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Budget impact analysis of routinely using whole-genomic sequencing of six multidrug-resistant bacterial pathogens in Queensland, Australia

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ABSTRACT

Objective To predict the cost and health effects of routine use of whole-genome sequencing (WGS) of bacterial pathogens compared with those of standard of care.

Design Budget impact analysis was performed over the following 5 years. Data were primarily from sequencing results on clusters of multidrug-resistant organisms across 27 hospitals. Model inputs were derived from hospitalisation and sequencing data, and epidemiological and costing reports, and included multidrug resistance rates and their trends.

Setting Queensland, Australia.

Participants Hospitalised patients.

Interventions WGS surveillance of six common multidrug-resistant organisms (*Staphylococcus aureus*, *Escherichia coli*, *Enterococcus faecium*, *Klebsiella pneumoniae*, *Enterobacter* sp and *Acinetobacter baumannii*) compared with standard of care or routine microbiology testing.

Primary and secondary outcomes Expected hospital costs, counts of patient infections and colonisations, and deaths from bloodstream infections.

Results In 2021, 97 539 patients in Queensland are expected to be infected or colonised with one of six multidrug-resistant organisms with standard of care testing. WGS surveillance strategy and earlier infection control measures could avoid 36 726 infected or colonised patients and avoid 650 deaths. The total cost under standard of care was $A170.8 million in 2021. WGS surveillance costs an additional $A26.8 million but was offset by fewer costs for cleaning, nursing, personal protective equipment, shorter hospital stays and antimicrobials to produce an overall cost savings of $30.9 million in 2021. Sensitivity analyses showed cost savings remained when input values were varied at 95% confidence limits.

Conclusions Compared with standard of care, WGS surveillance at a state-wide level could prevent a substantial number of hospital patients infected with multidrug-resistant organisms and related deaths and save healthcare costs. Primary prevention through routine use of WGS is an investment priority for the control of serious hospital-associated infections.

Strengths and limitations of this study

- To the best of our knowledge, this is the first study to assess the projected budget impact for a local government to invest in routine whole-genome sequencing of serious bacterial pathogens to assist hospital infection control teams.
- Analyses relied on recent outcomes from sequencing data to identify clusters, hospitalisation data, prevalence of healthcare-associated infections and detailed costing of all hospital resources, while sensitivity analyses assessed variation in inputs and stability of results.
- Projected cost savings of a whole-genome sequencing strategy rely on the success of infection control teams to act decisively and effectively on the information of patient clusters.

INTRODUCTION

Healthcare-associated infections (HAIs) are the most common complications among hospitalised patients in Australia.[1] The associated economic burden is enormous, resulting in longer hospital stays, higher treatment costs, and in severe cases intensive care unit stays and bed closures. Rates of bacterial infections causing septicaemia and deaths rose from the 1980s but have stabilised since 2000.[2] Consequently, substantial resources are devoted to controlling HAIs, especially for multidrug-resistant organisms (MROs), with strict infection control practices operating in most hospitals.

Whole-genome sequencing (WGS) of pathogens can identify genetically related isolates and identify patients involved in an outbreak. WGS can confirm or refute suspected related cases of infectious pathogens, discriminate between different strains and classify novel pathogens.[3] By detecting different strains with varied transmissibility,

patients can be better managed by the infection control team. Currently, usual laboratory tests to confirm infectious pathogens do not provide this granular information on different strains. Through WGS, multiple isolates can be analysed together to uncover the evolution of the pathogen (phylogenetics) and transmission history (who infected whom). In the future, sequencing is expected to identify information about resistance to certain antibiotics, which has potential to guide antibiotic treatment.

There is an emerging body of work on the economic value of WGS surveillance in hospital practice.[4–6] While WGS of human tissue can be expensive,[7] bacterial and viral genomes are less complex and the sequencing cost is less than one-tenth that for a human genome.[5] Nevertheless, whole hospital WGS screening is not yet economical so more judicious uses of pathogen WGS in a confirmatory role have been evaluated. In general, health economic studies have demonstrated favourable cost-effectiveness of WGS compared with standard of care. WGS can lead to reduced transmission and infection rates and lower overall costs.[4–6] These promising findings pave the way for a budget analysis to be performed to quantify the actual cost outlays required to adopt WGS on a population-wide scale.

Queensland is the second largest and third most populous state in Australia with a population of over five million. The network of public hospitals spans a large geographical area across 16 hospital and health services. For WGS surveillance in infection control to be routinely implemented in publicly funded Queensland hospitals, a budget impact analysis can assist in resource allocation and planning. The purpose of this study was to undertake a 5-year budget impact analysis of WGS surveillance compared with standard of care using an epidemiological approach from the state government perspective.

