Antimicrobials on the Horizon

(A Microbiologists/Pharmacologists Perspective)

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A Patient With a Multi-Drug Resistant (MDR) Urinary Infection

- 78y M with prostatic hypertrophy and urinary infection symptoms
- Already taking ciprofloxacin without any benefit x 10 days
- Recent travel to India, no prior history of urinary infection
- Urine culture from one week ago grew *E. coli*
- Pelvic, rectal and kidney ultrasound normal

Lagacé-Wiens and Zhanel. JAC 2006; 57:1262-3.

This MDR *E. coli* is a Superbug!

Ampicillin	R
TMP/SMX	R
Ciprofloxacin	R
Gentamicin	R
Tobramycin	R
Amikacin	R

Cefazolin	R
Cefuroxime	R
Cefotaxime	R
Ceftazidime	R
Meropenem	S

Lagacé-Wiens and Zhanel. JAC 2006; 57:1262-3.

How Should We Treat This Patient ?

- **Amoxicillin-Clavulanate 500mg/125mg** po TID and his symptoms resolve in 4 days
- Repeat cultures at 8 weeks were negative
- We got lucky !!!

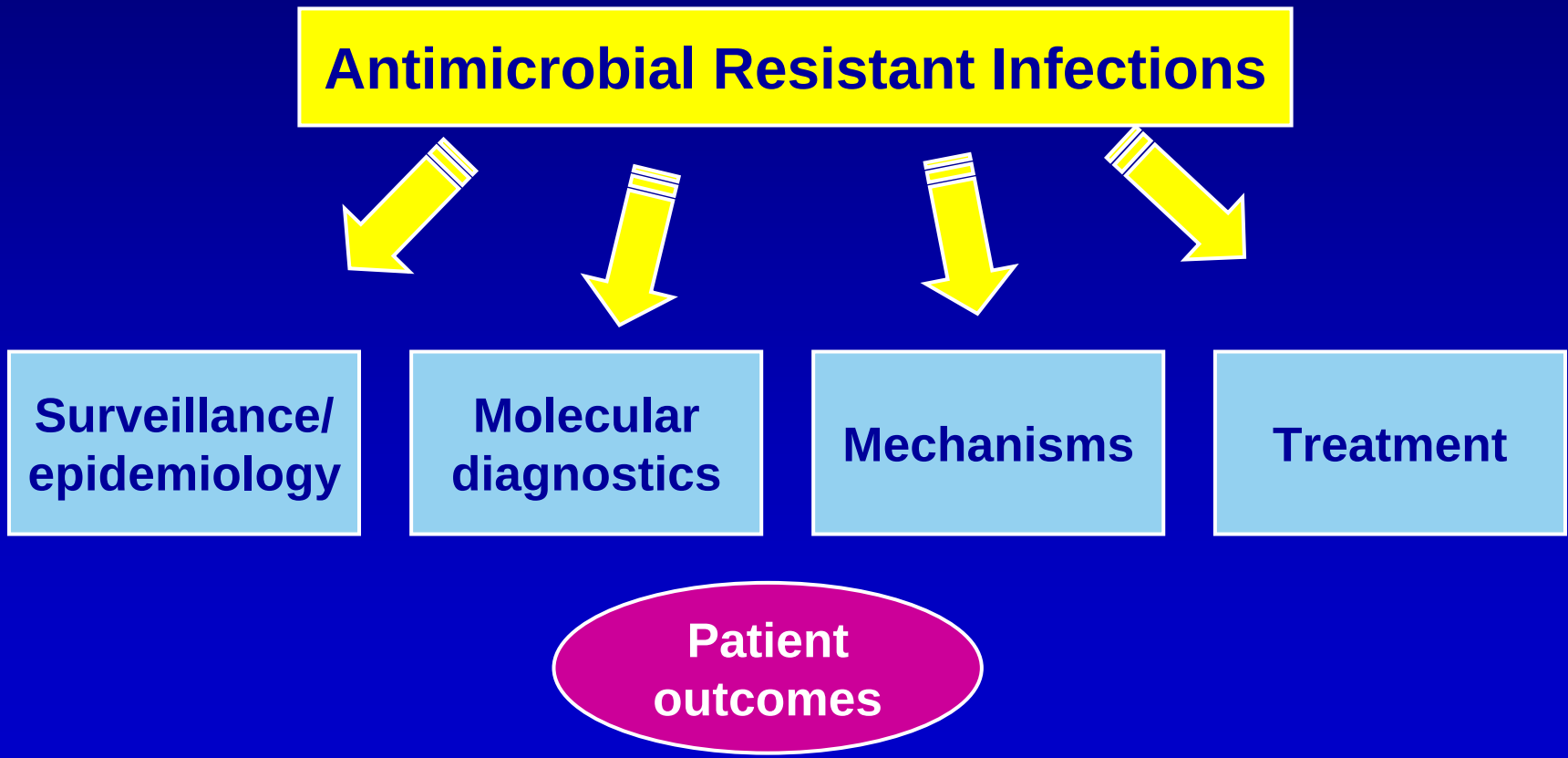
Lagacé-Wiens and Zhanel. JAC 2006; 57:1262-3.

Why are Antibiotic Resistant Superbug Infections Important to You ?

- Greater morbidity and mortality
- Hospitalization and supportive care
- Increased use of:
  - Laboratory and diagnostic tests
  - Infection control procedures
  - More expensive antimicrobials
  - Length of hospital stay and lost work days

Rubinstein and Zhanel. Lancet Infect Dis 2007.
Lynch and Zhanel. Sem Resp Crit Care Med 2005.
Cohen. Science 1992.

Canadian Antimicrobial Resistance Alliance (CARA)



