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**Use of a Victorian statewide surveillance program to evaluate the burden of healthcare-associated *Staphylococcus aureus* bacteraemia and *Clostridioides difficile* infection in patients with cancer**

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**Running head:** SAB and CDI rates in cancer patients

**Key words:** Haematology, oncology, surveillance, *Staphylococcus aureus*, *Clostridioides difficile*

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## Abstract

**Background:** Patients with cancer are at high risk for infection, but the epidemiology of healthcare-associated *Staphylococcus aureus* bacteraemia (HA-SAB) and *Clostridioides difficile* infection (HA-CDI) in Australian cancer patients has not previously been reported.

**Aims:** To compare the cumulative aggregate incidence and time trends of HA-SAB and HA-CDI in a predefined cancer cohort with a mixed statewide patient population in Victoria, Australia.

**Methods:** All SAB and CDI events in patients admitted to Victorian healthcare facilities between 1<sup>st</sup> July 2010 and 31<sup>st</sup> December 2018 were submitted to the Victorian Healthcare Associated Infection Surveillance System Coordinating Centre. Descriptive analyses and multilevel mixed-effects Poisson regression modelling were applied to a standardised data extract.

**Results:** In total, 10,608 and 13,118 SAB and CDI events were reported across 139 Victorian healthcare facilities, respectively. Of these, 89 (85%) and 279 (88%) were healthcare-

associated in the cancer cohort compared to 34% (3,561/10,503) and 66% (8,403/12,802) in the statewide cohort. The aggregate incidence was more than two-fold higher in the cancer compared to the statewide cohort for HA-SAB (2.25 [95% CI: 1.74-2.77] vs. 1.11 [95% CI: 1.07-1.15] HA-SABs/10,000 OBDs) and three-fold higher for HA-CDI (6.26 [95% CI: 5.12-7.41] vs. 2.31 [95% CI: 2.21-2.42] HA-CDIs/10,000 OBDs). Higher quarterly diminishing rates were observed in the cancer cohort than the statewide data for both infections.

**Conclusions:** Our findings demonstrate a higher burden of HA-SAB and HA-CDI in a cancer cohort when compared with state data and highlight the need for cancer-specific targets and benchmarks to meaningfully support quality improvement.

**Key words:** Haematology, oncology, surveillance, *Staphylococcus aureus*, *Clostridioides difficile*

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### Previous presentations

This research was presented in part at the 21<sup>st</sup> ICHS Symposium on Infections in the Immunocompromised Host in Melbourne, Victoria, Australia, 17<sup>th</sup> – 19<sup>th</sup> February 2021.

### Data Sharing and Data Accessibility

Data sharing is restricted to the researchers, clinical staff and the individual patient's healthcare provider participating in the project analysis. The ethics approval (LNR/58426/PMCC-2019) maintains that public data provision is contingent on authorisation from the Principal Investigator (J.C.V.) and associated ethics applications to the Peter MacCallum Cancer Centre Human Research Ethics Committee for researchers who meet the criteria for access to confidential data. Contact details to which data requests may be sent are [Jake.Valentine@petermac.org](mailto:Jake.Valentine@petermac.org) or [ethics@petermac.org](mailto:ethics@petermac.org).

### Abstract

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**Conclusions:** Our findings demonstrate a higher burden of HA-SAB and HA-CDI in a cancer cohort when compared with state data and highlight the need for cancer-specific targets and benchmarks to meaningfully support quality improvement.

**Key words:** Haematology, oncology, surveillance, *Staphylococcus aureus*, *Clostridioides difficile*

**Introduction**

*Staphylococcus aureus* bacteraemia (SAB) and *Clostridioides difficile* infection (CDI) are significant healthcare-associated infections leading to morbidity and mortality in hospitalised patients.<sup>1-4</sup> Immunocompromised patients are at increased risk for acquisition of infections and complications.<sup>5</sup> Surveillance and reporting of these infections are necessary to support prevention programs in healthcare as well as enabling meaningful inter-hospital comparisons and review of quality improvement activities.

