The monitoring system of antimicrobial resistance and control outbreaks of polyresistant pathogens: Lessons from Israel

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Novel Carbapenem-Hydrolyzing β-Lactamase, KPC-1, from a Carbapenem-Resistant Strain of *Klebsiella pneumoniae*

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SEBASTIAN ALBERTI,[4] KAREN BUSH,[2] AND FRED C. TENOVER[1]*

- First report of KPC (later corrected to be KPC-2)
- Isolated from a patient with nosocomial infection in and ICU in a North-Carolina hospital (1996?)
  - No particular attention to the isolate initially
- Examined when collection of isolates was tested in the CDC as part of the ICARE project (routine surveillance)

AAC 2001

Outbreak of *Klebsiella pneumoniae* Producing a New Carbapenem-Hydrolyzing Class A β-Lactamase, KPC-3, in a New York Medical Center

Neil Woodford,[1]* Philip M. Tierno, Jr.,[2] Katherine Young,[3] Luke Tysall,[1] Marie-France I. Palepou,[1] Elaina Ward,[1] Ronald E. Painter,[3] Deborah F. Suber,[3] Daniel Shungu,[3] Lynn L. Silver,[3] Kenneth Inglima,[2] John Kornblum,[4] and David M. Livermore[1]

History and control of the outbreak. Twenty-four patients in ICUs at the Tisch Hospital, NYU Medical Center, were colonized or infected with carbapenem-resistant *K. pneumoniae* between April 2000 and April 2001 (Table 2). Klebsiellae with this phenotype had not been detected in the hospital previously. All infections were nosocomially acquired, with the patients having been hospitalized from 9 to 374 days prior to isolation of the organism. Risk factors for acquisition included prolonged hospitalization, an ICU stay, and ventilator usage. Carbapenem-resistant organisms were isolated predominantly from respiratory secretions but also from urine and blood. Fourteen of the 24 patients were infected, and 8 of these died, with the *Klebsiella* infection considered causative or contributory. The isolates were also broadly resistant to many antibiotic

2000-2001
24 cases in
A single hospital:
33% CFR

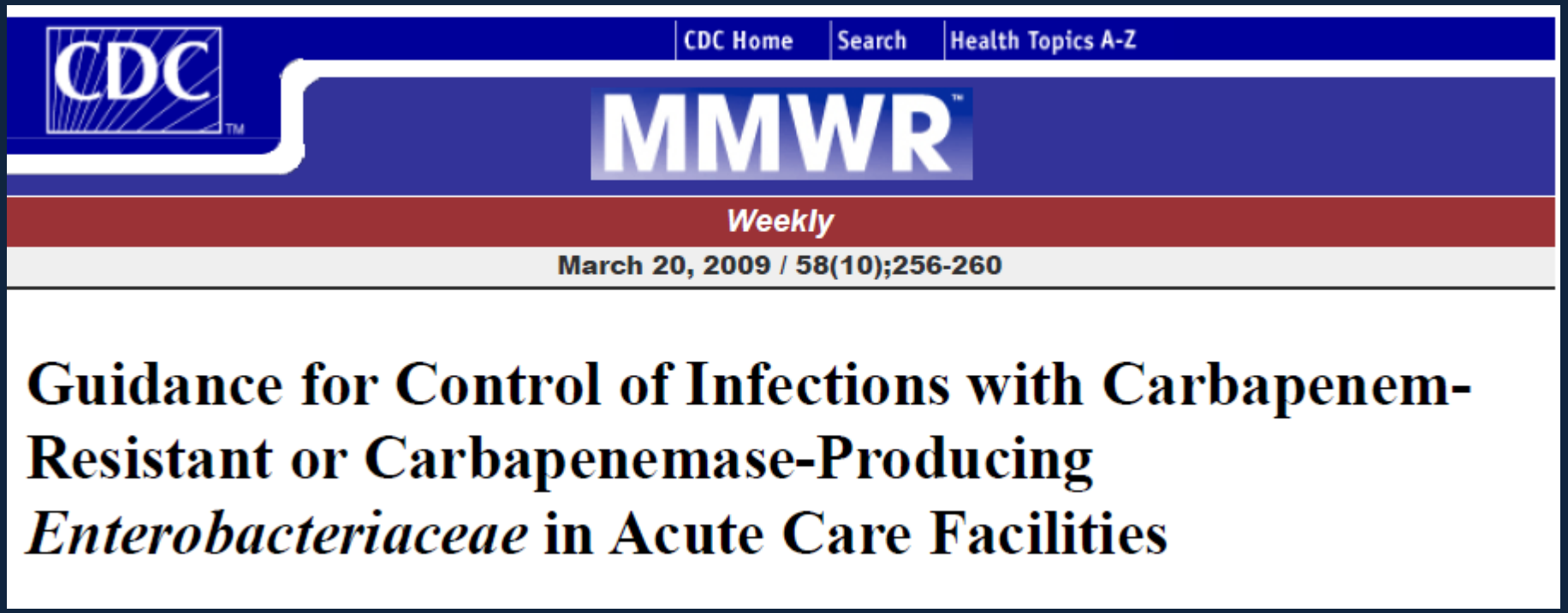
KPC-3
The outbreak contained by vigorous infection control and surveillance

