The most common cause of infectious diarrheal infection amongst hospitalized patients in North America and Europe is caused by *Clostridium difficile* infections (CDI) [1]. CDI has recently surpassed methicillin-resistant *Staphylococcus aureus* as a hospital acquired infection [2, 3]. The incidence, mortality and associated health care costs associated with CDI are significant, with 10-25% of all cases of antibiotic-associated diarrheal onset attributed to CDI [4]. Clinically, nosocomial CDI has been well-studied with several risk factors for acquisition including hospitalization at time of infection, prior hospitalization, older age (>65), antibiotic therapy (in particular fluoroquinolones, cephalosporins and clindamycin [5, 6]), use of nasogastric tubes, surgical procedures in the gastrointestinal tract, history of inflammatory bowel disease (IBD) and other states of immunosuppression [6, 7].

Recently, several studies have described the onset of community-acquired CDI (CA-CDI) [6]. The definition of CA-CDI requires the patient to not have been in a hospital or health care facility within the previous 12 weeks or to develop CDI symptoms within 48 hours of hospital admission [8]. CA-CDI rates are on the rise, with 20-45% [1, 9] of all CDI cases attributed to community onset, and a further 22% of patients having no history of antimicrobial several months prior to CDI onset [10]. CA-CDI patients are amongst those that are relatively free of traditional risk factors for nosocomial CDI, and include antibiotic-free patients, individuals with limited or no health care exposure, and younger children [9, 11-13]. A population-based study from the USA described the demographics of CA-CDI patients of those that are considerably younger (mean age of 50 compared to 72 years) and female (76% compared to 60%) [10]. CA- CDI rates amongst the pediatric population have also increased [14], with a case control study identifying exposure to an infant under the age of two years to be a potential risk factor [13]. However, infants and young children less than two years old have been established as asymptomatic carriers for *C. difficile*. Exposure to *C. difficile* in the outpatient setting may serve as a means of transmission to those with CA-CDI, with spore formation occurring even after completion of therapy [15]. Two-thirds of CA-CDI patients had some form of occupational exposure within health care fields that may have preceded their illness [16]. There is also evidence that food-borne exposure to *C. difficile* may be a means of transmission within the community as spores have been demonstrated to survive normal cooking temperatures [17]. Zoonotic reservoirs are elucidated possibility as asymptomatic *C. difficile* colonization has been observed amongst several animals including cattle and pigs [18-23].

The hypervirulent *C. difficile* strain (known as NAP1/ribotype 27) has been associated with several CDI outbreaks worldwide [23-25] with increased virulence possibly due to means of enhanced toxin production (16-23 times greater than any other *C. difficile* [26]). The impact of hypervirulent *C. difficile* strains in the community setting would be affect our ability to control transmission outside the hospital setting and serve as persistent reservoir. CA-CDI is associated with significant clinical complications with 40% of patients requiring hospitalization, 20% with severe infection, 4.4% with severe complications, 20% with treatment failure and 28% presenting with recurrent CDI [27]. This has tremendous impact on the health care system in terms of costs, patient outcomes and burden on already limited resources [23].

To better elucidate the impact of CA-CDI, the aim of this study is to identify CA-CDI cases in the metropolitan center of Calgary, which employs a single, centralized laboratory testing facility. Thus, the objectives and approaches to studying and characterizing CA-CDI are as follows:

1. *C. difficile* isolates are collected from clinical samples and to assess if truly community-acquired, a standardized telephone questionnaire that has already received ethical approval will be used to contact patients to identify risk factors or identifiable markers distinguishing community vs. hospital-acquired *C. difficile.*
2. Further characterization of true CA-CDI will be done with antibiotic susceptibility testing, pulsed field gel electrophoresis and whole genome sequencing. The aim of this is to determine if there are identifiable factors, in terms of molecular changes or pathogenic virulence factors that may distinguish CA-CDI.
3. Microbiome analysis from stool samples will be done on CA-CDI samples to ask the question whether gut dysbiosis was also present as has been seen in nosocomial CDI and if there were marked differences between these gut microbiomes, such as reduced bacterial diversity.
4. Finally, the inclusion of bioinformatics and epidemiological analysis will be required to distinguish if CA-CDI is truly distinguishable from nosocomial CDI and if there are changes with regards to pathogenicity and identifiable risk factors among this patient population.

