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A Bayesian spatiotemporal model for prevalence estimation of a VRE outbreak in a tertiary care hospital

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SUMMARY

Background: There was a nosocomial outbreak of vancomycin-resistant enterococci (VRE) at the hospital between 1st January 2018 and 31st July 2020. The goals of this study were to describe weekly prevalence, and to identify possible effects of the introduction of selected infection control measures.

Methods: A room-centric analysis of 12 floors (243 rooms) of the main hospital building was undertaken, including data on 37,558 patients over 22,072 person-weeks for the first 2 years of the outbreak (2018–2019). Poisson Bayesian hierarchical models were fitted to estimate prevalence per room and per week, including both spatial and temporal random effects terms.

Results: Exploratory data analysis revealed significant variability in prevalence between departments and floors, along with sporadic spatial and temporal clustering during colonization 'flare-ups'. The oncology department experienced slightly higher prevalence over the 104-week study period [adjusted prevalence ratio (aPR) 4.8, 95% confidence interval (CI) 2.6–8.9; $P<0.001$; compared with general medicine], as did both the cardiac surgery (aPR 3.8, 95% CI 2.0–7.3; $P<0.001$) and abdominal surgery (aPR 3.7, 95% CI 1.8–7.6; $P<0.001$) departments. Estimated peak prevalence was reached in July 2018, at which point a number of new infection control measures (including the daily disinfection of rooms and room cleaning with ultraviolet light upon patient discharge) were introduced that resulted in decreasing prevalence (aPR 0.89 per week, 95% CI 0.87–0.91; $P<0.001$).

Conclusion: Relatively straightforward but personnel-intensive cleaning with disinfectants and ultraviolet light provided tangible benefits in getting the outbreak under control. Despite additional complexity, Bayesian hierarchical models provide a more flexible platform to study transmission dynamics.

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Background

The multi-drug-resistant organism vancomycin-resistant *Enterococcus faecium* colonizes the intestinal tract mainly via ingestion. Infections associated with vancomycin-resistant enterococci (VRE) are associated with increased mortality, morbidity and higher hospital costs [1,2]. However, most cases are carriers, with very few leading to infections requiring antibiotic treatment. VRE were responsible for a large outbreak in the authors' hospital group from 1st January 2018 to 31st July 2020 [3,4] as a result of rapid intra- and interhospital spread.

A number of previous studies have described the risk factors for VRE colonization, which include length of hospital stay, duration and type of antibiotic use, proximity to a colonized or infected patient, contact with environmental contamination, and immunosuppression or haematologic malignancy [5—9]. Previous publications have documented the active surveillance screening and patient isolation processes implemented at the study hospital to reduce the risk of infection [4,10]. In summary, and in line with other settings [11,12], during the outbreak, VRE-positive (colonized or infected) patients were isolated, and a proactive 'contact tracing' process was introduced, whereby people were screened if they had been hospitalized in the same room and ward (and therefore potentially exposed) as a newly detected VRE-positive patient in the preceding 7 days. During the outbreak, cleaning was intensified with measures such as daily disinfection and ultraviolet (UV) light cleaning procedures (amongst others).

A modelling approach was adopted, taking into account potential clustering effects in the data. A 2014 review found 22 such studies using spatiotemporal specific methods for the analysis of healthcare-associated infections [13]. Yu *et al.* presented a rudimentary analysis of severe acute respiratory syndrome as far back as 2005 [14]. Starr *et al.* and Pai *et al.* investigated *Clostridioides difficile* transmission on a single ward [15] and in a tertiary care hospital [16], respectively. Methicillin-resistant *Staphylococcus aureus* (MRSA) (amongst others) was the subject of a study by Rushton *et al.* in an intensive care setting [17]. The present authors decided to follow a Bayesian modelling approach as this allows a more intuitive hierarchical decomposition of the data, and promised more flexibility in terms of considering both spatial and temporal clustering.

