

Antimicrobial Resistance and Nosocomial Pathogens in Canada May 30th, 2023

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Adjunct Professor, University of Manitoba, Medical Microbiology and Infectious Disease



Conflicts of Interest

None

Overview

- Antimicrobial Resistance and Nosocomial Infections (ARNI)
- AMR Surveillance

Genomics

New AMR Surveillance Initiatives

ARNI Reference Services

- Confirmatory testing (phenotypic and genotypic)
 - Identification of rare or novel resistance mechanisms
 - Testing for new antimicrobials
 - Passive surveillance
- Outbreak investigation support
 - WGS for hospital outbreaks
 - Advice to hospital/provincial/federal epidemiologists and microbiologists
 - Support to other countries
- Proficiency Testing and Standards

ARNI Basic and Applied Research

Characterization of novel resistance mechanisms

- Development of assays to rapidly identify and type pathogens from specimens
- Whole genome sequencing to better understand transmission routes

- Genetic mechanisms of epidemic strains
 - Genomic and proteomic studies

ARNI Surveillance

- Canadian Nosocomial Infection Surveillance Program (CNISP)
- Canadian Integrated Program for Antimicrobial Resistance Surveillance (CIPARS)
- AMRNet
- Carbapenemase-Producing Organisms CPHLN
- CANWARD
- Neisseria gonorrhoeae
- Streptococcus
- Wastewater

PHAC AMR Priority Organisms 2020

- Methicillin-resistant Staphylococcus aureus
- Vancomycin-resistant *Enterococcus*
- Carbapenemase-producing Enterobacterales
- Clostridioides difficile
- Neisseria gonorrhoeae
- Mycobacterium tuberculosis (different NML Lab, Hafid Soulahine)
- Streptococcus pneumoniae
- Streptococcus pyogenes
- Typhoidal and non-typhoidal Salmonella enterica
- Acinetobacter species
- Campylobacter species
- Escherichia coli

https://www.canada.ca/en/public-health/services/publications/drugs-health-products/canadian-antimicrobial-resistance-surveillance-system-2020-report.html

Overview

 Life in the Antimicrobial Resistance and Nosocomial Infections Unit (ARNI)

AMR Surveillance

Genomics

New AMR Surveillance Initiatives

Canadian Nosocomial Infection Surveillance Program (CNISP)

CNISP is a collaboration between the

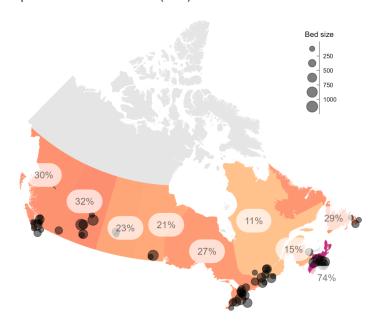
- □ Public Health Agency of Canada (PHAC) including the National Microbiology lab (NML)
- Association of Medical Microbiology and Infectious Disease (AMMI)
 Canada
- Sentinel hospitals across Canada

In 2022, CNISP has expanded to include 88 hospitals in 10 provinces and 1 territory including rural, community and northern hospitals

In 2023, potential expansion to 110 hospitals

Overview of CNISP

Participating CNISP sites in 2009 Proportion of acute care beds (27%)



Current CNISP Surveillance Projects

 Clostridioides difficile infection (CDI)

Cerebrospinal fluid shunt SSI

- Methicillin-resistant Staphylococcus aureus (MRSA) bloodstream infection (BSI)
- Pediatric Cardiac SSI

- Methicillin-susceptibile Staphylococcus aureus (MSSA) BSI
- Candida auris

 Vancomycin-resistant enterococci (VRE) BSI Carbapenemase-producing organisms (CPO)

Central Line-Associated Bloodstream Infections (CLABSI)

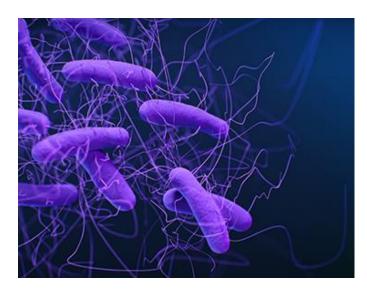
Antimicrobial Use

- Hip and knee Surgical Site Infections (SSI)
- Antibiogram

Point prevalence surveys

Viral Respiratory Infections (VRI) - COVID-19

CNISP surveillance of Clostridioides difficile infection (CDI)



https://www.cdc.gov/hai/organisms/cdiff/cdiff_infect.html

- 2004-2005 Pilot study
- HCA-CDI surveillance since 2007
- CA-CDI since 2015
- Stool samples submitted March+April for adult (year round for Peds)
- Primary *C. difficile* isolation
- AST (Etest)
- Toxin PCR
- Ribotyping (replaced PFGE 2018)
- Moving into WGS 2022



Clostridioides difficile infection (CDI)

Communityassociated CDI



Range: 1.57-1.83 per 10,000 PD

Healthcareassociated CDI



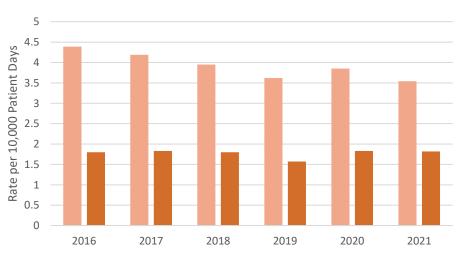
24%

CDI attributable mortality



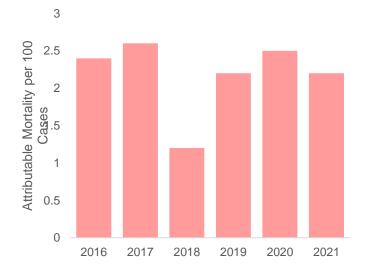
Range: 1.2%-2.6%

Inpatient healthcare-associated (HA) & community-associated (CA) CDI rates



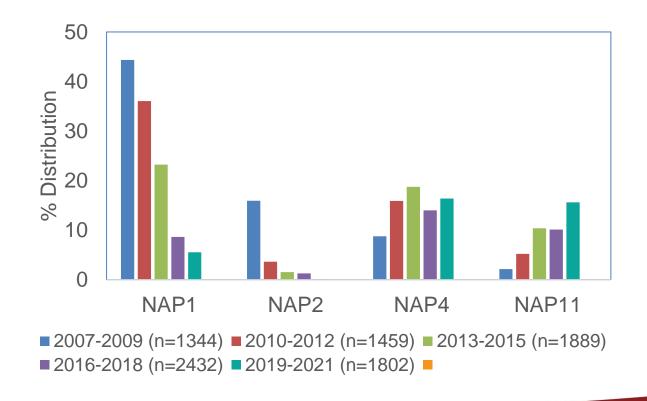
■ Healthcare-associated ■ Community-associated

