Furuya-Kanamori, Luis; McKenzie, Samantha J; Yakob, Laith; Clark, Justin; Paterson, David L; Riley, Thomas V; Clements, Archie C; (2015) Clostridium difficile infection seasonality: patterns across hemispheres and continents - a systematic review. PloS one, 10 (3). e0120730-. ISSN 1932-6203 DOI: https://doi.org/10.1371/journal.pone.0120730

Downloaded from: http://researchonline.lshtm.ac.uk/id/eprint/2130298/

DOI: https://doi.org/10.1371/journal.pone.0120730

Usage Guidelines:

Please refer to usage guidelines at https://researchonline.lshtm.ac.uk/policies.html or alternatively contact researchonline@lshtm.ac.uk.

Available under license: http://creativecommons.org/licenses/by/2.5/
Reprint Article

Clostridium difficile Infection Seasonality: Patterns across Hemispheres and Continents – A Systematic Review

Luis Furuya-Kanamori1*, Samantha J. McKenzie2, Laith Yakob3, Justin Clark4, David L. Paterson5, Thomas V. Riley6, Archie C. Clements1

1 Research School of Population Health, The Australian National University, Canberra, Australian Capital Territory, Australia, 2 School of Population Health, The University of Queensland, Herston, Queensland, Australia, 3 London School of Hygiene and Tropical Medicine, Department of Disease Control, London, United Kingdom, 4 Drug ARM Australasia, Annerley, Queensland, Australia, 5 The University of Queensland, UQ Centre for Clinical Research, Herston, Queensland, Australia, 6 Microbiology & Immunology, The University of Western Australia and Department of Microbiology PathWest Laboratory Medicine, Queen Elizabeth II Medical Centre, Nedlands, Western Australia, Australia

* Luis.Furuya-Kanamori@anu.edu.au

Abstract

Background

Studies have demonstrated seasonal variability in rates of Clostridium difficile infection (CDI). Synthesising all available information on seasonality is a necessary step in identifying large-scale epidemiological patterns and elucidating underlying causes.

Methods

Three medical and life sciences publication databases were searched from inception to October 2014 for longitudinal epidemiological studies written in English, Spanish or Portuguese that reported the incidence of CDI. The monthly frequency of CDI were extracted, standardized and weighted according to the number of follow-up months. Cross correlation coefficients (XCORR) were calculated to examine the correlation and lag between the year-month frequencies of reported CDI across hemispheres and continents.

Results

The search identified 13, 5 and 2 studies from North America, Europe, and Oceania, respectively that met the inclusion criteria. CDI had a similar seasonal pattern in the Northern and Southern Hemisphere characterized by a peak in spring and lower frequencies of CDI in summer/autumn with a lag of 8 months (XCORR = 0.60) between hemispheres. There was no difference between the seasonal patterns across European and North American countries.
**Conclusion**

CDI demonstrates a distinct seasonal pattern that is consistent across North America, Europe and Oceania. Further studies are required to identify the driving factors of the observed seasonality.

**Introduction**

_Clostridium difficile_ is the most common cause of antibiotic-associated diarrhea among hospital inpatients [1]. The incidence and severity of _C. difficile_ infection (CDI) have increased worldwide in the last two decades [2].

Understanding the seasonal patterns of infectious diseases is crucial to identify factors associated with an increased risk of infection and to implement control measures during the time of year when interventions are likely to have the greatest impact [3]. Epidemiological studies have documented a seasonal variation in the frequency of CDI, yet the mechanisms responsible for its variability remain poorly understood. Specifically, in the USA and Canada, the incidence of CDI has been reported to increase during boreal winter months (February–March) [4–6]. Antibiotic exposure is strongly associated with CDI [7–10]; consequently, it has been proposed that the observed CDI seasonality in the Northern Hemisphere is associated with the higher incidence of respiratory infections, which leads to an increase in antibiotic prescriptions during winter months [11,12].

In Australia, even though antibiotic consumption also peaks during winter (August) [13]; recent epidemiological studies have found that the seasonal pattern of _C. difficile_ is not characterized by an increased number of CDI during winter months [14,15]. This indicates that CDI in Australia may not conform to currently proposed mechanisms of _C. difficile_ seasonality, suggesting that factors in addition to antibiotic exposure might be driving the seasonality. Therefore, the aim of the current review was to pool the existing evidence to describe the global patterns of CDI seasonality and to facilitate improved understanding of underlying mechanisms.

**Methods**

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were followed in this systematic review [16]. A systematic search was undertaken in three medical and life sciences databases (PubMed, Embase and Latin American and Caribbean Health Sciences Literature [LILACS]) from their inception to October 1st, 2014 for longitudinal epidemiological studies that reported the incidence of CDI. Search terms included were “Clostridium difficile” and “season”, the specific keywords and connectors used in the systematic search strategy for each database are listed in S1.A Search strategy.

