A Trial of Automated Outbreak Detection to Reduce Hospital Pathogen Spread

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CLUSTER (**C**luster **L**inkage **U**sing **S**tatistics to **T**rigger and **E**valuate **R**esponse)
The CLUSTER Trial Protocol

1.0 Background and Goals

1.1 Outbreaks and Patient Safety in Hospitals

Healthcare-associated infections (HAIs) are a leading cause of preventable morbidity and mortality.[1] Some of these infections occur as part of outbreaks resulting from transmission of microorganisms from patient-to-patient via healthcare personnel, contaminated medical equipment, or supplies.[2] For patient safety, The Joint Commission requires hospital infection prevention programs to include outbreak detection and response protocols.[3] Nevertheless, there are no standardized, validated outbreak detection and response strategies.[4]

1.2 The Problem of Detecting Hospital-Associated Outbreaks

Despite the critical importance of identifying hospital-associated outbreaks as early as possible in order to limit their spread,[5-7] there are currently no standardized approaches to outbreak detection.[4] Ideally, outbreak detection methods not only detect HAIs, but also hospital acquisition of colonizing pathogens even before infection occurs. For this reason, clinical microbiology laboratory results are most commonly used for outbreak detection, since these can reflect both colonizing and infecting pathogens regardless of patient symptoms.

In this proposal, we refer to the co-occurrence of similar organisms as “clusters”; some of these represent true outbreaks. Many infection prevention programs rely on infection preventionists noticing unusual clustering of organisms on manual review of microbiology results. Other programs employ a fixed rule method,[8,9] commonly using ≥3 isolates of a hospital-associated organism within 2 weeks detected on the same unit to indicate a cluster. Although a wide variety of pathogens can spread in hospitals,[10-12] resource limitations typically limit outbreak detection to a small set of multidrug-resistant organisms (MDROs) such as methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant enterococcus (VRE), and resistant gram-negative bacteria such as extended-spectrum beta-lactamase producers (ESBLs). Another major limitation of fixed rules is their inability to account for the background prevalence of specific organisms, leading to both over- and under-identification of true outbreaks.

The lack of national investments in this important problem is reflected by the paucity of validated outbreak detection tools and high quality studies to assess existing tools or rules. Ideally, an outbreak detection tool would provide timely alerts, high sensitivity and specificity, ease of operating in real time, and cluster containment.[4,8,13,14] To address these needs, our research group has developed and refined a tool to provide standardized, automated, statistically-based and reliable outbreak detection.

1.3 WHONET-SaTScan as a Solution for Detecting and Tracking Hospital-Associated Clusters

The use of space-time and higher dimensional scan statistics is a promising method to improve hospital-associated cluster detection.[15-17] Our team has developed a statistically-based cluster detection tool by integrating two publicly available software programs created by members of our investigative team and prior faculty collaborators for use in public health epidemiology and clinical microbiology analytics.[8,18-22] WHONET is an analytics software program for management and descriptive analysis of microbiology data, including complex bacterial antibiotic resistance patterns.[23] It has been used for over 25 years in 90+ countries for developing antibiograms and other reports for clinical microbiology laboratories. SaTScan is a disease surveillance software containing various spatial and space-time scan statistics which has been widely used to detect and evaluate geographical disease clusters .[15,16,24-27] The integrated tool (WHONET-SaTScan) has been successfully used to detect clusters across South America and other large regions.[8,18,28,29] It not only detects clusters when pre-specified parameters are reached, but also determines when an cluster has resolved based upon cessation of statistically relevant signals.

We retrospectively applied WHONET-SaTScan to five years of daily microbiology laboratory data from Brigham and Women’s Hospital (BWH), a 793-bed academic medical center.[8] WHONET-SaTScan identified an average of 12 clusters annually. All were deemed to be of clinical interest by hospital epidemiologist reviewers and one-third would have warranted investigation or active intervention had the alerts occurred in real time. Half of the clusters involved gram-negative bacteria that were not routinely tracked by the infection control program. WHONET-SaTScan identified all previously known clusters that had undergone confirmation by genetic typing methods. In each of those clusters, WHONET-SaTScan identified the cluster several days prior to routine surveillance methods.

