Emerging multi-resistant pathogens where do they come from ? How to treat the patient ? How to limit the spread ?

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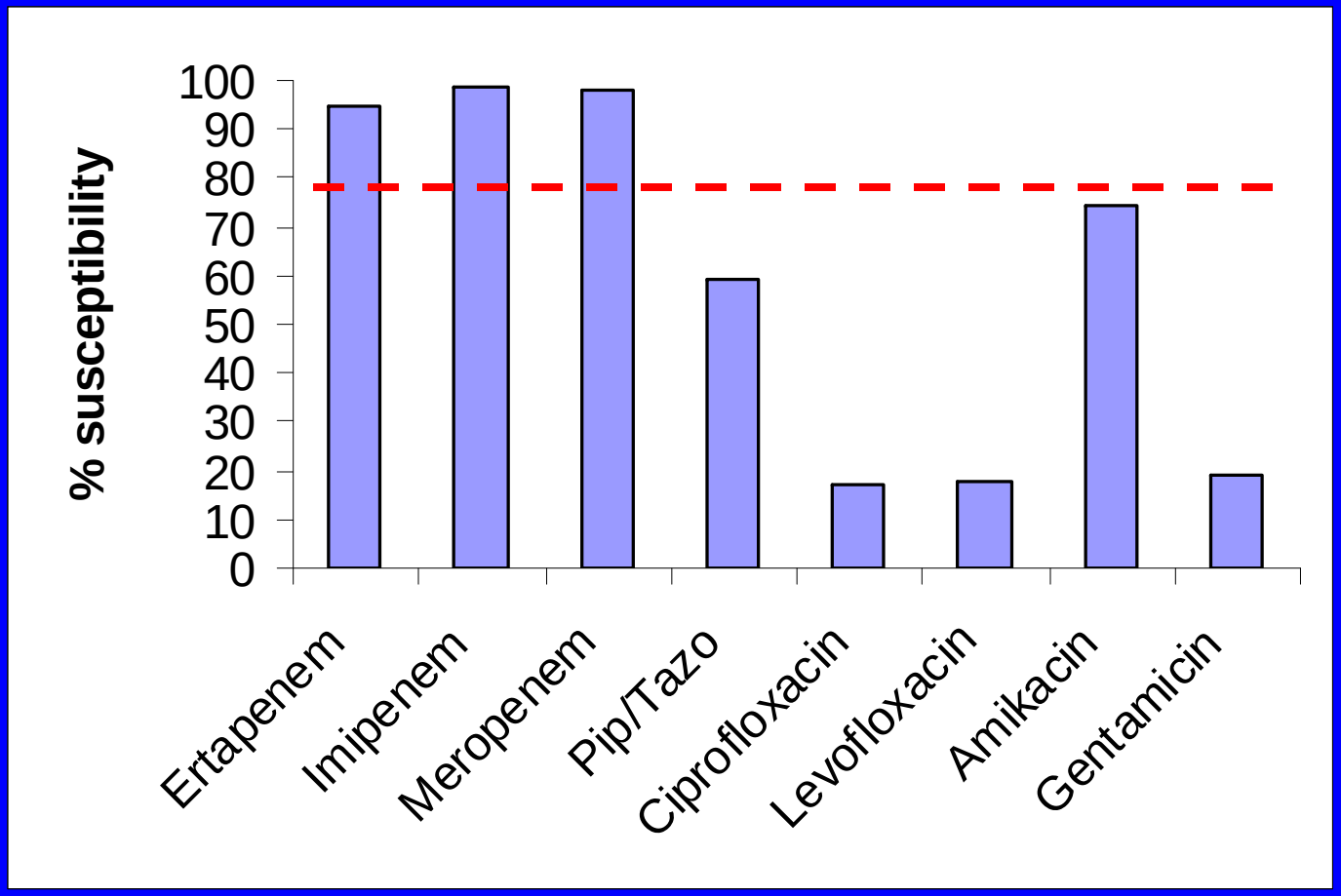
Emerging MDR Gram negative rods (GNR)

- ESBL producing Enterobacteriaceae
- Carbapenem resistant GNR
  - *P. aeruginosa*
  - *A. baumannii* (will not be discussed)
  - Enterobacteriaceae

ESBLs are MDR

Susceptibilities of 1,030 ESBL producing *E. coli* & *Klebsiella* spp.



Colodner R. DMID 2007

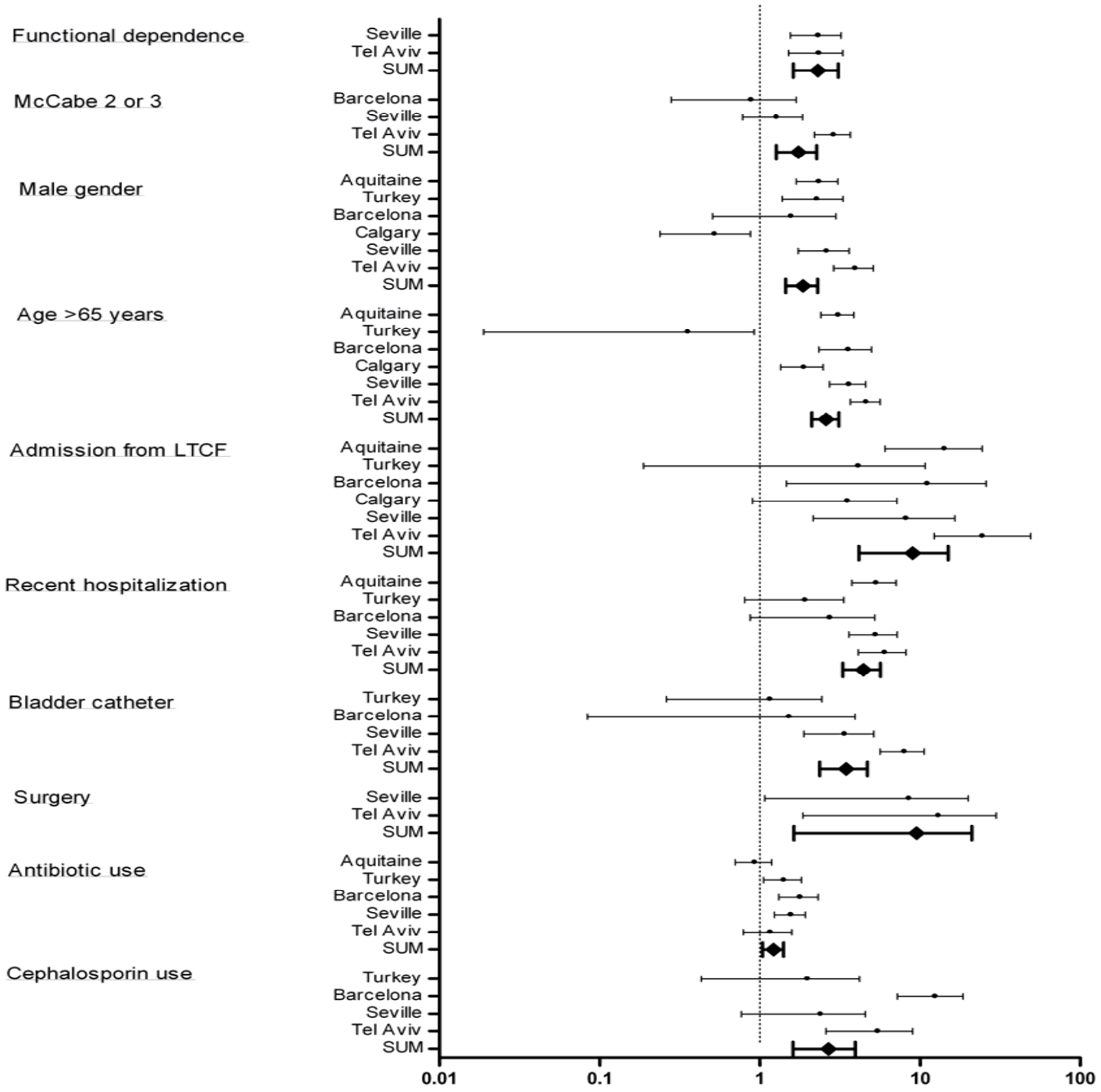
ESBL producers

- TEM and SHV – were seen primarily in *Klebsiella pneumoniae* and were primarily hospital/LTCF acquired
- CTX-M has become the most common and important ESBL
  - Acquired several times during evolution from *Kluivera* spp.
  - seen in all species but most importantly in *E. coli*
  - Acquired in healthcare setting
  - Significant spread in the community
    - Food chain
    - Success of genes (CTX-M 14 and 15) and clones (ST 131)