METHODS

Overview

The analysis focused on six MROs: methicillin-resistant *Staphylococcus aureus* (MRSA), extended spectrum beta-lactamase (ESBL)-producing *Escherichia coli* (ESBL *E. coli*), vancomycin-resistant *Enterococcus faecium* (VRE), ESBL-producing *Klebsiella pneumoniae* (ESBL *K. pneumoniae*), carbapenemase-producing *Enterobacterales* (CPE) and carbapenem-resistant *Acinetobacter baumannii* (CRAB). These organisms were selected because they are subject to hospital outbreaks with serious consequences and accounted for 95% of all sequenced isolates. A review of Australian hospital infection data, government reports and published studies provided the estimates for the analysis. Sequencing data to identify clusters were examined over 2 years. Costs were aggregated for the state of Queensland based on the expected number of MRO isolates arising in Queensland hospital patients. Costs were calculated annually across 5 years from the base year 2020. The International Society for Pharmacoeconomics and Outcomes Research good practice guidelines for budget impact analyses provided the framework for this work.[8]

Estimated patients infected with MROs

Each quarter, there are 409 972 hospitalisations in Queensland, and these figures were assumed to be stable over the next 5 years with full hospital capacity.[9] A recent Australian study showed that the point prevalence of HAIs in Australia was 9.9% of all hospitalisations.[10] Using Russo *et al*'s[10] data on 363 HAIs, the frequency of organisms detected was 50 (14%) *S. aureus*, 32 (9%) *E. coli*, 21 (6%) *E. faecium*, 16 (4%) *K. pneumoniae*, 7 (2%) *E. cloacae* and 4 (1%) *A. baumannii* (with 216 (62%) other organisms making up the remainder). Although these HAI data were national and the prevalence varied between hospitals, variations were within expected statistical limits to conclude HAIs could reasonably apply to Queensland.[10]

For each pathogen, the multidrug resistance rates were based on Wozniak *et al*,[11] according to site of infection—bloodstream, urinary tract and respiratory tract[11]—and the Australian Group on Antimicrobial Resistance Sepsis Outcomes Programs: 2018 Report.[12]

We estimated the total number of Queensland patients colonised or infected (N) for each of the six organisms of interest using Equation 1,

$$N = \frac{TH \times \%HAIs \times \%Org \times \%MDR}{I/(I+C)} \quad (1)$$

where *TH* is the total number of hospitalisations, *HAIs* is healthcare-associated infections, *Org* is the organism of interest, *MDR* is multidrug resistance and the denominator is the infection fraction (I/(I+C)). The infection fraction is the number of infections (I) as a fraction of the total number of colonisations (C) and infections (I). This is required on the denominator to increase the N and account for colonisations and infections as the true burden of HAI numbers. The infection fraction was calculated from 5 years of MRO surveillance data from the Royal Brisbane and Women's Hospital (RBWH), Australia (table 1). The RBWH is the largest public hospital in Australia. Sensitivity analyses were performed on the 95% CI for each of these separate variables.

Trends in multidrug resistance

Multidrug resistance rates are monitored over time in Australia and differ according to state, type of organism and antimicrobial agents used. For this analysis, annual changes to drug resistance were integrated in the analyses and were 0.3 percentage points for MRSA, 0.009 for ESBL *E. coli*, −2.8 for VRE (decreasing resistance) and 1.0 for ESBL *K. pneumoniae*.[12 13] No change in resistance rates was used for CPE and CRAB.[12]

WGS surveillance estimates and detection of clusters

Data from isolates that were sequenced came from a research demonstration project of prospective WGS for isolates of suspected outbreaks, to detect clusters before they became established as larger outbreaks. The routine use of WGS for widespread adoption would also be in

Table 1 Parameter values used in estimating the number of hospitalised patients affected by MROs