The inclusion of studies was restricted to human studies, full-text articles or abstracts written in English, Spanish or Portuguese. Studies with at least 12 months follow-up that reported the incidence of CDI or the proportion of stool specimens examined in which _C. difficile_ was detected, per month or per season, were included. CDI intervention studies were excluded from the review because of the interference that interventions might have on transmission dynamics. Exclusions were also made for studies that reported the number of positive samples detected for _C. difficile_ without reporting the total number of samples that were tested; unless the authors stated that the number of stool samples examined per month was constant across the...
follow-up period. Corresponding authors were contacted for further information regarding the total number of samples examined per month/season. The characteristics of the excluded studies are listed in S1 Table.

Two authors (LFK and LY) independently examined all the citations by title and abstracts for studies that met the inclusion criteria. Full-text version articles of all potentially relevant studies were retrieved and independently extracted. Data presented in a graphical format were extracted using Plot Digitizer version 2.6.6 (http://plotdigitizer.sourceforge.net/). Data from all the included studies were extracted and summarized in a spreadsheet. The extracted data were cross-checked by the two authors, discrepancies during the selection of studies or data extraction were resolved through discussion and consensus. The quality of the selected studies was assessed independently by the same two authors using the Newcastle-Ottawa scale (NOS) [17].

The extracted data (incidence of CDI or proportion of positive stool specimens for *C. difficile*) were standardized to have a mean = 0, a minimum value = −1, and a maximum value = 1 for comparison across studies. A weight between zero and 1 was assigned to each study proportional to the number of months of follow-up. The number of months of follow-up for each study were divided by the number of months of follow-up of the study with the longest follow-up period; this ensured that the study with the longest follow-up period received a weight of 1.

The weighted average of the standardized monthly incidence were then plotted by hemispheres and continents to compare the seasonal patterns of CDI in each setting. An additional plot in which weighted average of the standardized CDI data from the Southern Hemisphere was shifted 6 months to align the meteorological seasons between hemispheres was created for ease of comparison.

Cross correlation coefficients (XCORR) were used to examine the correlation and lag value (in months) between the weighted average of standardized monthly incidence of CDI across hemispheres and continents using the extracted temporal data.

Results

The search identified 244 publications; after screening the publications by title and abstract, 171 publications were excluded. After a full-text review of 41 publications was conducted, 20 studies met the inclusion criteria and were selected for the review (Fig. 1). Of the 20 studies, 18 were conducted in Northern Hemisphere countries and only 2 in the Southern Hemisphere. Among the studies from the Northern Hemisphere, 13 were from North America and 5 from Europe. The 2 studies from the Southern Hemisphere were from Oceania (Australia; Tables 1 and 2). No studies from South America, Africa or Asia were identified despite additional efforts to target these regions in our search strategy (S1.B Search strategy). Using the NOS, all the studies but two were identified as high quality (≥80% NOS score; Table 1 and S2 Table).

A similar seasonal pattern was observed between the Northern and Southern Hemisphere. In the Northern Hemisphere, CDI rates peaked during March − April (early boreal spring) and were at their lowest during the second half of the year. CDI increased in the Southern Hemisphere during the second half of the year and peaked in the last trimester of the year (October − November, the mid austral spring − Fig. 2A and 2B). The XCORR peaked (0.60) at lags = 8, indicating that the rise in the weighted average of the standardized monthly incidence of CDI in the Southern Hemisphere lagged the Northern Hemisphere by 8 months (i.e. it occurred two months later relative to the onset of spring in the Southern Hemisphere as compared to the Northern Hemisphere). The lowest value was identified (−0.76) at lag = 1, which indicates that at lag = 1 month the weighted average of the standardized monthly incidence of CDI in the Northern Hemisphere decreases while it increases in the Southern Hemisphere.
When the studies were grouped by continents, a similar trend was observed in the Northern Hemisphere between North American and European countries. This observation was confirmed by the peak of XCORR = 0.69 at lag 0 months. Both presented a higher frequency of CDI during the first half of the year, with peaks of CDI in March and April in Europe and North America, respectively (Fig. 3).

Discussion
The findings of the current systematic review suggested that the Northern and Southern Hemisphere countries exhibit similar seasonal patterns characterized by CDI peaking in spring and being at their lowest during summer/autumn months. Antibiotic consumption in the community also follows a seasonal pattern. In North American and European countries the consumption of antibiotics mainly peaked in January-February, whereas in Australia antibiotic consumption peaked in August [13]. Hensgens et al. found that after cessation of antibiotic therapy, patients remain at higher risk of CDI for up to 3 months [18]. Therefore, the observed seasonality may indicate a lag of 2–3 months between antibiotic exposure and CDI. It is not surprising that several studies have found co-seasonality of CDI and respiratory tract infection [11,12,19]. In these studies, the respiratory infections often lead CDI by 1 month which could be explained by the corresponding incidence of respiratory tract infection and antibiotic prescription in the community [20].

