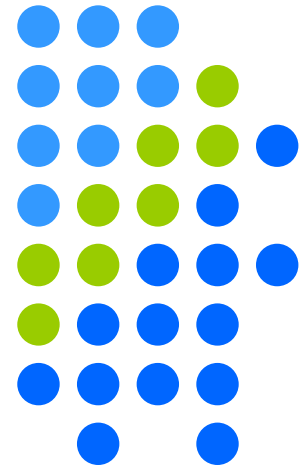


# Presentation of the Infectious Diseases Society of America (IDSA)

*Padma Natarajan, MPH, MS  
Program Officer for Science and Research  
Infectious Diseases Society of America  
Arlington, Virginia*



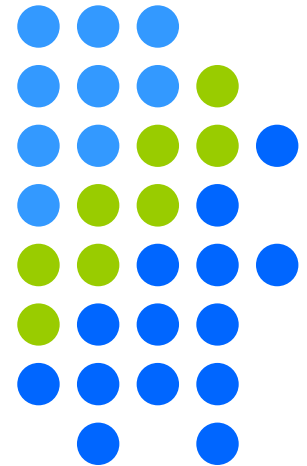
**FDA Tropical Disease Priority Review Voucher  
Hearing—December 12, 2008**



# Objectives

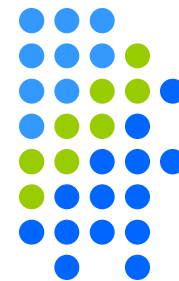
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- ❖ ***CONVEY URGENCY OF RESISTANCE IN GRAM-NEGATIVE INFECTIONS***
- ❖ ***CLARIFY REASONS FOR DIMINISHING DRUG PIPELINE***
- ❖ ***EMPHASIZE WHY GRAM-NEGATIVE INFECTIONS SHOULD BE ADDED TO THE PRIORITY REVIEW VOUCHER PROGRAM***

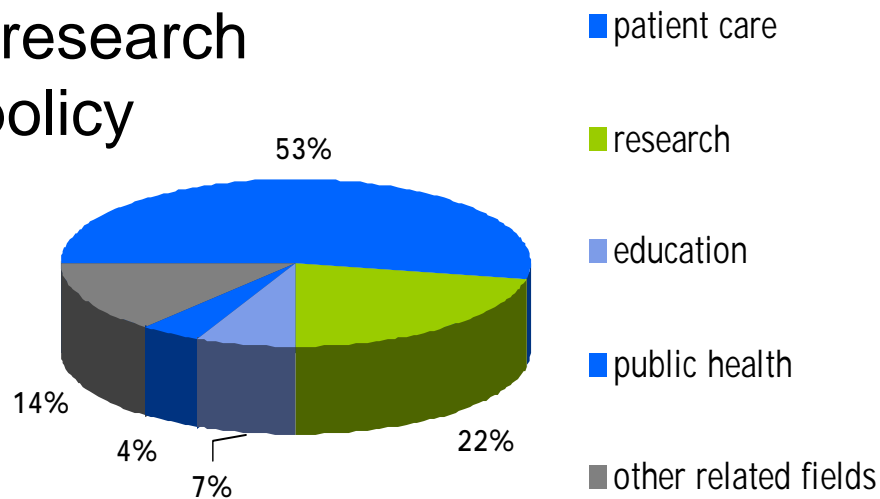




# About IDSA

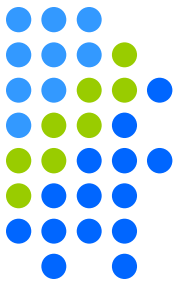


- Over 8,000 physicians, scientists, and other health care professionals who specialize in infectious diseases
- IDSA Goals
  - Serve our members
  - Promote clinical expertise
  - Enhance education and research
  - Advocate sound public policy





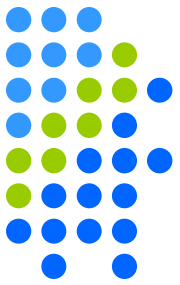
# IDSA Committees Focused on Antimicrobial Resistance



- Antimicrobial drug/diagnostics R&D
  - Antimicrobial Availability Task Force
    - Chair: John Bartlett, MD
- Antimicrobial resistance
  - Research on Resistance Work Group
    - Chair – Louis Rice, MD
  - Antimicrobial Resistance Work Group
    - Chair – Neil Fishman, MD

