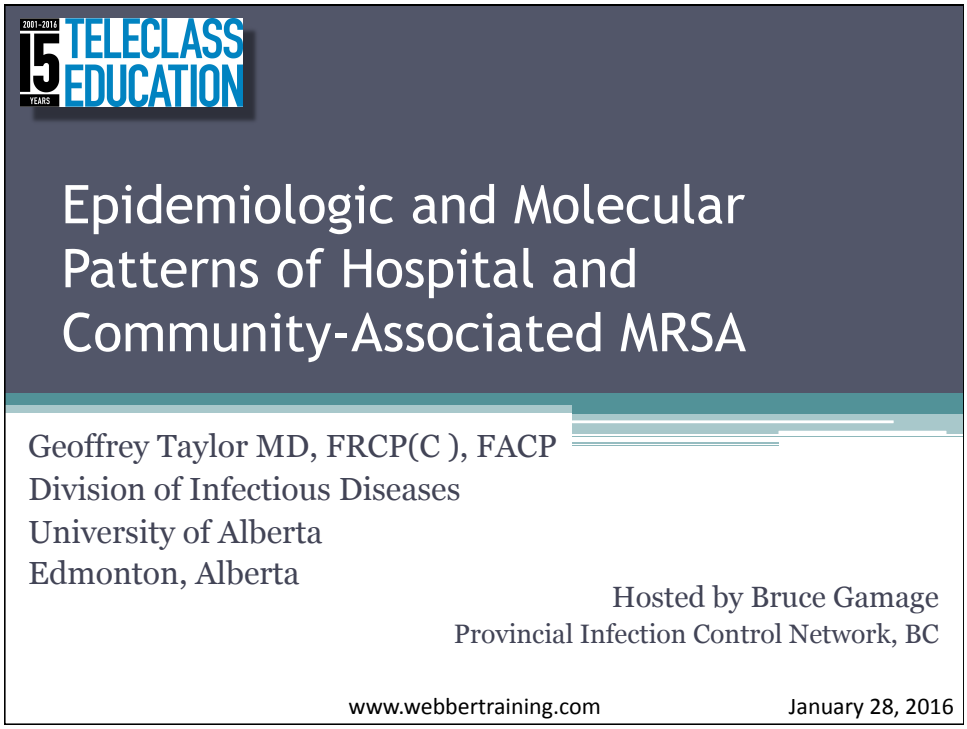
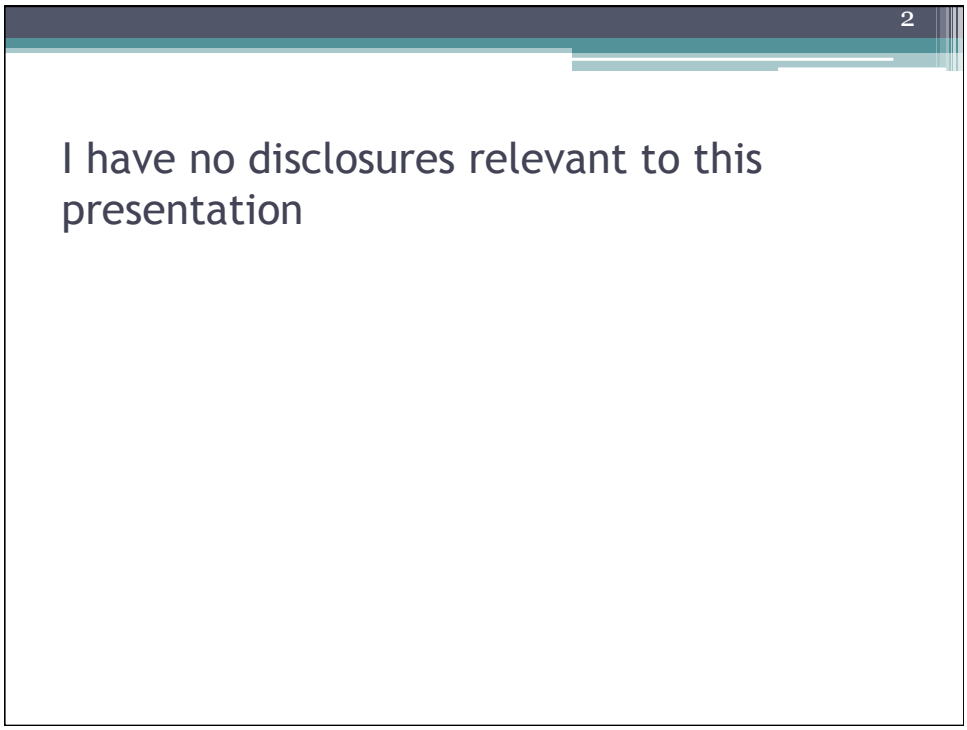
Epidemiologic and Molecular Patterns of Hospital and Community-Associated MRSA
Prof. Geoffrey Taylor University of Alberta
A Webber Training Teleclass