This study focused on the main bed tower of a tertiary care hospital, with the objective of describing trends in the prevalence of VRE over the first 2 years of the outbreak (2018—2019). Specifically, the authors were interested in how colonization propagates spatially and temporally over time in terms of prevalence, addressing the following key questions:

- Were specific departments/floors/wards/rooms more affected by the outbreak than others?
- Was there a noticeable effect from the introduction of outbreak prevention measures?
- For floors housing multiple departments, was there evidence of transmission based on geographical proximity, irrespective of department? This would imply a 'floor transmission effect' potentially precluding healthcare employee transmission (e.g. through shared ancillary employees such as hotel services and cleaning).
- For those departments spread across multiple floors, was there similar prevalence on all floors despite lack of geographical proximity (i.e. an 'employee transmission effect')?

Methods

Study population

This retrospective study investigated the prevalence of VRE during the period of the outbreak from January 2018 to December 2019 at the University Hospital in Bern, Switzerland (also known as the Inselspital), a 950-bed tertiary hospital. The study analysed data from the main bed tower of the hospital alone, including information from 37,558 patients (43% of all patients) and 86,391 individual 'room stays' from 243 rooms over 12 floors (Figure S1, see online supplementary material) from 12 departments. Floors house single or multiple departments, with some departments spread over several (often not vertically adjacent) floors. For example, the oncology department is located on two wings of Floor O and one wing of Floor R.

Approval for this study was obtained from the Cantonal Ethics Committee (Bern, Project ID 2020-00173).

Definitions

VRE acquisition was defined as an infection or colonization confirmed by testing [culture initially, and then from mid-2018 onwards using polymerase chain reaction (PCR), with subsequent confirmatory cultures for unclear and positive PCR results]. Wherever possible, colonized patients were placed in a single room with a sign indicating the isolation, and cohorted at one end of the affected ward.

For the analysis, colonized patients were considered positive 7 days prior to a positive test, then afterwards throughout the remainder of their current hospital stay. Furthermore, all rooms in which a colonized patient stayed during their current hospitalization were assumed to be contaminated for that time period. However, rooms were assumed to be disinfected after a colonized patient's stay, so that there was no carryover to the next patient(s) hospitalized in a 'colonized' room. The spatial unit for the study was defined to be one of the 243 patient rooms. Floors in the main hospital building which had few or no patient beds (Floors A—E) were excluded.

The primary endpoint of the study was the prevalence of VRE per room in each of the 104 weeks of the 2-year period, whereby the numerator was the number of colonized, or potentially colonized, patients, and the denominator was the number of patient-days at risk per room and week.

Layout of the main bed tower

To standardize the model structure, all floors were assumed to have 22 single or multiple occupancy rooms, situated in three building wings; north having four rooms, the long middle corridor having 14 rooms, and south having four rooms (refer to Figure S2A of the online supplementary material for Floor O). The majority of patient rooms are situated on one side of the corridor, with clinical staff and other utility rooms on the other side of the corridor (Figure S2B, see online supplementary material). For the spatial analysis, the digital architectural

schematics were used to construct a (22 x 22 room) symmetric matrix containing the Euclidean distance between the centroids of the rooms.

Isolation and other precautionary measures during the period of the VRE outbreaks were defined on a departmental basis, meaning they applied to part of a floor (i.e. a ward), a complete floor or multiple (parts of) floors. Specific rooms were often reserved for cohorting colonized patients (e.g. Room 123 of the middle corridor on Floor O), but in this regard, the specific room varied by department.

Data extraction

Diverse data were gathered from electronic medical records generated during the period of the outbreak, covering room characteristics such as floor, building wing (north, middle, south), number of beds in a room, room area (in m^2), room type and department, along with temporal measures (week, season). The time period granularity was chosen to be on a weekly basis as this was the approximate median length of hospitalization. VRE acquisitions (colonized or infected) were labelled as 'VRE positive' according to the definition above, and all other patients were assumed to be VRE negative.

Exploratory data analysis

Plots of crude prevalence per room and floor were used to visually investigate spatial, temporal and spatiotemporal trends, which were then confirmed using appropriate statistical tests [Moran's *I* test (spatial), Durban–Watson test (temporal) and Knox test (spatiotemporal)]. Room-centric uni- and multi-variable covariate adjusted Poisson models were fitted to determine risk factors for colonization. Sandwich-type standard errors were calculated to compensate for rooms being included multiple times in the analysis. An interrupted time series model was fitted to determine the potential effect of the introduction of specific interventions during the outbreak.

