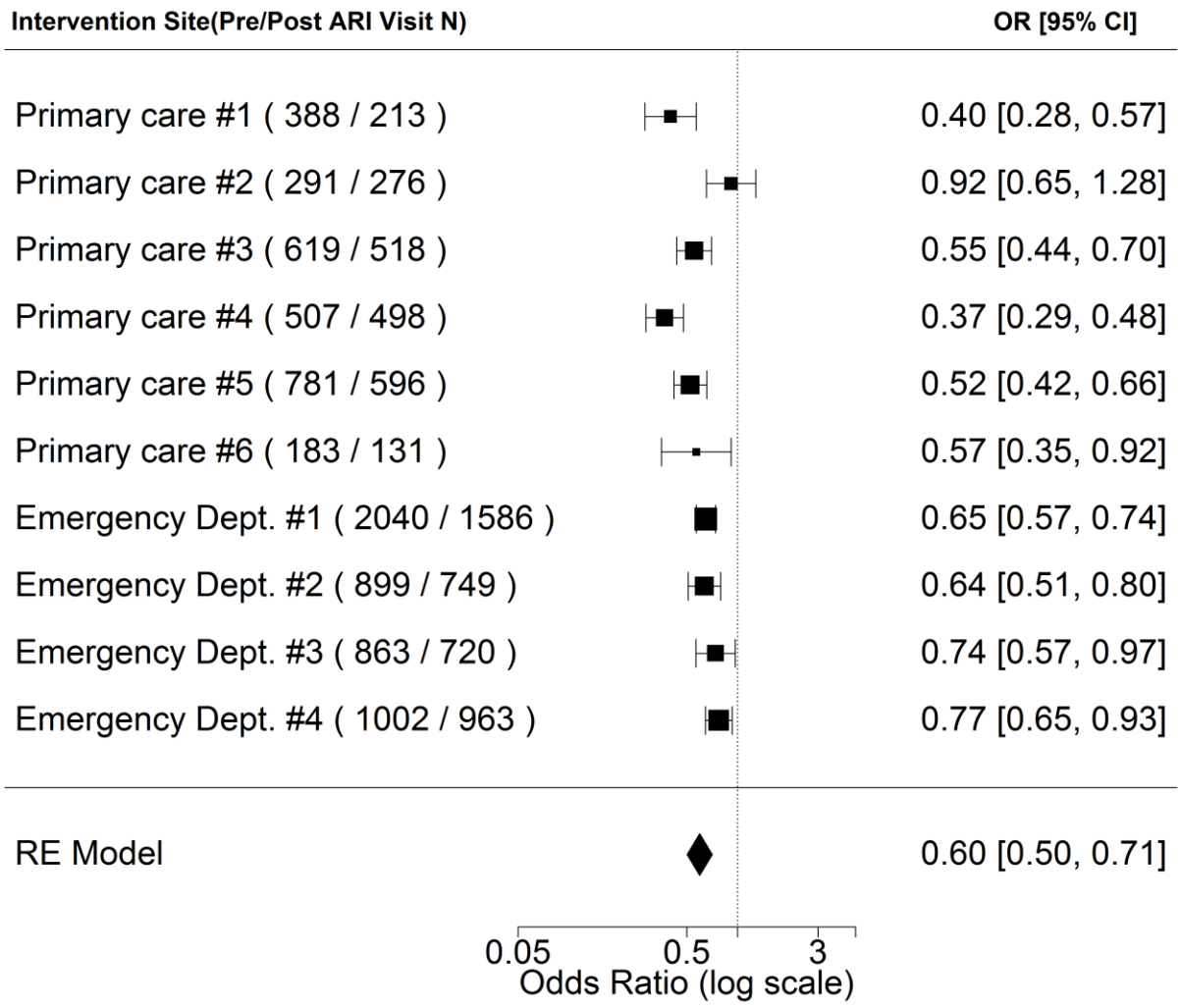

Figure 3 Legend: Odds ratio (adjusted) to receive an antibiotic for uncomplicated ARI within intervention sites for 12 months post-implementation compared to the preceding pre-implementation time-period. The summary OR was estimated using a random-effects model.

Additional Appendices Materials

A. Suggested approach for sites participating in the study.

B. Diagnostic codes for ARIs, Comorbidities, and Outcomes