Furthermore, when comparing clusters of MRSA determined by routine hospital infection prevention surveillance (using the 3-in-2-week fixed rule) versus WHONET-SaTScan, we found that many more MRSA clusters were triggered by the fixed rule criteria (n=73) than by the WHONET-SaTScan statistical thresholds (n = 7) over a five-year period.[8] Similar findings were noted for other pathogens such as VRE. This suggests that many fixed rule alerts may represent random variation rather than true clusters when the baseline prevalence of these pathogens is considered. This has implications for hospital infection prevention resources since programs using non-statistically-based, fixed rule triggers may be allocating limited resources to investigation and containment of false clusters while the majority of statistically unusual events are missed.

We recently expanded this single center retrospective study to 43 geographically diverse hospitals, including both academic medical centers and community hospitals.[30] The cluster detection tool detected an average of 1 cluster/100 beds/year. Based on survey responses, infection preventionists would have wanted to be notified about 81% of the clusters. Half of the clusters increased in size after detection, which would have allowed cluster response interventions to potentially curtail the clusters. All infection preventionists indicated that an automated tool would improve cluster detection at their hospital.

1.4 The Need for a Trial of Cluster Detection Strategies

Until now, there has been no robust alternative to fixed rule cluster detection methods despite the many limitations described above. Current vendor software programs either do not offer cluster detection, fail to separate out community-associated events from healthcare-associated events, or use undisclosed proprietary software. In addition, hospitals do not have standard guidance for how to respond to clusters.[4]

We aim to validate a publicly available system that has already shown promise in over 40 hospitals and to develop a standardized protocol for cluster response.[8,30] In this proposal, we will first conduct a prospective pilot to develop and test the standardized cluster response protocol. Then, we will conduct a cluster randomized trial to compare the impact of the statistical cluster detection tool to the impact of routine cluster detection methods when using the standardized response protocol.

1.5 Defining Valid Cluster Detection

The confirmation of a cluster is usually based upon both epidemiologic investigation that finds a common source and genomic testing that confirms transmission of a clonal strain. Unfortunately, formal investigation and genetic confirmation is uncommonly pursued by infection prevention programs due to time and resource constraints and insufficient training to appropriately conduct either evaluation. For these reasons, standard operating procedure usually dictates responses based solely on total numbers of apparently related isolates.[8] For this proposal, we will use a pragmatic outcomes-based approach to define the validity of our cluster detection tool, namely that responding to the alerts significantly reduces cluster size and duration.

1.6 Evaluate a Statistically-based Cluster Detection Tool to Identify Clusters

This study will be a novel validation of a statistically-based cluster detection tool. Although the tool has been assessed in retrospective evaluations, this will be the first prospective, cluster-randomized trial to assess impact and validity. The **WHONET-SaTScan Cluster Detection Tool** merges two Harvard-developed, publicly available software products which have been re-designed to assess hospital clusters. WHONET,[23] originally developed for management and descriptive analysis of microbiology data, includes a data conversion utility, BacLink, which standardizes and imports data from nearly all microbiology systems into the WHONET format. SaTScan software contains spatial and space-time scan statistics and is widely used to detect and evaluate geographical disease clusters.[15,16,24-27] The tool uses space-time permutation and Poisson software with a novel function that accommodates multiple additional dimensions, including antibiograms, units, services, and sets of units or services that share personnel. Thus another innovation is the ability to pre-specify groups of services or units that are part of the a priori search for clusters (e.g. cardiac surgery and cardiology).

1.7 Development of a Standardized Cluster Response Protocol

The approaches that hospital infection prevention programs use to respond to possible outbreaks vary widely.[4] Responses include, but are not limited to, watchful waiting, alerting unit personnel, increasing cleaning frequency, increased attention to hand hygiene compliance, implementation of unit-wide contact precautions, and screening of asymptomatic patients and/or health care workers to identify carriers. Decisions about when to intervene and which approaches to take vary widely between hospitals and even within hospitals over time. We have assembled a working group of healthcare epidemiology subject matter experts from geographically diverse academic and community hospitals to develop a standardized response protocol to cluster alerts.

2.0 Trial Study Design & Population

The CLUSTER trial will be the first randomized clinical trial to assess the impact of a hospital-based cluster detection system compared to routine cluster detection approaches when combined with a

standardized response protocol. If successful, this trial could provide the first evidence-based protocol for efficient cluster detection and response in U.S. hospitals.

2.1 Hypothesis

Using the refined cluster response protocol and implementation techniques from the pilot study in Aim 1, we hypothesize that the use of WHONET-SaTScan for cluster detection coupled with a robust response protocol will enable rapid containment of hospital clusters as measured by a reduction in cluster size and duration compared to routine infection prevention cluster detection methods combined with the same robust response protocol.