Meta-synthesis for risk factors for ESBLs in non-hospitalized patients

- 191 articles identified
- 8 met the inclusion criteria, 6 were able to participate
  - 3 tertiary level hospitals (two from Spain [Seville and Barcelona] and one from Israel
  - 1 networks of medical facilities in studies from Canada (Calgary Health Region)
  - France (28 private laboratories)
  - Turkey (15 geographically dispersed medical centers)

Ben Ami R. CID 2009



340 ESBL Isolates:

87% *E. coli*

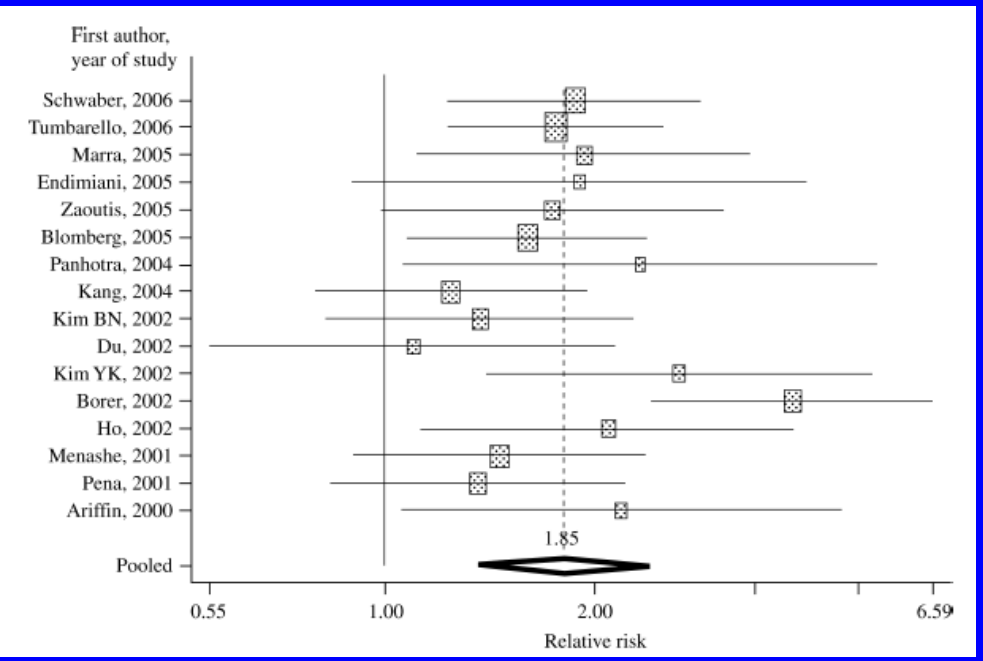
269 ESBL identified

65% CTX-M

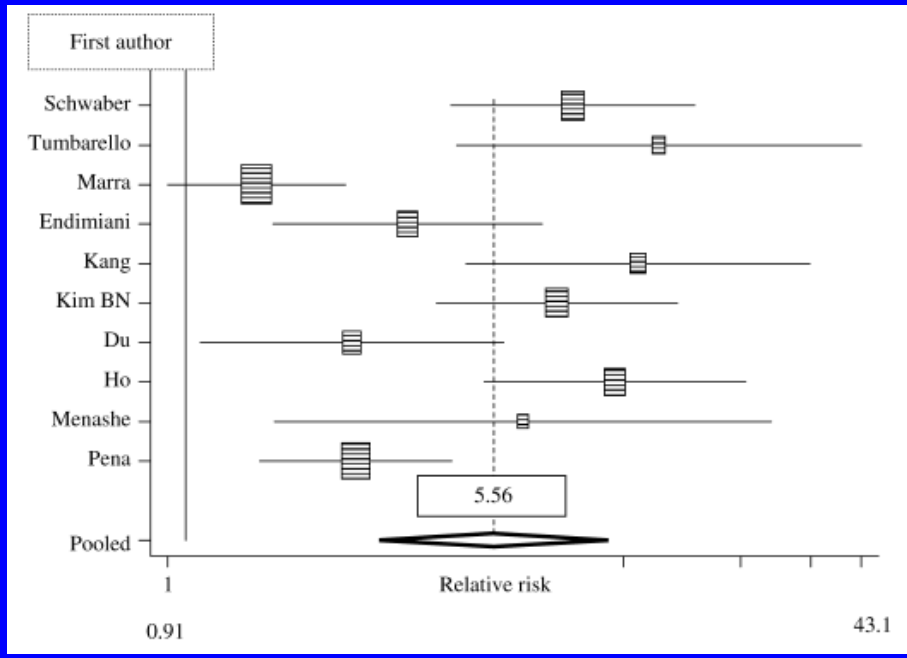
Ben-Ami R. CID 2009.

Mortality and delay in effective therapy associated with extended-spectrum β-lactamase production in Enterobacteriaceae bacteraemia: a systematic review and meta-analysis

Mitchell J. Schwaber[1]* and Yehuda Carmeli[1,2]



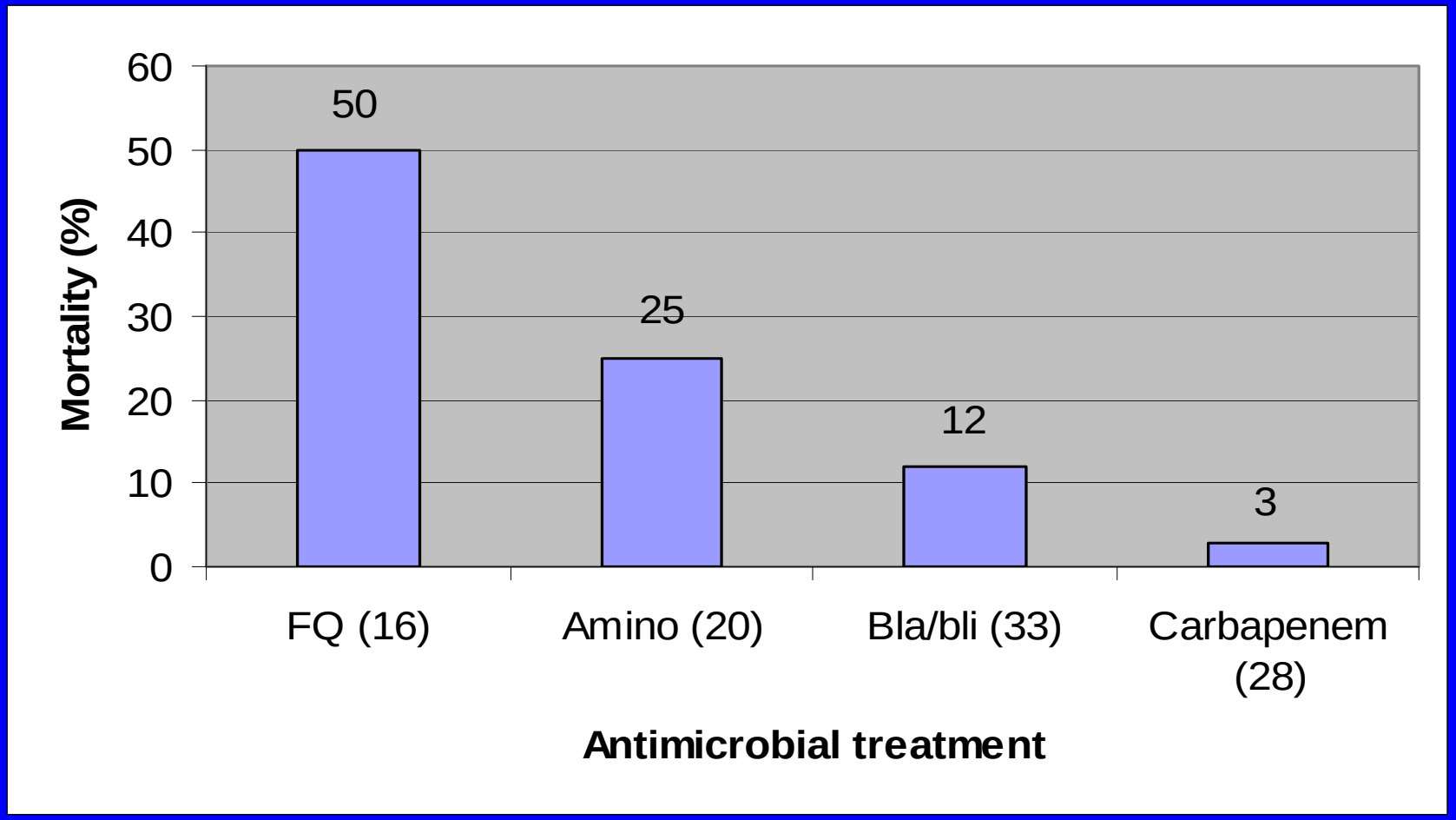
Mortality pOR=1.85



Delay in effective therapy pOR=5.56

JAC 2007

Mortality among 97 patients with adequate empiric therapy



Tumbarello M. AAC 2007

Preventive measures

- Based on local epidemiology
  - Specific targeted nfections control measures
    - Where in-hospital spread is important and community spread is limited
  - Formulary interventions
    - Primarily cephalosporins and quinolones restriction

