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PHO Rounds: Describing the Burden of Antimicrobial Resistance in Ontario

Kevin Brown, PhD
Nick Daneman, MD, MSc

World Antimicrobial Awareness Week

November 22, 2022

Overview

We will describe 4 Ontario-wide AMR projects:

- Antibiotic susceptibility of urine culture specimens
- Prevalence and mortality of bloodstream pathogens
- Association of AMR and mortality in E.coli bacteremia
- Clinical Antibiotic Resistance Index

Along the way we will:

- Demonstrate the value of population-based AMR research and surveillance
- Describe some of the key data sources and methods that make this work possible
- Highlight some of the challenges of this approach

Core strategies to address AMR

Public Health Agency of Canada. Tackling antimicrobial resistance and antimicrobial use: a Pan-Canadian framework for action [Internet]. Ottawa, ON: Her Majesty the Queen in Right of Canada; 2017 [cited 2022 Nov 22]. Available from: https://www.canada.ca/content/dam/hc-sc/documents/services/publications/drugs-health-products/tackling-antimicrobial-resistance-use-pan-canadian-framework-action/tackling-antimicrobial-resistance-use-pan-canadian-framework-action.pdf

COMBAT-AMR

- Comprehensive Ontario Microbiology LaBoratory Administrative daTa for AntiMicrobial Resistance

- Purpose
  - Identify incidence and prevalence of AMR
  - Measure the attributable mortality of each form of AMR
  - Combine into Clinical Antimicrobial Resistance Index

- Work funded by CIHR, PHO, and NML

Antibiotic Susceptibility of Urine Culture Specimens in Ontario, Canada

Antibiotic Susceptibility of Urine Culture Specimens in Ontario, Canada

Marchand-Austin A, Lee SM, Langford BJ, Daneman N, MacFadden DR, Diong C, et al. Antibiotic susceptibility of urine culture specimens in Ontario: a population-based cohort study. CMAJ Open. 2022. Forthcoming.

Background and rationale 1 of 2

- Over 30% of antibiotic prescribing is for presumptive urinary tract infection
- Treatment is often empiric, and isn’t necessarily based on local resistance rates
- US (IDSA) and European (ESCMID) guidelines for uncomplicated UTI emphasize the importance of accounting for local resistance

Background and rationale 2 of 2

- *E. coli* is the dominant uropathogen
- Resistance to *E. coli* guides empiric treatment of urinary tract infection
- Weighted Incidence Syndromic Combination Antibiogram
  - Idea is examine examine “marginal” resistance across all urinary pathogens (instead of just E. coli).

Objective

- Measure the prevalence of antimicrobial resistance in urinary isolate in Ontario
- Compare outpatient, inpatient, and long-term care
- Compare the *E. coli* antibiogram vs WISCA

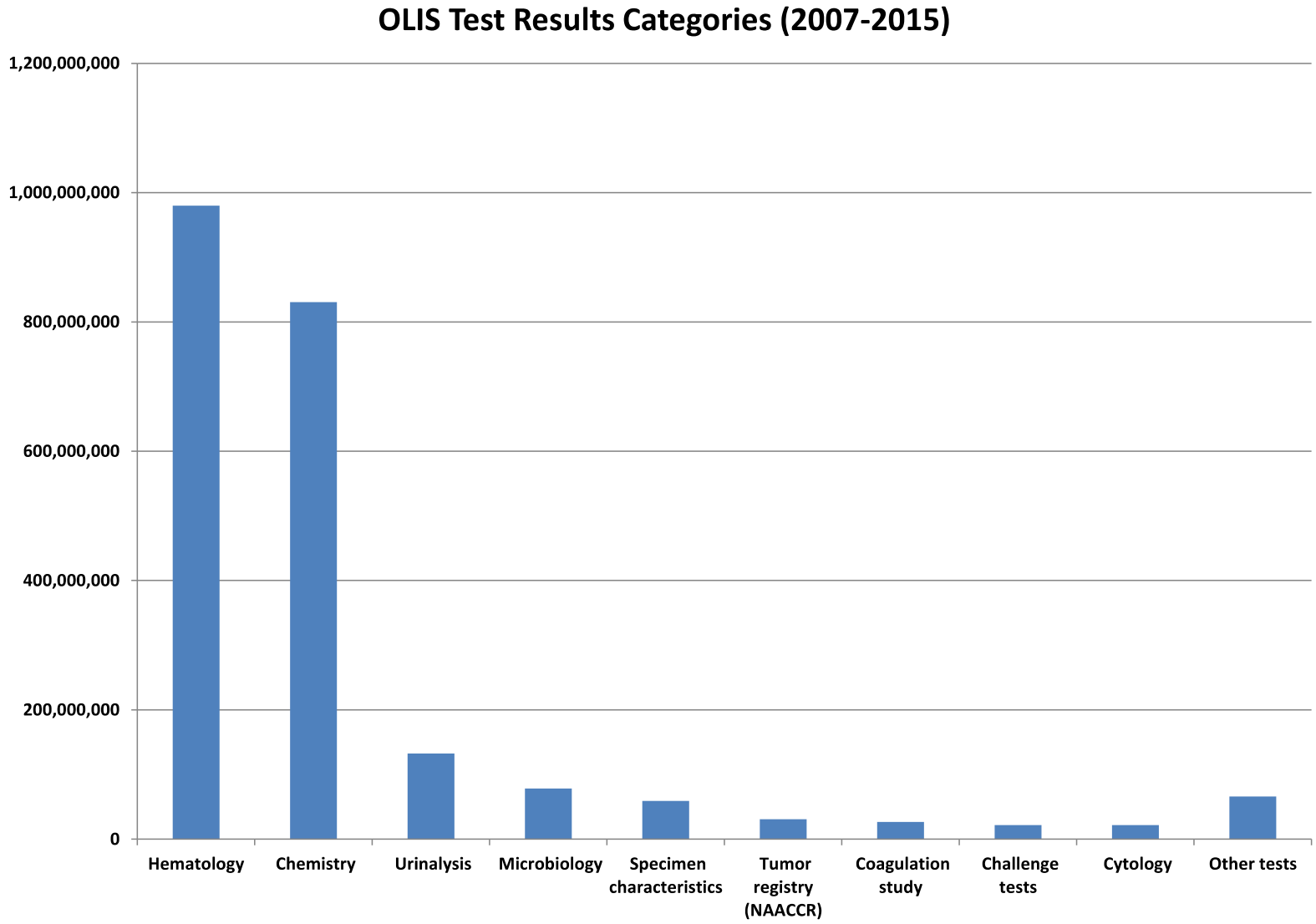
Marchand-Austin A, Lee SM, Langford BJ, Daneman N, MacFadden DR, Diong C, et al. Antibiotic susceptibility of urine culture specimens in Ontario: a population-based cohort study. CMAJ Open. 2022. Forthcoming.

Methods

- Data sources (ICES)
  - OLIS – Ontario Laboratory Information System -- cleaned culture and susceptibility data
  - Registered Persons Database (RPDB), Discharge Abstract Database (DAD)
- Covariates
  - Age, sex, setting, health region [LHIN]

Marchand-Austin A, Lee SM, Langford BJ, Daneman N, MacFadden DR, Diong C, et al. Antibiotic susceptibility of urine culture specimens in Ontario: a population-based cohort study. CMAJ Open. 2022. Forthcoming.

OLIS Data is Massive



OLIS Data Structure

- OLIS data consists of 3 linked data tables
  - Observations (observation codes, coded via LOINC)
    - Includes the free text result
    - Specimen source
    - Timing of result
  - Test requests (test request codes)
  - Orders

- LOINC
  - Logical Observation Identifiers Names and Codes
  - Idenfitying culture and susceptibility data in OLIS
    - Culture LOINC list
    - Susceptibility LOINC list

OLIS Culture and Susceptibility LOINC Lists

LOINC	loincfullyspecifiedname	frequency	priority	testype
634-6	BACTERIA IDENTIFIED:PRID:PT:XXX:NOM:AEROBIC CULTURE	9216722	1	C
6463-4	BACTERIA IDENTIFIED:PRID:PT:XXX:NOM:CULTURE	7087153	1	C
43409-2	BACTERIA IDENTIFIED:PRID:PT:ISOLATE:NOM:CULTURE	2167222	1	C
626-2	BACTERIA IDENTIFIED:PRID:PT:THRT:NOM:CULTURE	1246629	1	C
630-4	BACTERIA IDENTIFIED:PRID:PT:URINE:NOM:CULTURE	940225	1	C
600-7	BACTERIA IDENTIFIED:PRID:PT:BLD:NOM:CULTURE	673178	1	C
625-4	BACTERIA IDENTIFIED:PRID:PT:STOOL:NOM:CULTURE	294157	1	C
17928-3	Bacteria identified:Prid:Pt:Bld:Nom:Aerobic culture	284073	1	C
18998-5	TRIMETHOPRIM+SULFAMETHOXAZOLE:SUSC:PT:ISOLATE:ORDQN	2552324	1	S
18955-5	NITROFURANTOIN:SUSC:PT:ISOLATE:ORDQN	2409756	1	S
18928-2	GENTAMICIN:SUSC:PT:ISOLATE:ORDQN	2391134	1	S
18906-8	CIPROFLOXACIN:SUSC:PT:ISOLATE:ORDQN	2324269	1	S
18864-9	AMPICILLIN:SUSC:PT:ISOLATE:ORDQN	2211872	1	S
18900-1	CEPHALOTHIN:SUSC:PT:ISOLATE:ORDQN	1572324	1	S
18878-9	CEFAZOLIN:SUSC:PT:ISOLATE:ORDQN	1173398	1	S

OLIS Data Complexity

- Culture Results
  - 4,552,482 test result records in 2014
  - 63,312 unique values
  - 1 every 70 records are unique
- Susceptibility Results
  - 3,823,864 test result records in 2014
  - 2,217 unique values
  - 1 out of 1700 records are unique

OLIS Coding

- Culture Tests
  - Over 70 unique organisms
  - Multiple organisms
  - Not classified
- Susceptibility Tests
  - Susceptible
  - Intermediate
  - Resistant
  - Other (MIC values, etc)
  - Not classified

- Coding conducted with regular expressions. Searched and encoded organism names and susceptibility test results.