In Australia, hospital-level reporting of these infections is recommended nationally and supported by state programs.<sup>6</sup> Aggregated SAB data for public hospitals are reported annually through the Australian Institute of Health and Welfare's MyHospitals national reporting platform.<sup>7</sup> In contrast, and in recognition of differences in risks and outcomes, some international groups specifically report rates of these infections in immunocompromised cohorts.<sup>8-10</sup> To date, this approach has not been proposed or tested in Australia.

The objective of this study was to compare rates and time trends of SAB and CDI in a cancer-specific cohort in Victoria with a mixed statewide cohort using continuous surveillance data.

## Methods

### *Study design*

This study was a retrospective, longitudinal, cohort study of all laboratory-confirmed cases of SAB and CDI across 139 participating healthcare facilities in Victoria, Australia, including one dedicated cancer centre. Surveillance data regarding SAB and CDI captured for the period 1<sup>st</sup> July 2010 to 31<sup>st</sup> December 2018 were extracted retrospectively from the Victorian Healthcare Associated Infection Surveillance System (VICNISS) Coordinating Centre.<sup>11</sup> Study design was consistent with criteria endorsed in the STrengthening the Reporting of OBServational studies in Epidemiology (STROBE) statement (Supporting Information, Table S1).

### *Definitions*

A *cancer-specific* population was defined as patients admitted to the Peter MacCallum Cancer Centre (n=1 hospital). The *mixed patient* population comprised the statewide cohort (n=138 hospitals), which consisted of 43 large ( $\geq 100$  beds) and 95 small ( $< 100$  beds) healthcare facilities across Victoria. Infection rates and time trends for SAB and CDI were evaluated for the overall mixed patient population as well as the large and small healthcare facility groups.

Each SAB and CDI event was classified and reported by the VICNISS Coordinating Centre as either healthcare-associated (HA) or community-acquired using surveillance definitions endorsed by the Australian Commission for Safety and Quality in Health Care<sup>12, 13</sup> and the Centers for Disease Control and Prevention<sup>10</sup> (Supporting Information, Table S2). For CDI, a positive result for *C. difficile* toxin A or B or the presence of a toxin-producing *C. difficile*

organism in a diarrhoeal specimen was a requirement for a confirmed diagnosis. In accordance with state legislation<sup>14</sup> and the Victorian Health Service Performance Monitoring Framework,<sup>15</sup> continuous hospital-wide SAB and CDI surveillance during the study period was mandatory for all public health services and voluntary for private health services in Victoria.

### *Statistical analysis*

#### *Proportion of reported infection*

Healthcare-associated and community-associated SAB and CDI were reported as a proportion of total cases. The proportion of intravascular device-related or methicillin-resistant HA-SAB events was calculated as a proportion of the sum of SAB cases classified according to VICNISS Definitions 1 and 2 (Supporting Information, Table S2).

#### *Cumulative aggregate incidence and time trends*

The cumulative aggregate incidence comprised the cumulative count of HA-SAB and HA-CDI events spanning 2010-2018 and was calculated and reported per 10,000 occupied bed-days (OBD).<sup>16</sup> Occupied bed-day data were sourced from the Victorian Admitted Episodes Dataset. Multilevel mixed-effects Poisson regression models were used to model total counts of HA-SAB and HA-CDI, stratified by each evaluable cohort, where the total number of OBDs formed the offset exposure variable. To evaluate time trends, quarterly counts of HA-SAB and HA-CDI were fitted to the Poisson models. Linear regression models were subsequently fitted to predict overall linear time trends. Given that specific hospital characteristic data were not available, the hospital identifier was modelled as a random effect to adjust for inter-hospital heterogeneity. Infection counts were tested for overdispersion. A dummy variable that distinguishes the cancer-specific from the statewide cohort was included

as a binary explanatory covariate in the regression models to deduce any statistical significance in infection time trends between the groups.