AAC 2004

Outcomes

- Crude Mortality
  - Resistant *Klebsiella* – 44%
- 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
- Meta-analysis of 985 patients:
  - attributable mortality 26-44%
- Mortality with bacteremia >70%

Schwaber , AAC, 2008
Finkelstein, ECCMID 2007
Borer, ICHE 2009
Falagas, EID 2014



- Too late
- Too little

By Anne Godlasky, USA TODAY; Source: Centers for Disease Control and Prevention

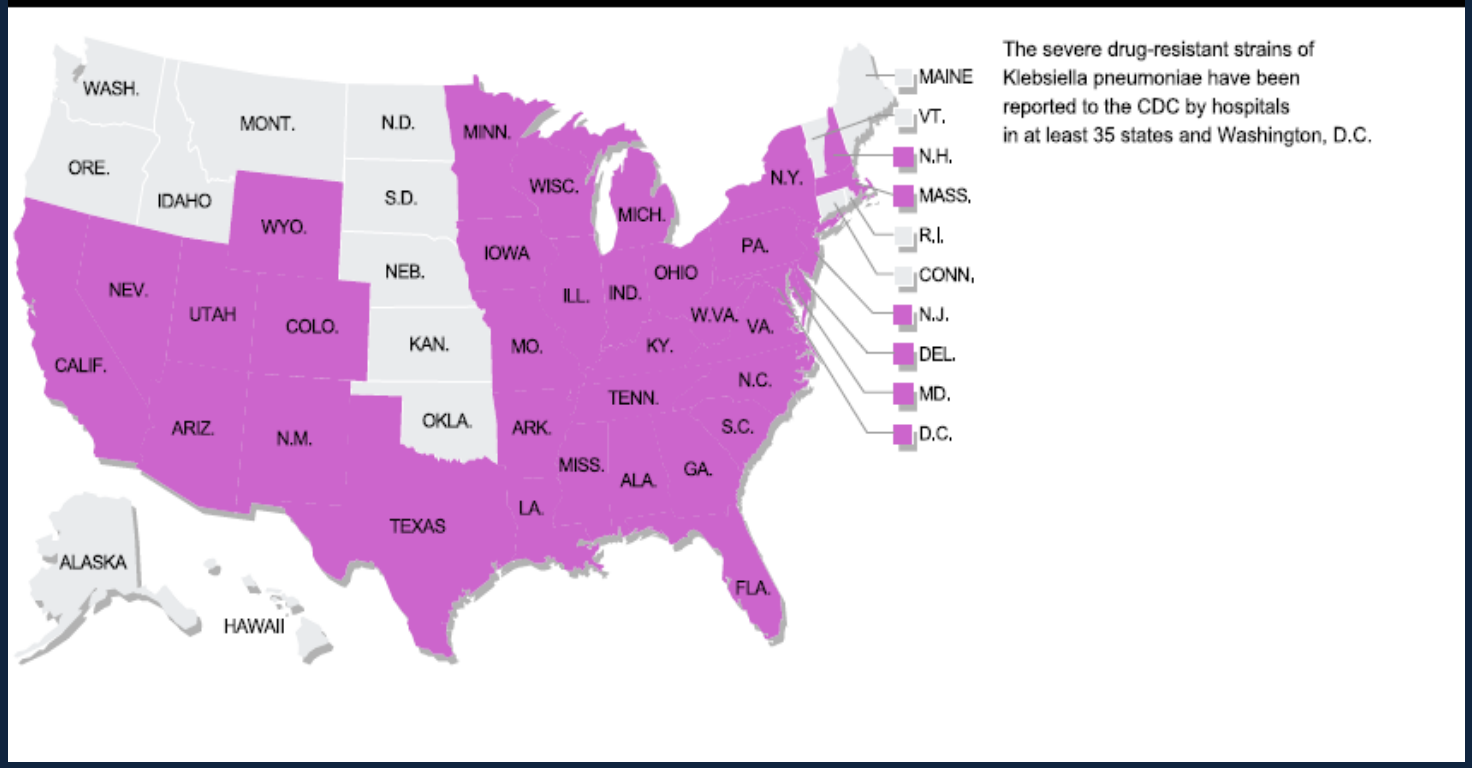
Drug-resistant 'superbugs' hit 35 states, spread worldwide