2.2 Health System Partner and Decision Support Software Systems

Hospital Corporation of America (HCA Healthcare) is the largest private inpatient healthcare organization in the U.S. with over 160 primarily community-based hospitals in 20 states. HCA provides 5% of all U.S. inpatient care. HCA's national scope and centralized infrastructure make it an ideal partner for healthcare-associated infection research. Its largely community-based hospitals are more representative of U.S. hospitals than academic medical centers and its centralized electronic data warehouse enables collection of standardized data from all hospitals throughout its health system.

HCA maintains a centralized corporate data warehouse including hospital and unit census data, patient demographic data, nursing documentation, admission and discharge information, diagnosis and procedure codes, and laboratory and microbiology data derived from the clinical information system (MEDITECH). HCA uses TheraDoc (Premier Inc.), clinical decision support software for infection surveillance, tracking, and reporting.

2.3 Study Design and Population

The CLUSTER Trial (**C**luster **L**inkage **U**sing **S**tatistics to **T**rigger and **E**valuate **R**esponse) is an 82-hospital cluster-randomized trial to evaluate the impact of the WHONET-SaTScan cluster detection system and response protocol on reducing the size and duration of signaled clusters. The study population will include all patients hospitalized at 82 HCA-affiliated hospitals between February 2017 and January 2022 (Table 1).

Table 1. CLUSTER Trial - Design and Outcomes

Study Design	Cluster-randomized clinical trial
Unit of Randomization	Hospitals*
Study Population	All patients in 82 participating HCA hospitals
Exclusions	HCA hospitals not in U.S.
Group Assignments **Arm 1 (N=41)** **Arm 2 (N=41)**	Routine cluster detection and response protocol for infection prevention programs WHONET-SaTScan cluster alerts, routine cluster detection and response protocol for infection prevention programs
Study Period	**24-Month Full Baseline Period** (Retrospective Data): February 2017 - January 2019 (Note: we will utilize a 24-month lookback period preceding baseline period for the WHONET-SaTScan analysis) **30-Month Intervention Period:** July 2019-January 2022
Primary Outcome	Size of cluster (number of cases added to a cluster after the first signal)
Secondary Outcome	Duration of cluster (number of days from the first signal to the last isolate collection date in a cluster)

* patient-level data will be analyzed by hospital

2.4 Installation of WHONET-SaTScan

The HCA corporate-wide use of the TheraDoc infection prevention surveillance and decision support system will enhance the implementation of WHONET-SaTScan alerts. Dr. Stelling will work with Premier Inc. to facilitate data feeds from TheraDoc that will integrate into WHONET-SaTScan. Output will flow back to a TheraDoc tracker board. Since TheraDoc requires standardized laboratory feeds, we do not anticipate any unresolved microbiology terminology. We will work with local infection preventionists to map units that share in patient care in order to evaluate clusters that occur across related units. Clusters will be presented to infection preventionists within the daily work flow of TheraDoc, including cluster details, line lists, and option to annotate. Infection preventionists will follow the progression of the cluster using the TheraDoc "tracker board".

2.5 Recruitment

HCA will use its leadership and communications systems to inform hospital decision makers (chief executive officers, chief medical officers, chief nursing officers, infection prevention directors) about the trial and to advocate for participation. Solicitation for hospital participation will be extended to all 165 HCA hospitals. We will also provide webinars through HCA's webhosting system to introduce the trial and the process for participation. Participation will be confirmed by an electronic eligibility survey and a signed letter of participation from each hospital's senior leadership.

2.6 Randomization

Randomization will be performed at the hospital level in order to detect clusters at the hospital and unit levels.[63] Randomizing entire hospitals will ensure uniform cluster detection and response practices within each hospital. During randomization, we will evaluate the need to account for hospital case mix using general hospital data (e.g., average daily census, median length of stay, average elixhauser score) and baseline outcome measures (e.g., number of preventable isolates or preventable days), among others, to improve balance across the arms. We will use a novel approach we developed for a prior cluster randomized trial.[64] In this approach, we will calculate the weighted Mahalanobis distance between pairs of facilities across all key variables for weights representing importance of achieving balance and choose the pairings with the minimum average within-pair distance. We will then assign one member of each pair to each arm.

