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Antibiotic Treatment of Outpatient UTI in 2020: What to Do ?

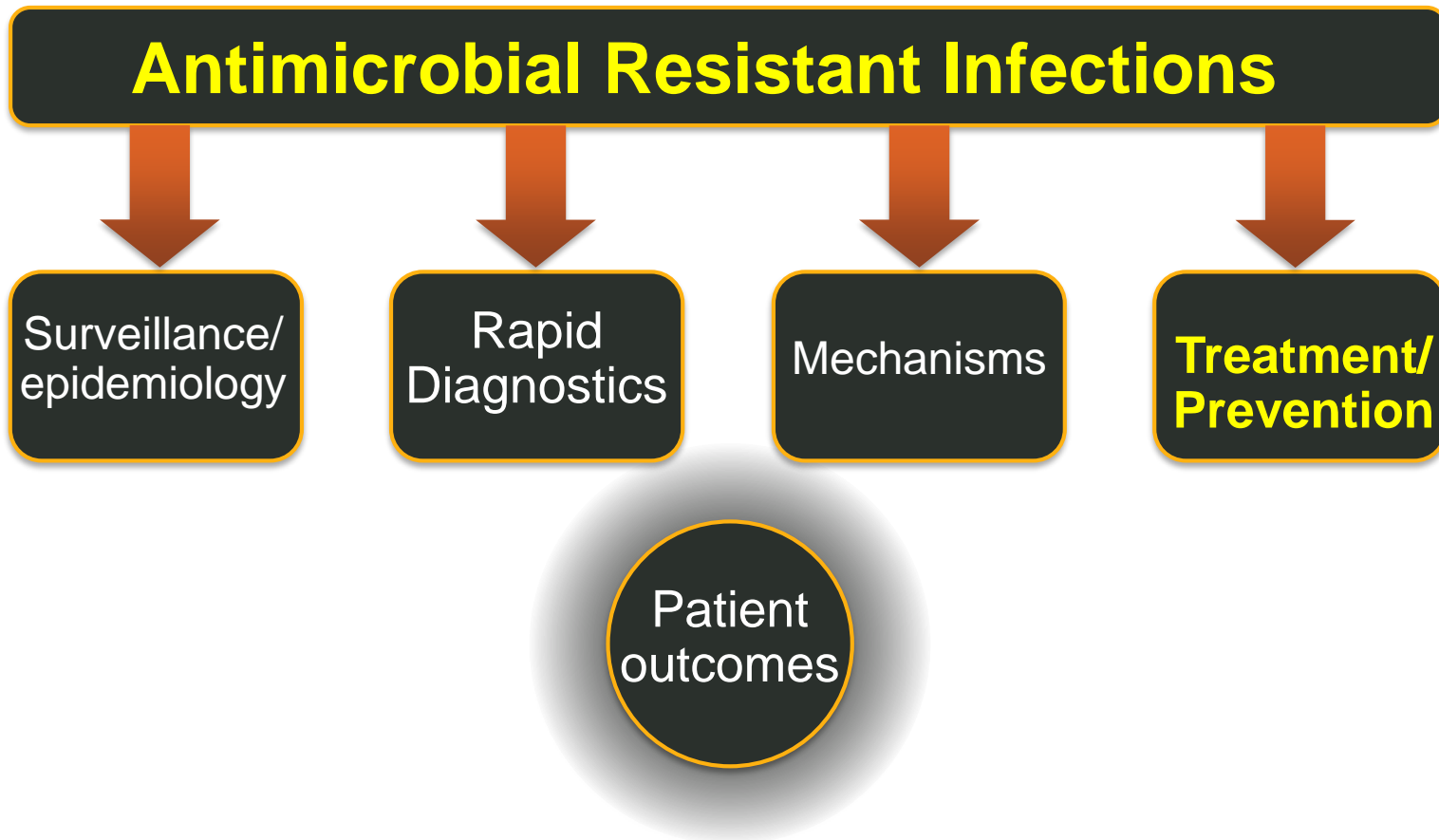


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(Microbiologist/Pharmacologist)

Professor: Department of Medical Microbiology/Infectious Diseases, Max Rady College of Medicine, University of Manitoba

Director: Canadian Antimicrobial Resistance Alliance (CARA www.can-r.com), Max Rady College of Medicine, University of Manitoba Winnipeg, Canada

Canadian Antimicrobial Resistance Alliance (CARA)



Welcome

The Canadian Antimicrobial Resistance Alliance (CARA) launched a website in early 2007, CAN-R (www.can-r.ca). The site is an online research portal designed to aid and educate Canadian healthcare providers on the escalating issue of antimicrobial resistance in Canada.

Providing current and comprehensive information, the site includes a variety of features and tools on antimicrobial resistance in Canada including:

- Surveillance of pathogens and infections from the national CANWARD study
- Surveillance of antimicrobial resistance in CANWARD
- Antimicrobial susceptibility data
- Activity of novel and new antimicrobials
- Current research presented at major conferences
- Publications from evidence-based medical literature
- Videos: antimicrobial mechanisms of action and resistance (see EDUCATION)