www.can-r.ca

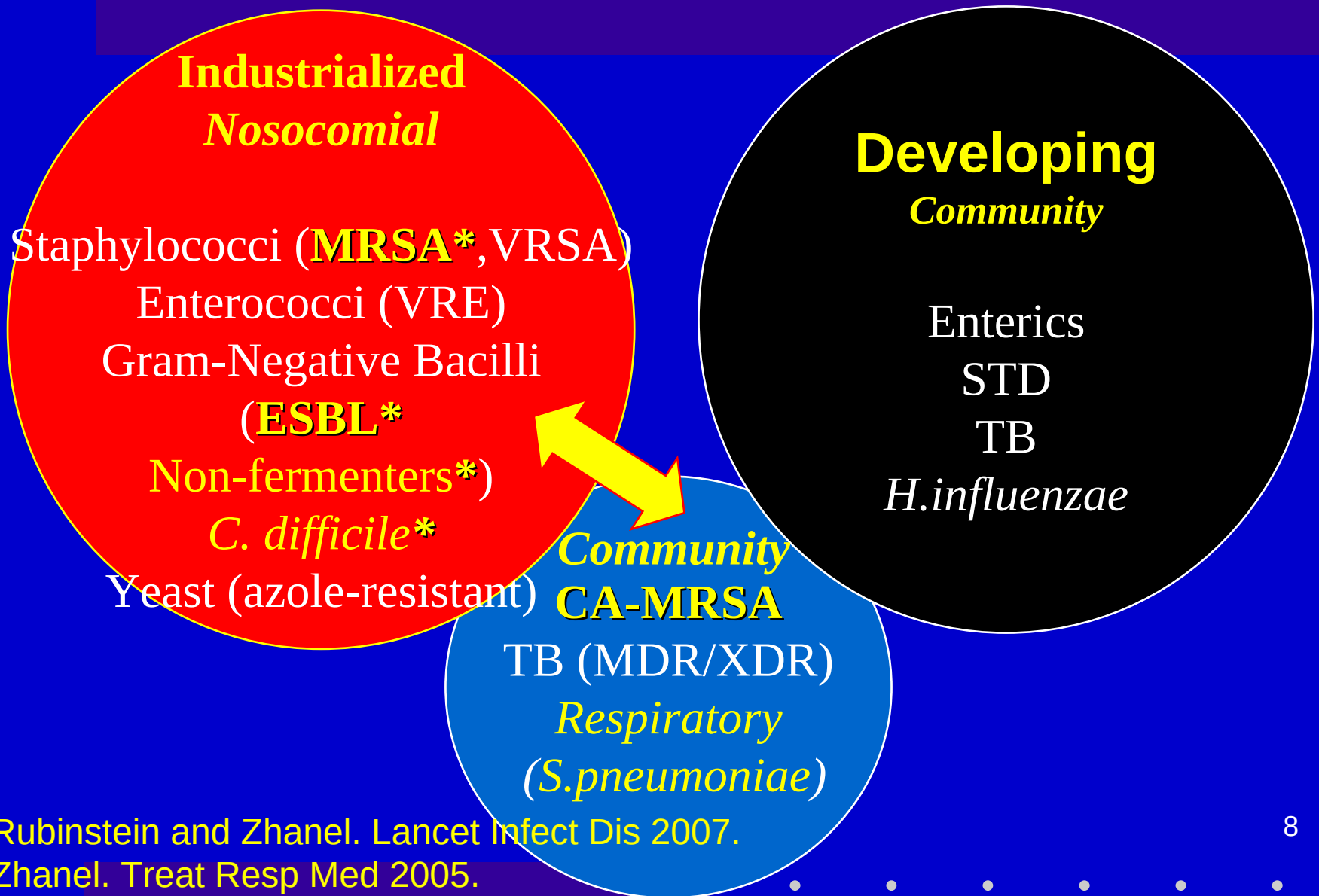
CARA Research Funding

- **NIH/CIHR/NSERC**
- **Health Canada**
- **MHRC**
- **MMSF**
- **MICH**
- **Manitoba Health**

- **Pharmaceutical Industry**
  - Abbott
  - Affinium
  - Apotex
  - Arpida
  - Astellas
  - Astra Zeneca
  - Bayer
  - Bristol Myers Squibb
  - Cangene
  - Cerexa
  - Chiron
  - Daiichi
  - GlaxoSmithKline

- **Pharmaceutical Industry**
  - Leo
  - Janssen Ortho/Ortho McNeill
  - Kane BioTech
  - Merck
  - Migenix
  - Novartis
  - Novexel
  - Novopharm
  - Optimer
  - Oryx
  - Pfizer
  - Procter and Gamble
  - Roche
  - Sanofi-Aventis
  - Schering-Plough
  - TaiGen
  - Targanta
  - Wyeth

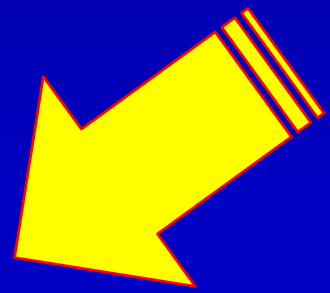
Antibiotic Resistant Pathogens are Spreading Across the World

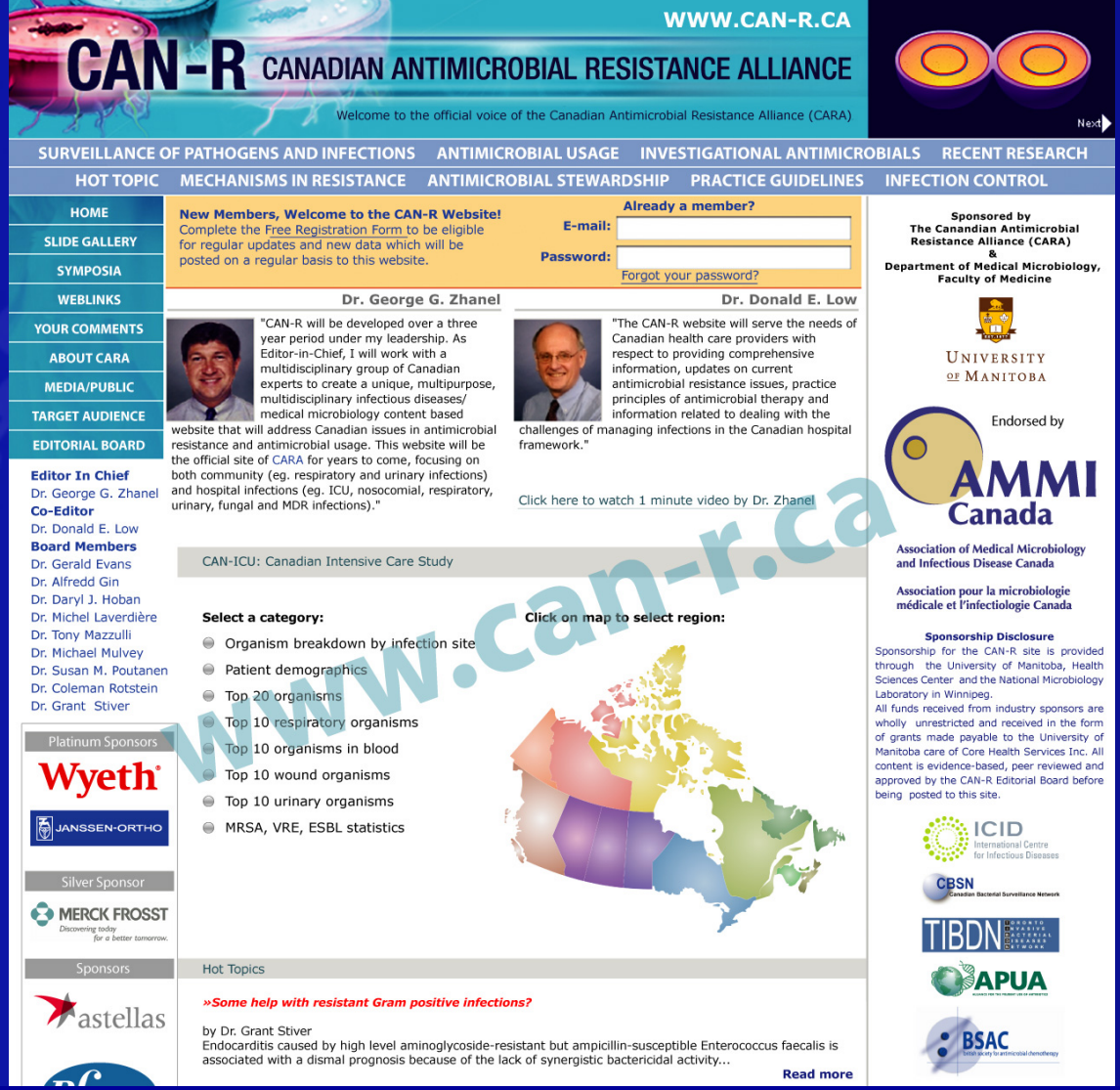


Rubinstein and Zhanel. Lancet Infect Dis 2007.
Zhanel. Treat Resp Med 2005.