Hosted by Bruce Gamage, PICNet, BC
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MRSA – a potpouri of recent cases

- 21 year old male with relapsing skin/soft tissue infection following long board crash
  - Wound culture: MRSA , (R) clox, clinda, (S) vanco, doxy, tmp-smx
    - Rx wound management, IV vancomycin , step down to po doxycycline
- 45 yr old IDU , previous MRSA endocarditis, admitted after recent discharge AMA for recurrent MRSA endocarditis. At last discharge given po linezolid but may not have taken it
  - Multiple blood cultures: MRSA, (R) clox, clinda, (S) vanco (MIC 1.0), linezolid

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MRSA cases - continued

- 35 year old male with AML post Rx for Hodgkins Lymphoma. Multiple hospitalizations in multiple sites since 2008. Prior MRSA colonization. In hosp receiving chemotherapy, ANC <0.5. Developed abscess in axilla
  - Culture: MRSA , (R) clox, clinda, (S) vanco, tmp-smx, doxy

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Outline

- Evolution of betalactam resistance in Staphylococcus aureus
- S aureus microbiology
  - Methicillin resistance in S. aureus
  - S aureus toxins
  - Non-betalactam susceptibility
  - Genetic profiles of MRSA
  - Clinical profiles of MRSA strains
- Evolution of epidemiologic patterns of MRSA in hospital and community settings in North America
  - MRSA in Alberta

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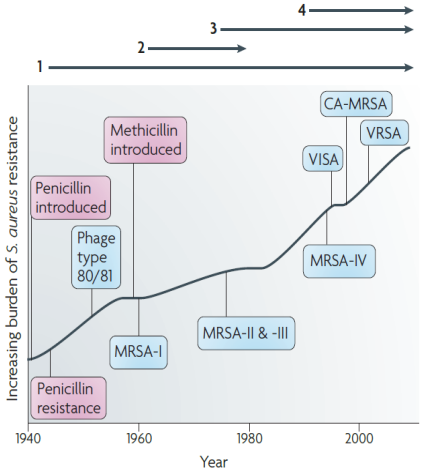
Evolution of antibiotic resistance in *S. aureus*

Chambers and Delo, Nat Rev Microbiol 2009

1. 1940's – 1960's: emergence and spread of penicillin resistance due to penicillinase production
2. 1959 – 1980's : emergence and spread, primarily in Europe, of semisythethic penicillin (methicillin) resistance due to PBP mutation (PBP2')
3. 1980's: Emergence and spread of novel MDR strains of MRSA (such as USA100/CMRSA 2)
4. *Late 1990's: Emergence and spread of community based MRSA strains (such as USA300/CMRSA 10)*



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MRSA 101
Microbiology

- Methicillin resistance is a genetic trait in *S. aureus* based on chromosomal *mecA* gene
  - mecA encodes a mutant Penicillin Binding Protein (PBP) 2 (a cell wall enzyme) designated PBP2'
  - *mec*A is part of a larger a larger chromosomal cassette (SCC), with 8 types (SCC*mec*I-VIII)
  - Results in resistance to all betalactam antibiotics
  - Imposes no fitness burden on *S aureus*

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S aureus: non-betalactam resistance

- Vancomycin
  - Very little full resistance (MIC >/= 16)
  - 'non-susceptible' isolates with elevated MIC (>/= 2) may fail Rx
    - A result of transient increase in cell wall thickness after prolonged non-curative vancomycin exposure
- Oral agents:
  - In the past hospital isolates typically MDR, community isolates have broader susceptibility
    - Clindamycin
      - Variable. Inducible resistance
    - Trimethoprim – sulfamethoxazole, Tetracyclines
      - Reasonable choices for non-invasive infections in susceptible strains. Ineffective for co-existing Streptococci
    - Linezolid (IV/po). Little resistance. Pneumonia. Endocarditis? Limited by toxicity
- Novel parenteral alternatives to vancomycin
  - Daptomycin
  - Telavancin
  - Ceftaroline
  - …

