Outbreak in Alberta of community-acquired (USA300) methicillin-resistant *Staphylococcus aureus* in people with a history of drug use, homelessness or incarceration

Mark Gilbert, Judy MacDonald, Dan Gregson, Jennifer Siushansian, Kunyan Zhang, Sameer Elsayed, Kevin Laupland, Tom Louie, Karen Hope, Michael Mulvey, John Gillespie, Diane Nielsen, Virginia Wheeler, Marie Louie, Agnes Honish, Gloria Keays, John Conly

Published at www.cmaj.ca on June 27, 2006.

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ABSTRACT

Background: The USA300 strain of community-acquired methicillin-resistant *Staphylococcus aureus* (CA-MRSA) can cause severe infection and is increasingly recognized as a cause of community outbreaks. In 2004, an outbreak was identified in the Calgary Health Region (CHR).

Methods: MRSA isolates were identified with standard methods at a central regional laboratory and typed via pulsed-field gel electrophoresis (PFGE). Isolates were tested by PCR for *mecA*, Panton–Valentine leukocidin (PVL), *SCCmec*, and *spa* genes. Cases were defined as such if a clinical isolate of the USA300 strain was noted between January 1 and September 30, 2004, and the patient had lived or traveled in CHR within 2 years before symptom onset. Demographic, clinical and risk data on all such cases were collected from several sources for statistical analysis. A case was defined as high-risk if the patient had a history of drug use, homelessness or incarceration.

Results: Of 40 isolates with the USA300 PFGE pattern, all tested positive for PVL, *SCCmec* type IVa and *spa* type 008. Almost all infections (39/40, 98%) involved skin and soft tissues, except for 1 death from necrotizing hemorrhagic pneumonia; a notable proportion (38%) required hospital admission or intravenous antimicrobial therapy. The outbreak centred on the high-risk population in CHR (70%; risk ratio 169.4, 95% confidence interval 86.1–333.0).

Interpretation: People with histories of illicit drug use, homelessness or recent incarceration were at highest risk for infection with CA-MRSA. The emergence and spread of this virulent strain has important implications for treatment and public health in Canada.

CMJ 2006;175(2):149–54

In 2004, an investigation of an outbreak of community-acquired (CA) methicillin-resistant *Staphylococcus aureus* (MRSA) infections caused by the USA300 strain in the Calgary Health Region identified that those at highest risk had histories of illicit drug use, homelessness or recent incarceration.

The USA300 strain of methicillin-resistant *Staphylococcus aureus* (MRSA) has been increasingly associated with multiple outbreaks in the United States involving prison inmates, men who have sex with men, military recruits and, most recently, professional athletes.^{1–4} This strain possesses the small mobile staphylococcal cassette chromosome (SCC) *mec* type-IV genetic element, which contains the *mecA* resistance gene, with or without other antibiotic resistance determinants.⁵ This element is more easily transferred to other strains of *S. aureus* than the larger *SCCmec* elements (types I–III) prevalent in health care–acquired MRSA strains.⁵ USA300 strains may also possess the Panton–Valentine leukocidin determinant (PVL), a virulence factor associated with primary skin infections and pneumonia.⁶ The emergence of these CA-MRSA strains and their outbreak potential is thought to pose a threat to public health.^{1,3,4}

In May through July 2004, a physician working at Corrections Facility A, a local corrections facility in Calgary, Alberta, noted an increased number of MRSA-positive skin infections among recently admitted inmates. A similar observation was made by physicians working in microbiology laboratories and hospitals in the Calgary Health Region (CHR). The cause of the infections was determined to be the USA300 strain of CA-MRSA (labelled CMRSA10 under Canadian nomenclature). We describe the results of our outbreak investigation demonstrating the introduction and dissemination of the USA300 strain into a marginalized population in the CHR, and describe hypotheses for its transmission within this population.