# Gram-Negative Bacteria

## No ESKAPE!



*Enterococcus faecium*\*

*Staphylococcus aureus*

*Klebsiella pneumoniae*

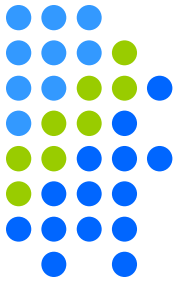
*Acinetobacter baumannii*

*Pseudomonas aeruginosa*

*Enterobacter spp.*

- Gram's Staining Protocol – Gram-negative bacteria do not retain crystal violet dye in their cell wall (Gram-positive bacteria do – e.g. MRSA)
- High patient morbidity and mortality from gram-negative infections
- High levels of antimicrobial resistance, and resistance is increasing

# Bad Bugs!!



RESEARCH

## Multidrug-resistant *Acinetobacter baumannii*

Aharon Abbo,\* Shiri Navon-Venezia,\* Orly Hammer-Muntz,\* Tami Krichali,\*  
Yardena Siegman-Igra,\* and Yehuda Carmeli\*

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Sept. 2005, p. 3734–3742  
0066-4804/05/\$08.00+0 doi:10.1128/AAC.49.9.3734–3742.2005  
Copyright © 2005, American Society for Microbiology. All Rights Reserved.

Vol. 49, No. 9

### Multidrug-Resistant *Pseudomonas aeruginosa* Strain That Caused an Outbreak in a Neurosurgery Ward and Its *aac(6′)-Iae* Gene Cassette Encoding a Novel Aminoglycoside Acetyltransferase

Jun-ichiro Sekiguchi,<sup>1</sup> Tsukasa Asagi,<sup>2</sup> Tohru Miyoshi-Akiyama,<sup>1</sup> Tomoko Fujino,<sup>1</sup>  
Intetsu Kobayashi,<sup>3</sup> Koji Morita,<sup>4</sup> Yoshihiro Kikuchi,<sup>2</sup> Tadatoshi Kuratsuji,<sup>1,5</sup>  
and Teruo Kirikae<sup>1\*</sup>

Commentary

### “Future” Threat of Gram-negative Resistance in Singapore

Thuan Tong Tan,<sup>1</sup> MBBS, MRCP (UK), PhD (Lund, Sweden)

JOURNAL OF CLINICAL MICROBIOLOGY, Feb. 2006, p. 518–524  
0095-1137/06/\$08.00+0 doi:10.1128/JCM.44.2.518–524.2006  
Copyright © 2006, American Society for Microbiology. All Rights Reserved.

### Extensive Hospital-Wide Spread of a Multidrug-Resistant *Enterobacter* *cloacae* Clone, with Late Detection Due to a Variable Antibigram and Frequent Patient Transfer

Maurine A. Leverstein-van Hall,\* Hetty E. M. Blok, Armand Paauw, Ad C. Fluit, Annet Troelstra,  
Ellen M. Mascini,† Marc J. M. Bonten, and Jan Verhoef

Eijkman-Winkler Institute for Microbiology, Infectious Disease and Inflammation,  
University Medical Center Utrecht, Utrecht, The Netherlands

### Antimicrobial resistance of *Neisseria gonorrhoeae* in Japan, 1993–2002: continuous increasing of ciprofloxacin-resistant isolates

satoshi Tanaka<sup>a,\*</sup>, Hiroshi Nakayama<sup>b</sup>, Takashi Notomi<sup>a</sup>, Shin-ichiro Irie<sup>a</sup>,  
Yuichi Tsunoda<sup>a</sup>, Aya Okadome<sup>a</sup>, Takeshi Saika<sup>c</sup>, Intetsu Kobayashi<sup>c</sup>

ment of Urology, Fukuoka University School of Medicine, 7-45-1 Nanakama, Jonan-ku, Fukuoka 814-0180, Fukuoka, Japan  
<sup>b</sup> Nakayama Urologic Clinic, Fukuoka, Japan

## The New England Journal of Medicine

Copyright © 2001 by the Massachusetts Medical Society

VOLUME 345

OCTOBER 4, 2001

NUMBER 14



### WIDESPREAD DISTRIBUTION OF URINARY TRACT INFECTIONS CAUSED BY A MULTIDRUG-RESISTANT *ESCHERICHIA COLI* CLONAL GROUP

M.P.H., JAMES R. JOHNSON, M.D., BETSY FOXMAN, PH.D., TIMOTHY T. O'BRYAN,  
KATHLEEN E. FULLERTON, M.P.H., AND LEE W. RILEY, M.D.