Variable	Estimate (95% CI)	Source
Number of Queensland hospital admissions per quarter	409 972 (348 476 to 462 243)	Queensland Health[9]
Prevalence of all hospitalisations with HAI (%)	9.9 (8.8 to 11.0)	Russo *et al*[10]
Species of all HAIs* (%)		
Staphylococcus aureus	13.8 (10.2 to 17.3)	Russo *et al*[10]
Escherichia coli	8.8 (5.9 to 11.7)	
Enterococcus faecium	5.8 (3.4 to 8.2)	
Klebsiella pneumoniae	4.4 (2.3 to 6.5)	
Enterobacter cloacae	1.9 (0.5 to 3.3)	
Acinetobacter baumannii	1.1 (0.0 to 2.2)	
Multidrug-resistant† (%)		
MRSA	14.4 (13.3 to 17.2)	Wozniak *et al*[11]
ESBL *E. coli*	5.3 (4.5 to 6.5)	
VRE	37.8 (26.7 to 49.2)	
ESBL *K. pneumoniae*	4.1 (3.6 to 7.7)	
CPE	4.1 (3.9 to 4.3)	Coombs *et al*[12]
CRAB	3.2 (2.7 to 3.7)	
Annual change of species incidence (% points)		
MRSA	0.3	
ESBL *E. coli*	0.9	
VRE	–2.8	Australian Commission on Safety and Quality in Health Care[13]
ESBL *K. pneumoniae*	1.0	Coombs *et al*[12]
CPE	0.0	
CRAB	0.0	
Infection fraction‡ (%)		
MRSA	20.6 (18.6 to 22.5)	Hospital/clinical data
ESBL *E. coli*	30.0 (23.9 to 36.1)	
VRE	4.6 (2.9 to 6.3)	
ESBL *K. pneumoniae*	27.6 (21.1 to 34.0)	
CPE	35.9 (20.8 to 51.0)	
CRAB	15.2 (4.8 to 25.6)	
Cluster frequency§		
MRSA, ESBL *E. coli*, ESBL *K. pneumoniae*	0.02	
VRE	0.05	Sequencing data records
CPE, CRAB	0.06	
Decreased cluster size (95% CI)		
MRSA§	5.38 (1.37 to 9.38)	
ESBL *E. coli*§	10.25 (2.94 to 17.56)	
VRE	8.29 (3.89 to 12.68)	Sequencing data records
ESBL *K. pneumoniae*	3.25 (1.23 to 5.27)	This is the estimated drop in cluster size with WGS use.
CPE	6.33 (–1.20¶ to 13.87)	

Continued

Table 1 Continued

Variable	Estimate (95% CI)	Source
CRAB	4.00 (–1.88¶ to 9.88)	

*The HAI percentage of each organism; the denominator is total HAIs.
†The denominator is the total number of the organism detected.
‡The fraction of infections to infections plus colonisations.
§The probability of a cluster detected from all isolates sequenced for that species.
¶The negative number does not denote an increase in isolates. Two isolates are required to identify the cluster, so this negative value means that no clusters are identified.
**
CPE, carbapenemase-producing *Enterobacterales*; CRAB, carbapenem-resistant *Acinetobacter baumannii*; ESBL, extended spectrum beta-lactamases; HAI, healthcare-associated infection; MRO, multidrug-resistant organism; MRSA, methicillin-resistant *Staphylococcus aureus*; VRE, vancomycin-resistant *enterococci*; WGS, whole-genome sequencing.

this context and not for indiscriminate testing. Two years of sequencing data outcomes on MROs were available from December 2017 to December 2019. MROs were sequenced at a central facility from 27 hospitals across Queensland. Of the 1783 isolates that were sequenced during the period, 90% were from three of the largest Queensland hospitals: RBWH, Queensland Children's Hospital and Princess Alexandra Hospital. Genetic relatedness was determined by examining the number of core genome single nucleotide polymorphisms (SNP) that differ between any two isolates (pair-wise core genome SNP distance). Genetically related isolates were subdivided into clusters when the SNP distance between them was under a predefined threshold, adjusted for genome size (5 SNPs/Mb).[14 15] Clustering was evident in all six pathogens, and isolates within these clusters demonstrate a high probability that pathogen transmission occurred between patients in the hospital.

Identifying SNP differences, through WGS, to investigate MRO outbreaks has become instrumental in revealing the routes of transmission and guiding the infection control response strategy.[16 17] The number of isolates in a cluster required to begin a response differs with each MRO. Based on current clinical practice, a cluster was acted on when two related isolates of an MRO were identified, except for MRSA and ESBL *E. coli*, where three related isolates were required. The number of clusters ranged from 2 to 18 across the pathogens, with an average number of patients in each cluster ranging from 5 to 13 (table 1).

Effectiveness of WGS surveillance

The effectiveness of WGS was estimated when clusters were identified and the information was provided to the infection control team, an outbreak was confirmed, and appropriate infection control measures mobilised. The effectiveness of WGS was a factor of the number of isolates that comprise a cluster, the number of clusters identified and the expected success of intervening to break the chain of transmission. An implicit assumption in this analysis is that the chain of transmission is broken when the WGS data are acted on immediately. Pathogen transmission is prevented with effective environmental cleaning, patient isolations and contact tracing, which we assume occur in all cases.

