# 30 minutes of abbreviations and understanding common antibiotic resistance

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# disclosure

- No conflict of interests to declare

# objectives

After this presentation, participants will be able to:

(1) Define antimicrobial resistance and it's impact on multiple aspects of society

(2) Explain the current state of antimicrobial resistance in Canada

(3) Identify contributors to antimicrobial resistance and potential remedies of antimicrobial resistance

# case

56M

T2DM, recurrent nephrolithiasis, UTIs
metformin, atorvastatin

Fever and dysuria for 5 days
Presents now due to transient episodes of gross hematuria

O/E – Unwell. No CVA tenderness. +supra-pubic tenderness. DRE warm, boggy, tender prostate.

LABS - WBC 16k/$mm^3$, Cr 127, UA +LE +nit

Started on ciprofloxacin 500mg PO bid x 14 d

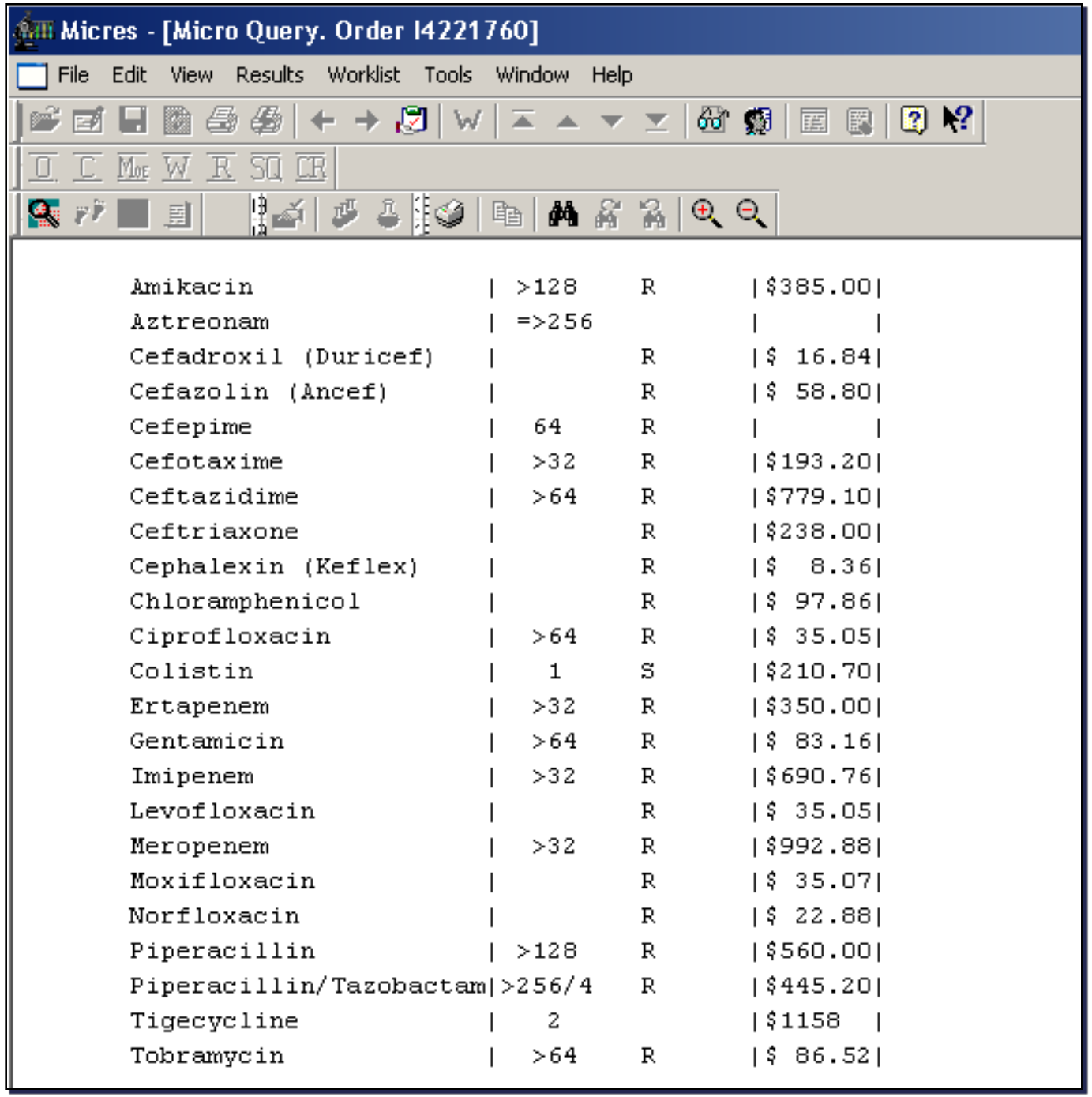
*Pseudomonas aeruginosa* >$100x10^6$ CFU/L

| | ***Pseudomonas aeruginosa*** |
|---|---|
| Aztreonam | R |
| Ceftazidime | R |
| Ciprofloxacin | R |
| Gentamicin | S |
| Imipenem | R |
| Meropenem | R |
| Piperacillin-tazobactam | R |
| Tobramycin | S |

**MICROBIOLOGIE/MICROBIOLOGY**

Req#P5100551 Specimen received:19/03/10 09:19
**Source: NOS Body Flu** Specimen plated: 19/03/10 10:48
**Site: pig tail (L) abd**
Antibiotics:
Comments: please add ceftolozane/tazobactam ( if patient grows Pseudo.)

| **ORGANISM** | **Ps. aerug** | | |
|---|---|---|---|
| Antibiotics | MIC | Int | Cost |
| Amikacin | | S | $385.00 |
| Aztreonam | | R | |
| Ceftazidime | | R | $779.10 |
| Ceftolozane/Tazobactum | 2 | S | |
| Ciprofloxacin | | R | $ 35.05 |
| Colistin | | R | $210.70 |
| Gentamicin | | S | $ 83.16 |
| Levofloxacin | | R | $ 35.05 |
| Meropenem | | R | $992.88 |
| Moxifloxacin | | R | $ 35.07 |
| Piperacillin/Tazobactam | | R | $445.20 |
| Tobramycin | | S | $ 86.52 |
| Trimethoprim/Sulfa | | R | $ 1.71 |




| | | | |
|---|---|---|---|
| Amikacin | >128 | R | $385.00 |
| Aztreonam | =>256 | | |
| Cefadroxil (Duricef) | | R | $ 16.84 |
| Cefazolin (Ancef) | | R | $ 58.80 |
| Cefepime | 64 | R | |
| Cefotaxime | >32 | R | $193.20 |
| Ceftazidime | >64 | R | $779.10 |
| Ceftriaxone | | R | $238.00 |
| Cephalexin (Keflex) | | R | $ 8.36 |
| Chloramphenicol | | R | $ 97.86 |
| Ciprofloxacin | >64 | R | $ 35.05 |
| Colistin | 1 | S | $210.70 |
| Ertapenem | >32 | R | $350.00 |
| Gentamicin | >64 | R | $ 83.16 |
| Imipenem | >32 | R | $690.76 |
| Levofloxacin | | R | $ 35.05 |
| Meropenem | >32 | R | $992.88 |
| Moxifloxacin | | R | $ 35.07 |
| Norfloxacin | | R | $ 22.88 |
| Piperacillin | >128 | R | $560.00 |
| Piperacillin/Tazobactam | >256/4 | R | $445.20 |
| Tigecycline | 2 | | $1158 |
| Tobramycin | >64 | R | $ 86.52 |

# defining resistance

- **Resistance** – the ability of a microorganism to demonstrate growth *in vitro* in the presence of an antimicrobial, by means of various mechanisms, which correlates with *in vivo* clinical treatment failure and progression of micro-organism mediated disease.