Increased Carbapenem consumption

- Likely to occur where ESBL become common
- Leads to fear of emergence and spread of carbapenem resistance
- Carbapenems are very effective agents resistant to hydrolysis by most beta-lactamases

Determinants of carbapenem Resistance

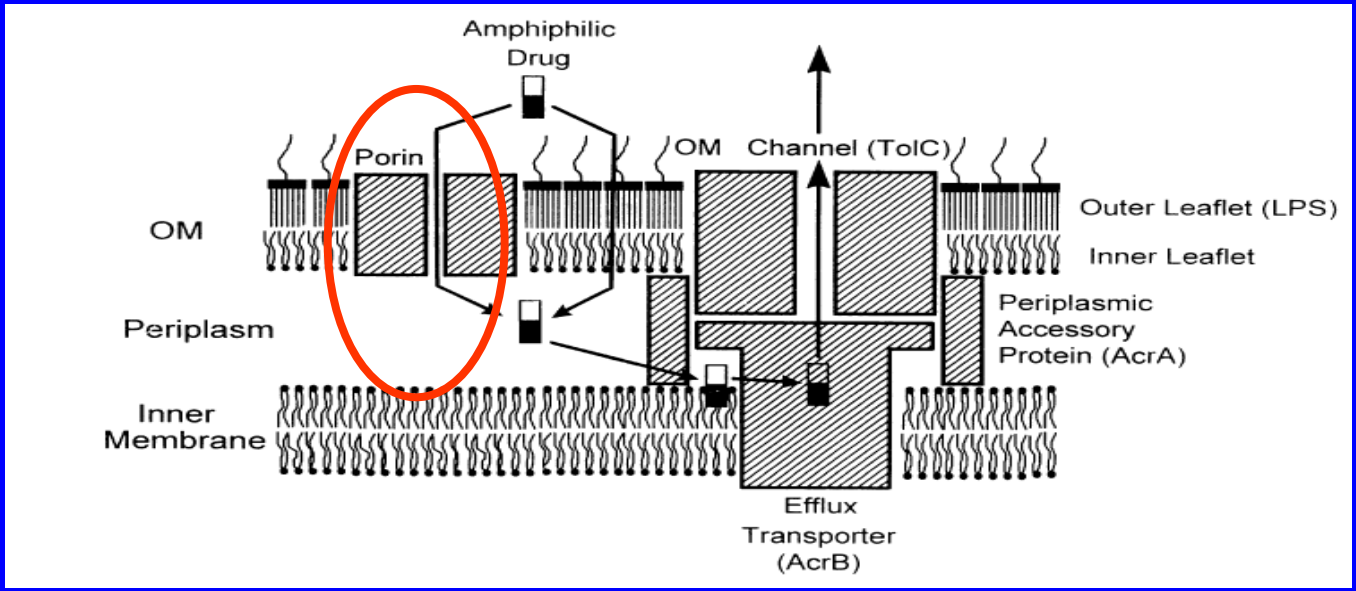
- An efficient carbapenamase or

  Combination of non-efficient beta-lactamase + porin loss +/- efflux
- Carbapenem entry to the cell (porins)
  - *P. aeruginosa* OprD – a specific porin used for influx of basic amino acids
  - Enterobacteriaceae - major porins
  - *A. baumannii* – various porins

Carbapenamases producers vs. porin mutants

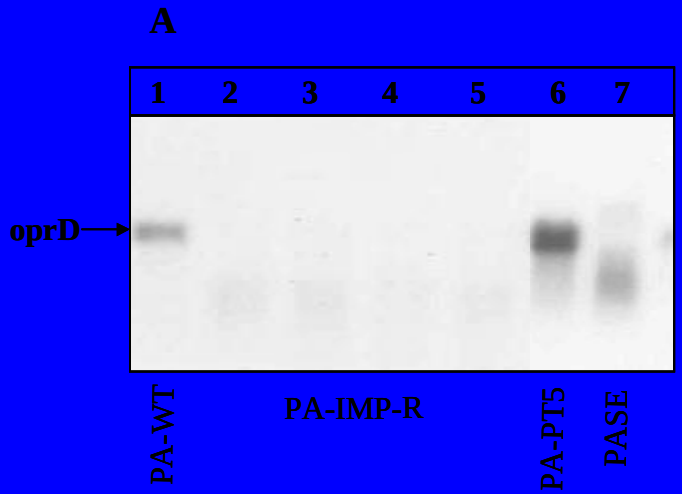
- Carbapenamases
  - Almost all are plasmid mediated
  - Can be transferred and reach successful clones
  - Do not cause impairment to the bacteria
  - Are associated with outbreaks and clonal/gene spread
- Porin mutants
  - Selected under abx pressure
  - Lead to metabolic impairment
  - When major porin is lost, not associated with outbreaks

Imipenem resistance in *P. aeruginosa* due to OprD loss:

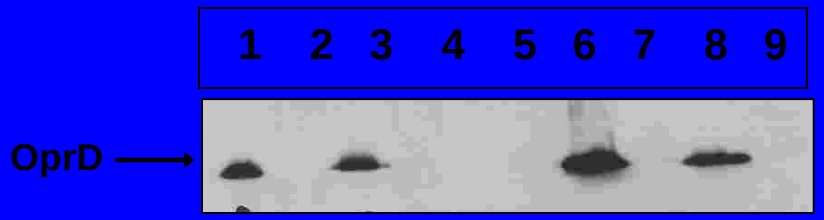


Nikaido H. Semin Cell Develop Biol. 2001;12;215

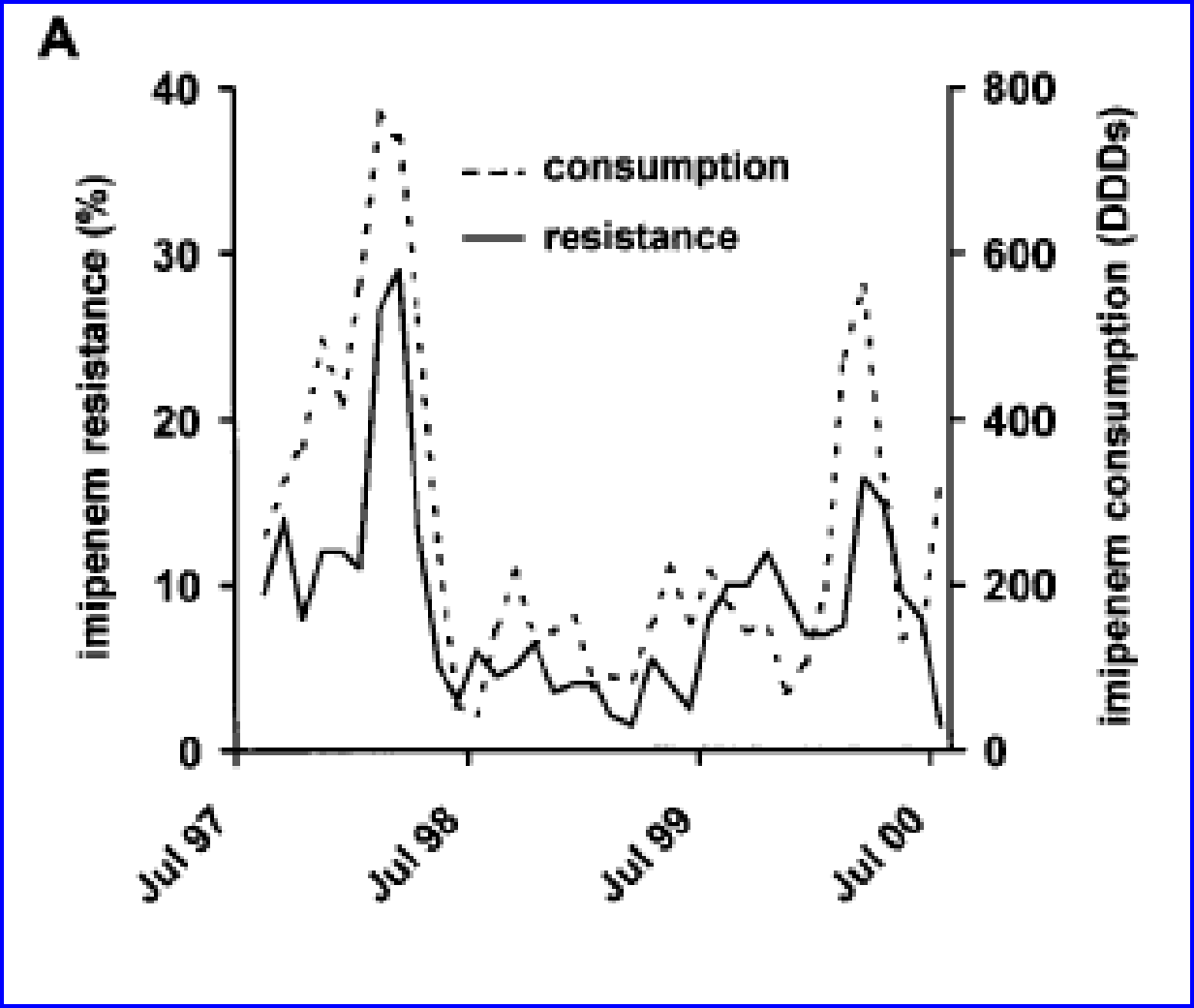
Northern blot



Western blot



Correlation between group 2 carbapenem and imipenem resistant *P. aeruginosa*



Lapper PM. AAC 2002

Prevention

- Primarily control group 2 carbapenem use
- In case of evident in-hospital transmission targeted infection control measures