Bayesian hierarchical model

A room-centric multi-level Poisson Bayesian hierarchical model (BHM) was fitted to take into account the spatial and temporal clustering by including appropriate random effects terms. The dependent variable was defined to be the total number of confirmed colonized patient cases in a room with:

$$\text{Cases}_{it} \sim \text{Poisson}(\mu_{it}),$$

for room *i* and week *t*. The denominator (offset) for the model was defined to be the total number of patient-days in the respective room and week. Spatial correlation was modelled using an intrinsic conditional autoregressive approach by including an adjacency matrix for the rooms on each floor (e.g. Besag *et al.* [18]); elements of the matrix were defined to be 1 if the distance between the centroids of each room was less than a pre-specified distance *D*, and 0 otherwise. Temporal effects were captured using a simple first-order random walk process. Appendix B (see online supplementary material) describes the model in more detail.

Two versions of the model were fitted:

- Model M1 ('single floor'): each floor was modelled separately, and the mean effect estimates per floor were combined using a random effects meta-analysis.
- Model M2 ('all floors'): all floors were modelled at the same time.

Markov–Chain Monte Carlo simulation with Gibbs sampling was implemented to estimate posterior distributions of the unknown model parameters. An initial burn-in period of 4000 iterations was followed by sampling of 10,000 iterations for the estimation of posterior distributions. WinBUGS code is provided in Appendix D (see online supplementary material). Model convergence was investigated using the *CODA* package in R [19].

Supplementary analyses included an investigation of the effect of varying the adjacency distance parameter (*D*), the influence of fitting an informative prior on the floor level estimates, and consideration of missing data issues (Appendix B, see online supplementary material).

OpenBUGS Version 3.6.3 was used for fitting the BHM [20], and R Version 3.6.1 was used for statistical analyses [21]. A statistical level of 5% was considered significant throughout, unless stated otherwise.

Results

Exploratory data analysis

Plots of crude prevalence indicated significant differences between departments and floors, with the cardiac, oncology and nephrology departments exhibiting slightly higher levels over the whole time period (Figure S3, see online supplementary material). A more indepth analysis on a monthly basis revealed differences between floors, with colonization 'flare-ups', followed by periods with no or few cases (Figure S4, see online supplementary material). Both temporal and spatial correlation is apparent during the flare-ups [e.g. Floor O (oncology and cardiac) in Figure S5, see online supplementary material]. These findings were confirmed using Moran's *I* statistic with crude prevalence values; Floors O, Q and R exhibited some degree of spatial correlation [$P<0.001$ (Floor O) and $P=0.01$ (Floors Q and R)]. The fitted Poisson model indicated that approximately half of the 104 weeks (53.4%) showed some degree of spatial correlation (i.e. Bonferroni corrected *P*-values <0.05), and the Durban–Watson test revealed that approximately 58% of the 243 rooms showed some degree of temporal correlation (corrected *P*-values <0.05). The Knox test performed for each floor and week revealed similar findings, with Floors G, O and Q exhibiting evidence of spatiotemporal correlation ($P<0.005$).

Estimated peak outbreak prevalence was reached in July 2018, which was followed by the introduction of a number of new infection control measures, including the daily disinfection of rooms (instead of cleaning with a detergent), and room cleaning with UV light upon patient discharge (the latter in October 2018). Interrupted time series analysis with the 'interruption' defined as July 2018 (outbreak week 29) showed a significant decrease in prevalence following this time point [adjusted prevalence ratio (aPR) 0.89 per week, 95% confidence interval (CI) 0.85–0.93; $P<0.001$; Figure 1]. Multi-