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MRSA typing & nomenclature

- Typing MRSA isolates is not required for clinical management , but is useful to explain and describe epidemiologic relationships: outbreaks or emerging epidemiologic patterns
- Typing methods:
  - Multilocus sequence typing (MLST)
  - Pulsed-field gel electrophoresis (PFGE)
  - *spa*-typing
- Nomenclature:
  - USA 100/CMRSA2 – classic HA-MRSA
  - USA 400/CMRSA7 – initial CA-MRSA, first described in children
  - USA 300/CMRSA10 – predominant CA-MRSA, unrelated to USA 400 or USA 100

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Biologic distinctions between typical Community and typical Hospital MRSA strains

Antimicrobial susceptibility

- USA 100/CMRSA2: only reliably susceptible to vancomycin (and novel agents such as linezolid, daptomycin , telavancin, ceftaroline)
- USA300/CMRSA 10: typically also susceptible to tmp-smx, tetracycline, fuscidic acid +/- clindamycin

Presence of virulence factors

- USA 300 has increased prevalence of:
  - Paton Valentine Leucocidin (PVL)
    - Associated with skin/soft tissue infection ("spider bite") and severe-hemorrhagic pneumonia
  - α-haemolysin
    - Associated with endocarditis and pneumonia

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Issues in MRSA Surveillance data

- Surveillance intensity
  - Numbers of cases you find can depend on how hard you look – especially colonization
- Clinical status
  - Some infections are treated without obtaining cultures
  - In lab based surveillance it can be difficult to distinguish infection from colonization
    - Eg - skin/wounds, sputum
    - No debate about significance of positive blood culture
- Source of MRSA
  - Hospital vs Community acquisition of MRSA is often speculative since acquisition is usually silent
  - Source of infection is easier to determine based on standard definition

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MRSA – USA

Carrel et al Emerging Inf Dis 21:1973, (2015)
Rhee et al Infect Control Hosp Epidemiol 36:1417 (2015)

- USA 100 has been present for many years in US hospitals. Since ~ 2007 it has been in relative decline in several regions (coincident with increased attention to IPC)
- USA 300 was introduced in the late 1990's but did not emerge simultaneously: starting in western states and spreading east
  - Disproportionately affects children , incarcerated and inner city populations

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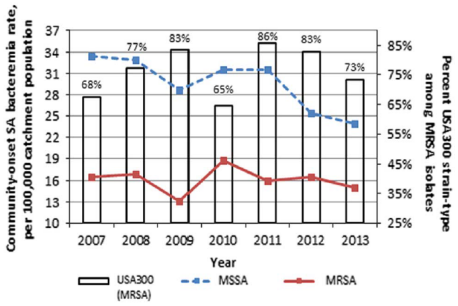
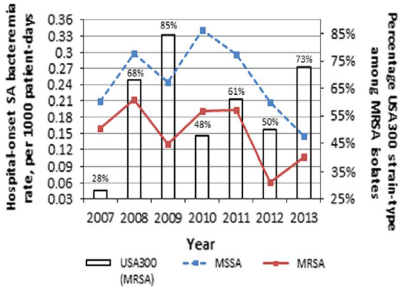
MRSA BSI in a large Chicago hospital 2007-2013

Community Onset BSI



Hospital Onset BSI



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Emergence of MRSA in a network of Canadian Hospitals (CNISP)

(Simor et al , ICHE , 2010)

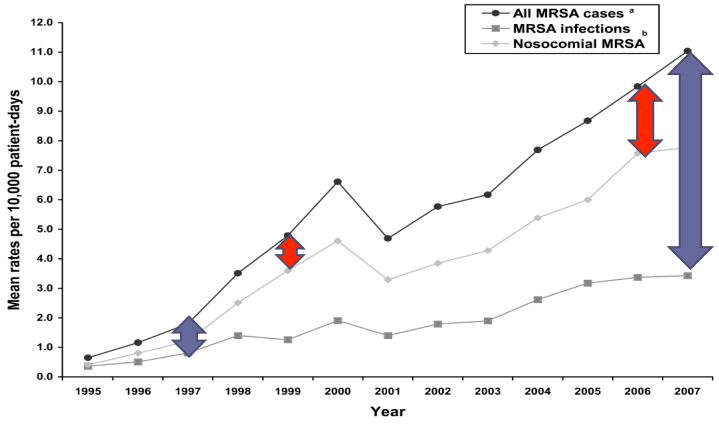

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TABLE 4. Laboratory Characterization of Canadian Strains of Methicillin-Resistant *Staphylococcus aureus* (MRSA) Identified in the Canadian Nosocomial Infection Surveillance Program, 1995–2007