Updated 9/17/2010 5:05 PM | Comments 467 | Recommend 51 E-mail | Print | Reprints & Permissions | RSS

By Steve Sternberg, USA TODAY

Share

USA TODAY Sept 2010



NHSN report 2009-2010: 12.5% of all Klebsiella reported from HAI are CRE

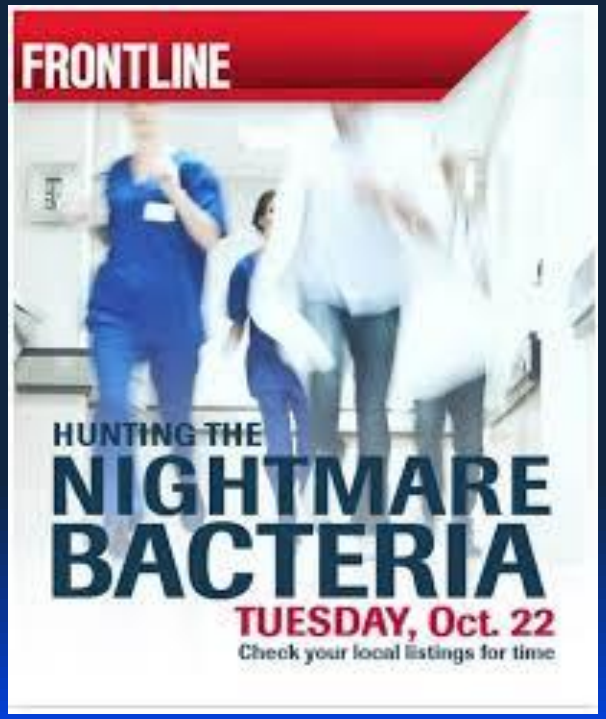
Silvert DM. ICHE 2013

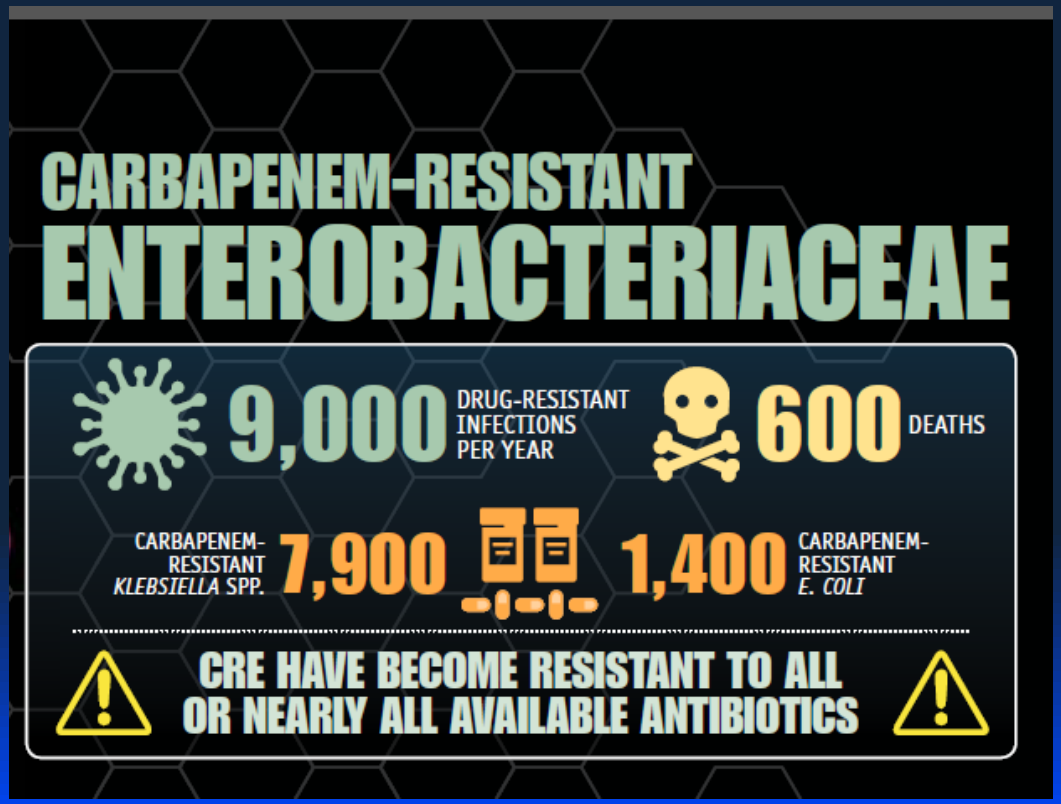
Press Release

For Immediate Release: March 5, 2013

CDC: Action needed now to halt spread of deadly bacteria

*"CRE are **nightmare bacteria**. Our strongest antibiotics don't work and patients are left with potentially untreatable infections,"* said CDC Director Tom Frieden, M.D., M.P.H.