- **Important concepts**
  - Micro-organisms, not patients, become resistant to antimicrobials.
  - Resistant micro-organisms does not imply more virulent micro-organisms; but, sometimes it does.

- **AMU** – Antimicrobial utilization
- **AMR** – Antimicrobial resistance

- **MDRO** – Multi-Drug Resistant Organism
- **XDRO** – Extensively Drug Resistant Organism

# defining resistance

| Virus | Resistance |
|---|---|
| Influenza | Antigenic drift, antigenic shift |
| HIV | Point mutations, M184V – NRTIs |
| CMV | UL97 kinase mutation – GCV-R |

| Parasite | Resistance |
|---|---|
| Malaria | PfCRT mutations – chloroquine-R |
| PCP / PJP | DHPS mutations – SXT-TMP-R |

| Fungus | Resistance |
|---|---|
| Candida spp | ERGx expression – fluconazole-R |

| MDR TB | XDR TB |
|---|---|
| Resistance to INH, RIF | Resistance to INH, RIF, FQs, AND at least 1 of 3 second line injectables |

| MDRO | | XDRO | |
|---|---|---|---|
| Definition | Antimicrobial groups | Definition | Antimicrobial groups |
| Enterobacteriaceae | | | |
| Resistance to THREE OR FOUR of the SIX antimicrobial groups | Tobramycin OR[a] gentamicin[b] | Resistance to FIVE OR SIX of the antimicrobial groups | Tobramycin OR gentamicin |
| | Piperacillin-tazobactam | | Piperacillin-tazobactam |
| | Imipenem OR meropenem[c] | | Imipenem OR meropenem |
| | Cefotaxime OR ceftriaxone OR ceftazidime | | Cefotaxime OR ceftriaxone OR ceftazidime |
| | Ciprofloxacin | | Ciprofloxacin |
| | Trimethoprim-sulfamethoxazole | | Trimethoprim-sulfamethoxazole |
| Organisms: *Pseudomonas aeruginosa* OR *Acinetobacter* species | | | |
| Not applicable | Not applicable | Resistance to ALL FIVE antimicrobial groups | Ciprofloxacin |
| | | | Piperacillin-tazobactam[d] |
| | | | Ceftazidime |
| | | | Imipenem OR meropenem |
| | | | Tobramycin |

German GJ *et al.* (2018) Can Commun Dis Rep 44: 29-34. Published online 2018 Jan 4.

# causes of antimicrobial resistance

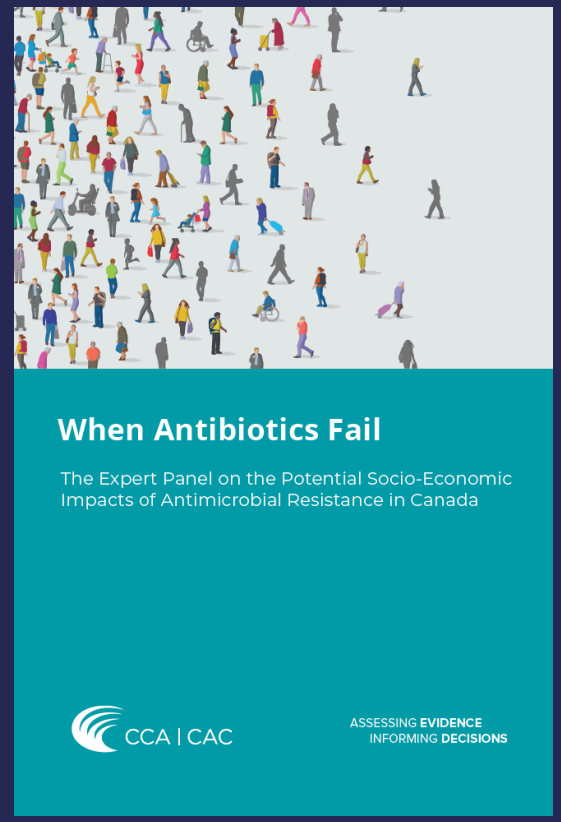
- Over utilization / Over prescription → Increased selective pressure
- Improper utilization (dosing)
- Abuse of antimicrobials in livestock and fish farming
- Lapses in infection control
- Poor food hygiene, personal hygiene and sanitation

# Impact of antimicrobial resistance

"Eventually, if resistance continues to rise, they will lead to substantial financial implications for Canada's healthcare system, fundamentally changing the delivery of most service and eroding the public trust."

- Current situation
  - 26% of bacterial infections are resistant to first line antimicrobials
  - AMR impact on productivity → ↓ GDP $2 billion
  - $1.4 billion cost attributable to AMR in Canadian healthcare system

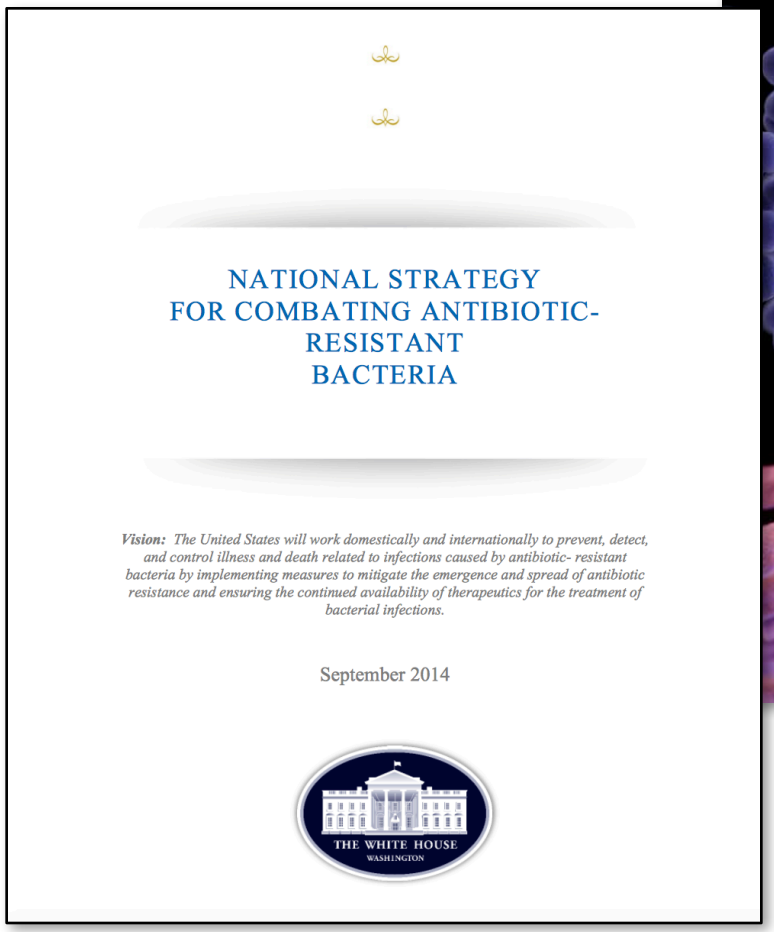
- Forecasted impact on the future (by 2050)
  - ↑40% of bacterial infections are resistant to first line antimicrobials
  - Canadian economy would shrink by 0.7%
  - AMR impact on productivity → ↓$13-21 billion/yr, ↓$388 billion
  - Potentially $6-8 billion cost attributable to AMR in Canadian healthcare system
  - AMR negatively impacts society




Council of Canadian Academies, (2019) *When Antibiotics Fail*. Ottawa (ON): The Expert Panel on the Potential Socio-Economic Impacts of Antimicrobial Resistance in Canada, Council of Canadian Academies.