CDI attributable mortality



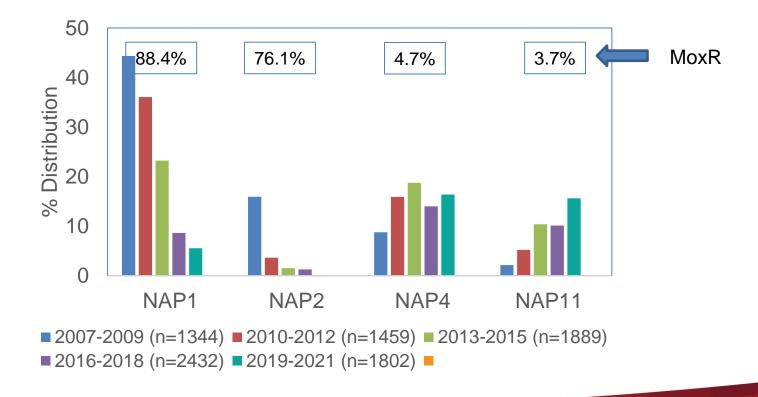


Changing Molecular Epidemiology of *C.difficile* 2007-2021





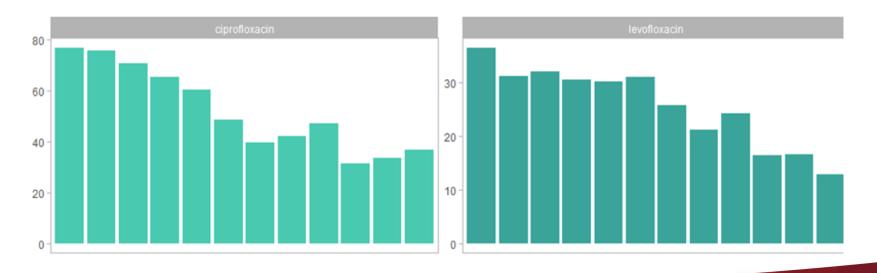
Declining Fluoroquinolone Resistant Strain Types and Emerging Susceptible Types



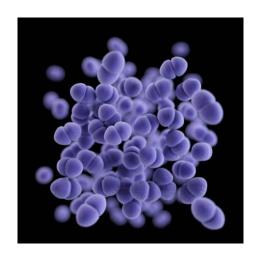
CNISP: Antibiotics with the greatest absolute decreases

Stewardship highlight for C. difficile NAP1

Rate of AMU per 1,000 patient days/ Taux d'AMU pour 1 000 jours-patients

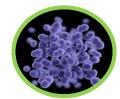


Vancomycin Resistant Enterococci (VRE) bloodstream infection (BSI)



CDC/Dan Higgins - Medical Illustrator, 2013

- Surveillance of infections and colonizations since 1999
- Surveillance of only BSI beginning 2018
- AST sensititre
- Van PCR
- WGS (all to be sequenced)



Vancomycin Resistant Enterococci (VRE) bloodstream infection (BSI)

Healthcare-associated VRE



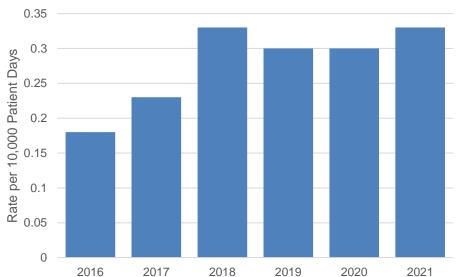
83%

VRE all-cause mortality

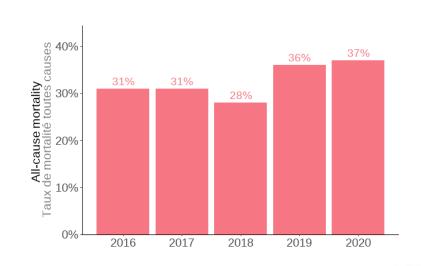


Range: 28%-37%

Inpatient healthcare-associated (HA) VRE rates

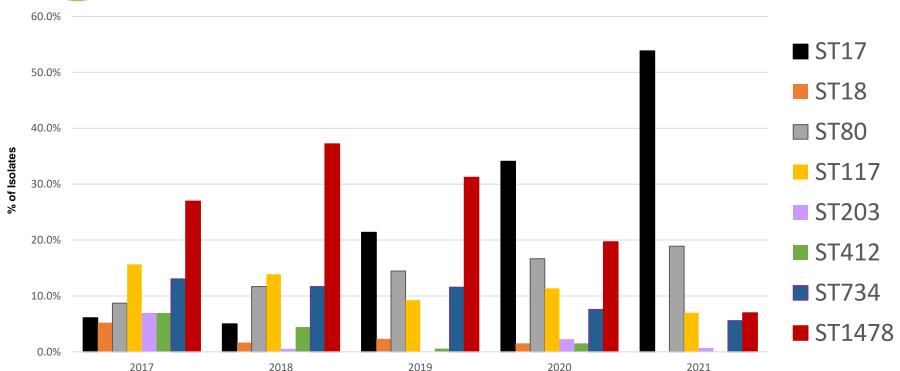


VRE all-cause mortality

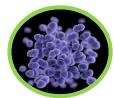




Distribution of VRE Sequence Type by Year, 2017-2021

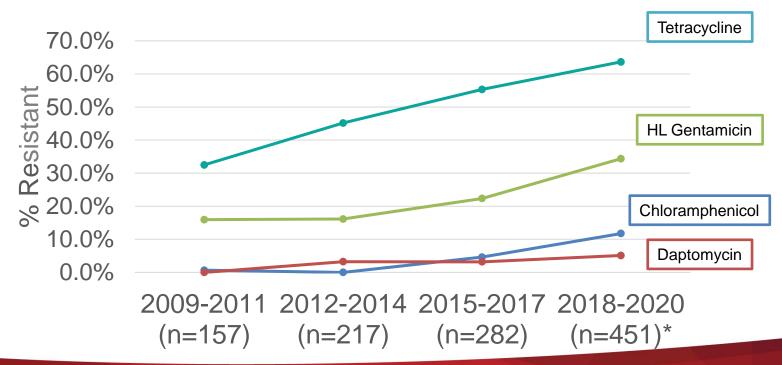


AMMI/CACMID 2023 P033 McCracken et al.

