A Pragmatic Stepped-wedge, Cluster-controlled Trial of Real-time Pneumonia Clinical Decision Support

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ND, CV, BW, SB, and TA participated in ePNa development and study design. ND, CV, JR, BW, NJ, MW, and TA supported ePNa deployment. JA and ML developed the CheXED image processing model and directed its use in the study. ND and CV managed the study. JL, AJ, JJ, JR, JC, NJ, MW, BW and ND participated in data collection, AB performed statistical analysis. ND wrote the first draft and revisions, CV, JC, SB, NJ, BW, JJ, AB, and TA provided critical review and editing.

Impact: In this pragmatic, stepped-wedge, cluster controlled clinical trial, severity adjusted mortality was 38% lower among emergency department patients with pneumonia after deployment of an electronic clinical decision support tool (ePNa) across 16 community hospitals. This result helps validate the 2007 and 2019 American Thoracic Society and Infectious Diseases Society of America pneumonia treatment guidelines on which ePNa logic is

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based and demonstrates the impact of real-time clinical decision support integrated into standard workflows. We are developing a SMART on FHIR version of ePNa to be interoperable among different electronic health records and allow validation outside of Intermountain Healthcare.

At a Glance Commentary

Care of emergency department patients with pneumonia can be challenging. Treatment recommendations have been published in American Thoracic Society and Infectious Disease Society of America guidelines but adoption into clinical practice is challenging. In this 3-year, pragmatic stepped-wedge, cluster-controlled study in 16 community hospitals, we report improved processes of care and 38% lower severity adjusted 30-day all-cause mortality following deployment of electronic, open loop, clinical decision support embedded within the electronic health record (ePNa). ePNa extracts both real-time and historical data to guide diagnosis, risk stratification, microbiology studies, site of care and antibiotic therapy. ePNa requires minimal input from clinicians and gathers/displays data to aid decision making and smooth transitions of care.

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Following ePNa deployment, there was a 17% increase in outpatient disposition and decreased intensive care unit admission without safety concerns. Antibiotic administration was earlier and more aligned with guideline recommendations. Vancomycin begun empirically was mostly discontinued after hospital admission.

These findings replicate the lower mortality observed in our earlier prospective, quasi-experimental, controlled trial.[12] and validate the pneumonia treatment guidelines on which ePNa logic is based. We are developing a SMART on FHIR version of ePNa to be interoperable among different electronic health records and allow validation outside of Intermountain.

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Abstract

Rationale: Care of emergency department patients with pneumonia can be challenging. Clinical decision support may decrease unnecessary variation and improve care.

Objectives: Report patient outcomes and processes of care following deployment of ePNa: comprehensive, open loop, real-time clinical decision support embedded within the electronic health record.

Methods: Pragmatic, stepped-wedge, cluster-controlled trial with deployment at 2-month intervals into 16 community hospitals. ePNa extracts real-time and historical data to guide diagnosis, risk stratification, microbiology studies, site of care and antibiotic therapy. We included all adult emergency department patients with pneumonia over three years identified by ICD-10 discharge coding confirmed by chest imaging.

Measurements and Main Results: Median age of the 6848 patients was 67 years (interquartile range 50-79), 48% female; 64.8% were hospital admitted. Unadjusted mortality was 8.6% before and 4.8% after deployment. A mixed-effects logistic regression model adjusting for severity of illness with hospital cluster as the random effect showed adjusted odds ratio of 0.62 (0.49, 0.79, P<0.001) for 30-day all-cause mortality after deployment. Lower mortality was

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consistent across hospital clusters. ePNa concordant antibiotic prescribing increased from 83.5 to 90.2% (P<0.001). Mean time from emergency department admission to first antibiotic was 159.4 (156.9, 161.9) minutes at baseline and 150.9 (144.1, 157.8) after deployment (P<0.001). Outpatient disposition from the emergency department increased from 29.2% to 46.9% while 7-day secondary hospital admission was unchanged, 5.2% versus 6.1%. ePNa was utilized by emergency department clinicians in 67% of eligible patients.

Conclusions: ePNa deployment was associated with improved processes of care and lower mortality.

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Introduction

Pneumonia is the eighth leading cause of death in the United States, with more than six million cases annually, one million hospitalizations, and over $7 billion dollars for inpatient treatment costs alone.[1,2] When a patient is suspected of having pneumonia, clinicians must (1) assess symptoms and clinical findings to determine whether pneumonia is likely compared to other diagnoses, (2) identify the most appropriate treatment site (home, hospital, or intensive care unit (ICU) and 3) determine whether causative bacteria may be resistant to commonly prescribed antibiotics. These decisions are critical for patient safety but given their complexity and the fundamental limitations of human decision-making, care often deviates from best practice. Studies have consistently demonstrated variability in hospital admission rates between different institutions and between physicians in a single emergency department (ED).[4,5,6] Electronic clinical decision support may decrease unnecessary variation and improve care.[7]

Well-established scientific guidelines help clinicians diagnose and treat pneumonia, but they are underused.[8] The 2007 and 2019 American Thoracic Society/Infectious Disease Society of America (ATS/IDSA) pneumonia guidelines form the knowledge base within our electronic pneumonia clinical decision support tool (ePNa).[9,10] ePNa extracts real-time and

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historical data from the electronic health record (EHR) to guide diagnosis, risk stratification, ordering of microbiology studies, site of care decisions, and treatment. A detailed description of ePNa function is provided in supplementary file #2 and has been previously published.[11]

ePNa was first deployed into four hospital EDs in 2011. A quasi-experimental study demonstrated lower all-cause, 30-day mortality among patients with community-acquired pneumonia compared to 3 nearby usual care hospitals (OR: 0.53; 95% CI: 0.28 to 0.99).[12] Patients with severe illness were more likely to be admitted to ePNa hospitals for treatment and to receive guideline recommended antibiotics compared with nearby usual care hospitals.