	No. (%) of isolates				
Laboratory characteristic	Overall (1995–2007)	1995–1999	2000–2003	2004–2007	*P*
PFGE genotype					
Total no. of isolates typed	13,648	2,607	4,266	6,775	
CMRSA-1 (USA600; ST45; CC45)	2,589 (19)	1,109 (43)	1,136 (27)	344 (5)	<.001
CMRSA-2 (USA100/800; ST5; CC5)	6,370 (47)	373 (14)	2,051 (48)	3,946 (58)	<.001
CMRSA-3/6 (ST241/ST239; CC8)	1,603 (12)	622 (24)	437 (10)	544 (8)	<.001
CMRSA-7 (USA400; ST1; CC1)	340 (2)	18 (1)	72 (2)	250 (4)	<.001
CMRSA-10 (USA300; ST8; CC8)	1,175 (9)	1 (0.4)	32 (1)	1,142 (17)	<.001
Other types	1,571 (11)	484 (19)	538 (13)	549 (8)	
SCCmec type					
Total no. of isolates typed	3,269	339	637	2,293	
Type I	18 (1)	9 (3)	4 (1)	5 (0.2)	
Type II	1,765 (54)	202 (60)	434 (68)	1,129 (49)	<.001
Type III	283 (9)	64 (19)	71 (11)	148 (6)	<.001
Type IV	1,151 (35)	63 (18)	96 (15)	992 (43)	<.001
Other types	52 (1)	1 (0.3)	32 (5)	19 (1)	

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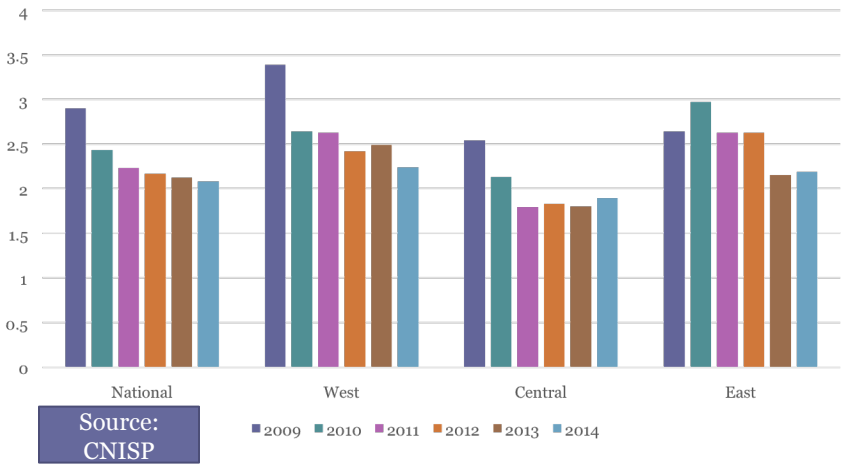
MRSA Infections/1,000 admissions in Sentinel Canadian Hospitals



Source: CNISP

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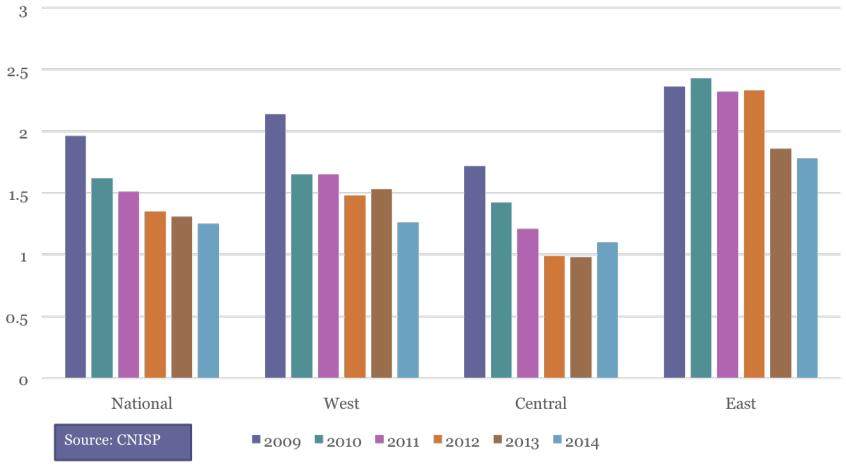
Healthcare Associated MRSA Infections in Sentinel Canadian Hospitals