Risk factors in addition to antibiotic exposure such as environmental variables (temperature, precipitation, altitude, etc.) could also be involved in the observed seasonality as they have also been demonstrate to affect the dynamics of numerous infectious diseases [3,21]. In a previous study we found that the odds of CDI infection increased by 9% (OR: 1.09; 95%CI: 1.02 to 1.17) per 100 mm increase in monthly rainfall in Queensland, Australia [14]. Respiratory tract infection transmission dynamics are highly dependent on environmental factors [21];
therefore, caution is advised for future studies drawing an association between CDI and environmental factors because of the possible confounder of co-seasonality in CDI and respiratory infections. Because CDI was traditionally viewed as a nosocomial disease, studies that assess the relationship between environmental factors and CDI are scant and this is a research gap that requires substantial development. The observed difference of two-month lag between the Southern and Northern Hemisphere (relative to the onset of spring) may be explained by the

---

**Table 1. Characteristics of included studies.**

| Location | Data source | Start | Finish | Follow-up (months) | NOS scores |
|----------|-------------|-------|--------|--------------------|------------|
| Archibald et al., 2004 [4] | National Nosocomial Infections Surveillance System | Jan 1987 | Dec 2001 | 180 | 3/5 |
| Brown et al., 2013 [11] | U.S. National Hospital Discharge Survey | Jan 1993 | Dec 2008 | 192 | 8/9 |
| Burckhardt et al., 2008 [40] | State of Saxony Surveillance | Jan 2002 | Dec 2006 | 60 | 4/5 |
| Camacho-Ortiz et al., 2009 [41] | Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubiran | Jan 2003 | Dec 2007 | 60 | 4/5 |
| Damani et al., 2011 [42] | Craigavon Area Hospital | Jan 2007 | May 2010 | 41 | 3/5 |
| Deorari et al., 1999 [34] | Alberta Children’s Hospital | Apr 1993 | Mar 1995 | 24 | 9/9 |
| Dubberke et al., 2009 [43] | Five hospitals | Jul 2000 | Jun 2006 | 72 | 5/5 |
| Faires et al., 2014 [44] | A community hospital in Southern Ontario | Aug 2006 | Feb 2011 | 55 | 5/5 |
| Furuya-Kanamori et al., 2014 [14] | Sullivan Nicolaides Pathology | May 2003 | Dec 2012 | 117 | 4/5 |
| Gilca et al., 2010 [5] | MED-ECHO and Quebec's provincial surveillance | Apr 1998 | Mar 2006 | 97 | 4/5 |
| Gilca et al., 2012 [12] | Quebec's provincial surveillance | Jan 2005 | Dec 2008 | 48 | 8/9 |
| Jagai and Naumova, 2009 [6] | Centers for Medicare and Medicaid Services | Jan 1993 | Dec 2004 | 144 | 4/5 |
| MacDonald et al., 1993 [45] | A tertiary care referral hospital | May 1990 | May 1992 | 23* | 5/5 |
| McFarland et al., 2007 [46] | Veterans Administration Puget Sound Health Care System | Jan 2004 | Dec 2004 | 12 | 8/9 |
| Reil et al., 2012 [47] | Synlab Medical Care Service Centre Wieden | Jan 2000 | Dec 2009 | 120 | 4/5 |
| Reveles et al., 2014 [48] | U.S. National Hospital Discharge Survey | Jan 2001 | Dec 2010 | 120 | 4/5 |
| Sliming et al., 2014 [15] | 450 public hospitals | Jan 2011 | Dec 2012 | 24 | 5/5 |
| Sonnenberg, 2009 [49] | Hospital Episode Statistics | Apr 1995 | Mar 2006 | 132 | 4/5 |
| von Muller et al., 2011 [50] | The University of Saarland Hospital | Apr 2008 | Jun 2010 | 27 | 4/5 |
| Wong-McClure et al., 2012 [30] | A tertiary care hospital | Jan 2009 | Jun 2011 | 30 | 4/5 |

NOS: Newcastle-Ottawa Scale, NR: Not reported, MO: Missouri, MA: Massachusetts, OH: Ohio, IL: Illinois, UT: Utah
* January 1991 not included, a nursing strike made data unretrievable.

doi:10.1371/journal.pone.0120730.001
climatic zones where the studies included in the review are located. Australia, which is located in tropical and sub-tropical zones was the only country included in the review from the Southern Hemisphere; whereas the Northern Hemisphere countries included were mainly located in a temperate zone (USA, Canada, Germany, Ireland, and England). Von Boeckel et al. found that countries further from the equator (temperate zone) have a prominent seasonal pattern in antibiotic consumption characterized by peaks during winter, whereas antibiotic consumption is fairly constant across the months in countries located in tropical and sub-tropical zones [13]. Furthermore, Tamerius et al. described a similar one-month lag between the start of influenza epidemic in temperate Northern Hemisphere countries (November, end of boreal autumn) and the start of influenza epidemic in Australia (June, start of austral winter) [22]. In both cases, the influenza epidemic starts 3–4 months before the peak of CDI (March – April in Northern Hemisphere and October – November in Southern Hemisphere).