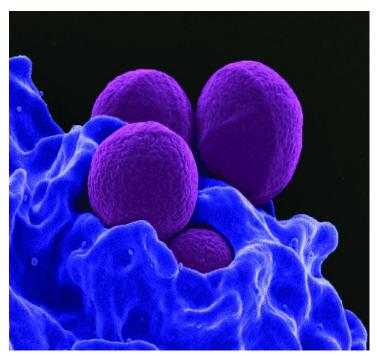


Vancomycin Resistant Enterococci (VRE) bloodstream infection (BSI)

Increasing Antimicrobial Resistance Trends in VRE



CNISP Surveillance of MRSA bloodstream infection (BSI)



NIAID https://doi.org/10.1371/journal.pbio.2003775.g002

- Surveillance since 1995
 - Previously included colonization and other infections
 - Currently just BSI (2018 on)
- Surveillance year round
- AST (Sensititre)
- rtPCR (mec, nuc, PVL)
- Spa typing (2008+)
- PFGE
- Moving into WGS 2022



Methicillin-resistant Staphylococcus aureus (MRSA) bloodstream infection (BSI)

Communityassociated MRSA



69.4%

Healthcareassociated MRSA



Range: 0.43-0.50 per 10,000 PD

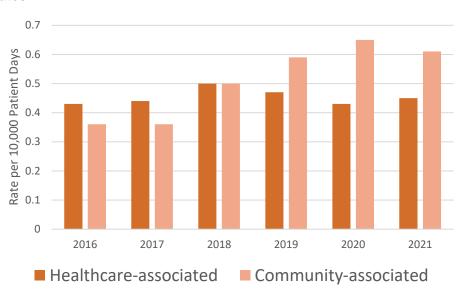
MRSA all-cause mortality

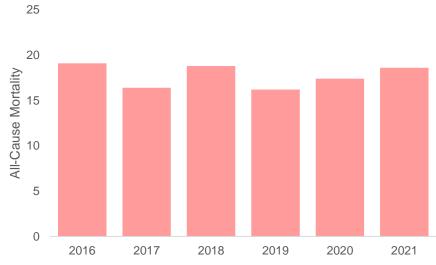


Range: 16.2%-18.8%

Inpatient healthcare-associated (HA) & community-associated (CA) MRSA rates

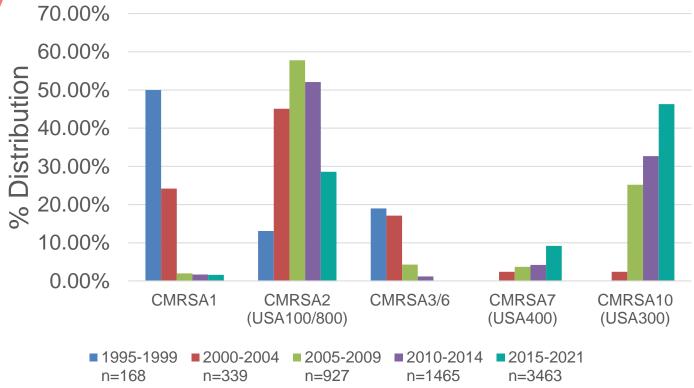






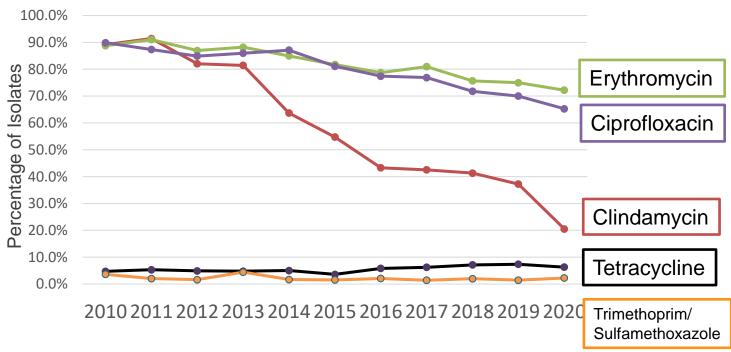


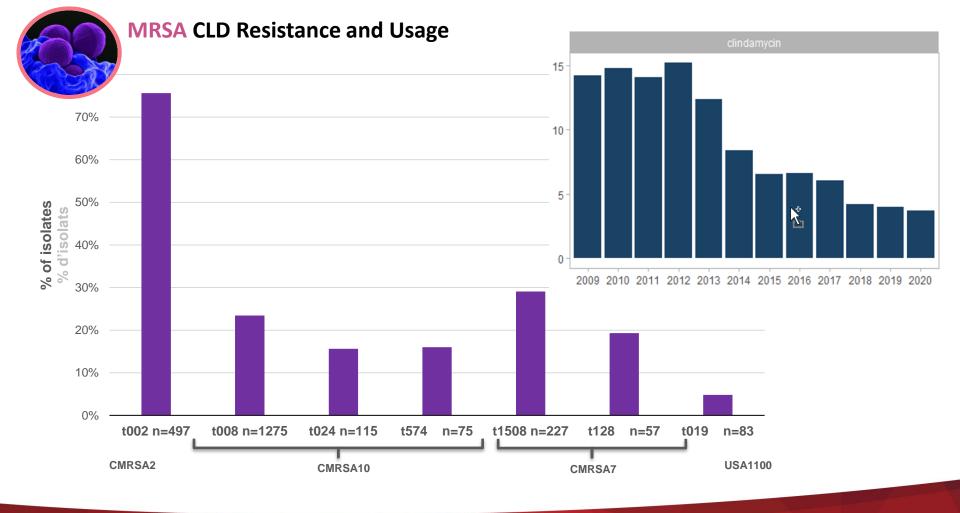
National Distribution of Select Canadian MRSA Epidemic Strains from Bacteremia Cases (CNISP, 1995-2021)