Methods

In the laboratory, isolates of MRSA were identified on mannitol salt agar screen plates supplemented with oxacillin (6 mg/L), confirmed by detection of the *mecA* and *nuc* genes via a polymerase chain reaction (PCR) assay.⁷ Susceptibility testing was done with VITEK (bioMérieux, Inc. Haselwood, Mo.) or Kirby Bauer methods, plus a D-test for clindamycin susceptibility.⁸ Typing was done with pulsed-field gel electrophoresis (PFGE) after DNA extraction and digestion with *Sma*I in a standard protocol.⁹ All isolates were further tested to confirm methicillin resistance and for the presence of PVL with a triplex PCR assay, which simultaneously detects *lukS-PV*, *lukF-PV* and *mecA* genes.¹⁰ The MRSA isolates were typed for *SCCmec* with a multiplex PCR *SCCmec* typing assay into subtypes I, II, III, IVa, IVb, IVc, IVd and V.¹¹ Isolates were typed for *spa* (a polymorphism of the *S. aureus* protein-A gene),^{12,13} and a representative selection of isolates was further tested with multilocus sequence typing (MLST).¹⁴ The identification of MRSA isolates matching the USA300 strain was based on the similarity of PFGE patterns to control strains provided by the National Microbiology Laboratory of the Public Health Agency of Canada.

For case findings and definitions, we used laboratory reports provided by the regional laboratory of USA300 MRSA isolates to identify potential cases; in those with more than one positive isolate, the first report was used. This laboratory processes all specimens submitted from community physicians, clinics, hospitals and long-term care facilities in the CHR. A study case was defined as a patient with a positive isolate for the USA300 strain of MRSA between Jan. 1 and Sept. 30, 2004; a clinical infection; and a history of residence in or

travel to the CHR during the 2 years before symptom onset. We used a history of one of the following during the 2 years before symptom onset to assign patients a high-risk status: illicit drug use (i.e., heroin, cocaine, crack cocaine, or abuse of morphine or other prescription opiates); incarceration in Alberta anytime since Jan. 1, 2002; or homelessness (having no fixed address, or staying in homeless shelters). Patients without any such history were identified as low-risk.

For demographic, clinical and risk information, we used chart reviews of medical records at hospitals, primary care clinics and a local corrections facility; an electronic search of the provincial Corrections Services admission database, HIV and hepatitis C registries, and hospital admission databases; and interviews with patients and their primary care providers. The information collected on potential risk factors included the presence of comorbid disease and histories of incarceration, use of group-living community facilities (detoxification centres or homeless shelters), travel, drug-use behaviours and types of drugs used, wound-care behaviours and previous hospital admissions.

We used EpiData version 3.0 (The EpiData Association, Denmark) to collect data, which was then analyzed with Epi-INFO6 version 6.04 (US Centers for Disease Control and Prevention) and SPSS version 12.0.1. To compare medians, we used the Wilcoxon rank-sum test; to compare proportions, the χ^2 test or Fisher's exact test, as appropriate.

We calculated the cumulative incidence of USA300 MRSA infection using CHR population estimates from Alberta Registry population data (from the Calgary Health Region internal Web site; accessed 2005 Aug. 10): 15 540 for the high-risk population (6000 homeless persons, 3540 injection drug users and 6000 individuals admitted to the local corrections

Fig. 1: Typing results for outbreak-related clinical isolates of methicillin-resistant *Staphylococcus aureus* (MRSA) in the Calgary Health Region (CHR). **Left panel:** Staphylococcal cassette chromosome *mec* (*SCCmec*) typing results. Lanes 1–6, representative outbreak-associated clinical isolates; lane M, molecular size markers, 1 Kb Plus DNA Ladder (Invitrogen). Control strains used: types I (NCTC10442), II (N315), III (85/2082), IVa (CA05), IVb (8/6–3P), IVc (MR108), IVd (JCSC4469) and V (WIS [WBG8318]-JCSC3624), corresponding to distinct amplicon sizes of 613, 398, 280, 776, 493, 200, 881 and 325 bp, respectively. In addition, a 147-bp *mecA* gene (methicillin-resistant determinant) amplicon was present in all strains. Note: bp = base pairs. **Right panel:** Pulsed-field gel electrophoresis patterns of USA300 strains of MRSA circulating in the CHR between Jan. 1 and Sept. 30, 2004. Lane 1, pattern A (31 of 40 cases, 78%); lane 2, USA300 reference strain pattern; lane 3, pattern B (7 cases, 18%); lane 4, pattern C (2 cases, 5%).

