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Seasonal peaks in *Escherichia coli* infections: possible explanations and implications

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Abstract

Escherichia coli is a common cause of infections in all populations and countries of the world, causing an enormous burden of disease. In this issue of *Clinical Microbiology and Infection*, Al-Hasan *et al.* describe seasonal peaks in the incidence of *E. coli* bloodstream infection (BSI) during the summer for a population of 125 000 in Minnesota, USA. We discuss the probability that similar seasonal peaks in the incidence of *E. coli* BSI occur in other populations and geographical regions. Second, we discuss possible underlying explanations for these findings in terms of seasonal changes in human behaviour and the effect of temperature on the ability of *E. coli* to survive in the environment. Finally, we discuss some of the possible implications of *E. coli* BSI being a seasonal illness. More specifically, we discuss how better understanding the reasons for seasonality may potentially help us to better understand the dominant routes by which human populations are exposed to clonal groups of *E. coli* associated with urinary tract infection.

Escherichia coli is a common cause of infections in all populations and countries of the world. In fact, it is the most common cause of community-onset bloodstream infection (BSI) in persons 65 years of age or older, accounting for 150 BSIs/100 000 persons/year in the USA [1]. Although *E. coli* infections are commonly encountered in all areas of healthcare, there is much about their epidemiology that remains poorly understood. For example, the precise reservoirs for strains of *E. coli* associated with BSI and urinary tract infections (UTI) are not known, and the dominant routes by which humans are exposed to these strains are not well understood [2].

In light of the preceding gaps in our understanding, reports suggesting that the incidence rate of BSI as a result of *E. coli* follows a seasonal epidemic pattern are intriguing and deserve our attention. In this issue of *Clinical Microbiology and Infection,* Al-Hasan *et al.* report that the incidence rate of *E. coli* BSI increased by 35% per month during the 4 summer months in Olmsted County, Minnesota, compared with the other 8 months of the year [3]. More specifically, Al-Hasan *et al.* estimated that a 7% increase in the average monthly incidence of *E. coli* BSI occurred for every 10° Fahrenheit increase in average monthly temperature. Even though these observations were made by studying people in one county with a population of *c.* 125 000, Al-Hasan *et al.* conclusions are supported by similar findings made by authors of other recent studies. For example, Perencevich *et al.* noted that the incidence of *E. coli* isolation from an array of clinical specimens (including blood) collected in a large urban hospital in Baltimore increased by 12% during the summer [4]. Similar seasonal increases in the incidence of infection have also been described for other species of *Enterobacteriaceae*. For example, *E. cloacae* infections increase by over 40% during the summer months [4] and Anderson *et al.* showed that increasing environmental temperature was independently associated with an increased incidence of *K. pneumoniae* BSI [5].

Other species of Gram-negative bacteria also cause seasonal infections. During the warm wet season in tropical climates, melioidosis and community-acquired infections as a result of *Acinetobacter* species increase [6,7]. In temperate climates, an association has also been described between temperature and the incidence of infection caused by *Pseudomonas aeruginosa* and *Acinetobacter baumanii* [4]. Finally, significant increases in the rates of *Acinetobacter* bloodstream infection (67%) and pneumonia (47%) occur during the summer [8].

The preceding seasonal fluctuations in the incidence of disease as a result of various species of Gram-negative bacteria in different populations and geographical regions suggest that the seasonality of *E. coli* BSI reported by Al-Hasan *et al.* is more than just a localized phenomenon. However, the underlying reasons for this phenomenon remain enigmatic. For Gram-negative bacterial species that are acquired predominantly from the environment such as *Acinetobacter* spp, *P. aeruginosa* and *B. pseudomallei*, a positive correlation between environmental temperature and the incidence of disease is plausible, because temperature is likely to have a direct effect on the survival and multiplication of these

bacteria in the environment. Increased density of these bacteria in the environment is likely to increase the probability that humans will be exposed to these organisms and subsequently become infected. However, for Gram-negative bacteria that are human commensal species such as *E. coli*, potential mechanisms by which environmental temperature might affect the incidence of infection are less obvious. Although it is well known that *E. coli* readily survives and multiplies in the environment, the extent to which *extraintestinal E. coli* infections such as BSI are acquired as a result of exposure to strains in the environment is uncertain [2].

What is known is that different strains of *E. coli* vary widely in their propensity to cause disease. Pathogenic strains of *E. coli* that cause diarrhoea (such as enterotoxigenic *E. coli* and enterohemorrhagic *E. coli*) seldom cause asymptomatic colonization whereas strains of *E. coli* that cause extraintestinal infections colonize the intestinal tract prior to causing disease [9]. Furthermore, not all colonizing strains of *E. coli* have the same propensity to cause extraintestinal infections. The majority of extraintestinal *E. coli* infections are caused by strains that carry more virulence genes than typical strains of *E. coli* that colonize the intestinal tract [10]. These 'extraintestinal pathogenic *E. coli*' strains (ExPEC) [11] are also the predominant colonizing strain in the intestinal tract of up to 20% of healthy people [12].

