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Economic Evaluation

Clinical and Economic Outcomes of Genome Sequencing Availability on Containing a Hospital Outbreak of Resistant *Escherichia coli* in Australia

Xing J. Lee, PhD, Thomas M. Elliott, MHEcon, Patrick N.A. Harris, PhD, Joel Douglas, BAppSc (MedLabSc), Belinda Henderson, MAHCP Infection Control, Catherine Watson, MHealth Practice, David L. Paterson, PhD, Deborah S. Schofield, PhD, Nicholas Graves, PhD, Louisa G. Gordon, PhD*

ABSTRACT

Objectives: To evaluate the outbreak size and hospital cost effects of bacterial whole-genome sequencing availability in managing a large-scale hospital outbreak.

Methods: We built a hybrid discrete event/agent-based simulation model to replicate a serious bacterial outbreak of resistant *Escherichia coli* in a large metropolitan public hospital during 2017. We tested the 3 strategies of using whole-genome sequencing early, late (actual outbreak), or not using it and assessed their associated outbreak size and hospital cost. The model included ward dynamics, pathogen transmission, and associated hospital costs during a 5-month outbreak. Model parameters were determined using data from the Queensland Hospital Admitted Patient Data Collection (N = 4809 patient admissions) and local clinical knowledge. Sensitivity analyses were performed to address model and parameter uncertainty.

Results: An estimated 197 patients were colonized during the outbreak, with 75 patients detected. The total outbreak cost was A$460 137 (US$317 117), with 6.1% spent on sequencing. Without sequencing, the outbreak was estimated to result in 352 colonized patients, costing A$766 921 (US$528 547). With earlier detection from use of routine sequencing, the estimated outbreak size was 3 patients and cost A$65 374 (US$45 054).

Conclusions: Using whole-genome sequencing in hospital outbreak management was associated with smaller outbreaks and cost savings, with sequencing costs as a small fraction of total hospital costs, supporting the further investigation of the use of routine whole-genome sequencing in hospitals.

Keywords: bacterial infectious disease, healthcare associated infections, agent-based modeling, discrete event modeling, cost consequences.

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Introduction

Enterobacteriaceae, which encompasses a large family of gram-negative bacteria, are common causative organisms of healthcare-associated infections (HAIs).[1] Resistant gram-negative bacteria are of particular concern[2,3] because of their relative ease in transferring plasmid-based antibiotic-resistance gene elements across specie, and increasing carbapenemase-producing *Enterobacteriaceae* (CPE) infections worldwide with large mortality estimates (44%-70%).[4,5] There are comparatively fewer reports of CPE in Australia. As such, it is important that stringent detection and infection control practices for CPE are promoted to avoid its widespread establishment.[6]

A key infection control aim is the timely identification of pathogens and their susceptibility to minimize adverse patient outcomes. Microbiological screening is used to identify colonized and infected patients and to facilitate appropriate treatment and infection control measures. Current methods rely on cultivating a positive culture from suspected patients and takes 1 or 2 days, with further characterization determined using typing methods such as pulsed-field gel electrophoresis and multilocus sequence typing. Multiplex polymerase chain reaction (PCR) assays use multilocus sequence typing to quickly identify the particular genes for which they are specifically designed.[7] Whole-genome sequencing (WGS) is a relatively new method receiving attention as it has substantially greater discrimination power compared with conventional typing methods.[8,9] WGS identifies pathogens when other typing methods fail to and consequently helps infection control staff to manage patients by identifying transmission clusters[8] and determine novel pathogen outbreaks in hospital settings.

Conventional intervention trials to evaluate the effectiveness and cost-effectiveness of new technologies are particularly challenging for hospital outbreaks because of their stochastic nature. Although mathematical simulation models of pathogen

* Address correspondence to: Louisa G. Gordon, PhD, QIMR Berghofer Medical Research Institute, 300 Herston Rd, Herston, Queensland Q4006, Australia. Email: louisa.gordon@qimrberghofer.edu.au

transmission dynamics are recommended for such evaluations,[10–12] there are few economic evaluations using these models.[13] For instance, Knight et al[14] found that a combination of culture and multiplex PCR was optimal in detecting carbapenemase-producing carbapenem-resistant *Enterobacteriaceae* in a low-prevalence, nonoutbreak setting using an individual-based simulation model.

There is little information on the cost-effectiveness of WGS in managing hospital outbreaks. We found one 2019 study[15] that evaluated the cost-effectiveness of routine WGS to detect methicillin-resistant *Staphylococcus aureus* using a decision tree model rather than the recommended simulation models. The authors assumed the sequencing effectiveness, citing a lack of published data. As such, it is unclear whether a strong recommendation to fund new genomic sequencing technologies is appropriate given scarce resources in health services.[16] This economic evaluation used mathematical simulation modeling to assess the value of WGS in containing a large-scale hospital outbreak of a multidrug-resistant *Escherichia coli* strain that had not been previously reported in Queensland public hospitals. The strain carried a gene encoding OXA-181 carbapenemase, which mediates resistance to our most effective class of antibiotics, carbapenems, and cannot be identified alone by cultures and multiplex PCR assays.[17] OXA-181 carbapenemases are rarely encountered in Australia. Evidence generated here is important to inform initiatives to prevent the resistant gram-negative strain from becoming endemic in Australia and increasing the burden of resistant infection.