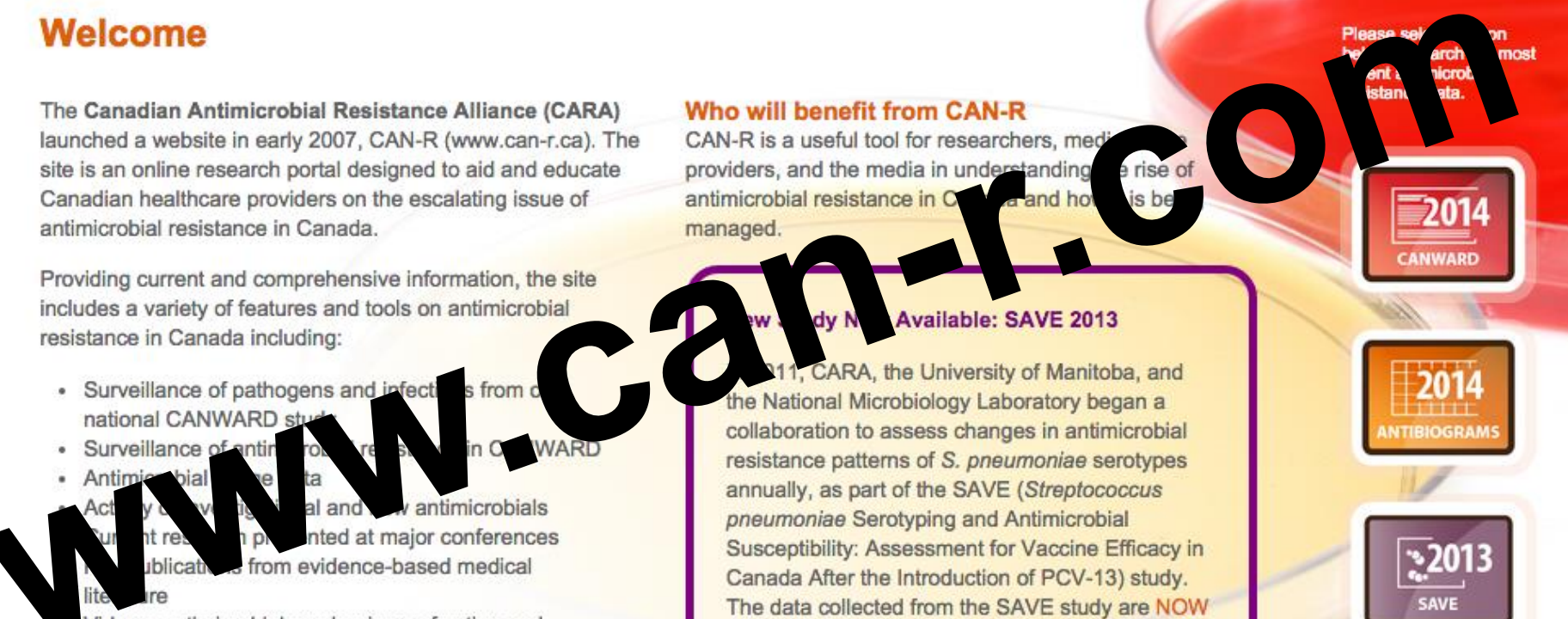
Who will benefit from CAN-R

CAN-R is a useful tool for researchers, medical providers, and the media in understanding the rise of antimicrobial resistance in Canada and how it is being managed.

New Study Now Available: SAVE 2013

In 2011, CARA, the University of Manitoba, and the National Microbiology Laboratory began a collaboration to assess changes in antimicrobial resistance patterns of *S. pneumoniae* serotypes annually, as part of the SAVE (*Streptococcus pneumoniae* Serotyping and Antimicrobial Susceptibility: Assessment for Vaccine Efficacy in Canada After the Introduction of PCV-13) study. The data collected from the SAVE study are **NOW AVAILABLE** as an interactive experience. Antimicrobial susceptibility/resistance data can be reviewed by serotype, patient age or a combination of the two parameters.

Please select a year on the left to view antimicrobial resistance data.



Faculty/Presenter Disclosure

- **Faculty:** [Dr. George G. Zhanel]
- **Relationships with financial sponsors:**
 - **Grants/Research Support:** Avir, Basilea, Cipher, Ferrer, Galderma, Iterum, Merck, Nabriva, Orbital Dx, Paladin Labs, Paratek, Pfizer, Red Leaf Medical, Sandoz, Shionogi, Sunovion, TetraPhase, Verity, Zambon, Zoetis

Mitigation of bias



1. Disclose conflicts of interest
2. Evidence based presentation
3. Impartial presentation

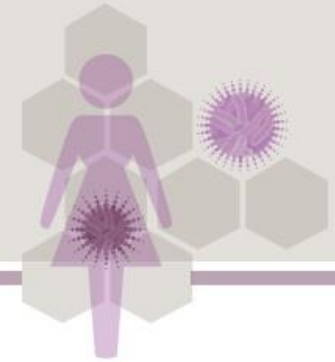
OBJECTIVES - ANTIBIOTIC TREATMENT OF OUTPATIENT UTI

1. Review current antibiotic treatment of **acute uncomplicated cystitis**
2. Discuss the only 2 situations where you treat **asymptomatic bacteriuria**
3. Review current antibiotic treatment of **acute uncomplicated pyelonephritis**

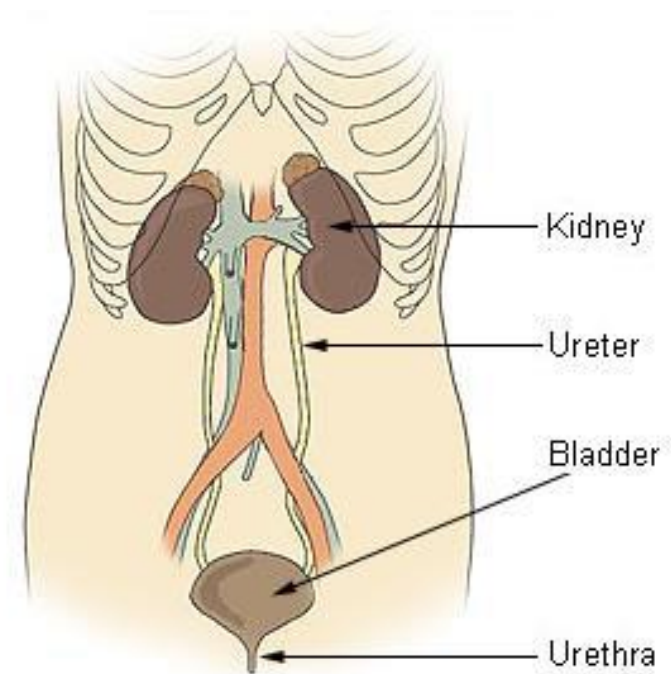
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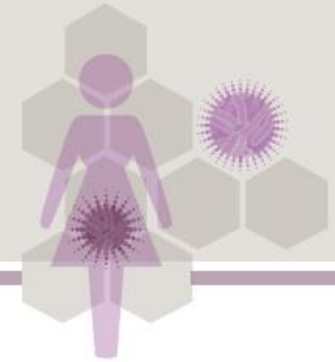
Classification of UTIs



- **Based on location:**
 - Upper (pyelonephritis)
 - Lower (cystitis)
- **Based on condition of the urinary tract or the patient:**
 - Uncomplicated
 - Complicated
- **Based on evolution:**
 - Acute
 - Chronic (symptoms persist over time)
 - Recurring (relapse or reinfection)



Uncomplicated vs. Complicated UTIs



- **Uncomplicated UTIs**

- Occurs in patients with normal genitourinary tracts
- Usually nonpregnant premenopausal women of childbearing age

- **Complicated UTIs**

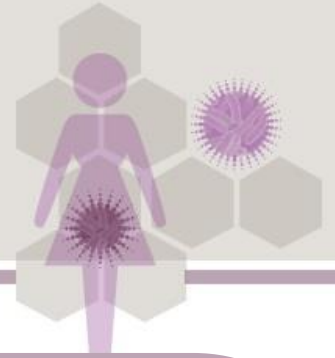
- Structural or functional abnormality of the genitourinary tract
- Pregnant women, elderly, men, children
- Chronic symptoms
- Comorbid illness or immunocompromised
- Upper UTIs (pyelonephritis)

Mazzulli T. *Can J Urol*. 2012;19 Suppl 1:42-48.