2.7 Implementation and Compliance

WHONET-SaTScan will run daily in the intervention arm. Alerts will display in TheraDoc with weekday monitoring by infection preventionists. Alerts will also be accessible to investigators and research coordinators who will follow up with compliance assessments. In the control arm, WHONET-SaTScan will be run daily in the background, on all microbiology and census data in the baseline and intervention period to identify clusters that would have been detected had WHONET-SaTScan been running in real time. The output will be saved to a secure folder to which study staff will have no access. On a monthly basis, a de-identified version of this output will be uploaded to the HCA Research Server for a quality assurance check, to confirm that the program is running appropriately.

2.8 Data Collection and Outcomes

Clusters will be identified based upon WHONET-SaTScan analyses occurring in real time, in both intervention hospitals and in routine surveillance hospitals. The primary outcome is cluster size: the number of cluster cases identified after the initial cluster signal from the WHONET-SaTScan software. The secondary outcome is the cluster duration: the number of days from the initial cluster signal through the last cluster case. Additional data will include the number of clusters, cluster type (unit or meta-unit with antibiotic profile when available), pathogen type (gram-positive, gram-negative, fungal) and pathogen species.

2.9 Standardized Cluster Response Protocol for Real Time Implementation

We will leverage the infrastructure of infection prevention programs at participating hospitals to implement the response protocol when a cluster alert is triggered by WHONET-SaTScan in intervention hospitals or when a cluster is detected by routine methods in both control and intervention hospitals. Both intervention and control hospitals will use the same response protocol and receive the same support from study investigators and HCA corporate leaders. The protocol will be predicated on alerting unit personnel to the cluster, assessing and improving compliance with hand hygiene and appropriate precautions, and enhanced environmental cleaning until the cluster ceases (Table 2).

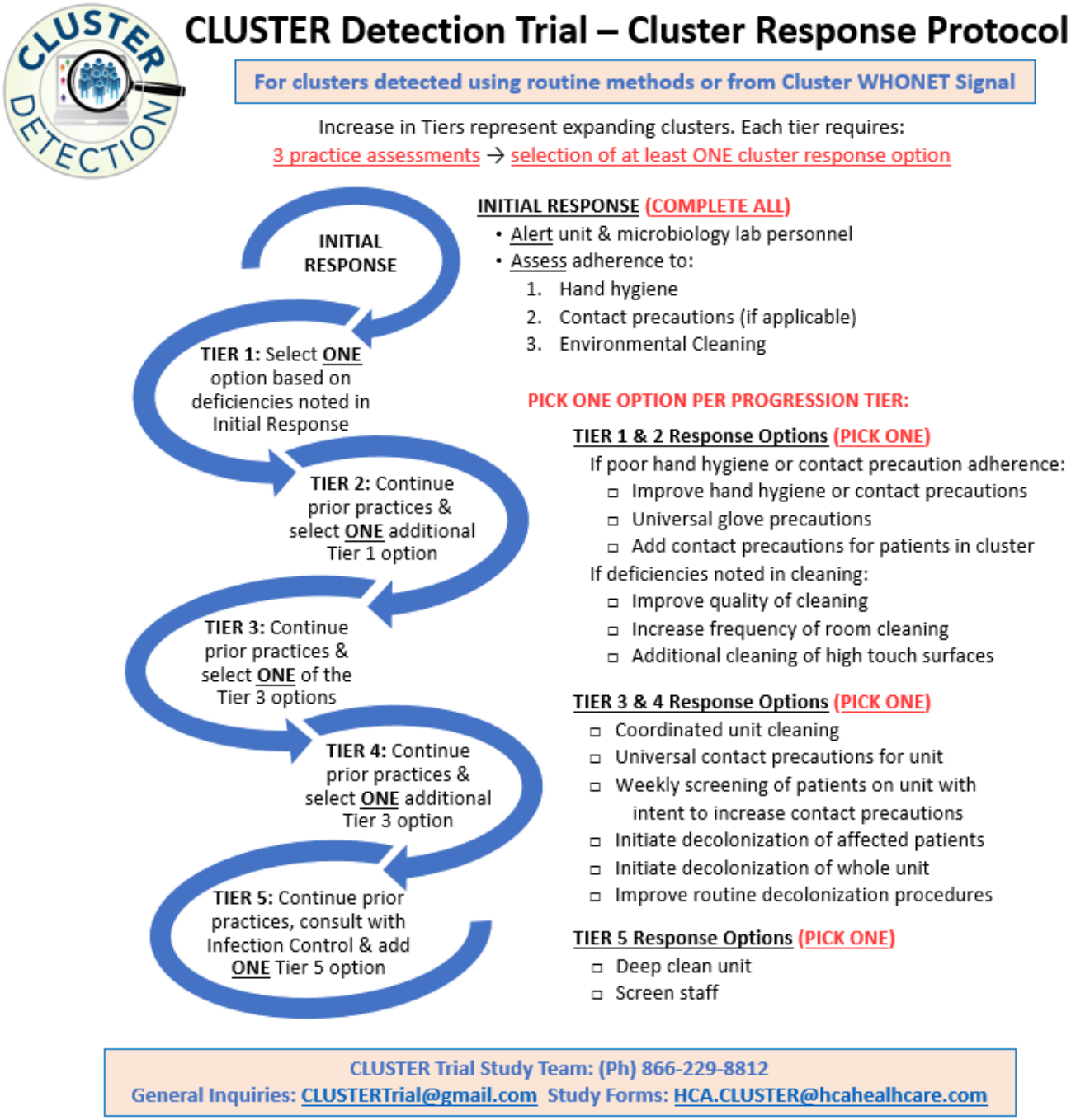
Table 2. Elements of the Standardized Cluster Response Protocol