CDC/PCAST estimated at least
2,049,442 illnesses
23,000 deaths in the USA
attributed to
**antibiotic resistance**

Up to $20 billion in excess in
direct healthcare costs
Lost of productivity $35 billion/yr



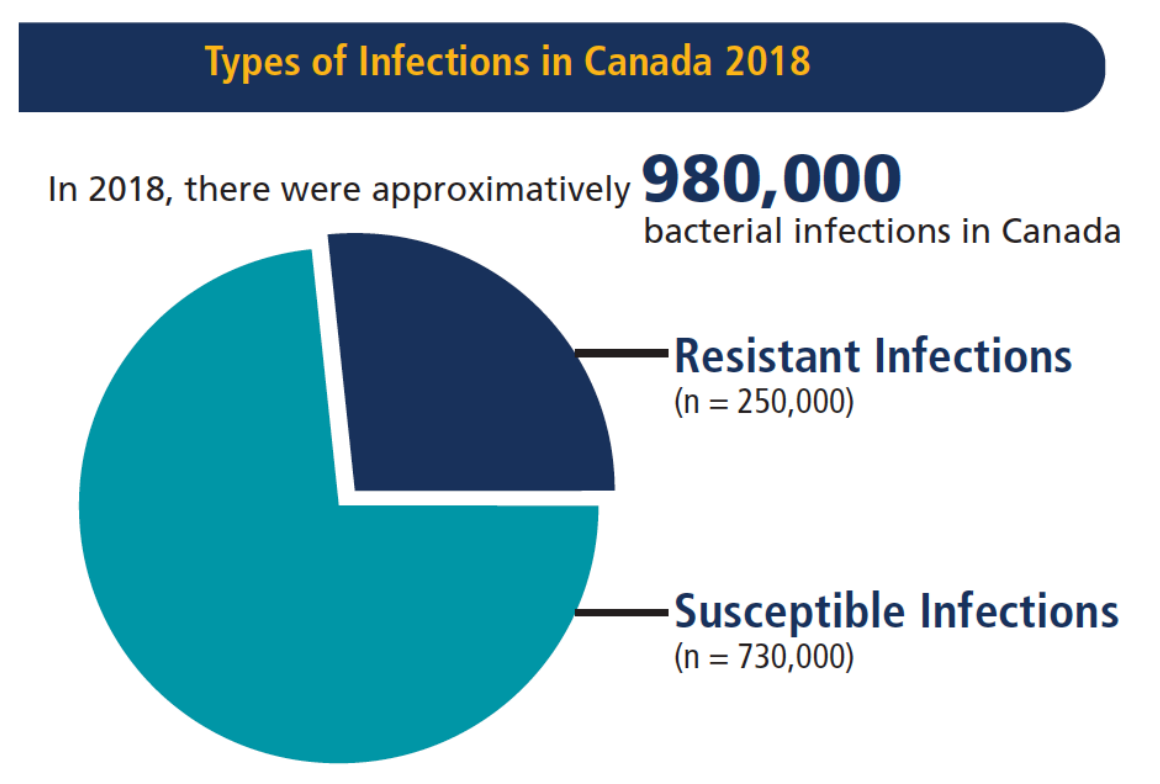
NATIONAL STRATEGY
FOR COMBATING ANTIBIOTIC-
RESISTANT
BACTERIA

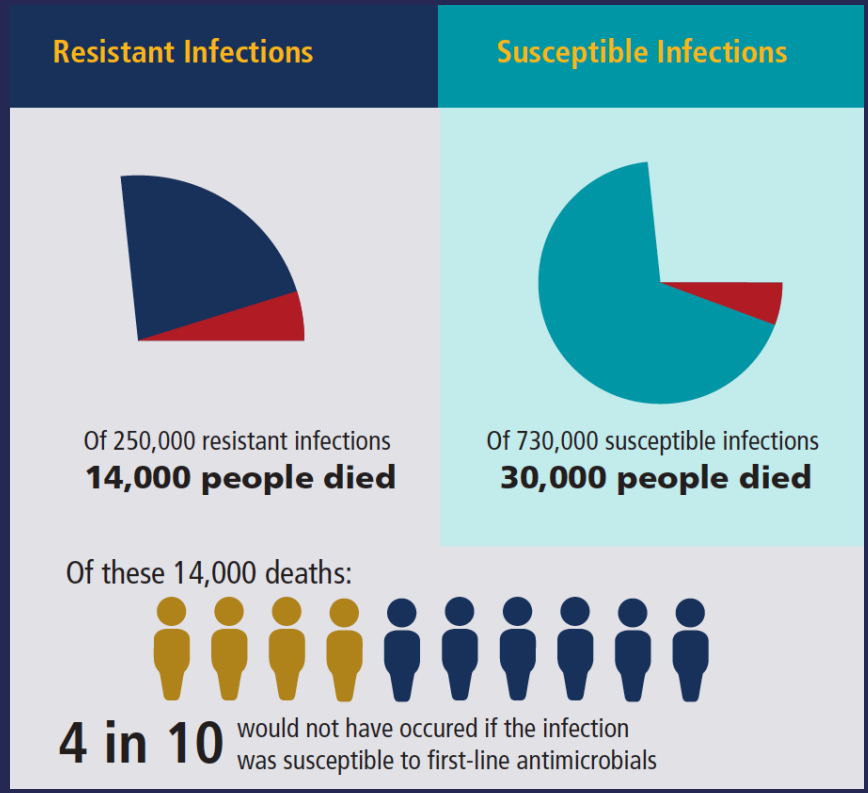
*Vision: The United States will work domestically and internationally to prevent, detect, and control illness and death related to infections caused by antibiotic- resistant bacteria by implementing measures to mitigate the emergence and spread of antibiotic resistance and ensuring the continued availability of therapeutics for the treatment of bacterial infections.*