facility at least once per year) and 1 127 825 for the low-risk population.¹⁵ Relative risks of infection were calculated with 95% confidence intervals (CIs).

To identify people with USA300 infections that were potentially health care-acquired, we used criteria from the Canadian Nosocomial Infections Surveillance Program (i.e., patients with infections that developed ≥ 3 days after admission to hospital, or who stayed in a hospital or resided in a long-term care facility at any time during the 12 months before symptom onset).¹⁶

Results

Laboratory results

Between Jan. 1 and Sept. 30, 2004, we identified 42 patients with laboratory isolates of the USA300 strain of MRSA. (In comparison, between Jan. 1, 2002 and Dec. 31, 2003, only 7 individuals with this strain were identified.) Antimicrobial susceptibility profiles revealed the strains were uniformly resistant to oxacillin, erythromycin and ciprofloxacin, but susceptible to gentamicin, clindamycin, trimethoprim-sulfamethoxazole, tetracycline and vancomycin. None of the isolates exhibited inducible clindamycin resistance on the D-test. All 42 isolates tested positive for the PVL determinant, carried the *SCCmec* type-IVa genetic element (Fig. 1, left panel) and were of the same *spa* type. Selected isolates were also determined to have identical MLST types (sequence type 8). PFGE analysis (Fig. 1,

right panel) divided isolates into 3 patterns, all belonging to a single clonal group identical to USA300.¹⁷

Epidemiologic results

Of these 42 isolates, 40 met the case definition (95%; Fig. 2. Excluded isolates were from screening swabs or CHR nonresidents). Twenty-eight of these 40 cases (70%) had a history of illicit drug use, homelessness and/or incarceration (i.e., were at high risk). Interviews were less likely to occur with people at high (6/28, 21%) than at low risk (11/12, 92%, $p < 0.001$). The cumulative incidence of USA300 infection among high-risk cases (240.2 per 100 000 population) was found to be higher than that of low-risk cases (1.4 per 100 000). The relative risk of infection in high-risk compared with low-risk cases was 169.4 (95% CI 86.1–333.0).

Characteristics of these 40 cases are presented in Table 1. Almost all (39/40, 98%) were treated for skin and soft-tissue infections (SSTI) of varying severity. One person (3%) presented with rapidly progressive hemorrhagic necrotizing pneumonia, and died from this infection. Patients classified as being at high risk were more likely to have hepatitis C infection (14/28 [50%] v. 0/12, $p < 0.05$).

Fourteen (35%) of the 40 patients with USA300 MRSA infections met criteria for their case to be considered a potential health care-acquired infection. Three of these (7.5%) had onset of infection ≥ 3 days after admission to hospital (range 6–44 d). Although 10 (25%) had been admitted to a hospital

Fig. 2: Number of cases that furnished the USA300 strain of methicillin-resistant *Staphylococcus aureus* (MRSA) in the Calgary Health Region by month of specimen collection, from Jan. 1, 2004 through Sept. 30, 2004 ($n = 40$; 7 historical isolates were included for comparison). A further 310 infections were identified through ongoing surveillance up to Dec. 31, 2005 (8–34 cases per month).

during the 12 months before the onset of infection, most of these patients had short hospital stays or were in units at low risk of MRSA infection; of these, one had an infection appear 10 days after discharge from a surgical ward adjacent to a