Despite contrasting antibiotic prescribing practices in outpatients between North America and Europe, the results indicate a similar seasonal pattern between European and North American countries. Patrick et al. found that the antibiotic consumption in the community was higher in British Columbia, Canada, than in Sweden, Germany, United Kingdom, Denmark and The Netherlands [23]. Of particular interest is the high consumption rate found in Canada compared to Denmark for some antibiotic classes such as fluoroquinolones (1.44 versus 0.15

---

**Table 2. Measures of monthly C. difficile infection incidence.**

| Study                  | Measure                        | Jan  | Feb  | Mar  | Apr  | May  | Jun  | Jul  | Aug  | Sep  | Oct  | Nov  | Dec  |
|------------------------|--------------------------------|------|------|------|------|------|------|------|------|------|------|------|------|
| Archibald et al., 2004| (Cases/10,000 patient-days)    | 4.25 | 4.46 | 4.69 | 3.21 | 3.93 | 2.53 | 2.28 | 1.97 | 1.01 | 2.60 | 1.19 | 2.15 |
| Brown et al., 2013     | (Cases/1,000 discharges)       | 8.36 | 8.42 | 8.67 | 8.75 | 8.65 | 8.35 | 8.19 | 8.22 | 8.27 | 7.97 | 7.71 | 7.90 |
| Burckhardt et al., 2008| (Cases/100,000 persons)        | 6.15 | 6.15 | 6.67 | 6.67 | 6.67 | 6.50 | 5.60 | 5.60 | 6.28 | 6.28 | 6.28 | 6.15 |
| Camacho-Ortiz et al., 2009| (Cases/1,000 discharges)     | 7.97 | 9.63 | 7.08 | 10.55| 8.85 | 11.06| 9.92 | 14.37| 16.44| 3.97 | 5.06 | 5.46 |
| Damani et al., 2011    | (Percentage of positive samples)| 10.48| 10.36| 10.16| 6.58 | 7.53 | 9.30 | 11.17| 13.43| 12.93| 11.96| 15.40| 12.98 |
| Deorari et al., 1999   | (Percentage of positive samples)| 22.64| 14.64| 9.36 | 19.73| 0.09 | 33.18| 41.91| 35.36| 44.27| 49.91| 42.27| 25.55 |
| Dubberke et al., 2009  | (Cases/10,000 patient-days)    | 9.02 | 9.30 | 9.39 | 10.03| 9.17 | 9.13 | 8.28 | 9.32 | 9.32 | 9.43 | 9.36 | 9.28 |
| Faires et al., 2014    | (Cases/10,000 patient-days)    | 0.18 | 0.79 | 0.90 | 1.66 | 1.59 | 1.50 | 1.45 | 1.18 | 1.49 | 0.70 | 1.50 | 1.11 |
| Furuya-Kanamori et al., 2014| (Percentage of positive samples)| 13.42| 13.39| 12.55| 10.07| 11.24| 13.39| 13.08| 13.33| 12.84| 14.22| 14.09| 14.67 |
| Gilca et al., 2010     | (Cases/1,000 discharges)       | 11.29| 10.10| 9.08 | 8.29 | 7.83 | 6.92 | 7.31 | 8.02 | 8.63 | 10.05| 10.43| 11.50 |
| Gilca et al., 2012     | (Cases/1,000 discharges)       | 12.76| 11.82| 11.85| 11.04| 10.09| 8.99 | 8.70 | 7.65 | 7.30 | 7.70 | 8.12 | 8.40 |
| Jagai and Naumova, 2009| (Cases/10,000 persons)         | 0.53 | 0.48 | 0.49 | 0.51 | 0.50 | 0.46 | 0.50 | 0.50 | 0.49 | 0.54 | 0.47 | 0.54 |
| MacDonald et al., 1993 | (Cases/100,000 patient-days)   | 2.97 | 5.49 | 2.39 | 5.49 | 4.33 | 5.92 | 8.97 | 3.98 | 4.96 | 4.93 | 9.50 | 2.94 |
| McFarland et al., 2007 | (Cases/10,000 patient-days)    | 21.90| 40.51| 42.70| 28.47| 36.86| 15.33| 11.31| 23.36| 24.09| 34.67| 34.67| 31.02 |
| Reil et al., 2012      | (Percentage of positive samples)| 10.99| 10.99| 10.96| 10.96| 10.96| 11.44| 11.44| 11.44| 10.94| 10.94| 10.94| 10.99 |
| Reveles et al., 2014   | (Cases/1,000 discharges)       | 6.60 | 7.00 | 7.60 | 6.70 | 7.30 | 7.00 | 6.80 | 7.00 | 6.70 | 7.10 | 6.00 | 6.90 |
| Slimming et al., 2014  | (Cases/10,000 patient-days)    | 3.32 | 3.32 | 3.80 | 3.80 | 3.80 | 3.53 | 3.53 | 3.53 | 4.27 | 4.27 | 4.27 | 3.32 |
| Sonnenberg, 1993       | (Cases/100,000 patient-days)   | 0.80 | 0.92 | 1.03 | 1.03 | 0.92 | 0.76 | 0.68 | 0.60 | 0.69 | 0.58 | 0.69 | 0.66 |
| von Muller et al., 2011| (Percentage of positive samples)| 7.35 | 7.06 | 8.42 | 9.12 | 6.51 | 9.26 | 5.11 | 7.91 | 10.34| 6.36 | 11.29| 10.74 |
| Wong-McClure et al., 2012| (Cases/10,000 patient-days)  | 10.68| 15.19| 6.69 | 12.62| 7.53 | 8.02 | 8.67 | 4.13 | 7.41 | 5.14 | 9.74 | 8.50 |