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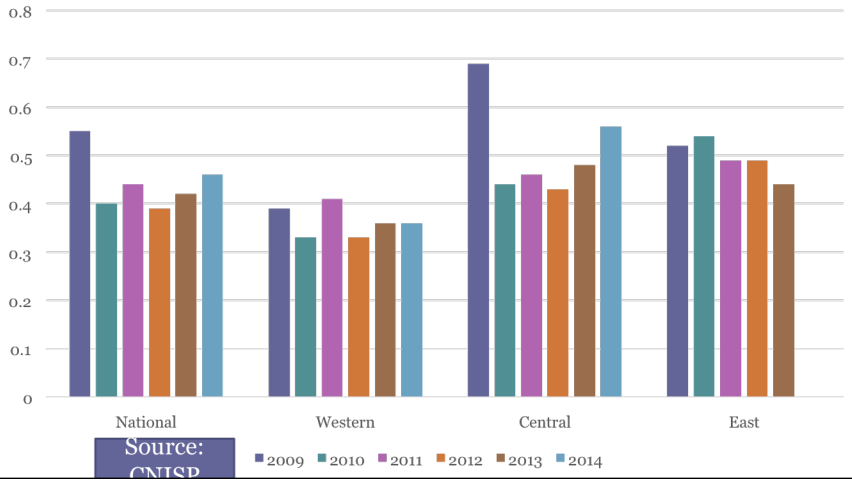
MRSA BSI in Sentinel Canadian Hospitals/ 1000 Admissions



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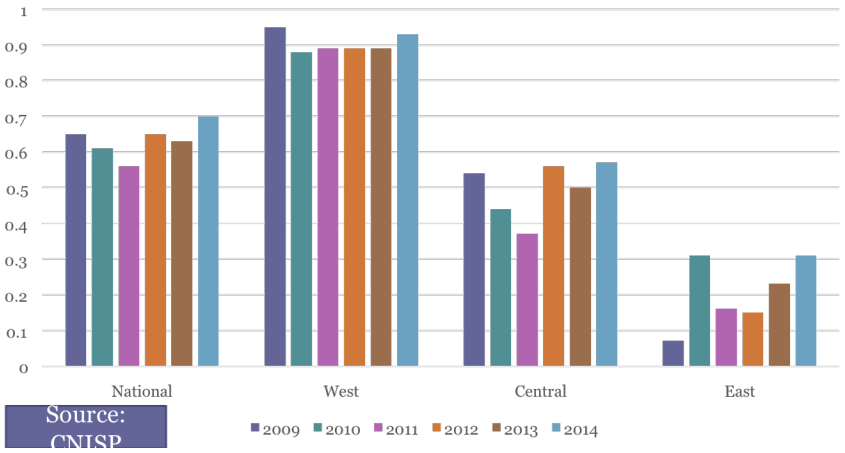
Community Acquired MRSA Infections in Sentinel Canadian Hospitals/1000 Admissions



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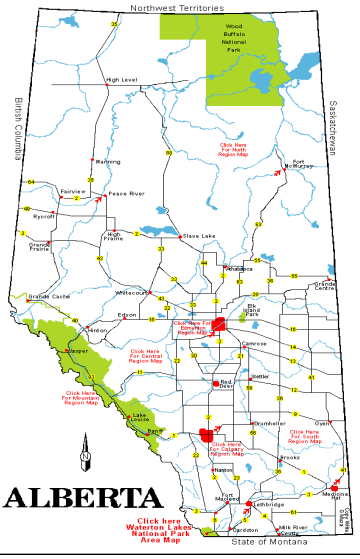
Alberta

- Population 4.2 million (2014)
- 2 major urban centres (Edmonton, Calgary) with 68% of population
- 2 medical schools
- Academic medical centres in Edmonton and Calgary