The number of patients in whom infection or colonisation could have been prevented was calculated after WGS identified a cluster (two or three patients) and began control measures. The turnaround time for WGS testing was 7 days; this is the time required for WGS to be processed and the results made available to the physicians. For example, if the cluster was identified after two patients were detected, and the cluster size was five, then three patients could potentially avoid infection, providing 7 days had elapsed between patients 2 and 3 in the cluster (table 1, online supplemental figure 1).

Expected deaths

Data on the frequency of deaths in hospital from patients infected with any of the six MROs were obtained from the Australian Group on Antimicrobial Resistance Sepsis Outcomes Programs: 2018 Report[12] and ranged from 6.7% for CPE to 36.6% for VRE *E. faecium*. Sensitivity analyses were performed on the 95% confidence limits of these mortality rates.

Resource use and costs

Patients who were colonised with an MRO accrued hospital costs for health professional personal protective equipment (PPE), microbiology tests, cleaning and extra infection control nursing time associated with contact precautions. Patients who were infected and showed symptoms accrued these same costs, plus costs for antibiotic treatments and bed closures. PPE was valued at $50 per day for each patient isolated.[18] The colonisation and infection mean length of stay for each MRO ranged from 9 to 43 days (table 2).[19–24] Published estimates for extra length of stay due to infection were used to calculate the additional hospitalisation costs for each MRO (table 2).[20 21 23] These were valued at $246 per day.[25] Antibiotic treatments were estimated from clinical advice (for infected symptomatic patients only), and their costs sourced from hospital pharmacy records, the Pharmaceutical Benefit Scheme and published studies.[11 26 27]

Table 2 Variables used in estimating the cost of MRO screening and treatments

Variable	Estimate (95% CI)	Comment/source
Cost of screening for pathogens		
Usual screening: microbiology test and PCR	$82 ($58 to $107)	Elliott *et al*[5]
WGS: microbiology test, PCR and WGS	$437 ($309 to $565)	Elliott *et al*[5]
Cleaning and extra nurse time per detection*	$122 ($90 to $155)	Elliott *et al*[5]
PPE per day in isolation	$50 ($35 to $65)	Otter *et al*[18]
Closed-bed day	$246 ($151 to $342)	Page *et al*[25]†
Cost of antibiotic treatment per infected patient		
MRSA (vancomycin)‡	$580 ($409 to $750)	SA guideline[26]/hospital pharmacy
ESBL *Escherichia coli* (meropenem)§	$321 ($227 to $416)	Wozniak[28] and hospital pharmacy pricing
VRE (linezolid and daptomycin)¶	$3433 ($2424 to $4443)	
CPE (colistin+meropenem** and gentamicin/amikacin††)	$2920 ($2061 to $3778)	Pharmacy infection network[27] and hospital pharmacy pricing
CRAB (colistin+tigecycline‡‡ and colistin+meropenem**)	$3199 ($2258 to $4139)	Viehman *et al*[29] and hospital pharmacy pricing
MRSA		
Colonisation LOS	29.2 (16.4 to 51.9)	Kirwin *et al*[20]
Infection LOS	42.7 (23.6 to 77.2)	Kirwin *et al*[20]
ESBL *E. coli*		
Colonisation LOS	16.0 (8.0 to 31.0)	Suzuki *et al*[23]
Infection LOS	33.0 (18.0 to 64.0)	Suzuki *et al*[23]
VRE		
Colonisation LOS	15.0 (9.0 to 30.0)	Tan *et al*[30]
Infection LOS	34.0 (29.6 to 38.4)	Lloyd-Smith *et al*[21]
ESBL *Klebsiella pneumoniae*		
Colonisation LOS	16.0 (8.0 to 31.0)	Suzuki *et al*[23]
Infection LOS	33.0 (18.0 to 64.0)	Suzuki *et al*[23]
CPE		
Colonisation LOS	12.0 (3.0 to 21.0)	Rodriguez-Acevedo *et al*[22]†
Infection LOS	29.0 (22.7 to 35.3)	Zhen *et al*[24]
CRAB		
Colonisation LOS	9.0 (6.0 to 22.0)	Álvarez-Marín *et al*[19]
Infection LOS	21.5 (11.5 to 42.8)	Álvarez-Marín *et al*[19]
Closed-bed days§§		
MRSA	35.2 (16.3 to 69.4)	Kirwin *et al*[20]
ESBL *E. coli*	16.6 (3.6 to 30.4)	Suzuki *et al*[23]
VRE	13.8 (10.0 to 16.9)	Lloyd-Smith *et al*[21]
ESBL *K. pneumoniae*	16.6 (3.6 to 30.4)	Suzuki *et al*[23]
CPE	14.5 (11.4 to 17.6)	Assumption¶¶
CRAB	10.8 (5.8 to 21.4)	Assumption¶¶