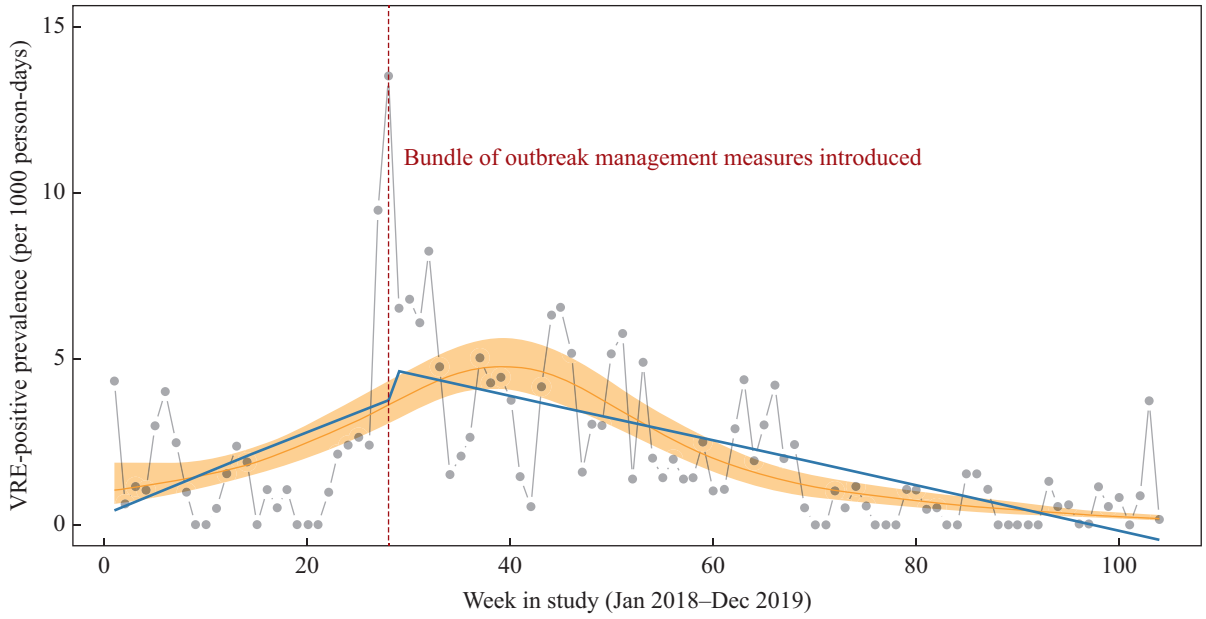

Figure 1. Crude prevalence of vancomycin-resistant enterococci (VRE) colonization (grey) with fitted unadjusted general additive model (restricted cubic spline with six knots) and 95% confidence intervals (orange, shaded), and interrupted time series (blue solid) with 'interruption' defined as the time of the introduction of the first bundle of outbreak management measures in July 2018 (red dashed).

variable Poisson models revealed that prevalence was marginally higher in summer (aPR 2.3, 95% CI 1.6–3.2; $P<0.001$; Table I) and autumn (aPR 2.2, 95% CI 1.6–3.0; $P<0.001$), even after adjusting for time with both linear and spline regression terms. The oncology department, where the outbreak was thought to have started, experienced slightly higher prevalence (aPR 4.8, 95% CI 2.6–8.9; $P<0.001$; compared with general medicine), as did both the cardiac surgery (aPR 3.8, 95% CI 2.0–7.3; $P<0.001$) and abdominal surgery (aPR 3.7, 95% CI 1.8–7.6; $P<0.001$) departments.

The authors were also interested in testing the potential effect of employee movements between floors of the same department, such as when people work on multiple floors during their shift. In subgroup analyses of the five departments distributed across two or more floors, there was no discernible overall difference in prevalence between different floors from the same department ($P=0.4$). This apparent homogeneity may infer transmission via employees, but this could not be shown definitively. Furthermore, two departments split across multiple floors did show a difference in prevalence between their constituent floors, and one of them, oncology, was known not to share employees between floors [Oncology Floor O (reference) compared with Oncology Floor F, PR 2.6, 95% CI 1.6–4.3; $P<0.001$]. This would seem to tentatively support the hypothesis that prevalence is similar across a department split across multiple floors when employees move between these floors, perhaps indicating that VRE colonization is transferable between floors with employees as the vector. Of course, this has disregarded possible transmission by non-ward-specific employees, such as those performing hotel services and cleaning tasks.