Methods

Setting

The study hospital is a 780-bed, tertiary hospital in Queensland, Australia, with wards composed of 4-bed, 2-bed, and single-bed accommodation combinations. The outbreak affected 13 wards between May 2017 and August 2017, with 75 patients detected colonized with the OXA-181 *E coli* strain using a combination of culture, PCR, and WGS.[18] No patients were seriously ill or died as a direct consequence of this outbreak.

The outbreak strain in the index patient was first identified from WGS performed as part of a separate outbreak management at the hospital. The index patient was able to be retrospectively identified with high certainty through contact tracing due to the novel strain involved. The hospital performed WGS on a cluster of 5 *E coli* patients detected 40 days after the index case, after noticing their distinct antibiogram was similar to the index patient. WGS confirmation of identical *E coli* strains with the index patient expedited the hospital's formal outbreak management plan, compared with routine practice, where the infection control team would need additional time to deliberate on whether these cases form a substantial outbreak requiring a formal outbreak management plan. Additional outbreak details are included in the Supplementary Materials (found at https://doi.org/10.1016/j.jval.2020.03.006).

Evaluation

We evaluated the performance of different WGS availabilities using a simulation model on these key outcome measures: outbreak size (estimated number of colonized patients), total detected colonized patients, and total hospital cost. Multiplex PCR assay was not included as a comparator because the OXA-181 strain is a foreign variant that would not have been tested for without prior suspicion of its presence. We additionally investigated 2 clinically relevant alternatives that could not be captured directly from the outbreak data using scenario analyses (Table 1).

Scenario 1 is the model re-creation of the observed outbreak with WGS used regularly after detection of the 5 patients with the OXA-181 strain as described earlier (late sequencing). Culture and PCR were used otherwise.

Scenario 2 involved no sequencing and served as the usual case scenario for most Australian public hospitals. Without sequencing information, local clinical staff reported that outbreaks are typically declared when a statistical increase from baseline numbers is detected and deliberated by the infection control team. In this instance, identification of 7 to 15 similar *E coli* strains would be

Table 1. List of scenario analyses considered in this evaluation of WGS availability in a large hospital outbreak.

Scenario (scenario number)	Condition to declare outbreak	Scenario-specific parameter	Parameter value	Source
Actual outbreak (1)	5 WGS results with OXA-181	—	—	—
No WGS (2)	2 to 5 days after 7 to 15 patients detected with same pathogen	Outbreak number	Uniform(7, 15)	Expert clinical opinion*
		Days post outbreak number reached	Uniform(2, 5)	Expert clinical opinion*
Early sequencing (3)	First anomalous (OXA-181) WGS results	—	—	—
Environmental transmission with no sequencing (4)	As in scenario 2	Environmental transmission odds ratio	2.65	[19]
Environmental transmission with early sequencing (5)	As in scenario 3	Probability that bed contamination spreads to other beds in room	0.50	Assumption
		Bed contamination duration	5 to 10 days	[20]
Virulent model with no sequencing (6)	As in scenario 2	Infection probability	0.165	[21]
Virulent model with early sequencing (7)	As in scenario 3	Days until infection	27 (SD 11)	[21]
		Mortality probability	0.40 (SD.0.5)	[22]

WGS indicates whole-genome sequencing.
*Infection control and prevention staff including 2 infection control nurses and a microbiologist.

considered as a sufficient increase, and deliberations take between 2 to 5 days. This outbreak definition is consistent with Australia's national guidelines[23] but is higher than the Australian CPE recommendation[6] because of the original determination of the pathogen being common and low risk (*E coli*). Scenario 3 assumed an optimal early sequencing scenario in which WGS was used, routinely allowing an outbreak to be declared with the first positive anomalous strain (early sequencing).

Scenarios 4 (no sequencing) and 5 (early sequencing) evaluated the impact of WGS availability in scenarios where the pathogen can spread through contaminated patient beds, a situation that may happen with imperfect, albeit plausible, environmental cleaning. Scenarios 6 (no sequencing) and 7 (early sequencing) involved a hypothetical pathogen with increased virulence causing colonized patients to develop an infection and a proportion subsequently dying in hospital. Increased pathogenicity is plausible given the relative ease of gram-negative pathogens to acquire genes via mobile genetic elements and the large mortality estimates for CPE-related infections.[4,5]

These scenarios were developed to compare the impact of WGS within each outbreak condition. It is inappropriate to compare across the actual, environmental contamination and increased virulence outbreak scenarios as the alternatives involved increased transmission potential and naturally resulted in larger outbreaks.