Hypothesizing that ePNa would improve mortality (primary outcome) and processes of care (secondary outcomes), we deployed ePNa across all remaining adult Intermountain Healthcare (Utah, USA) community hospitals ranging from 20 to 310 inpatient beds. Intermountain is an integrated non-profit healthcare system with hospital EDs staffed by family practice physicians, nurse practitioners, physician assistants, and board-certified emergency medicine physicians. Annual ED volumes range from 5090 to 60,000 patients with a staff of 5 to 37 clinicians at each

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hospital. We staged implementation with ED leadership support, active clinician engagement in tool development and deployment, educational meetings, academic detailing, and ongoing technical support. Local champions taught and encouraged use of ePNa and study authors conducted audit and feedback at regular intervals. We have previously published the implementation science methods and qualitative results.[11,13]

Here we report 30-day, all-cause mortality and processes of care in ED patients with pneumonia following deployment of ePNa in a pragmatic, stepped wedge cluster-controlled trial.[14] Some of the results of this study have previously been reported.[15]

Methods

Study Design (see supplementary files 1 and 3 for details)

We deployed ePNa into 6 geographic clusters of 16 Intermountain hospital EDs at 2-month intervals between December 2017 and November 2018 according to a prespecified plan (ClinicalTrials.gov Identifier: NCT03358342), figure 1. We chose the stepped-wedge cluster-controlled design to deploy ePNa because our prior study demonstrated decreased mortality[12] and implementation requires intensive education, monitoring, and feedback on ePNa utilization facilitated by focusing on a few hospitals at a time.[14] We grouped hospitals into 6 clusters by

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geographic proximity to each other and need to encompass ED, hospital, and critical care clinicians providing care at >1 hospital. Cluster order enacted our previous commitment to prioritize usual care hospitals from the prior study because of decreased mortality. Deployment had been delayed because Intermountain's legacy EHR had differences that prevented ePNa from functioning beyond where first deployed. We began deployment after Intermountain had transitioned to the Cerner EHR and ePNa was re-programmed. The baseline period lasted 18 months prior to deployment in each cluster beginning June 2016. We excluded pneumonia patients for 2 months after deployment to allow uptake of ePNa into clinical practice. Data were collected until June 2019, 18 months after first cluster deployment.

Patient identification and data

We included all ED patients ≥18 years old with radiographic pneumonia on ED chest imaging plus discharge ICD-10 pneumonia codes.[16,17] Severely ill ED patients transferred from smaller Intermountain hospitals to regional referral centers were attributed to their initial cluster.

We gathered data through queries of Intermountain's enterprise data warehouse. Mortality data were collected from Intermountain medical records and death certificate data from state departments of health. Missing data (most commonly ED mental status and oxygen

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supplementation during SpO2 measurement) were identified by manual chart review; missing data ultimately were <1%. The Cerner EHR does not reliably record ePNa use after the current encounter. Percent ePNa utilization was therefore calculated from physician review (ND, CV, JC, NJ, MW) of individual ED clinician notes identified by pneumonia ICD-10 codes and ED chest imaging, as previously described.[13]

The Intermountain Institutional Review Board approved ePNa deployment and data collection with waiver of individual patient consent (#1050688). Intermountain's Office of Research provided a supporting grant but had no role in study design, conduct, or analysis.

Statistical Analysis

Because ePNa use is not recorded in Cerner and exact time of implementation in each cluster varied by provider meeting schedules, we analyzed the clusters employing the intention-to-treat principle by planned deployment time. *A priori,* we had estimated that approximately 9,370 subjects would be needed to measure a 2% absolute decrease in 30-day mortality with 80% power (see supplementary file 3 for details). Our primary analysis used a mixed effects model to evaluate the relationship between ePNa deployment and severity-adjusted 30-day mortality. To account for secular trends, we included scheduled implementation time as a fixed effect. To

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account for regional differences in practice patterns and patient characteristics, cluster was analyzed as both a random and a fixed effect using validated severity adjustors.

To thoroughly explore possible influence of secular trends on mortality, we conducted several post-hoc sensitivity analyses. We first truncated data to 12 months before and 12 months after the washout period at each cluster, and then further truncated to six months before and after. To further differentiate secular trends from intervention-specific effect, we conducted an additional sensitivity analysis to compare predicted (risk-adjusted) mortality with observed mortality, before and after implementation. This was performed using a mixed effects model with factors influencing mortality (listed in below) but excluding the pre/post-implementation variable, to estimate predicted mortality for each patient and compare with the actual observed outcomes. We also explored using segmented regression to conduct a post-hoc interrupted time series analysis, but the number of events were insufficient for model accuracy (see online supplement 4 for details).

Patient disposition from the ED was compared with what PNa would have recommended (regardless of whether PNa was actually used). Change in disposition after ePNa deployment was adjusted for illness severity using the same mixed methods model as for mortality. Hospital

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length of stay included only admitted patients who survived to hospital discharge. Seven-day secondary hospital admission includes patients with initial outpatient disposition who were admitted to any Intermountain hospital for any reason within 7 days after first ED visit. R version 4.1.0 was used for these analyses.[18]

Results

Out of 7641 patients with discharge ICD-10 pneumonia codes confirmed by ED chest imaging consistent with radiographic pneumonia, we excluded 342 patients from washout periods, 37 who died in the ED or were directly transferred to hospice, one patient with missing mortality information, and 413 transferred to non-Intermountain hospitals for admission where subsequent data were not available, leaving 6848 patients of whom 4536 were before and 2312 after deployment. Figure 1 illustrates the step wedge study timeline and number of patients included in each cluster. Median age was 67 (IQ range 50-79), 48% female, 94% white including 7% Hispanic, Latino, or Spanish origin, and 64.8% were initially admitted to the hospital. Patient demographics are detailed in Table 1.