Preliminary results have established the presence of CA-CDI with specific epidemiological factors associated with these cases, suggesting a subset of CDI that may have been previously misunderstood or attributed to nosocomial transmission. The relevance of this project in *C. difficile* research is two-fold. Firstly, it will increase our understanding and knowledge of CA- CDI, a clinical entity that is only recently being elucidated as a major player within the background of traditional nosocomial CDI. Secondly, enhanced knowledge of CA-CDI will help with to target treatment, therapy and infection prevention control both within the hospital setting and out in the community.

References:

1. Bartlett JG: Clinical practice. Antibiotic0associated diarrhea. *The New England Journal of Medicine* 2002, 346 5:334-339.
2. Miller BA, Chen LF, Sexton DJ, Anderson DJ: Comparison of the burdens of hospital0onset, healthcare facility0associated Clostridium difficile Infection and of healthcare0associated infection due to methicillin-resistant Staphylococcus aureus in community hospitals. *Infection Control and Hospital Epidemiology: the Official Journal of the Society of Hospital Epidemiologists of America* 2011, 32 4:387-390.
3. Zilberberg MD, Shorr AF, Kollef MH: Growth and geographic variation in hospitalizations with resistant infections, United States, 2000-2005. *Emerging Infectious Diseases* 2008, 14:1756-1758.
4. Beaugerie L, Flahault A, Barbut F, Atlan P, Lalande V, Cousin P, Cadilhac M, Petit JC, Study G: Antibiotic-associated diarrhoea and Clostridium difficile in the community. *Alimentary Pharmacology & Therapeutics* 2003, 17 7:905-912.
5. Kandel C, Moayedi Y, Bunce PE: A woman with community0acquired Clostridium difficile infection. *CMAJ: Canadian Medical Association Journal* 2012, 184:1383-1385.
6. Lee L, Cohen, S.H.: Community0aquired Clostridium difficile infection: an emerging problem. *Curr Emerg Hosp Med Rep* 2013, 1:149-153.
7. Bauer MP, Goorhuis A, Koster T, NumanK Ruberg SC, Hagen EC, Debast SB, Kuijper EJ, van Dissel JT: Community-onset Clostridium difficile-associated diarrhoea not associated with antibiotic usage - two case reports with review of the changing epidemiology of