Potential Solutions to Infections Caused By Resistant Superbugs

- Knowledge about resistant infections **(www.can-r.ca)**
- Infection control (wash those hands !)
- Appropriate antibiotic use
- Vaccination (eg. Influenza and *S.pneumoniae*)
- ABC's of treating infectious diseases
- Probiotics
- Discover and develop **new antibiotics**





www.can-r.ca

Methods to Minimize Antibiotic Resistance

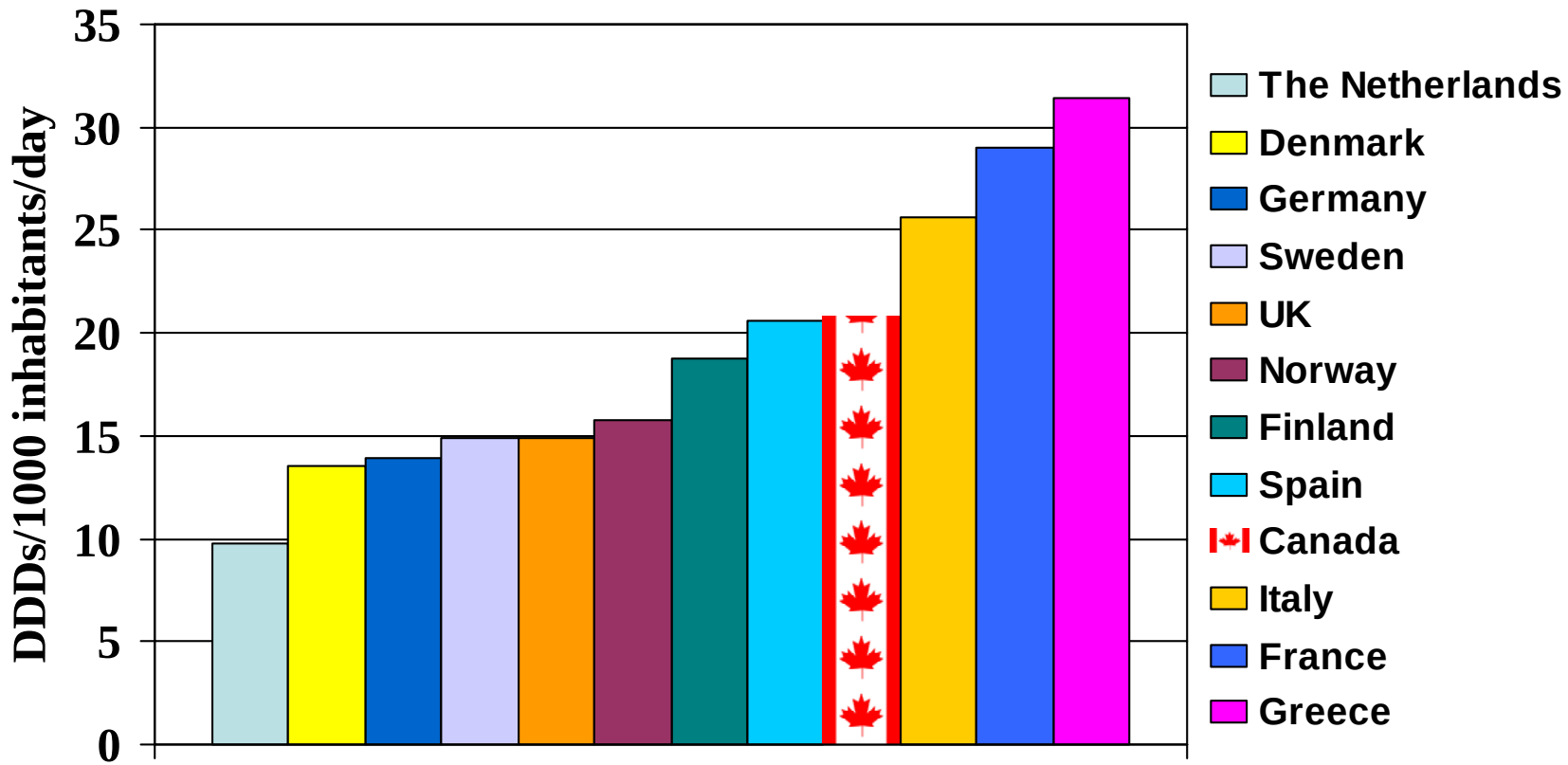
- Infection control (**wash those hands !**)

Scissors May Spread Resistant Organisms

- HCW (including surgeons) carry scissors (communal)
- Voluntary/permission
- Scissors swabbed/planted
- 78.4% (182/232) scissors colonized with organisms
- Organisms:
  - Gram-positive (*S. aureus*, *Enterococci* spp)
  - Gram-negative (*P. aeruginosa*, Acinetobacter)
- **Cleaning scissors with alcohol swab disinfected them.**

Embil, Hoban and Zhanel. Inf Cont Hosp Epid 2003;23:147-151.