Nicolle L, et al. *Can Fam Physician*. 2006;52:612-618.

Nicolle LE, et al. *Can J Infect Dis Med Microbiol*. 2005;16(6):349-360.

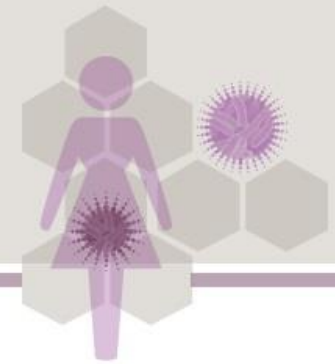
Case 1: Melissa – Acute Uncomplicated Cystitis



- **Patient presentation and history**

- 21-year-old woman comes to the office with a **2-day** history of **pain (“burning”)** during urination and urinary **frequency** along with “smelly urine”
- She is sexually active with her new boyfriend
- She had a similar episode on 1 previous occasion, a year ago
- No history or risk factors of STIs

Signs and Symptoms of UTIs



- **Dysuria**
- **Urinary frequency**
- **Urinary urgency**
- Suprapubic pain
- Hematuria
- Nocturia
- * Above in the absence of vulvar or vaginal discharge or irritation

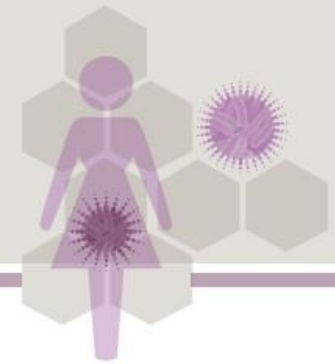
- **Upper UTI** symptoms include fever, flank pain, chills, nausea, and vomiting

Dason S, et al. *Can Urol Assoc J.* 2011;5(5):316-322.

Epp A, et al. *J Obstet Gynaecol Can.* 2010;32(11):1082-1101.

Mazzulli T. *Can J Urol.* 2012;19 Suppl 1:42-48.

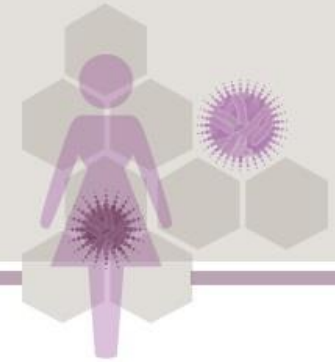
Diagnosis: Rapid In-office Lab Testing



- Urinalysis by dipstick testing
 - Mostly interested in the detection of **nitrites** and **leukocytes** produced by infection
 - Detection of **leukocytes** is sensitive but not specific
 - Detection of **nitrites** is reasonably sensitive for gram-negative bacteria but highly specific
 - **Combined detection of leukocytes and nitrites is sensitive and specific**
 - Red blood cell detection is not sensitive or specific



Validated Clinical Decision Aid for Uncomplicated Lower UTIs in Women



- **Simple 3-item decision aid:**
 1. **Symptoms** suggestive of UTI (dysuria, frequency, urgency)
 2. Presence of **leukocytes** (greater than a trace amount)
 3. Presence of **nitrites** (any positive amount including trace)

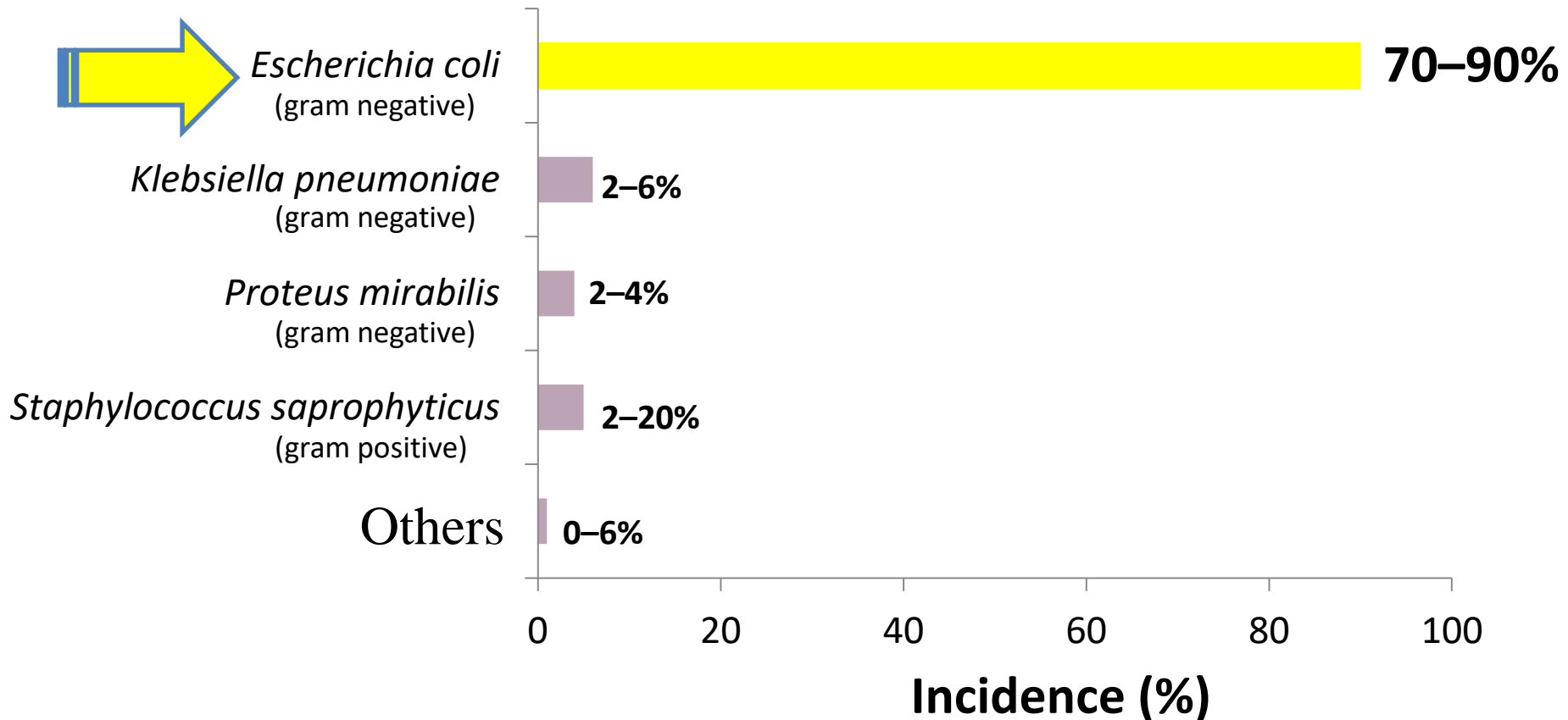
Meta-Analysis of Clinical Efficacy in Acute Uncomplicated Cystitis – AUC (If Pathogen Susceptible)