- Verification against all unique values to ensure we weren't misclassifying values

- Mechanisms to reduce uniqueness (removal of special characters, placeholders for numeric values)

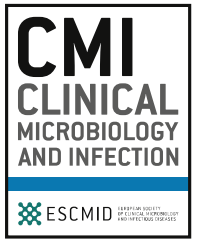
Methods

- Imputation
  - Some drugs missing due to variable testing practices (Langford et al. 2021)

Contents lists available at ScienceDirect

Clinical Microbiology and Infection

journal homepage: www.clinicalmicrobiologyandinfection.com



Original article

Antibiotic susceptibility reporting and association with antibiotic prescribing: a cohort study

Bradley J. Langford [1, *], Nick Daneman [2], Christina Diong [3], Alex Marchand-Austin [3], Kwaku Adomako [4], Arezou Saedi [4], Kevin L. Schwartz [5], Jennie Johnstone [6], Derek R. MacFadden [7], Larissa M. Matukas [8], Samir N. Patel [9], Gary Garber [10], Kevin A. Brown [5]

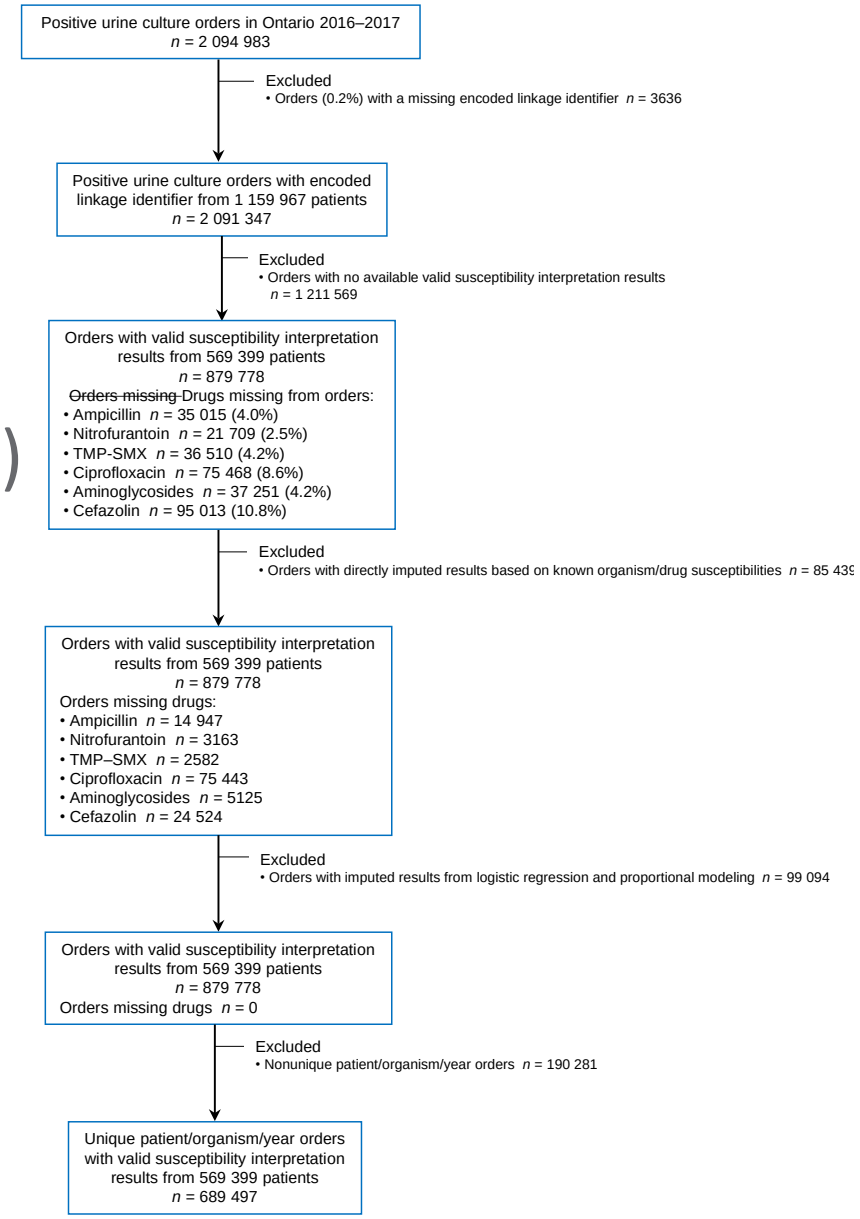
Langford BJ, Daneman N, Diong C, Marchand-Austin A, Adomako K, Saedi A, et al. Antibiotic susceptibility reporting and association with antibiotic prescribing: a cohort study. Clin Microbiol Infect. 2021;27(4):568-75. Available from: https://doi.org/10.1016/j.cmi.2020.10.001

Methods

- Solution was to do imputation – 3 models, depending on availability of data
  - 1. Full model (age, sex, setting, health region, organism, all drugs)
  - 2. Patient characteristics only model (age, sex, setting, health region, organism)
  - 3. Intercept only model

Urine culture susceptibility

- Ontario – 2 year period: 2016-2017
- 2.1 million urine culture orders
- 689,000 unique cultures (patient/organism/year)



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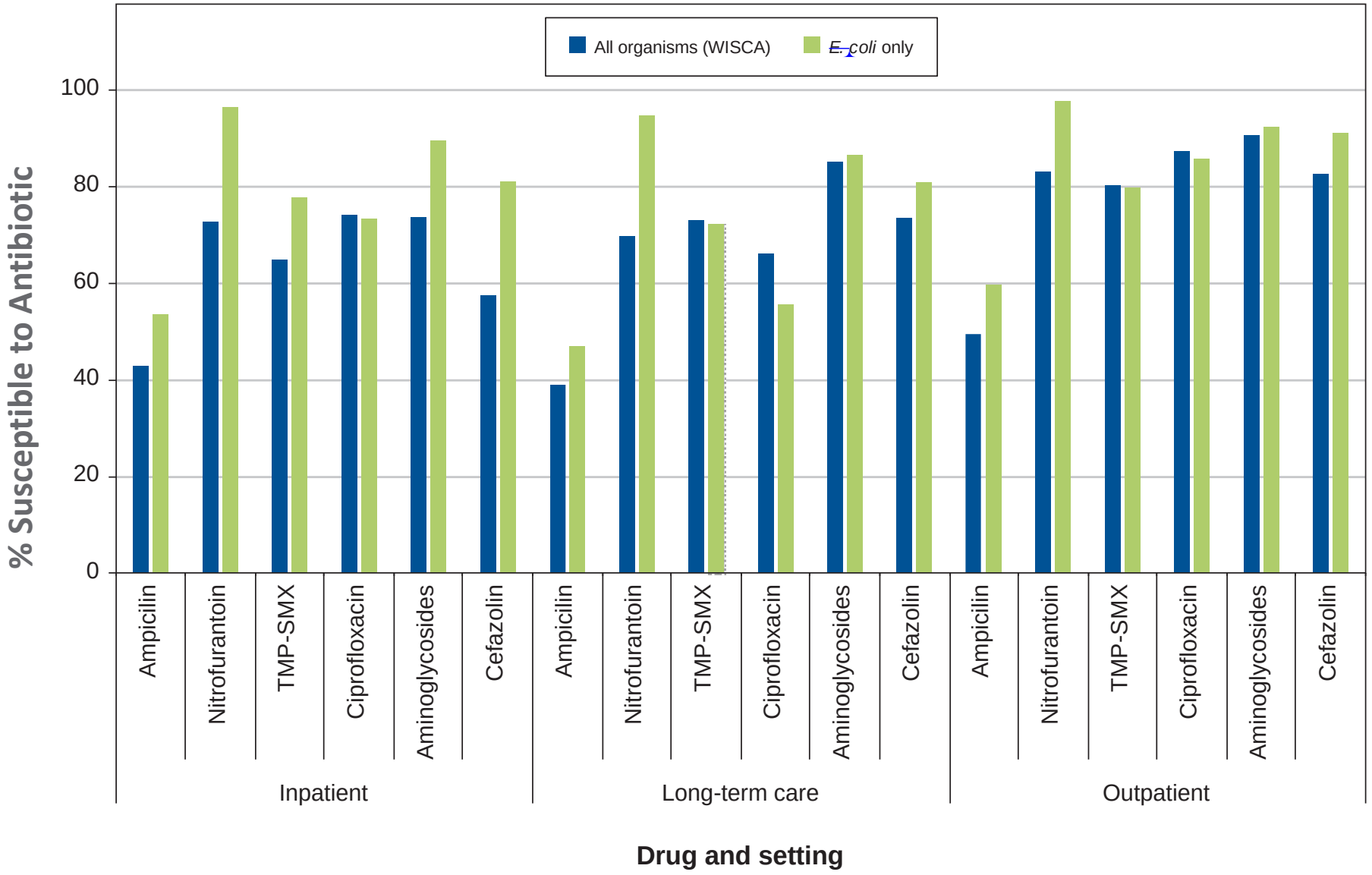


Marchand-Austin A, Lee SM, Langford BJ, Daneman N, MacFadden DR, Diong C, et al. Antibiotic susceptibility of urine culture specimens in Ontario: a population-based cohort study. CMAJ Open. 2022. Forthcoming.