September 2014

THE WHITE HOUSE
WASHINGTON


# current antimicrobial resistance in Canada

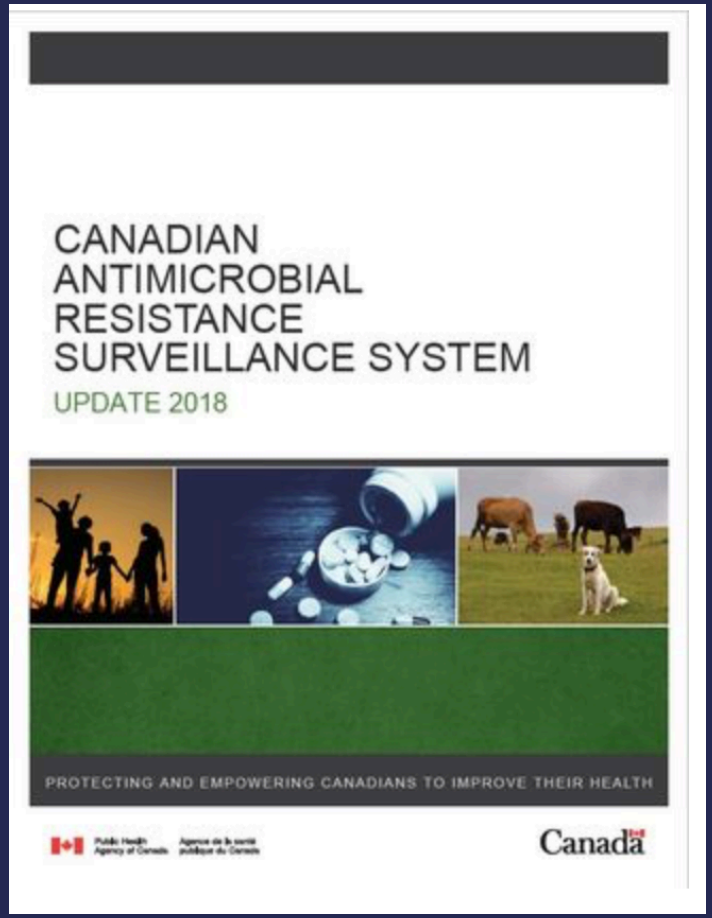



Council of Canadian Academies, 2019. *When Antibiotics Fail.* Ottawa (ON): The Expert Panel on the Potential Socio-Economic Impacts of Antimicrobial Resistance in Canada, Council of Canadian Academies.

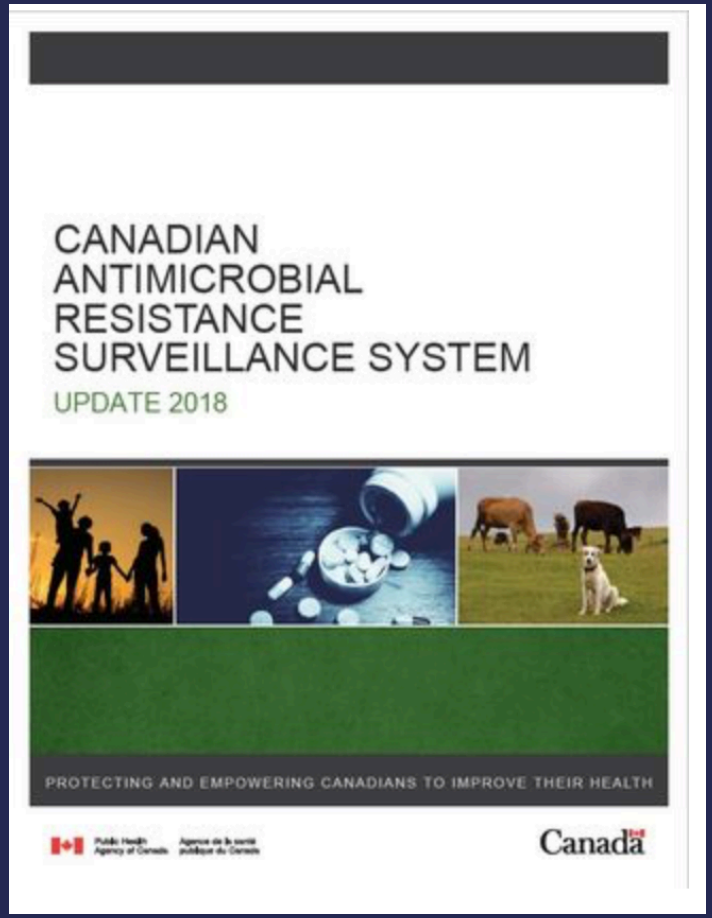
# Key findings from the Canadian Antimicrobial Resistance Surveillance System (CARSS)-Update 2018

- **Increase** in colonization by carbapenemase-producing organisms in both hospitals and the community setting;
- Healthcare-associated C. *difficile* infection rates continue to **decline**;
- The rate of methicillin-resistant Staphylococcus aureus (MRSA) infections coming from the community has nearly doubled;
- MRSA bloodstream infections remain high in paediatric hospitals;
- Increasing rates of vancomycin-resistant enterococci infections are still being seen in hospitalized patients;



# Key findings from the Canadian Antimicrobial Resistance Surveillance System (CARSS)-Update 2018

- Azithromycin resistance in Neisseria gonorrhoeae has doubled;
- Prescriptions for adults 60 years and older have continued to increase over time and represent the age group with the greatest use of antimicrobials;
- There was no reported use of fluoroquinolones or third-generation cephalosporins by sentinel chicken farms, consistent with recent policy changes that introduced a ban on the preventative use of Category I antimicrobials on poultry farms across Canada;
- A decrease in the prevalence of resistance to third-generation cephalosporins was observed in non-typhoidal Salmonella spp. collected from chickens, chicken meat, and humans.



# principal bacterial culprits

***E****nterococcus faecium*

***S****taphylococcus aureus*

***K****lebsiella pneumoniae*

***A****cinetobacter baumannii*

***P****seudomonas aeruginosa*

***E****nterobacter* spp.

**mechanisms of resistance**

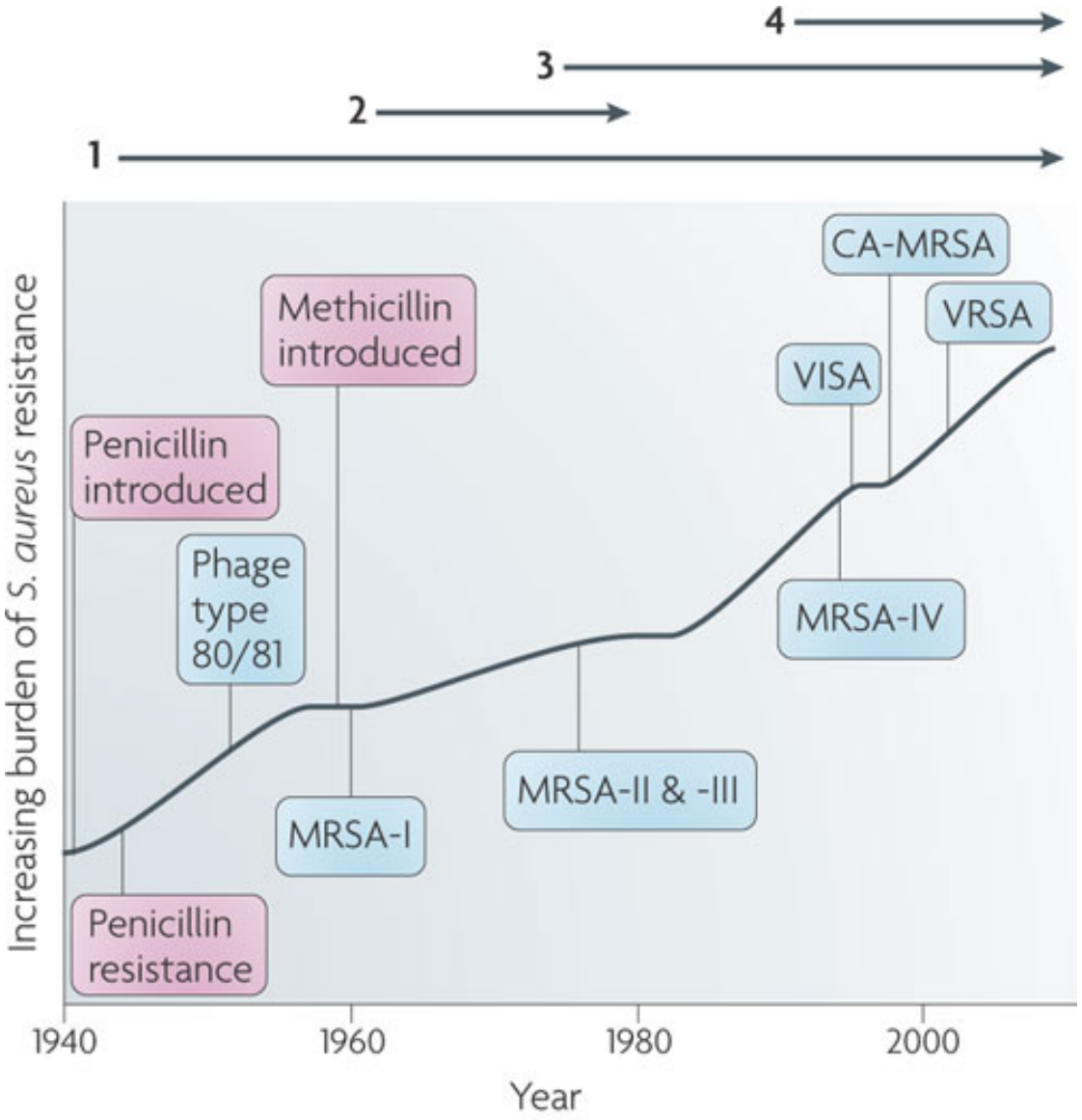
- Drug inactivation through enzymatic cleavage
- Modification of antibiotic binding/target site
- Reducing accumulation of drug via altered cell wall permeability or by molecular efflux pump
- Biofilm formation altering antibiotic penetration and bacterial metabolism
  - Mediated through intrinsic mechanisms, acquired genes (plasmids, transposons, etc)