Drug	Dosage	% Clinical Cure	Evidence Level
TMP/SMX	1 DS BID X 3–7 days	<u>91</u>	A-I
Nitrofurantoin	100 mg BID x 5–7 days	<u>92</u>	A-I (7 d)
Fosfomycin	3 g single dose	<u>91</u>	A-I
Fluoroquinolones	3–7 days	<u>90</u>	B-III
β -lactams	7 days	<u>86</u>	A-III

Escherichia coli Is the Most Common Pathogen in UTIs



- Most UTIs are caused by gram-negative bacteria



Mclsaac WJ, et al. *Can J Infect Dis Med Microbiol*. 2013;24(3):143-149.

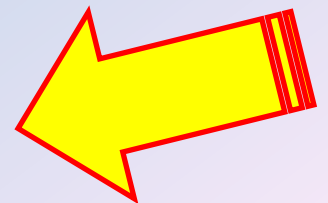
Pezzlo MA. *Clin Microbiol Newsl*. 2014;36(12):87-93.

CANWARD 2007- Present

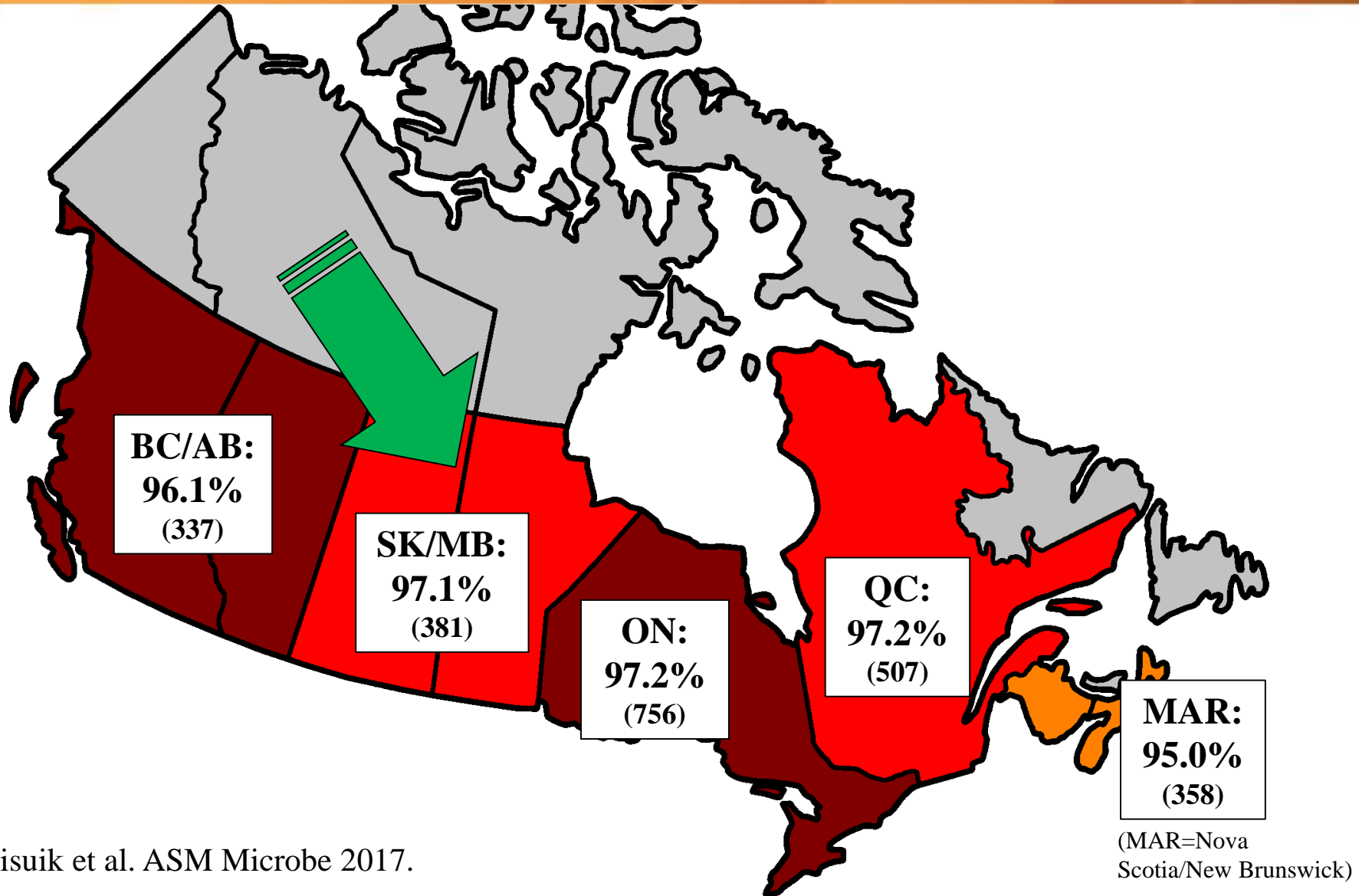
George Zhanel, Heather Adam, Mel Baxter, Melissa McCracken, Laura Mataseje, Michael R Mulvey, Matt Gilmour, Karen Wake, Ravi Vashisht, Sali Biju, Nancy Laing, James Karlowsky, Kim Nichol, Andrew Denisuik, Alyssa Golden, Rachel Hink, Philippe Lagacé-Wiens, Andrew Walkty, Frank Schweizer, Jack Johnson, the Canadian Antimicrobial Resistance Alliance (CARA) and Daryl J Hoban