Trends in MRSA AMR



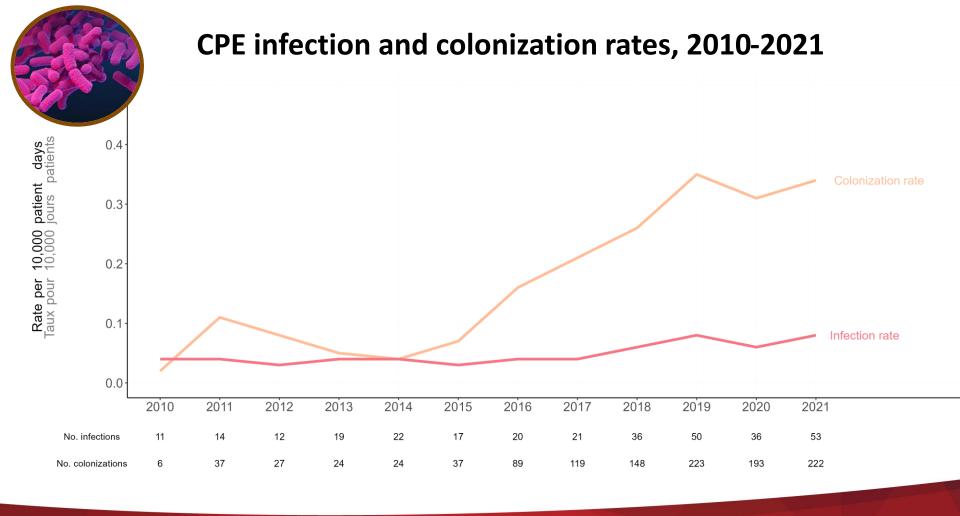


CNISP surveillance of Carbapenemase-producing *Enterobacterales* (CPE)



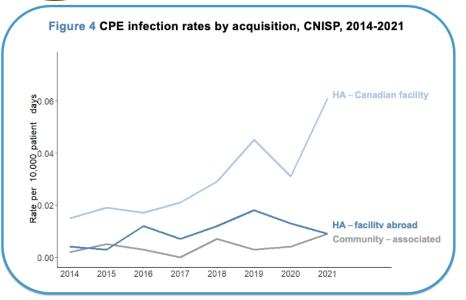
Stephanie Rossow, Centers for Disease Control and Prevention/Antibiotic Resistance Coordination &

- Surveillance of CPE infections and colonizations since 2010
- Select Environmental
- WGS
- **AST Sensititre**





CNISP CPE Surveillance



AMMI/CACMID 2023, P036 R. Mitchell et al.; P042 L. Matasje et al.



32% (96/300) reported international travel in the 12 months prior to positive culture



27% (80/294) received healthcare while abroad, most commonly in South Asia (46%, 33/71)



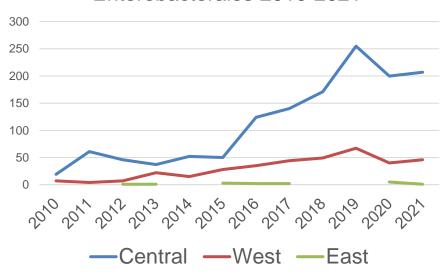
24% of inpatients (67/285) were in an **intensive care unit** at the time of positive culture or were admitted following positive culture

17%
30-day all-cause mortality

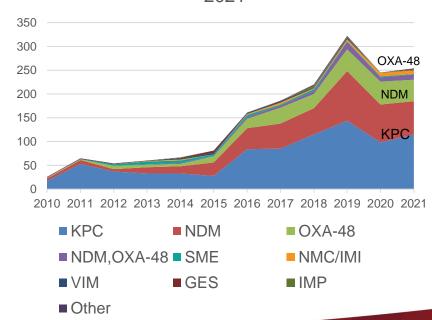


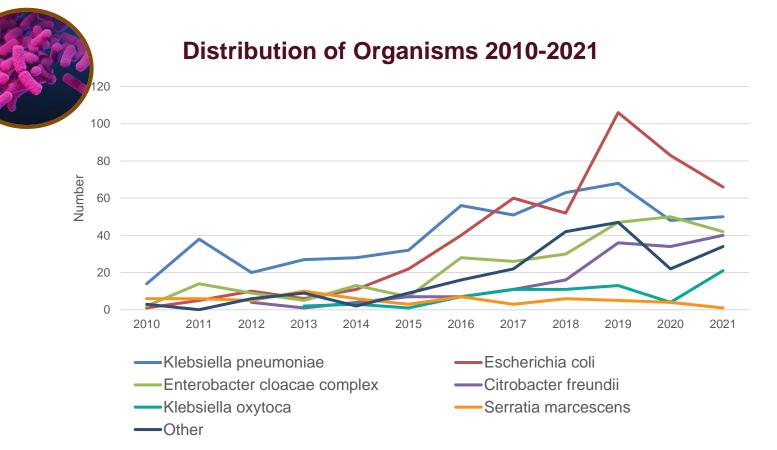
CPE

Total Carbapenemase Producing Enterobacterales 2010-2021



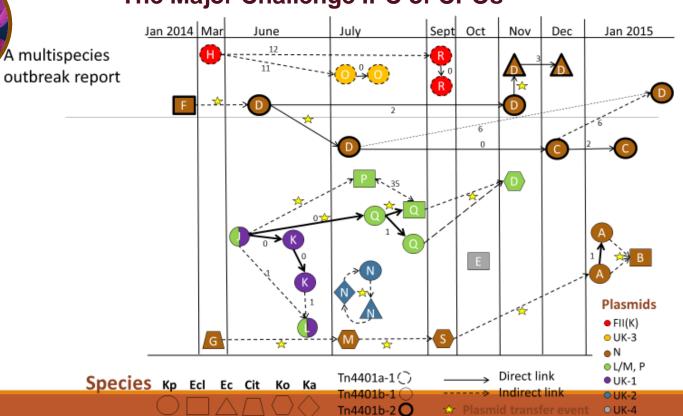
All Carbapenemases Reported 2010-2021



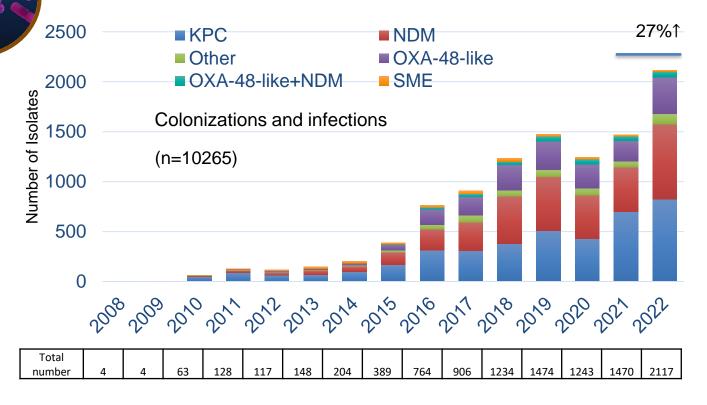


Similar to some Provincial reports there is a decline in E.coli

The Major Challenge IPC of CPOs



CPE in Canada: CPHLN Data. L. Mataseje





CIPARS: Carbapenemase Surveillance Drs. Amrita Bharat and Audrey Charlebois

- Only Canadian human case S. London OXA-48, NB, travel history to Morocco (2018)
- Only Canadian animal case S. London IMP-64 clinical pig isolates MB (2016)

