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Epidemiology of *Clostridium difficile* infections in Australia: enhanced surveillance to evaluate time trends and severity of illness in Victoria, 2010–2014

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SUMMARY

Background: With epidemic strains of *Clostridium difficile* posing a substantial healthcare burden internationally, there is a need for longitudinal evaluation of *Clostridium difficile* infection (CDI) events in Australia.

Aim: To evaluate time trends and severity of illness for CDI events in Australian healthcare facilities.

Methods: All CDI events in patients admitted to Victorian public hospitals between 1st October 2010 and 31st December 2014 were reported to the Victorian Healthcare Associated Infection Surveillance System. CDI was defined as the isolation of a toxin-producing *C. difficile* organism in a diarrhoeal specimen, and classified as community-associated (CA-CDI) or healthcare-associated (HA-CDI). Severe disease was defined as admission to an intensive care unit, requirement for surgery and/or death due to infection. Time trends were examined using a mixed-effects Poisson regression model, and the Walter and Edward test of seasonality was applied to evaluate potential cyclical patterns.

Findings: In total, 6736 CDI events were reported across 89 healthcare facilities. Of these, 4826 (71.6%) were HA-CDI, corresponding to a rate of 2.49/10,000 occupied bed days (OBDs). The incidence of HA-CDI was highest in the fifth quarter of surveillance (3.6/10,000 OBDs), followed by a reduction. Severe disease was reported in 1.66% of events, with the proportion being significantly higher for CA-CDI compared with HA-CDI (2.21 vs 1.45%, $P = 0.03$). The highest and lowest incidence of HA-CDI occurred in March and October, respectively.

Conclusions: A low incidence of HA-CDI was reported in Victoria compared with US/European surveillance reports. Seasonality was evident, together with diminishing HA-CDI rates in 2012–2014. Severe infections were more common in CA-CDI, supporting future enhanced surveillance in community settings.

Introduction

Clostridium difficile infection (CDI) is the most common cause of healthcare-associated diarrhoea.[1] Epidemic strains of *C. difficile* have caused outbreaks in North America, Europe,

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Asia and Central America,[2] and hypervirulent strains have been associated with hospital outbreaks of severe infection, frequent relapses and high mortality.[3]

Acquisition of infection due to organism strains associated with hypervirulence was first identified in Victoria in 2010.[4] Subsequently, a review of national data for 2011–2012 indicated an increasing incidence of infections due to *C. difficile*.[5] However, the severity of illness was not evaluated, and it is not known if the burden of severe disease has increased or changed in tandem with changes in overall CDI rates.

In 2010, Victorian healthcare facilities commenced mandatory surveillance for CDI using a nationally agreed case definition for infection.[6] Given the potential for CDI disease trends observed internationally to be mirrored in Australia, particularly the rapid emergence of hospital outbreaks due to severe disease, enhanced surveillance was instituted. This included assessment of illness severity for all reported CDI cases, time and place of onset, and differentiation between healthcare- and community-associated cases.[7]

The objectives of this study were to evaluate the time trends for the incidence of CDI and, secondly, the severity of illness of CDI events reported by public and private hospitals participating in the Victorian Healthcare Associated Infection Surveillance System (VICNISS) between 2010 and 2014.

Methods

Target population

Since 2010, all public healthcare facilities in Victoria have been required to collect data regarding hospital-identified CDI to the VICNISS Coordinating Centre. The current study analysed data from 1st October 2010 to 31st December 2014.

The CDI surveillance module has been described in detail previously.[7] In brief, cases of infection are identified by infection prevention staff in Victorian healthcare facilities, and data are submitted using a web-based data collection form, including non-identifying demographic data, specimen collection date, if the organism was cultured, identification of strain type, and where the infection was thought to have originated. Data are reported back to participating hospitals on a quarterly basis.

Definitions

All cases of laboratory-confirmed CDI were included in the surveillance. 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 required for diagnosis of CDI.[6,8] Infants aged <2 years were excluded from surveillance due to frequent asymptomatic carriage of *C. difficile* in this population. Consistent with recommendations of the Centers for Disease Control and Prevention,[9] cases were classified using the following criteria for time/place of onset:

1. healthcare associated, healthcare facility (HCF) onset – defined as >48 h after admission;
2. healthcare associated, community onset – defined as onset within 48 h of HCF admission and within four weeks of discharge from an HCF;
3. community associated – defined as symptom onset in the community or within 48 h of admission where symptom onset was >12 weeks after discharge from an HCF;
4. indeterminate exposure – defined as onset in the community between four and 12 weeks of discharge from an HCF; and
5. unknown exposure.

Healthcare-associated infections (HA-CDI) were defined as those with HCF or community onset (i.e. Criterion 1 or 2 above). Illness severity was reported according to criteria proposed by McDonald *et al.*:[9] 'severe disease' was defined as either admission to an intensive care unit (ICU), surgery for CDI-related complications, or death attributed to CDI within 30 days of symptom onset.

Statistical analysis

Rates of healthcare-associated infection were calculated per 10,000 occupied bed days (OBDs), sourced from the Victorian Admitted Episodes Dataset.[7] Community-associated cases (CA-CDI) were reported as counts rather than rates of infection, given the fact that length of hospitalization would not be an appropriate measure of time at risk for patients residing in the community. Severe CDI was reported as a proportion of total CDI cases.

Categorical variables were summarized using frequency and percentages. Continuous variables were summarized using mean and standard deviation or median and interquartile range (IQR), as appropriate. A longitudinal mixed-effects Poisson regression was used to model trends in counts of CDI over time where the aggregate number of OBDs formed the offset exposure variable. In the absence of explicit data regarding individual hospital characteristics that may differ systematically between contributing sites (e.g. case-mix), the hospital identifier was included in the mixed model as a random effect to adjust for unobserved intersite heterogeneity. CDI counts were tested for overdispersion. Effect size was quantified as the risk ratio (RR).

To evaluate potential periodic, cyclical patterns in CDI rates, the Walter and Edward test of seasonality[10] was applied to monthly infection count data submitted between 2012 and 2014 to avoid inclusion of early data with potential ascertainment bias (2010–2011). This pattern suggested a predictable annual cycle consisting of a single peak and trough separated by an interval of six months, as described by a regression model specified as a function of one sine and one cosine function. This assumption supporting a base model describing a periodic, sinusoidal annual cycle was tested formally against models extended to include additional period harmonics. Competing trigonometric models were compared using an Akaike and Bayesian Information Criterion, assessment of the coefficient of determination (R^2), a likelihood ratio test and visual analysis of residual plots. The base model describing a single peak and trough was found to return the best fit in terms of minimizing the residual square error ($P < 0.0001$, $R^2 = 0.314$) relative to either an extended model containing an additional harmonic ($P < 0.0001$, $R^2 = 0.228$) or an additional two harmonics ($P = 0.0214$, $R^2 = 0.187$).

For all analyses, $P < 0.05$ was considered to indicate significance. Analysis was undertaken using Stata Version 14