Outpatient Antibiotic Use Compared to Europe*
2003

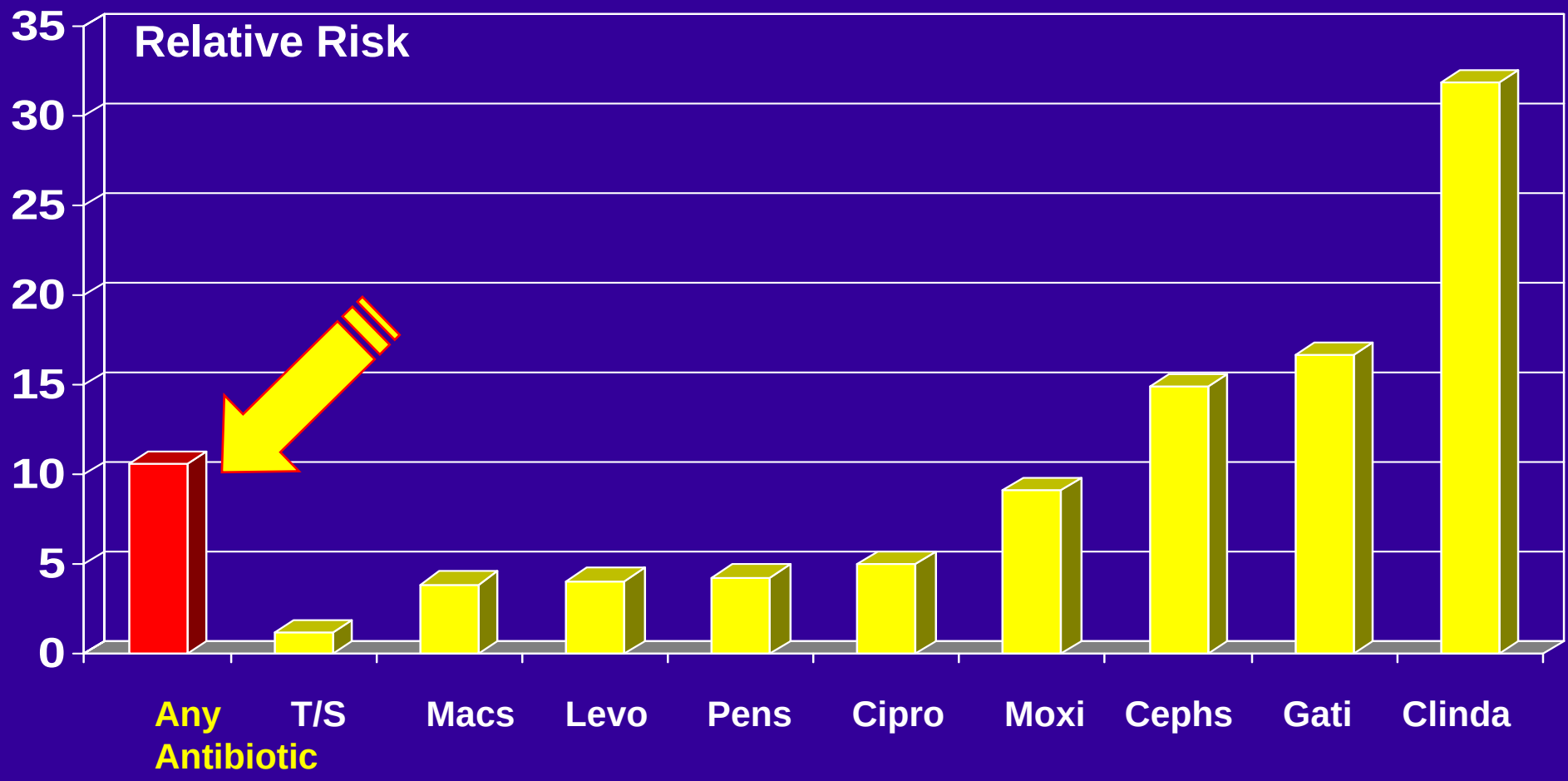


*selected countries
European data from the www.esac.ua.ac.be/
DDD=defined daily dose (WHO ATC)
Antibiotic use derived from data from IMS Health Canada

www.can-r.ca

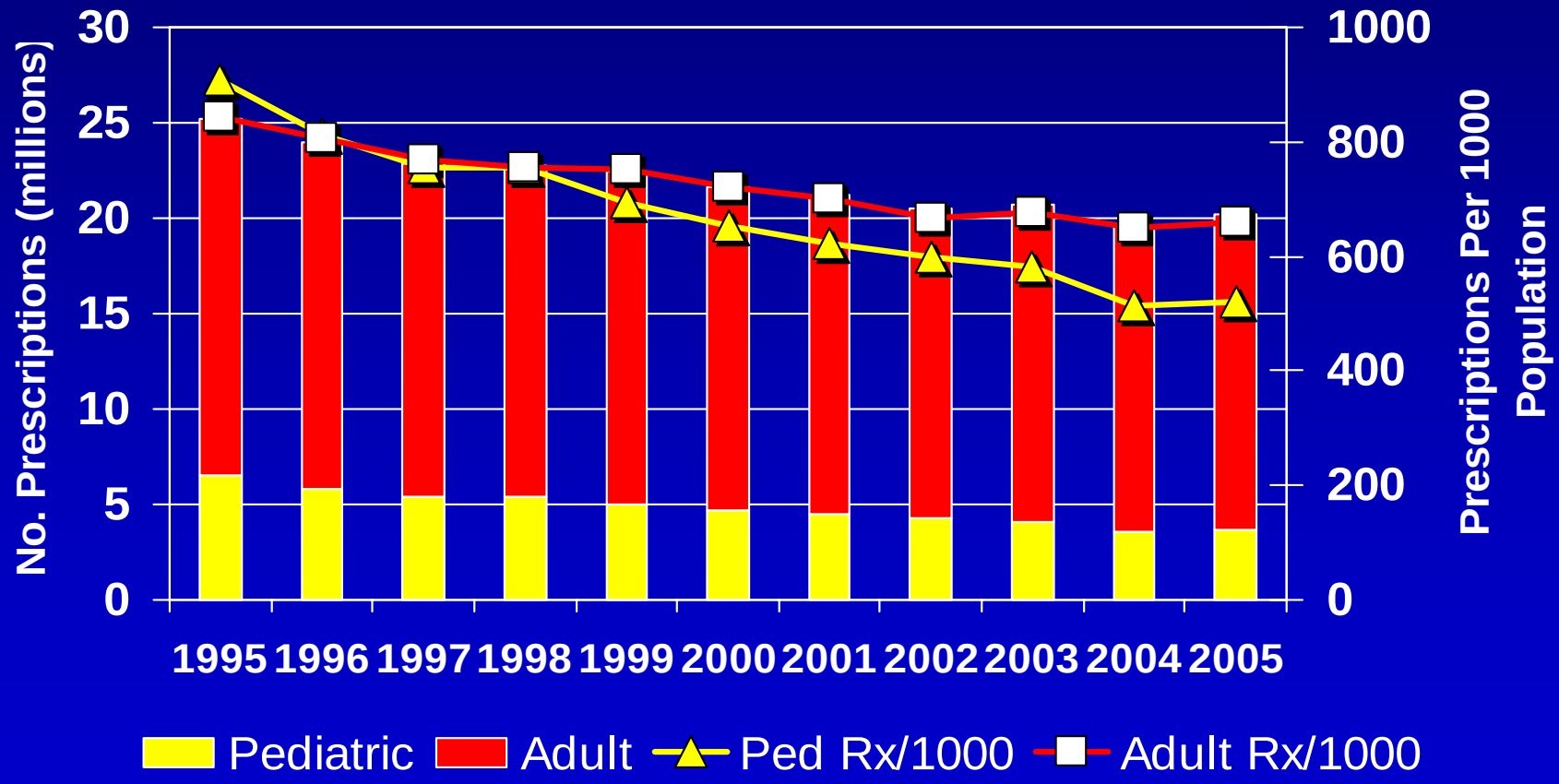
Relative Risk of *Clostridium difficile* Infection

(Antibiotic Exposure 45 days before index date)



Dial et al. CMAJ 2008;179(8): 767-772.

Adult and Pediatric Antibiotic Prescriptions in Canada (1995-2005)



Gin and Zhanel. ICAAC 2008/2006; www.can-r.ca.

Potential Solutions to Infections Caused By Resistant Superbugs

- Vaccination (eg. Influenza and *S.pneumoniae*)

Potential Solutions to Infections Caused By Resistant Superbugs

- ABC's of treating infectious diseases
  - Treat immediately
  - Kill the pathogen
  - If patient critically ill, you can not be wrong
  - Combinations if necessary (*P. aeruginosa*)

Probiotics

- Definition: live organisms that when administered in adequate amounts confer a health benefit to the host
- Normal, healthy, non-virulent bacteria
- Eg. *Lactobacillus* spp., *Saccharomyces boulardii*, *Bifidobacterium* spp.
- Available as foods, dietary supplements or as pharmaceuticals
- Tested vs untested products
  (eg. yogurt vs. specific probiotic product)

Use of Probiotics in Diarrhea

Type of Diarrhea	Effectiveness	Organism
Treatment-Infectious Adult/pediatric	**A**	*S. boulardii*, LGG
Prevention of diarrhea	B	*S. boulardii*, LGG
Prevention of AAD	**A**	*S. boulardii*, LGG, *Lactobacillus* spp.
Treatment of recurrent CDAD	B	*S. boulardii*, LGG
Prevention of CDAD	B	*S. boulardii*, LGG

Floch et al. J Clin Gastronter 2008;42 (Suppl 2):1-4-108.