*Cleaning is for decontamination of the room and nursing time is for isolating the patient, contact precautions and so on.
†Australian study/data.
‡Flucloxacillin administered at 2 g intravenously 6-hourly initially and vancomycin at 2 g.
§Meropenem administered at 1.0–2 g three times daily.
¶Linezolid administered at 2×0.6 g for 14 days and daptomycin 0.6 g daily.
**Colistin administered at 275 mg for 14 days and meropenem administered at 1.0–2 g three times daily.
††Gentamicin administered at 5–7 mg/kg for 14 days and amikacin administered at 15 mg/kg.
‡‡Colistin administered at 275 mg for 14 days and tigecycline administered at 100 mg followed by 50 mg every 12 hours.
§§Closed-bed days were estimated by excess LOS for infections by each species.
¶¶Extra LOS was assumed to be 50% of the infection LOS.
CPE, carbapenemase-producing *Enterobacterales*; CRAB, carbapenem-resistant *Acinetobacter baumannii*; ESBL, extended spectrum beta-lactamases; LOS, length of stay; MRO, multidrug-resistant organism; MRSA, methicillin-resistant *Staphylococcus aureus*; PPE, personal protective equipment; SA, South Australia Health; VRE, vancomycin-resistant *enterococci*; WGS, whole-genome sequencing.

Where necessary, costs were inflated to 2019 prices using the Hospital Pricing Index. Sensitivity analyses were performed on the 95% confidence limits of the values and for treatment costs, ±15%.

Analyses

Analyses comprised aggregated total of the costs for current practice compared with a WGS surveillance strategy for the six MROs. Analyses were performed in Excel. Multiway sensitivity analyses were undertaken for each variable (eg, organism frequency, MRO rate, cluster frequency, infection fraction and so on), and the high and low values for the six organisms were used simultaneously for each variable. These values were varied within the 95% confidence limits and the results were shown for the overall cost difference between current practice (no WGS) and WGS surveillance (table 1). A sensitivity analysis was performed on a quicker 4-day turnaround time for WGS testing. Outcomes were reported for the number of expected patients with colonisations and infections, the associated hospitalisation costs and the expected deaths.

Patient and public involvement

The research study did not involve patients and the public.

RESULTS

An estimated 8003 patients in Queensland hospitals will be infected with one of six common MROs and 89 535 will be colonised, for a total of 97 539 patients in the first year. MRSA and VRE made up the majority of the six MROs (table 3). The expected number of deaths was 2032 in year 1. Over 5 years, the number of patients infected with these MROs decreased by 15% and the number of colonisations decreased by 27% overall, primarily due to decreasing drug resistance for VRE (table 3).

This compares with a strategy of routine WGS surveillance, with a turnaround time of 7 days, where WGS use could avoid 2085 infected patients and 34 641 colonised patients (table 4). In total, WGS would avoid 36 726 patients infected/colonised in year 1, decreasing to 26 984 avoided patient infections/colonisations by year 5. The number of patient deaths avoided was estimated at 650 in year 1 to 502 by year 5.

The total cost for the current management of these colonised and infected patients was an estimated $170.8 million in year 1, comprising $8.0 million for conventional microbiology screening, $11.9 million for cleaning and nursing time, $44.8 million for closed-bed days, $91.1 million for the cost of PPE and $15.0 million for antibiotic treatments (table 4).

Compared with a strategy of routine WGS surveillance, the sequencing and microbiology cost would be $26.8 million ($18.5 million more than the standard of care), but is offset in the same year by fewer costs for cleaning and nursing, length of stay, PPE and antibiotic treatments (table 4). The total cost savings were $30.9 million in year 1, dropping to $22.1 million by year 5. The cost saved for each avoided patient infection was $6917 and for each colonisation $475 in year 1.

