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A longitudinal analysis of methicillin-resistant and sensitive *Staphylococcus aureus* incidence in respect to specimen source, patient location, and temperature variation

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SUMMARY

Objective: Seasonal variations in temperature exert strong selective pressure on microorganism population dynamics and should be taken into account in epidemiological studies. The objective of the present study was to characterize the seasonal variation of staphylococcal infections in respect to patient location, specimen source, month of year, and temperature variation.
Methods: A retrospective longitudinal time-series analysis of methicillin-resistant and methicillin-sensitive *Staphylococcus aureus* (MRSA and MSSA) was conducted in northeastern Ohio over a 5-year period. Multivariable time-series analyses were performed to detect the variations in the monthly incidence based on location of patients (inpatient, outpatient, and nursing homes), source of specimen (wound, respiratory tract, and urine), time of year (January–December), and temperature variation (average monthly over 5 years).
Results: The results indicated a gradual increase in both MRSA and MSSA infections, with outpatient cases representing the majority of cases. If present, the seasonal nature of MRSA infections varied based on specimen source and patient location, with wound infections from outpatients more prevalent in warmer months, and respiratory infections among inpatients more prevalent during colder months.
Conclusions: The current report provides a longitudinal analysis of staphylococcal epidemiology, and in the process, identifies the seasonal nature of infections to be multifactorial, depending on such variables as specimen source and patient location. The seasonal nature of staphylococcal infections appears to be the product of a complex interaction among host, pathogen, and environment.

1. Introduction

Staphylococcus aureus is a Gram-positive bacterium that is the most common cause of skin infections in the USA. According to the Centers for Disease Control and Prevention (CDC), about 33% of the population carries *S. aureus* as part of the normal flora in their nasal cavity.[1] Staphylococcal infections can be treated effectively with antibiotics; however, within the last three decades, an increasing number of *S. aureus* species have become resistant to a wide array of antibiotics across the world.[2,3] The first reports of methicillin-resistant *S. aureus* (MRSA) go back to Europe in 1961, only 1 year after the introduction of methicillin.[4,5] In the 1970s, MRSA was first recognized as a serious nosocomial infection in the USA.[6] By the early-1990s, hospital-acquired MRSA (HA-MRSA) infections, which were directly associated with hospitals and long-term healthcare facilities, had become one of the most prevalent nosocomial infections worldwide.[7] By the late 1990s, new strains, referred to as community-associated MRSA (CA-MRSA), were identified among individuals with no apparent risk factors.[8,9] Today, MRSA infections are no longer considered strictly of nosocomial origin, since infections are frequently found in schools and daycare centers.[10,11] This epidemiological change in distribution of MRSA is alarming and must be addressed. Since the underlying dynamics of MRSA infections are not completely understood, further studies are required to improve the current understanding of MRSA epidemiology and the host–pathogen interaction in order to advance the current surveillance and preventive measures.

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Previous reports have demonstrated some seasonal trends associated with MRSA incidence. In 2010, Frei and colleagues reported the emergence of MRSA in pediatric populations across the USA.[12] The data accounted for 616 375 pediatric patients with skin and soft tissue infections in hospitals between 1996 and 2006. Over that period, the rate of hospitalization for MRSA increased dramatically from less than 1 case to 25.5 cases per 100 000 per year. All regions across the country showed seasonality of infection, with the peak incidence occurring between the months of May and December.[12] Another study in a military training site in Georgia found that MRSA skin and soft tissue infections had an increased rate of occurrence from July to September,[13] while in a study of a younger population that was conducted in Maricopa County, Arizona, strong annual MRSA seasonality was found with peak incidences occurring in early September.[14] In addition, a 1-year study of cutaneous MRSA infections at Johns Hopkins Hospital found that during the first 6 months of the study (November–April), up to 33% of total staphylococcal infections were MRSA, while the proportion increased to 65% during the last 6 months (May–October).[15] Interestingly, a national observational study conducted by Klein and colleagues used a combination of national hospitalization and surveillance data on drug susceptibility to infer trends associated with MRSA hospitalization rates from 2005 to 2009.[16] Seasonal patterns of MRSA-related hospitalizations were found, with phenotypically different MRSA infections peaking during different times of the year.[16] Lastly, a 1998 Connecticut study looked at community-onset *S. aureus* bacteremia, finding 15% of infections to be MRSA. Over the 1-year period, no seasonal pattern for MRSA infections was detected.[17]