doi:10.1371/journal.pone.0120730.t002
Fig 2. (a) Weighted average of the standardized monthly incidence of *C. difficile* infection by hemisphere. (b) Weighted average of the standardized monthly incidence of *C. difficile* infection by hemispheres. For ease of comparison, the Southern Hemisphere plot was moved 6 months (in the x-axis) thus the meteorological seasons align between hemispheres.

doi:10.1371/journal.pone.0120730.g002
defined daily doses [DDDs]/1000 inhabitant-days), macrolides (1.59 versus 0.92 DDDs/1000 inhabitant-days), and cephalosporins (1.86 versus 0.02 DDDs/1000 inhabitant-days) as these antibiotic classes have been associated with an increased risk of community-acquired CDI [7,8]. A similar trend in antibiotic prescribing was observed in children; higher rates of use of cephalosporins (89.1 versus 0.2 prescriptions/1000 children), lincosamides (2.3 versus 0.1 prescriptions/1000 children), macrolides (148.0 versus 42.6 prescriptions/1000 children), and fluoroquinolones (1.4 versus 0.5 prescriptions/1000 children) were reported in Canada compared to Denmark [24]. This finding supports the need to investigate additional factors (other than antibiotic exposure [11,12]) that would contribute towards a broader understanding of CDI seasonality.

Exposure to proton pump inhibitor (PPI) [25] and glucocorticoid [26] has been associated with an increased risk of CDI, however no study has yet examined the temporal relationship between monthly PPIs or glucocorticoids prescription rates and CDI seasonality. Additional factors such as the introduction of new strains of the pathogen via trade in livestock, commodities and/or movement of people (asymptomatic colonized patients such as tourists or business travellers, or hospital transfers) across boundaries should be evaluated when assessing possible factors associated with the seasonality of CDI [27]. Rodriguez-Palacios et al. reported a possible seasonality in contamination of retail meat in Canada with higher prevalence of C. difficile in January – February (11.5%) compared to other months of the study (4.0%) [28]. Riley has implicated the importation of onions and garlic from USA and Mexico into Australia in the increase in CDI during October – December in Western Australia [29].

![Fig 3. Weighted average of the standardized monthly incidence of C. difficile infection by Northern Hemisphere continents.](doi:10.1371/journal.pone.0120730.g003)
Although a comprehensive review was carried out, several limitations were noted. First, only two studies were identified that reported the seasonality of CDI in Southern Hemisphere countries [14,15]. Furthermore, both studies were conducted in Australia. This may limit the generalizability of the findings for Southern Hemisphere countries only to Australia. However, the identified gap in information should encourage further investigation particularly in countries in South America, Africa and Asia. Second, there was a small number of studies from countries located between the Tropic of Cancer and the Tropic of Capricorn. The study conducted by Wong-McClure et al. [30] in Costa Rica was the only study from the Northern Hemisphere located in a tropical zone, precluding the comparison between the seasonality of CDI in temperate and sub-tropical/tropical climates. Despite the documented changes in CDI epidemiology [2], the increase in community-acquired CDI [31], and the different risk profiles between community- and hospital-acquired CDI patients [32], our study was also limited by the inability to compare the community- and hospital-acquired CDI seasonal patterns. Despite the increasing incidence of CDI among the paediatric population [33] only one study (Deodari et al. [34]) was identified that described the CDI seasonality in children; therefore, generalizability of the findings may be limited among this population. Potential factors that may contribute to differences in monthly CDI incidence that could not be accounted for in this review, such as hospital characteristics (e.g. staffing, overcrowding), CDI diagnosis ascertainment, severity of underlying illness, infection control practices, and CDI strain need to be assessed in future studies.