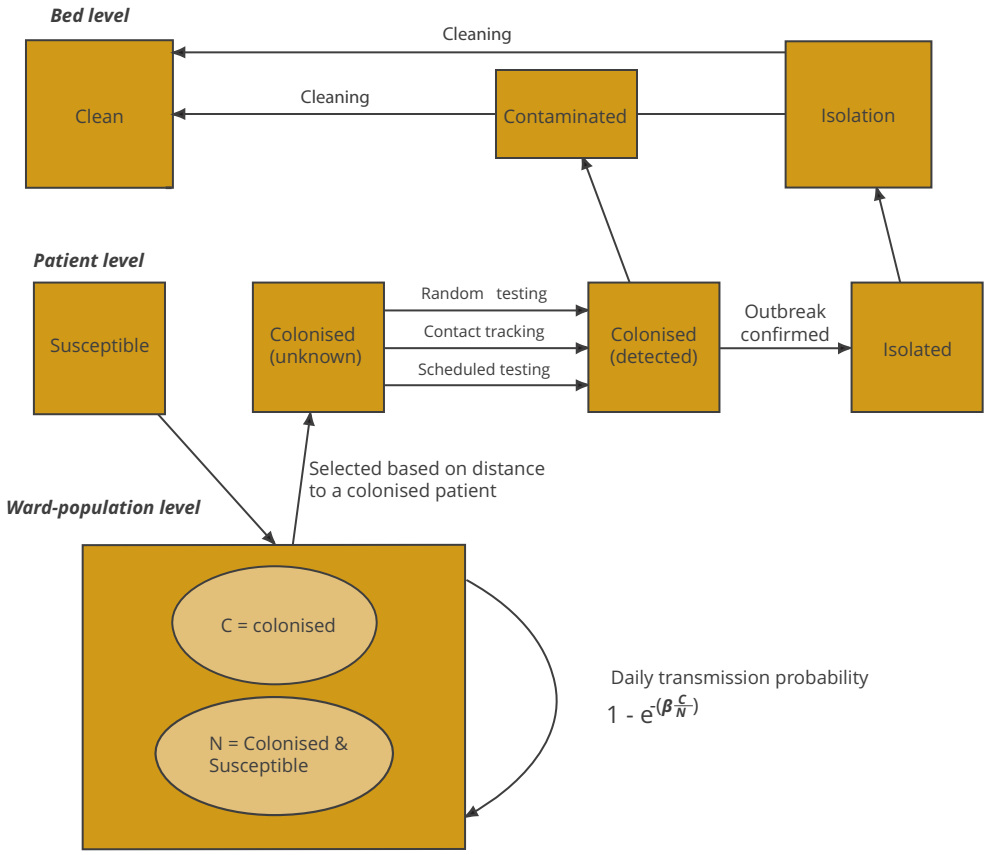
Model Structure

We built a stochastic hybrid discrete-event, agent-based simulation model using AnyLogic to re-create the outbreak and investigate the impacts of different WGS availabilities (Fig. 1). The model interweaves discrete-event simulation for ward-level pathogen transmission dynamics and agent-based models for individual-level dynamics for patient hospitalizations and outbreak management actions. The simulation model covers patient dynamics in the wards affected by the outbreak, with all other hospital wards aggregated to an "other wards" group dynamics to alleviate computational burden and minimize the number of assumptions made for unobserved processes. The model can be viewed online at https://cloud.anylogic.com/model/6fe44e5b-6276-44fd-95c8-ba93b3975262?mode=SETTINGS&tab=GENERAL. Full details on the technical specifications and calibration of the model are available in a complementary article.24

Model simulations were initiated with the index colonized patient's admission. Subsequent patient admissions occurred at ward-specific daily rates, and patients were assumed susceptible on admission as this pathogen was a novel strain to the state and hospital. Patients were monitored daily to determine if they were screened, transferred to a different ward, or discharged. Patient beds were modeled as part of the patient hospitalization flow (Fig. 1).

Pathogen transmission dynamics were modeled at the ward level in the absence of data on patient contact rates to inform individual-level modeling. We modeled new daily colonizations as a binomial random variable with sample size S and probability $1 - \exp\left\{\frac{-\beta C}{N}\right\}$, where the exponent is derived from the frequency-dependent transmission term,[25] with transmission parameter (β), number of susceptible patients (S), number of colonized patients (C), and the number of patients in the ward (N), excluding isolated patients. Patient OXA-181 acquisition was

Figure 1. Schematic of hybrid simulation model.



based on their proximity to a colonized patient. We assumed that once colonized, patients remained colonized for the rest of their hospitalization.

The model triggered 3 outbreak management actions when a colonized patient was detected. First, the patient was isolated, or cohorted if no single rooms were available. We assumed this was 100% effective for this evaluation. Patients in the same room were screened and their beds flagged for cleaning after their discharge. Lastly, the colonized patient's bed was closed until all contact screening swabs were reported as negative. Bed closures occurred when a colonized patient left the bed due to isolation or discharge, and in cases where the patient occupied a multibed room, multiple beds were closed as a result of a single detection. Additional model details are provided in the Supplementary Materials.