Mortality

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Observed 30-day all-cause mortality including both outpatients and inpatients was 8.6% before deployment versus 4.8% after deployment of ePNa. A mixed-effects logistic regression model adjusting for severity of illness with cluster as the random effect demonstrated lower mortality post-deployment with odds ratio (OR) 0.62 (95% CI 0.49, 0.79, P <.001), table 2. This estimate was unchanged when modeling cluster as a fixed effect OR 0.62, (0.49, 0.79, P <.001), reflecting consistent changes in mortality among the 6 clusters. Between-cluster variance was 0.63 (SD 0.79), adjusted Intraclass Correlation Coefficient (ICC) was 0.17, and the conditional ICC 0.13.

Results from sensitivity analyses to evaluate for possible secular trend in mortality by limiting enrollment were consistent with the primary analysis – when truncated to 12 months before and 12 months after the washout period at each cluster, OR was 0.66 (0.51, 0.87, P =0.003); when truncated to six months OR was 0.64 (0.44, 0.93, P =0.02). The addition of hospital type to the primary analysis as a random effect resulted in minor changes in estimates and p-values, but no changes to the ultimate conclusions (see online supplement 4 for details). In the mixed effects sensitivity model, *observed* (actual) mortality decreased by 3.8% after ePNa deployment (8.6% pre-deployment vs 4.8% post), which was greater than the 1.4% difference in *predicted* (adjusted) mortality (7.8% pre-deployment vs 6.4% post). Mortality reduction was greatest in

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patients directly admitted to ICUs from the emergency department (OR 0.32, CI 0.14, 0.77, P =0.01), compared to those admitted to the medical floor (OR 0.53, 0.25, 1.1, P =0.09) and with outpatient disposition (figure 2).

Antibiotic use

Among patients admitted to the hospital, guideline/ePNa concordant antibiotic prescribing increased in the 8 hours after ED arrival from 79.5% to 87.9%, after severity adjustment OR 1.9 (1.54, 2.30), P < 0.001. Use of broad-spectrum antibiotics (active against methicillin resistant *Staphylococcus aureus* (MRSA)and/or *Pseudomonas aeruginosa*) within 8 hours was not significantly different, with 27% before and 25% after ePNa deployment, after severity adjustment OR 0.88 (0.75, 1.04), P=0.14. However, administration of antibiotics active against MRSA (mostly vancomycin) decreased from 13% before deployment to 10% after deployment, 15% to 8% between 8 and 72 hours, and from 6% to 3% after 72 hours, all P <.001). Mean time from ED admission to first antibiotic was 159.4 (CI 156.9, 161.9) minutes at baseline and 150.9 (144.1, 157.8) after ePNa deployment (P <0.001).

Disposition

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Overall outpatient disposition for treatment of pneumonia from the emergency department increased from 29.2% before ePNa to 46.9%; a similar increase was observed in patients for whom ePNa recommended outpatient care (49.2% pre-deployment vs 66.6% afterwards). Reciprocally, hospital ward disposition (57.3 vs 47%) and ICU disposition (13.5% to 6.1%) both decreased after ePNa deployment. These changes in disposition after ePNa deployment were significant different after severity adjustment (P =0.036). Despite increased outpatient disposition, neither severity adjusted 7-day secondary hospital admission (69 patients, 5.2% versus 66 patients, 6.1%, OR 1.20 (0.84, 1.71), P= 0.31), nor severity adjusted 30-day mortality were significantly different before versus after ePNa deployment (1.4% versus 2.0% OR 1.4, 0.72, 2.72, P =0.32).

Outpatient disposition also increased (from 15.1% to 24.2% after ePNa deployment) in patients recommended for hospital ward admission by ePNa. Both 30-day mortality (7.2%) and seven-day secondary hospital admission (7.7%) were higher among patients recommended for hospital ward admission but discharged home from the ED, compared with patients recommended by ePNa for outpatient care (0.46%, and 5.7% respectively). To understand this result, ED clinician notes for 52 (25%) randomly selected patients were individually reviewed by ND. ePNa was less commonly utilized than overall, only 10/52 (19%). The most common

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indication for admission in this subset of patients was hypoxemia in 34 patients (65%), of whom 22 (65%) were prescribed or continued home oxygen. eCURB predicted mortality was ≥ 5% (a criterium for hospital admission used by ePNa) in 11 patients (21%), mostly older patients with elevated blood urea nitrogen. Pleural effusions were present in 7 patients (13%) and 20 patients (38%) reportedly declined their clinician's recommendation of hospital admission.

Utilization

Overall, ePNa was utilized by the ED clinician in 67% of eligible patients with pneumonia after deployment. Utilization was 69% in the 6 larger hospitals but 36% in the 10 smaller, rural hospitals. Figure 3 shows ePNa utilization by cluster over time after the washout period.

Discussion

Deployment of ePNa real-time, comprehensive, electronic clinical decision support across 16 community hospitals in a pragmatic, stepped wedge cluster-controlled trial was associated with a 38% relative reduction in 30-day, all-cause mortality among ED patients with pneumonia. The largest reduction in mortality associated with ePNa deployment was observed among patients directly admitted from the emergency department to ICUs. Guideline-concordant antibiotic therapy increased and was administered sooner in the ED. A significantly higher percentage of

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ED pneumonia patients were safely triaged to pneumonia management at home, without significantly worsening 7-day secondary hospital admission readmission or mortality. This represents an important reduction in unnecessary healthcare utilization and cost-savings, while simultaneously improving outcomes overall among ED patients. An intriguing possibility is that lower risk ED pneumonia patients might do better at home than on hospital wards, and on hospital wards than in ICUs due to less nosocomial impact.