As the studies included in the review reported the measures of monthly CDI using different units, the values were standardized to compare the monthly CDI incidence across the studies. By doing so, the magnitude of the seasonality measured by the amplitude between the peak and the trough was lost. Although, the magnitude of the seasonality could be masked, the observed patterns should not be affected by the standardization. Finally, the weight allocated to each study was based on the number of follow-up months and not on the sample size as the number of participants or stool samples examined during the study period was not available for all the studies included in this review.

Understanding the seasonality of an infectious disease and the driving factors are of utmost importance for planning prevention and control strategies [21,35]. Recently, several epidemiological models of CDI have been constructed to inform control strategies for this disease of increasing incidence and severity [36–39]. However, none has yet incorporated the effects of seasonality and this will be difficult to achieve without better understanding of the underlying mechanisms. The current review provided evidence of a similar CDI seasonal pattern across hemispheres which differs from the seasonality that was previously proposed. Further studies are required to identify exposure to medications and environmental factors associated with the observed seasonality.

**Supporting Information**

**S1 PRISMA Checklist.**

(DOC)

**S1 Table. Excluded studies.**

(DOCX)

**S2 Table. Study quality assessment.**

(DOCX)

**S1 Text. Search Strategy.**

(DOCX)
Acknowledgments

The authors would like to thank Professor Lutz von Müller, Dr. Alexander Halfmann and Dr. Kelly Reveles for kindly provide us with additional data from their studies.

Author Contributions

Conceived and designed the experiments: LY. Analyzed the data: LFK SM AC. Wrote the paper: LFK SM LY JC DP TR AC. Conducted the systematic review: JC.

References

1. Bartlett JG (2002) Antibiotic-Associated Diarrhea. N Engl J Med 346: 334–339. PMID: 11821511
2. Freeman J, Bauer MP, Baines SD, Corver J, Fawley WN, Goorhuis B, et al. (2010) The changing epidemiology of Clostridium difficile infections. Clin Microbiol Rev 23: 529–548. doi: 10.1128/CMR.00082-09 PMID: 20610822
3. Grassey NC, Fraser C (2006) Seasonal infectious disease epidemiology. Proc Biol Sci 273: 2541–2550. PMID: 16959647
4. Archibald LK, Banerjee SN, Jarvis WR (2004) Secular trends in hospital-acquired Clostridium difficile disease in the United States, 1987–2001. J Infect Dis 189: 1585–1589. PMID: 15116293
5. Gilca R, Hubert B, Fortin E, Gaulin C, Dionne M (2010) Epidemiological patterns and hospital characteristics associated with increased incidence of Clostridium difficile infection in Quebec, Canada, 1998–2006. Infect Control Hosp Epidem 31: 939–947. doi: 10.1086/655463 PMID: 20677973
6. Jagai J, Naumova E (2009) Clostridium difficile-associated disease in the elderly, United States. Emerg Infect Dis 15: 343–344. PMID: 19193291
7. Brown KA, Khanafer N, Daneman N, Fisman DN (2013) Meta-analysis of antibiotics and the risk of community-associated Clostridium difficile infection. Antimicrob Agents Chemother 57: 2326–2332. doi: 10.1128/AAC.02176-12 PMID: 23478961
8. Deshpande A, Pasupuleti P, Thota P, Pant C, Rolston DDK, Sierra TJ, et al. (2013) Community-associated Clostridium difficile infection antibiotics: A meta-analysis. J Antimicrob Chemother 68: 1951–1961. doi: 10.1093/jac/dkt129 PMID: 23620467
9. Slimings C, Riley TV (2014) Antibiotics and hospital-acquired Clostridium difficile infection: update of systematic review and meta-analysis. J Antimicrob Chemother 69: 881–891. doi: 10.1093/jac/dkt477 PMID: 24324224
10. Thomas C, Stevenson M, Riley TV (2003) Antibiotics and hospital-acquired Clostridium difficile-associated diarrhoea: a systematic review. J Antimicrob Chemother 51: 1339–1350. PMID: 12746372
11. Brown KA, Daneman N, Arora P, Moineddin R, Fisman DN (2013) The co-seasonality of pneumonia and influenza with Clostridium difficile infection in the United States, 1993–2008. Am J Epidemiol 178: 118–125. doi: 10.1093/aje/kws463 PMID: 23660799
12. Gilca R, Fortin E, Frenette C, Longtin Y, Gourdeau M (2012) Seasonal variations in Clostridium difficile infections are associated with influenza and respiratory syncytial virus activity independently of antibiotic prescriptions: a time series analysis in Quebec, Canada. Antimicrob Agents Chemother 56: 639–646. doi: 10.1128/AAC.05411-11 PMID: 22106208
13. Van Boeckel TP, Gandra S, Ashok A, Caudron Q, Grenfell BT, Levin SA, et al. (2014) Global antibiotic consumption 2000 to 2010: an analysis of national pharmaceutical sales data. Lancet Infect Dis 14: 742–750. doi: 10.1016/S1473-3099(14)70780-7 PMID: 25022435
14. Furuya-Kanamori L, Robson J, Soares Magalhaes R, Yakob L, McKenzie SJ, Paterson DL, et al. (2014) A population-based spatio-temporal analysis of Clostridium difficile infection in Queensland, Australia over a 10-year period. J Infect 69: 447–455. doi: 10.1016/j.jinf.2014.06.014 PMID: 24984276
15. Slimings C, Armstrong P, Beckingham WD, Bull AL, Hall L, Kennedy KJ, et al. (2014) Increasing incidence of Clostridium difficile infection, Australia, 2011–2012. Med J Aust 200: 272–276. PMID: 24641152
16. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group (2009) Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med 6: e1000097. doi: 10.1371/journal.pmed.1000097 PMID: 19621072
17. Wells GA, Shea B, O’Connell D, Peterson J, Welch V, Losos M, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomized studies in meta-analyses. Available: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp. Accessed 2015 February 2.
18. Hensgens MPM, Goorhuis A, Dekkers OM, Kuipers EJ (2012) Time interval of increased risk for *Clostridium difficile* infection after exposure to antibiotics. J Antimicrob Chemother 67: 742–748. doi: 10.1093/jac/dks087 PMID: 22146873