Rice L. B. (2008). Federal funding for the study of antimicrobial resistance in nosocomial pathogens: no ESKAPE. J. Infect. Dis. 197, 1079–1081
Mulani, MS *et al (2019). Emerging Strategies to Combat ESKAPE Pathogens in the Era of Antimicrobial Resistance: A Review. Front Microbiol. 10; 539. Published online 2019 Apr 1* doi: 10.3389/fmicb.2019.00539

# resistant *Staphylococcus aureus*

- **MRSA** – Methicillin Resistant *Staphylococcus aureus*
  - Resistance to all beta-lactam based antimicrobials
  - Screening by cefoxitin resistance, oxacillin resistance, and molecular detection
  - *mecA* gene encoding PBP-2a
  - Strain types CA-MRSA (USA300, CMRSA10; USA400, CMRSA7), HA-MRSA (USA100, CMRSA2)
- **VISA** - Vancomycin Intermediate *Staphylococcus aureus*
  - Vancomycin MIC = 4-8 mcg/ml
  - Successive mutations resulting in a D-ala-D-ala moiety stacking (pseudotargets) and thicker cell wall/clogging
- **VRSA** – Vancomycin Resistant *Staphylococcus aureus*
  - Vancomycin MIC ≥ 16 mcg/ml
  - 14 isolates in USA as of 2015 CDC report
  - Acquire *Van* gene

Public Health Agency of Canada. *Methicillin-resistant Staphylococcus aureus in Canadian acute-care hospitals: Surveillance Report January 1, 2008 to December 31, 2012.* Centre for Communicable Diseases and Infection Control, Public Health Agency of Canada, 2014.
Walters M, *et al.* Investigation and Control of Vancomycin-resistant Staphylococcus aureus: A Guide for Health Departments and Infection Control Personnel. Atlanta, GA 2015. Available at: http://www.cdc.gov/hai/pdfs/VRSA-Investigation-Guide-05_12_2015.pdf



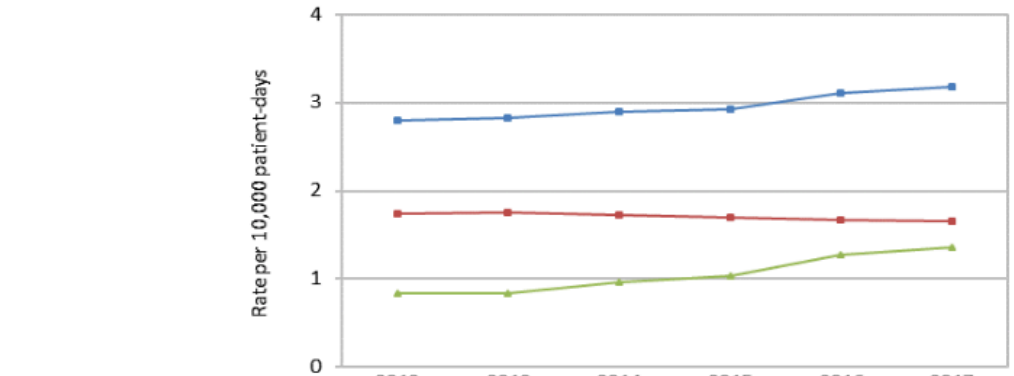

Nature Reviews | Microbiology

Chambers and Leo (2009) Nature Reviews Microbiology **7**, 629-64

# resistant *Staphylococcus aureus*

- MRSA
  - ↑ rate of MRSA infections by sentinel hospitals: 2.8/10000 pt-d (2012) → 3.2/10000 pt-d (2017)
  - ↑ rate of MRSA infections attributed to ↑ rate of CA-MRSA infections by 60% despite ↓ rate of HA-MRSA
  - Overall ↑ rate of MRSA bloodstream infections 0.30/10000 pt-d (2012) → 0.44/10000 pt-d (2017)
  - Doubling of the rate of MRSA bloodstream infections originating from the community
  - Universally susceptible to vancomycin and linezolid
  - < 1% resistance to daptomycin
  - Annual decrease in clindamycin resistance

**Figure 9: Rate of healthcare-associated and community-associated MRSA infection, 2012-2017**




| | 2012 | 2013 | 2014 | 2015 | 2016 | 2017 |
|---|---|---|---|---|---|---|
| Overall MRSA | 2.8 | 2.83 | 2.89 | 2.93 | 3.11 | 3.17 |
| Healthcare-associated MRSA | 1.74 | 1.75 | 1.72 | 1.70 | 1.67 | 1.65 |
| Community-associated MRSA | 0.84 | 0.84 | 0.96 | 1.04 | 1.28 | 1.36 |

# vancomycin resistant *Enterococcus*

TABLE 2. Characteristics of phenotypes of glycopeptide-resistant enterococci[a]

| Characteristic | Phenotype | | | | |
|---|---|---|---|---|---|
| | VanA | VanB | VanC | VanD | VanE |
| Vancomycin MIC (μg/ml) | 64–>1,000 | 4–1,024 | 2–32 | 128 | 16 |
| Teicoplanin MIC (μg/ml) | 16–512 | ≤0.5 | ≤0.5 | 4 | 0.5 |
| Most frequent enterococcal species | *E. faecium*, *E. faecalis* | *E. faecium*, *E. faecalis* | *E. gallinarum*, *E. casseliflavus*, *E. flavescens* | *E. faecium* | *E. faecalis* |
| Genetic determinant | Acquired | Acquired | Intrinsic | Acquired | Acquired |
| Transferable | Yes | Yes | No | No | No |

Cetinkaya, y *et al*. (2000) Vancomycin-Resistant Enterococci. Clin Microbiol Rev 13: 686-707