Data Sources

Information on patient ward transfers was obtained from the Queensland Hospital Admitted Patient Data Collection (QHAPDC) for all 4250 patient admissions between April 1, 2017, and August 1, 2017, and the 559 patients already in the affected wards on April 1, 2017. QHAPDC is a routinely collected patient data collection accessed through the Queensland government health department. Local clinical staff provided details of the historical outbreak management plan, expert knowledge about an ideal WGS implementation, and likely outbreak management plan without sequencing information. This study was approved by the QIMR Berghofer Medical Research Institute Human Research Ethics Committee (P2353) and the Queensland Government Public Health Act Human Research Ethics Committee (RD007427).

Model Parameter Estimation

We estimated ward-specific admission rates directly from the QHAPDC data. Patient ward stay durations were estimated from the QHAPDC data as gamma distributions using the methods of moments.[26] Screening duration and frequency were informed by local clinical staff and relevant guidelines.[27]

The transmission parameter β governs how readily the outbreak spreads and is determined by how the pathogen is transferred from a contact between a transmission source and a susceptible patient and how frequently such contacts occur. These 2 factors likely differ across hospital wards (eg, wards where patients are more immunocompromised or require more frequent medical attention are likely have large β values). We assumed there were separate β parameters for each hospital floor, rather than for each ward, because of the small number of detected colonized patients at the ward level, making it infeasible to calibrate ward-specific β values. We calibrated the β parameters to generate simulations matching the outbreak's detected colonized patient numbers on each hospital floor at key time points corresponding to when the outbreak was starting out (day 69), reaching its peak (day 83), and tapering off (day 111).[24] These time points and the total outbreak number became the calibration target estimates. The function used to generate randomness in the model controlled for the pathogen transmission processes to reduce the variability between simulations with the same parameters.[24] This process of blocking ensured the pathogen spread would occur identically across simulations[28] and that the outcomes produced were due to the intervention and not variation in the outbreak.

Healthcare costs were assigned to WGS, microbiology tests, dedicated nursing time, bed closures, cleaning, and executive infection control meetings using a combination of administrative data, expert opinion, and literature estimates. Costs were calculated in 2018 Australian dollars (US$1 = A$1.45).[29] WGS cost was A$354.70, estimated using micro-costing on a sampling load of 100 per month, and included costs for sample preparation, sequencing, analysis, and labor. The microbiology screening cost (A$79.23) included the medical services fee set by the Australian government and the hospital costs for PCR.[30] Cleaning cost (A$70) comprised labor, curtain replacement, and cleaning agents costs. The bed closure cost of A$216 is a willingness-to-pay estimate, from the Australian hospital chief executive officers' perspective.[31] A higher published bed day cost[32] of A$800 was tested in a sensitivity analysis. Daily executive meetings were estimated to cost A$462.03. An hourly nursing cost of A$40.33 was attributed to contact precaution, patient isolation, environmental decontamination, and wider patient screening activities. Model inputs are summarized in Table 2 with additional details in the Supplementary Materials.

Analysis

We fitted appropriate statistical distributions to the model parameters to represent associated parameter uncertainty.[26] Costs and ward stays were assigned gamma distributions, and probabilities were assigned beta distributions. We used uniform distributions to represent uncertainty in parameters for which we know only their plausible range. We sampled 1000 parameter sets from the fitted distributions to perform 1000 model simulations for each scenario in a probabilistic sensitivity analysis. Total costs of the outbreak were for the management of the outbreak duration rather than a specified study population size. To address uncertainty in isolation effectiveness, we simulated scenarios 1, 2, and 3 with imperfect isolation such that each patient isolated outside level 5 ward D had a 10% chance of being infective and continued to contribute to the colonization formulae. We recalibrated the outbreak parameters in order for scenario 1 to match to the real outbreak assuming imperfect isolation (Supplementary Table 6).

Results

Our analyses indicated that the hospital identified 38.1% of 197 colonized patients during the outbreak (scenario 1; Table 3). The outbreak resulted in 419 bed closures and 79 sequencing tests performed. Without WGS (scenario 2), we estimated 352 colonized patients (with 152 detected) and 902 bed closures for this outbreak. With early sequencing (scenario 3), the estimated outbreak size was 3 patients with 1 detected patient and 11 bed closures. The total hospital costs savings over the length of the outbreak for scenario 1 were A$306 785 (standard deviation [SD]: A$338 055; US$211 430, SD: US$232 981) and for scenario 3 were A$701 547 (SD: A$337 897; US$483 492, SD: US$232 872) when each was compared with scenario 2.