Although ExPEC strains sporadically cause infections in normal and abnormal hosts, there is evidence that endemic and epidemic spread of single ExPEC clonal groups occurs within larger human populations [13]. For example, single ExPEC clonal groups have been recovered from localized geographical clusters of UTI in community settings [14] as well as from cases of community-acquired UTI in different geographical regions [15]. Furthermore, humans are not the only reservoir of ExPEC strains. ExPEC strains have been recovered from environmental and animal sources such as livestock, water and meat products [16]. For example, Johnson *et al.* recovered ExPEC strains from 46% of raw poultry sampled in Minnesota [17]. In another study, an isolate of *E. coli* from a cow was found to be closely related to an ExPEC clonal group known to cause UTI in humans [18].

The preceding observations support the notion that environmental sources such as water and products of the food chain play an important role in the acquisition of ExPEC strains. If indeed this is the case, then increases in the levels of contamination with ExPEC strains in water and food during warm summer conditions may lead to an increased incidence of colonization with ExPEC strains and ultimately, to seasonal increases in BSIs as a result of *E. coli*.

Nevertheless, although it is plausible that increased contamination of food and water sources with ExPEC strains during summer explains the seasonality of *E. coli* BSI, this hypothesis may be overly simplistic. Correlations between temperature and the incidence of disease may be confounded by a huge number of unmeasured variables. Furthermore, seasonal increases in *exposure* to *E. coli* are not the only mechanism by which the incidence of BSI might increase. Seasonal changes in *vulnerability to disease* within a population are also possible. Such seasonal changes in vulnerability to disease might be as a result of seasonal changes in immune function or seasonal changes in the expression of virulence factors in colonizing *E. coli*. However, seasonal changes in host immunity or the virulence phenotype for *E. coli* have not been well defined nor have they been demonstrated to occur.

Finally, summer peaks in the incidence of *E. coli* BSI may be as a result of complex seasonal changes in human behaviour. Seasonal changes in behaviour could affect both the risk of exposure to *E. coli* present in the environment as well as the risk of exposure to *E. coli* carried by other humans. Potentially relevant examples include seasonal changes in travel, sexual activity, water consumption, recreational water exposure, or in dietary or food preparation practices.

These numerous confounding variables make evaluating the relative importance of environmental variables such as temperature on the seasonality of *E. coli* and other infections a daunting and almost impossible task. In order to help address these challenges, Naumova *et al.* have proposed a standardized, systematic approach for describing and quantifying seasonality [19]. This approach involves defining the magnitude and timing of seasonal peaks. In subsequent analyses, *daily* temperatures are used rather than average monthly temperatures. By taking such an approach, seasonal peaks will more likely be detected and more precisely defined.

Further studies that use such an approach are needed to evaluate the seasonality of *E. coli* infections in different populations and geographical regions. Seasonality and the relationship between the incidence of *E. coli* BSI and temperature should be evaluated in tropical regions. Furthermore, the relationship between the incidence of *E. coli* BSI and other environmental variables such as *humidity* and *precipitation* should be examined in both tropical and temperate regions.

Primary sites of infection leading to BSI should be differentiated in future studies and the seasonality of infection at each site should also be analysed separately. In the study by Al-Hasan *et al.*, most *E. coli* bloodstream infections were secondary to UTI (80%) and over half the infections were community acquired (59%). Therefore, the increase in *E. coli* BSI during the summer may have been the result of a large seasonal fluctuation in the incidence of primary infection of the urinary tract.

Future studies should also systematically collect isolates of *E. coli* throughout the year. Isolates could then be assessed for ExPEC status [11] and compared for genetic relatedness by performing typing studies. Such collections of isolates could be recovered from BSI or UTI throughout the year or alternatively, colonizing isolates of *E. coli* could be recovered throughout the year by systematically taking rectal swabs from asymptomatic individuals. Isolates recovered during the summer could then be compared with isolates recovered during the winter. If for example, ExPEC strains were found to colonize significantly greater proportions of the same cohort of asymptomatic individuals during the summer than during the winter, then this would support the notion that increases in exposure to ExPEC strains occurs during the summer. Furthermore, if colonizing ExPEC strains were found to be identical to isolates from BSI, this would provide compelling evidence that seasonal increases in rates of BSI are the result of seasonal increases in exposure to ExPEC strains.