**University of Manitoba, Health Sciences Centre,
National Microbiology Lab, Winnipeg, Canada and International Health Management
Associates (IHMA), Chicago, USA**

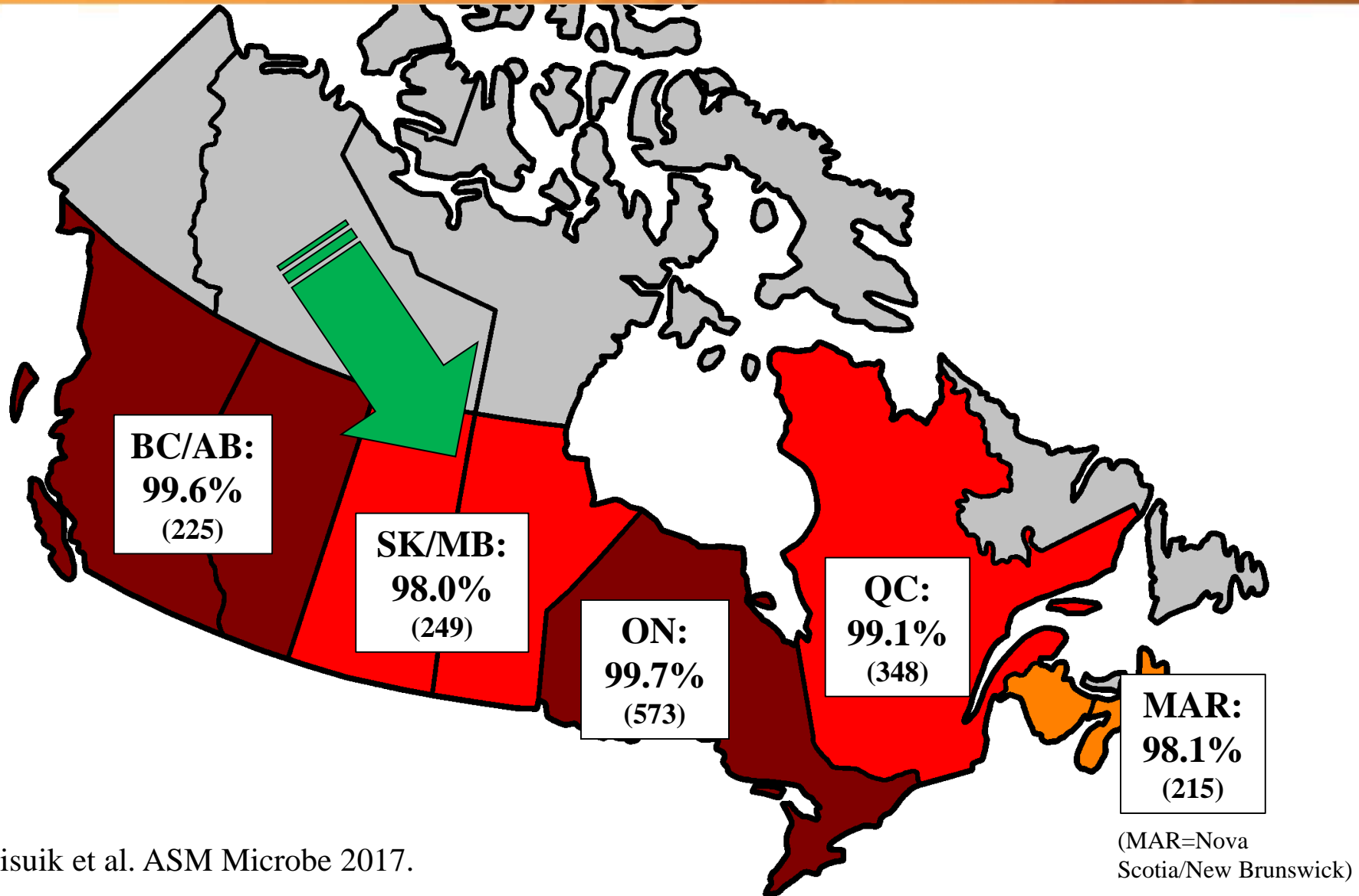
**Supplements in CJIDMM 2009, DMID 2011, JAC 2013, JAC 2019.
www.can-r.com.**



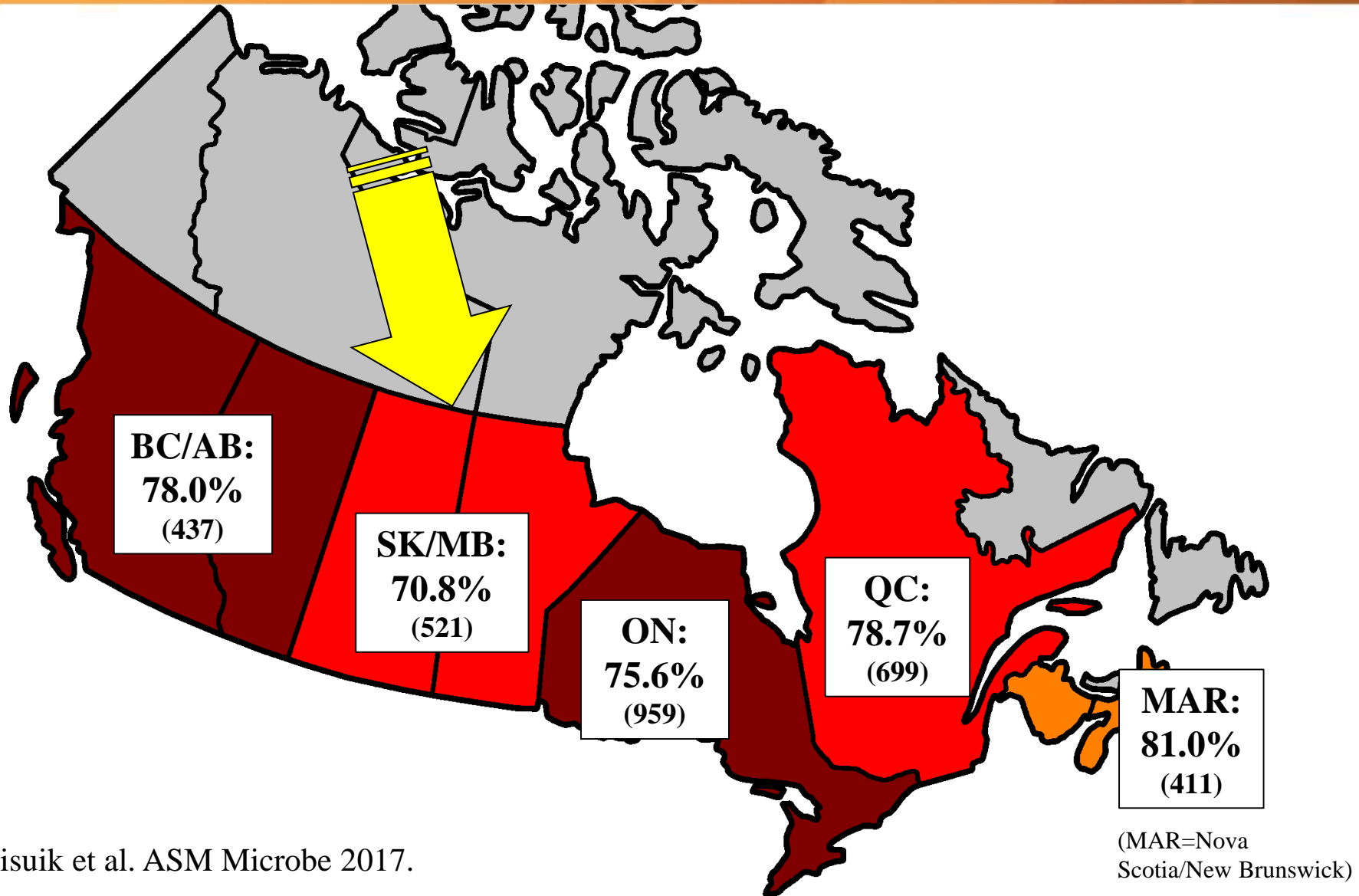
Nitrofurantoin Susceptibility in UTI *E. coli* - CANWARD 2007-2016