To this end, further supplementary analysis investigated potential transmission across department boundaries within the same floor, but the results were largely inconclusive (Figure S6 in Appendix C, see online supplementary material).

In summary, the exploratory analysis revealed considerable differences in prevalence between rooms, floors and departments. This, along with the presence of spatial and temporal correlation, modest overdispersion in the fitted Poisson models, and the many weeks/rooms having few or no cases (i.e. so-called 'zero inflation') recommended fitting a more flexible Bayesian hierarchical model.

Bayesian hierarchical model

Comparison of the two model implementations revealed that both fitted the observed data rather well. The 'single-floor meta-analysis' approach (M1) followed crude average prevalence more closely (Figure 2), whereas the 'all-floors average' model (M2) dampened the amplitude of the peaks somewhat, smoothing weekly transmissions (Figure S7A, see online supplementary material); here, the focus is on the results from Model M1. In terms of goodness of fit, and referring to Figure 2, the majority of observed prevalence estimates (in grey) are contained within the 95% credible intervals from the model (in pink), with the model having most difficulty predicting the outcome in weeks with very low or no recorded VRE cases.

Supplementary analyses

Altering the definitions used for the adjacency matrix changed the fitted estimates for both the fixed and random effects, but the estimates remained within the 95% CI for the baseline model presented in the Results (results not shown).

As expected, fitting an informative prior in the model, based on prevalence in the oncology department, increased the

Table I
Prevalence risk estimates from the fitted Poisson model per room and week

Dependent variable: VRE acquired Offset = log(time at risk)	Univariable (*N*=243 rooms, 22,702 weeks)		Multi-variable (*N*=243 rooms, 22,702 weeks)	
Room and patient in room characteristics	PR (95% CI)	*P*-value	PR (95% CI)	*P*-value
Time (weeks)[a]	1.0 (1.0–1.0)	<0.001	1.0 (1.0–1.0)	<0.001
Season				
Winter	1 (reference)		1 (reference)	
Spring	1.8 (1.2–2.8)	0.005	-	NS
Summer	4.1 (2.8–6.0)	<0.001	2.3 (1.6–3.2)	<0.001
Autumn	3.0 (2.2–4.2)	<0.001	2.2 (1.6–3.0)	<0.001
Building wing				
Middle	1 (reference)			
North	-	NS		
South	-	NS		
Capacity (number of beds)	0.9 (0.7–1.0)	0.07	-	NS
Area (m^2)	1.0 (1.0–1.0)	0.08	-	NS
Room type (22 types)				
All other rooms	1 (reference)			
Room 108	0.3 (0.1–0.8)	0.02	0.5 (0.3–0.9)	0.01
Room 109	0.2 (0.1–0.8)	0.02	0.3 (0.1–0.7)	0.005
Room 112	0.2 (0.1–1.0)	0.05	0.3 (0.2–0.6)	<0.001
Room 127	0.3 (0.1–1.2)	0.08	0.4 (0.2–0.9)	0.04
Room 128	0.3 (0.1–1.1)	0.08	-	NS
Department[b]				
General internal medicine	1 (reference)		1 (reference)	
Cardiac	8.4 (4.4–16.1)	<0.001	7.4 (3.8–14.5)	<0.001
Ear, nose and throat	0.1 (0.0–0.5)	0.01	0.1 (0.0–0.6)	0.01
Cardiology/angiology		NS		
Nephrology and hypertension	15.0 (8.0–29.2)	<0.001	15.2 (8.2–28.3)	<0.001
Neurology	0.4 (0.2–0.9)	0.03	0.4 (0.2–0.8)	0.02
Oncology	6.0 (3.0–11.7)	<0.001	5.4 (3.0–10.0)	<0.001
Orthopaedics	-	NS	-	NS
Plastics and hand surgery	-	NS	-	NS
Pneumology	-	NS	-	NS
Visceral surgery and medicine	3.3 (1.7–6.6)	<0.001	2.7 (1.4–5.3)	0.002
Mixed floor				
Single department floor	1 (reference)			
Multiple department floor	1.4 (0.9–2.2)	0.1	-	NS
Department split across multiple floors				
Single floor department	1 (reference)			
Multiple floor department	-	NS		