### *Model selection*

The goodness-of-fit  $\chi^2$  test, McFadden's pseudo  $R^2$  and the simplified quasi-likelihood information criterion (QIC<sub>v</sub>)<sup>17</sup> were used to assess the fit and correlation structure of each mixed-effects Poisson regression model. To determine the proportion of the variation in the hospital identifier variable, the intraclass correlation coefficient<sup>18</sup> was calculated (Supporting Information, Table S3). To model the response of specifying random effect distributions (i.e. hospital identifier) on the outcome parameter (i.e. healthcare-associated infection rates), deviance residuals for the fixed effects and mixed effects models were calculated and plotted against fitted linear predictions of both the fixed and random effects (Supporting Information, Table S3).<sup>19</sup>

Exact binomial 95% confidence intervals were calculated for all proportion estimates. A two-sided  $p$  value  $<0.05$  was considered statistically significant. All statistical analyses were undertaken using Stata/SE v15.1 (StataCorp® LLC, College Station, Texas, U.S.A.).

### *Ethics*

Ethics approval was granted by the Peter MacCallum Cancer Centre Human Research Ethics Committee (project number: 19/216L) and the need for informed consent was waived in accordance with the National Statement on Ethical Conduct in Human Research 2007 (Updated May 2015).<sup>20</sup>

## Results

### *Healthcare-associated SAB*

#### *Distribution and rates of infection*

Overall, 10,608 SAB events were identified during the study period, with 105, 10,503, 747 and 9,756 events in the cancer-specific, statewide, small and large healthcare facility cohorts, respectively. A larger proportion of SAB events were healthcare-associated in the cancer cohort (89/105 [85%]), compared with the statewide (3,561/10,503 [34%]), small (227/747 [30%]) and large (3,334/9,756 [34%]) healthcare facility cohorts (Table 1, Figure 1).

#### *Epidemiology of infection*

Of all HA-SAB events, 56% (95% CI: 45, 67; 50/89), 66% (95% CI: 65, 68; 2,360/3,561), 58% (95% CI: 51, 65; 132/227) and 67% (95% CI: 65, 68; 2,228/3,334) had infection onset >48-hours of hospital admission or <48-hours of hospital discharge (VICNISS Definition 1; Supporting Information, Tables S2 and S4)<sup>12</sup> in the cancer-specific, statewide, small and large healthcare facility cohorts, respectively. The proportion of intravascular device-related HA-SAB cases was approximately two-fold higher in the cancer-specific cohort (74% [95% CI: 63, 83]; 65/88) than the statewide comparator (42% [95% CI: 41, 44]; 1,384/3,275), of which 40% and 28% were associated with central venous catheter use, respectively. The proportion of methicillin-resistant HA-SAB isolates was comparable across all studied cohorts (cancer-specific, 20% [95% CI: 13, 30], 18/88; statewide, 18% [95% CI: 17, 20],

605/3,275; small healthcare facility, 25% [95% CI: 19, 32], 50/200; large healthcare facility, 18% [95% CI: 17, 19], 555/3,075).

### *Cumulative aggregate incidence and time trends*

The cumulative aggregate incidence of HA-SAB was approximately two-fold higher in the cancer-specific cohort compared with the statewide comparator (2.25 [95% CI: 1.74, 2.77] vs. 1.11 [95% CI: 1.07, 1.15] HA-SABs/10,000 OBDs), and approximately 1.2 and 2.1-times higher than the small and large healthcare facility cohorts, respectively (Table 1, Figure 2).

A statistically significant difference in quarterly HA-SAB time trends was detected between the cancer-specific and state aggregate cohorts ( $p<0.001$ ). The highest quarterly rate reduction (per 10,000 OBDs) was detected in the cancer-specific cohort (-0.04 [95% CI: -0.06, -0.03];  $p<0.001$ ), followed by small healthcare facilities (-0.03 [95% CI: -0.04, 0.02];  $p<0.001$ ), large healthcare facilities (-0.02 [95% CI: -0.02, -0.02];  $p<0.001$ ) and the state aggregate (-0.01 [95% CI: -0.02, -0.008];  $p<0.001$ ) (Table 1, Figure 3).

### ***Healthcare-associated CDI***

#### *Distribution and rates of infection*

Overall, 13,118 CDI events were identified during the study period, with 316, 12,802, 859 and 11,943 events detected in the cancer-specific, statewide, small and large healthcare facility cohorts, respectively. A larger proportion of CDI events were healthcare-associated in the cancer cohort (279/316 [88%]), compared to statewide comparator (8,403/12,802 [66%]), small (511/859 [59%]) and large (7,892/11,943 [66%]) healthcare facility data (Table 1, Figure 1, Supporting Information, Table S4).