# vancomycin resistant *Enterococcus*

- Colonization rates substantially greater than invasive infection rates
- Debate as to whether VRE patients need to be isolated
- ↑ rate of VRE bloodstream infections 0.18/10000 pt-d (2016) → 0.23/10000 pt-d (2017)
- ↑ non-BSI infections due to VRE for the first time in 2017 after steady annual declines since 2012
- ↑ daptomycin resistance – 9%
- ↑ high level gentamicin resistance, ↓ high level streptomycin resistance
- 3x ↑ in nitrofurantoin resistance between 2012-2017 – 45%

# resistant *Enterobacteriaceae*

- ESBL – Extended Spectrum Beta-Lactamase
- AmpC resistance – inducible
- CRE – Carbapenem Resistant *Enterobacteriaceae*
  CPE – Carbapenemase Producing *Enterobacteriaceae*
  CRO – Carbapenem Resistant Organism

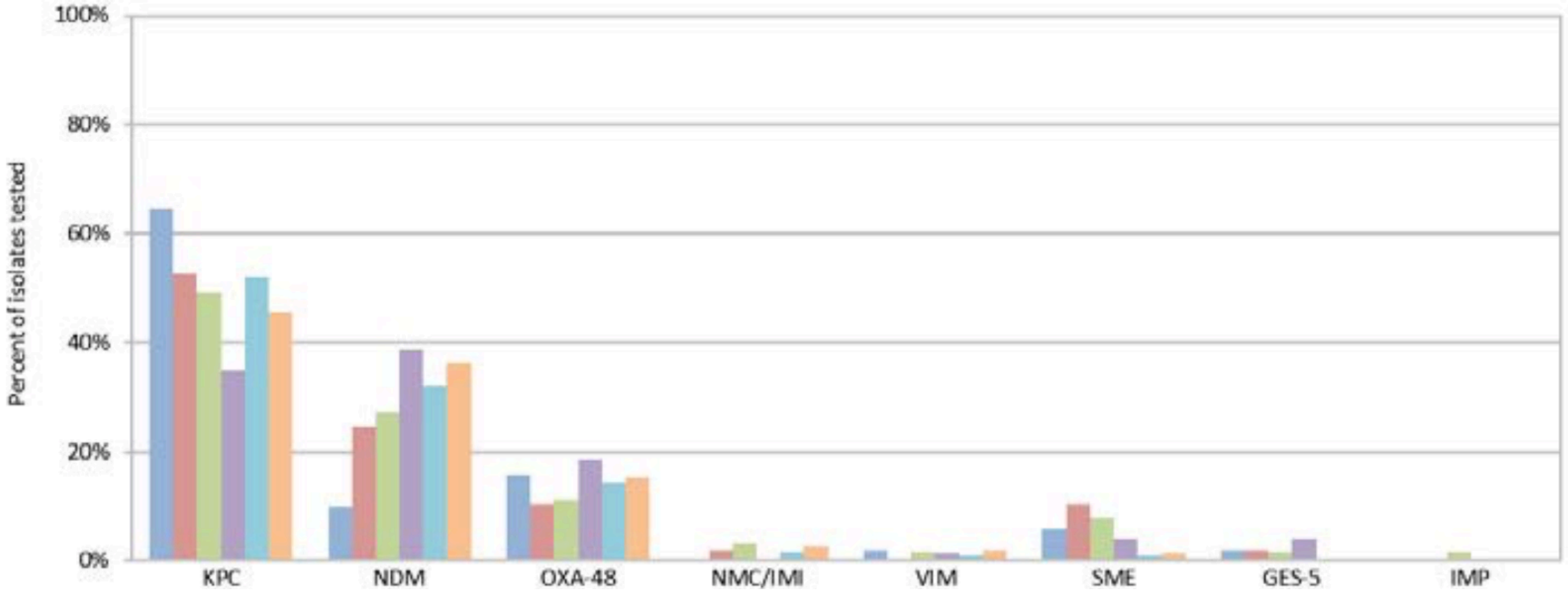
| | ESBL / AmpC | CRE |
|---|---|---|
| Penicillin based BL | R | R |
| Beta lactam-BLi | S/R | R |
| Cephalosporin | R | R |
| Carbapenem | S | R |
| Fluoroquinolones | ? | ? |
| SXT-TMP | ? | ? |

# Rate of CPE cases (infections and colonizations) per 10,000 patient-days, 2012-2017


| | 2012 | 2013 | 2014 | 2015 | 2016 | 2017 |
|---|---|---|---|---|---|---|
| CPE Colonization | 0.05 | 0.04 | 0.03 | 0.05 | 0.10 | 0.14 |
| CPE Infection | 0.03 | 0.03 | 0.03 | 0.03 | 0.03 | 0.03 |

Canadian Antimicrobial Resistance Surveillance System Update 2018

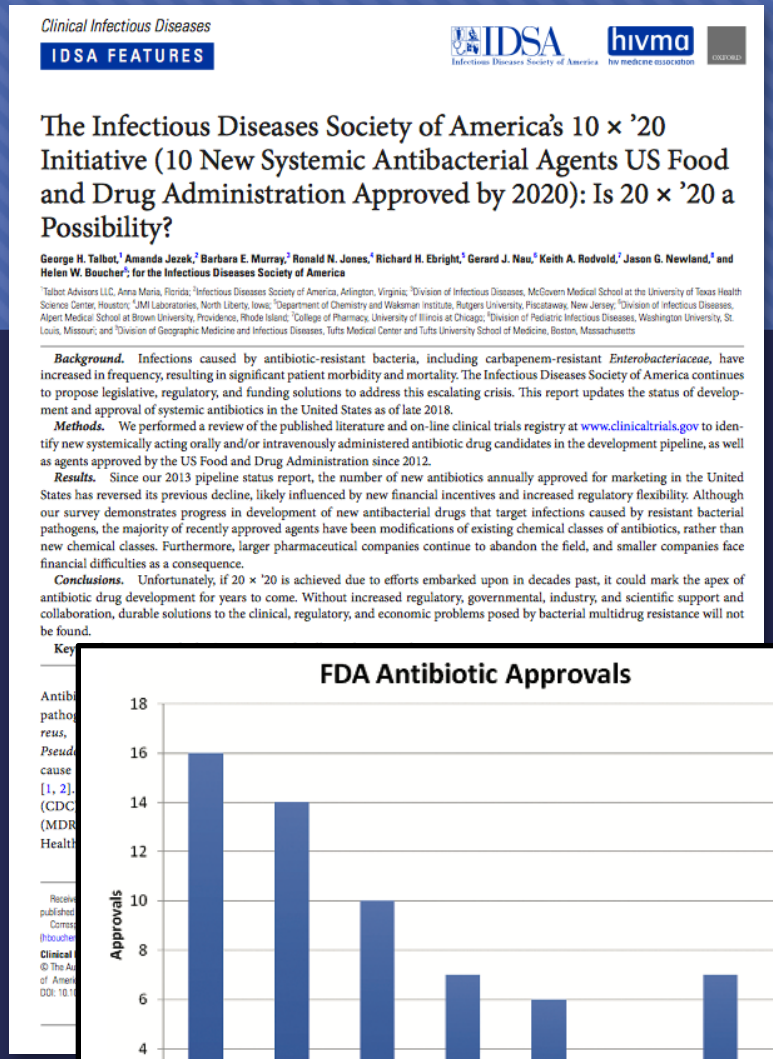
# Figure 3: CPE resistance gene prevalence, 2012-2017




Canadian Antimicrobial Resistance Surveillance System Update 2018

# is this the end?

- Next generation antimicrobials vs Gram negative agents
  - Ceftolozane-tazobactam / Ceftazidime-avibactam
  - Meropenem-verbobactam / Imipenem-cilastatin-relebactam
  - Tigecylcine / Eravacycline / Omadacycline
  - Plazomicin
- Older antimicrobials
  - Fosfomycin PO / Fosfomycin IV
  - Aminoglycosides
  - Chloramphenicol
  - Colistin / polymyxins



Clinical Infectious Diseases

IDSA FEATURES

The Infectious Diseases Society of America's 10 × '20 Initiative (10 New Systemic Antibacterial Agents US Food and Drug Administration Approved by 2020): Is 20 × '20 a Possibility?