Mechanisms of Carbapenem Resistance in Enterobacteriaceae

- Efficient carbapenamases
  - Metallo-beta-lactamases (Class B)
    - VIM, IMP, NDM
  - Serine carbapenamses (Class 2f)
    - KPC, SME, NMC
- Other beta-lactamases (inefficient carbapenamses) + porin loss
  - Certain ESBLs + major porin loss
  - AmpC + major porin loss

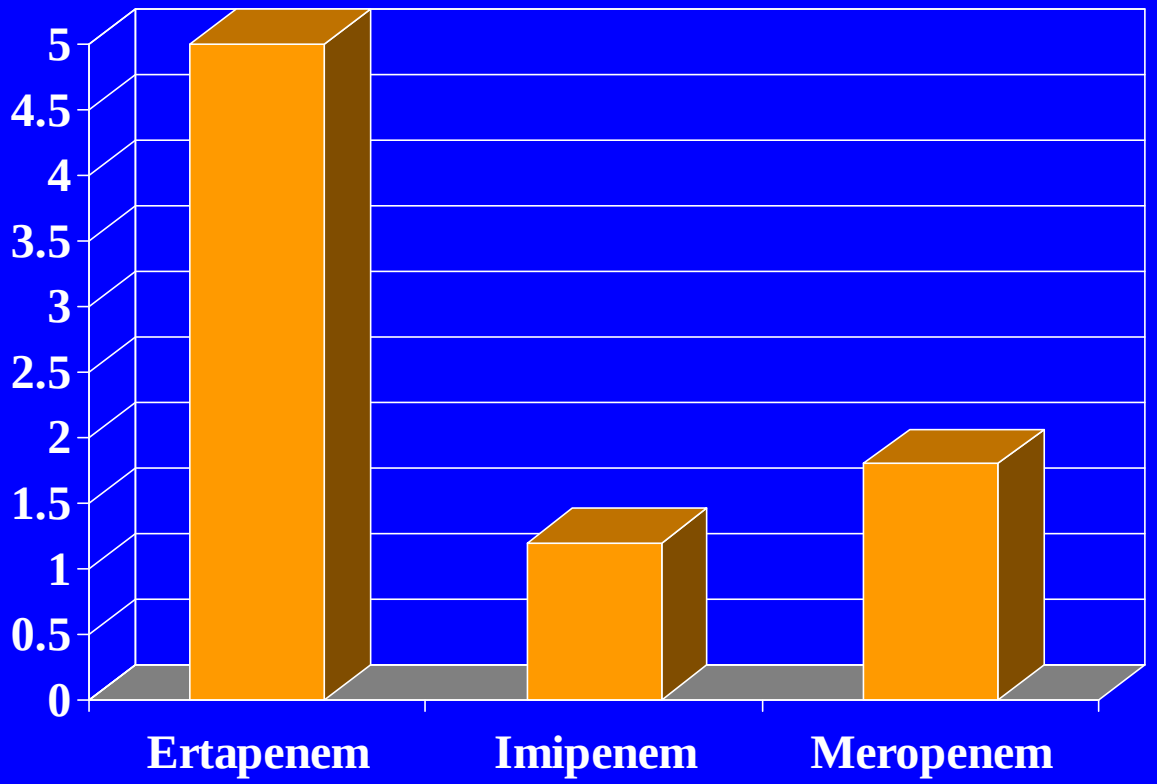
} Not associated with outbreaks

The Israeli experience with KPCs

- Carbapenem resistance in Enterbacteriaceae almost non-existing before 2006
- We have seen sporadic cases of KPC producing *Enterobacter* (NICU outbreak – imported by a mother) and *E. coli* in 2004-2005
- During 2006 large nationwide outbreak of KPC producing *K. pneumoniae*

% non-susceptibly to carbapenems of 1,030 ESBL producing *E. coli* & *Klebsiella* spp. Collected during 2004 (10 hospitals)

All detected as ESBL + porin loss,
No Carbapenamse, polyclonal



Adapted from Colodner R. DMID 2007; Leavit A, AAC 2009

Imipenem Resistant Enterobacter

- Seen for the first time in TASMC in Jan 2004 isolated from the urine of a surgical patient
  - Patient discharge before result – went unnoticed
- No other cases until Jun 2004
- Jun 30, 2004 – Outbreak in the NICU, three cases of late neonatal sepsis
  - 3 other carriers
- Traced to a mother which was GI carrier of the strain

Enterobacter KPC

- 2004 no further cases during 6 months
- 2005-2007:
  - 30 new cases, only two small (3 patients) time and space clusters
  - In hospital mortality 33%
    - Typical phenotype – quinolone and amikacin S
  - 18 isolates typed
    - 3 PFGE genotypes all produce KPC-2
      - 11 clone A
      - 5 clone B
      - 2 clone C

    } Similar plasmid encoding also for qnr B2
  - Repeated investigation did not identify the source
  - No association with carbapenem Rx

Marchaim D AAC 2008
Chmelintzky I. AAC 2009

KPC-2 producing *E. coli*

Patient	Isolate	Isolation Date	Infection site	LOS prior to IPM-R-*E. coli*	LOS	antibiotic treatment		Infection/ Colonization	Outcome
						1 m prior to *E. coli* isolation	**After *E. coli* isolation**		
1	157	2/2005	Urine	10 d	14 d	FQ	No treatment	Colonization	Recovered
2	329	9/2005	Blood	1d *	3 d	No treatment	Empiric iv CRO	Infection	Died
3	339	9/ 2005	Sub-phrenic abscess	30 d	4 m	Broad-spectrum cephalosporins, FQ, metronidazole, VAN, Followed with 14d IPM until 2 w before isolation, and then TZP, AMK	TZP, AMK	Infection	Recovered
4	360	10/ 2005	Urine	2 d *	18 d	CXM [a]	VAN, AMK, metronidazole	Colonization	Recovered

Navon-Venezia S. AAC 2006

IC at Dec 2005 in Tel Aviv

- KPC-2 in *E. coli* and *Enterobacter* spp.
- Mostly sporadic events
- High risk isolates
  - Single patient rooms
  - Contact isolation
  - Isolate on readmission admissions
- Presented to hospital management twice as a major threat
  - Questions regarding detection ability of the clinical micro lab (Vitek II system)