Elements	Description
Alert unit personnel	Standardized email and call to unit nursing and/or medical directors
Assess compliance with prevention practices	Audits
Hand hygiene	Appropriately performed
Contact Precautions	Check appropriate use, donning and doffing
Adequacy of environmental cleaning	Mark high touch room surfaces and verify next day removal
Interventions	Based on deficiencies noted during audits (see Figure 1)

Cluster alerts will trigger an activation checklist for designated responders and rapidly assess adherence to basic infection prevention practices to identify performance gaps. The on-site responders (infection preventionists or unit director) will perform audits of the rooms of patients belonging to the cluster to assess compliance with hand hygiene and contact precautions, and assess the thoroughness of environmental cleaning by applying an ultraviolet (UV) or ATP bioluminescence marker to high touch room surfaces and assessing the adequacy of removal after daily cleaning.[31-35] Deficiencies noted during these initial assessments will trigger selection and implementation of pre-defined interventions (Tier 1), including improved hand hygiene, improved or enhanced contact precautions (if appropriate), and improved or enhanced environmental cleaning (see Figure 1). Project coordinators at HPHCI will support the on-site responders by encouraging use of the cluster response protocol guidance and forms, and tracking assessment results and interventions. If the cluster progresses, audits will be reinstituted for all patients in the cluster and the response

will be intensified to consider additional Tier 2 through 5 responses, such as pre-emptive precautions, isolation of patients involved in the cluster, screening of asymptomatic patients and healthcare workers, and/or closure of the unit for deep cleaning (Figure 1).

Figure 1. CLUSTER Pilot Study Cluster Response Protocol



3.0 Statistical Analysis

3.1 Background

The CLUSTER (**C**luster **L**inkage **U**sing **S**tatistics to **T**rigger and **E**valuate **R**esponse) Trial is a cluster-randomized trial in 82 HCA Healthcare (HCA) affiliated hospitals designed to assess a statistically-based automated method for detecting clusters of hospital acquired infections, compared to routine assessment. The CLUSTER Trial will assess the impact of a space-time statistical software tool, WHONET-SaTScan, on guiding response and containment of hospital-based clusters.

Hospitals have been randomized to:

- **Arm 1**–Routine cluster detection coupled with an evidence-based cluster response protocol
- **Arm 2**–Enhanced cluster detection using an automated cluster detection tool and routine cluster detection, coupled with an evidence-based cluster response protocol

Trial Outcomes

Clusters will be identified based upon WHONET-SaTScan analyses occurring in real time, in both intervention hospitals and in routine surveillance hospitals. The primary outcome is cluster size: the number of cluster cases identified after the initial cluster signal from the WHONET-SaTScan software. The secondary outcome is the cluster duration: the number of days from the initial cluster signal through the last cluster case. WHONET-SaTScan identifies the beginning of a cluster using a p-value threshold, and we define the end of a cluster as the date of the last case meeting the p-value threshold, by the close of the 180 day window, or end of the trial, whichever date is earlier.

Trial outcomes are found in the below table.