These results were achieved using intention to treat principles despite incomplete utilization of ePNa by ED clinicians, explored in prior work published by our group.[11,13,19] These findings replicate the lower mortality observed in our earlier prospective, quasi-experimental, controlled trial in 7 Intermountain hospitals (see introduction).[12] They also are a real-world validation of the 2007 and 2019 ATS/IDSA pneumonia treatment guidelines on which ePNa logic is based. While the 2019 guideline was not published until after study completion, ND's guideline committee membership allowed adoption of recommendations before ePNa deployment.

Emergency department disposition to home also significantly increased in patients recommended for hospital admission, but this subgroup experienced higher mortality than patients recommended by ePNa for outpatient disposition. Case review revealed oxygen

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prescribing for home use in selected patients that ePNa recommended for hospital admission because of hypoxemia. Prior studies have shown that hypoxemic patients with pneumonia have increased risk of mortality,[20,21] but no randomized trial of home oxygen versus hospital admission has been published. Patients in this subgroup who declined their clinician's recommendation of hospital admission might benefit from future plans to provide patient centered severity of illness estimates calculated by ePNa.

The absolute difference in antibiotic prescribing after ePNa deployment was small, perhaps because Intermountain has had a paper-based guideline for community acquired pneumonia in place for 20 years yielding a relatively high guideline concordant antibiotic use at baseline compared to published reports.[22, 23, 24] We hypothesize that ePNa guidance (DRIP score, see supplementary file #2)) for prescribing broad spectrum antibiotics may have targeted patients at risk for drug resistant pathogens. MRSA nasal swab testing recommended by ePNa for patients receiving Vancomycin led to its discontinuation after hospital admission per pharmacy protocol.[25] Some of the observed residual broad spectrum antibiotic use is attributable to early prescribing for sepsis prior to chest imaging, as well as antibiotic allergy history.

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Year to year variation in pneumonia severity reflects differences in circulating respiratory viruses, bacterial serotypes, weather, and air pollution levels. Mean age was 5 years younger after deployment despite inclusion and exclusion criteria being unchanged. Utah has the fastest growing (2% net population increase per year during the study period) and youngest population of any American state (88.6% are less than 65 years old).[26] Age is a severity adjustor in the mixed effects logistic regression model for mortality (Table 2).

Smaller cluster randomized trials of pneumonia clinical decision support have demonstrated increased outpatient disposition but without reduction in mortality. The CAPITAL trial studied a critical pathway with the Pneumonia Severity Index manually calculated by ED nurses and showed an 18% increase in outpatient disposition.[27] Mortality at baseline was about 5% and did not change although patients with severe pneumonia and many with comorbid illnesses were excluded. The EDCAP study implemented a project-developed guideline for initial site of treatment based on the Pneumonia Severity Index and performance of evidence-based processes of care at the emergency department level.[8] Three different strategies with escalating intensity of guideline implementation were utilized, none involving electronic clinical decision support. Outpatient disposition increased by 23% in the moderate and high-intensity hospital clusters. Twenty percent of eligible patients were not enrolled. Mortality reported only in high-

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risk patients was unchanged at ~9%. Compared to the CAPITAL and EDCAP studies, our study cohort had more community hospital patients exposed to the intervention and more severely ill patients where the largest mortality benefit was observed. Unlike prior studies, ePNa is automated, electronic health record based, and displays information to clinicians without requiring manual calculation since it only uses data routinely available in ED encounters.

Limitations

The trial was confined to a single healthcare system in one region of the United States with a patient population that may differ from other regions. Our decision not to randomize by cluster (see first paragraph of methods) may have affected the results. Patients were identified after their encounters by pneumonia discharge codes plus ED radiographic imaging; a method with high specificity but sensitivity of 68% versus physician review.[12] While this approach enrolls higher risk patients unable to provide individual consent, we cannot determine whether results would be different if additional patients with pneumonia were included. Our inclusion criteria do not capture ED patients diagnosed with pneumonia and admitted to the hospital but discharged with a different diagnosis such as pulmonary embolism or cryptogenic organizing pneumonia. We were not able to perform a sensitivity analysis restricted to patients where ePNa was utilized

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due to limitations of the Cerner EHR. Since the DRIP score cannot be retrospectively calculated and was not stored within Cerner, we are not able to specifically link DRIP to antibiotic selection in individual patients.

Conclusion

Deployment of ePNa clinical decision support in 16 community hospitals in a pragmatic, stepped wedge cluster-controlled trial was associated with improved processes of care and lower mortality in ED patients with pneumonia.

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Table 1: Patient demographics.

P-values for categorical variables were obtained using Fisher's exact test. P-values for continuous variables were obtained using T-test. *White race includes 7% Latino/Hispanic. †eCURB = electronically calculated percent predicted 30-day all-cause mortality[17] §PaO2/FiO2 = Oxygen arterial partial pressure divided by fraction of inspired oxygen. **sCAP = American Thoracic Society/Infectious Disease of America minor severe Community-Acquired-Pneumonia criteria, an ordinal scale of 9 criteria[8,9] ††HCAP = Health Care Associated Pneumonia criteria used as a severity adjustor. §§COPD = chronic obstructive pulmonary disease.