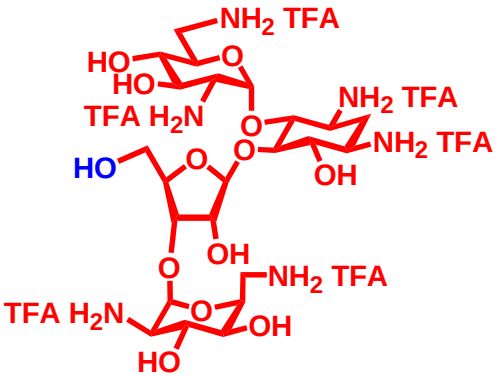
Probiotics - Unresolved Questions

- What is the best product(s) to use ?
- Does the method of delivery matter ?
- What dose to take ?
- What is the duration of treatment or prevention ?
- Other than imuunosuppressed individuals any other contra-indications or problems ?
- What is their role in human health ?

New Antimicrobials on the Horizon

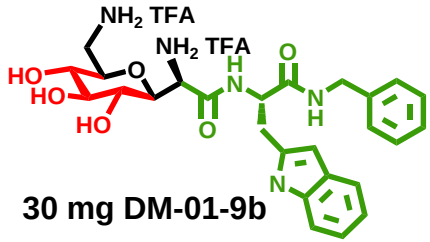
- **New fluoroquinolones/Topo Inh** (**nemonoxacin**, flinafloxacin, JNJ-Q2, ACH-702)
- **Ketolides/Macs** (**cethromycin**, CEM-101, EDP-420)
- **Oxazolidinones** (JNJ-416457, TR-700)
- **Glycylcyclines** (PTK0796)
- **Cephalosporins** (**ceftobiprole**, ceftaroline, CXA-101)
- **Carbapenems** (**doripenem**, faropenem, sulopenem, **PZ-601**, ME1036)
- **Monobactams** (BAL30072)
- **Novel β-lactamase inhibitors** (**NXL-104**, **Pip/BLI-489**, Me1071)
- **Glyco/lipopeptides** (**oritavancin**, **dalbavancin, telavancin,** MX-2401)
- **FabI inhibitors** (**AFN-1252,** MUT37307)
- **Peptide/Peptide Mimetics** (Arenicin-3, BL-2060, CSA-13, EA-230)
- **Peptide Deformylase Inhibitors** (VRC4887/NVP-PDF713, BB 83698)
- **Antisense** (Phosphorodiamidate morpholin oligomers-PMO's)
- **Chorismate synthase inhibitors** ("Round Up" derivatives)
- **Bacteriophages**
- **Monoclonals** (tefibazumab)
- **GSQ 7302** (SMAT-Small Molecule Anti-genomic Therapeutic)
- **Diaminopyridines** (**Iclaprim**, BAL30543-5)
- **Efflux inhibitors** (M-Pex – **MP601205**)
- **Hybrids** (FQ/Rif, Glyco/Ceph)

ICAAC 2007-8



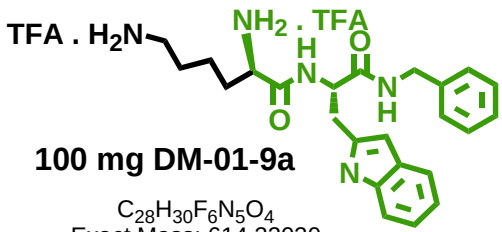
Neomycin B (TFA)$_6$

$C_{35}H_{46}F_{18}N_6O_{19}$
Exact Mass: 1196.25303
Mol. Wt.: 1196.73980
C, 35.13; H, 3.87; F, 28.58; N, 7.02; O, 25.40



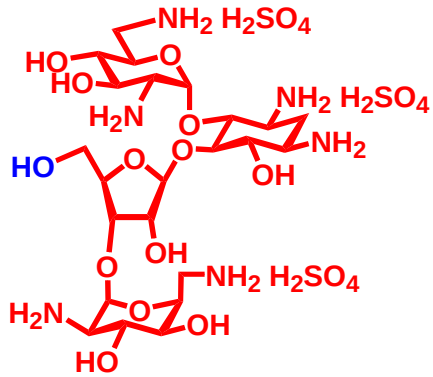
30 mg DM-01-9b

$C_{30}H_{32}F_6N_5O_8$
Exact Mass: 704.21551
Mol. Wt.: 704.59420
C, 51.14; H, 4.58; F, 16.18; N, 9.94; O, 18.17



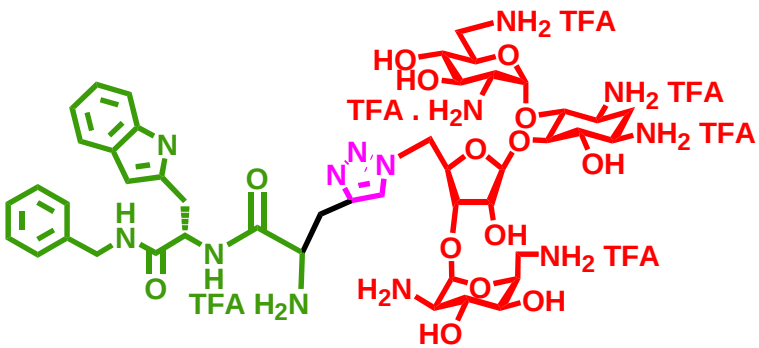
100 mg DM-01-9a

$C_{28}H_{30}F_6N_5O_4$
Exact Mass: 614.22020
Mol. Wt.: 614.55932
C, 54.72; H, 4.92; F, 18.55; N, 11.40; O, 10.41



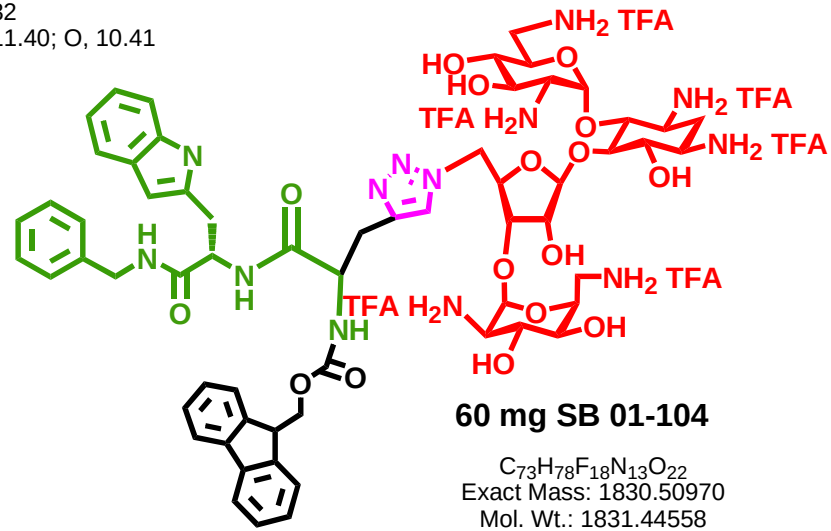
Neomycin B (H_2SO_4)$_3$

$C_{23}H_{52}N_6O_{25}S_3$
Exact Mass: 908.21443
Mol. Wt.: 908.87918
C, 30.39; H, 5.77; N, 9.25; O, 44.01; S, 10.58