Table 1: Description of the 40 cases of infection with the USA300 strain of MRSA in the Calgary Health Region (CHR) between Jan. 1 and Sept. 30, 2004*

Characteristic	No. (%) of patients/cases†		
	All n = 40	High-risk‡ n = 28	Low-risk n = 12
Male	27 (68)	20 (71)	7 (58)
Age, median, yr	37.0	38.5	26.5
Age, range, yr	< 1-93	18-63	< 1-93
Primary residence outside CHR	4 (10)	2 (7)	2 (17)
Clinical presentation			
Skin and soft-tissue infections	39 (98)	27 (96)	12 (100)
Abscess ± cellulitis	18 (45)	13 (46)	5 (42)
Infected wound or ulcer	9 (23)	8 (29)	1 (8)
Cellulitis ± ulceration	5 (13)	4 (14)	1 (8)
Bursitis, septic arthritis	2 (5)	1 (4)	1 (8)
Furuncle	2 (5)	1 (4)	1 (8)
Other¶ [p < 0.1]	3 (8)	0 (0)	3 (25)
Severe SSTI§ [p < 0.05]	34 (85)	26 (93)	8 (67)
Pneumonia	1 (3)	1 (4)	0 (0)
Outcomes of infection			
Outpatient IV therapy**	8 (20)	6 (21)	2 (17)
Hospital admission (HAdm)	7 (18)	6 (21)	1 (8)
HAdm or outpatient IV therapy	15 (38)	12 (43)	3 (25)
Sepsis	1 (3)	1 (4)	0 (0)
Death	1 (3)	1 (4)	0 (0)
No complication	25 (63)	16 (57)	9 (75)
Comorbid disease			
Hepatitis C [p < 0.05]	14 (35)	14 (50)	0 (0)
HIV	1 (3)	1 (4)	0 (0)
Diabetes	2 (5)	1 (4)	1 (8)
None identified [p < 0.1]	23 (58)	12 (43)	11 (92)
Risk factors for health care-acquired MRSA			
Symptom onset • 3 d after HAdm	3 (8)	3 (11)	0 (0)
Resident of long-term care facility	1 (3)	0 (0)	1 (8)
HAdm during preceding 12 mo	10 (25)††	7 (25)	3 (25)
None identified	26 (65)	18 (64)	8 (67)

Note: MRSA = methicillin-resistant *Staphylococcus aureus*, ± = with or without, SSTI = skin and soft-tissue infection, IV = intravenous, HAdm = hospital admission.

*Data were collected from clinic or hospital medical records (55% of 40 cases), review of medical charts at the local corrections facility (40%) and interviews with primary care providers (50%) and directly with patients (42%).

†Unless otherwise indicated.

‡Considered to be at high risk were those patients with a history of illicit drug use, homelessness or incarceration within the 2 years before symptom onset.

§Abscess, ulcer, cellulitis, bursitis, septic arthritis.

¶Periungual infection, impetigo.

**The Home Parenteral Therapy Program (*J Infus Nurs* 2002;25:372-8), CHR.

††Of these 10 patients, 9 were admitted to CHR hospitals for an average stay of 3.1 days, at a mean 21 weeks before onset of symptoms of MRSA.

ward where another patient was being treated for an infection with USA300.

Additional characteristics of the 28 high-risk cases are presented in Table 2. Eighteen (64%) of these patients had a history of recent incarceration in the Alberta corrections system, the majority having passed through local Correction Facility A (range, 1–20 incarcerations/person). Furthermore, of the 18 patients who had been incarcerated (for a range of 5–11 weeks), 3 had onset of their infection during their incarceration.