Variable	Before Deployment	After Deployment	P-values
N	4536	2312	
Age (years)	68 (53-79)	63 (45-77)	<.001
Female	2175 (48%)	1146 (50%)	0.21
Race, % white*	4293 (95%)	2164 (94%)	0.088
eCURB† (mean)	7% +/- 10	4% +/- 7	<.001
PaO2/FiO2§ (standardized)	314 (252-362)	319 (271-390)	0.002
sCAP**	1 (1-2)	1 (0-2)	<.001
HCAP††	939 (21%)	507 (22%)	0.25
Pleural Effusion	3% (128)	5% (123)	<.001
Diabetes	1628 (36%)	736 (32%)	<.001
Chronic renal disease	1386 (31%)	541 (23%)	<.001
Chronic liver disease	943 (21%)	471 (20%)	0.71

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Chronic heart disease	1568 (35%)	626 (27%)	<.001
COPD§§	1258 (28%)	545 (24%)	<.001
No comorbid illnesses	1433(32%)	894 (39%)	<.001
Unadjusted mortality	389 (8.58%)	112 (4.84%)	<.001
Length of hospital stay (days)	3.2 (2.1, 5.3)	2.6 (1.8, 4.0)	<.001

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Table 2: Mixed effects logistic regression model for 30-day all-cause mortality using intent to treat principles adjusted for severity of illness with cluster as the random effect.

*Season = November 1st to June 1s, †eCURB = electronic CURB-65, §PaO2/FiO2 = Oxygen arterial partial pressure divided by fraction of inspired oxygen, ††HCAP = Health Care Associated Pneumonia used as a severity of illness adjustor, §§COPD = chronic obstructive pulmonary disease.

Variable	Odds Ratio (95% CI)	P values
Intercept	0.00 (0.00, 0.01)	<.001
Post	0.62 (0.49, 0.79)	<.001
Season*	1.16 (0.94, 1.44)	0.171
Age (y)	1.03 (1.02, 1.03)	<.001
Female	0.90 (0.74, 1.10)	0.288
eCURB†	1.05 (1.04, 1.06)	<.001
PaO2/FiO2§ (standardized)	0.67 (0.60, 0.75)	<.001
HCAP††	2.08 (1.68, 2.57)	<.001
Pleural effusion	2.23 (1.49, 3.35)	<.001
Diabetes	0.90 (0.72, 1.11)	0.304
Chronic renal disease	0.91 (0.73, 1.14)	0.415
Chronic liver disease	1.59 (1.27, 1.99)	<.001

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Chronic heart disease	1.54 (1.23, 1.92)	<.001
COPD§§	0.97 (0.78, 1.21)	0.811

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Figure Legends

Figure 1: Stepwise deployment into 6 hospital clusters at 2-month intervals. The pre deployment period was 18 months prior to deployment in each cluster. Post deployment began after the 2-month washout period and ended June 2019. Number of pneumonia patients per cluster per period are contained within the bars. Three larger urban hospitals with intensive care units staffed by critical care physicians are included in clusters 1, 2, and 3; five medium sized hospitals in smaller cities and suburbs with intensive care units staffed by hospitalists in consultation with telemedicine critical care physicians are included in clusters 2 through 5; eight smaller rural hospitals whose family practice clinicians transfer patients to hospitals with intensive care units in consultation with telemedicine critical care physicians are included in clusters 2 through 6.

Figure 2: Severity adjusted mortality by site of care following emergency department discharge. Before ePNa deployment versus after ePNa deployment was 1.4% versus 2.0% for patients with outpatient disposition, 6.0% versus 4.6% for hospital ward disposition, and 15.0% versus 7.4% for intensive care unit disposition.

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Figure 3: ePNa utilization based on individual case reviews by cluster at intervals following the washout periods.

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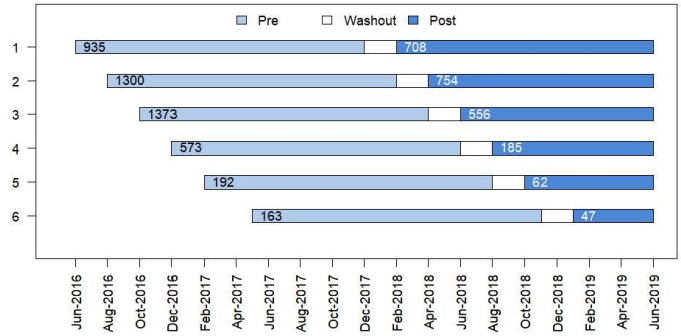

Figure 1 legend: Stepwise deployment into 6 hospital clusters at 2-month intervals. The pre deployment period was 18 months prior to deployment in each cluster. Post deployment began after the 2-month washout period and ended June 2019. Number of pneumonia patients per cluster per period are contained within the bars. Three larger urban hospitals with intensive care units staffed by critical care physicians are included in clusters 1, 2, and 3; five medium sized hospitals in smaller cities and suburbs with intensive care units staffed by hospitalists in consultation with telemedicine critical care physicians are included in clusters 2 through 5; eight smaller rural hospitals whose family practice clinicians transfer patients to hospitals with intensive care units in consultation with telemedicine critical care physicians are included in clusters 2 through 6.

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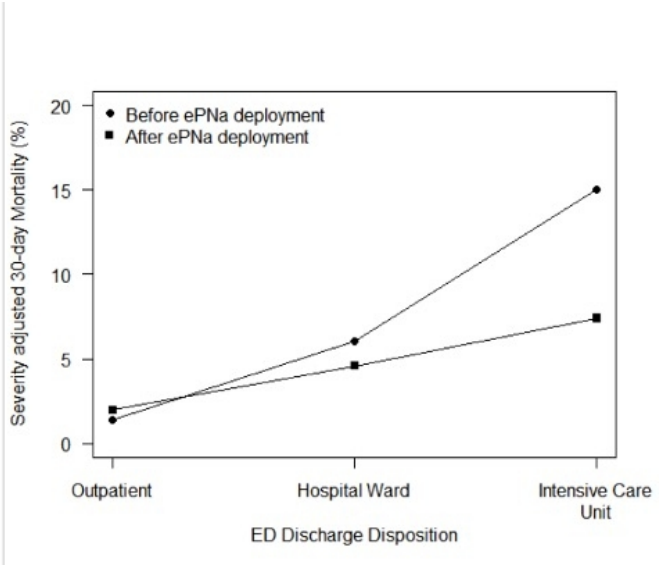