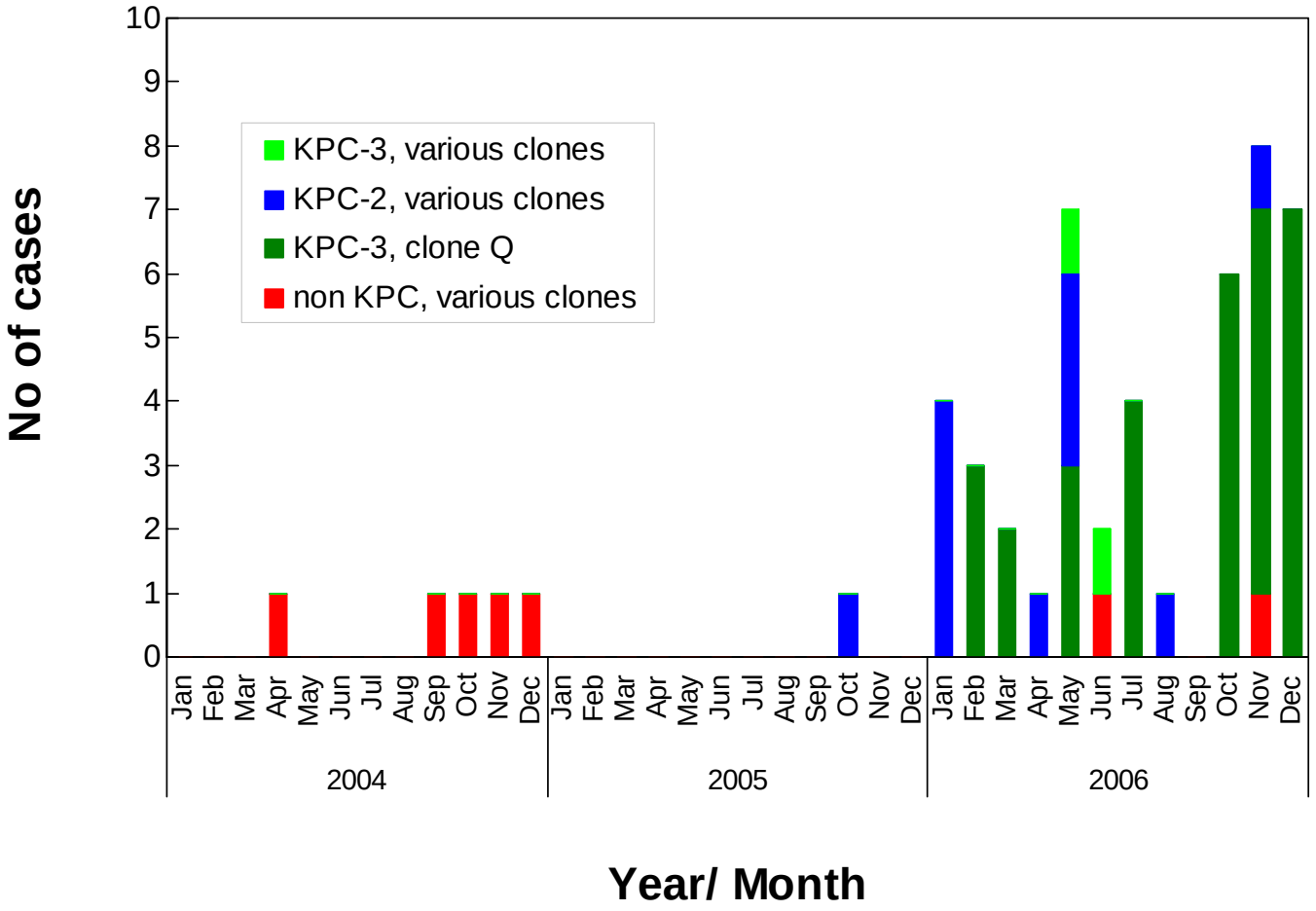
Antimicrobial susceptibility testing of 15 KPC-positive *K. pneumoniae* isolates

Method (software)	Card/panel	Imipenem results (n = 15)			Meropenem results (n = 15)		
		Resistant	Intermediate	Susceptible	Resistant	Intermediate	Susceptible
Broth microdilution	In-house frozen panel	13	2	0	14	1	0
Disk diffusion	BDDS disks	3	11	1	10	5	0
MicroScan (LabPro1.51, Alert 1.50)	Neg combo 32	7	7	1	13	1	1
Phoenix (4.05W/3.81A)	NMIC/ ID-104	5	8	2	12	1	2
Sensititre AutoReader (3.0.8 SP2)	GN2F	0	2	13	0	3	12
VITEK (R10.01)	Superflex GNS 122 and 127	5	0	10	2	3	10
VITEK 2* (R04.01)	GN07	4	6	5	4	4	5

5 (33%) of 15 KPC-pos *K. pneumoniae* isolates were reported as susceptible to imipenem by VITEK 2

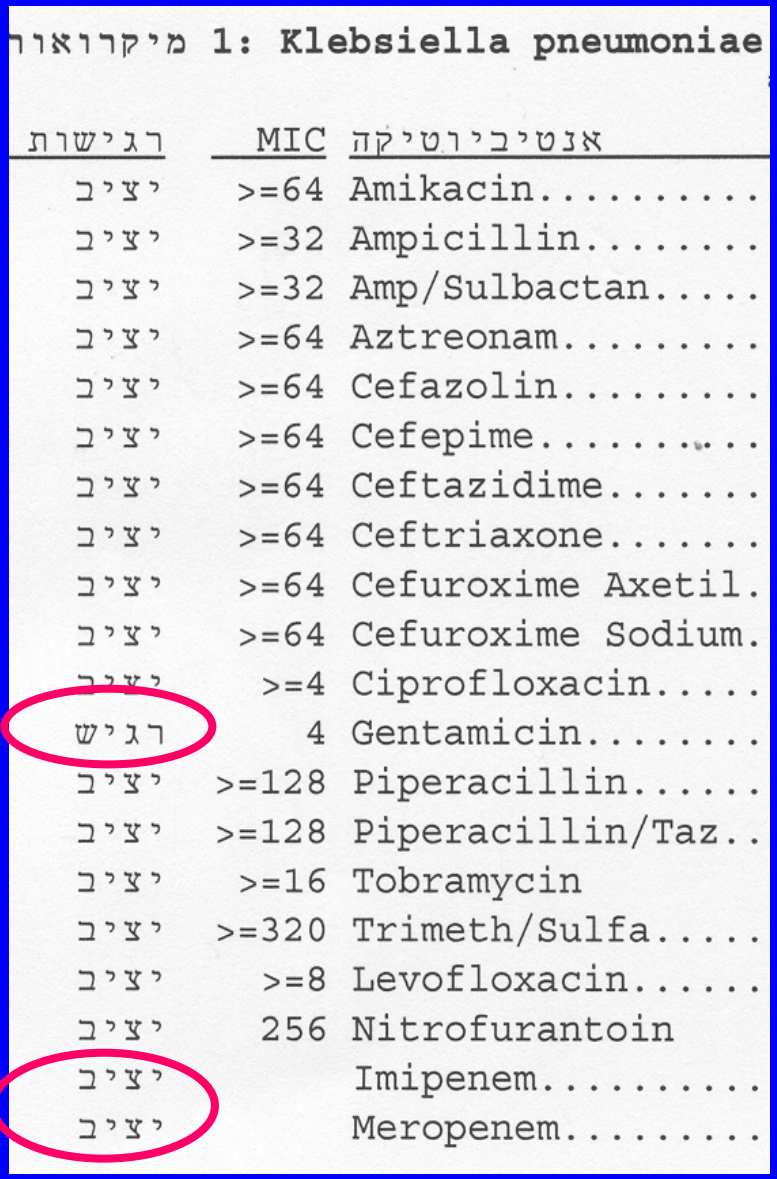
Tenover et al, EID 2006

Molecular epidemiology and emergence of KPC in carbapenem-resistant *K. pneumoniae*



Leavitt A., AAC, 2007

Israeli epidemic KPC-3 producing *Klebsiella*



מיקרואור 1: **Klebsiella pneumoniae**

רגישות	MIC	אנטיביוטיקה
יציב	>=64	Amikacin.....
יציב	>=32	Ampicillin.....
יציב	>=32	Amp/Sulbactan.....
יציב	>=64	Aztreonam.....
יציב	>=64	Cefazolin.....
יציב	>=64	Cefepime.....
יציב	>=64	Ceftazidime.....
יציב	>=64	Ceftriaxone.....
יציב	>=64	Cefuroxime Axetil.
יציב	>=64	Cefuroxime Sodium.
יציב	>=4	Ciprofloxacin.....
רגיש	4	Gentamicin.....
יציב	>=128	Piperacillin.....
יציב	>=128	Piperacillin/Taz..
יציב	>=16	Tobramycin
יציב	>=320	Trimeth/Sulfa.....
יציב	>=8	Levofloxacin.....
יציב	256	Nitrofurantoin
יציב		Imipenem.....
יציב		Meropenem.....

S

R

Outcomes

- Crude Mortality
  - Resistant *Klebsiella* – 21 died (44%)
  - Susceptible *Klebsiella* – 7 died (13%)
  - No *Klebsiella* – 1 died (2%)
- Adjusted impact of CRKP on mortality:
  - Compared with hospital controls – OR 5.0 (1.7-14.8), p=0.004
  - Compared with susceptible *Klebsiella* – OR 3.9 (1.1-13.6), p=0.03
- Mortality with bacteremia >70%