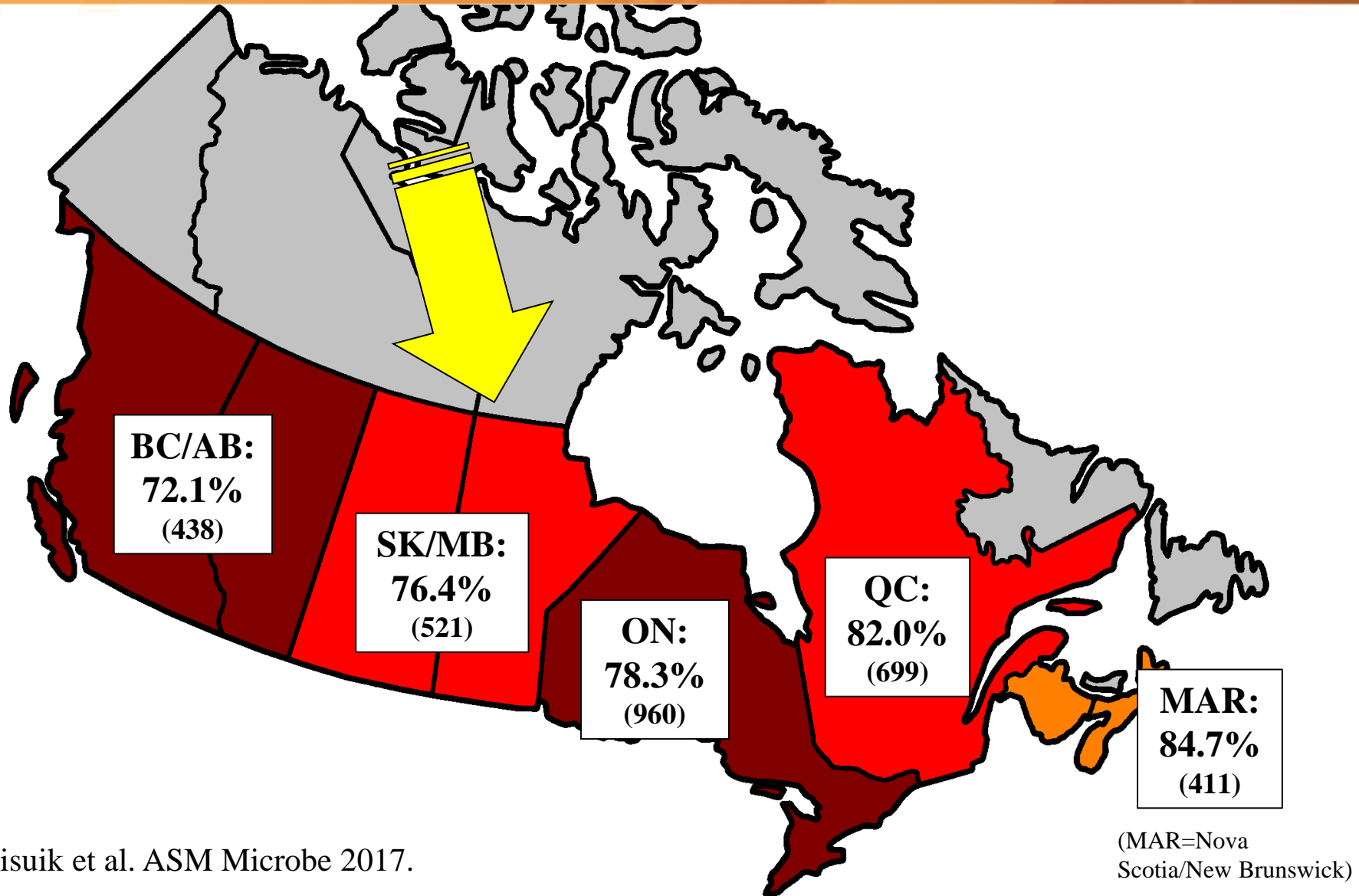
Fosfomycin Susceptibility in UTI *E. coli* - CANWARD 2007-2016



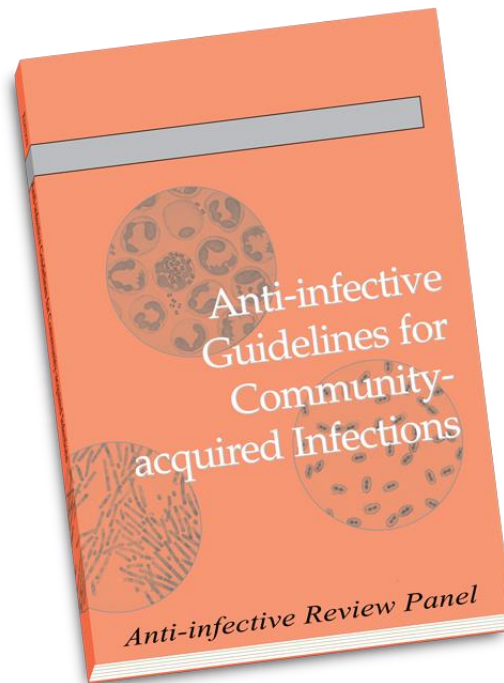
Trimethoprim-Sulfa Susceptibility in UTI *E. coli* - CANWARD 2007-2016



Ciprofloxacin Susceptibility in UTI *E. coli* - CANWARD 2007-2016



Canadian Guidelines Acute Uncomplicated Cystitis



Anti-Infective Guidelines for Community-acquired Infections. 2019 Edition.