### *Cumulative aggregate incidence and time trends*

The cumulative aggregate incidence was approximately three-fold higher for HA-CDI in the cancer-specific cohort compared to the statewide comparator (6.26 [95% CI: 5.12, 7.41] vs. 2.31 [95% CI: 2.21, 2.42] HA-CDIs/10,000 OBDs), and approximately 6 and 2.5-times higher than the small and large healthcare facility cohorts, respectively (Table 1, Figure 2).

A statistically significant difference in quarterly HA-CDI time trends was detected between the cancer-specific and state aggregate cohorts ( $p < 0.001$ ). Quarterly rate reductions (per 10,000 OBDs) were observed for all subgroups and were highest in the cancer-specific cohort (-0.05 [95% CI: -0.09, -0.006];  $p = 0.008$ ), followed by the state aggregate (-0.02 [95% CI: -0.03, -0.001];  $p = 0.034$ ), large healthcare facilities (-0.02 [95% CI: -0.04, -0.003];  $p = 0.353$ ), and small healthcare facilities (-0.008 [95% CI: -0.02, -0.001];  $p = 0.025$ ) (Table 1, Figure 4).

## Discussion

Our findings demonstrate the incidence of HA-SAB and HA-CDI to be more than two-fold higher in the cancer-specific cohort when compared with a mixed patient population using standardised case definitions. We also observed the relative burden of healthcare-associated events to be higher than community-associated events in the cancer-specific cohort. Diminishing rates of HA-SAB and HA-CDI were observed across Victorian facilities, with the largest quarterly rate reduction reported in the cancer-specific cohort.

There are a number of potential reasons for our observations regarding differences in SAB and CDI rates between cancer and statewide cohorts. For SAB, cancer cohorts frequently require indwelling medical devices for administration of chemotherapy and other treatments.<sup>21</sup> Specific cancer subgroups are also known to have high prevalence of colonisation with *S. aureus*, contributing to risk of invasive infection.<sup>22</sup> Furthermore, patients with cancer may require frequent and prolonged hospitalisation, contributing to risk of *S. aureus* acquisition. Risks for CDI are also increased in cancer cohorts, and our data are consistent with a higher burden of illness.<sup>2</sup> This is potentially related to frequent use of broad-spectrum antibiotics in patients with cancer, alterations in gut microbiome, frequent and prolonged periods of hospitalisation, use of proton-pump inhibitors and cancer-related gastrointestinal surgery.<sup>2</sup> In particular, higher SAB and CDI rates in the cancer-specific as compared to the small healthcare facility cohort were unsurprising, given small health services are less likely to manage a complex patient casemix.

Overall, the proportion of SAB and CDI events that were healthcare-associated (85% and 88%, respectively) in cancer patients were comparable to international reports.<sup>3, 22-25</sup> Of note, the cumulative aggregate incidence of HA-CDI (6.26 CDIs [95% CI: 5.12, 7.41] per 10,000 OBDs) was approximately half that of interstate and international estimates in patients with cancer (15-17.9 HA-CDI/10,000 OBDs).<sup>26-28</sup> However, notwithstanding reported HA-SAB incidence rates spanning 0.36-0.85 per 1,000 hospital admissions in haematology-oncology patients,<sup>29</sup> the paucity of literature documenting rates according to bed-day occupancy limits any meaningful comparison with our HA-SAB incidence estimates. Lower infection rates in our cancer cohort may be a consequence of specific infection prevention measures and screening programs implemented at our centre, including clinical practice guidelines regarding insertion and management of central venous catheters,<sup>30</sup> accommodation of patients in single rooms<sup>31</sup> and a hospital-wide antimicrobial stewardship program.<sup>32</sup> A larger proportion of HA-SAB cases were detected <48-hours of hospitalisation in the cancer-specific compared to the statewide cohort (43% versus 26%; Supporting Information, Table S4). We propose that this may be ascribed to a large number of haematology-oncology patients who frequently require indwelling medical devices in the community as part of cancer care, meaning increased community exposure to *in situ* catheterisation likely increases the risk for early onset HA-SAB <48-hours of admission at our centre compared with other facilities.