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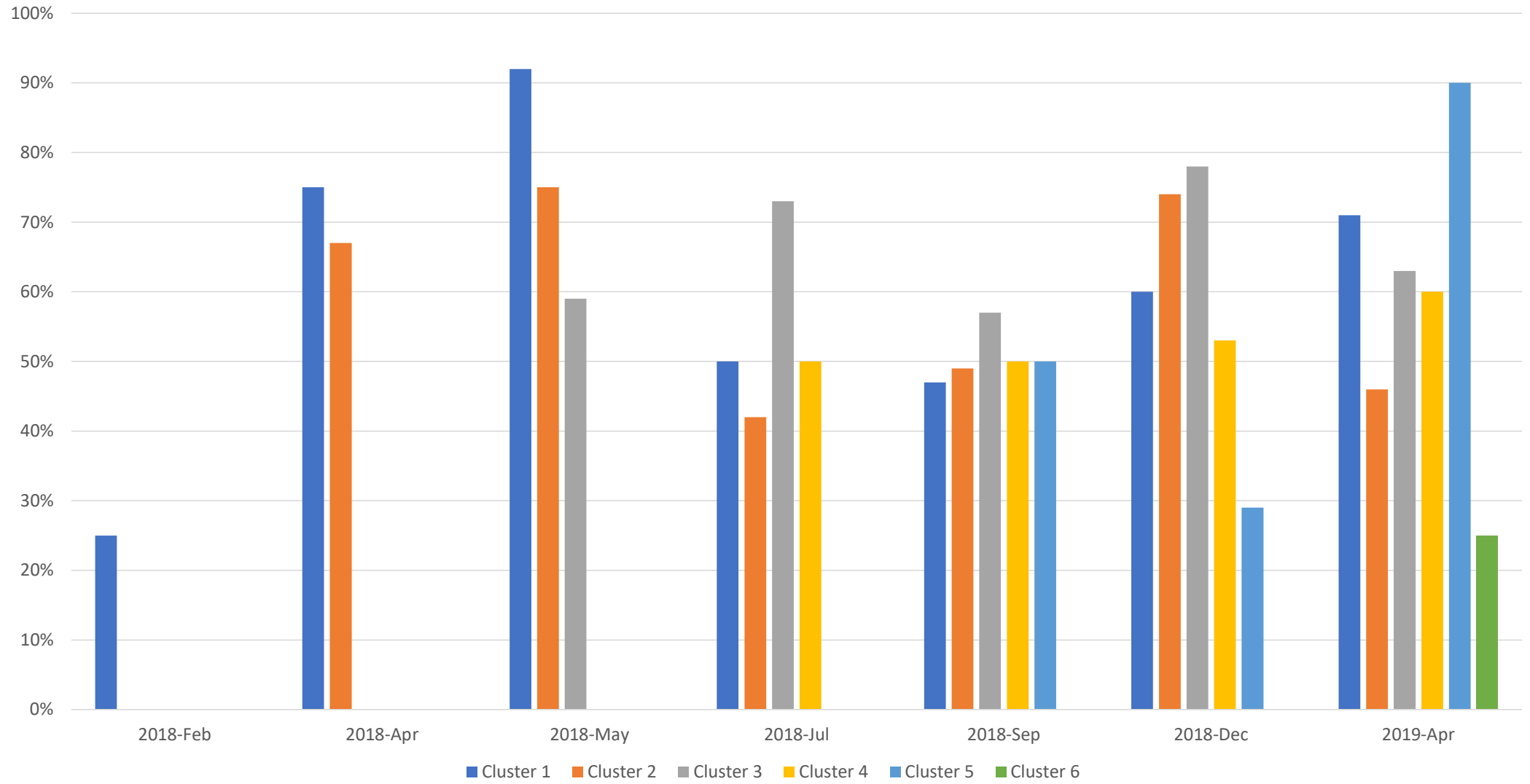
Figure 3



ePNa utilization based on individual case reviews by cluster at intervals following the washout periods.

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Online Data Supplement

Supplementary File 1: Detailed patient inclusion criteria

We used the following codes for patient inclusion: pneumonia ICD-10 codes A48.1, B01.2, J10.0, J11.0, J85.1, J12.*, J13.*, J14.*, J15.*, J16.*, and J18.* We also included patients with primary sepsis codes A40*, A41*, R78.81, R65.20 and R65.21 and/or respiratory failure codes J96.0*, J96.2*, J96.6* and J80 with pneumonia codes in any position. For outpatients we searched for the discharge ED code, for inpatients the hospital discharge code.

Of patients identified by one of these codes, about 75% had possible or likely radiographic evidence of pneumonia. If more than one chest imaging study were available we hierarchically selected computed tomography (CT) studies (mostly CT pulmonary angiograms), then posterior-anterior/lateral 2-view studies, then the first portable CXR if no higher quality study was available. Chest X-rays were classified by the CheXED artificial intelligence model applied retrospectively to CXR images. Accuracy of CheXED is superior to natural language processing and approaches accuracy of radiologist consensus review of chest images.[1] Chest CT clinical radiology reports were categorized for pneumonia elements by study authors (ND, BW, CV, and JC) blinded to date and location of study since CheXED is not currently validated for CT images. Kappa agreement on a sample of 50 reports between authors for radiographic pneumonia was 0.93 (0.79,1.0). We have previously reported that these inclusion criteria have high specificity (0.99), but lower sensitivity (0.68) compared to physician consensus for pneumonia diagnosis.[2] We included only the first episode of pneumonia within 12 months periods.