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[1]Talbot Advisors LLC, Anna Maria, Florida; [2]Infectious Diseases Society of America, Arlington, Virginia; [3]Division of Infectious Diseases, McGovern Medical School at the University of Texas Health Science Center, Houston; [4]JMI Laboratories, North Liberty, Iowa; [5]Department of Chemistry and Waksman Institute, Rutgers University, Piscataway, New Jersey; [6]Division of Infectious Diseases, Alpert Medical School at Brown University, Providence, Rhode Island; [7]College of Pharmacy, University of Illinois at Chicago; [8]Division of Pediatric Infectious Diseases, Washington University, St. Louis, Missouri; and [9]Division of Geographic Medicine and Infectious Diseases, Tufts Medical Center and Tufts University School of Medicine, Boston, Massachusetts

***Background.*** Infections caused by antibiotic-resistant bacteria, including carbapenem-resistant *Enterobacteriaceae*, have increased in frequency, resulting in significant patient morbidity and mortality. The Infectious Diseases Society of America continues to propose legislative, regulatory, and funding solutions to address this escalating crisis. This report updates the status of development and approval of systemic antibiotics in the United States as of late 2018.

***Methods.*** We performed a review of the published literature and on-line clinical trials registry at www.clinicaltrials.gov to identify new systemically acting orally and/or intravenously administered antibiotic drug candidates in the development pipeline, as well as agents approved by the US Food and Drug Administration since 2012.

***Results.*** Since our 2013 pipeline status report, the number of new antibiotics annually approved for marketing in the United States has reversed its previous decline, likely influenced by new financial incentives and increased regulatory flexibility. Although our survey demonstrates progress in development of new antibacterial drugs that target infections caused by resistant bacterial pathogens, the majority of recently approved agents have been modifications of existing chemical classes of antibiotics, rather than new chemical classes. Furthermore, larger pharmaceutical companies continue to abandon the field, and smaller companies face financial difficulties as a consequence.

***Conclusions.*** Unfortunately, if 20 × '20 is achieved due to efforts embarked upon in decades past, it could mark the apex of antibiotic drug development for years to come. Without increased regulatory, governmental, industry, and scientific support and collaboration, durable solutions to the clinical, regulatory, and economic problems posed by bacterial multidrug resistance will not be found.

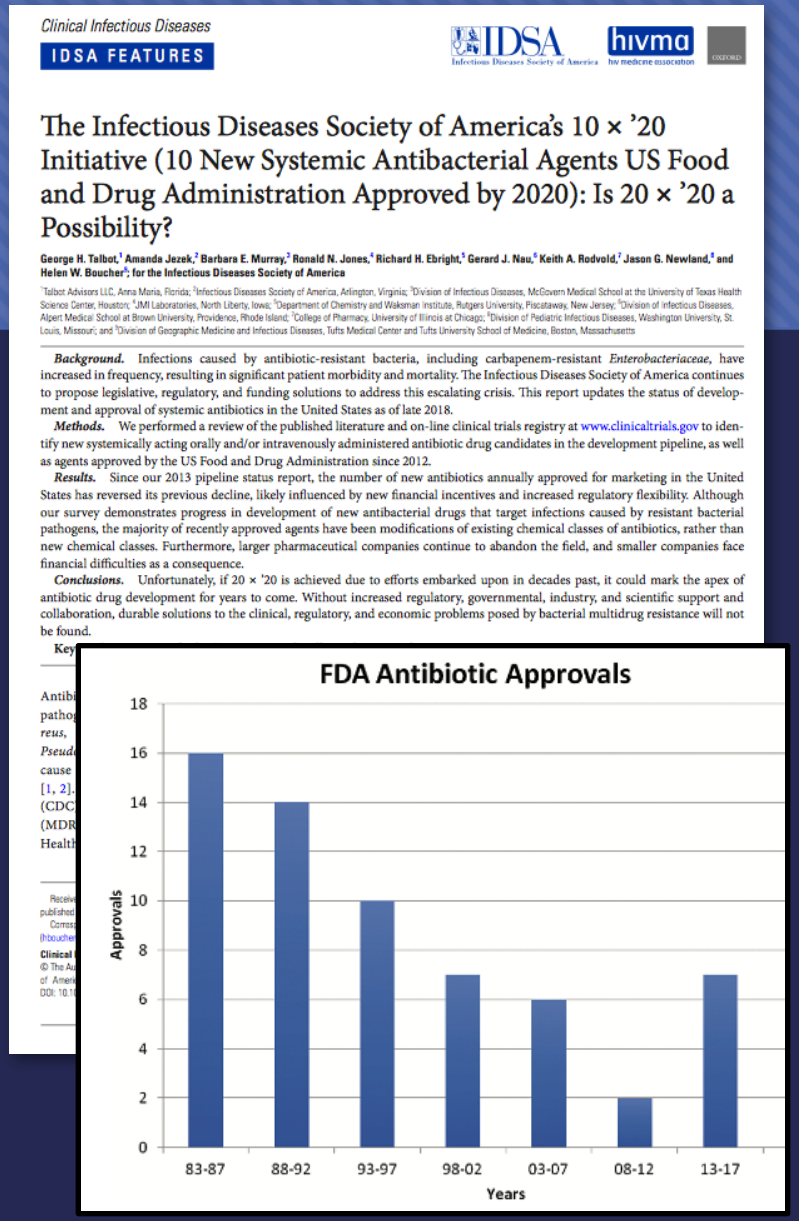



The Sanford Guide to Antimicrobial Therapy 2019. David N Gilbert Editor

Talbot, GH *et al.* (2019) The Infectious Diseases Society of America 10x'20 Initiative (10 New Systemic Antimicrobial Agents US Food and Drug Administration Approved by 2020); Is 20x'20 a Possibility? Clin Infect Dis 69(1); 1-11.