The proportion of healthcare-associated MRSA bacteraemia cases in the cancer-specific cohort (20%) is marginally lower than published estimates spanning 21-39% in neutropenic haematology-oncology patients.<sup>3, 23</sup> This may reflect effectiveness and continuous refinement of antimicrobial-prescribing guidelines,<sup>33-35</sup> peripheral intravenous cannulae insertion and

maintenance,<sup>30</sup> improved access to infectious disease consultation<sup>36</sup> and implementation of a hospital-wide sepsis pathway at our centre.<sup>32</sup>

A higher proportion of intravascular device-related HA-SABs in the cancer versus mixed patient cohort highlights the need to consider dedicated reporting of infections in cancer populations. We observed that 74% of HA-SABs in the cancer-specific cohort were associated with insertion of tunnelled devices, approximately two-fold higher than the state aggregate (42%). These data are unadjusted estimates given hospitalised cancer patients require frequent insertion of indwelling devices (e.g. for intravenous administration of chemotherapy), placing patients at greater risk of HA-SAB compared to an immunocompetent population.<sup>37</sup> Earlier works have demonstrated an up to 36% decrease in HA-SAB incidence after adjusting for device exposure in admitted haematology patients.<sup>38, 39</sup> Epidemiological differences, particularly for HA-SAB, between malignant and non-malignant groups provide a compelling argument to consider cancer-specific reporting of infection data that reflects the aetiology of healthcare-associated infection in hospitalised cancer patients.

We identified greater statistically significant quarterly incidence rate reductions for HA-SAB and HA-CDI in the cancer-specific compared to the mixed statewide cohort. Beyond the mounting evidence supporting the effect of coordinated statewide surveillance programs in reducing rates of HA-SAB and HA-CDI in Victoria,<sup>40-42</sup> more pronounced quarterly rate reduction of both infections at our centre in the cancer-specific cohort may reflect multiple risk-reduction processes previously described. Comparable rate reductions for both infections

in the small and large healthcare facility cohorts (Table 1) likely speaks to continuous refinement in infection prevention practices across all patient casemixes in Victoria.<sup>40,41</sup>

While state and national targets have been proposed for SAB rates,<sup>7, 43</sup> these have been structured for application to healthcare facilities rather than specific or high-risk populations. We propose that rates and the epidemiology of infections are different within cancer cohorts, and that these differences support the need for targeted reporting of surveillance data for high-risk patients. While our centre is a unique population of patients with cancer, haematology-oncology units within tertiary healthcare facilities specifically could report SAB and CDI using currently captured denominator data (e.g. occupied bed-days or patient-days). This would enable similar populations to be compared using standardised methods for calculating infection rates in cancer cohorts within different facilities.

Effective infection prevention programs are predicated on risk-adjusted longitudinal data to monitor trends over time and quality improvement within target populations. We note that diminishing rates of HA-SAB and HA-CDI in the cancer cohort were higher than that of the statewide comparator (Table 1; Figures 3 and 4). Despite this, application of cancer-specific and risk-adjusted benchmarks provide more meaningful targets to measure patient safety according to infection risk, enabling a more targeted approach to infection prevention.<sup>39,44</sup> Of note, Tong *et al.*<sup>45</sup> and Thompson *et al.*<sup>46</sup> maintain that specification of more granular medical service provision data (e.g. haematology versus oncology wards) provides a more robust risk-adjusted estimate on healthcare-associated infection rates given the underlying propensity of their casemix to develop healthcare-associated infection. Differences in the distribution of *hospital*-level healthcare-associated SAB data across Victorian facilities have

previously been identified, meaning that comparison with a static *population*-level benchmark may not adequately reflect the impact of local infection prevention initiatives upon infection outcomes,<sup>47</sup> particularly for hospitals treating complex cancer patients.

