

Antimicrobials on the Horizon

(A Microbiologists/Pharmacologists Perspective)

George G. Zhanel

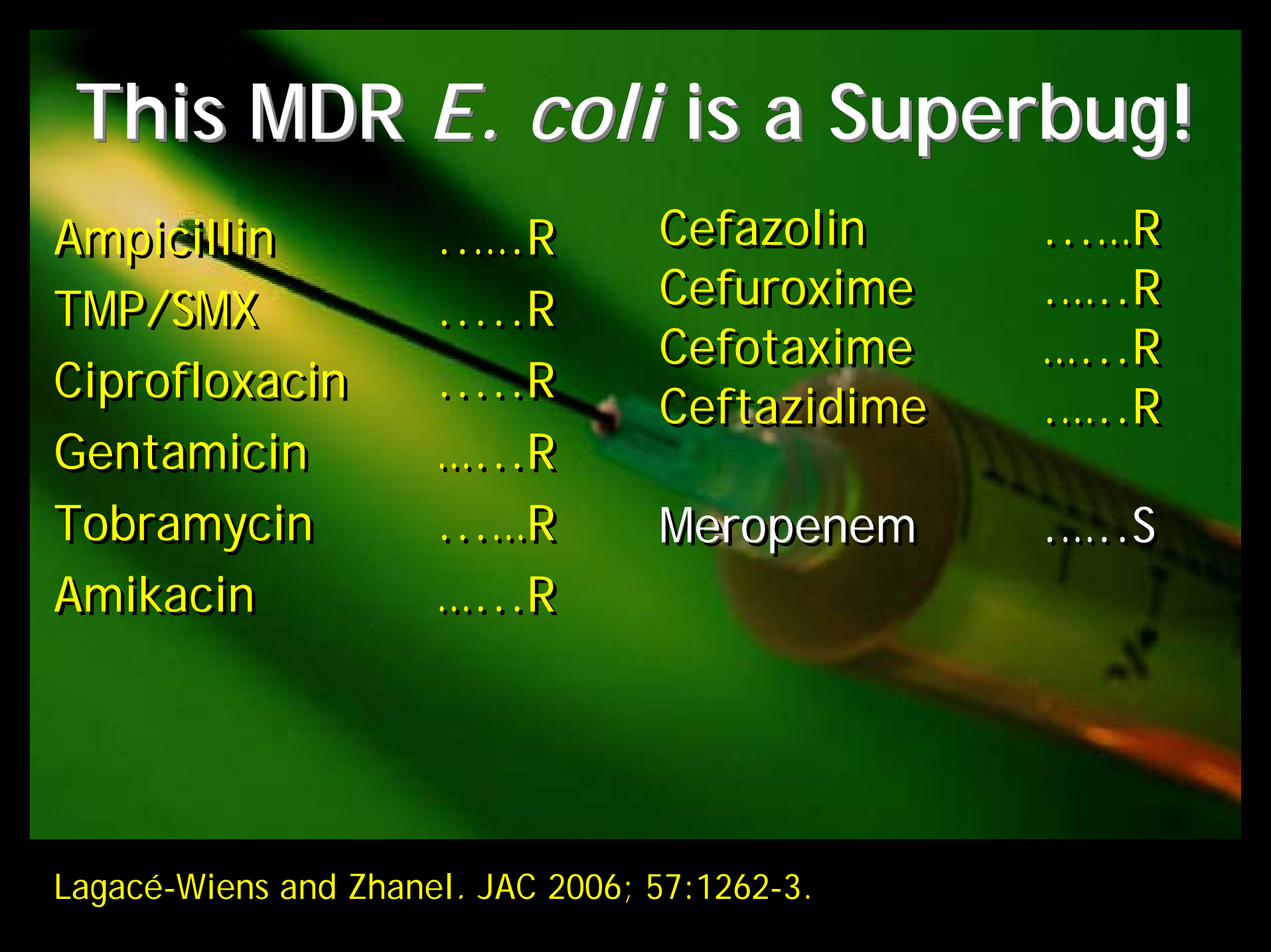
**Professor, Dept. of Medical Microbiology/Infectious Diseases
University of Manitoba;**

**Coordinator-Antibiotic Resistance Program, Dept. of Medicine/Microbiology
Health Sciences Centre, Winnipeg, Canada**

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

This MDR *E. coli* is a Superbug!



AmpicillinR	CefazolinR
TMP/SMXR	CefuroximeR
CiprofloxacinR	CefotaximeR
GentamicinR	CeftazidimeR
TobramycinR	MeropenemS
AmikacinR		

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 !!!