Imported Seafood 2,584 samples screened 10 CPE identified (2011-15)

| Gene Description | Speciation | n | Origin of sample (n) | Sample Types |
|---|---|--------|--------------------------------|-------------------------------|
| $bla_{ m NMC}$ | Enterobacter cloaceae Enterobacter aerogenes | 2 1 | Vietnam (2); Bangladesh (1) | CIPARS retail shrimp n=832 |
| $bla_{ m VCC}$ | Vibrio cholerae | 2 | India (2) | |
| | | | | Niche market seafood |
| $bla_{	ext{NDM},}bla_{	ext{TEM},}bla_{	ext{OXA-1}} \ bla_{	ext{NMC}}$ | Enterobacter cloaceae Enterobacter cloaceae | 2 3 | Vietnam (2) Vietnam (3) | Clams n=101 |

Janecko et al., 2016 Emerg Infect Dis 22:1675-77 Mangat et al., 2016 AAC 60:1819-25

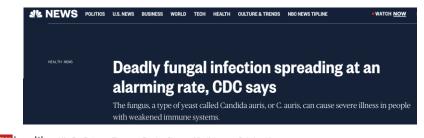
Candida auris – Dr. Amrita Bharat



Potentially deadly fungus spreading rapidly in US health care facilities

Cases of Candida auris doubled in 2021, according to a new CDC report.





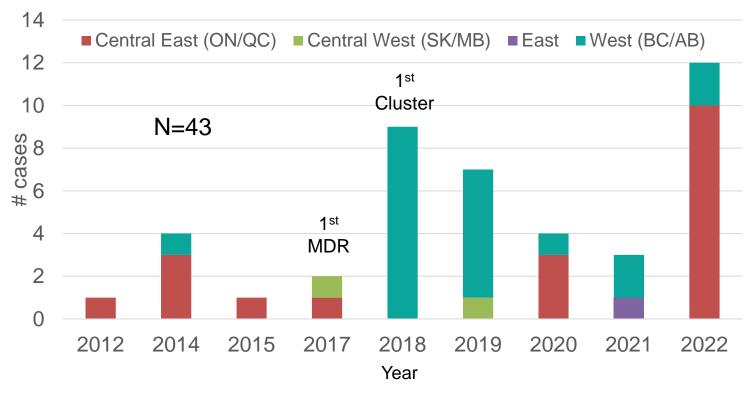


By Janelle Chavez, CNN
Published 5:01 PM EDT. Mon March 20, 2023



Doctors are warning about the emerging threat of Candida auris, a deadly fungal infection that resists treatment and tends to thrive in hospital settings and long-term care facilities.

Number of *C. auris* cases in Canada, 2012-2022



Schwartz and Hammond. Can Commun Dis Rep. 2017; 43:150-153.

Rapid Response to MDR C. auris in Canada

CANWARD Mycology Surveillance Drs. Jeff Fuller and George Zhanel Ended 2016



2017 Canadian Nosocomial Infection Surveillance Program (CNISP) *C. auris* Interest Group



~45 participating hospitals

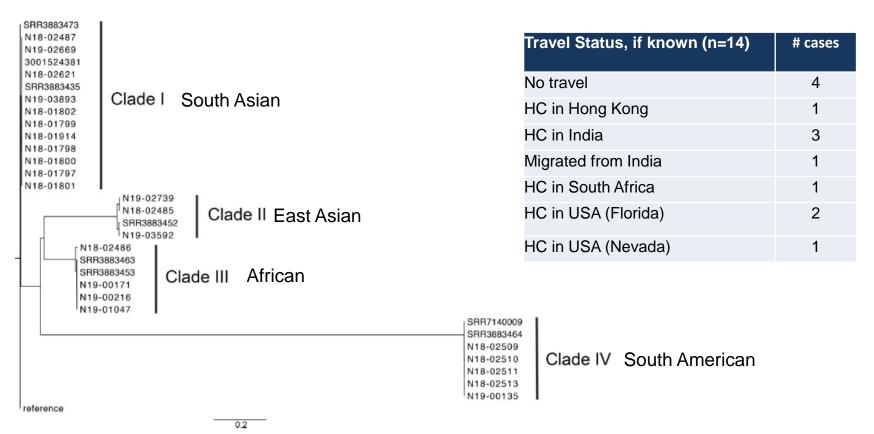


2017 Canadian Public Health Laboratory Network (CPHLN) Mycology Working Group

Co-led by Philippe Dufresne and Amrita Bharat

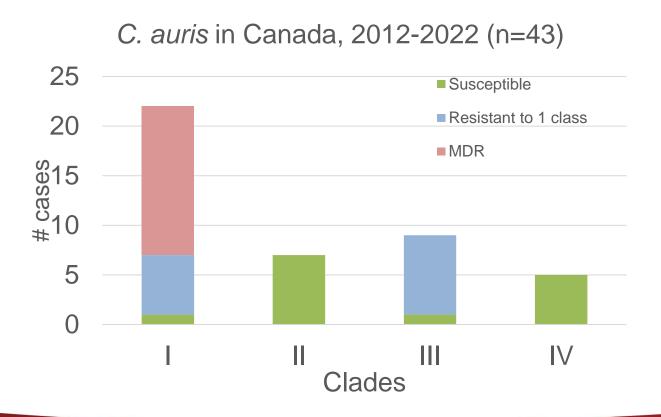
Linda Hoang, BC Centres for Disease Control, BC Tanis Dingle, Alberta Health Services, AB Kathy Malejczyk, Saskatchewan Shared Health, SK David Alexander, Cadham Provincial Laboratory, MB Julianne Kus, Public Health Ontario, ON Caroline Sheitoyan-Pesant, Centre Hospitalier Universitaire Dr Georges-L.-Dumont, NB David Haldane, QEII Health Science Centre, NS Lei Jiao, Eastern Health, NL Greg German, Health PEI, PEI