Vol. 44, No. 2

Chinese Medical Journal 2008; 121(17):1611-1616

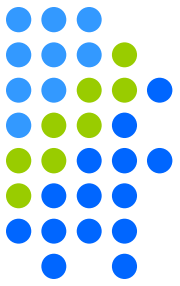
## Original article

### Characterization of multidrug-resistant and metallo-beta- lactamase-producing *Pseudomonas aeruginosa* isolates from a paediatric clinic in China

DONG Fang, XU Xi-wei, SONG Wen-qi, LÜ Ping, YU Sang-jie, YANG Yong-hong and SHEN Xu-zhuang

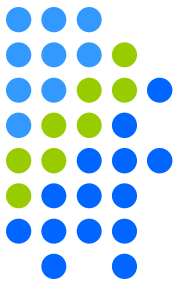


# The “Gram-Negative” Crisis



- Increasing Numbers of People at Risk
  - Elderly
  - Immunosuppressed
  - Infants/Children
  - Military
- Approved Drugs
  - Fewer and fewer in number
  - Poor stewardship leads to increased resistance
- The Drug Development Pipeline: Weak

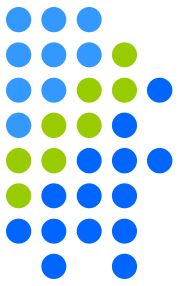
# Mechanisms of resistance



- Inactivation of drugs by bacterial enzymes – (e.g. beta-lactamases, carbapenemase)
- Decreased penetration of Abx into bacterial cell
- Efflux - bacteria pump Abx out of the cell
- Changes in the targets for Abx (e.g. cell wall or enzymes)
- The result: Increasing frequency of multi-drug-resistant (MDR) gram-negative infections

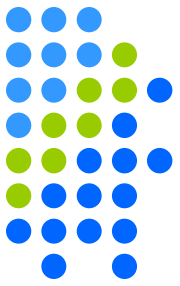


# Antimicrobial Resistance in the Hospital Setting



- Greater proportion of hospital-acquired infections due to drug-resistant pathogens\*
- Increase in MDR and extremely drug-resistant (XDR) strains
- Use of one antibiotic may lead to resistance to many other antibiotics