Schwaber et al, AAC, 2008
Finkelstein, ECCMID 2007

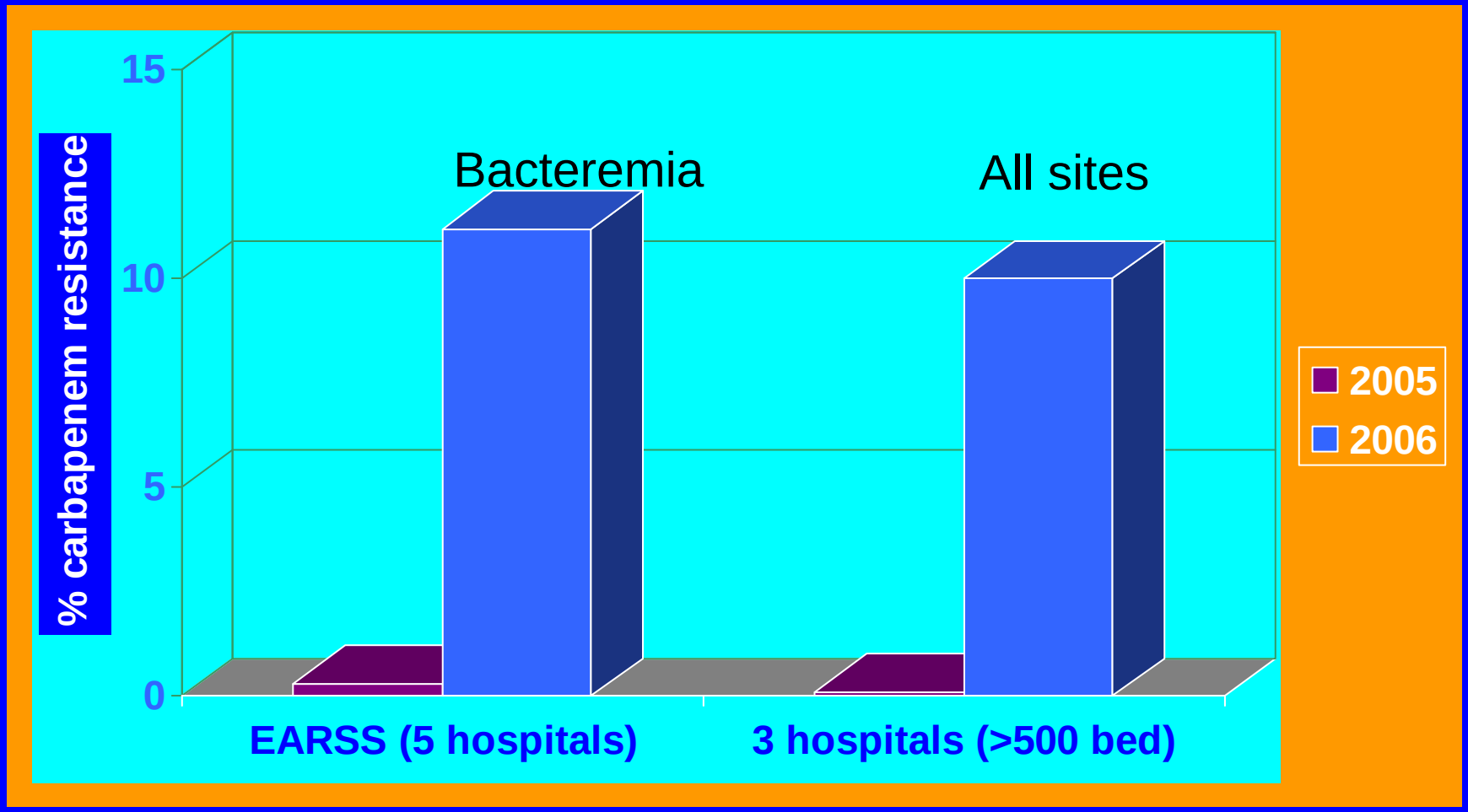
Mid February

- Ministry of health approached to intervene at a national level
- Guidelines were written by IC society and embraced by the ministry of health mandating
  - Isolation
  - Cohorting with dedicated staff and equipment
  - Reporting daily on cases and isolation
  - National task force to control KPCs

Mode of action of the Task force

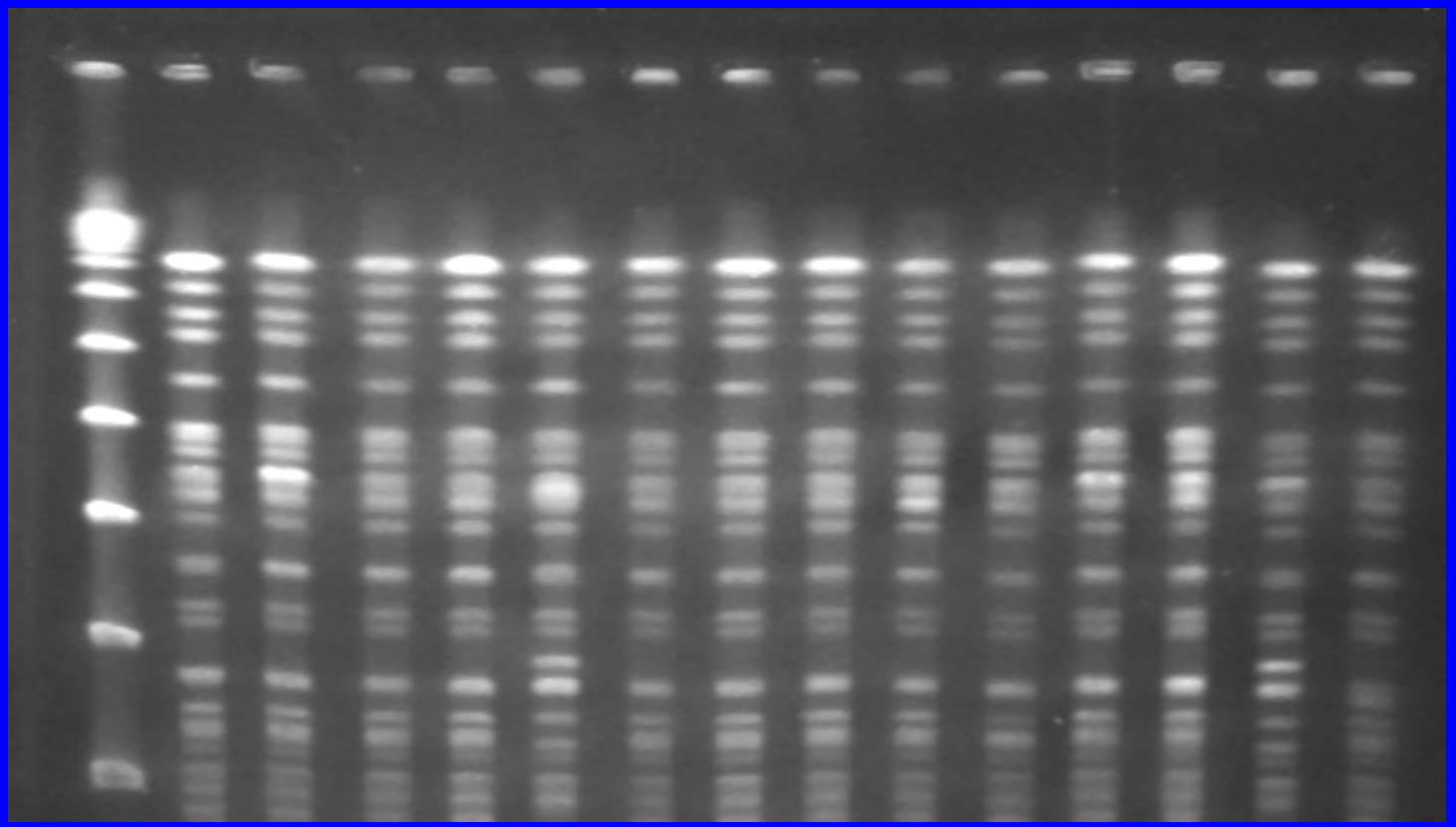
- Coordinated regional measures
- Collaborative effort of the entire IC community
- Refer to hospital CEO's as responsible for control of CRE
- All formal communications are with the CEO's
- Daily feedbacks for non-adherence
- Visits at all sites (30 per year)

Nationwide emergence of carbapenem-resistant Kpn - Israel



Incidence: 60-100 cases per 1,000 hospital beds/year
Total number of cases: ~1000 (per 7 million population) mortality 44%