Limitations to the current study include the fact that a mixed population of hospitalised patients was used as the comparator for the cancer-specific cohort. Mixed and general hospital patient populations will be comprised of patients with a range of underlying diseases, including cancer. It is therefore likely that our observations represent an underestimate of the true difference in rates of healthcare-associated infections in cancer and non-cancer populations. Second, only cancer populations in a single cancer centre were evaluated, leading to lower statistical power and inflated effect size estimation when comparing infection rates between each cohort. Moreover, infection practices at our centre may not be representative of other facilities providing cancer care. Third, voluntary participation in SAB and CDI surveillance activities by private healthcare facilities may mean that data submitted by participating health services are not representative of the entire private sector and may introduce self-selection bias<sup>49</sup> into the current study. Lastly, we were unable to adjust for any time-variant confounders in our modelling since exposure to chemotherapy or other quantitative measures of immunosuppression are not a minimum data requirement in existing surveillance systems, and were therefore absent from our data collection.

## Conclusion

Although standardised surveillance methods are used within many Australian healthcare facilities for reporting of healthcare-associated infections, we demonstrate that reporting of infection rates in high-risk cancer cohorts is required to support benchmarking activities and facilitate quality improvement programs in cancer care. An evaluation of the feasibility of capturing and collating cancer-specific data across the range of Australian healthcare providers is therefore required. Looking ahead, we propose that existing surveillance infrastructure be modified to enable numerator and denominator data specific to haematology-oncology units in general hospitals be extracted to allow reporting and meaningful comparison of high-risk subpopulations across multiple health services.

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## Figure legends

**Figure 1.** Proportion (in percent) of *Staphylococcus aureus* bacteraemia and *Clostridioides difficile* infection cases by surveillance definition and hospital cohort. Numbers in parentheses denote the sum of infections within each hospital group. CDI, *Clostridioides difficile* infection; SAB, *Staphylococcus aureus* bacteraemia.

**Figure 2.** Cumulative aggregate incidence (2010-2018) with 95% confidence intervals of healthcare-associated *Staphylococcus aureus* bacteraemia and *Clostridioides difficile* infection in each cohort.

**Figure 3.** Quarterly incidence rates (per 10,000 occupied bed-days) and linear trend of healthcare-associated *Staphylococcus aureus* bacteraemia in the cancer-specific and statewide cohort in Victoria, 2010-2018. OBD, occupied bed-days.