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)

Antimicrobial Resistant Infections

```
graph TD; A[Antimicrobial Resistant Infections] --> B[Surveillance/epidemiology]; A --> C[Molecular diagnostics]; A --> D[Mechanisms]; A --> E[Treatment]; B --> F([Patient outcomes]); C --> F; D --> F; E --> F;
```

Surveillance/
epidemiology

Molecular
diagnostics

Mechanisms

Treatment

Patient
outcomes

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
 - Novoxel
 - Novopharm
 - Optimer
 - Oryx
 - Pfizer
 - Procter and Gamble
 - Roche
 - Sanofi-Aventis
 - Schering-Plough
 - TaiGen
 - Targanta
 - Wyeth

Antibiotic Resistant Pathogens are Spreading Across the World

Industrialized *Nosocomial*

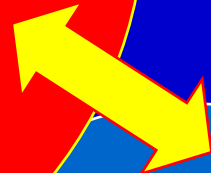
Staphylococci (**MRSA***, VRSA)
Enterococci (VRE)
Gram-Negative Bacilli
(**ESBL***
Non-fermenters*)
*C. difficile**
Yeast (azole-resistant)

Developing *Community*

Enterics
STD
TB
H.influenzae

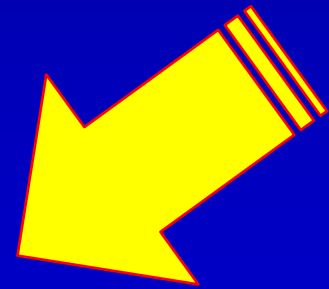
Community **CA-MRSA**

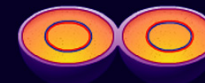
TB (MDR/XDR)
Respiratory
(*S.pneumoniae*)



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**





Next

- SURVEILLANCE OF PATHOGENS AND INFECTIONS
 - ANTIMICROBIAL USAGE
 - INVESTIGATIONAL ANTIMICROBIALS
 - RECENT RESEARCH
- HOT TOPIC
 - MECHANISMS IN RESISTANCE
 - ANTIMICROBIAL STEWARDSHIP
 - PRACTICE GUIDELINES
 - INFECTION CONTROL

- HOME
- SLIDE GALLERY
- SYMPOSIA
- WEBLINKS
- YOUR COMMENTS
- ABOUT CARA
- MEDIA/PUBLIC
- TARGET AUDIENCE
- EDITORIAL BOARD

New Members, Welcome to the CAN-R Website!
Complete the Free Registration Form to be eligible for regular updates and new data which will be posted on a regular basis to this website.


Already a member?

E-mail:

Password:


[Forgot your password?](#)

Dr. George G. Zhanel



"CAN-R will be developed over a three year period under my leadership. As Editor-in-Chief, I will work with a multidisciplinary group of Canadian experts to create a unique, multipurpose, multidisciplinary infectious diseases/medical microbiology content based website that will address Canadian issues in antimicrobial resistance and antimicrobial usage. This website will be the official site of CARA for years to come, focusing on both community (eg. respiratory and urinary infections) and hospital infections (eg. ICU, nosocomial, respiratory, urinary, fungal and MDR infections)."

Dr. Donald E. Low



"The CAN-R website will serve the needs of Canadian health care providers with respect to providing comprehensive information, updates on current antimicrobial resistance issues, practice principles of antimicrobial therapy and information related to dealing with the challenges of managing infections in the Canadian hospital framework."

[Click here to watch 1 minute video by Dr. Zhanel](#)

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CAN-ICU: Canadian Intensive Care Study

- Select a category:**
- Organism breakdown by infection site
 - Patient demographics
 - Top 20 organisms
 - Top 10 respiratory organisms
 - Top 10 organisms in blood
 - Top 10 wound organisms
 - Top 10 urinary organisms
 - MRSA, VRE, ESBL statistics



Hot Topics

»Some help with resistant Gram positive infections?

by Dr. Grant Stiver
Endocarditis caused by high level aminoglycoside-resistant but ampicillin-susceptible Enterococcus faecalis is associated with a dismal prognosis because of the lack of synergistic bactericidal activity...

[Read more](#)