Characteristic	Frequency (%)	Susceptibility to antibiotics, %						Resistant to ≥ 3 drug categories, %
		Ampicillin	Nitrofurantoin	TMP–SMX	Ciprofloxacin	Aminoglycosides*	Cefazolin	
Setting								
All combined	689 497 (100.0)	48.3	81.7	79.0	85.3	89.3	80.6	20.6
Inpatient	40 547 (5.9)	42.8	72.7	64.8	74.1	73.6	57.5	42.1
Long-term care	39 249 (5.7)	39.2	69.7	73.1	66.2	85.1	73.5	32.8
Outpatient	609 701 (88.4)	49.3	83.1	80.3	87.2	90.6	82.6	18.4
Organism								
Escherichia coli	497 646 (72.2)	58.9	97.5	79.4	83.8	92.1	90.3	14.0
Klebsiella pneumoniae	61 333 (8.9)	0	35.4	92.6	96.3	97.2	95.2	9.3
Proteus mirabilis	27 795 (4.0)	84.8	0.0	85.1	91.6	93.6	93.2	14.7
Pseudomonas aeruginosa	11 252 (1.6)	0	0	0	88.4	91.8	0	100.0
Citrobacter koseri	10 562 (1.5)	0	78.5	99.0	99.4	99.5	0.8	22.4
Enterobacter cloacae	10 275 (1.5)	0	39.3	89.6	96.0	97.1	0	64.3
Klebsiella sp. other	9888 (1.4)	0	43.2	94.5	94.7	97.8	94.0	8.9
Enterococcus sp. other	9650 (1.4)	91.6	92.0	0.1	51.9	0.0	0	100.0
Klebsiella oxytoca	8205 (1.2)	0.0	82.5	94.8	96.8	97.7	50.6	14.1
Staphylococcus aureus	8146 (1.2)	2.0	82.6	99.2	50.3	0.0	85.1	58.8
Enterococcus faecalis	6857 (1.0)	99.6	98.9	0.1	73.6	0.1	0	100.0
Enterobacter erogenes	6330 (0.9)	0	15.8	97.7	98.5	99.2	0	84.6
Citrobacter freundii	6293 (0.9)	0	94.6	87.2	94.5	95.2	0	19.5
Morganella sp.	4907 (0.7)	0.1	0.1	81.2	88.1	89.5	0	99.9
Staphylococcus sp. other	2348 (0.3)	24.8	81.4	77.5	48.9	0	63.0	66.3
Serratia sp.	2297 (0.3)	0.1	0.8	97.5	95.3	87.2	0.1	99.3
Other†	1682 (0.2)	17.8	31.6	90.8	91.4	93.9	13.1	60.4
Citrobacter sp. other	1663 (0.2)	0.1	80.6	93.9	95.7	97.3	0.3	26.1
Enterococcus faecium	982 (0.1)	10.3	25.1	0.1	8.5	0.1	0.1	100.0
Acinetobacter sp. other	797 (0.1)	0.3	0.0	91.3	92.9	95.4	0.1	99.8
Proteus vulgaris	589 (0.1)	0.2	0.3	86.8	98.0	98.3	0.2	99.5
Age, yr								
< 18	38 820 (5.6)	53.3	85.4	78.2	72.9	89.9	84.1	22.7
18–64	349 652 (50.7)	51.6	86.3	79.7	89.6	90.6	84.8	16.5
≥ 65	301 025 (43.7)	43.9	75.9	78.2	81.8	87.6	75.3	25.1
Sex								
Male	99 126 (14.4)	39.3	69.0	72.2	77.9	80.2	62.4	37.7
Female	590 355 (85.6)	49.9	83.9	80.1	86.5	90.8	83.7	17.7
Year								
2016	337 560 (49.0)	48.4	81.6	79.1	85.4	89.6	81.2	20.2
2017	351 937 (51.0)	48.3	81.8	78.8	85.2	88.9	80.0	20.9

Marchand-Austin A, Lee SM, Langford BJ, Daneman N, MacFadden DR, Diong C, et al. Antibiotic susceptibility of urine culture specimens in Ontario: a population-based cohort study. CMAJ Open. 2022. Forthcoming.

Discussion 1 of 2

- In outpatients -- 80%–85% of positive urine cultures were susceptible to nitrofurantoin, trimethoprim–sulfamethoxazole TMP-SMX, cephalexin and ciprofloxacin
- WISCA method vs *E. coli* approach
  - Similar results in outpatient settings
  - *E. coli* antibiogram underestimates resistance in inpatient settings

Marchand-Austin A, Lee SM, Langford BJ, Daneman N, MacFadden DR, Diong C, et al. Antibiotic susceptibility of urine culture specimens in Ontario: a population-based cohort study. CMAJ Open. 2022. Forthcoming.

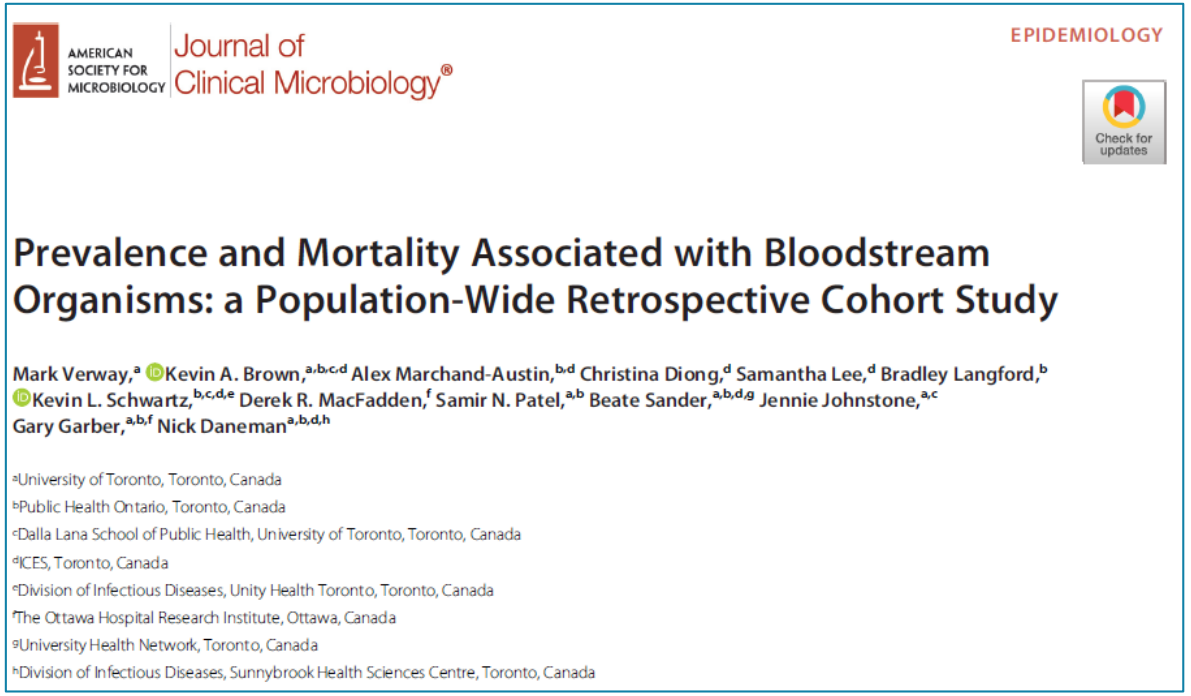
Discussion 2 of 2

- Harnessing population-level susceptibility data and tailoring antibiograms to the local population to support improved antibiotic decision making

- Embedded and available -- Ontario Urinary Antibiogram
  - https://www.publichealthontario.ca/en/health-topics/antimicrobial-stewardship/asp-comparison-tool

Marchand-Austin A, Lee SM, Langford BJ, Daneman N, MacFadden DR, Diong C, et al. Antibiotic susceptibility of urine culture specimens in Ontario: a population-based cohort study. CMAJ Open. 2022. Forthcoming.

Prevalence and Mortality of Bloodstream Pathogens in Ontario



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EPIDEMIOLOGY

Check for updates

Prevalence and Mortality Associated with Bloodstream Organisms: a Population-Wide Retrospective Cohort Study

Mark Verway,[a] Kevin A. Brown,[a,b,c,d] Alex Marchand-Austin,[b,d] Christina Diong,[d] Samantha Lee,[d] Bradley Langford,[b] Kevin L. Schwartz,[b,c,d,e] Derek R. MacFadden,[f] Samir N. Patel,[a,b] Beate Sander,[a,b,d,g] Jennie Johnstone,[a,c] Gary Garber,[a,b,f] Nick Daneman[a,b,d,h]

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[d]ICES, Toronto, Canada
[e]Division of Infectious Diseases, Unity Health Toronto, Toronto, Canada
[f]The Ottawa Hospital Research Institute, Ottawa, Canada
[g]University Health Network, Toronto, Canada
[h]Division of Infectious Diseases, Sunnybrook Health Sciences Centre, Toronto, Canada

Verway M, Brown KA, Marchand-Austin A, Diong C, Lee S, Langford B, et al. Prevalence and mortality associated with bloodstream organisms: a population-wide retrospective cohort study. J Clin Microbiol. 2022;60(4):e0242921. Available from: h_ttps://doi.org/10.1128/jcm.02429-21

Background and Rationale 1 of 2

- Bloodstream infections (BSIs) are common and lethal
  - 600,000 cases/year in North America
  - 90,000 deaths/year in North America
  - ranks among top 7 causes of death

- Surveillance networks have been established to track BSIs, but they have many limitations:
  - rely on voluntary contributions from participating hospitals
    - under-representation of non-academic hospitals
    - under-representation of BSIs outside of hospital sector
  - lab data are usually separate from clinical data
    - lack information on patient characteristics and outcomes

Goto M, Al-Hasan MN. Overall burden of bloodstream infection and nosocomial bloodstream infection in North America and Europe. Clinical Microbiology and Infection. 2013;19(6):501-9.