A thorough and meaningful characterization of staphylococcal infections in respect to patient location, specimen source, and seasonal temperature variation may provide a better understanding of the host–pathogen interaction and may lead to the development of more effective surveillance and infection control measures.[16,18] However, with only four MRSA studies briefly addressing the effect of climate,[19–22] little to no research has been done on the seasonal influence due to climate and temperature variation. Temperature data are a key factor in seasonality, and temperature has either not been taken into account, or seasons have only been defined as specific calendar periods that may reflect different temperature patterns. In the current study, a longitudinal time-series analysis was conducted in which MRSA and methicillin-sensitive *S. aureus* (MSSA) infections were categorized systematically based on patient sex, source of specimens, location of patients, month of year, and weather-related temperature variation for five consecutive years. This report further clarifies the mechanisms that link the seasonal and environmental variations to staphylococcal infection dynamics and may aid in forecasting long-term health risks and developing new strategies for controlling infections caused by MRSA and similar antibiotic-resistant pathogens.

2. Materials and methods

This study was reviewed and approved by Kent State University Institutional Review Board (IRB 08-355).

A survey was performed of all cases of MRSA and MSSA infection diagnosed by the Ashtabula County Medical Center (ACMC) Clinical Laboratory from January 2006 to December 2010. ACMC is a private, non-profit hospital providing both inpatient and outpatient services for northeastern Ohio. This 241-bed medical center is the largest in Ashtabula County and has been serving an estimated population of over 100 000 for over a century. The ACMC laboratory routinely processes clinical samples from Ashtabula County nursing homes and from the ACMC network of family practice physicians and clinics. At the time of this survey, ACMC did not operate an MRSA admission screening policy. All the surveyed cases were clinical samples sent for microbial identification to the ACMC laboratory to confirm a presumptive initial diagnosis of an infection by a physician.

A total of 5178 cases (3085 MRSA and 2093 MSSA) were included in the study. To prevent duplicate samples from the same patient, clinical samples from the same patient and from the same sample source that were collected/processed within a 6-month period were counted as one occurrence. The diagnosis of MRSA versus MSSA sources of infection was determined based on clinical laboratory culture findings and antibiotic resistance screening. Antibiotic resistance results were interpreted in accordance with the Clinical and Laboratory Standards Institute (CLSI).

Clinical data on staphylococcal infection from various sources (i.e., wound, respiratory tract, urine) were divided into three different categories: (1) inpatient: samples collected at various ACMC hospital wards, (2) nursing homes: samples sent from 22 Ashtabula County long-term care and rehabilitation facilities, and (3) outpatients: samples processed by ACMC emergency rooms, and a local network of family practice physicians and/or clinics. Since more than 95% of specimens were only from three sources (wound, respiratory tract, and urine), only these three sources were included in the analysis.

The unequal numbers of days in the month were adjusted by using an offset that divides the number of infections in each month by the number of days in that month to give a daily rate. Multivariable time-series analyses were performed to explain variations in the monthly incidence of MRSA and MSSA infections in respect to patient sex, patient location, and specimen source.

Data were analyzed using SAS 9.3 (SAS Institute, Cary, NC, USA) and Excel (Microsoft, Redmond, WA, USA). Means of the different treatments were separated using the Waller–Duncan *k*-ratio *t*-test after it was determined that there was a significant treatment effect ($p < 0.05$) using the general linear model procedure. Seasonal trends for MRSA and MSSA infections were measured as described previously.[23] Briefly, by placing the independent variable data (i.e., total specimens from each source) on the *x*-axis and the dependent variable (i.e., MRSA or MSSA occurrences each month) on the *y*-axis, a scatter chart was generated. For linear trend curves, the 'best fitting' trend-line of the selected trend curve was generated by minimizing the sum of the squared vertical distances from each data point to the trend-line. The concept behind the calculation of seasonal variations was to determine the part of the annual total that is due to each of the 12 months of the year in which the random factors that can arise in a given year is considered independently of what might occur the following year. For instance, if there is a heat wave in February of a given year, this random factor is considered independent of any factor that might happen in February of the following year, or in any other February. If they are added for February from a number of years, the perturbations caused by casual factors compensate each other. After adjustment for random variation, what remained would be seasonal variation, which can be expressed by a coefficient or index of seasonality. For the purpose of description, the R^2 values were divided arbitrarily into four descriptive qualitative categories (Table 1).

Table 1
Descriptive terms for the R^2 value

R^2	Descriptive term
>0.8	Strong correlation
0.6–0.79	Moderate correlation
0.4–0.59	Weak correlation
<0.39	No correlation