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Association of Medical Microbiology and Infectious Disease Canada
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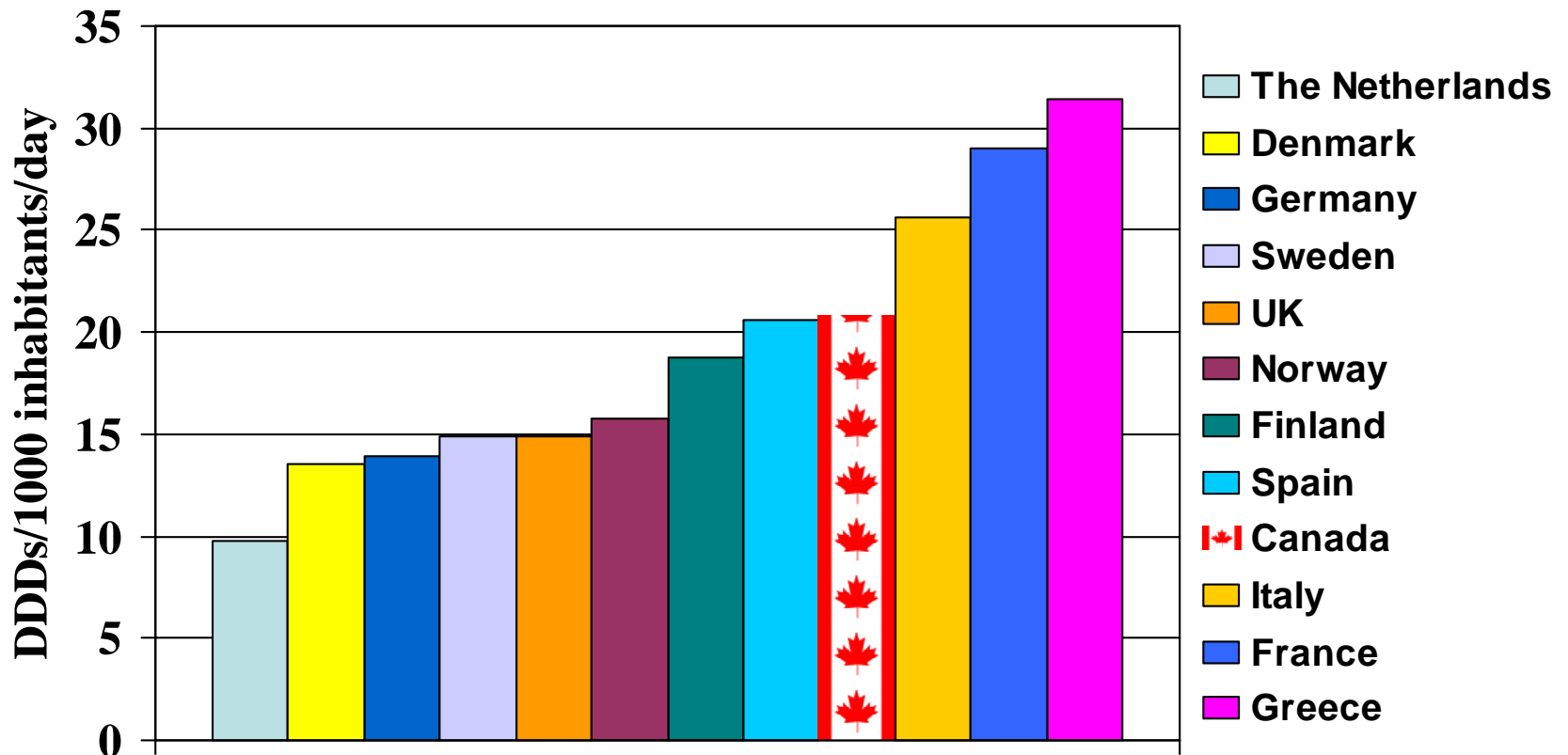
Methods to Minimize Antibiotic Resistance