Diekema DJ, Hsueh PR, Mendes RE, Pfaller MA, Rolston KV, Sader HS, Jones RN. The microbiology of bloodstream infection: 20-year trends from the SENTRY antimicrobial surveillance program. Antimicrobial agents and chemotherapy. 2019;63(7):e00355-19.

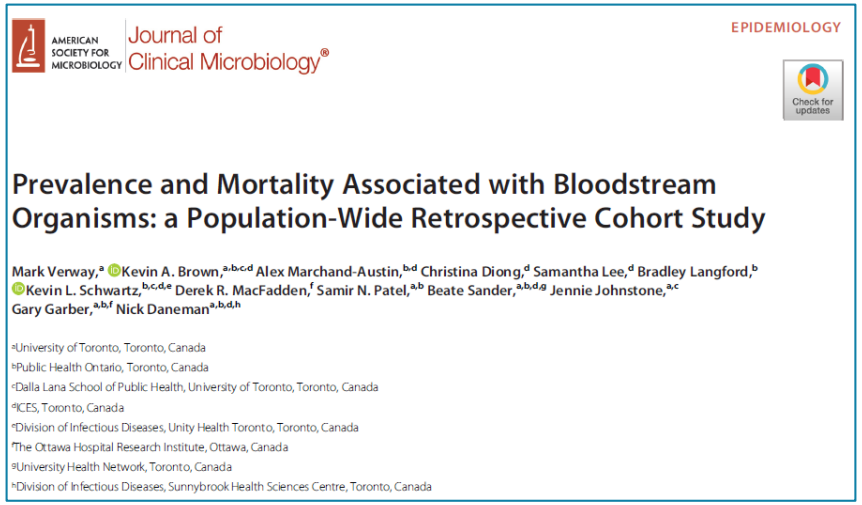
Background and Rationale 2 of 2

- In Ontario we now have:
  - cleaned OLIS data for population-wide microbiology data
    - acute care hospitals, long term care, community/outpatient setting
  - linked (within ICES) to health care datasets at the patient level
    - patient characteristics
    - outcomes

Objectives

1. quantify the prevalence of BSIs across all health sectors
2. examine the relative prevalence of BSI organisms across these sectors
3. examine the odds of mortality associated with each organism

Methods



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- Ontario, Canada
- calendar year 2017

- Data sources
  - Ontario Lab Information System (OLIS)
  - hospital data (CIHI-DAD)
  - emergency department data (NACRS)
  - vital statistics (RPDB)

Verway M, Brown KA, Marchand-Austin A, Diong C, Lee S, Langford B, et al. Prevalence and mortality associated with bloodstream organisms: a population-wide retrospective cohort study. J Clin Microbiol. 2022;60(4):e0242921. Available from: https://doi.org/10.1128/jcm.02429-21

Methods

- Definition of blood culture episode
  - positive and negative blood cultures were clustered into episodes if collected within 7d of an initial sample
  - for common contaminant species we required two positive sets for inclusion
    - coagulase negative staphylococci
    - *Bacillus spp*
    - *Micrococcus spp*
    - *Corynebacterium spp*
    - *Paenibacillus spp*
    - *Lactobacillus spp*
    - *Propionobacterium spp*

Verway M, Brown KA, Marchand-Austin A, Diong C, Lee S, Langford B, et al. Prevalence and mortality associated with bloodstream organisms: a population-wide retrospective cohort study. J Clin Microbiol. 2022;60(4):e0242921. Available from: https://doi.org/10.1128/jcm.02429-21

Methods

- Aggregated most organisms by genus for ease of display
  - exceptions – some common *Staphylococci* and *Streptococci* reported at species level

- Rates per 100,000 population calculated using Ontario denominator 13,278,784 from RPDB in 2017
- Two comparisons to determine adjusted odds of mortality:
  - compared to patients with negative blood cultures
    - logistic regression (age, sex, location, hospitalized days in last 90d)
    - generalized estimating equations to account for multiple episodes/pt

  - compared to Ontarians without bloodstream infection
    - hard-matching to up to 10 other Ontarians by age (+-2yrs), sex, healthcare location, Deyo-Charlson comorbidity score, days hospitalized in last 90d
    - generalized estimating equations to account for matching

Verway M, Brown KA, Marchand-Austin A, Diong C, Lee S, Langford B, et al. Prevalence and mortality associated with bloodstream organisms: a population-wide retrospective cohort study. J Clin Microbiol. 2022;60(4):e0242921. Available from: https://doi.org/10.1128/jcm.02429-21

Results:
Number of blood culture episodes and bloodstream infections

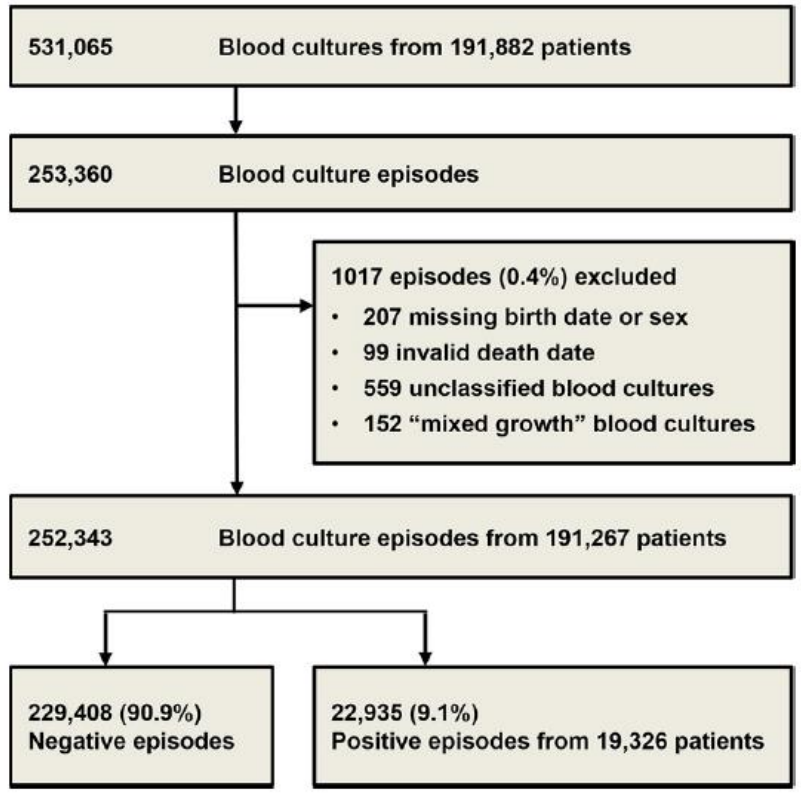


FIG 1 Flow diagram of blood culture data processing. Blood culture data collected was first clustered into episodes, followed by exclusion of episodes for which there was incomplete or incorrect data. Remaining episodes were divided into negative or positive episodes. Percentages are expressed relative to the preceding total.

Verway M, Brown KA, Marchand-Austin A, Diong C, Lee S, Langford B, et al. Prevalence and mortality associated with bloodstream organisms: a population-wide retrospective cohort study. J Clin Microbiol. 2022;60(4):e0242921. Available from: https://doi.org/10.1128/jcm.02429-21

Results:
Characteristics of Ontario patients with bloodstream infection

TABLE 1 Characteristics of patients undergoing blood culture collection and experiencing bloodstream infection episodes

Demographic characteristic	Total culture episodes (n = 252,343)		Positive BSI episodes (n = 22,935)	
	No.	%	No.	%
Age				
0–3 mo	5,810	2.3	188	0.8
3 mo–1 yr	1,934	0.8	65	0.3
1–5 yr	7,648	3.0	176	0.8
6–10 yr	2,998	1.2	76	0.3
11–19 yr	5,531	2.2	194	0.8
20–29 yr	13,493	5.3	790	3.4
30–39 yr	16,997	6.7	1,217	5.3
40–49 yr	19,645	7.8	1,598	7.0
50–59 yr	32,422	12.8	3,088	13.5
60–69 yr	42,187	16.7	4,417	19.3
70–79 yr	45,525	18.0	4,914	21.4
80+ yr	58,153	23.0	6,212	27.1
Sex				
Female	122,520	48.6	10,320	45.0
Male	129,823	51.4	12,615	55.0
Days in hospital[a]				
0	181,857	72.1	15,272	66.6
1–4	19,953	7.9	1,805	7.9
5–9	18,688	7.4	1,988	8.7
10–90	31,845	12.6	3,870	16.9
Location				
Community	85,982	34.1	3,921	17.1
Acute care hospital	117,574	46.6	12,205	53.2
Intensive care unit	45,502	18.0	6,561	28.6
Long-term care	3,285	1.3	248	1.1

[a]Number of days admitted to hospital in the 90 days prior to blood culture collection date.