Genomic Clades of *C. auris*



D. DeLuca et al. 2022. Medical Mycology. 60:myab079. doi: 10.1093/mmy/myab079

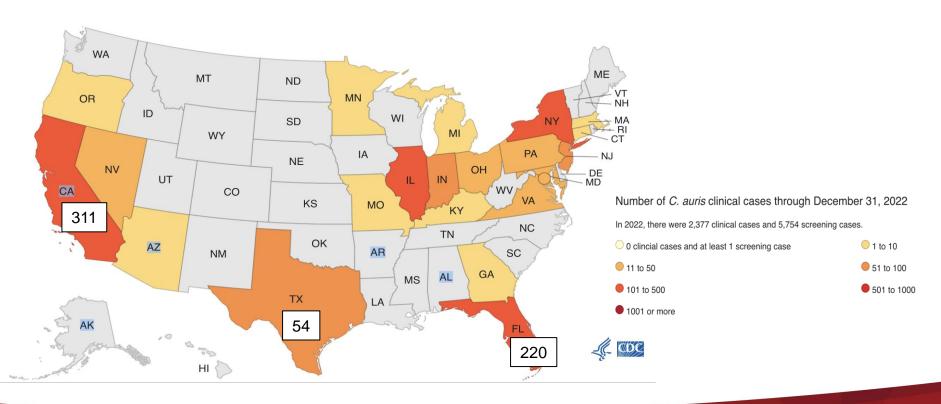
Antifungal resistance was associated with clades I and III



~ one-third of isolates each were resistant to

- 0 classes (susceptible)
- 1 class (azoles)
- 2 classes (azoles and Amphotericin B) MDR
- All MDR isolates were in clade I

USA C. auris cases in 2022



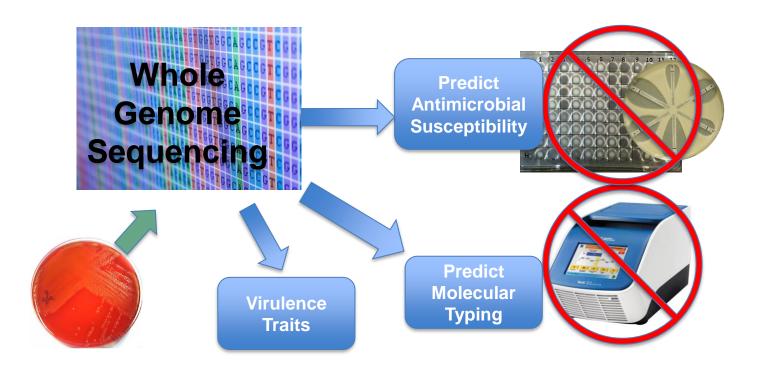
Overview

- Life in the Antimicrobial Resistance and Nosocomial Infections Unit (ARNI)
- AMR Surveillance

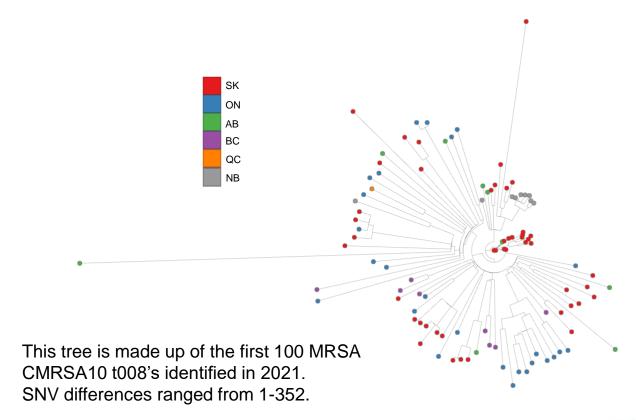
Genomics

New AMR Surveillance Initiatives

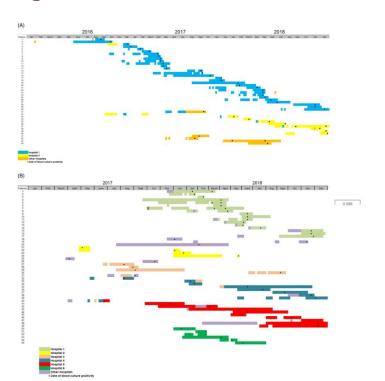
The Transition to Whole Genome Sequencing

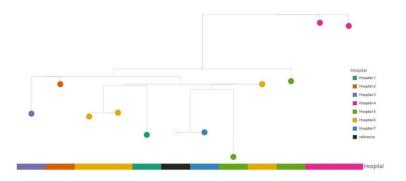


WGS vs traditional spa typing for MRSA



Emergence of VRE ST1478





Evidence of both intrahospital and regional interhospital spread.

Kleinman DR et al. Infect Control Hosp Epidemiol. 2023 Jan;44(1):17-23.

ARNI Genomics

- Isolates being sequenced and/or analysed at ARNI for surveillance:
 - All human Salmonella isolates sequenced by PulseNet Canada and Enteric Disease Program
 - Most Salmonella food and animal isolates
 - All CNISP VRE (1999-present) and MRSA (2018-present) blood isolates, C. difficile (on-going), and all CNISP CPE and CPA (2010 onward)
 - All N. gonorrhoeae being sequenced (Nov 2022 onward)
 - All S. pneumoniae and Group A Strep (Nov 2022 onward)
 - All C. auris sequenced
- Also sequencing all outbreak isolates submitted to ARNI
- Vision is to sequence all isolates submitted to ARNI Lab
- Incorporating machine learning into our bioinformatics tools (AMR prediction and surveillance/outbreak analysis)

Genomics AMR Prediction

- Predicting AMR for surveillance:
 - Salmonella harmonized with NARMS USA Program
 - S. pneumoniae
 - N. gonorrhoeae
 - Build safeguards to detect new resistance mechanisms
- Studies for predicting AMR
 - Escherichia coli (SIR validation)
 - Campylobacter (SIR validation)
 - Pseudomonas aeruginosa
 - Enterococcus spp.
 - MRSA

Genomics Clinical Diagnostics



Contents lists available at ScienceDirect

journal homepage: www.elsevier.com/locate/ygeno



Genomics

J Antimicrob Chemother doi:10.1093/jac/dkx067

Journal of **Antimicrobial** Chemotherapy

WGS to predict antibiotic MICs for Neisseria gonorrhoeae

David W. Eyre^{1-3*}, Dilrini De Silva¹⁻³, Kevin Cole^{4,5}, Joanna Peters^{4,5}, Michelle J. Cole⁶, Yonatan H. Grad^{7,8}, Walter Demczuk⁹, Irene Martin⁹, Michael R. Mulvey⁹, Derrick W. Crook^{1-3,5}, A. Sarah Walker¹⁻³. Tim E. A. Peto¹⁻³ and John Paul^{2,4,5}