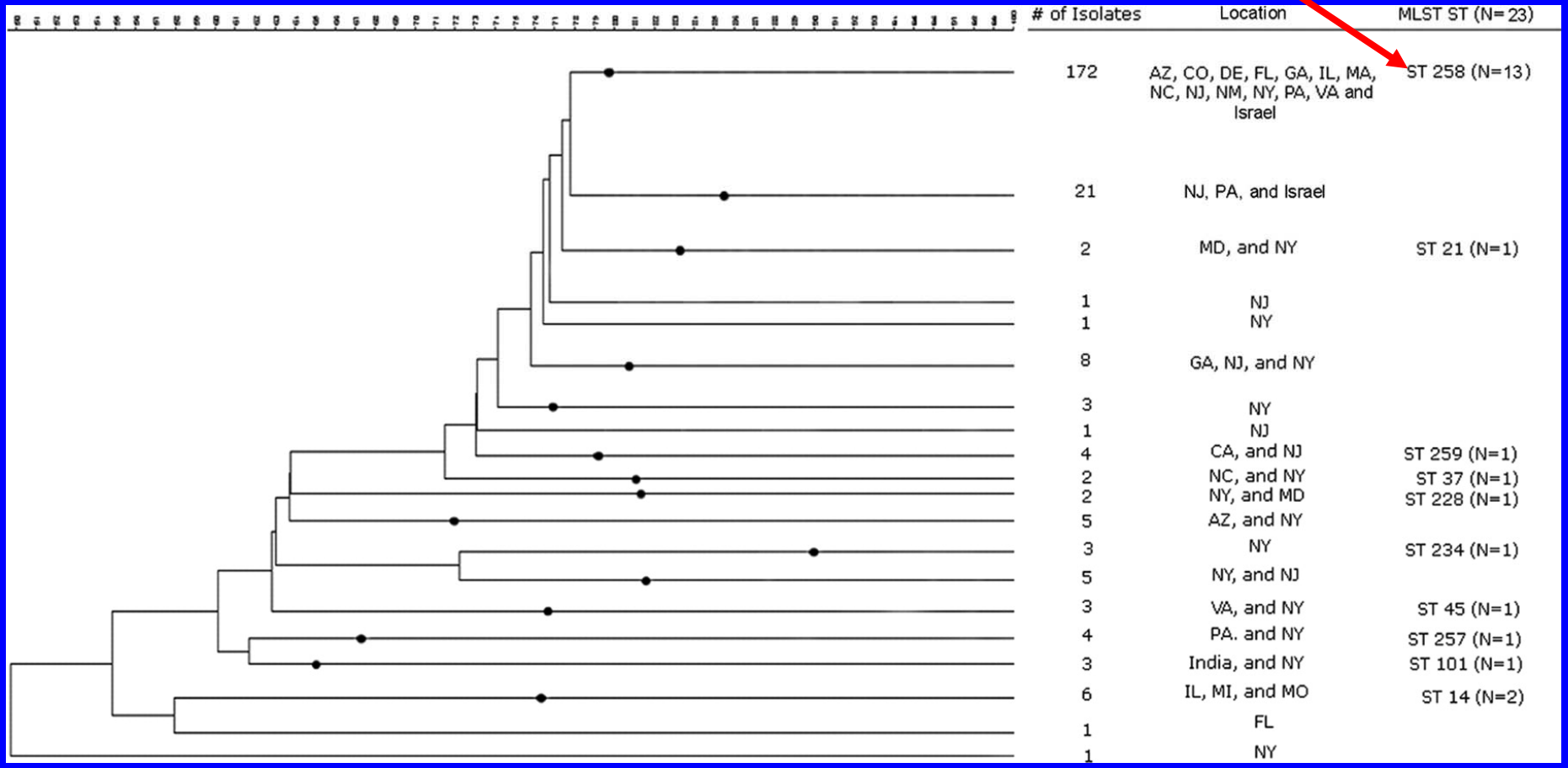
PFGE of isolates from 8 hospitals and 5 LTCFs:



Navon-Venezia et al, ICAAC, 2007

Dendrogram of the CDC's KPC-producing *K. pneumoniae* PFGE database (n = 248)

Predominance of a single clone - ST258



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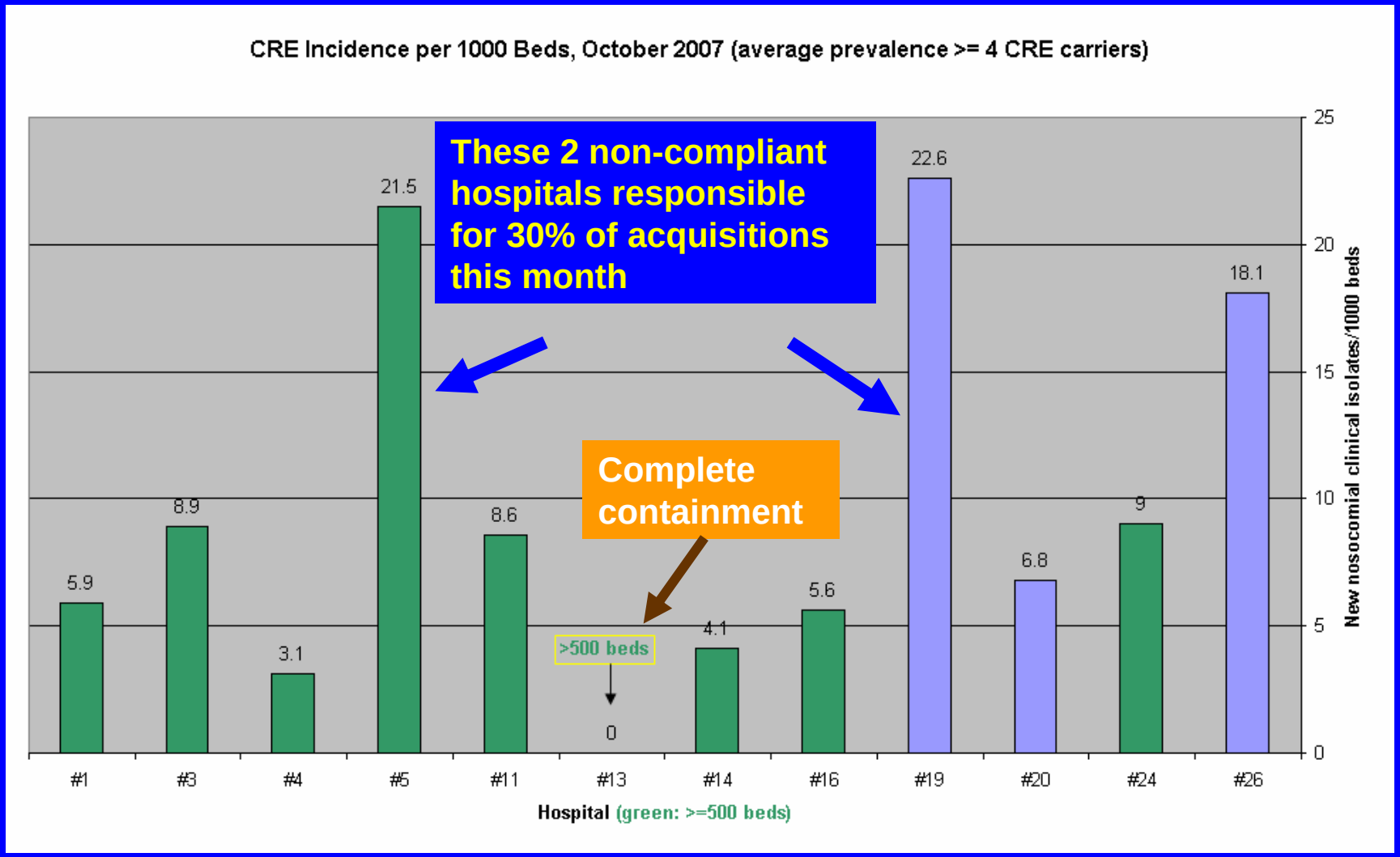
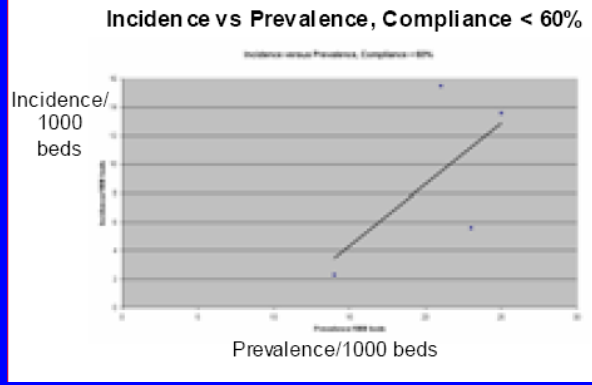
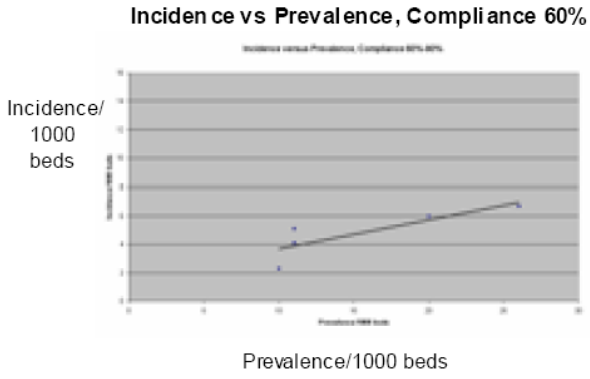
Kitchel et al, AAC, 2009

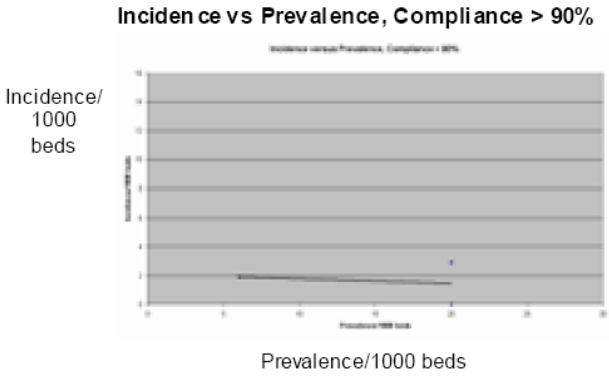
Compliant hospitals succeed in containing spread; non-compliant hospitals do not