Verway M, Brown KA, Marchand-Austin A, Diong C, Lee S, Langford B, et al. Prevalence and mortality associated with bloodstream organisms: a population-wide retrospective cohort study. J Clin Microbiol. 2022;60(4):e0242921. Available from: https://doi.org/10.1128/jcm.02429-21

Results: Incidence of top pathogens

Overall rate:

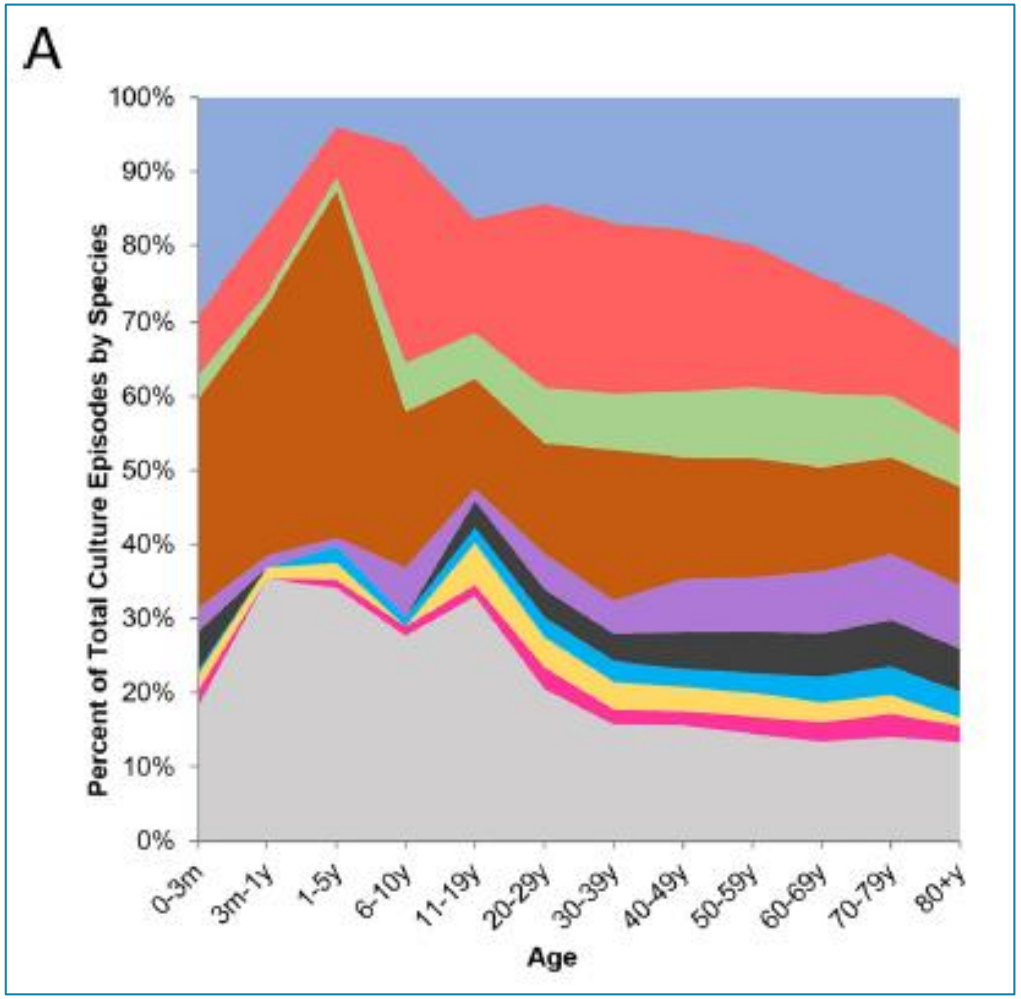
150 episodes/
100,000p/yr

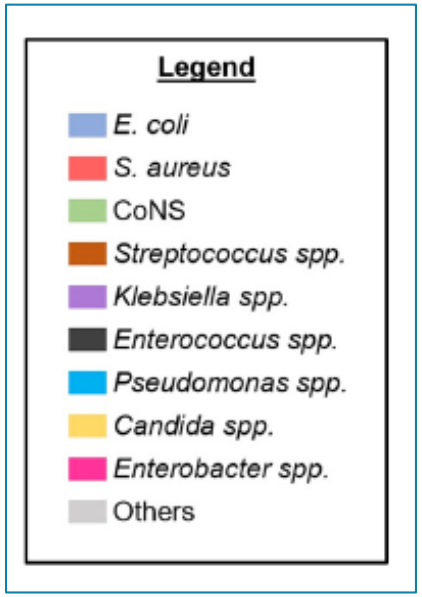
Verway M, Brown KA, Marchand-Austin A, Diong C, Lee S, Langford B, et al. Prevalence and mortality associated with bloodstream organisms: a population-wide retrospective cohort study. J Clin Microbiol. 2022;60(4):e0242921. Available from: https://doi.org/10.1128/jcm.02429-21

TABLE 2 Positive BSI episodes by organism isolated

Organism	Positive BSI episodes (n = 22,935)		Patients (n = 19,326)		Annual rate/100,000 population
	No.	%	No.	%	
Escherichia coli	5,864	26.9	5,450	28.2	40.24
Staphylococci	5,455	25.1			
Staphylococcus aureus	3,455	15.9	3,035	15.7	22.41
Staphylococcus lugdunensis	74	0.3	68	0.4	0.50
Staphylococcus saprophyticus	15	0.1	15	0.1	0.11
Other CoNS	1,911	8.8	1,632	8.4	12.05
Streptococci	3,412	15.7			
Streptococcus pneumoniae	691	3.2	672	3.5	4.96
Streptococcus agalactiae	508	2.3	487	2.5	3.60
Viridans group *Streptococcus*	469	2.2	431	2.2	3.18
Streptococcus pyogenes	438	2.0	415	2.2	3.06
Group G/C *Streptococcus*	329	1.5	312	1.6	2.30
Streptococcus mitis	133	0.6	123	0.6	0.91
Other streptococci	844	3.9	785	4.1	5.80
Klebsiella species	1,794	8.2	1,505	7.8	11.11
Enterococcus species	1,267	5.8	963	5.0	7.11
Pseudomonas species	749	3.4	602	3.1	4.45
Enterobacter species	568	2.6	461	2.4	3.40
Candida species	561	2.6	357	1.9	2.64
Proteus species	394	1.8	369	1.9	2.72
Bacteroides fragilis	292	1.3	268	1.4	1.98
Serratia species	226	1.0	175	0.9	1.29
Haemophilus influenzae	195	0.9	190	1.0	1.40
Bacillus species	171	0.8	136	0.7	1.00
Clostridium species	168	0.8	154	0.8	1.14
Citrobacter species	148	0.7	127	0.7	0.94
Acinetobacter species	128	0.6	106	0.6	0.78
Salmonella non-*Typhi/Paratyphi*	128	0.6	126	0.7	0.93
Actinomyces species	96	0.4	91	0.5	0.67
Stenotrophomonas maltophilia	84	0.4	55	0.3	0.41
Aerococcus species	80	0.4	77	0.4	0.57
Fusobacterium species	78	0.4	73	0.4	0.54
Corynebacterium species	69	0.3	59	0.3	0.44
Salmonella Typhi/Paratyphi	69	0.3	67	0.4	0.49
Morganella species	68	0.3	65	0.3	0.48
Bacteroides species	66	0.3	60	0.3	0.44
Others	813	3.7	737	3.8	5.44

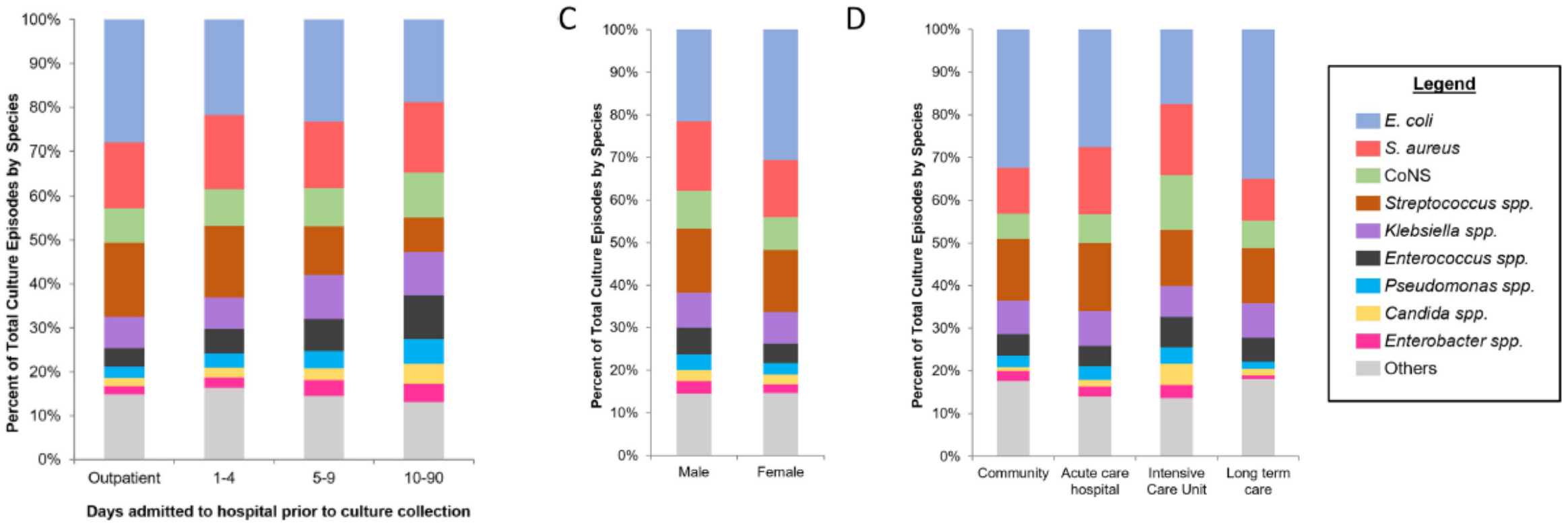
Results:
Top pathogens by age groups





Verway M, Brown KA, Marchand-Austin A, Diong C, Lee S, Langford B, et al. Prevalence and mortality associated with bloodstream organisms: a population-wide retrospective cohort study. J Clin Microbiol. 2022;60(4):e0242921. Available from: https://doi.org/10.1128/jcm.02429-21

Results:
Top pathogens by hospital exposure, sex, location of collection



Verway M, Brown KA, Marchand-Austin A, Diong C, Lee S, Langford B, et al. Prevalence and mortality associated with bloodstream organisms: a population-wide retrospective cohort study. J Clin Microbiol. 2022;60(4):e0242921. Available from: https://doi.org/10.1128/jcm.02429-21

Results:

Crude short-term and long-term mortality rates

Verway M, Brown KA, Marchand-Austin A, Diong C, Lee S, Langford B, et al. Prevalence and mortality associated with bloodstream organisms: a population-wide retrospective cohort study. J Clin Microbiol. 2022;60(4):e0242921. Available from: https://doi.org/10.1128/jcm.02429-21

Supplementary Table 1: Percent Mortality in One Year Following BSI Episodes.