- 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.**

Outpatient Antibiotic Use Compared to Europe* 2003



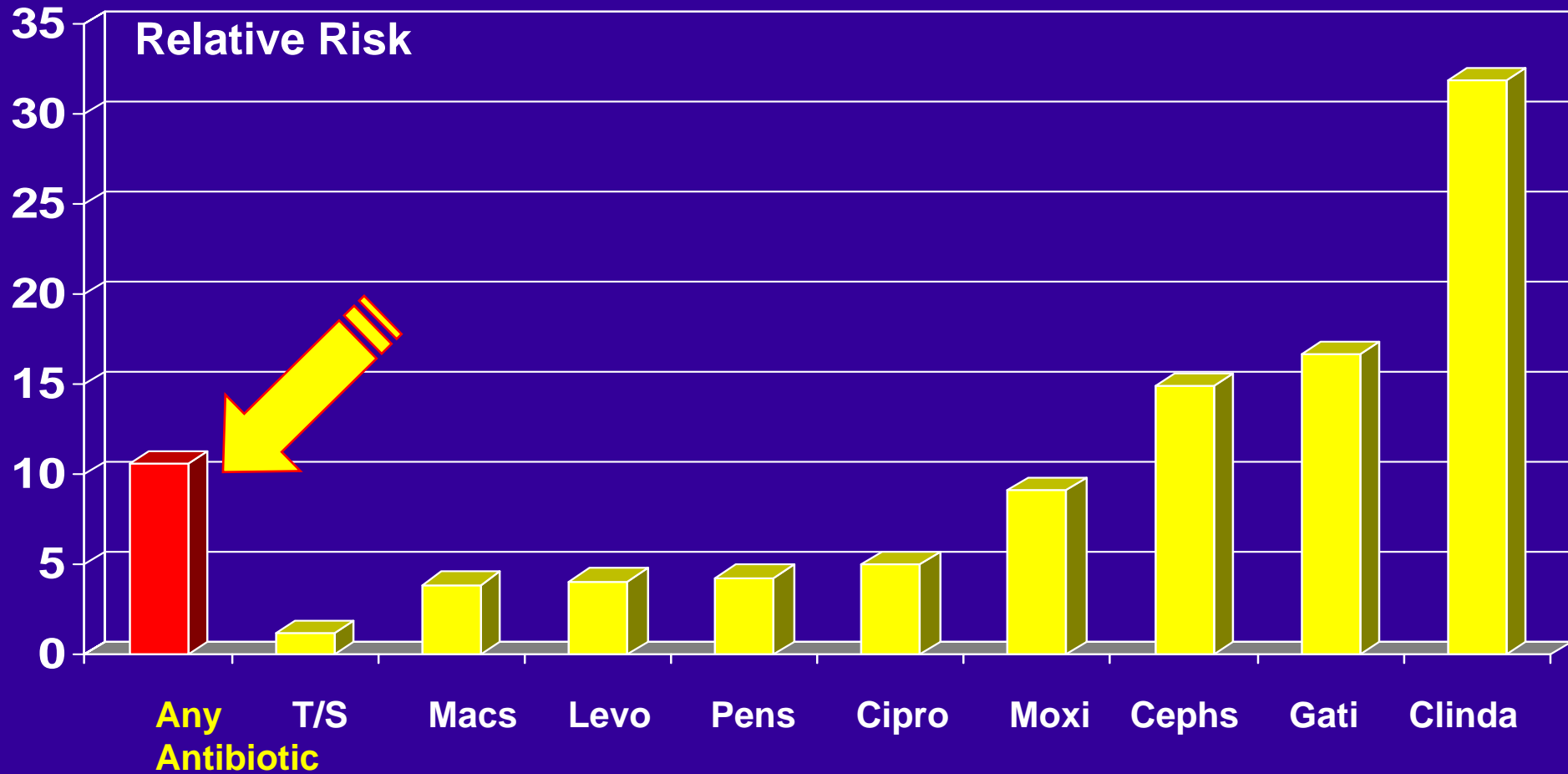
*selected countries

European data from the www.esac.ua.ac.be/

DDD=defined daily dose (WHO ATC)

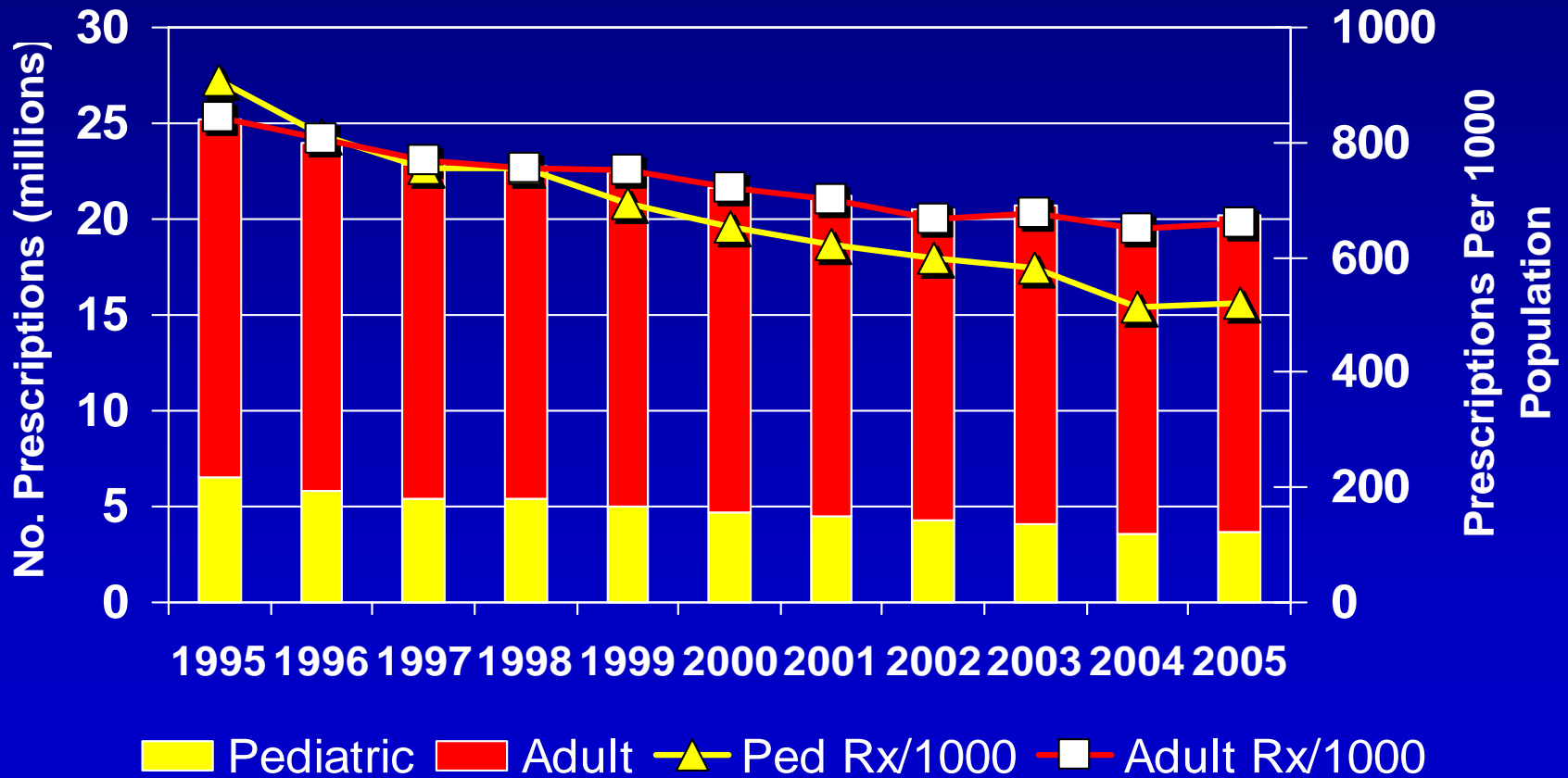
Antibiotic use derived from data from IMS Health Canada