Not all-or-nothing: greater compliance yields greater containment

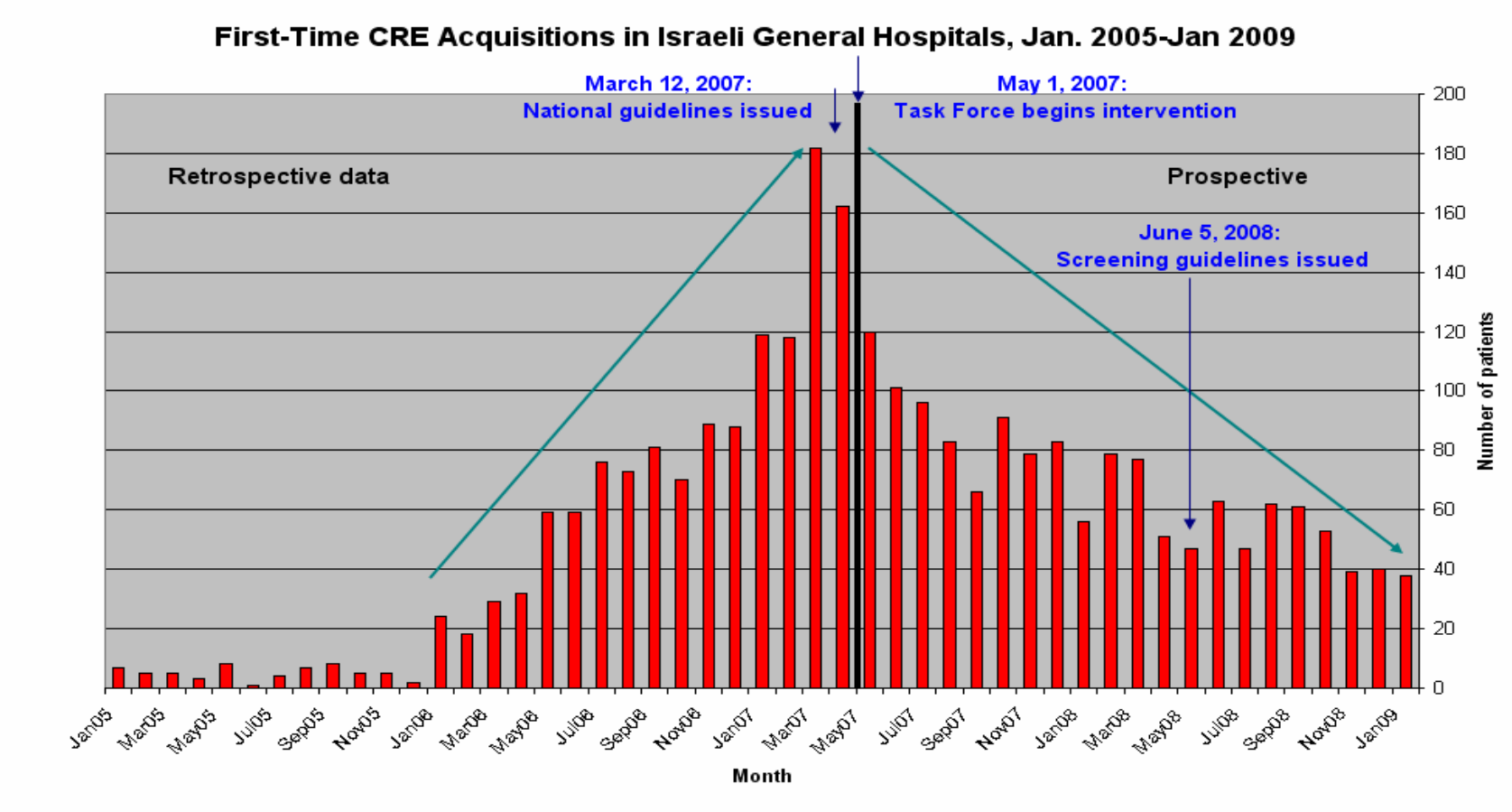






Schwaber et al. ICAAC 2008

Effect of nationwide infection control intervention



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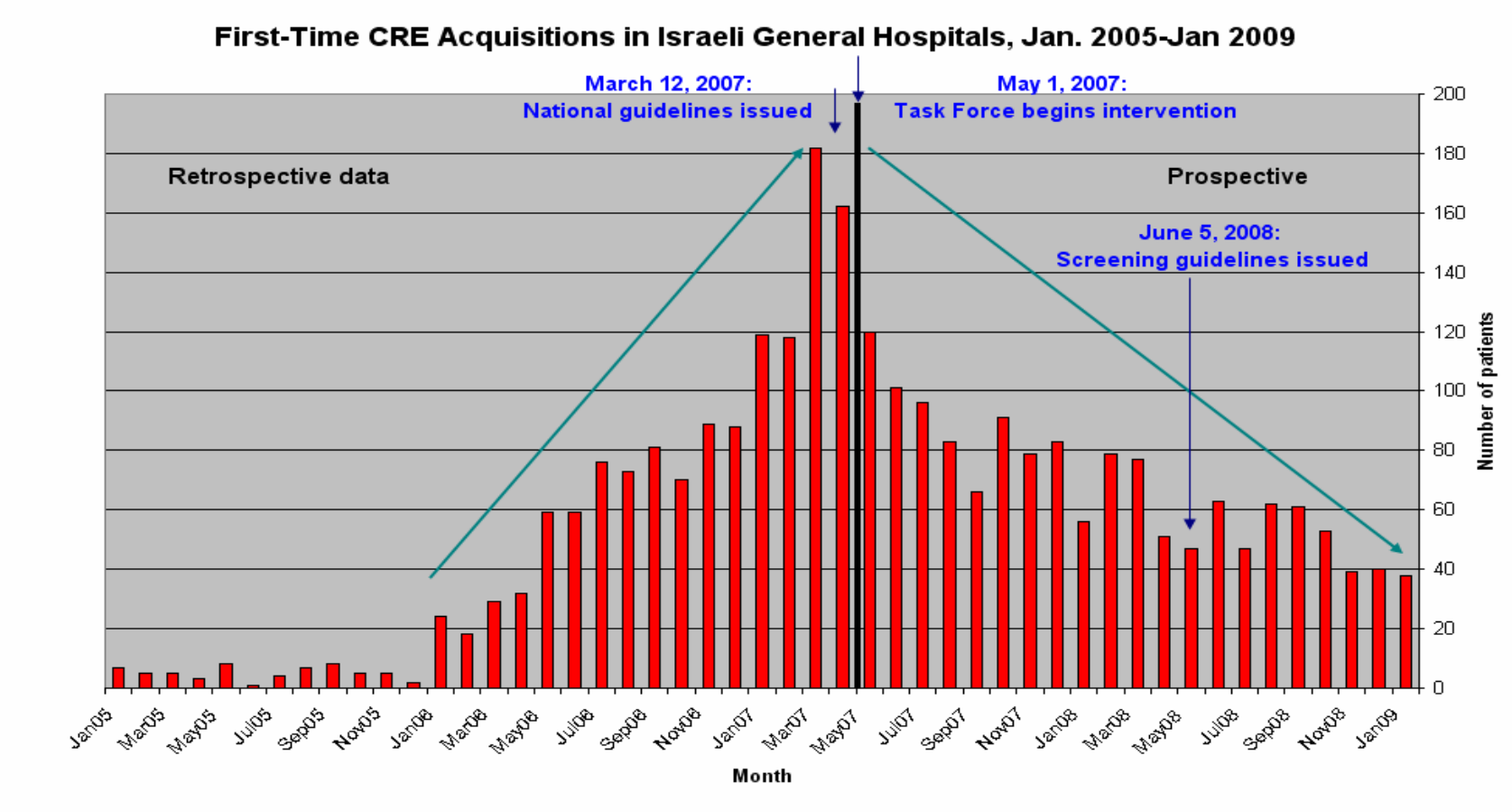

Schwaber M. ICCAC 2009

Summary

- ESBL
  - Come from the community + healthcare spread
  - Serious infections should be treated with carbapenems
  - Prevention: Formulary interventions +/- targeted IC (local epidemiology)
- Porin loss mutants (primarily *P. aeruginosa*)
  - Caused by selective pressure
  - Treatment ?
  - Prevention: primarily abx control
- Carbapenemases
  - Come from other countries (or affected institutions)
  - Treatment?
  - Prevention: early detection and strict infection control measures