Microorganism	Percent Mortality Following Positive Culture Episodes (%)*				
	7 days	30 days	60 days	90 days	365 days
Staphylococci					
Staphylococcus aureus	13.3	22.8	28.1	30.6	39.7
Staphylococcus lugdunensis	9.5	17.6	20.3	23.0	33.8
Other CoNS	8.7	19.6	25.6	28.6	42.2
Escherichia coli	6.9	12.3	15.7	18.2	27.3
Streptococci					
Streptococcus pneumoniae	9.4	15.3	17.8	19.2	26.2
viridans group streptococcus	7.7	14.1	18.3	20.9	33.5
Streptococcus agalactiae	8.5	14.0	16.9	19.1	28.0
Group G/C Streptococcus	9.7	14.6	16.7	19.5	31.6
Streptococcus pyogenes	11.9	15.5	16.9	18.0	22.8
Streptococcus mitis	7.5	12.8	18.8	21.1	33.1
Other Streptococci species	10.2	16.5	20.7	22.5	32.8
Klebsiella species	9.5	17.6	23.5	26.7	39.6
Enterococcus species	10.7	23.6	31.7	35.8	50.3
Pseudomonas species	14.4	25.0	31.2	33.9	49.7
Enterobacter species	9.2	19.2	23.4	28.0	42.6
Candida species	17.8	31.9	37.6	40.3	57.4
Proteus species	11.4	20.3	25.6	30.2	45.7
Bacteroides fragilis	16.4	25.3	29.5	32.5	42.5
Serratia species	10.2	20.4	25.7	29.2	38.9
Haemophilus influenzae	14.4	19.5	21.5	23.1	29.2
Bacillus species	5.8	13.5	17.0	18.7	26.3

TABLE 3 30-day mortality and adjusted mortality odds ratios by microorganism

Organism	30-day mortality		Mortality OR compared to matched patients without blood culture testing[a]		Mortality OR compared to patients with negative cultures[b]	
	Deaths	% of episodes	Adjusted OR (95% CI)	*P* value	Adjusted OR (95% CI)	*P* value
All positive episodes	3509	17.0	2.62 (2.52, 2.73)	<0.0001	1.47 (1.41, 1.54)	<0.0001
Staphylococci						
Staphylococcus aureus	764	22.8	★ 3.53 (3.23, 3.86)	<0.0001	2.14 (1.94, 2.36)	<0.0001
Staphylococcus lugdunensis	13	17.6	3.39 (1.85, 6.19)	<0.0001	1.69 (0.83, 3.45)	0.1469
Other CoNS	365	19.7	2.62 (2.31, 2.97)	<0.0001	1.36 (1.19, 1.55)	<0.0001
Escherichia coli	699	12.1	1.68 (1.54, 1.83)	<0.0001	0.96 (0.87, 1.05)	0.3270
Streptococci						
Streptococcus pneumoniae	105	15.4	2.49 (1.99, 3.11)	<0.0001	1.46 (1.15, 1.86)	0.0017
Streptococcus agalactiae	70	13.8	2.17 (1.66, 2.84)	<0.0001	1.35 (1.01, 1.79)	0.0397
Viridans group *Streptococcus*	66	14.2	2.18 (1.64, 2.89)	<0.0001	1.33 (0.99, 1.78)	0.0612
Streptococcus pyogenes	66	15.8	★ 3.19 (2.38, 4.28)	<0.0001	1.88 (1.39, 2.54)	<0.0001
Group G/C *Streptococcus*	47	14.5	2.03 (1.45, 2.85)	<0.0001	1.14 (0.81, 1.62)	0.4457
Streptococcus mitis	17	13.0	2.06 (1.24, 3.43)	0.0054	1.23 (0.68, 2.22)	0.4869
Other streptococci species	139	16.7	2.80 (2.31, 3.39)	<0.0001	1.58 (1.28, 1.96)	<0.0001
Klebsiella species	307	17.6	2.20 (1.92, 2.51)	<0.0001	1.32 (1.15, 1.52)	0.0001
Enterococcus species	290	23.6	2.86 (2.46, 3.31)	<0.0001	1.68 (1.44, 1.96)	<0.0001
Pseudomonas species	181	24.7	2.82 (2.36, 3.37)	<0.0001	1.83 (1.50, 2.23)	<0.0001
Candida species	171	32.0	★ 4.51 (3.66, 5.56)	<0.0001	2.40 (1.93, 2.99)	<0.0001
Enterobacter species	109	19.8	2.46 (1.97, 3.08)	<0.0001	1.31 (1.03, 1.68)	0.0286
Proteus species	79	20.7	2.42 (1.84, 3.18)	<0.0001	1.41 (1.07, 1.87)	0.0148
Bacteroides fragilis	73	25.3	4.40 (3.26, 5.95)	<0.0001	2.19 (1.59, 3.00)	<0.0001
Clostridium species	70	41.9	★ 6.94 (4.87, 9.89)	<0.0001	5.81 (4.00, 8.44)	<0.0001
Serratia species	46	20.7	2.76 (1.95, 3.90)	<0.0001	1.30 (0.88, 1.90)	0.1864
Haemophilus influenzae	38	19.5	3.48 (2.41, 5.02)	<0.0001	2.14 (1.40, 3.27)	0.0005
Citrobacter species	22	15.6	2.12 (1.36, 3.30)	0.0010	1.11 (0.67, 1.82)	0.6842
Bacillus species	21	13.1	2.57 (1.53, 4.29)	0.0003	1.20 (0.72, 1.99)	0.4860
Acinetobacter species	19	15.5	2.18 (1.30, 3.67)	0.0033	1.44 (0.82, 2.51)	0.2061
Actinomyces species	19	20.0	3.33 (2.07, 5.36)	<0.0001	2.38 (1.30, 4.34)	0.0049
Stenotrophomonas maltophilia	19	23.2	3.37 (1.87, 6.09)	<0.0001	2.25 (1.20, 4.18)	0.0109
Corynebacterium species	18	27.3	4.64 (2.48, 8.68)	<0.0001	3.00 (1.59, 5.68)	0.0007
Aerococcus species	11	13.9	2.16 (1.09, 4.29)	0.0273	0.94 (0.46, 1.93)	0.8750
Fusobacterium species	10	13.0	3.87 (1.76, 8.51)	0.0008	2.37 (1.11, 5.08)	0.0264

[a]Compared to up to 10 individuals without blood culture testing matched by age, sex, health care location, Charlson comorbidity score, and number of days in hospital in the 90 days prior to blood culture.

[b]Calculated using a generalized linear mixed model (GLMM) adjusting for age, sex, health care location, and number of days hospitalized in prior 90 days.