# Multi-Drug Resistant (MDR) Gram-Negative Bacteria: Definition

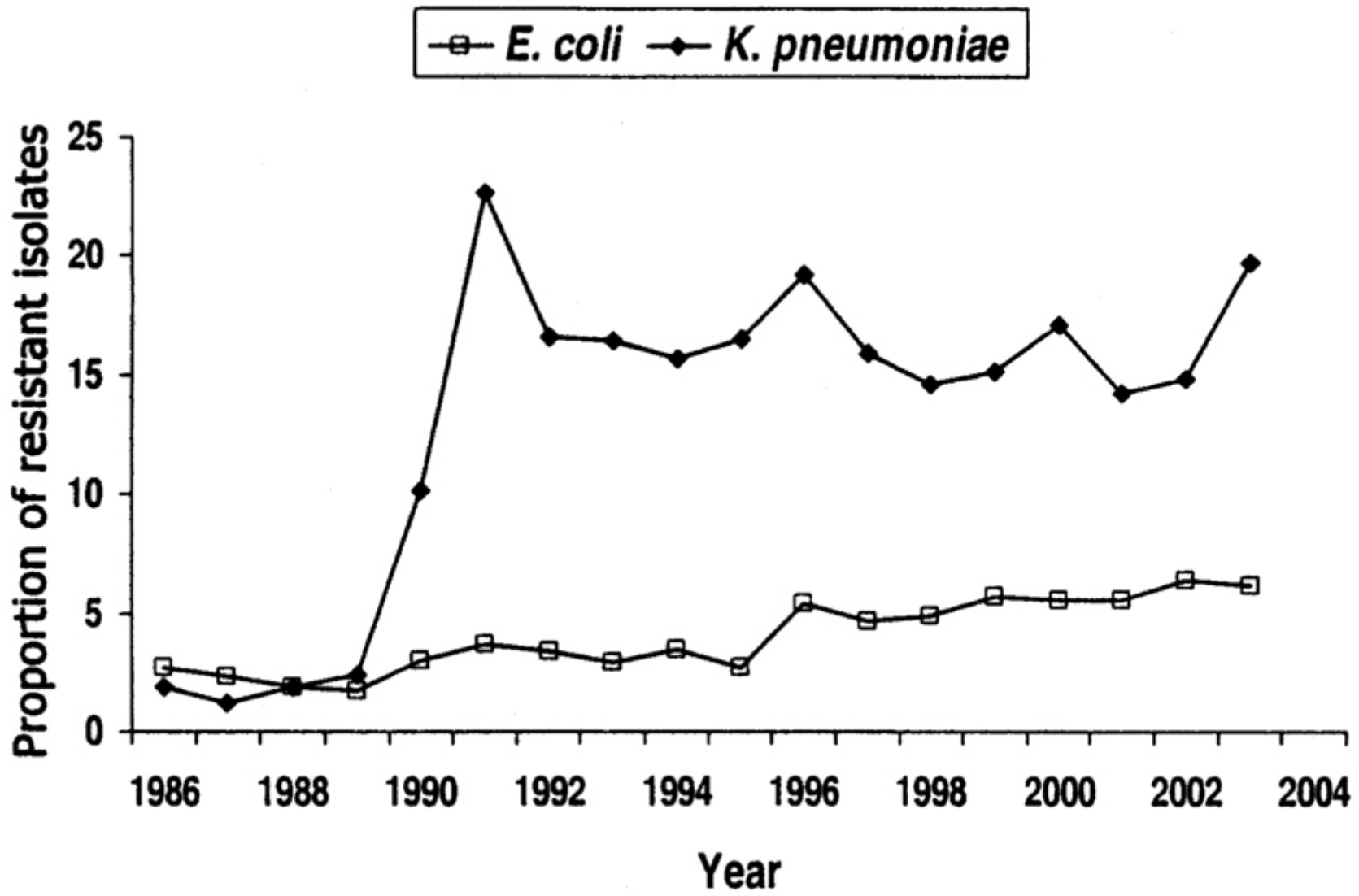