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Supplementary File 2: Description of ePNa Clinical Decision Support

ePNa integrates pneumonia detection with a management tool that presents needed information to ED clinicians assessing patients with suspected pneumonia. ePNa first identifies ED patients with possible pneumonia based on their presenting symptoms, coded nurse exam findings, laboratory and radiographic findings.[1] ePNa uses natural language processing to identify information in free-text radiology reports to determine radiographic pneumonia. A Bayesian probabilistic algorithm calculates and displays percent likelihood of pneumonia and the pertinent data elements directly to ED clinicians. ePNa alerts clinicians when pneumonia probability is ≥ 40%, chosen to produce a true positive rate of 50% and balance sensitivity versus specificity. The clinician chooses either to launch ePNa or not; use was encouraged after deployment but was not mandatory. Launch of ePNa within the Cerner EHR requires 3 clicks independent of the alert and utilizes data available at the time of launch without requiring all elements be present.

ePNa then calculates illness severity using automated versions of established tools:

- Estimates 30-day mortality risk using a validated electronic severity score (eCURB) with patient age, initial systolic blood pressure, initial respiratory rate, altered mental status, and blood urea nitrogen level as continuous, weighted variables.[2]
- Calculates arterial blood oxygenation compared to inspired oxygen fraction (PaO2/FiO2) from percutaneous oxygen saturation (SpO2).[3] ePNa uses arterial blood gas measurement of PaO2 preferentially when available.
- Tabulates the 9 minor criteria for severe pneumonia (sCAP), summed into an ordinal score.[4]

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- Identifies patients with a small or larger parapneumonic pleural effusion by natural language processing of the chest imaging report.

Site of care

Patients with eCURB predicted mortality ≥ 5%, PaO2/FiO2 < 280 mm Hg adjusted for altitude, or pleural effusion are recommended for hospital admission in accordance with previously validated criteria.[5,6,7] Patients with >3 severe sCAP criteria, or PaO2/FiO2 <120 mm Hg are recommended for intensive care unit (ICU) admission. Severity data are displayed to ED clinicians with the site of care recommendation. ePNa's open loop design allows the clinician to accept or reject recommendations; if rejected, clinicians select from a list of common reasons or inputs free text.

Antibiotic resistant pathogens

Drug Resistance in Pneumonia (DRIP) is a 10-factor ordinal score that measures risk for antibiotic resistant bacterial pathogens developed at Intermountain and externally validated.[8] In 2014, we replaced Health Care Associated Pneumonia logic with ePNa electronic calculation of DRIP to better guide antibiotic treatment recommendations. Antibiotic selection is based on site of care and whether the DRIP score is >3. ePNa recommends doxycycline or amoxicillin +/- azithromycin for outpatients at low risk for resistance with the option of ceftriaxone 1 gm prior to discharge. Most inpatients receive ceftriaxone plus intravenous azithromycin. Vancomycin and cefepime replace ceftriaxone for patients with a DRIP score >3, linked with a recommendation for blood and sputum/tracheal aspirate cultures and urine antigens for legionella and pneumococcus. Patients given vancomycin also receive a nasal swab for MRSA; vancomycin is usually discontinued after the

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initial dose when the swab is negative.[9] In accord with 2019 ATS/IDSA guideline recommendations, during the study period ePNa recommended empiric antibiotics in all patients diagnosed with pneumonia regardless of suspected viral or bacterial etiology.[10] ED clinicians enact ePNa recommendations by clicking an embedded button for one of 6 computerized pneumonia order sets. Percent likelihood of pneumonia, severity scores, radiology results, DRIP score and the ED clinician's response to ePNa recommendations (including their reason for disagreement) are automatically loaded into both the ED and admitting clinician notes, thereby smoothing transitions of care. A more detailed description of ePNa function has been previously published.[11]

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Supplementary File 3: Details of *a priori* power analyses.

Two clinically relevant outcomes were considered when powering this study: mortality, and 7-day secondary hospital admission, and results were compared across a range of effects and heterogeneity. The team ultimately selected mortality since it was the most critical endpoint and we estimated that approximately 9,370 subjects would be needed to measure a 2% absolute decrease in 30-day mortality with 80% power. (E table 1) The power analyses were computed using the weighted average of the previously reported baseline rates in the study Intermountain hospital EDs and accounted for expected imbalance of patient enrollment (E table 2) with heterogeneity among clusters and allowed for a variety of time effects (Equation 1). This avoided artificial inflation of power at the study design stage. R version 3.3.3 was used for these analyses. [1] Power was estimated by Monte Carlo simulation of logistic regression controlling for secular trends and region, with statistical significance determined by $p < 0.05$ by a Generalized Likelihood Ratio Test against a null logistic regression.

$$Y_{ijt} = \frac{1}{1 + e^{-(\mu + \alpha_j + \beta_1 t + \beta_2 t^2 + \theta x_{ijt})}}$$

E table 1: Absolute decrease in mortality of varying degrees

Intraclass Correlation Coefficient	1.5%	2%	2.5%
0.01	15,800	8,160	5,080
0.10	14,100	9,370	4,910
0.20	13,900	7,840	5,510

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E table 2: Anticipated Annual ED Volumes at Each of Six Clusters

	Annual Adult ED patient volumes	Proportion of Study Population
Cluster 1	52,220	0.1415
Cluster 2	67,588	0.1831
Cluster 3	52,316	0.1417
Cluster 4	26,127	0.0532
Cluster 5	19,629	0.0361
Cluster 6	13,319	0.0708
Total	231,199	1.0000

[1] R Core Team (2020). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. https://www.R-project.org/.

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Supplementary File 4

Reviewers asked for additional analyses to explore and confirm results reported in the manuscript. Results of these analyses were robust to the primary reported results. We report these results here for interested readers.