53 mg SB 01-100

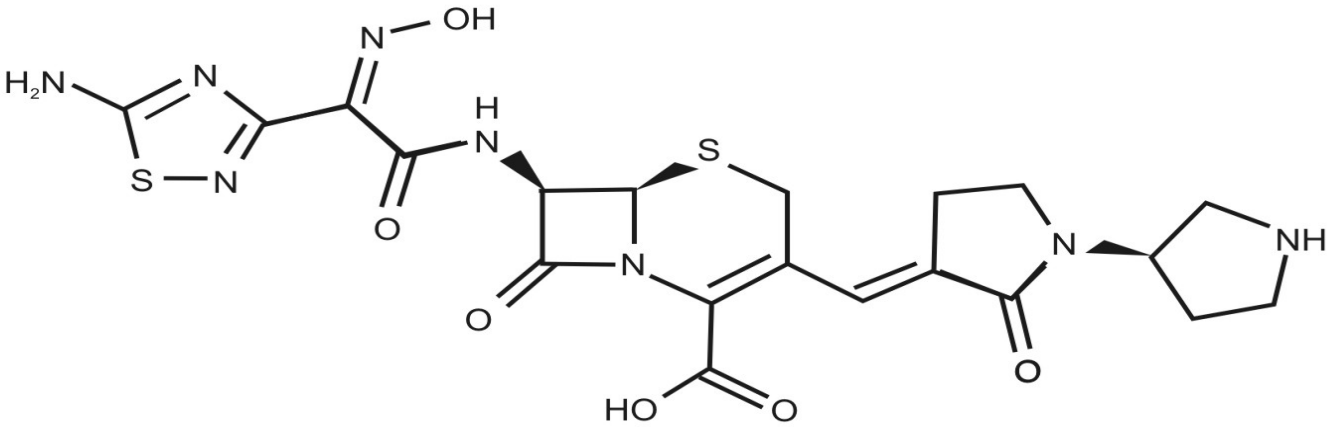
$C_{58}H_{68}F_{18}N_{13}O_{20}$
Exact Mass: 1608.44162
Mol. Wt.: 1609.20688
C, 43.29; H, 4.26; F, 21.25; N, 11.32; O, 19.88



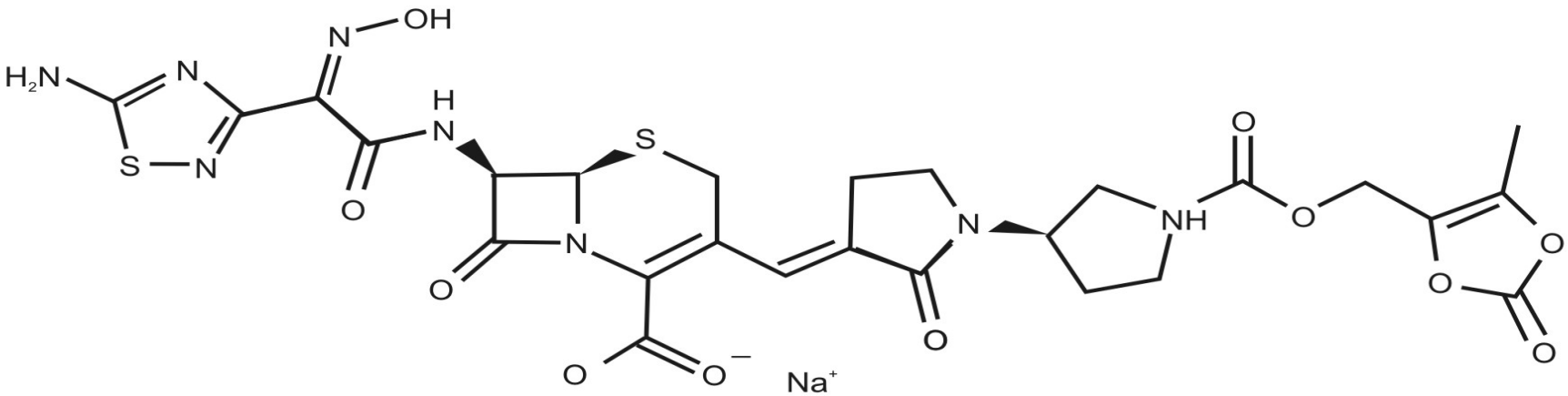
60 mg SB 01-104

$C_{73}H_{78}F_{18}N_{13}O_{22}$
Exact Mass: 1830.50970
Mol. Wt.: 1831.44558
C, 47.87; H, 4.29; F, 18.67; N, 9.94; O, 19.22

Schweizer and Zhanel. J Med Chem 2008.



Ceftobiprole



Ceftobiprole medocaril

Zhanel et al. Am J Clin Derm 2008;9(4):245-254.

Ceftobiprole (Zeftera ®)

CANWARD 2007
(Zhanel et al. CJIDMM 2009 and www.can-r.ca)

Top 10 Organisms Causing Bacteremia

National

Rank	Organism	n	% of Total
1	*E. coli*	795	21.9
2	*S. aureus* - MSSA	487	13.4
3	*K. pneumoniae*	266	7.3
4	CNS / *S. epidermidis*	257	7.1
5	*S. pneumoniae*	232	6.4
6	*S. aureus* - MRSA	169	4.7
7	*E. faecalis*	154	4.2
8	*P. aeruginosa*	148	4.1
9	*C. albicans*	100	2.8
10	*E. cloacae*	88	2.4

CANWARD 2007

(Zhanel et al. CJIDMM 2009 and www.can-r.ca)

Top 10 Organisms Causing Skin/Soft Tissue Infections (Wounds)

National

Rank	Organism	n	% of Total
1	*S. aureus* - MSSA	204	33.1
2	*S. aureus* - MRSA	76	12.3
3	*P. aeruginosa*	63	10.2
4	*E. coli*	57	9.2
5	*S. pyogenes*	31	5.0
6	CNS / *S. epidermidis*	26	4.2
7	*Enterococcus spp.*	25	4.1
8	*E. cloacae*	21	3.4
9	*S. agalactiae*	20	3.2
10	*K. pneumoniae*	18	2.9

CANWARD 2007

(Zhanel et al. CJIDMM 2009 and www.can-r.ca)