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)



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	<i>S. boulardii</i> , LGG
Prevention of diarrhea	B	<i>S. boulardii</i> , LGG
Prevention of AAD	A	<i>S. boulardii</i> , LGG, <i>Lactobacillus</i> spp.
Treatment of recurrent CDAD	B	<i>S. boulardii</i> , LGG
Prevention of CDAD	B	<i>S. boulardii</i> , LGG

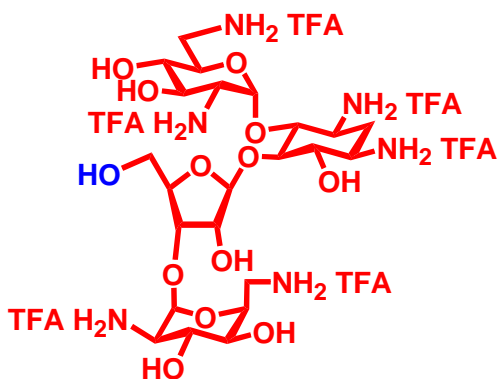
Probiotics - Unresolved Questions

- 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 immunosuppressed individuals any other contra-indications or problems ?
- What is their role in human health ?

New Antimicrobials on the Horizon

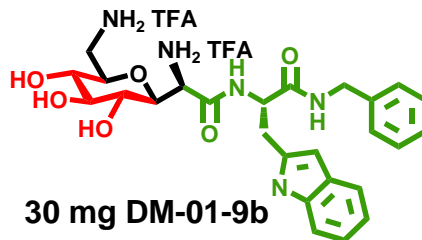
- **New fluoroquinolones/Topo Inh** (nemonoxacin, flinafloxacin, JNJ-Q2, ACH-702)
- **Ketolides/Macs** (cethromycin, CEM-101, EDP-420)
- **Oxazolidinones** (JNJ-416457, TR-700)
- **Glycylcyclines** (PTK0796)
- **Cephalosporins** (ceftobiprole, ceftaroline, CXA-101)
- **Carbapenems** (doripenem, faropenem, 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