The environmental contamination scenario analysis without sequencing (scenario 4) resulted in 123 colonized patients detected out of 234 colonized patients and 33 contaminated hospital beds, on average. We estimated that the outbreak resulted in 2 colonized patients, no contaminated beds, and 4 sequencing tests for the environmental contamination scenario with early sequencing (scenario 5). The total hospital costs were A$651 649 (SD: A$364 223) in scenario 4 and $64, 971 (SD: A$2822) in scenario 5, creating cost savings over the length of the outbreak with early sequencing of A$586 659 (SD: A$364 027) (US$404 313, SD: US$250 880).

The scenario with increased virulence without sequencing (scenario 6) resulted in 256 colonized patients with 119 detected patients (46.4%). Forty-one colonized patients developed an infection and a subsequent 6 died. With early sequencing in the increased virulence scenario (scenario 7), we estimated that the outbreak resulted in 3 colonized patients, with 1 colonized patient detected with an infection, and 2 sequencing tests performed. The

Table 2. Parameter values used in the hybrid simulation model.

Parameter	Value	Source	Notes
Initial starting population	551	QHAPDC	
Population entry rate, patients per day	24	Calibration	Calibration range 24 to 28
Ward admission, transfers, and stays	See Supplementary Material	QHAPDC	Gamma distribution assigned to ward stays
Microbiology test processing time, days	2	Expert clinical opinion*	
WGS processing time, days (SD)	7 (0.5)	Expert clinical opinion*	Normal distribution
Transmission parameter β	Level 5 = 0.153, level 2 = 0.14, SIU = 0.086, GARU = 0.086	Calibration	Calibration range 0.0001 to 0.25
Frequency of executive meetings during outbreak	Daily	Expert clinical opinion*	Weekly when <5 colonized patients
Daily probability of patient being screened	Level 5 = 0.041, level 2 = 0.043, GARU = 0.055, SIU = 0.056	Calibration	Calibration range 0.01 to 0.07 as advised by expert opinion*
Routine hospital screening ward 5D, ward 2E	On entry to ward, and weekly thereafter	Queensland Health guidelines[27]	Hospital screening protocol
Outbreak control screening	Weekly in GARU, SIU, and contact tracing for patients in same room	Clinical staff	Additional hospital-wide screening on 29 days after outbreak identification, if outbreak is not contained
WGS cost, A$ (SD)	354.70 (53.2)	Clinical records	Sample preparation A$15, sequencing A$105, analysis/ storage A$18, scientist A$102.50, isolate handling A$5, labor administration A$33.33, biostatistics A$75.85
Microbiology test cost, A$ (SD)	79.23 (11.88)	MBS item 69306, PCR cost[30]	MBS item 69306 charge A$33.75 PCR cost A$45.48
Bedroom cleaning cost, A$ (SD)	70 (10.5)	Cleaning staff	Hospital cleaning staff, labor hourly rate A$31.24, curtains A$33, consumables A$5
Bed closure, A$ (SD)	216 (23)	Page et al, 2017[31]	
Hourly wage for infection control nurse, A$ (SD)	40.33 (6.05)	Clinical staff and Queensland Health wage rates[33]	Registered nurse level 5
Combined hourly wages of staff involved in executive infection control meeting,[1] A$	462.03 (69.3)	Clinical staff and Queensland Health wage rates[33]	3 senior consultants A$215.10, infection control nurse A$59.03, senior administrator A$65.10, manager A$45.81
Infection treatment costs, A$	2650	[22]	Scenarios 6 and 7 only
Death cost, A$	19 696	[34]	Scenarios 6 and 7 only

GARU indicates geriatric assessment and recovery unit; MBS, Medicare benefits schedule; PCR, polymerase chain reaction; QHAPDC, Queensland Health Admitted Patient Data Collection; SD, standard deviation; SIU, spinal injury unit.
*Infection control and prevention staff including 2 infection control nurses and a microbiologist.

total hospital costs were A$875 594 (SD: A$460 589) and A$67 373 (SD: A$4046) in scenarios 6 and 7, respectively, with hospital cost savings of A$808 227 (SD: A$460504; US$557 014, SD: US$317370).

Microbiology screening costs were the largest cost component across all scenarios, ranging from 44.3% of the total hospital costs for scenario 6 to 89.2% for scenarios 3 and 5. Bed closure costs were smaller in scenarios with early sequencing, between 2.0% to 3.1%, compared with 17.2% to 25.5% in other scenarios. WGS costs ranged from 1.1% to 6.1% of the total hospital costs when used (scenarios 1, 3, 5, 7).

In sensitivity analyses with increased bed closure unit cost, estimated bed closure costs accounted for most of the total hospital costs in scenarios without early sequencing, ranging from 43.3% for scenario 6 to 55.8% in scenario 2, followed by the microbiology testing costs (30.3% for scenario 6 to 37.1% in scenario 1) (Fig. 2). For scenarios with early sequencing, microbiology screening was still the largest cost component (81.3% for scenario 2 to 82.8% for scenario 7), and bed closure costs represented between 6.9% (scenario 7) and 12.2% (scenario 2) of the total costs. Sequencing costs accounted for between 1.0% (scenarios 2 and 7) to 4.0% (scenario 1) of the total hospital cost for scenarios with WGS in the sensitivity analyses.