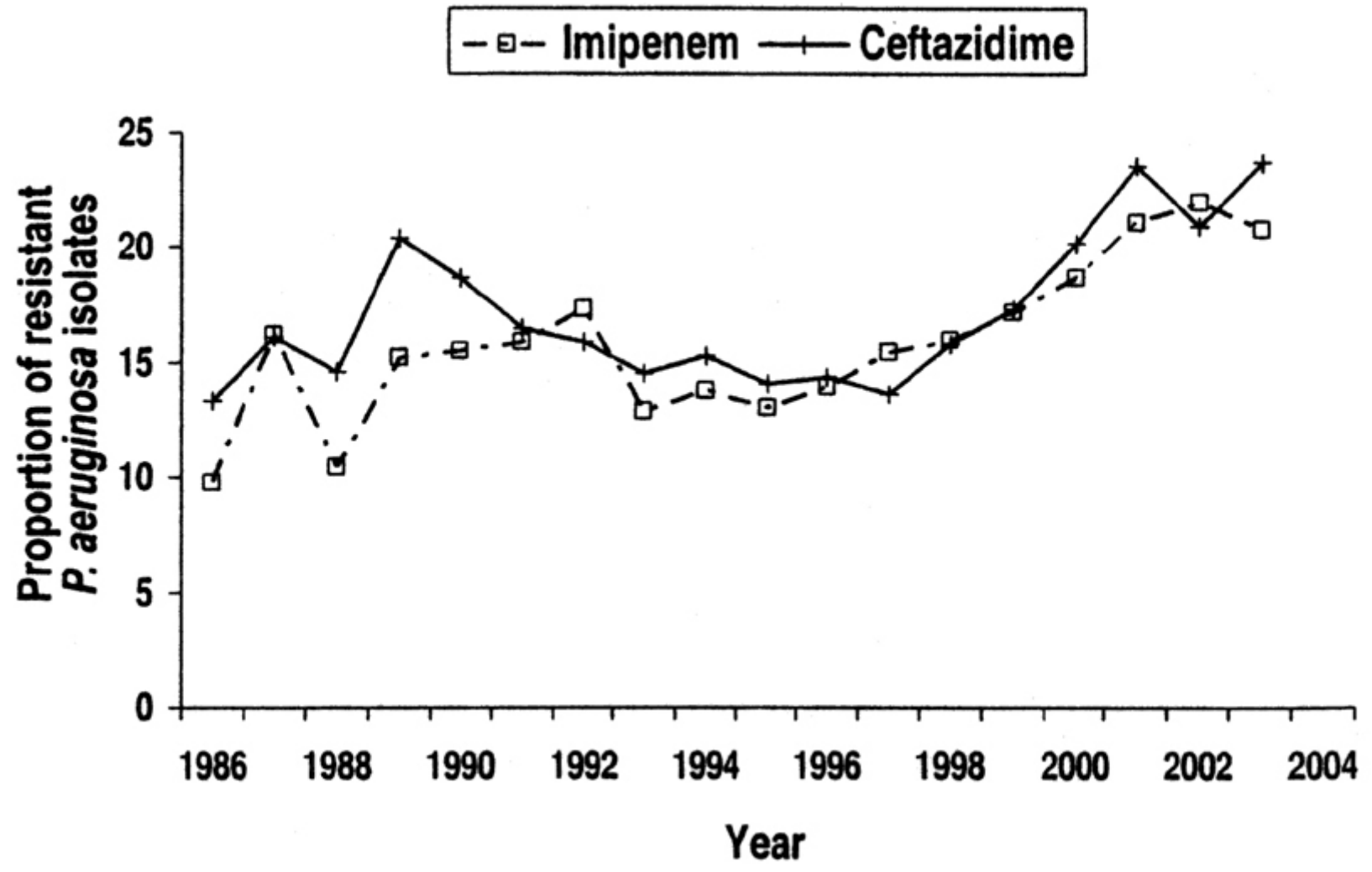
MDR: Resistant to  $\geq 3$  classes\*