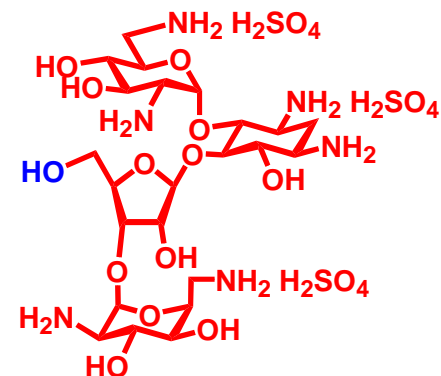
Neomycin B (TFA)₆

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



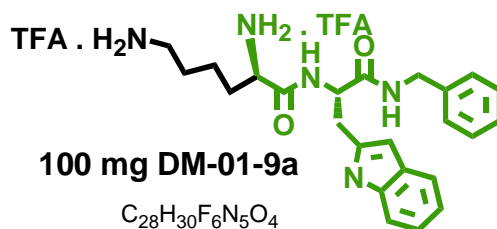
30 mg DM-01-9b

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



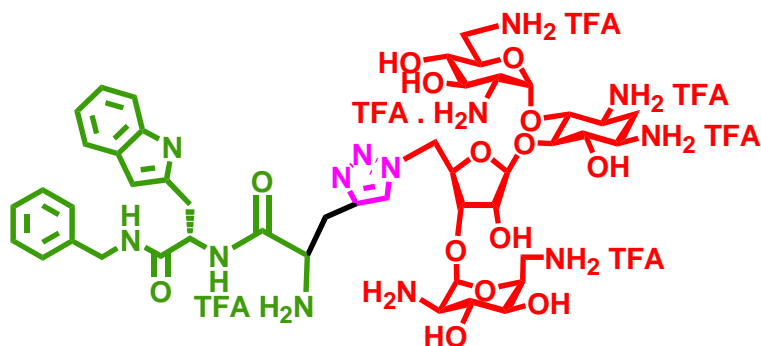
Neomycin B (H₂SO₄)₃

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



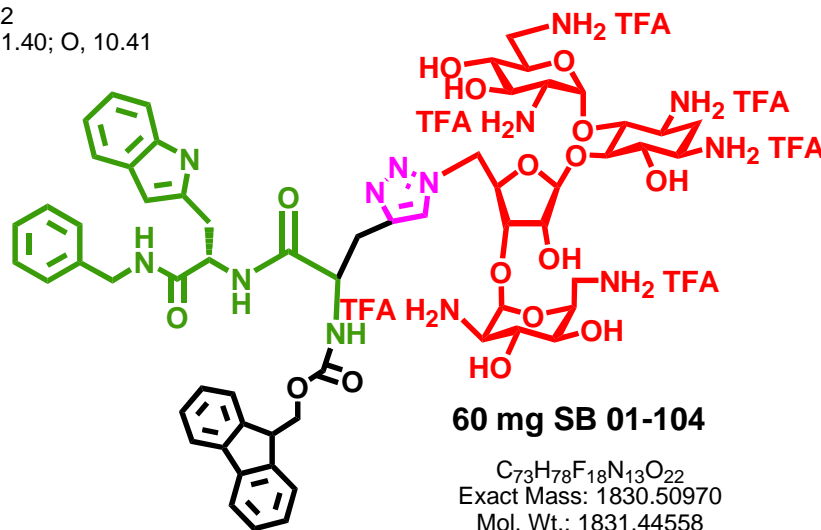
100 mg DM-01-9a

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



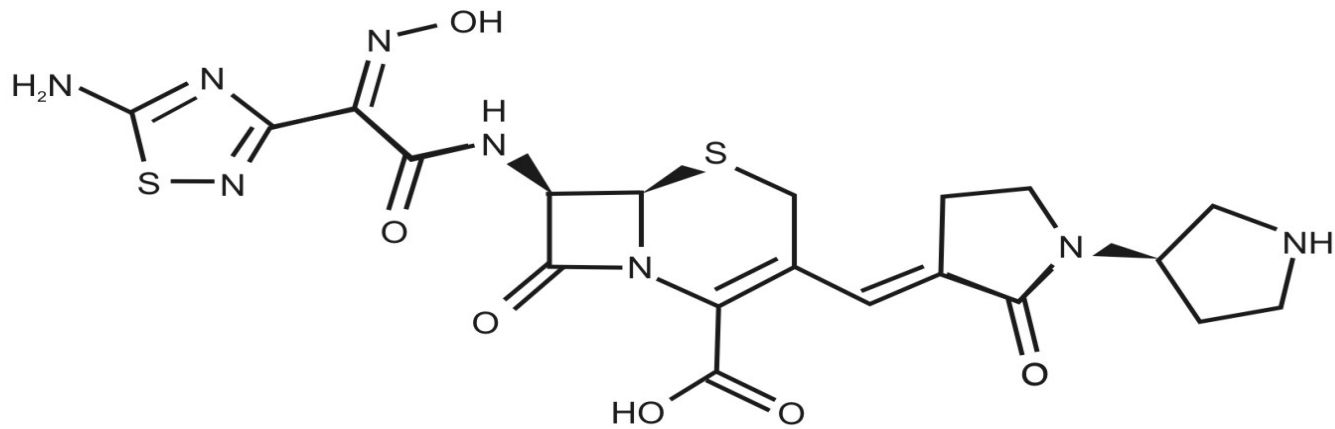
53 mg SB 01-100

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

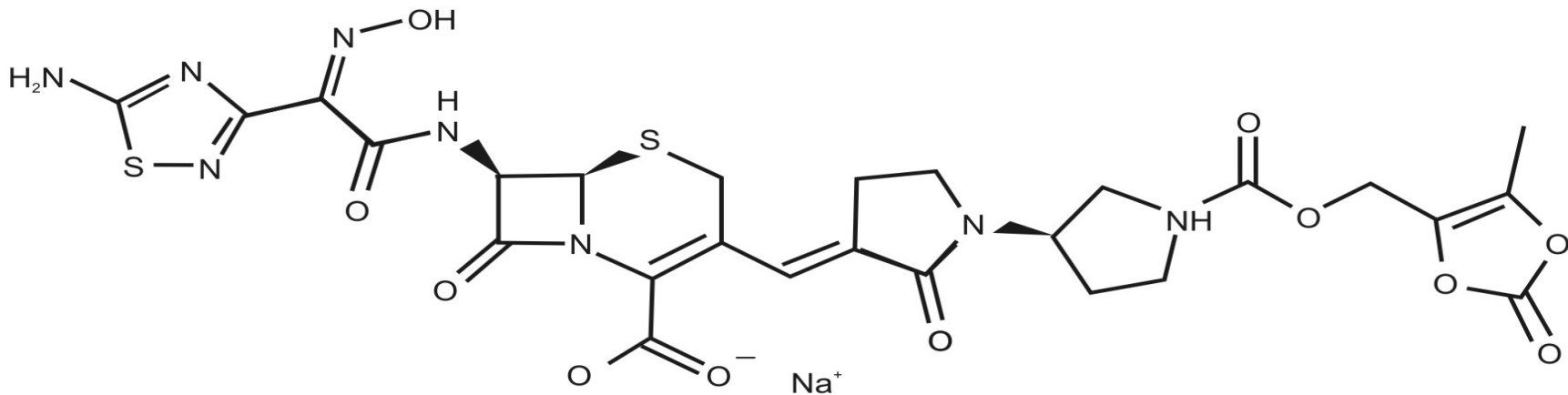


60 mg SB 01-104

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



Ceftobiprole



Ceftobiprole medocartil

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	<i>E. coli</i>	795	21.9
2	<i>S. aureus</i> - MSSA	487	13.4
3	<i>K. pneumoniae</i>	266	7.3