VRE, vancomycin-resistant enterococci; PR, prevalence ratio; NS, not significant at the 5% level; CI, confidence interval.
[a] Estimates for spatial coordinates and their interaction with time, along with time^2, time^3 and the cubic spline fit (with six knots) from the general additive model were all significant at the 5% level (not shown).
[b] Floor not fitted as collinear with department.

estimated prevalence per floor considerably (Figure S7B, see online supplementary material). However, this particular scenario was deemed to be overly pessimistic in terms of prevalence estimation, and therefore the baseline modelling assumptions were preferred and presented in the results.

Discussion

A number of approaches were applied sequentially to characterize a VRE outbreak in the main bed tower of the hospital, choosing prevalence as the endpoint as the authors were interested in how colonization propagates in such a setting. The oncology department, where the outbreak was first detected, was particularly affected, as were the cardiac surgery (co-located with oncology) and abdominal surgery departments. However, there were periods of time on these wards with low or no cases, followed by 'flare-ups' involving several rooms over a period ≥2 weeks. Peak outbreak prevalence was estimated to have occurred in July 2018, after which there was a steady decline in cases until the end of 2019. This decrease followed the introduction of a number of relatively straightforward but personnel-intensive room cleaning measures, although this association was not definitely attributable to the decline. Other bundles of measures were introduced later in the outbreak, and it can certainly be argued that these also contributed to the reduction in prevalence over time. This study was underpowered to detect potential transmission between departments on the same

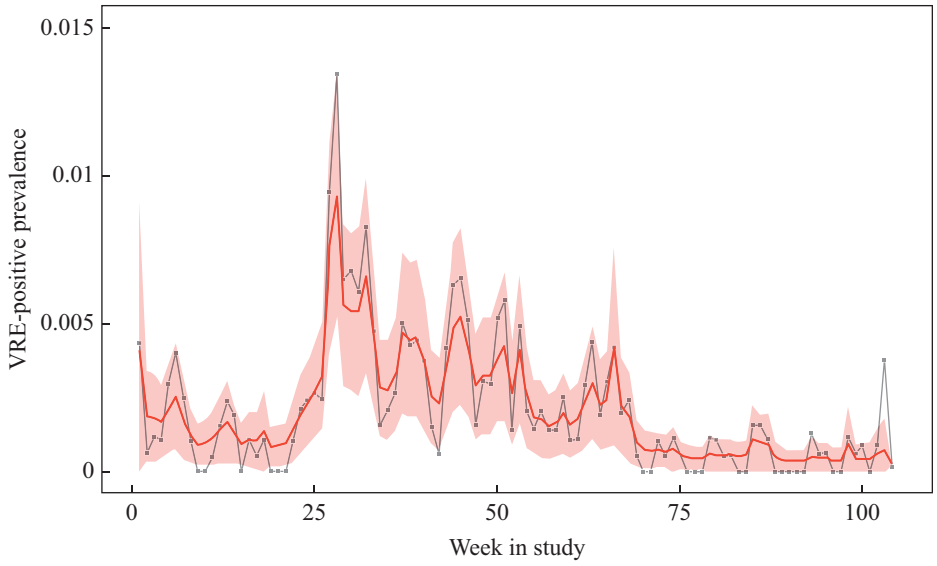

Figure 2. Crude prevalence per week (solid, grey) and posterior distribution weekly estimates from the single-floor meta-analysis approach (Model M1, solid red) with 95% credible intervals shown shaded in pink. VRE, vancomycin-resistant enterococci.

floor or between floors of the same department; this is a potentially interesting area for prospective investigations involving employee screening.