Canadian/Ontario Recommendations: Treatment of Acute **Uncomplicated Cystitis (AUC)** in Women

- **First-line**

- – Fosfomycin 3 g single dose
- – Nitrofurantoin 100 mg BID x 5 – 7 days
- – **TMP/SMX 1 DS BID (TMP 200 mg Daily) x 3 days**

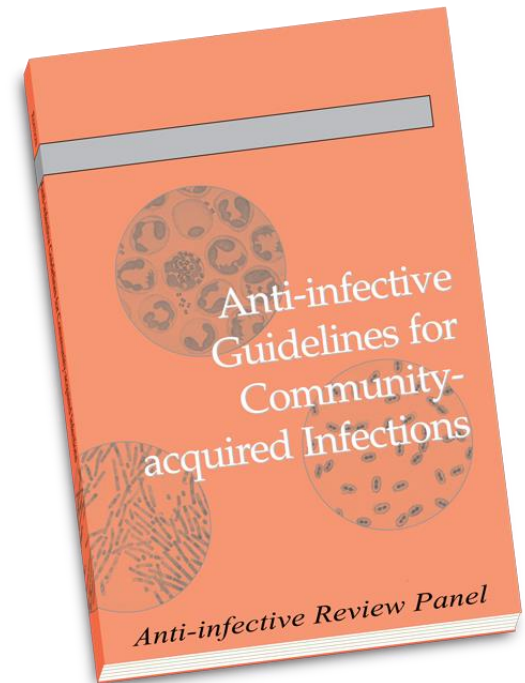
- **Second-line**

- – Amoxicillin 500 mg TID x 7 days
- – Ciprofloxacin 250 mg BID x 3 days (500 mg XL OD)
- – Norfloxacin 400 mg BID x 3 days

- **Third-line**

- – Cephalexin 500 mg BID x 7 days
- – Levofloxacin 250 mg OD x 3 days

→ **TMP/SMX only if resistance < 20%**



Fosfomycin PO and IV

Review Article CJIDMM 2016.

Fosfomycin: A First-Line Oral Therapy for Acute Uncomplicated Cystitis

George G. Zhanel, Andrew J. Walkty, and James A. Karlowsky

Review Article CJIDMM 2018.

Intravenous Fosfomycin: An Assessment of Its Potential for Use in the Treatment of Systemic Infections in Canada

George G. Zhanel , Michael A. Zhanel, and James A. Karlowsky 

Why do Clinicians like ORAL Fosfomycin for Treatment of Acute Uncomplicated Cystitis

- 99% *E. coli* susceptible
- Proven clinical efficacy, recommended by Guidelines
- ~40 years of proven safety (internationally)
- **Single dose treatment** (100% compliance)
- No clinically relevant drug interactions
- No dose adjustment for age, renal or hepatic dysfunction
- Safe in all trimesters of pregnancy and lactation

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Canadian/Ontario Recommendations: Treatment of Acute Asymptomatic Bacteriuria-ABU in Women

• ONLY screen and treat ABU in **PREGNANCY** and/or **PRE-OPERATIVE GU PROCEDURES...THATS IT !!!**

1. Safe in all trimesters
2. Not at term; not in renal dysfunction
3. Not in 1st trimester or last 6 weeks pregnancy



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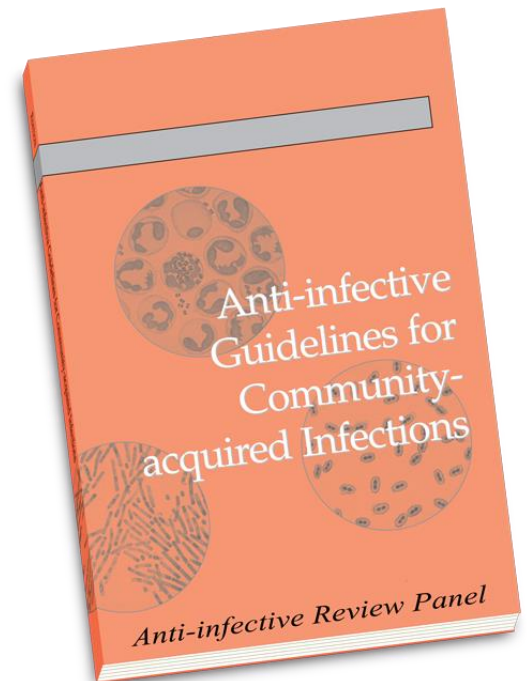
Canadian/Ontario Recommendations: Treatment of Acute **Uncomplicated Pyelonephritis** in Women

- **First-line**

- **TMP/SMX 1 DS BID (TMP 200 mg Daily) x 10-14 days**
- **Ciprofloxacin 500 mg BID x (1g XL OD) x 7 days**
- **Norfloxacin 400 mg BID x 7 days**
- **Levofloxacin 750 mg OD x 5 days**

- **Second-line**

- **Amoxicillin/Clavulanate 500 mg TID (875 BID) x 10-14 days**




Overall Conclusions - UTI 2020

- **Acute uncomplicated cystitis**
 - Fosfomycin
 - Nitrofurantoin
- **Screen/Treat asymptomatic bacteriuria**
 - Pregnancy
 - Pre-operative GU procedures
- **Acute uncomplicated pyelonephritis**
 - Fluoroquinolones (cipro/levo)
 - TMP/SMX

NEW/Investigational Agents vs. MDR Gram-negative Pathogens - UTI

- Ceftolozane/tazobactam-IV
 - Fosfomycin-PO/IV
 - Ceftobiprole-IV
 - Amox/clav-IV
- YES**

-
- Ceftazidime-avibactam-IV
 - Meropenem-vaborbactam-IV
 - Imipenem-relebactam-IV
 - Aztreonam-avibactam-IV
- ???**

- Ceftaroline-IV
 - Eravacycline-IV/Omadacycline-PO/IV
 - Plazomicin-IV
 - Delafloxacin-PO/IV
 - Cefiderocol-IV
 - Sulopenem-PO/Tebipenem-PO
- 

Peri et al. DMID 2019.