Outcome	Metric
Primary Trial Outcome	
Cluster size	Number of cases identified after the initial cluster signal through the last cluster case
Secondary Trial Outcome	
Cluster duration	Number of days from the initial cluster signal through the last cluster case

3.2 Analysis

Our primary analysis will be an unadjusted generalized linear mixed model that assumes a negative binomial distribution and accounts for groupings of clusters within each hospital. Model terms will include arm (intervention or routine surveillance group), trial period (baseline vs. intervention) and an interaction term between trial period and arm. The assessment of trial success in decreasing the size of clusters will be determined by the significance of the interaction term, which assesses whether the difference in cluster size between the baseline and intervention period differs significantly between the two arms. This model will be used for both the primary and the secondary outcome.

We can write this model symbolically as:

$$\log(y_{ij}) = \beta_0 + \beta_1 Arm_{ij} + \beta_2 Period_{ij} + \beta_3 Arm_{ij} * Period_{ij} + b_{0i} + b_{1i} * Period_i$$

where i is a hospital, j is a signal within the hospital, Arm and $Period$ are indicator variables and are = 0 for signals in a hospital in the routine surveillance arm or baseline period and 1 if in the intervention arm or period. The b_{0i} and b_{1i} are random effects, and account for the clustering within a given hospital, equivalent to usual length or size of cluster at each hospital. These may differ in the baseline and intervention periods. The ultimate effect of the intervention is assessed through β_3: as parameterized, if it is negative and has p-value < .05 (or 95% CI excluding 0) then the intervention reduces the size (primary outcome) or duration (secondary outcome) of clusters.

Subsequent analyses will include as-treated and adjusted models. As treated models in this setting correspond to coding hospitals according to whether they actually implemented the WHONET-SaTScan system. All analyses will be performed using current versions of SAS (9.3, as of writing, SAS Institute, Cary NC) and/or R (3.6.1, as of writing).[36] These analyses will not be included in formal multiple comparisons adjustment because these are non-independent assessments related to the as-randomized unadjusted analyses. Results will be reported only as estimated effects and confidence limits, in keeping with current recommendations.[37] Types of clusters based on pathogen type will be provided as descriptive tables without including statistical analysis.

3.3 Power Assessment

In many settings, an analytic approach to power is possible given that the assumptions of the model (e.g., logistic regression) are met and a relatively simple solution exists. However, generating the expected values to plug in may be difficult. In addition, some settings are complex enough that closed-form solutions may be difficult to generate. Many cluster-randomized designs fall into this class. In cluster-randomized

studies, it is also difficult to obtain reliable estimates of the additional parameters that are required, most notably the between-cluster variance or, equivalently, the intra-class correlation coefficient.

We assessed power using a custom-built simulation/resampling approach. This allowed us to incorporate detailed information from data collected from the hospitals in the study. Briefly, to calculate power by simulation, we 1) generated data under the alternative hypothesis-the data we anticipated seeing; 2) fit the model we planned to fit in the actual study; and 3) recorded whether we rejected the null hypothesis of no detectable effect in the simulated data. We repeated this process many times, and the proportion times we rejected the null hypothesis was used as an estimate of the power under the alternative hypothesis which we used to simulate the data.

Our simulation is based on the actual arm assignments for the trial. For the simulated baseline period in each arm, we use the observed clusters, rather than simulating new clusters; we assume that all clusters are as observed, with a probability of additional cases or days in each arm. In the simulated intervention period, the routine surveillance arm has the observed number of cases from the observed data, while the intervention arm has the effect described below.

We assumed that the intervention would have no effect in 20% of the intervention hospitals. Using the clusters observed in the baseline period within each hospital, we assumed that we prevent 30-50% of the cases after an initial signal during the intervention period in the intervention hospitals, with the actual reduction chosen by a uniform distribution over the described range on a per-outbreak basis. We also assumed that we would shorten the clusters by 50-70% of the observed length after an initial signal in the intervention period in the intervention hospitals. In addition, the extra days and cases added probabilistically to each cluster in the baseline period are not added in the intervention period. Thus, the simulation assumes a secular effect of smaller and shorter clusters.

We then fit the model described above. For our primary analysis, we achieved a power of 100% (95% CI 99.6%,100%) for the main (size) outcome and power of 79% (95% CI 77%, 82%) for the secondary duration outcome. Other assumptions reflected in this estimate include an alpha error level of 0.05.

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