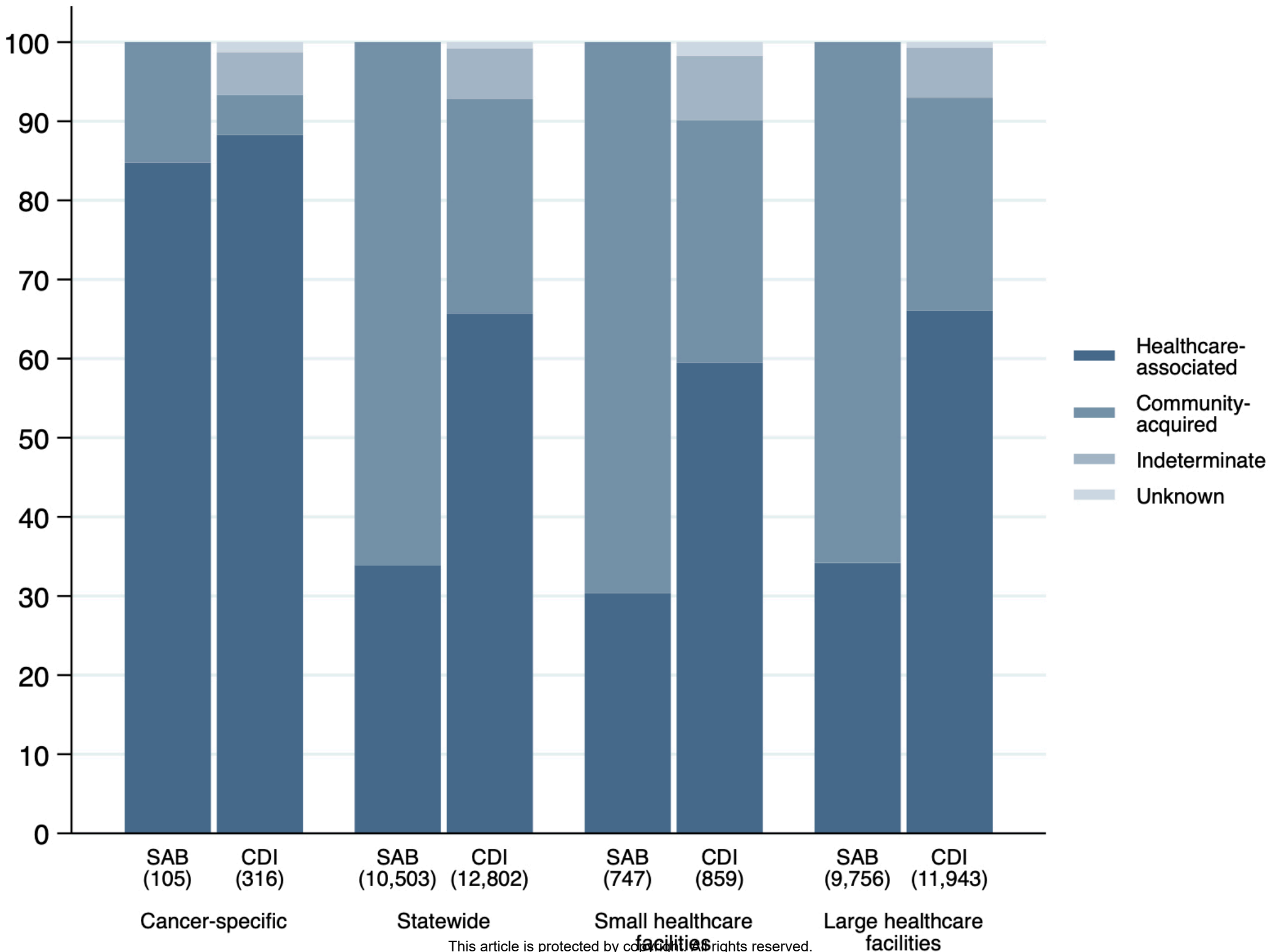
**Figure 4.** Quarterly incidence rates (per 10,000 occupied bed-days) and linear trend of healthcare-associated *Clostridioides difficile* infection in the cancer-specific and statewide cohort in Victoria, 2010-2018. OBD, occupied bed-days.