MECHANISMS OF RESISTANCE



Equations To Predict Antimicrobial MICs in Neisseria gonorrhoeae Using Molecular Antimicrobial Resistance Determinants

Walter Demczuk,^a Irene Martin,^a Pam Sawatzky,^a Vanessa Allen,^b Brigitte Lefebvre,^c Linda Hoang,^d Prenilla Naidu,^e Jessica Minjon, Paul VanCaeseele, David Haldane, David W. Evre, U.K. Michael R. Mulvey





Linear Regression Equations To Predict β -Lactam, Macrolide, Lincosamide, and Fluoroquinolone MICs from Molecular Antimicrobial Resistance Determinants in Streptococcus pneumoniae

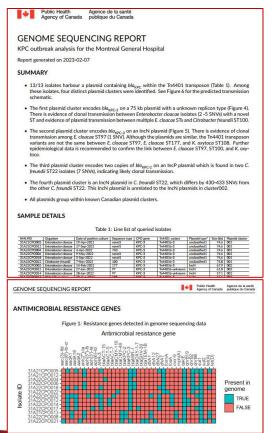
💿 Walter Demczuk,* Irene Martin,* Averil Griffith,* Brigitte Lefebvre,^b Allison McGeer,¢ Gregory J. Tyrrell,⁴ 💿 George G. Zhanel,* 😊 Julianne V. Kus, ^{6,8} Linda Hoang, ⁵ Jessica Minion, ¹ Paul Van Caeseele, ¹ Rita Raafat Gad, ^k David Haldane, ¹ George Zahariadis, ⁵ Kristen Mead," Laura Steven, Lori Strudwick, Michael R. Mulvey

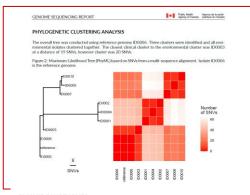


Identification of bacterial and fungal pathogens directly from clinical blood cultures using whole genome sequencing



ARNI Nosocomial Outbreak Reports





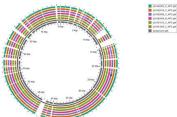
PLASMID PANGENOMES

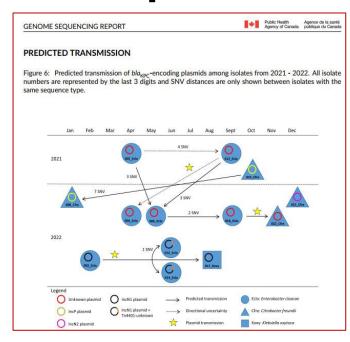
Plasmid coding sequence content was compared within each plasmid cluster by creating a pangenome plot of all genes found within each plasmid. Core genes are present within each plasmid whereas variable accessory genes present only in select isolates will be indicated by gaps. The pangenome of the bla_{KPC-3}-encoding plasmids in cluster001 are shown in Figure 4. Plasmid CDSs are

identical except for two IS3 family transposases from 10.7 kb - 12.1 kb in 31A22CPO022. The pangenome of the bla_{KPC-3} -encoding IncN plasmids in cluster002 are shown in Figure 5. Plasmid CDSs

are identical except for a 10 kb island from 27.5 - 38 kb containing duplicates of folP, emrE, pspF, and yghA found in 31A22CPO002 and 31A22CPO017.

Figure 4: Plasmid pangenome analysis for blagge-a-encoding 75 kb plasmids with unclassified replicon type





Collaboration with Dr. Hoang BCCDC

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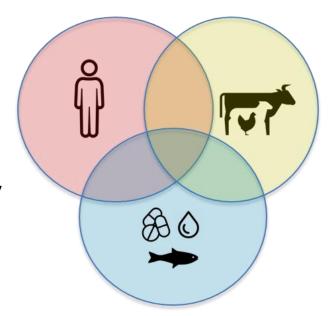
Genomics

New AMR Surveillance Initiatives



Drs. Wallice Rudnick, Shamir Mukai, and Michael Mulvey

- PHAC-funded lab-based AMR surveillance program under development
- Collaboration between PHAC, provincial/territorial public health, and human/animal labs
- Captures existing information on antimicrobial susceptibility testing from human clinical and veterinary labs
- Includes all bacterial and fungal organisms
- One-health, integrated approach



AMRNet*

Where we are now....

CCDR overview & publication of **AMRNet data in CARSS Report**

Daily automatic data transfers



16.7 million human & 200K vet results

AMRNet webpage

https://health-infobase.canada.ca,amrnet/ https://sante-infobase.canada.ca/resram/



Agreements with 6 provinces/territories



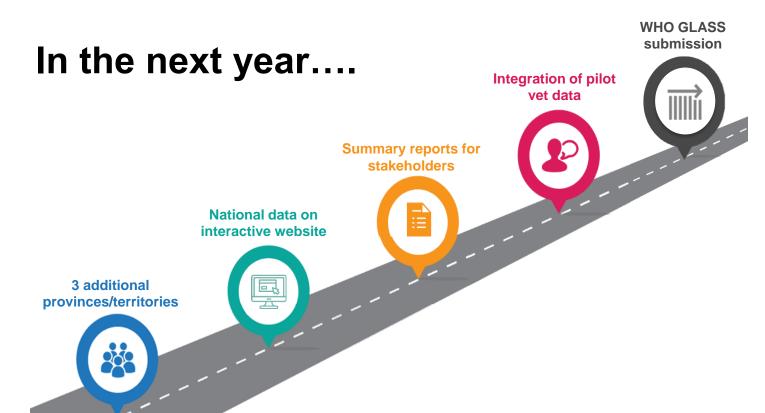




Overview of Canada's Antimicrobial Resistance Network (AMRNet): A data-driven One Health approach to antimicrobial resistance surveillance

Rudnick et al. 2022 48:522-28





AMRITECTION Mock Data Antimicrobial Susceptibilty Testing Summary PHAC AMRNet 08 March, 2023 E. coli Please note that displicates have been removed for all analyses presented here. Between 2016 and 2021, data on 10,000 E. coli isolates were submitted and included in the analysis below. De-duplication method: Only the 1st E. col isolate from a given patient in a given calendar year is included.