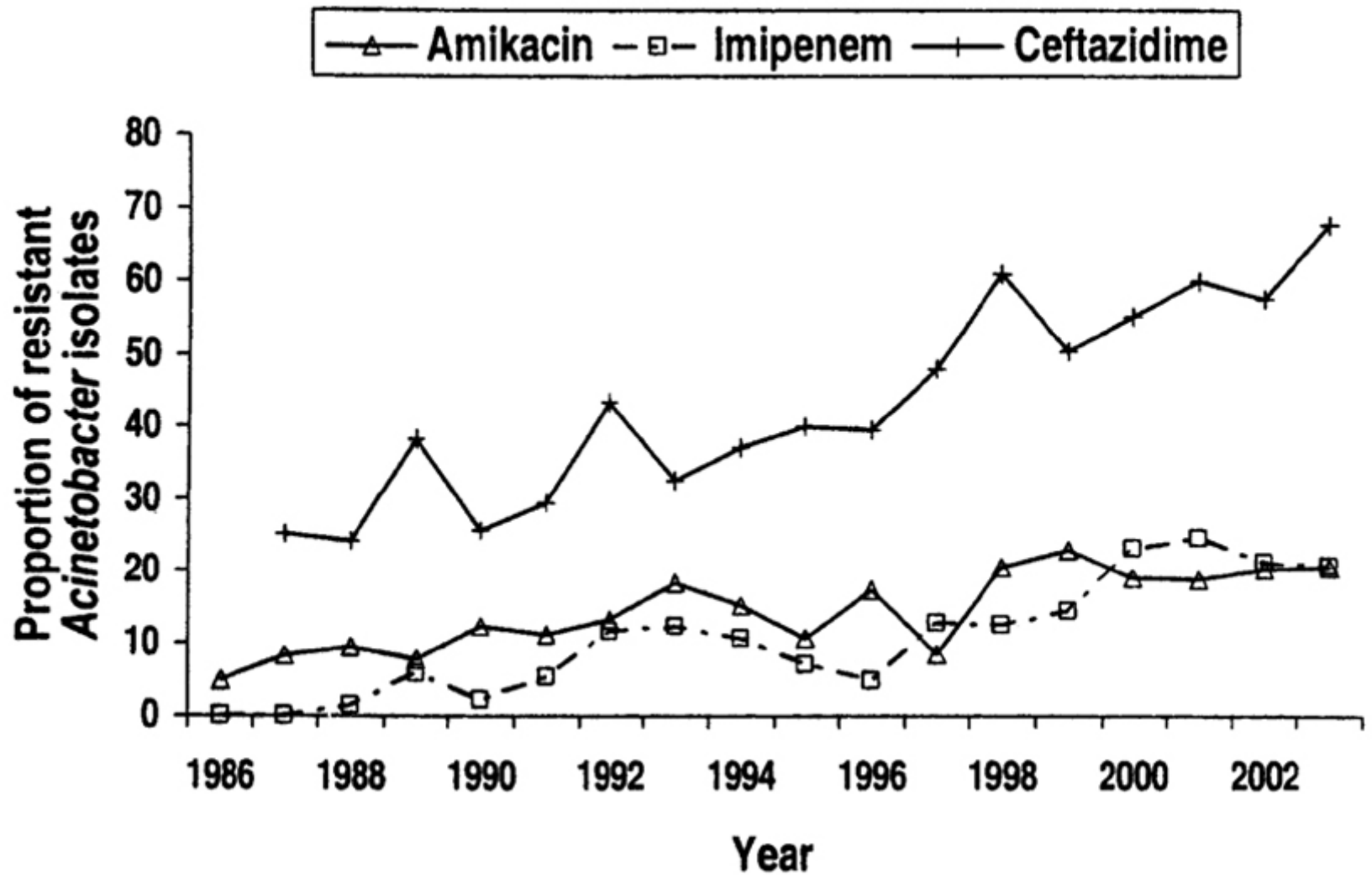
XDR: Susceptible to  $\leq 2$  agents commonly used to treat infection