Results:
Putting it all together to identify biggest public health threats

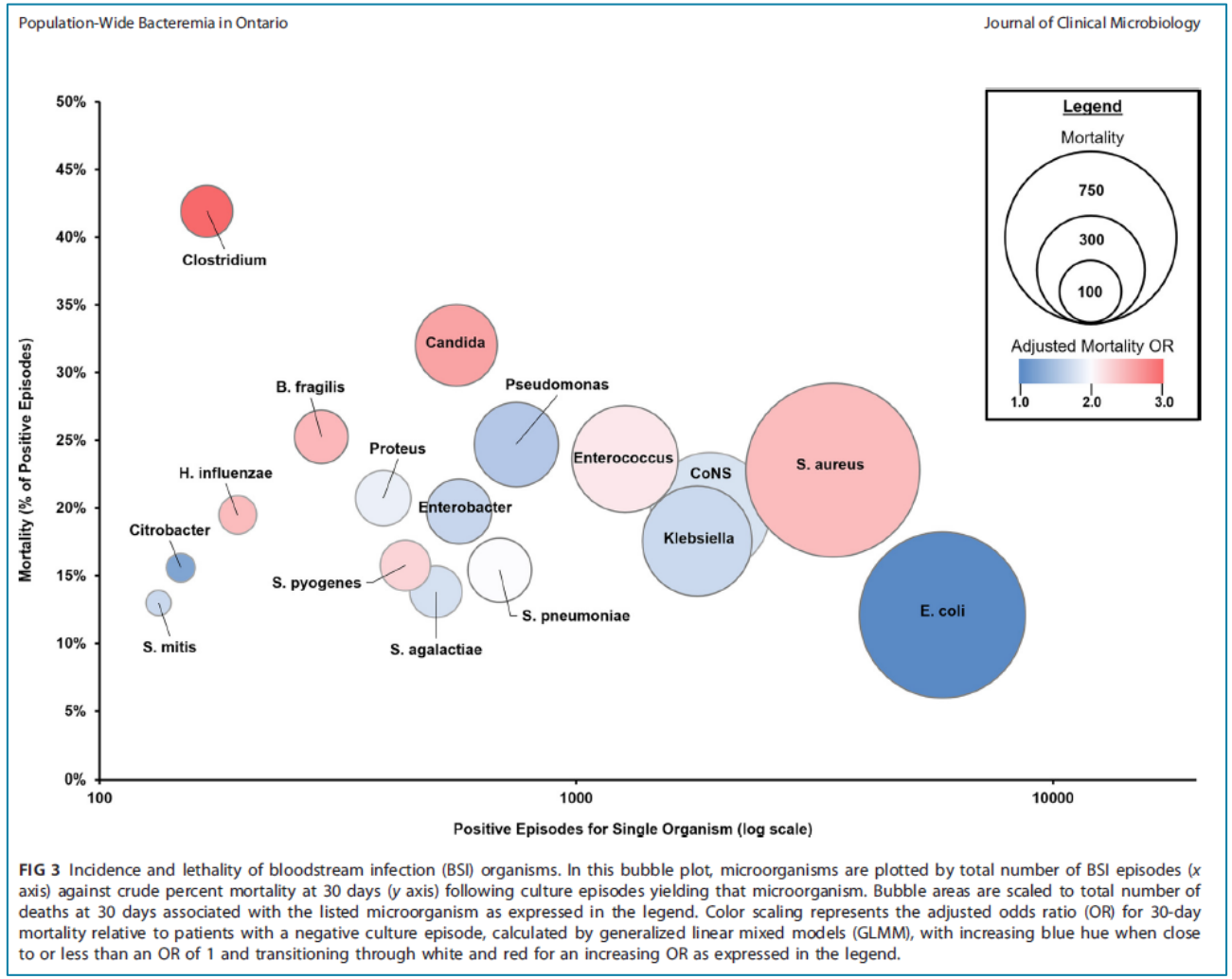


FIG 3 Incidence and lethality of bloodstream infection (BSI) organisms. In this bubble plot, microorganisms are plotted by total number of BSI episodes (*x* axis) against crude percent mortality at 30 days (*y* axis) following culture episodes yielding that microorganism. Bubble areas are scaled to total number of deaths at 30 days associated with the listed microorganism as expressed in the legend. Color scaling represents the adjusted odds ratio (OR) for 30-day mortality relative to patients with a negative culture episode, calculated by generalized linear mixed models (GLMM), with increasing blue hue when close to or less than an OR of 1 and transitioning through white and red for an increasing OR as expressed in the legend.

Verway M, Brown KA, Marchand-Austin A, Diong C, Lee S, Langford B, et al. Prevalence and mortality associated with bloodstream organisms: a population-wide retrospective cohort study. J Clin Microbiol. 2022;60(4):e0242921. Available from: https://doi.org/10.1128/jcm.02429-21

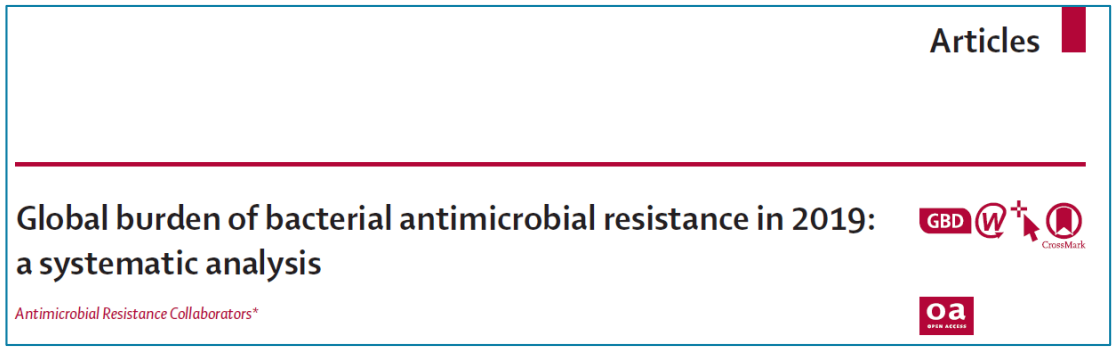
Discussion

- bloodstream infections are common in Ontario
  - >22,000 episodes/year
  - 150/100,000 people/year
- mortality rates are high
  - 1.5-fold adjusted odds of death compared to patients with negative blood cultures
  - 2.6-fold adjusted odds of death compared to matched patients without bloodstream infection
- burden varies according to pathogen
- *Staph aureus* stands out as high burden pathogen across multiple domains

Verway M, Brown KA, Marchand-Austin A, Diong C, Lee S, Langford B, et al. Prevalence and mortality associated with bloodstream organisms: a population-wide retrospective cohort study. J Clin Microbiol. 2022;60(4):e0242921. Available from: https://doi.org/10.1128/jcm.02429-21

Antimicrobial Resistance and Mortality Following *E.coli* bacteremia

Background and Rationale 1 of 3

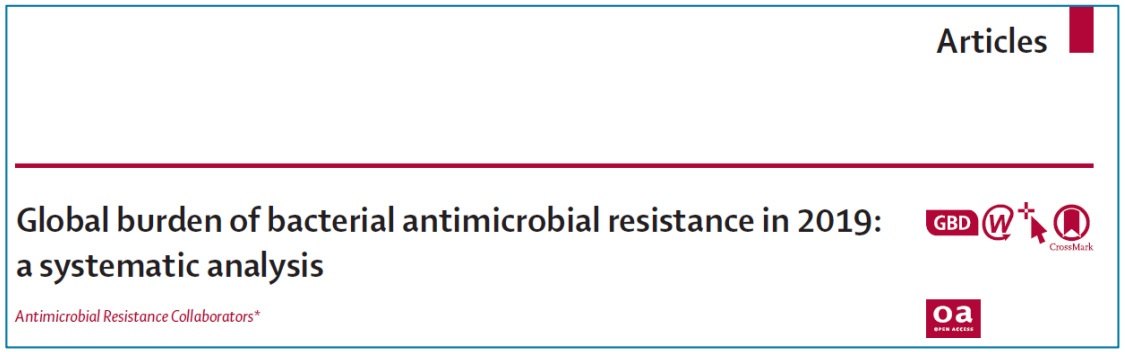


- Antimicrobial Resistance Collaborators
- most comprehensive global estimate of AMR mortality
- calendar year 2019

- estimated deaths and disability-adjusted-life-years attributable to and associated with AMR
- 23 pathogens
- 88 bug-drug combinations
- 204 countries
- 471 million individual records or isolates

Antimicrobial Resistance Collaborators. Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. Lancet. 2022;399(10325):629-55. https://doi.org/10.1016/S0140-6736(21)02724-0

Background and Rationale 2 of 3



- 4.95 million (3.62-6.57) deaths *associated* with bacterial AMR
- 1.27 million (0.91-1.71) deaths *attributable* to bacterial AMR

- E.coli was number one pathogen
  - 829,000 AMR *associated* deaths
  - 219,000 AMR *attributable* deaths

Antimicrobial Resistance Collaborators. Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. Lancet. 2022;399(10325):629-55. https://doi.org/10.1016/S0140-6736(21)02724-0

Background and Rationale 3 of 3

- the Antimicrobial Resistance Collaborators had massive source data (471 million isolates)
- but data was relatively scarce for determining the relative risk of death for drug-resistant compared to drug-sensitive infection
- because most regions are unable to link microbiology results to patient characteristics and outcomes

Objective

- focusing on the most common pathogen (*E.coli*) we examined the extent to which AMR is associated with increased odds of death in the context of a well resourced healthcare system

Methods

- retrospective cohort study
- all Ontarians
- with *E.coli* bacteremia
- 2017-2020

- Data sources as per previous study
  - OLIS
  - CIHI-DAD
  - NACRS
  - OHIP
  - RPDB

Daneman N, Fridman D, Johnstone J, Langford BJ, Lee SM, et al. Antimicrobial resistance and mortality following E. coli bacteremia. eClinicalMedicine. 2022. Forthcoming.

Methods: Antimicrobial resistance

- antimicrobial resistant vs susceptible *E.coli*
- 8 classes of agents
  - aminopenicillins (ampicillin)
  - first generation cephalosporins (cefazolin)
  - third generation cephalosporins (ceftriaxone, ceftazidime)
  - beta-lactam beta-lactamase inhibitors (piperacillin-tazobactam)
  - carbapenems (ertapenem, meropenem)
  - fluoroquinolones (cipro-, levo-, moxifloxacin)
  - aminoglycosides (gentamicin, tobramycin)
  - sulphonamides (trimethoprim-sulfamethoxazole)
- Difficult to treat resistance (DTTR)
  - resistant to carbapenems, fluoroquinolones, and at least one of third generation cephalosporins or beta-lactam beta-lactamase inhibitors

Daneman N, Fridman D, Johnstone J, Langford BJ, Lee SM, et al. Antimicrobial resistance and mortality following E. coli bacteremia. eClinicalMedicine. 2022. Forthcoming.

Methods:
Antimicrobial resistance - The Challenge

- not all laboratories test and report the same panel of antibiotics
- even within a laboratory, reporting might be variably suppressed or released
- this is one of the front-loaded challenges of using routinely available microbiology data

Daneman N, Fridman D, Johnstone J, Langford BJ, Lee SM, et al. Antimicrobial resistance and mortality following E. coli bacteremia. eClinicalMedicine. 2022. Forthcoming.

Methods:
Antimicrobial resistance - Our solution

- rule-based imputation
  - some sensitive (S) results can be inferred by others
    - eg, if ampicillin-S then piperacillin-tazobactam-S
  - some resistance results can be inferred by others
    - eg, if ceftriaxone-R then cefazolin-R

- model-based imputation
  - logistic regression model accounting for overall rate of susceptibility to that antibiotic in the available results
  - as well as age, sex, location, results of other antibiotic classes

Daneman N, Fridman D, Johnstone J, Langford BJ, Lee SM, et al. Antimicrobial resistance and mortality following E. coli bacteremia. eClinicalMedicine. 2022. Forthcoming.