In terms of methodology, this study is most similar to those performed by Kong *et al.* [22,23]. They also adopted a BHM approach, albeit applied to an MRSA outbreak rather than VRE. Furthermore, a recent genomic surveillance noted that 'subtypes carried by multiple patients were particularly associated with contamination of communal bathrooms and medical devices' [24], which highlights the oral transmission path associated with VRE, and confirms its longevity, especially on surfaces. Consequently, the present authors were particularly interested in determining the degree of spatial (i.e. between rooms/wards/departments) correlation, and the results support the findings from this earlier study.

This study has a number of limitations. It might be argued that incident transmission, rather than prevalence, is of more interest. The authors decided to focus on prevalence and the outwards propagation of cases, as this accurately reflects the burden of disease, and also in terms of demands on hospital resources. Transmission dynamics from the VRE outbreak were investigated in a previous study [10]. The authors were particularly interested in spatial clustering of cases but, once a VRE case was detected, ward-level 'cohorting' of colonized patients was implemented. Therefore, in this analysis, it is not possible to disentangle clustering as a result of this enforced cohorting from that due to an outbreak in a contaminated room.

This study focused on the rooms in the main bed tower of the hospital, which constituted approximately 43% of all patients in the hospital. As such, some medical fields were not represented in the study, such as intensive care wards. Perhaps most importantly, with the exception of the oncology department, regular screening of patients on a ward was not implemented during the study. This meant that there is certainly a degree of under-reporting in the number of observed VRE-positive cases; the authors attempted to adjust for this by performing an analysis with an informative prior on the prevalence level per floor, but nonetheless a definitive 'gold standard' is lacking for the number and location of cases. Finally, it is acknowledged that whole-genome sequencing would have provided valuable additional information in terms of mode of transmission and causes.

In conclusion, relatively straightforward but personnel-intensive cleaning with disinfectants and UV light provided tangible benefits in getting the outbreak under control. Despite additional complexity, BHMs provide a more flexible platform for studying transmission dynamics. Finally, every investigation has at least one eye on the next potential outbreak. The hospital is soon to open a new building, which is essentially a cube structure with multiple co-located departments on each floor; the study methods are certainly applicable to this complicated environment.

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Author contributions

AA was responsible for the concept and methodology, and performed data curation, analysis, and prepared the first draft of the manuscript. BE was responsible for data extraction and checking. TK/VP provided expertise with regards to infection control procedures and the hospital. MZ reviewed and provided input for the analysis. JM supervised the work. All authors were responsible for reviewing and editing the manuscript.

Conflict of interest statement

None declared.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhin.2021.12.024.