The percent of isolates tested represents the percent of isolates in a category with any susceptibility testing results that have been tested for the specific antimicrobial or combination. AMRNet does not collect information on isolates that do not undergo susceptibility testing.

The map below show the number of isolates included in the analyses in 2021 by FSA. Please note that number of submitted isolates change year

Please note that duplicates have been removed for all analyses presented here. Between 2016 and 2021, data on 10,000 Pseudomonas isolates

The percent of solates tested represents the percent of solates in a category with any susceptibility testing results that have been tested for the specific antimicrobial or combination. AdRNet does not collect information on solates that do not undergo susceptibility testing.

Number of solates by FSA Unine Blood Respiratory Wound Non-blood All source

De-duplication method: Only the 1st Pseudomonas isolate from a given patient in a given calendar year is included.

Number of isolates

to year and differ between specimen types and FSAs.

C1N n=128

Pseudomonas

WHO GLASS submission Integration of pilot vet data nmary reports for stakeholders The percent of isolates tested represents the percent of isolates in a category with any susceptibility testing results that have been tested for the The percent of isolates reside represents are percent or reported to represent the percent of isolates to the percent of isolates The heatmap below includes E. coil from urine 2016 to 2021. Isolates from FSAs outside of PEI have been excluded. White text on the heatmap indicates fewer than 30 isolates represented. Percent (%) of Ignistes Tested 0 10 20 30 40 50 60 70 80 90 100 Queen & Kings excl. Charlottetown (C0A) Charlottetown (C1ABCE) Summerside (C1N) Prince County excl. Summerside (C0B) Queen & Kings excl. Charlottetown (C0A)

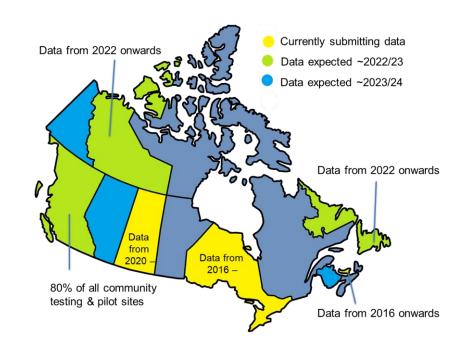
Prince County excl. Summerside (COB)

Queen & Kings excl. Charlottetown (C0A)



Summary

- Early days
- Stable long-term funding
- Very positive responses and early support at FTP level
- Pilot: SES factors collaboration with StatCan and SK
- Data sharing/requests:
 - Human: WHO GLASS, PHAC programs (CARSS, CNISP), Non-profit
 - Vet: CIPARS, industry-affiliated network
- AMRNet Vet pilots with ON, SK & PEI
- Federal data: C. difficile (CNISP), N. gonorrhoeae (ESAG), Salmonella (CIPARS) data transfer approved

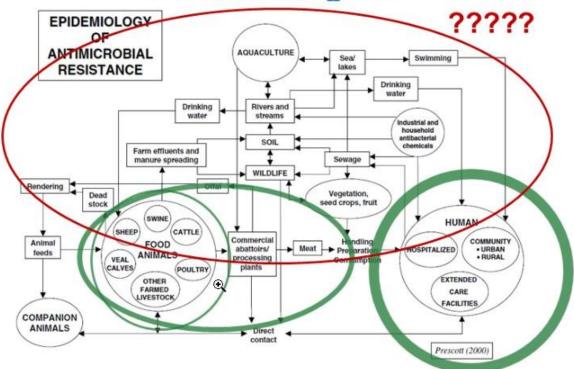


The "One-Health" AMR Model



http://www.phac-aspc.gc.ca/owoh-umus/index-eng.php

The 'Confusogram'



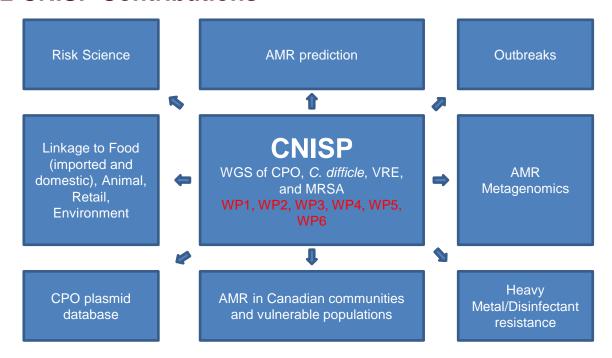
J. F. Prescott et al. (2000) Antimicrobial Therapy in Veterinary Medicine

Genomics Research Development Initiative (GRDI)

- 5 year funded interdepartmental shared priority project on AMR
- PHAC, AAFC, CFIA, DFO, ECCC
- 6 work packages to assess the dissemination of priority AMR pathogens affecting human and animal health across the farm to fork to clinic continuum



GRDI AMR2 CNISP Contributions



Wastewater AMR: Dr. Chand Mangat

- New surveillance program for AMR in wastewater
- Community-based surveillance is a gap in our current complement of tests
- Near-term technical goals
 - Develop a robust/stable method for tracking AMR genes, pathogens and plasmids (2 year)
 - qPCR panel to begin and transitioning to omics

Development plan

- qPCR -> metagenomics -> quantitative metagenomics > long-read
- 20 sites to be tested for weekly
- Technically aligned with developing US-CDC program
 - US-CDC qPCR panel is below, will choose 8 indicators
 - mcr-1, vanA, NDM, KPC, VIM, CTX-M (group 1), CMY-2, TEM, SHV, intl1, tetW, IMP

Establishment of a Phage Biobank at NML

- Alternatives to antimicrobial therapy
- Funding requested to establish a new lab to identify phage active against highly drug resistant AMR pathogens
- Phage therapy recently being approved for treatment of difficult to treat infections (compassionate use)
 - USA first case 2018
 - Canada first case 2022
 - Other countries ahead of Canada and USA
 - Clinical trials underway
- Why NML? Perfect location.
 - AMR pathogen collection for over 30 years
 - Wastewater collections and manure samples for isolation of phage
- Working with AMMI Canada Phage WG
- More info to come

Acknowledgements

- The ARNI Team
- Canadian Nosocomial Infection Surveillance Program
- Canadian Integrated Program for Antimicrobial Resistance Surveillance
- CANWARD
- The Canadian Public Health Laboratory Network
- Canadian Animal Health Laboratory Network
- All of the many clinical laboratories interested in working with ARNI