19. Polgreen PM, Yang M, Bohnett LC, Cavanaugh JE (2010) A time-series analysis of *Clostridium difficile* and its seasonal association with influenza. Infect Control Hosp Epidemiol 31: 382–387. doi: 10.1086/651095 PMID: 20175682

20. Fleming DM, Ross AM, Cross KW, Kendall H (2003) The reducing incidence of respiratory tract infection and its relation to antibiotic prescribing. Br J Gen Pract 53: 778–783. PMID: 14601353

21. Altizer S, Dobson A, Hosseini P, Hudson P, Pascual M, Rohani P (2006) Seasonality and the dynamics of infectious diseases. Ecol Lett 9: 467–484. PMID: 16623732

22. Tamerius J, Nelson M, Zhou S, Viboud C, Miller MA, Alonso WJ (2011) Global influenza seasonality: reconciling patterns across temperate and tropical regions. Environ Health Perspect 119: 439–445. doi: 10.1289/ehp.1002383 PMID: 21097384

23. Patrick DM, Marra F, Hutchinson J, Monnet DL, Ng H, Bowie WR (2004) Per capita antibiotic consumption: how does a North American jurisdiction compare with Europe? Clin Infect Dis 39: 11–17. PMID: 15206046

24. Marra F, Monnet DL, Patrick DM, Chong M, Brandt CT, Winters M, et al. (2007) A comparison of antibiotic use in children between Canada and Denmark. Ann Pharmacother 41: 659–666. PMID: 17374628

25. Cunningham R, Dale B, Undy B, Gaunt N (2003) Proton pump inhibitors as a risk factor for *Clostridium difficile* diarrhoea. J Hosp Infect 54: 243–245. PMID: 12855243

26. Furuya-Kanamori L, Stone JC, Clark J, McKenzie SJ, Yakob L, Paterson DL, et al. (2015) Comorbidities, Exposure to Medications, and the Risk of Community-Acquired *Clostridium difficile* Infection: A Systematic Review and Meta-analysis. Infect Control Hosp Epidemiol 36: 131–141.

27. Clements AC, Magalhaes RJ, Tatem AJ, Paterson DL, Riley TV (2010) *Clostridium difficile* PCR ribotype 027: assessing the risks of further worldwide spread. Lancet Infect Dis 10: 395–404. doi: 10.1016/S1473-3099(10)70080-3 PMID: 20510280

28. Rodriguez-Palacios A, Reid-Smith RJ, Stempfli HR, Daignault D, Janecko N, Avery BP, et al. (2009) Possible seasonality of *Clostridium difficile* in retail meat, Canada. Emerg Infect Dis 15: 802–805. doi: 10.3201/eid1505.081084 PMID: 19402975

29. Riley TV (2013) *Clostridium difficile* infection: the Australian experience. Available: http://www.hqsc.govt.nz/assets/Infection-Prevention/CIDI-workshop-Feb-2013-Riley.pdf. Accessed 2014 October 30.