In sensitivity analyses with imperfect isolation (Table 4), early sequencing (scenario 3) avoided 172 (SD: 199) colonized patients (with 102 detected) and 614 (SD: 637) bed closures compared with no WGS (scenario 2). The total hospital costs savings

Table 3. Result summaries for the outcomes measures from 1000 probabilistic simulations for each scenario.

	Scenarios*						
	1†	2	3	4	5	6	7
Colonized patients (SD)	197	352 (170)	3 (0)	234 (179)	2 (0)	256 (157)	3 (0)
Environmental contamination sites (SD)	—	—	—	33 (28)	0 (0)	—	—
Infected patients (SD)	—	—	—	—	—	41 (25)	1 (0)
Deaths (SD)	—	—	—	—	—	6 (5)	0 (0)
Detected patients (SD)	75	152 (75)	1 (0)	123 (86)	2 (0)	119 (70)	1 (0)
Sequencing tests (SD)	79	—	2 (0)	—	4 (0)	—	2 (0)
Bed closures (SD)	419	902 (486)	11 (2)	720 (508)	9 (1)	692 (424)	6 (2)
Total costs, A$ (SD)	460 137 (12 138)	766 921 (338 351)	65 374 (4556)	651 649 (364 223)	64 971 (2822)	875 594 (460 589)	67 373 (4046)
WGS costs, A$ (SD)	28 113 (568)	—	724 (74)	—	1422 (29)	—	725 (71)
Microbiology testing costs, A$ (SD)	261 268 (11 269)	422 141 (159 491)	58 333 (4007)	375 310 (172 828)	57 964 (2816)	387 888 (164 676)	58 748 (3672)
Cleaning costs, A$ (SD)	40 159 (1944)	83 861 (45 344)	1059 (296)	66 871 (47 459)	688 (85)	64 010 (39 468)	534 (287)
Nursing costs, A$ (SD)	4463 (264)	9085 (4663)	64 (12)	7194 (5340)	124 (8)	6993 (4381)	64 (13)
Infection control executive meetings costs, A$ (SD)	35 185 (633)	56 132 (28 943)	2810 (179)	45 921 (32 793)	2779 (49)	45 296 (26 885)	2803 (145)
Bed closure costs, A$ (SD)	90 949 (3583)	195 703 (105 052)	2385 (537)	156 352 (110 813)	1994 (201)	150 204 (92 225)	1322 (490)
Infection treatment costs, A$ (SD)	—	—	—	—	—	108 052 (67 020)	3177 (1057)
Death costs, A$ (SD)	—	—	—	—	—	113 151 (89 489)	0 (0)

SD indicates standard deviation; WGS, whole-genome sequencing.
*Scenarios: 1, actual outbreak; 2, no sequencing; 3, early sequencing; 4, environmental transmission (no sequencing); 5, environmental transmission (early sequencing); 6, virulent model (no sequencing); 7, virulent model (early sequencing).
†No standard deviations were reported for noncost outcome summaries in scenario 1 as the model was calibrated using this scenario with a fixed outbreak signaling condition. Variation observed in scenario 1's cost outcomes was due solely to the stochasticity of the cost parameters.

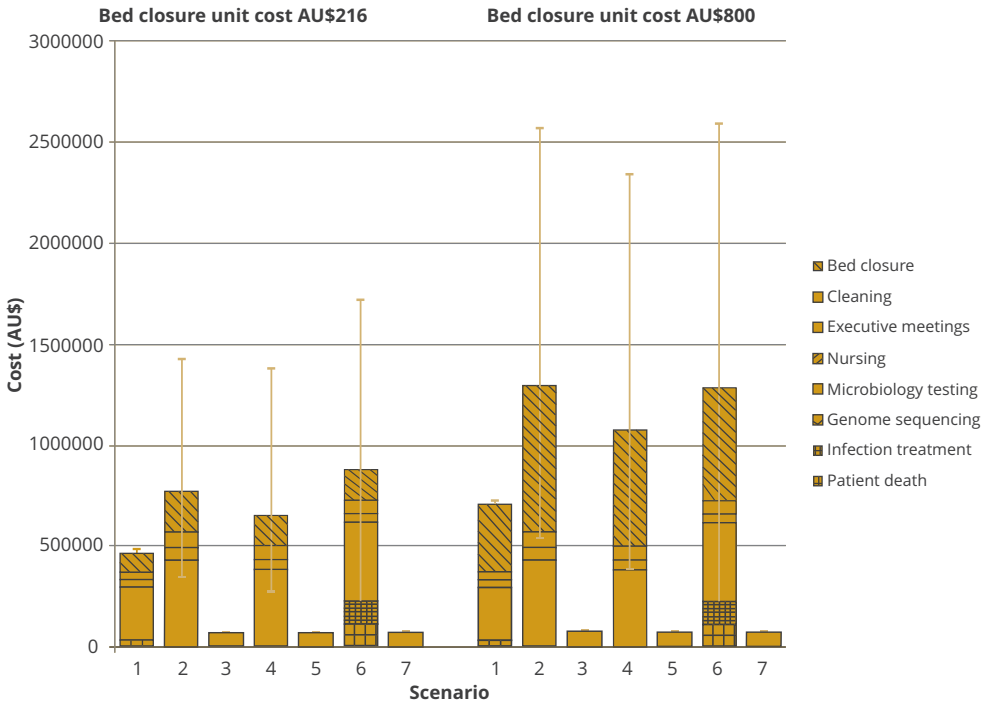
between scenario 2 and 3 over the length of the outbreak were A$540 082 (standard deviation [SD]: A$504 908; US$372 214, SD: US$347 972).