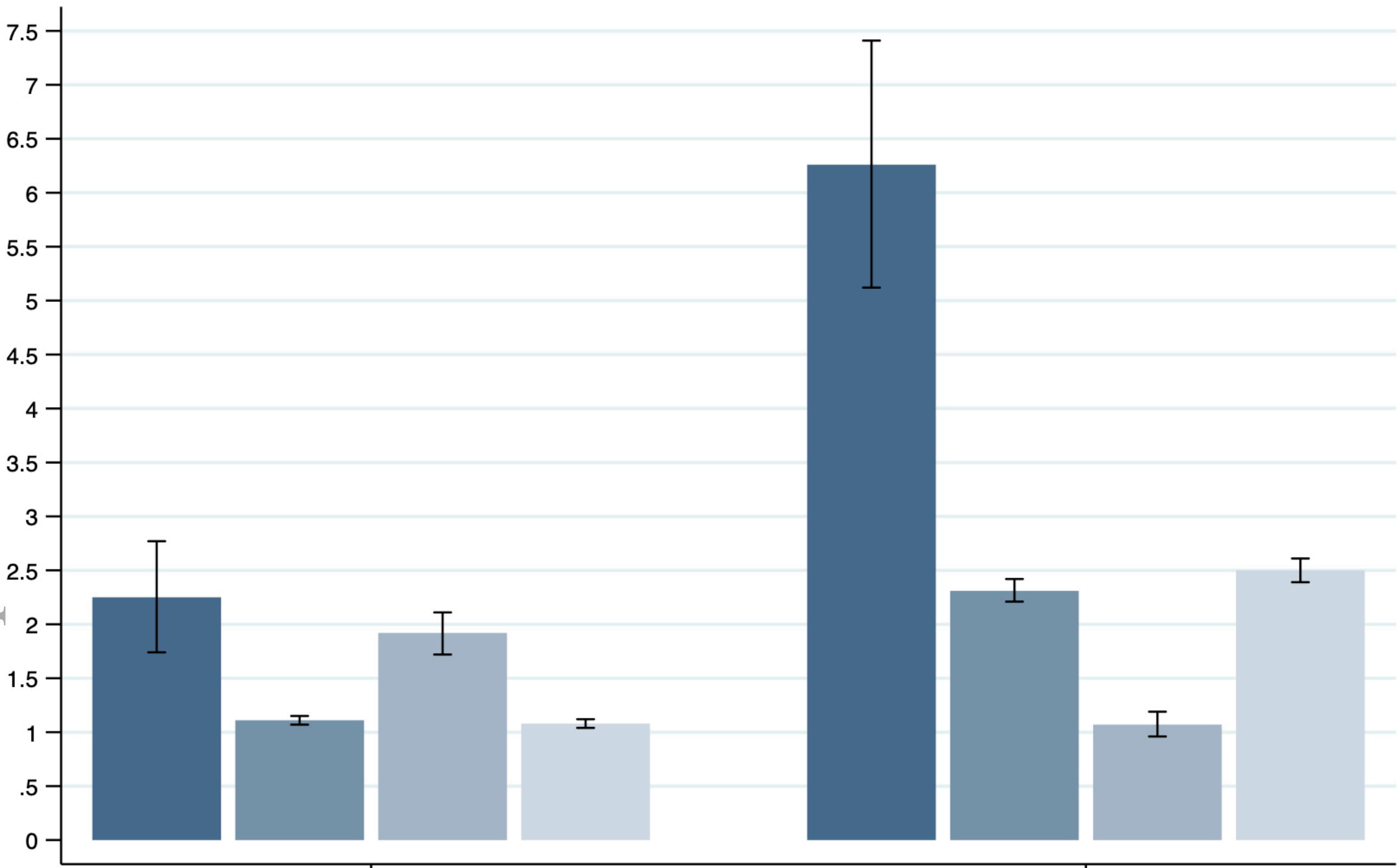
## Tables

**Table 1.** Healthcare-associated infection rates and time trends in cancer and comparator cohorts for *Staphylococcus aureus* bacteraemia and *Clostridioides difficile* infections, 2010-2018.

	<b>Infection</b>	<b>Cancer-specific (n=1)</b>	<b>Statewide (n=138)</b>	<b>Small healthcare facilities (n=95)</b>	<b>Large healthcare facilities (n=43)</b>
<b>Proportion (%) healthcare-associated [95% CI] (n/N total infection events)</b>	SAB	85 [76, 91] (89/105)	34 [33, 35] (3,561/10,503)	30 [27, 34] (227/747)	34 [33, 35] (3,334/9,756)
	CDI	88 [84, 92] (279/316)	66 [65, 66] (8,403/12,802)	59 [56, 62] (511/859)	66 [65, 67] (7,892/11,943)
<b>Aggregate incidence (per 10,000 occupied bed-days) [95% CI]</b>	HA-SAB	2.25 [1.74, 2.77]	1.11 [1.07, 1.15]	1.92 [1.72, 2.11]	1.08 [1.04, 1.12]
	HA-CDI	6.26 [5.12, 7.41]	2.31 [2.21, 2.42]	1.07 [0.96, 1.19]	2.50 [2.39, 2.61]
<b>Quarterly time trend (per 10,000 occupied bed-days) [95% CI]</b>	HA-SAB	-0.04 [-0.06, -0.03]	-0.01 [-0.02, -0.008]	-0.03 [-0.04, 0.02]	-0.02 [-0.02, -0.02]
	HA-CDI	-0.05 [-0.09, -0.006]	-0.02 [-0.03, -0.001]	-0.008 [-0.02, -0.001]	-0.02 [-0.04, -0.003]

CDI, *Clostridioides difficile* infection; CI, confidence interval; HA, healthcare-associated; SAB, *Staphylococcus aureus* bacteraemia





*Staphylococcus aureus* bacteraemia

*Clostridioides difficile* infection

Cancer-specific      Statewide      Small healthcare facilities      Large healthcare facilities