# is this the end?

- Next generation antimicrobials vs Gram positive agents
  - **Daptomycin** / Telavancin / Oritavancin / Dalbavancin
  - Linezolid / Tedizolid
  - Ceftaroline / Ceftobiprole
  - Omadacycline / Eravacycline / Tigecycline
  - Delafloxacin
- Older antimicrobials
  - Doxycycline / Minocycline / Tetracycline
  - Clindamycin
  - Chloramphenicol
  - Fosfomycin IV / Fosfomycin PO



*Clinical Infectious Diseases*

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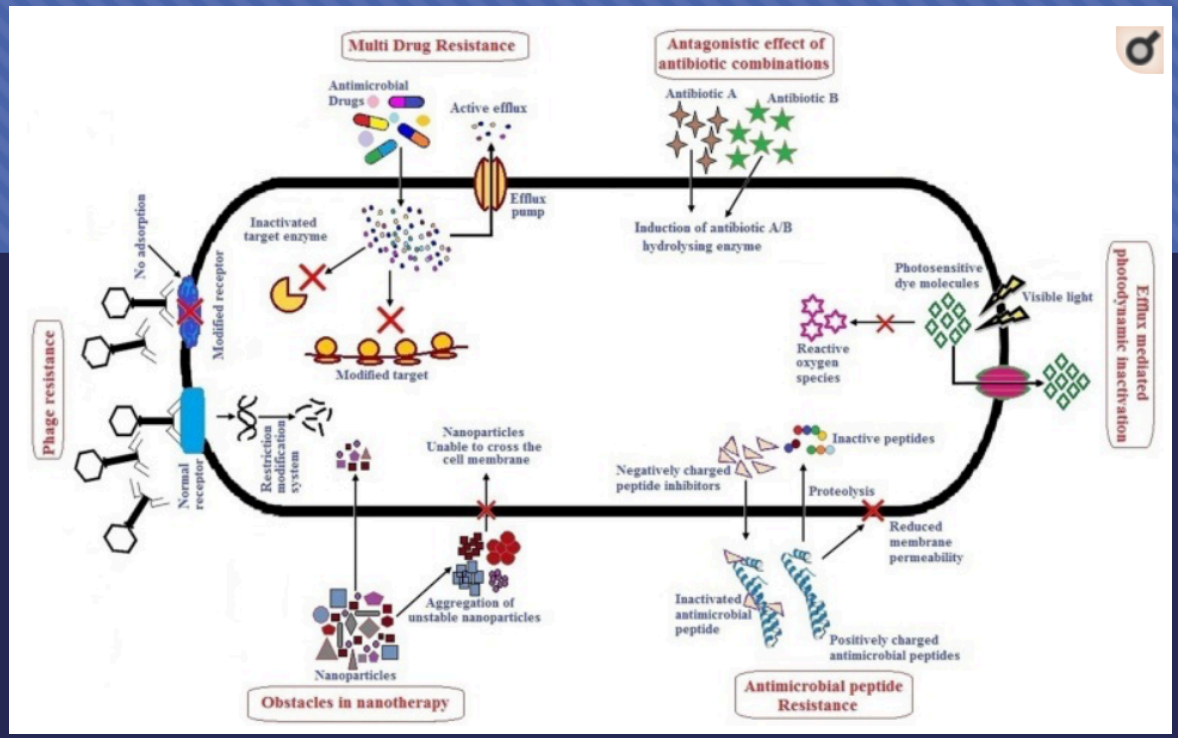
# Infection control

- Hand hygiene
- In hospital
  - Contact precautions – gowns and gloves
  - Chlorhexidine
  - Hydrogen peroxide spray
  - UV light
- In private office / Clinics / Diagnostic suites
  - "Last patient in"
  - Contact precautions – gowns and gloves, disposable coverings
  - Disinfection of high touch and grey zones between patients
  - Terminal cleaning
- Clinical
  - Decolonization protocols

# salvation?

- New antimicrobials
- Vaccines
- Phage therapy
- Lysins, peptides, nanoparticles
- Antimicrobial adjuvants
- Updated informatics, data handling, AI
- Veterinarian and agricultural paradigm shifts – "One Health" initiatives
- Educational campaigns
- Community responsibility – safe sex practices, "own stewardship"





Council of Canadian Academies, 2019. *When Antibiotics Fail.* Ottawa (ON): The Expert Panel on the Potential Socio-Economic Impacts of Antimicrobial Resistance in Canada, Council of Canadian Academies.

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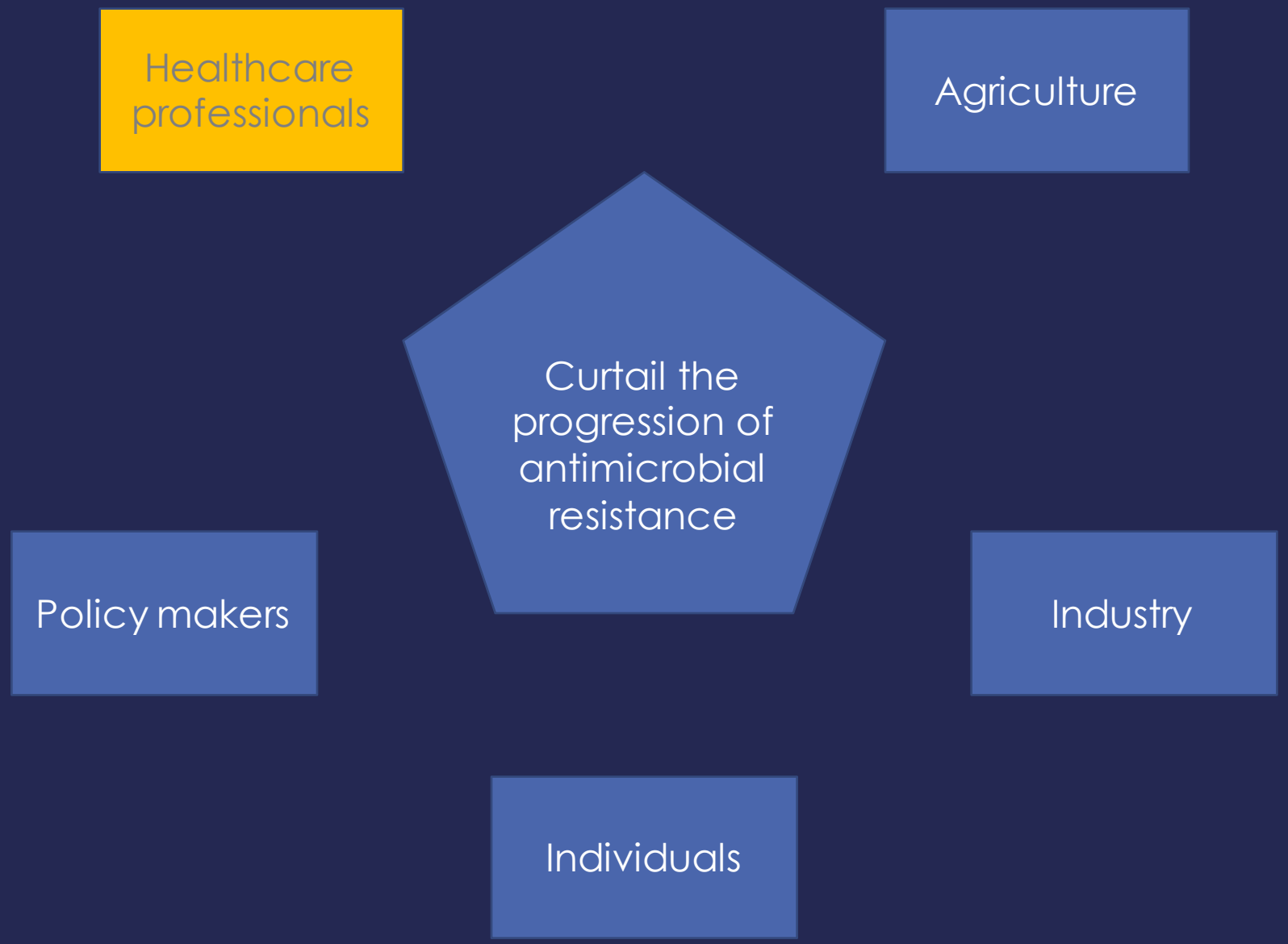
Healthcare professionals
Agriculture
Curtail the progression of antimicrobial resistance
Policy makers
Industry
Individuals