The sensitivity analyses showed that when plausible alternative values were used in the analyses, hospital cost savings were always retained, with one exception (figure 1). The findings were most sensitive to the

Table 3 Estimated number of Queensland patients with MROs and deaths from sepsis

	2021	2022	2023	2024	2025
Number of annual hospitalisations	1 639 888	1 639 888	1 639 888	1 639 888	1 639 888
Number of HAIs	162 349	162 349	162 349	162 349	162 349
Number of HAIs from MROs of interest	58 141	58 141	58 141	58 141	58 141
Number of patients infected with MROs*					
MRSA	3223	3290	3357	3424	3491
ESBL *Escherichia coli*	752	881	1009	1138	1267
VRE	3551	3288	3025	2762	2499
ESBL *Klebsiellapneumoniae*	292	364	435	507	578
CPE	128	128	128	128	128
CRAB	57	57	57	57	57
Total MROs of concern	8003	8008	8012	8017	8021
Total number of patients colonised with MROs	89 536	84 801	80 067	75 332	70 598
Total number of patients expected with infections/colonisations	97 539	92 809	88 079	83 349	78 619
Deaths from sepsis	2032	1982	1932	1881	1831

*Adjusted for change in drug resistance rate.
CPE, carbapenemase-producing *Enterobacterales*; CRAB, carbapenem-resistant *Acinetobacter baumannii*; ESBL, extended spectrum beta-lactamases; HAI, healthcare-associated infection; MRO, multidrug-resistant organism; MRSA, methicillin-resistant *Staphylococcus aureus*; VRE, vancomycin-resistant *enterococci*.

Table 4 Estimated differences in costs ($A) and patient deaths from current practice versus WGS surveillance

	2021	2022	2023	2024	2025
Current practice					
Total number of patients expected to have MRO infections/colonisation	97 539	92 809	88 079	83 349	78 619
Cost of microbiology screening	$8 028 283	$7 638 967	$7 249 651	$6 860 335	$6 471 019
Cost of cleaning and nursing time	$11 911 230	$11 333 618	$10 756 006	$10 178 394	$9 600 782
Cost of extra length of stay	$44 793 430	$45 297 162	$45 800 893	$46 304 625	$46 808 356
Cost of PPE	$91 162 386	$87 836 074	$84 509 762	$81 183 450	$77 857 139
Cost of antibiotic treatment of patients	$14 952 034	$14 152 425	$13 352 816	$12 553 207	$11 753 598
Total cost: current practice	$170 847 364	$166 258 246	$161 669 129	$157 080 012	$152 490 895
Expected number of patient deaths	2032	1982	1932	1881	1831
WGS surveillance					
Total number of potentially avoided infections with WGS (patients)	2085	2003	1921	1839	1757
Total number of potentially avoided colonisations with WGS (patients)	34 641	32 287	29 934	27 580	25 227
Total number of potentially avoided infected/colonised with WGS	36 726	34 290	31 855	29 419	26 984
Cost of WGS	$26 575 746	$25 573 072	$24 570 397	$23 567 723	$22 565 049
Cost of cleaning and nursing time	$7 426 340	$7 146 152	$6 865 964	$6 585 777	$6 305 589
Cost of extra length of stay	$36 149 780	$36 881 764	$37 613 748	$38 345 732	$39 077 716
Cost of PPE	$60 703 607	$59 267 592	$57 831 577	$56 395 563	$54 959 548
Cost of treating infected patients	$9 123 437	$8 713 828	$8 304 219	$7 894 610	$7 485 001
Total cost: WGS surveillance	$139 978 910	$137 582 408	$135 185 906	$132 789 404	$130 392 902
Expected number of patient deaths	1382	1369	1356	1342	1329
Cost savings with WGS surveillance	$30 868 454	$28 675 839	$26 483 223	$24 290 608	$22 097 992
Patient deaths avoided	650	613	576	539	502
Costs saved per avoided infection	–$14 805	–$14 317	–$13 787	–$13 210	–$12 579
Costs saved per avoided colonisation	–$891	–$888	–$885	–$881	–$876

MRO, multidrug-resistant organism; PPE, personal protective equipment; WGS, whole-genome sequencing.

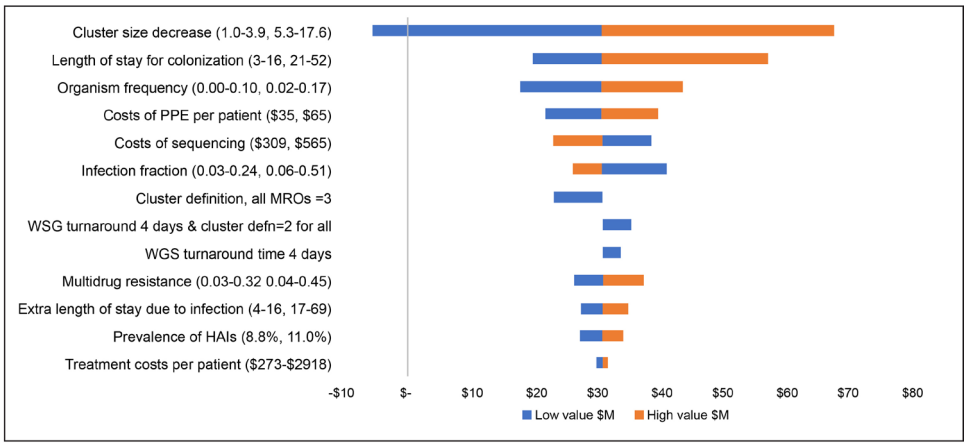

Figure 1 Tornado diagram of change in the main analysis cost savings of $A30.9 million, with higher and lower input values. HAIs, healthcare-associated infections; MROs, multidrug-resistant organisms; PPE, personal protective equipment; WGS, whole-genome sequencing.