Interpretation

CA-MRSA infections are being reported with increasing frequency, particularly those with the USA300 strain.^{1,18,19} We report an outbreak of infections by the USA300 strain of MRSA, centred on an urban CHR population with histories of illicit drug use, homelessness or recent incarceration. We used a strain-based case definition and described the clinical features and hypotheses for transmission of a single virulent strain of CA-MRSA. A single central laboratory performed all microbiologic testing, which allowed the identification of all patients who were infected with the USA300 strain and a direct estimation of population incidence.

Table 2: Characteristics of the 28 people at high risk for community-acquired MRSA infection (i.e., subjects with a history of illicit drug use, homelessness or incarceration)

High-risk behaviour or characteristic	No. (%)
Substance or illicit drug use*	
Any illicit drug use	20 (71)
Cocaine, crack cocaine	20 (71)
Morphine or other prescription opiates	8 (29)
Heroin	3 (11)
Other non-opiate prescription drugs	1 (4)
Alcohol use only†	4 (14)
Use of detoxification centres	3 (11)
Homelessness*	
Any history of homelessness	15 (54)
Living in homeless shelters	12 (43)
No fixed address	3 (11)
Incarceration‡	
Anywhere in Alberta	18 (64)
At Corrections Facility A	17 (61)
Risk factor combinations	
Illicit drug use, homelessness and incarceration	6 (21)
Illicit drug use only	5 (18)
Homelessness only	1 (4)
Incarceration only	3 (11)
Other risk factor	
Popping or lancing own skin infections	8 (29)

Note: MRSA = methicillin-resistant *Staphylococcus aureus*.

*Within the 2 years before symptom onset.

†People with excess alcohol use but no use of illicit drugs.

‡Since 2002 Jan. 1.

Because people in drug-using or homeless populations may tend to seek medical care at a later stage of infection,²⁰ the CHR's burden of illness from this strain of MRSA may be even greater than we have documented. Our ability to interview high-risk patients was limited, which may also have led to underreportage of the characteristics of this group (e.g., the percentage who reported drug use).

The overall population prevalence of MRSA colonization in the CHR is probably low, in keeping with that recently reported in the United States.²¹ Outbreaks or a high prevalence of CA-MRSA infections have, however, been previously found in marginalized populations (prison inmates,⁴ drug-using and homeless people,^{22,23} and low-income communities²⁴), where these strains may become endemic and difficult to control.²⁵ Ongoing surveillance of CA-MRSA (and USA300) in the CHR has identified a further 310 infections up to the end of 2005 (8–34 cases/mo), with at least 73% occurring in the high-risk or transient population, which suggests that the strain has become endemic in this setting. Transmission within these populations has been attributed to factors that are environmental (e.g., crowded living conditions, such as in homeless shelters or jails), social (e.g., belonging to drug-using networks) and behavioural (e.g., poor personal hygiene).^{23,26–29} Lancing one's own skin infections, with the accompanying possibility of environmental contamination and transmission to close contacts, may also be a route of spread in the CHR high-risk population. Given that 71% of the patients whose cases met our inclusion criteria reported use of cocaine or crack cocaine, transmission may also be increased by the more frequent use of these drugs, drug use in settings such as crack houses, or sharing contaminated drugs or drug paraphernalia (e.g., needles, crack pipes).^{23,27,28} Although none of 7 cultures that we did on 2 samples of crack cocaine seized by police in Calgary grew CA-MRSA, 4 of 12 crack pipes that we tested had results positive for methicillin-sensitive *S. aureus*, which suggests that pipes may be a potential vector.

The majority of infections were community-acquired. Possible nosocomial acquisition may be explained by mitigating factors in each case, or by confounding from high rates of hospitalization.^{20,30} The infections identified in this outbreak were severe, with a high proportion (38%) of cases requiring intravenous antimicrobial therapy or hospital admission, and one death from a rapidly progressing necrotizing pneumonia.^{6,31} The severity of the infections and the potential consequences of delays in the initiation of appropriate treatment led to recommendations for empiric antibiotic treatment of skin and soft-tissue infections in the high-risk population in the CHR.