Methods: Primary outcome

- the primary outcome was 90 day mortality (from date of collection of the *E.coli* blood culture)

Daneman N, Fridman D, Johnstone J, Langford BJ, Lee SM, et al. Antimicrobial resistance and mortality following E. coli bacteremia. eClinicalMedicine. 2022. Forthcoming.

Methods: Statistical analysis

- univariable logistic regression to examine crude association between AMR and mortality with resistant versus susceptible *E.coli*
  - 9 separate models for 8 classes + DTTR
- multivariable logistic regression accounting for:
  - age
  - sex
  - setting at time of blood culture (community, ward, ICU, LTC)
  - total days in hospital in prior year
  - total days in ICU in prior year
  - total days in LTC in prior year
  - total physician visits in prior year
  - source of bacteremia (UTI versus other)
  - immunosuppressive illness
  - 18 individual comorbidities

eClinicalMedicine in Revisions 2022

Results

- 14,548 eligible *E.coli* bloodstream infection episodes among 13,706 unique patients
  - community 2,382 (16.4%)
  - hospital wards 10,233 (70.3%)
  - ICUs 1,784 (12.3%)
  - long term care 149 (1.0%)
- median age 74yrs old
- women 55%
- urinary tract sources 47.5%

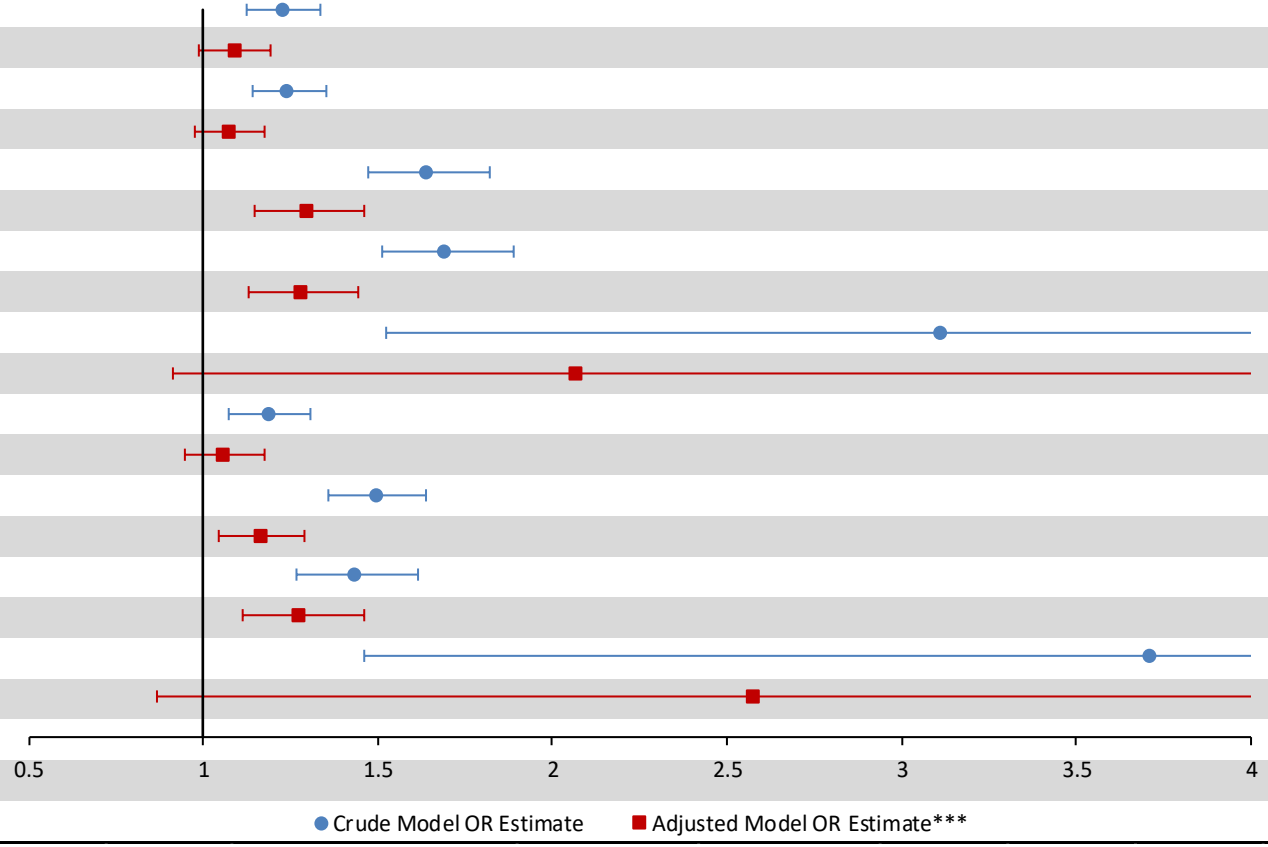
Daneman N, Fridman D, Johnstone J, Langford BJ, Lee SM, et al. Antimicrobial resistance and mortality following E. coli bacteremia. eClinicalMedicine. 2022. Forthcoming.

Results:
Antibiotic resistance rates among E.coli bloodstream infections

Daneman N, Fridman D, Johnstone J, Langford BJ, Lee SM, et al. Antimicrobial resistance and mortality following E. coli bacteremia. eClinicalMedicine. 2022. Forthcoming.

Results:
Odds of mortality associated with AMR

Antibiotic Class-Specific Resistance	OR	95% CI	
Aminopenicillin	1.22	1.12	1.33
	1.09	0.99	1.19
First Gen. Cephalosporin	1.24	1.14	1.35
	1.07	0.97	1.18
Third Gen. Cephalosporin	1.64	1.47	1.82
	1.29	1.15	1.46
Beta-lactam Beta-lactamase Inhibitor	1.69	1.51	1.89
	1.28	1.13	1.44
Carbapenem	3.11	1.52	6.34
	2.06	0.91	4.66
Sulfonamide	1.18	1.07	1.31
	1.06	0.95	1.18
Fluoroquinolone	1.49	1.36	1.64
	1.16	1.05	1.29
Aminoglycoside*	1.43	1.27	1.62
	1.27	1.11	1.46
Difficult to Treat Resistance**	3.71	1.46	9.41
	2.58	0.87	7.66



Daneman N, Fridman D, Johnstone J, Langford BJ, Lee SM, et al. Antimicrobial resistance and mortality following E. coli bacteremia. eClinicalMedicine. 2022. Forthcoming.

Discussion

- antimicrobial resistance surveillance can harness routinely available data from microbiology laboratories
- the main challenge is that not all labs report the same panel of antibiotics for all patients
- this can be overcome with rule-based and model-based imputation

Daneman N, Fridman D, Johnstone J, Langford BJ, Lee SM, et al. Antimicrobial resistance and mortality following E. coli bacteremia. eClinicalMedicine. 2022. Forthcoming.

Discussion

- AMR has not yet progressed in Ontario to the extent that we don't have effective therapeutic options for patients
  - eg, *E.coli* Carbapenem resistance 0.2%
  - eg, *E.coli* Difficult to treat resistance 0.1%

- but *E.coli* resistance is substantial for our most commonly used empiric agents
  - third generation cephalosporins 13.8%
  - beta-lactam beta-lactamase inhibitors 9.1%
  - fluoroquinolones 26.5%

Daneman N, Fridman D, Johnstone J, Langford BJ, Lee SM, et al. Antimicrobial resistance and mortality following E. coli bacteremia. eClinicalMedicine. 2022. Forthcoming.

Discussion

- AMR is associated with increased mortality for patients with *E.coli* bloodstream infection
  - especially for agents commonly used in empiric treatment
- adjustment for patient characteristics and prior healthcare utilization leads to attenuation in the association of AMR and mortality
- under-adjustment for these factors means most literature over-estimates the current burden of AMR
- nevertheless, AMR is already associated with substantial mortality risk

Daneman N, Fridman D, Johnstone J, Langford BJ, Lee SM, et al. Antimicrobial resistance and mortality following E. coli bacteremia. eClinicalMedicine. 2022. Forthcoming.

Future Work of the COMBAT-AMR Project

Objective

- To estimate the public health impact of antibiotic resistance in Ontario, across all pathogens and resistance profiles

Methods

- Population
  - 46 bacteria (31 Gram-negative and 15 Gram-positive)
- Exposures
  - 16 antibiotics per bacterium
  - 761 bacterium-antibiotic pairs
- Outcome
  - 90-day mortality
  - 30-day mortality

Methods

- Statistical analysis
  - Measure risk ratio for each bacteria-antibiotic pair and for each form of multidrug resistance
  - How to combine appropriately (due to variable prevalence)?
- Antimicrobial Resistance Impact Index
  - Leveraging the risk ratio, measure the population attributable fraction
  - Measure the incidence of mortality as if everyone had a susceptible infection (I_S)
  - Measure the incidence rate of mortality as if everyone had a observed resistance pattern infection (I_{asis})

Summary

- millions of routine microbiology testing results are unharnessed in individual laboratory archives

- amalgamating this data requires a large amount of up-front work
  - cleaning, imputing, linking to administrative datasets, …

- but this is an essential effort to COMBAT the global public health threat of antimicrobial resistance

Summary

- centralized population-wide microbiology data linked to clinical datasets provides
  - comprehensive information on pathogens and resistance
  - not limited to sentinel/voluntary hospital sites
  - spans across acute care, long term care, and community
  - offers potential for timely surveillance at facility, regional and provincial level
  - the linkage to clinical datasets at ICES provides, has the potential to make Ontario an epicentre of AMR research and surveillance

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  - Beate Sander
- COMBAT AMR ICES analytic team
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  - Samantha Lee
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  - Kwadwo Mponponsuo
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  - PHAC/NML

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