30. Wong-McClure RA, Guevara-Rodríguez M, Abarca-Gómez L, Solano-Chinchilla A, Marchena-Picado M, Shea M, et al. *Clostridium difficile* outbreak in Costa Rica: control actions and associated factors. Rev Panam Salud Publica 32: 413–418. PMID: 23370184

31. Kunstl JL, Chrischilles EA, Pendergast JF, Herwaldt LA, Polgreen PM (2011) Incidence of and risk factors for community-associated *Clostridium difficile* infection: a nested case-control study. BMC Infect Dis 11: 194. doi: 10.1186/1471-2334-11-194 PMID: 21762504

32. Pituch H (2009) *Clostridium difficile* is no longer just a nosocomial infection or an infection of adults. Int J Antimicrob Agents 33: S42–45. doi: 10.1016/S0924-8579(09)70016-0 PMID: 19303569

33. Khanna S, Baddour LM, Huskins WC, Kammer PP, Faubion WA, Zinsmeister AR, et al. (2013) The epidemiology of *Clostridium difficile* infection in children: a population-based study. Clin Infect Dis 56: 1401–1406. doi: 10.1093/cid/cit075 PMID: 23408679

34. Durair S, McConnell A, Tan KK, Jadavji N, Ma D, Church D, et al. (1999) Differential yield of pathogens from stool testing of nosocomial versus community-acquired paediatric diarrhea. Can J Infect Dis 10: 421–428. PMID: 22346400

35. Pascual M, Dobson A (2005) Seasonal Patterns of Infectious Diseases. PLoS Med 2: e5. PMID: 15696215

36. Codello J, Safdar N, Heffernan R, Alagoz O (2014) An Agent-based Simulation Model for *Clostridium difficile* Infection Control. Med Decis Making (Epub ahead of print).

37. Lanzas C, Dubberke ER (2014) Effectiveness of Screening Hospital Admissions to Detect Asymptomatic Carriers of *Clostridium difficile*: A Modeling Evaluation. Infect Control Hosp Epidemiol 35: 1043–1050. doi: 10.1086/677162 PMID: 25026622

38. Yakob L, Riley T, Paterson D, Clements A (2013) *Clostridium difficile* exposure as an insidious source of infection in healthcare settings: an epidemiological model. BMC Infect Dis 13: 376. doi: 10.1186/1471-2334-13-376 PMID: 23947736

39. Yakob L, Riley TV, Paterson DL, Marquess J, Clements ACA (2014) Assessing control bundles for *Clostridium difficile*: a review and mathematical model. Emerg Microbes Infect 3: e43.
40. Burckhardt F, Friedrich A, Beier D, Eckmanns T (2008) *Clostridium difficile* surveillance trends, Saxony, Germany. Emerg Infect Dis 14: 691–692. doi: 10.3201/eid1404.071023 PMID: 18394306

41. Camacho-Ortiz A, Galindo-Fraga A, Rancel-Cordero A, Macias AE, Lamothe-Molina P, Ponce de Leon-Garduno A, et al. (2009) [Factors associated with *Clostridium difficile* disease in a tertiary-care medical institution in Mexico: a case-control study]. Rev Invest Clin 61: 371–377. PMID: 20184096

42. Damani N, Trudy R, Markey M, Wallace S (2011) *C. difficile* associated diarrhoea-don't blame community or norovirus. BMC Proc 5(Suppl 6): P186.

43. Dubberke ER, Butler AM, Hota B, Khan YM, Mangino JE, Mayer J, et al. (2009) Multicenter study of the impact of community-onset *Clostridium difficile* infection on surveillance for *C. difficile* infection. Infect Control Hosp Epidemiol 30: 518–525. doi: 10.1086/597380 PMID: 19419269

44. Faires MC, Pearl DL, Ciccotelli WA, Berke O, Reid-Smith RJ, Weese JS (2014) Detection of *Clostridium difficile* infection clusters, using the temporal scan statistic, in a community hospital in southern Ontario, Canada, 2006–2011. BMC Infect Dis 14: 254. doi: 10.1186/1471-2334-14-254 PMID: 24885351

45. MacDonald KS, McLeod J, Nicolle L (1993) *Clostridium difficile* enteritis in a Canadian tertiary care hospital. Can J Infect Control 8: 37–40. PMID: 8400341

46. McFarland LV, Clarridge JE, Beneda HW, Raugi GJ (2007) Fluoroquinolone use and risk factors for *Clostridium difficile*-associated disease within a Veterans Administration health care system. Clin Infect Dis 45: 1141–1151. PMID: 17918075

47. Reil M, Hensgens MP, Kuijper EJ, Jakobiak T, Gruber H, Kist M, et al. (2012) Seasonality of *Clostridium difficile* infections in Southern Germany. Epidemiol Infect 140: 1787–1793. doi: 10.1017/S0950268811002627 PMID: 22152928

48. Reveles KR, Lee GC, Boyd NK, Frei CR (2014) Regional and seasonal variations in *Clostridium difficile* infections in United States hospitals, 2001 to 2010. Value in Health 17: A267.

49. Sonnenberg A (2008) Seasonal variation of enteric infections and inflammatory bowel disease. Inflamm Bowel Dis 14: 955–959. doi: 10.1002/ibd.20408 PMID: 18302273

50. Von Muller L, Speck K, Hermann M (2011) Surveillance analysis of *C. difficile* genotypes demonstrates decreasing frequencies of 027 infections in a tertiary care hospital. Clin Microbiol Infec 17: S577.