PanDR: Resistant to all Abx

\*Classes: Beta-lactams, Fluoroquinolones,  
Aminoglycosides, Carbapenems

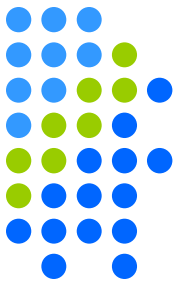








# *Klebsiella pneumoniae* carbapenemase (KPC)

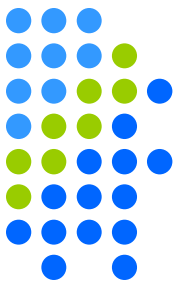


- Class of enzymes that inactivate drugs, especially carbapenems (a last resort for treatment of severe gram-negative infection)
- NYC hospital epidemic
  - 30 % of *K. pneumoniae* isolates in 2 hospitals
  - 15% of *K. pneumoniae* isolates in another
- Exponential growth in the Philadelphia region
- Organisms now seen in St. Louis and Chicago
- Increased mortality
- Fall-back is Colistin, an old, toxic antibiotic

(Personal communication)



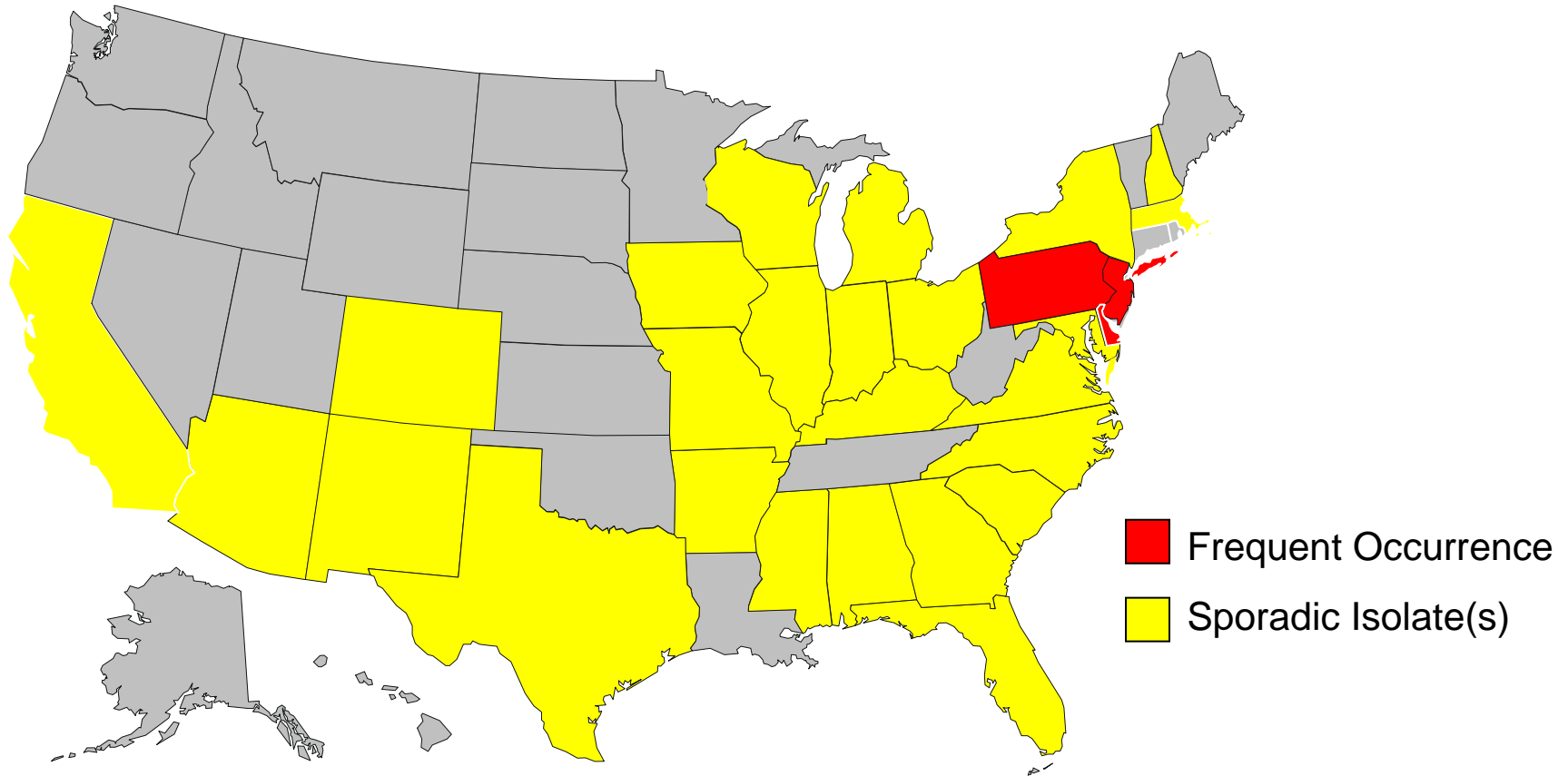
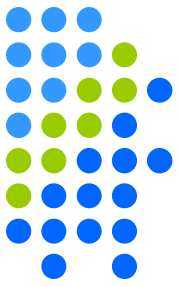
# Surrogate for Serious Infections due to MDR Gram-Negative Bacteria