Of concern was the identification of 12 cases outside of the high-risk population. This suggests that the USA300 strain may be present in the general population, as has been recently documented.¹⁹

Control measures have included education of health care providers and the high-risk population, and recommendations for improved infection control in homeless shelters, group living settings and the local corrections facility. Despite these measures, this strain has now become endemic

in this marginalized population in the CHR. We feel it is critical for Canadian physicians to be aware of our experience in the CHR with this strain of CA-MRSA which, with its considerable morbidity and mortality, quickly became endemic in a marginalized population and has the potential for inappropriate initial antibiotic selection, which may adversely affect outcomes.

This article has been peer reviewed.

From the Canadian Field Epidemiology Program (Gilbert, Siushansian), Public Health Agency of Canada, Ottawa, Ont.; the Centre for Antimicrobial Resistance (Zhang, Laupland, Conly), Calgary Laboratory Services (Gregson, Zhang, Elsayed, Laupland, Conly), Calgary Health Region (MacDonald, Gregson, Zhang, Elsayed, Laupland, T. Louie, M. Louie, Hope, Gillespie, Nielsen, Wheeler, Conly) and the Departments of Pathology and Laboratory Medicine (Gregson, Zhang, Elsayed, Laupland, T. Louie, M. Louie, Conly), Medicine (Gregson, Zhang, Laupland, T. Louie, M. Louie, Conly), Microbiology and Infectious Diseases (Zhang, Elsayed, T. Louie, M. Louie, Conly) and Community Health Sciences (MacDonald, Laupland), University of Calgary, Calgary; Alberta Provincial Laboratory for Public Health (M. Louie), Alberta Health and Wellness (Honish, Keys), Edmonton, Alta.; and the National Microbiological Laboratory (Mulvey), Public Health Agency of Canada, Winnipeg, Man.

Competing interests: None declared.

Contributors: Mark Gilbert was responsible for the design of the data collection tool and interviews, and data collation, epidemiologic analysis and preliminary interpretation for the outbreak investigation. Judy MacDonald and John Conly initiated, organized and coordinated the investigation, contributed to the study design and data analysis, and were responsible for the final interpretation of all aspects of the investigation. Jennifer Siushansian and Kevin Laupland contributed to the study design and epidemiologic analysis. Kunyan Zhang, Sameer Elsayed, Dan Gregson, Tom Louie, Marie Louie and Michael Mulvey contributed microbiologic or molecular typing data, molecular characterization of the strains and the interpretation of these data. John Gillespie, Virginia Wheeler, Diane Nielsen and Karen Hope were responsible for the identification of cases, acquisition of data and implementation of control measures. Agnes Honish and Gloria Keys contributed to the study design and epidemiologic analysis, and helped coordinate the investigation at the provincial level. Mark Gilbert, Judy MacDonald and John Conly drafted the initial manuscript. All of the authors revised the manuscript for critical content and approved the final version to be published.

Acknowledgements: The authors would like to acknowledge the contribution of the following individuals: L. Ward, Infection Prevention and Control, Calgary Health Region; J. McClure, Calgary Laboratory Services; E. Smith and I. Grigoriu, Alberta Corrections; D. Gravel, Nosocomial and Occupational Infections, Public Health Agency of Canada; L. Panaro, Canadian Field Epidemiology Program; and K. Hiramatsu and T. Ito, Jutendo University, Tokyo, for provision of control strains for SCCmec typing.

Dr. Mark Gilbert is a Field Epidemiologist with the Canadian Field Epidemiology Program at the Public Health Agency of Canada. His interests include research in communicable disease epidemiology, and in health issues related to marginalized populations, particularly sexual minority and substance-using populations.

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Correspondence to: Dr. John Conly, Department of Medicine, Centre for Antimicrobial Resistance, University of Calgary, Calgary Health Region, and Calgary Laboratory Services, Calgary AB T2N 2T9; fax 403 944-1095; jconly@ucalgary.ca

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