Top 10 Organisms Causing Respiratory Infections

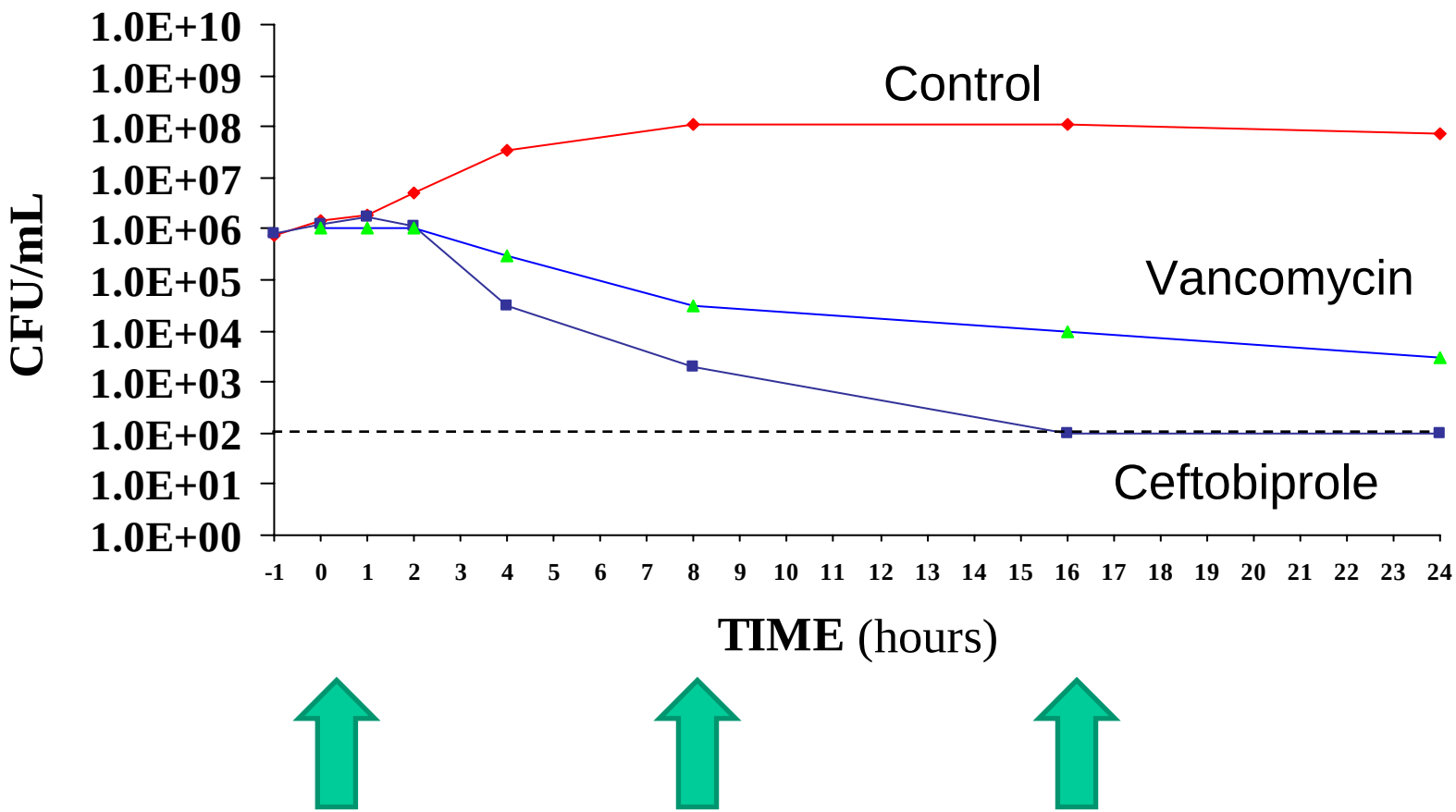
National

Rank	Organism	n	% of Total
1	*S. pneumoniae*	470	20.4
2	*S. aureus* - MSSA	383	16.6
3	*P. aeruginosa*	380	16.5
4	*H. influenzae*	321	13.9
5	*S. aureus* - MRSA	124	5.4
6	*E. coli*	102	4.4
7	*M. catarrhalis*	91	3.9
8	*S. maltophilia*	79	3.4
9	*K. pneumoniae*	61	2.6
10	*S. marcescens*	51	2.2

Ceftobiprole Killing of MRSA

(fC_{max} 30 ug/mL, t½ 3.5 hrs, MRSA 60392)

(Vancomycin 1, Clindamycin >8, Ceftriaxone >64, Ceftobiprole 1 ug/mL)



Zhanel et al. JAC in press 2009.

(MSSA,MRSA,VISA,VRSA)

Comparative Spectrum of Ceftobiprole: A New Broad-Spectrum Cephalosporin

Zhanel et al. Am J Clin Derm 2008;9(4):245-254; Zhanel et al. Drugs 2007

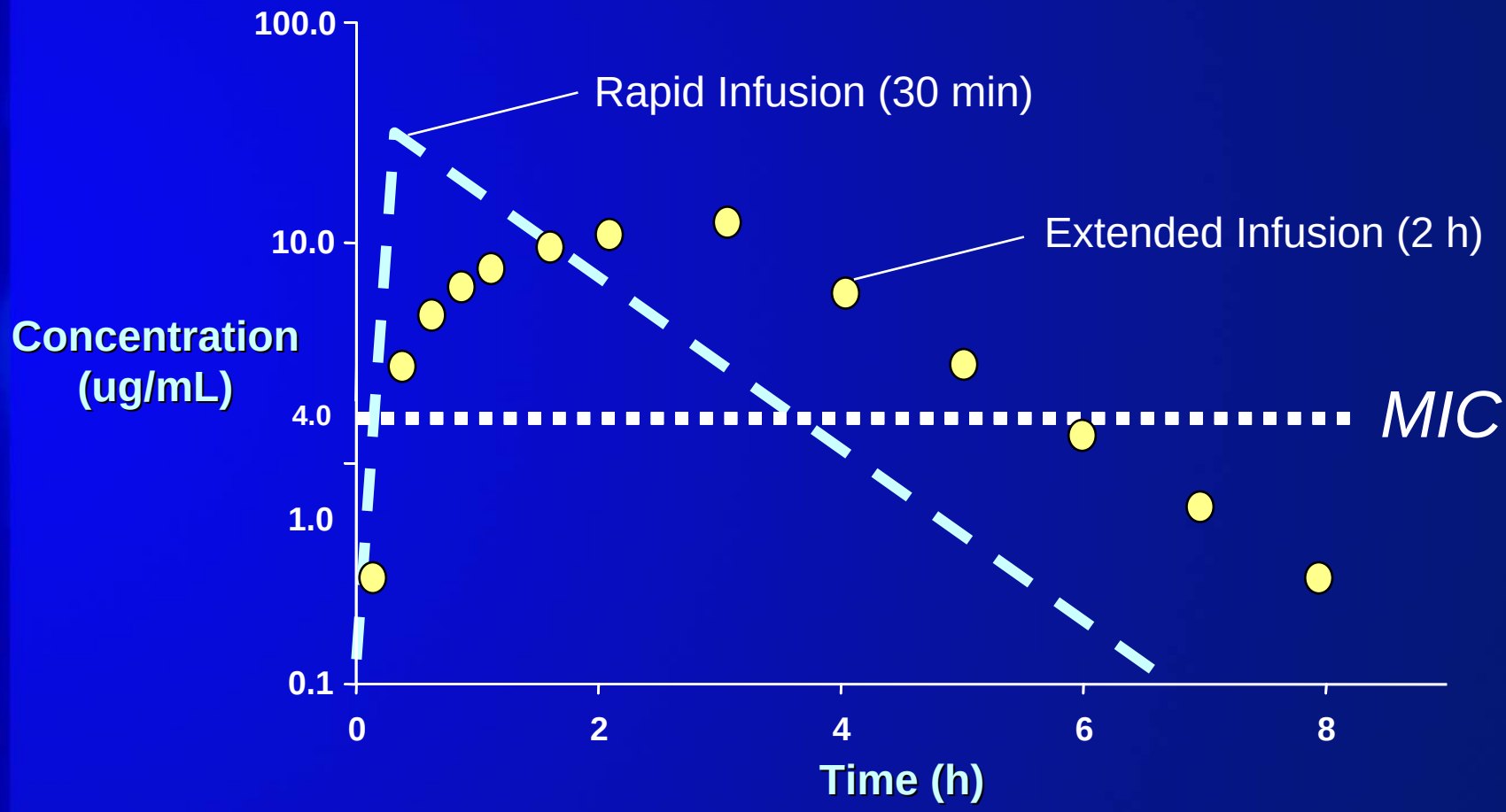
Antibiotic	MRSA	*E. faecalis*	GNB (*E. coli*)	*P. aeruginosa*	Anaerobes (*B. fragilis*)
Ceftobiprole	++++	++++	++++	++++	+
Ceftriaxone/ Cefotaxime	-	-	+++	++	+
Ceftazidime	-	-	+++	++++	+
Cefepime	-	-	++++	++++	+
Pip/Tazo	-	++++	++++	++++	++++
Meropenem	-	++	++++	+++	++++