## COLISTIN COURSES: Johns Hopkins Hospital

- In 2001, 6 patients – 6 courses of Colistin
- In 2007, 61 patients – 68 courses of Colistin
- Extrapolation of data shows that in 2015, 6000 patients will be treated with Colistin at Johns Hopkins alone
- Colistin is an old drug with high toxicity – **We need better alternatives**

# Increasing Geographical Distribution of KPC-Producers



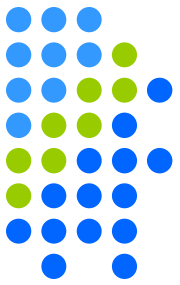


# Growing Problem Abroad

- KPC outbreaks first observed in healthcare settings in the Northeastern United States
- Now KPC-producing isolates reported all over the world:



# FDA's Critical Path Report, 2004



**“Product development in areas crucial to public health goals, such as antibiotics, has slowed significantly during the past decade.”**

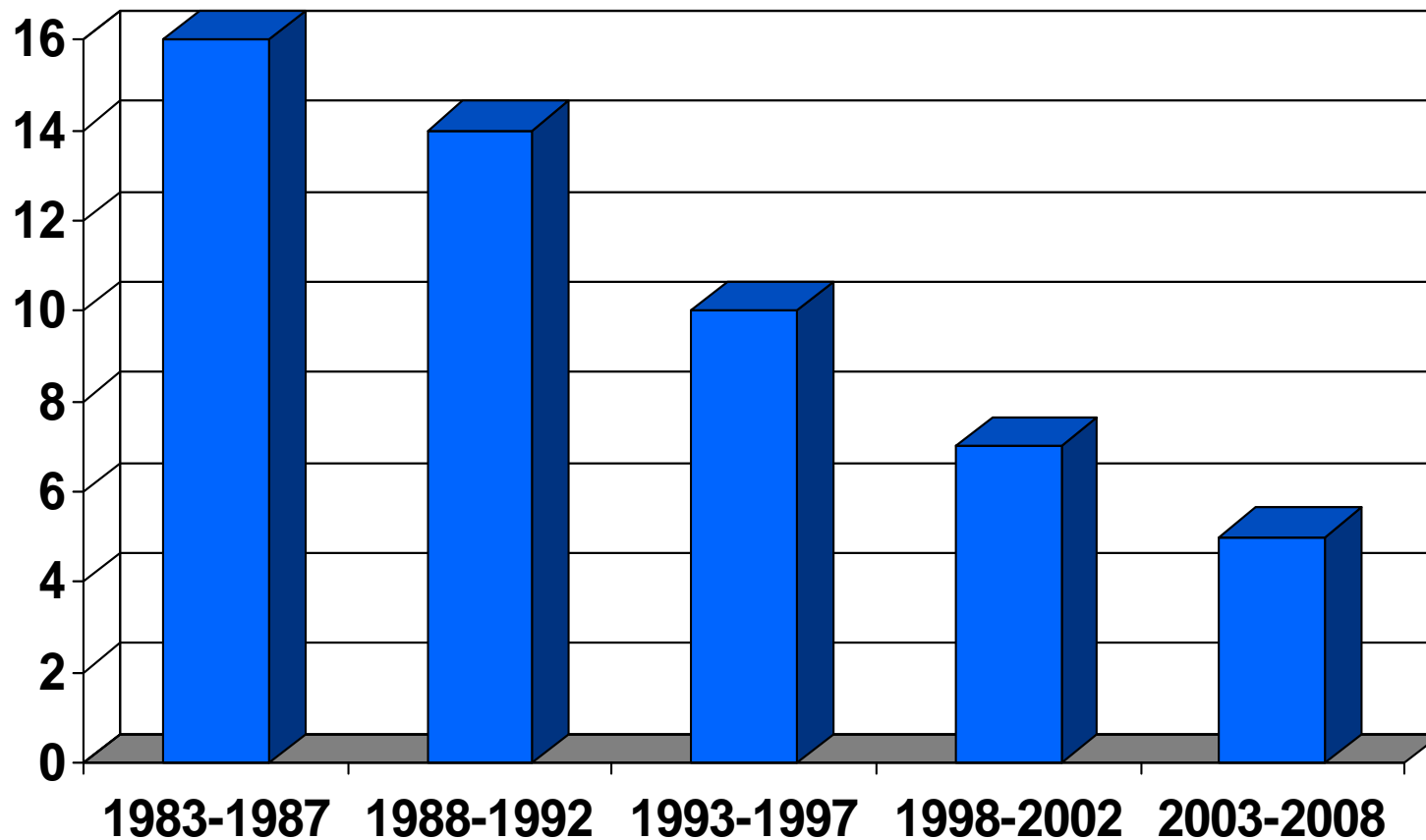
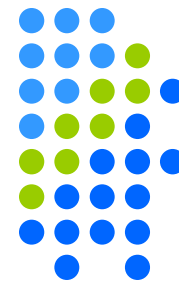
**U.S. Food and Drug Administration.**

***Innovation/Stagnation: Challenge and Opportunity on the Critical Path to New Medical Products*** March 2004





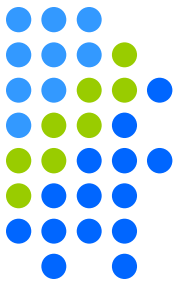
# New Antibacterial Drugs Approved By FDA



Spellberg, *CID* 2004, Modified

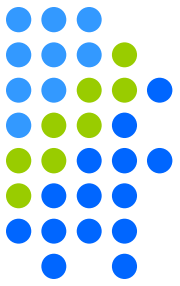


# Challenges in the Pathway to Antibiotic Approvals



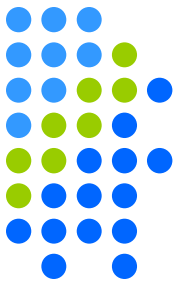
- Antibiotics used for short duration
- Science is difficult, especially with gram-negatives
- Lack of sufficient diagnostic tests
- Regulatory uncertainty
- Insufficient past research support
- Antimicrobial resistance
- Drugs in other markets (chronic disease, lifestyle) are more attractive

# Emerging Unanswered Crisis of Gram-Negative Infections



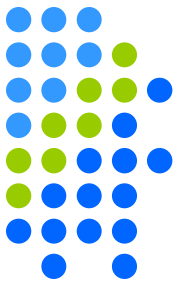
- Rapidly growing resistance
- Growing problem in United States and abroad
- Increasing numbers of patients at risk
- Empty medicine cabinets - Lack of effective drugs
- Pipeline is thin

# Summary



- Focused incentives must be provided to pharmaceutical companies to develop drugs for gram-negative infections
- Imperative for FDA to add gram-negative infections to the tropical disease priority review voucher program

# Acknowledgements



## IDSA Antimicrobial Availability Task Force

John Bartlett, MD (Chair)  
Helen Boucher, MD  
John Bradley, MD  
John Edwards Jr., MD  
David Gilbert, MD  
Robert Guidos, JD (IDSA Staff)  
W. Michael Scheld, MD  
Brad Spellberg, MD  
George Talbot, MD