4	CNS / <i>S. epidermidis</i>	257	7.1
5	<i>S. pneumoniae</i>	232	6.4
6	<i>S. aureus</i> - MRSA	169	4.7
7	<i>E. faecalis</i>	154	4.2
8	<i>P. aeruginosa</i>	148	4.1
9	<i>C. albicans</i>	100	2.8
10	<i>E. cloacae</i>	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	<i>S. aureus</i> - MSSA	204	33.1
2	<i>S. aureus</i> - MRSA	76	12.3
3	<i>P. aeruginosa</i>	63	10.2
4	<i>E. coli</i>	57	9.2
5	<i>S. pyogenes</i>	31	5.0
6	CNS / <i>S. epidermidis</i>	26	4.2
7	<i>Enterococcus spp.</i>	25	4.1
8	<i>E. cloacae</i>	21	3.4
9	<i>S. agalactiae</i>	20	3.2
10	<i>K. pneumoniae</i>	18	2.9

CANWARD 2007

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

Top 10 Organisms Causing Respiratory Infections

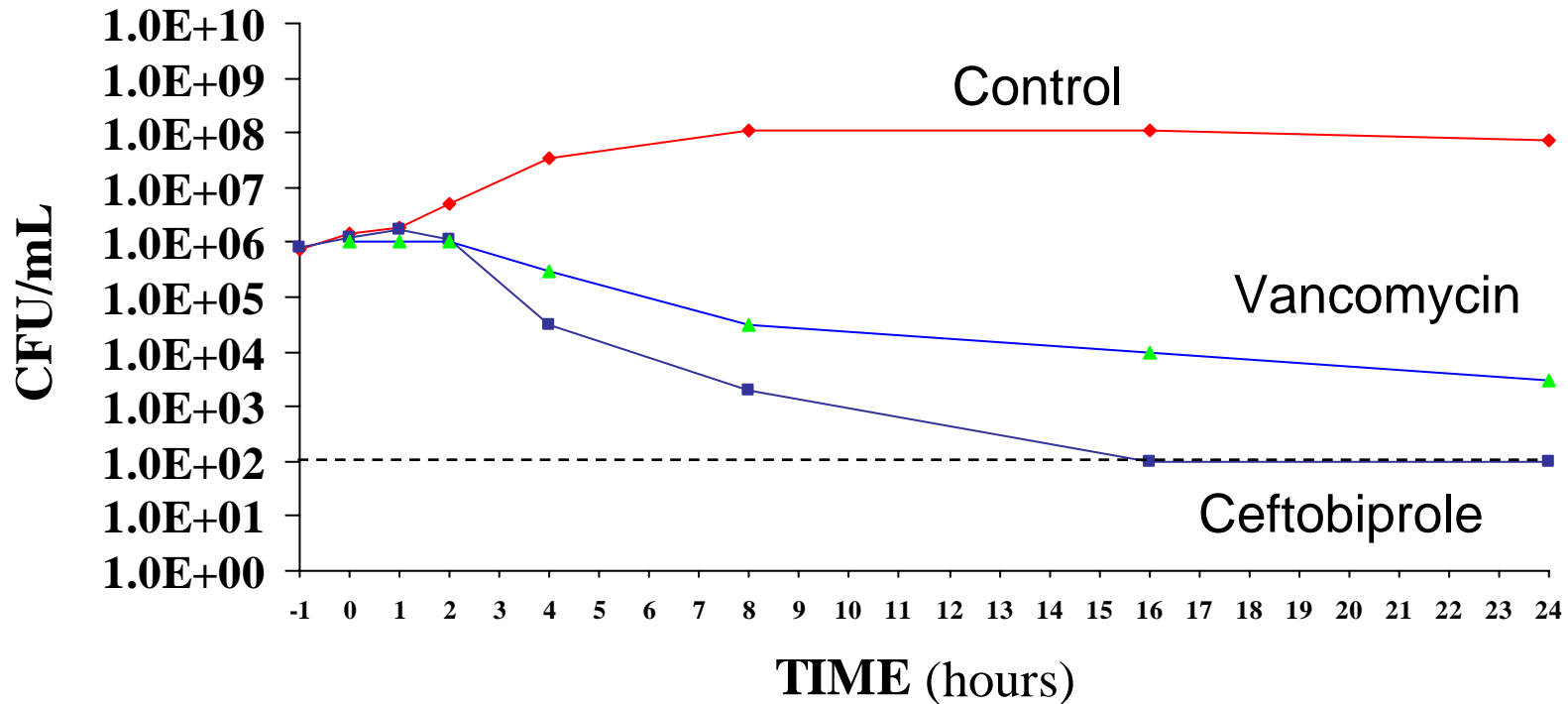
National

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

Ceftobiprole Killing of MRSA

(fC_{max} 30 ug/mL, $t_{1/2}$ 3.5 hrs, MRSA 60392)