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Alberta Health Services (AHS)

- As in other Canadian provinces all medically necessary healthcare is provided publically
- AHS founded in 2009 to provide **all medically necessary hospital care in Alberta**
- Currently (2015) provides 3.1 million annual inpatient days through
  - 2 tertiary hospitals
  - 2 pediatric hospitals
  - 1 cancer hospital
  - 7 large urban hospitals
  - 7 regional hospitals
  - 82 small suburban /rural hospitals

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MRSA in Alberta: a retrospective cohort study

Bush et al
Antimicrobial Resistance and Infection Control , 2015

Methods:

- Incident MRSA in AHS hospitals between 01/04/2011 and 31/03/2013
- Epidemiologic definitions of source of MRSA
  - Hospital Acquired
    - Identified >48 hr after hospital admission
  - Healthcare Associated (HCA)
    - <48 hr after admission, healthcare risk (eg LTC, hemodialysis)
  - Community Acquired
- Spa-typing and PFGE of a subset of isolates

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Results

- 4818 incident MRSA cases
  - 32.7% clinical, 67.4% screening
  - 41.1% HA, 20.8% HCA, 38.1% CA
  - 43.4% large urban, 23.6% small suburban rural
- 2248 (46.7%) isolates available for typing

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MRSA in Alberta by strain type and mode of acquisition

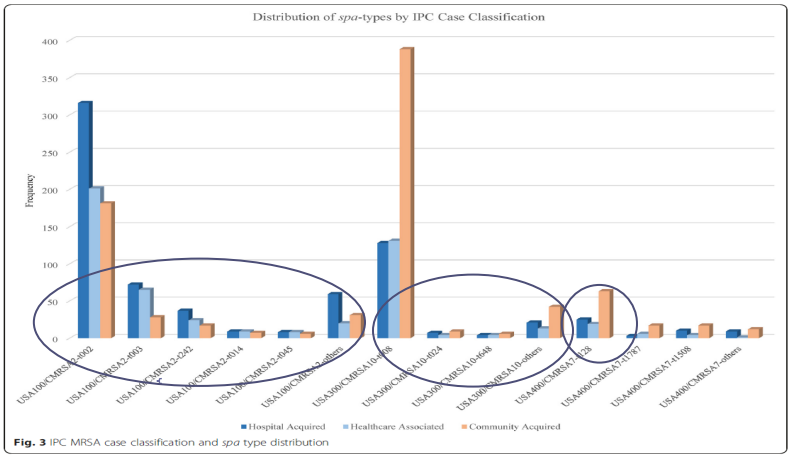

Fig. 3 IPC MRSA case classification and *spa* type distribution

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Epidemiology of MRSA BSI in Alberta

Taylor et al
J Hosp Infect, 2015

Background

- Focus is on infection
  - By surveying only BSI , avoids problems related to surveillance intensity, definition of clinical status and permits comparison to other jurisdictions
- Source = source of BSI not MRSA

Methods

- MRSA blood culture isolates between 04/11-03/13 were assessed by site based ICP's
- Isolates were *spa*-typed

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Table I
Meticillin-resistant *Staphylococcus aureus* (MRSA) bloodstream infections (BSI) in Alberta, Canada in 2011–2013 by location and setting of BSI acquisition

	Hospital acquired *N* = 99 (%)	Non-hospital acquired *N* = 200 (%)	All MRSA BSI *N* = 299 (%)	*P*-value for hospital acquired vs non-hospital acquired
Sex				
Male *N* (%)	60 (60.6)	116 (58.0)	176 (58.9)	0.67
Age				
Mean age in years (SD)	64.6 (16.6)	57.5 (20.0)	59.8 (19.4)	0.002
Facility type, *N* (%)				
Tertiary	36 (36.4)	55 (27.5)	91 (30.4)	0.12
Large urban	34 (34.3)	95 (47.5)	129 (43.1	0.03
Regional	19 (19.2)	34 (17.0)	53 (17.7)	0.64
Small suburban/rural	7 (7.1)	14 (7.0)	21 (7.0)	0.98
Paediatric	3 (3.0)	2 (1.0)	5 (1.7)	0.20
Geographic zone, *N* (%)				
Calgary	48 (48.5)	83 (41.5)	131 (43.8)	0.25
Edmonton	30 (30.3)	76 (38.0)	106 (35.5)	0.19
Remaining zones	21 (21.2)	41 (20.5)	62 (20.7)	0.89