References

[1] Chiang HY, Perencevich EN, Nair R, Nelson RE, Samore M, Khader K, et al. Incidence and outcomes associated with infections caused by vancomycin-resistant enterococci in the United States: systematic literature review and meta-analysis. Infect Control Hosp Epidemiol 2017;38:203—15.
[2] Prematunge C, MacDougall C, Johnstone J, Adomako K, Lam F, Robertson J, et al. VRE and VSE bacteremia outcomes in the era of effective VRE therapy: a systematic review and meta-analysis. Infect Control Hosp Epidemiol 2016;37:26—35.
[3] Wassilew N, Seth-Smith HMB, Rolli E, Fietze Y, Casanova C, Führer U, et al. Outbreak of vancomycin-resistant *Enterococcus faecium* clone ST796, Switzerland. Eurosurveillance 2018;19:23.
[4] Piezzi V, Wassilew N, Atkinson A, Kaspar T, Seth-Smith H, Casanova C, et al. Report of the first nosocomial outbreak of vancomycin-resistant *Enterococcus faecium* (VRE) ST796 in Europe. Eurosurveillance, submitted for publication.
[5] Monteserin N, Larson E. Temporal trends and risk factors for healthcare-associated vancomycin-resistant enterococci in adults. J Hosp Infect 2016;94:3.
[6] Suleyman G, Alangaden G, Bardossy AC. The role of environmental contamination in the transmission of nosocomial pathogens and healthcare-associated infections. Curr Infect Dis Rep 2018;20:12.
[7] Zhou MJ, Li J, Salmasian H, Zachariah P, Yang YX, Freedberg DE. The local hospital milieu and healthcare-associated vancomycin-resistant enterococcus acquisition. J Hosp Infect 2019;101:69—75.
[8] Correa-Martinez CL, Stollenwerk VB, Kossow A, Schaumberg F, Mellmann A, Kampmeier S. Risk factors for long-term vancomycin-resistant enterococci persistance — a prospective longitudinal study. Microorganisms 2019;7:400.
[9] Correa-Martinez CL, Tönnies H, Froböse NJ, Mellmann A, Kampmeier S. Transmission of vancomycin-resistant enterococci in the hospital setting: uncovering the patient environment interplay. Microorganism 2020;8:203.
[10] Atkinson A, Ellenberger B, Zahnd S, Piezzi V, Kaspar T, Salazar-Vizcaya L, et al. Precision medicine approach for innovative outbreak investigation using machine learning and graph theory: blueprint and application to a nosocomial outbreak of multi-drug resistant organisms. Infect Control Hosp Epidemiol 2021; submitted for publication.
[11] Wetterings V, van Oosten A, Nieuwkoop E, Nelson J, Voss A, Wintermans B, et al. Management of a hospital-wide vancomycin-resistant *Enterococcus faecium* outbreak in a Dutch general hospital, 2014—2017: successful control using a restrictive screening strategy. Antimicrob Resist Infect Control 2021;10:38.
[12] Frakking FNJ, Bril WS, Sinnige JC, Van't Klooster JE, de Jong BAW, van Hannen EJ, et al. Recommendations for the successful control of a large outbreak of vancomycin-resistant *Enterococcus faecium* in a non-endemic hospital setting. J Hosp Infect 2018;100:e216—25.
[13] Davis GS, Sevdalis N, Drumright LN. Spatial and temporal analyses to investigate infectious disease transmission within healthcare settings. J Hosp Infect 2014;86:227—43.
[14] Yu ITS, Wong TW, Chiu YL, Lee N, Li Y. Temporal-spatial analysis of severe acute respiratory syndrome among hospital patients. Clin Infect Dis 2005;40:1237—43.
[15] Starr JM, Campbell A, Renshaw E, Poxton IR, Gibson GJ. Spatio-temporal stochastic modelling of *Clostridium difficile*. J Hosp Infect 2009;71:49—56.
[16] Pai S, Polgreen PM, Segre AM, Sewell DK, Pemmaraju SV. Spatiotemporal clustering of in-hospital *Clostridioides difficile* infection. Infect Control Hosp Epidemiol 2021;41:418—24.
[17] Rushton SP, Shirley MDF, Sheridan EA, Lanyon CV, O'Donnell AG. The transmission of nosocomial pathogens in an intensive care unit: a space—time clustering and structural equation modelling approach. Epidemiol Infect 2010;138:915—26.
[18] Besag J, York J, Mollié A. Bayesian image restoration with two applications in spatial statistics. Ann Inst Stat Math 1991;43:1—59.
[19] Plummer M, Best N, Cowles K, Vines K. CODA: convergence diagnosis and output analysis for MCMC. R News 2006;6:7—11.
[20] Spiegelhalter D, Thomas A, Best N, Lunn D. OpenBUGS user manual. 2014. Available at: https://www.mrc-bsu.cam.ac.uk/software/bugs/openbugs/ [last accessed August 2021].
[21] R Core Team. R: a language and environment for statistical computing. R Foundation for Statistical Computing; 2019. Available at: https://www.R-project.org/.
[22] Kong F, Paterson DL, Coory M, Clements ACA. A multilevel model of methicillin-resistant *Staphylococcus aureus* acquisition within the hierarchy of an Australian tertiary hospital. Am J Infect Control 2012;40:787—93.
[23] Kong F, Paterson DL, Whitby M, Coory M, Clements ACA. A hierarchical spatial modelling approach to investigate MRSA transmission in a tertiary hospital. BMC Infect Dis 2013;13:449.
[24] Gouliouris T, Coll F, Ludden C, Blane B, Raven KE, Naydenova P, et al. Quantifying acquisition and transmission of *Enterococcus faecium* using genomic surveillance. Nat Microbiol 2020;6:103—11.