Discussion

Our dynamic simulation model results showed WGS use was associated with smaller outbreaks and lower associated hospital costs compared with no sequencing, consistent with the only other economic evaluation of routine WGS for a hospital pathogen.[15] Costs saving incurred from fewer colonized patients, and bed closures outweighed the sequencing costs. The estimated WGS costs were a small percentage of the total hospital costs for managing outbreaks when used as a second-line test.

These simulation-based economic evaluations are important given the increasing demand for health services when health budgets are finite.[35] The 2018 introduction of hospital-based financial penalties for excess hospital-acquired complications, including HAIs, in Australia[36] further motivates hospital decision makers to consider economic evidence when allocating resources, especially for common complications such as HAIs.[37] We acknowledge that this evaluation focused only on the direct impact of the outbreak, and there were broader costs and consequences that were out of scope. For example, outbreaks can result in temporary cessation of elective surgeries, restrict hospital transfers, and severely limit isolation room availability. This evaluation did not have sufficient data to quantify these potential flow-on effects nor the implied cost of routine WGS in early sequencing scenarios and other microbiological investigations performed that were not relevant to the outbreak. The results presented reflect the direct cost savings of using WGS for a single-outbreak management and should be interpreted accordingly. This OXA-181 outbreak did not cause significant harm to patients. The increased virulence scenario was designed to explore how potentially worse patient harm impacted the outcomes. Health outcomes were not measured, and it is uncertain how WGS availability for outbreak management would affect quality-adjusted life-years. The disutility associated with colonization has been treated the same as in noncolonized inpatients,[38] but research is emerging that isolation can have a negative impact on patients.[39] Future work could explore how WGS-guided

Figure 2. Hospital cost breakdown for the seven scenarios and two bed closure cost estimates.



infection control affects quality-adjusted life-years; however, for the time being, it remains important to capture the operational impacts within the hospital, which in turn affects patient well-being.

The main limitation of this retrospective evaluation is that it is based on a single hospital outbreak, limiting its generalizability. However, the simulation model can be adapted for similar outbreak evaluations at the hospital and potentially other

Table 4. Result summaries for imperfection isolation sensitivity analysis.

	Scenarios			Difference between scenarios 2 and 3
	Actual outbreak*	No sequencing	Early sequencing	
Colonized patients (SD)	150	226 (197)	54 (28)	172 (199)
Patient isolations failed (SD)	1	5.68 (6.00)	0.01 (0.11)	—
Detected patients (SD)	71	130 (111)	28 (17)	102 (112)
Sequencing tests (SD)	73	—	30 (18)	−30 (18)
Bed closures (SD)	425	792 (632)	178 (115)	614 (637)
Total costs, A$ (SD)	$473 116 ($13 015)	$823 812 ($497 814)	$283 229 ($106 179)	$540 082 ($504 908)
WGS costs, A$ (SD)	$284 757 ($12 105)	—	$10 814 ($6333)	$−10 814 ($6333)
Microbiology testing costs, A$ (SD)	$25 955 ($544)	$522 429 ($271 118)	$200 414 ($54 426)	$321 776 ($274 682)
Cleaning costs, A$ (SD)	$40 871 ($1855)	$74 382 ($59 701)	$16 787 ($10 752)	$57 562 ($60 106)
Nursing costs, A$ (SD)	$4163 ($240)	$7664 ($6867)	$1750 ($1082)	$5909 ($6916)
IC executive meetings costs, A$ (SD)	$25 006 ($461)	$47 743 ($40 740)	$14 849 ($10 709)	$32 809 ($41 934)
Bed closure costs, A$ (SD)	$92 364 ($3536)	$171 593 ($136 874)	$38 614 ($25 032)	$132 877 ($137 979)
Percentage of 1000 simulations where outbreak did not finish with 730 days	0.0%	19.6%	1.1%	18.7%

IC indicates infection control; SD, standard deviation; WGS, whole-genome sequencing.
*No standard deviations were reported for noncost outcome summaries in scenario 1 as the model was calibrated using this scenario with a fixed outbreak signaling condition. Variation observed in scenario 1's cost outcomes was due solely to the stochasticity of the cost parameters.