To the primary logistic regression analysis of mortality, we added site descriptors of 1 for the larger urban hospitals with intensive care units staffed by critical care physicians, 2 for medium sized hospitals in smaller cities and suburbs with intensive care units staffed by hospitalists in consultation with telemedicine critical care physicians, and 3 for smaller rural hospitals whose family practice clinicians transfer patients to category 1 and 2 hospitals in consultation with telemedicine critical care physicians. The makeup of the different clusters by hospital category is detailed in the figure 1 caption. The addition of hospital type as a random effect resulted in minor changes in estimates and p-values, but no changes to the ultimate conclusions.

Variable	Odds Ratio (95% CI)	P-values
Intercept	0.01 (0.00, 0.01)	<.001
Post	0.62 (0.49, 0.79)	<.001
Flu Season (Nov 1 - May 31)	1.16 (0.94, 1.44)	0.181
Age (y)	1.02 (1.02, 1.03)	<.001
Female	0.90 (0.73, 1.09)	0.284
eCURB (%)	1.05 (1.04, 1.06)	<.001
P:F ratio (standardized)	0.67 (0.59, 0.75)	<.001

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HCAP	2.08 (1.68, 2.57)	<.001
Pleural effusion	2.24 (1.47, 3.34)	<.001
Diabetes	0.89 (0.72, 1.11)	0.304
Chronic renal disease	0.91 (0.73, 1.15)	0.436
Chronic liver disease	1.58 (1.26, 1.98)	<.001
Chronic heart disease	1.54 (1.23, 1.92)	<.001
COPD	0.98 (0.79, 1.22)	0.871
Cluster (2 vs 1)	0.83 (0.62, 1.10)	0.192
Cluster (3 vs 1)	0.90 (0.68, 1.18)	0.438
Cluster (4 vs 1)	0.71 (0.44, 1.14)	0.159
Cluster (5 vs 1)	0.30 (0.10, 0.77)	0.022
Cluster (6 vs 1)	0.07 (0.00, 0.42)	0.015
Hospital type (ICU with hospitalists/TeleCCM vs ICU with intensivists)	0.93 (0.70, 1.23)	0.629
Hospital type (No ICU vs ICU with intensivists)	0.60 (0.24, 1.31)	0.227

Beyond the sensitivity analyses truncating the before and after periods to 12 months and 6 months, we performed an interrupted time series analysis. Because we didn't design or power the study as an interrupted time series analysis, the model doesn't have enough follow-up data points to confirm if the effects observed were significant. But it does suggest that while there was a down trend in mortality before ePNA, there was a large step down after deployment, followed by stable trend at a lower set point. Figure 1e shows the 30-day mortality percentage for cluster by quarter.

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Interrupted Time Series model for 30-day mortality (3-month time unit)

Variable	Odds Ratio (95% CI)	P-value
Intercept	0.093 (0.04, 0.19)	<.001
Baseline mortality trend before ePNa deployment	0.93 (0.87, 0.98)	0.009
Level change in mortality after ePNa deployment	0.68 (0.39, 1.14)	0.15
Post-Intervention trend in mortality after ePNa deployment	1.06 (0.93, 1.21)	0.37

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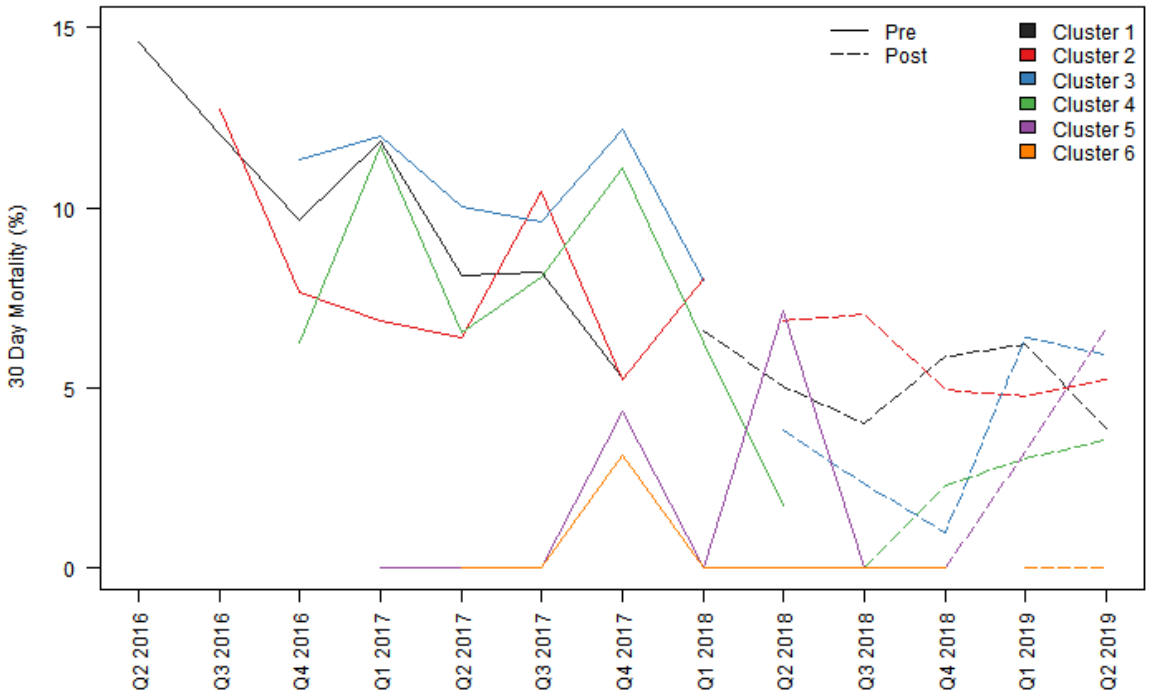
Supplementary Figure 1: Mortality at 3 month intervals from Interrupted Time Series analysis



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