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



Comparative Spectrum of Ceftobiprole: A New Broad-Spectrum Cephalosporin

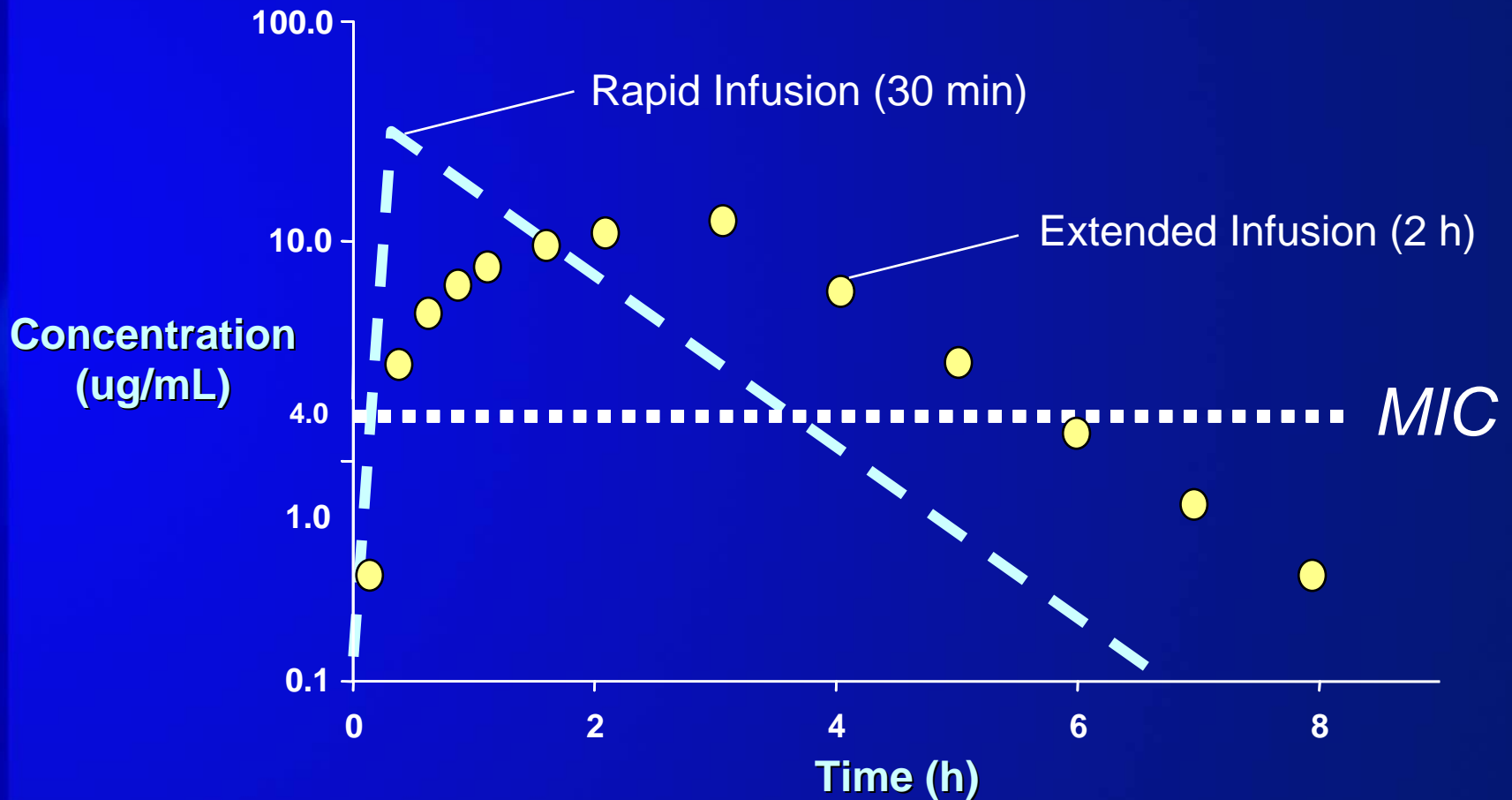
Zhanel et al. Am J Clin Derm 2008;9(4):245-254; Zhanel et al. Drugs 2007

Antibiotic	MRSA	<i>E. faecalis</i>	GNB (<i>E. coli</i>)	<i>P. aeruginosa</i>	Anaerobes (<i>B. fragilis</i>)
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

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



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* (\downarrow OprD and \uparrow *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

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 ?