Jackson et al. JAC 2018;73:1452-9.

ASM Microbe 2017-2019.

Butler, Blaskovich and Cooper. J Antibiot 2017;70:3-24.

Int Urogynecol J (2013) 24:127–134

DOI 10.1007/s00192-012-1853-5

ORIGINAL ARTICLE

Evaluation of a therapeutic vaccine for the prevention of recurrent urinary tract infections versus prophylactic treatment with antibiotics

M. F. Lorenzo-Gómez · B. Padilla-Fernández · F. J. García-Criado · J. A. Mirón-Canelo · A. Gil-Vicente · A. Nieto-Huertos · J. M. Silva-Abuin

Lorenzo-Gómez, Int Urogynecol J 2013.

MV140 (Uromune Vaccine)

• Whole-cell inactivated bacteria

- ✓ *Enterococcus faecalis* (25%)
- ✓ *Klebsiella pneumoniae* (25%)
- ✓ *Escherichia coli* (25%)
- ✓ *Proteus vulgaris* (25%)

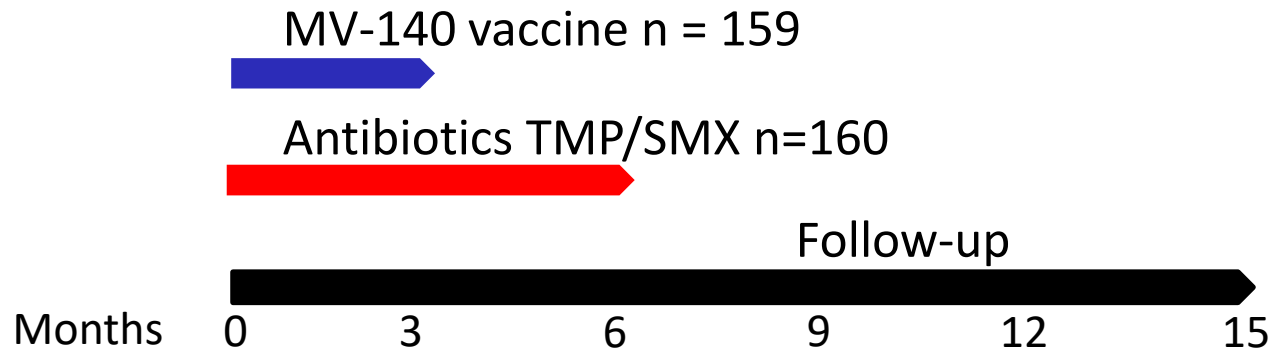
Concentration: 10^9 bacteria/mL

- Sublingual route – 2 sprays OD (10^8 bacteria/spray)
- Excipients: glycerol, pineapple essence, sodium chloride and water for injection



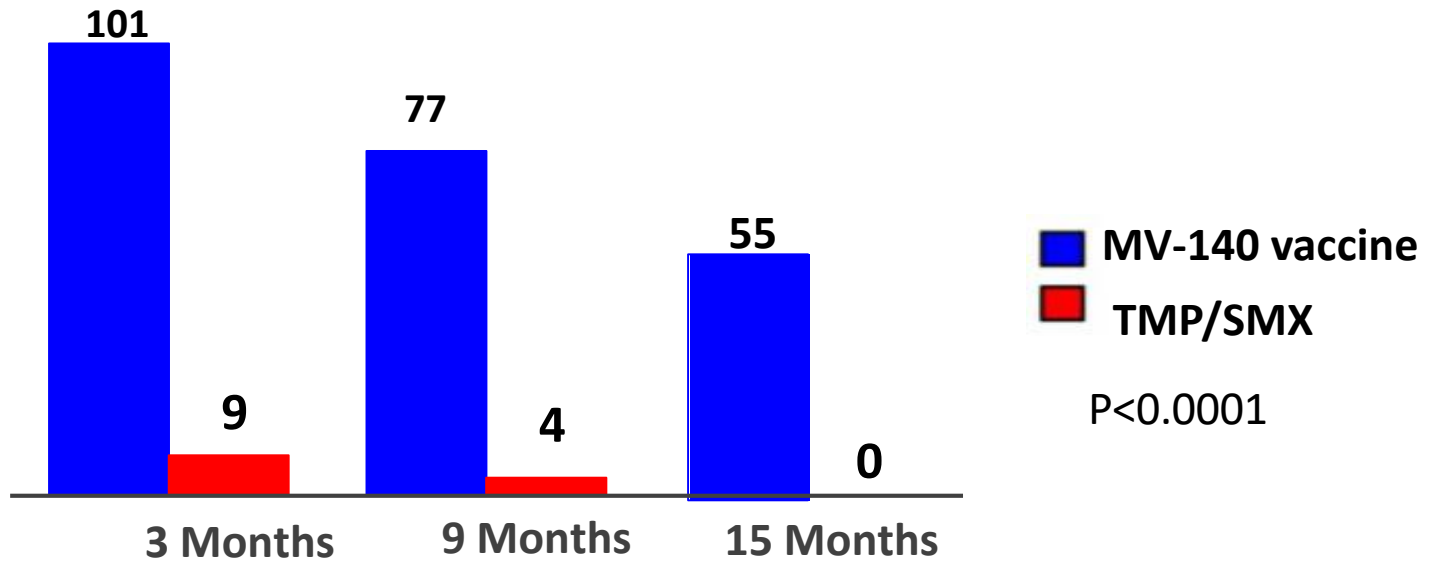
CLINICAL STUDY: MATERIAL & METHODS

Multicenter retrospective observational study Women with rUTIs



CLINICAL STUDY: RESULTS

Patients free of UTI



Summary – MV-140 Vaccine

- ✓ Potent immunostimulant effect
 - Cellular & systemic level
 - Specific & non-specific
- ✓ Efficacy in females with rUTIs
- ✓ Excellent safety profile
- ✓ **Potential to significantly reduce antibiotic consumption....less antibiotic resistance!**