variation in estimates of preventable patient infections if WGS is undertaken, and if this was the lowest value across all six MROs (simultaneously) it would cost an additional $5.0 million for the WGS strategy. The length of stay for colonisations and organism frequency also changed the base findings by ±$10.0 million, but overall cost savings remained. When higher and lower values were used for expected rates of deaths from the six MROs (simultaneously), the deaths potentially avoided ranged from 411 to 893 in year 1 to 316 to 694 in year 5.

DISCUSSION

To the best of our knowledge on the incidence of HAIs, MROs and drug resistance rates, nearly 100 000 patients will be infected or colonised with potentially serious bacterial infections in Queensland hospitals each year. This will cost the government $171 million per year to manage. By routinely using WGS to assist infection control teams in managing patients early in bacterial transmission, the expected cost savings will be $30.9 million per year. Not only will hospital costs be saved but thousands of patients will avoid suffering from infections and the associated risk of death.

Based on the information from WGS, we identified clusters to observe detection patterns of the six MROs among hospital patients. This differs from observing actual transmission among patients because WGS screening was not undertaken on every patient. Retrospectively, we found WGS was performed on between 13% and 93% of the MROs, with 13% for each of *S. aureus* and *E. coli*, the most common pathogens. The cost savings are heavily influenced by the cluster sizes and potential to avoid infections/colonisations, breaking the chain of transmission. A quicker testing turnaround is desirable for infection control processes. When we tested the turnaround time from 7 days to 4 days, we saw only two of the six MROs with notable reductions in patients infected, meaning detections in most patients screened were greater than a few days between the first two or three patients.

These findings align with other economic studies looking at the benefits of a WGS surveillance-based infection control programme. Kumar *et al*'s[6] findings from a single-institute US study found WGS surveillance to be less costly and more effective than standard of care. Their results were most sensitive to WGS cost and number of isolates sequenced each year. In the UK, Dymond *et al*[4] undertook an economic analysis that modelled MRSA genomic surveillance, compared with current practice, and found cost savings for genomic surveillance of ~£730 000 annually to the National Health Service. In Australia, our previous work on an ESBL *E. coli* outbreak in a single hospital also predicted significant cost savings and patient outcomes if WGS was implemented early as standard of care and avoided delays in response.[5] The major criticisms of the previous work in this area are the focus on single organisms or single institutions which can limit the generalisability of the findings and the studies are retrospective. Our cost analysis somewhat overcomes these issues by analysing data from Queensland hospitals for state-wide application, including six common MROs in our setting, and we estimated future trends based on expected changes in multidrug resistance rates.

The cluster information from WGS was not available in real time but part of a demonstration project of prospective WGS in response to suspected outbreaks, to detect clusters before they became established as larger outbreaks. The cluster analysis here was performed retrospectively within a research context. Our cost analysis shows the potential for proactive WGS surveillance to support infection control teams under the premise that testing infrastructure, staffing and fast turnaround times are in place on a wider scale. With the extensive COVID-19 pandemic preparations for widespread testing and additional sequencers now in place for Queensland, this would appear possible for more routine whole-genome pathogen sequencing. An additional benefit of genomic information is the contribution towards phylogenetic libraries and reporting to share knowledge and

information with other jurisdictions and the scientific community.