hospitals. The inherent time delay between transmission and detection meant that a few patients were transferred to other hospitals before they were detected. These patients were promptly identified and managed appropriately. Contact tracing did not detect outbreaks at the other hospitals. As such, model extension to include hospital transfer dynamics was not warranted for this evaluation, noting likely variations in hospital structures, infection control policies, and staffing. In addition, WGS use in this outbreak was suboptimal, with sequencing results delayed as samples were processed in batches for efficiency. We also assessed the impact of only a single pathogen, where it is plausible for hospitals to have multiple concurrent outbreaks of different pathogens. Future work is planned to identify the impact of WGS over an extended time period, encapsulating pathogens other than *E coli* and facilitating economies of scale. Both the cost per-sequenced pathogen and the testing turnaround time could decrease with increased WGS use.

A few modeling extensions were possible but outside the study scope. For instance, contact patterns between patients and healthcare workers are highly heterogeneous and structured,[40] which requires costly and time-consuming detailed contact data collection and was not available for this outbreak. We assumed, in the primary analysis, that patient isolation was 100% effective at preventing transmission given the strict infection control and heightened awareness during an outbreak. The imperfect isolation sensitivity analysis showed WGS use was still associated with a smaller outbreak (89% of simulations) and lower associated hospital costs (86% of simulations) compared with no sequencing. Incorporating an explicit environmental transmission pathway, beyond bed contamination, may be warranted for more environmentally hardy pathogens, but there is only moderate-to-low evidence level for environmental contamination transmission of *E coli*.[41]

The main strength of this study is the use of a comprehensive simulation model, informed by actual outbreak data, to replicate a real-world outbreak and test the impact of WGS on outbreak size and hospital costs in multiple potential scenarios. The disadvantages of purely stochastic models are the uncontrollable extent of randomness and potential occurrence of stochastic fade-outs, where the outbreak fails to spread.[42] We introduced deterministic characteristics in our model by calibrating the spread of the outbreak to real outbreak data, avoiding stochastic fade-outs as they do not reflect the efficacy of the infection control procedures in place. The deterministic characteristics of the simulation model ensure the real-world data were observed until the outbreak was identified, and the ongoing processes become stochastic predictions, as shown by the range of outcomes in scenario 2. We combined literature estimates and expert clinical opinions to address gaps in the available data to perform the evaluation. This is common in modeling studies and highlights a key strength of such studies, where we are able to interrogate a range of plausible scenarios.

We showed how WGS can be used in outbreak management to promptly and accurately identify strains and the source of outbreaks. In the future, WGS may have an important role in informing antibiotic selection through antimicrobial susceptibility testing. Antimicrobial susceptibility was not investigated in this outbreak as the clinical utility and application of WGS are still emerging.[43] In mid-2017, two-thirds of European countries were using WGS analysis in a limited capacity, either as a first- or second-line typing method for surveillance of the pathogens and antibiotic resistance.[44] Future work is planned to model in what capacity WGS can improve infection control. We showed that WGS was associated with reduced outbreak sizes and lower hospital costs. This study supports further investigation and evaluation of routine WGS use in hospital outbreak.

Supplemental Material

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.jval.2020.03.006.

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Author Affiliations: Australian Centre for Health Services Innovation, Institute of Health and Biomedical Innovations, School of Public Health and Social Work, Faculty of Health, Queensland University of Technology, Kelvin Grove, Queensland, Australia (Lee, Graves); QIMR Berghofer Medical Research Institute, Herston, Queensland, Australia (Elliott, Gordon); Queensland Health, Pathology Queensland, Herston, Queensland, Australia (Harris, Douglas, Gordon); University of Queensland Centre for Clinical Research, Herston, Queensland, Australia (Harris, Paterson); Infection Management Services, Princess Alexandra Hospital, Woolloongabba, Queensland, Australia (Henderson, Watson); Macquarie University, Macquarie Park, New South Wales, Australia (Schofield) ; Queensland University of Technology (QUT), School of Nursing, Kelvin Grove, Queensland, Australia (Gordon); School of Public Health, The University of Queensland, Herston, Queensland, Australia (Gordon)

Author Contributions: *Concept and design:* Elliott, Harris, Watson, Paterson, Graves, Gordon
Acquisition of data: Elliott, Harris, Douglas, Henderson, Watson, Gordon
Analysis and interpretation of data: Lee, Elliott, Watson, Schofield, Graves, Gordon
Drafting of the manuscript: Lee, Elliott, Harris, Watson, Schofield, Graves, Gordon
Critical revision of the paper for important intellectual content: Lee, Elliott, Harris, Henderson, Watson, Paterson, Schofield, Graves
Statistical analysis: Lee
Provision of study materials or patients: Harris, Douglas, Henderson, Paterson
Obtaining funding: Harris, Schofield, Gordon
Administrative, technical, or logistic support: Douglas, Henderson
Supervision: Gordon

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