Clinical Trials of Ceftobiprole

- **cSSSI (caused by GPC and/or GNB)**
- **DFI, wound, abscess, cellulitis**
- Ceftob 500mg q8h (**2hr inf**) vs. Vanco 1g q12h + ceftaz 1g q8h (2hr inf)
  - Cure: C (485) – 90.5% vs V/C (244) – 90.2%
  - Cure (DFI): C 86.2% vs. V/C 81.8%
- Microbiological eradication:
  - MRSA: C 89.7% (78/87) vs V/C 86.1% (31/36)
  - *P. aeruginosa*: C 86.7% (26/30) vs V/C 100% (9/9)
- AE: Similar

Noel et al. CID 2008;46;647-655.

Ceftobiprole 500 mg Administered as a 0.5 h or 2 h Infusion



Adapted from Zhanel et al. Am J Clin Derm 2008; 9(4):245-254.

Nosocomial Pneumonia-NP/ Ventilatory Acquired Pneumonia (VAP)

- Ceftob 500mg q8h (2hr inf) vs. Ceftazidime 2g q8h (2hr inf) + Linezolid 600mg q12h
- **NON-VAP**:
  - Cure: C (199) – 77.4% vs C/L (190) – 76.3%
- Microbiological eradication:
  - MSSA: C 79.0% (15/19) vs C/L 71% (22/31)
  - MRSA: C 41% (7/17) vs C/L 53% (10/19)
  - *P. aeruginosa*: 60% (9/15) vs C/L 55% (11/20)

Noel et al. ICAAC 2008.

Ceftobiprole: Summary/Role in Therapy

- Single agent with very bactericidal broad spectrum activity
  - Activity against MRSA, *E. faecalis*, GNB including *Acinetobacter* spp. and *P. aeruginosa*
- Safety of a cephalosporin
- Empiric treatment (instead of 2 agents)
  - cSSSI, CAP, NP
- Pathogen directed therapy
  - MRSA, GNB, *Acinetobacter* spp., *P. aeruginosa*

Doripenem-A new Carbapenem

- Gram-positive cocci activity similar to imipenem:
- Gram-negative bacilli activity similar to meropenem:
- Very active against *P. aeruginosa*
  - **More active and less resistance than meropenem/imipenem**
- Pharmacokinetics similar to imip/merop

Zhanel et al. Drugs 2007;67:1027-1052.
Zhanel and Hoban ICAAC/IDSA 2008.
Zhanel et al. CJIDMM 2009;20(Suppl A):1-72.

Doripenem-A new Carbapenem

- Clinical Trials:
  - **NP:**
  - Dori 500mg q8h (1hr inf) vs. P/T 4.5g q6h
    - Cure: D-81.3% vs P/T-79.8%
    - AE: Similar
  - **cIAI:**
  - Dori 500mg q8h (1hr inf) vs. Mero 1g q8h
    - Cure: D-85.9% vs P/T-85.3%
    - AE: Similar

Rea-Neto et al. Curr Med Res Opin 2008;24(7):2113-26.
Lucasti et al. Clin Ther 2008;30(5):868-883.

Doripenem-A new Carbapenem

Clinical Trials:

- **VAP:**
- Dori 500mg q8h (4hr inf) vs. Imip 500mg q6h (or 1g q8h)
  - Cure: D-68.3% vs I-64.2%
  - *P. aeruginosa*: ? Erad: D: 65% (18/28) vs. I: 38% (9/25)

Chastre et al. Crit Care Med 2008;36(4);1089-1096.

Doripenem is less likely to select for resistance in *P. aeruginosa* vs imipenem or meropenem

Strain	Imipenem	Meropenem	Doripenem
46139	32	>32	8
49674	>32	>32	16
59690	>32	>32	8
62958	>32	32	8
63930	>32	>32	8

Zhanel et al. CJIDMM 2009;20(Suppl A):1-72.

Tanimoto et al AAC 2008. Doripenem less likely than meropenem to select resistant *P. aeruginosa* (↓ OprD and ↑ *mexAB-oprM*).

Doripenem is less likely to select for resistance in *P. aeruginosa* vs imipenem or meropenem

Strain	Doripenem/ Levofloxacin	Doripenem/ Tobramycin	Doripenem/ Colistin
46139	0.5	1	2
49674	0.5	1	2
59690	0.5	1	1
62958	0.5	1	1
63930	0.5	1	2

Zhanel et al. CJIDMM 2009;20(Suppl A):1-72.

What Role Will Doripenem Play ???

- Serious infections in hospitalized patients
- Empiric treatment where both gram-positive and gram-negative coverage is required (ie. need a carbapenem)
  - Eg. HAP, VAP, cSSTI, IAI, ICU infections, etc
- **Imipenem/Meropenem but with better anti- *P. aeruginosa* properties ?**

Zhanel et al. Drugs 2007;67:1027-1052.
Zhanel and Hoban ICAAC/IDSAA 2008.
Zhanel et al. CJIDMM 2009;20(Suppl A):1-72.

FDA (?TPD) Issues with New Antimicrobials

- The standard for safety and efficacy has been raised
- New agents asked to “do more” studies:
  - Faropenem (vs. placebo ?)
  - Oritavancin
  - Dalbavancin
- Higher standards for study sites (eg. telithromycin, ceftobiprole)
- FDA asks is this new agent needed ?

Provincial Formulary Hurdles

- Lots of safety data wanted
- Superiority trials preferred (not inferiority)
  - proof vs. potential
- Very competitive price requested

- Worried about driving use of the class
- Worried about resistance development

A NO from the CDR is a death sentence,
but a YES may actually be a MAYBE

Hospital Formulary Hurdles

- Lots of safety data wanted
- Superiority trials preferred (not inferiority)
  - proof vs. potential
- Very competitive price requested
  - generics

- Worried about how/who to restrict use to minimize cost/resistance development

Big Pharma/Biotech Considerations (Antibiotics)

- Difficult to find new classes
- FDA hurdles
- Infrequently used
- Short duration treatments
- Formulary hurdles
- Lots of generics
- Restriction to Infectious Diseases
- What if resistance develops

Conclusions

- Reduction in Big Pharma agents
  - (acute vs chronic disease)
- Biotech agents
- FDA issues
- Formulary hurdles
- What to do with probiotics ?