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MRSA BSI in Alberta

Table II

Meticillin-resistant *Staphylococcus aureus* (MRSA) molecular profiles by site of acquisition

Canadian MRSA prototype	Community acquired *N* = 120 (%)	Healthcare associated *N* = 71 (%)	Hospital acquired *N* = 105 (%)	Total *N* = 296 (%)	*P*-value for hospital acquired vs community acquired
CMRSA 10 (USA300)	66 (55.0)	24 (33.8)	29 (27.6)	119 (40.2)	<0.001
CMRSA 2 (USA100/USA 800)	33 (27.5)	25 (35.2)	56 (53.3)	114 (38.5)	<0.001
CMRSA 3/6	0	0	1 (1.0)	1 (0.3)	0.27
CMRSA 7 (USA 400)	2 (1.7)	2 (2.8)	2 (1.9)	6 (2.0)	0.91
CMRSA 8	2 (1.7)	4 (5.6)	4 (3.8)	10 (3.4)	0.33
Not assigned	7 (5.8)[a]	3 (4.2)[b]	2 (1.9)[c]	12 (4.1)	0.33
Not tested	10 (8.3)	13 (18.3)	11 (10.5)	34 (11.5)	0.57
Total	120	71	105	296	

Spa types: [a]t19 (*N* = 5), t521 (*N* = 2); [b]t316, t437, t521; [c]t1346, t1839.

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Molecular and Epidemiologic Patterns of MRSA Conclusions

- MRSA epidemiology is in transition and varies geographically
- Across North America , there has been a decline in traditionally hospital acquired MRSA
- Community sourced MRSA is variable, but well established/predominant in several areas
- In Alberta, MRSA BSI is predominantly community onset
- While USA 300/CMRSA 10 is still predominantly a community strain and USA 100/CMRSA 2 is still predominantly a hospital strain, presumption of source of MRSA based on strain type is no longer viable

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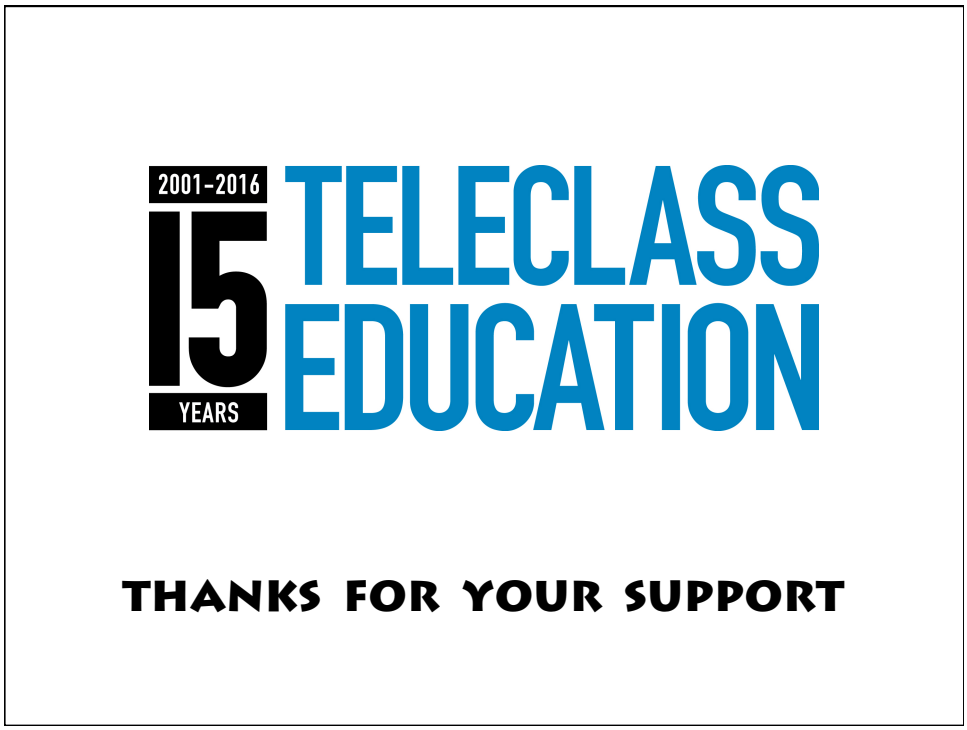

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