Clostridium difficile-associated diarrhoea. *The Netherlands Journal of Medicine* 2008, 66 5:207-211. 8. McDonald LC, Coignard B, Dubberke E, Song X, Horan T, Kutty PK, Ad Hoc Clostridium difficile Surveillance Working G: Recommendations for surveillance of Clostridium difficile-associated disease. *Infection Control and Hospital Epidemiology: the Official Journal of the Society of Hospital Epidemiologists of America* 2007, 28 2:140-145.
9. CDC: Surveillance for community0associated Clostridium difficile--Connecticut, 2006. *MMWR Morb Mortal Wkly Rep* 2006, 57 13:340-343.
10. Khanna S, Pardi DS, Aronson SL, Kammer PP, Orenstein R, St Sauver JL, Harmsen WS, Zinsmeister AR: The epidemiology of community-acquired Clostridium difficile infection: a population-based study. *The American Journal of Gastroenterology* 2012, 107 1:89-95.
11. CDC: Severe Clostridium difficile-associated disease in populations previously at low risk--four states, 2005. *MMWR Morb Mortal Wkly Rep* 2005, 54 47:1201-1205.
12. Kim J, Smathers SA, Prasad P, Leckerman KH, Coffin S, Zaoutis T: Epidemiological features of Clostridium difficile0associated disease among inpatients at children s hospitals in the United States, 2001-2006. *Pediatrics* 2008, 122 6:1266-1270.
13. Wilcox MH, Mooney L, Bendall R, Settle CD, Fawley WN: A case-control study of community-associated Clostridium difficile infection. *The Journal of Antimicrobial Chemotherapy* 2008, 62 2:388-396.
14. Khanna S, Baddour LM, Huskins WC, Kammer PP, Faubion WA, Zinsmeister AR, Harmsen WS, Pardi DS: The epidemiology of Clostridium difficile infection in children: a population-based study. *Clinical Infectious Diseases: an Official Publication of the Infectious Diseases Society of America* 2013, 56 10:1401-1406.
15. Sethi AK, Al‰Nassir WN, Nerandzic MM, Bobulsky GS, Donskey CJ: Persistence of skin contamination and environmental shedding of Clostridium difficile during and after treatment of C. difficile infection. *Infection Control and Hospital Epidemiology: the Official Journal of the Society of Hospital Epidemiologists of America* 2010, 31 1:21-27.
16. Chitnis AS, Holzbauer SM, Belflower RM, Winston LG, Bamberg WM, Lyons C, Farley MM, Dumyati GK, Wilson LE, Beldavs ZG *et al*: Epidemiology of community-associated Clostridium difficile infection, 2009 through 2011. *JAMA Internal Medicine* 2013, 173 14:1359-1367.
17. Rodriguez-Palacios A, Reid-Smith RJ, Staempfli HR, Weese JS: Clostridium difficile survives minimal temperature recommended for cooking ground meats. *Anaerobe* 2010, 16 5:540-542.
18. Avbersek J, Janezic S, Pate M, Rupnik M, Zidaric V, Logar K, Vengust M, Zemljic M, Pirs T, Ocepek M: Diversity of Clostridium difficile in pigs and other animals in Slovenia. *Anaerobe* 2009, 15 6:252-255.
19. Indra A, Lassnig H, Baliko N, Much P, Fiedler A, Huhulescu S, Allerberger F: Clostridium difficile: a new zoonotic agent? *Wiener klinische Wochenschrift* 2009, 121 34:91-95.
20. Keel MK, Songer JG: The distribution and density of Clostridium difficile toxin receptors on the intestinal mucosa of neonatal pigs. *Veterinary Pathology* 2007, 44 6:814-822.
21. Pirs T, Ocepek M, Rupnik M: Isolation of Clostridium difficile from food animals in Slovenia. *Journal of Medical Microbiology* 2008, 57 Pt 6:790-792.
22. Weese JS, Avery BP, Rousseau J, Reid‰Smith RJ: Detection and enumeration of Clostridium difficile spores in retail beef and pork. *Applied and Environmental*

Microbiology 2009, 75 15:5009-5011.
23. Gupta A, Khanna S: Community-acquired Clostridium difficile infection: an increasing public health threat. *Infection and Drug Resistance* 2014, 7:63-72.
24. Loo VG, Poirier L, Miller MA, Oughton M, Libman MD, Michaud S, Bourgault AM, Nguyen T, Frenette C, Kelly M *et al*: A predominantly clonal multi-institutional outbreak of Clostridium difficile-associated diarrhea with high morbidity and mortality. *The New England Journal of Medicine* 2005, 353 23:2442-2449.
25. McDonald LC, Killgore GE, Thompson A, Owens RC, Jr., Kazakova SV, Sambol SP, Johnson S, Gerding DN: An epidemic, toxin gene-variant strain of Clostridium difficile. *The New England Journal of Medicine* 2005, 353 23:2433-2441.
26. Warny M, Pepin J, Fang A, Killgore G, Thompson A, Brazier J, Frost E, McDonald LC: Toxin production by an emerging strain of Clostridium difficile associated with outbreaks of severe disease in North America and Europe. *Lancet* 2005, 366 9491:1079-1084.
27. Khanna S, Pardi DS, Aronson SL, Kammer PP, Baddour LM: Outcomes in community-acquired Clostridium difficile infection. *Alimentary Pharmacology & Therapeutics* 2012, 35 5:613-618.