In summary, although BSI as a result of *E. coli* are responsible for a huge burden of disease, many important gaps remain in our understanding of the epidemiology of these infections. The need to improve our understanding of these infections is underscored by increasing antibiotic resistance amongst *E. coli* worldwide [20]. Therefore the seasonality of *E. coli* BSI described by Al-Hasan *et al.* is an intriguing and potentially important finding that deserves to be explored further in other populations and geographical settings. Future studies that explore seasonality may help to shed light on the dominant routes by which ExPEC clonal groups spread in human populations. Although studies that attempt to unravel the precise reasons behind the seasonality of *E. coli* infections will undoubtedly be difficult to design and perform, the dividends of such studies may be potentially high. If seasonal epidemics of *E. coli* BSI are found to occur as a result of seasonal increases in contamination of specific food, water or environmental sources with *E. coli*, then strategies could in principle be designed to reduce such contamination and thereby reduce the incidence of these important infections.

References

1. Jackson LA, Benson P, Neuzil KM, Grandjean M, Marino JL. Burden of community-onset *Escherichia coli* bacteremia in seniors. *J Infect Dis* 2005; 191: 1523–1529.
2. Hooton T, Samadpour M. Is acute uncomplicated urinary tract infection a foodborne illness and are animals the source? *Clin Infect Dis* 2005; 40: 258–259.
3. Al-Hasan M, Lahr BD, Eckel-Passow JE, Baddour LM. Seasonal variation in *Escherichia coli* bloodstream infection: a population based study. *Clin Microbiol Infect* 2009; 15 (in this issue).
4. Perencevich EN, McGregor JC, Shardell M *et al.* Summer peaks in the incidence of Gram-negative bacterial infection among hospitalized patients. *Infect Control Hosp Epidemiol* 2008; 29: 1124–1131.
5. Anderson DJ, Richet H, Chen LF *et al.* Seasonal variation in *Klebsiella pneumoniae* bloodstream infection on 4 continents. *J Infect Dis* 2008; 197: 752–756.
6. Cheng AC, Currie BJ. Melioidosis: epidemiology, pathophysiology, and management. *Clin Microbiol Rev* 2005; 18: 383–416.
7. Chu YW, Leung CM, Houang ET *et al.* Skin carriage of acinetobacters in Hong Kong *J Clin Microbiol* 1999; 37: 2962–2576.
8. McDonald LC, Banerjee SN, Jarvis WR. Seasonal variation of *Acinetobacter* infections: 1987–1996. Nosocomial infections surveillance system. *Clin Infect Dis* 1999; 29: 1133–1137.
9. Yamamoto S, Tsukamoto T, Terai A *et al.* Genetic evidence supporting the fecal-perineal-urethral hypothesis in cystitis caused by *Escherichia coli*. *J Urol* 1997; 157: 1127–1129.
10. Johnson JR. Microbial virulence determinants and the pathogenesis of urinary tract infection. *Infect Dis Clin North Am* 2003; 17: 261–278.
11. Johnson JR, Murray AC, Gajewski A *et al.* Isolation and molecular characterization of nalidixic acid-resistant extraintestinal pathogenic *Escherichia coli* from retail chicken products. *Antimicrob Agents Chemother* 2003; 47: 2161–2168.
12. Johnson JR, Russo TA. Extraintestinal pathogenic *Escherichia coli*: 'The other bad *E. coli*'. *J Lab Clin Med* 2002; 139: 155–162.
13. Manges AR, Tabor H, Tellis P, Vincent C, Tellier P. Endemic and epidemic lineages of *Escherichia coli* that cause urinary tract infections. *Emerg Infect Dis* 2008; 14: 1575–1583.
14. Manges AR, Johnson JR, Foxman B *et al.* Widespread distribution of urinary tract infections caused by a multidrug-resistant *Escherichia coli* clonal group. *N Engl J Med* 2001; 345: 1007–1013.
15. Johnson JR, Manges AR, O'Bryan TT, Riley LW. A disseminated multidrug-resistant clonal group of uropathogenic *Escherichia coli* in pyelonephritis. *Lancet* 2002; 359: 2249–2251.
16. Smith JL, Fratamico PM, Gunther NW. Extraintestinal pathogenic *Escherichia coli*. *Foodborne Pathog Dis* 2007; 4: 134–163.
17. Johnson JR, Kuskowski MA, Smith K, O'Bryan TT, Tatini S. Antimicrobial-resistant and extraintestinal pathogenic *Escherichia coli* in retail foods. *J Infect Dis* 2005; 191: 1040–1049.
18. Ramchandani M, Manges AR, Debroy C *et al.* Possible animal origin of human-associated, multidrug-resistant, uropapathogenic *Escherichia coli*. *Clin Infect Dis* 2005; 40: 251–257.
19. Naumova EN, Jagai JS, Matyas B *et al.* Seasonality in six enterically transmitted diseases and ambient temperature. *Epidemiol Infect* 2007; 135: 281–292.
20. Canton R, Coque T. The CTX-M β-lactamase pandemic. *Curr Opin Microbiol* 2006; 9: 466–475.