This study should be viewed with some caution as it depends on the accuracy of the estimates used. For example, it is feasible that the estimates of deaths avoided with WGS may be conflated by the MRO not being the main cause of death if the patient's underlying clinical condition is severe and advanced. Other than the best available evidence for the estimates used in the analysis, the appropriate way to address this is through sensitivity analyses. To deal with the possible uncertainty in the estimates, 95% confidence limits were tested in sensitivity analyses. These found the cost savings were stable despite variation in all but one scenario (ie, low cluster sizes). Estimating the mean length of stay for infections or colonisations is difficult to measure and varies significantly depending on MRO type. Colonisation length of stay directly influences infection control nursing time and PPE costs and is shown to be a major driver of these findings, with high patient numbers. Further research is necessary to avoid measurement bias of length of stay estimates for HAIs.[22] A further issue is the assumption that WGS equipment and infrastructure were available at the outset as these costs are not included in an operational budget impact, but rather a capital investment. Economies of scale with wider testing and lower testing are seen in the sensitivity analyses covering a lower unit cost for WGS; however, further streamlining of workflows could see testing in the future as low as $A150 per isolate. Overall, we suggest the findings are conservative because WGS testing was only used infrequently as a total percentage of MRO isolates, and if screening were higher more infections and therefore higher cluster sizes would be apparent (at reasonable cost). The expected consequences of a WGS strategy are also likely to be conservative and other MROs were excluded in the analysis. Furthermore, it is possible that an organism can contribute to more than one type of HAI and therefore the impact of prevention may also be greater.

Implementation of WGS into routine infection control practice would require standardised algorithms leading to early alarms and detection of problems and intervention for all hospitals. Although many hospitals do have systems and decision rules currently in place, a key issue is whether infection control teams would immediately and effectively respond on receiving these advanced data. This is uncertain, as is any significant organisational change, and would require infection control teams to undergo training and time to transition to new protocols. Our analysis assumes full adherence to a new scenario as presented here, as if it were established, and it is recognised this is the result of effective change and uptake by hospitals. Nevertheless, predictions about resource use and costs that might result from routine WGS are useful for decision-makers to understand whether it is warranted on an economic basis to proceed further with new resource allocations.

CONCLUSION

The proactive use of WGS surveillance for infection control of common MROs was estimated to be cost-saving for hospitals and beneficial for patients. This study has implications for government resource allocation decisions and establishes a favourable value proposition for adopting pathogen WGS into routine clinical practice in Queensland.

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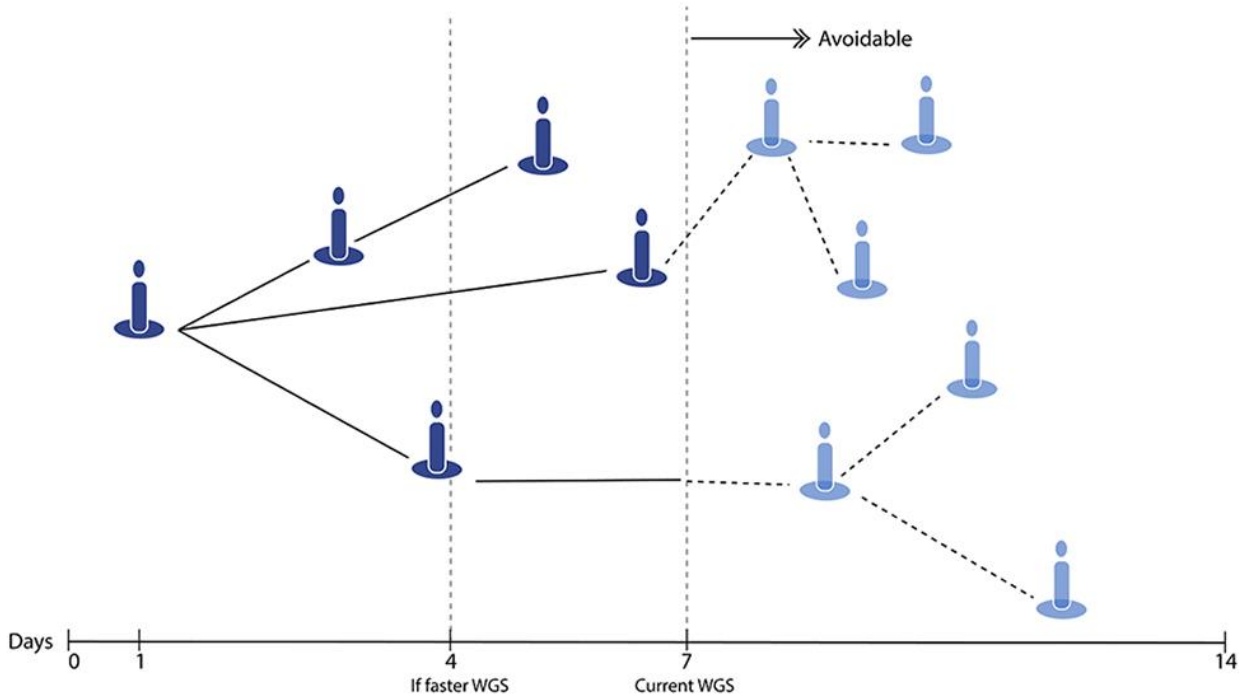
Avoidable
Days
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If faster WGS
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