Superbug found in California hospitals

March 28th, 2011

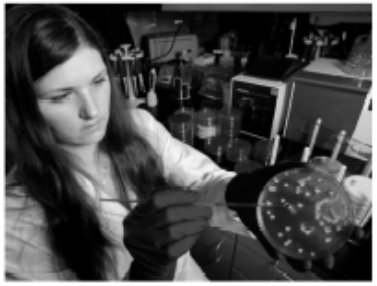
CNN Health

A deadly superbug, thought to be rare on the West Coast, is appearing in large numbers in Southern California, according to a new study.

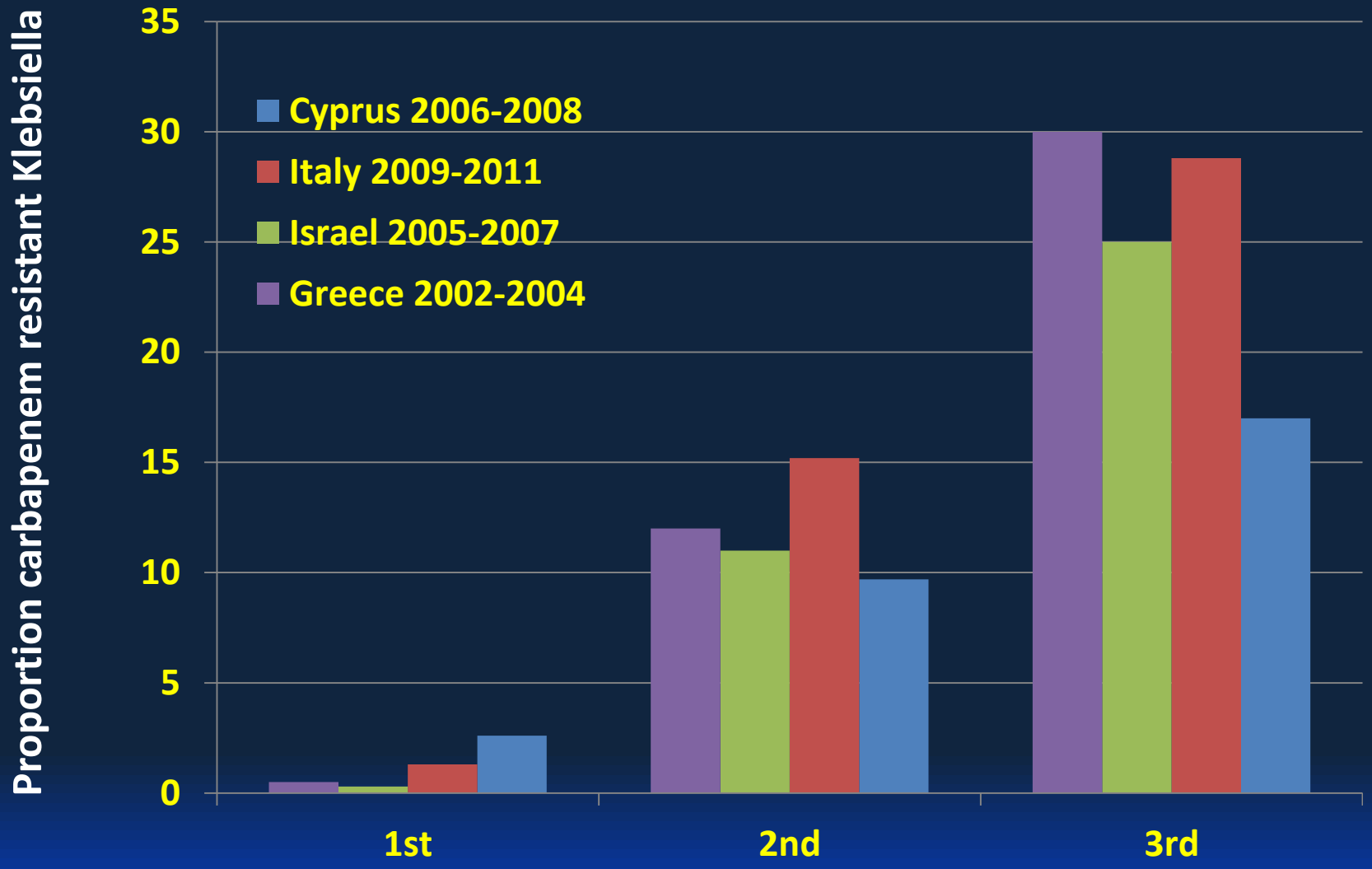
Estimated fatalities in 7 months: 356 X 35% = 125

'Nightmare bacteria' spread in Southeast

Laura Ungar, USA TODAY *7:43 p.m. EDT July 31, 2014*



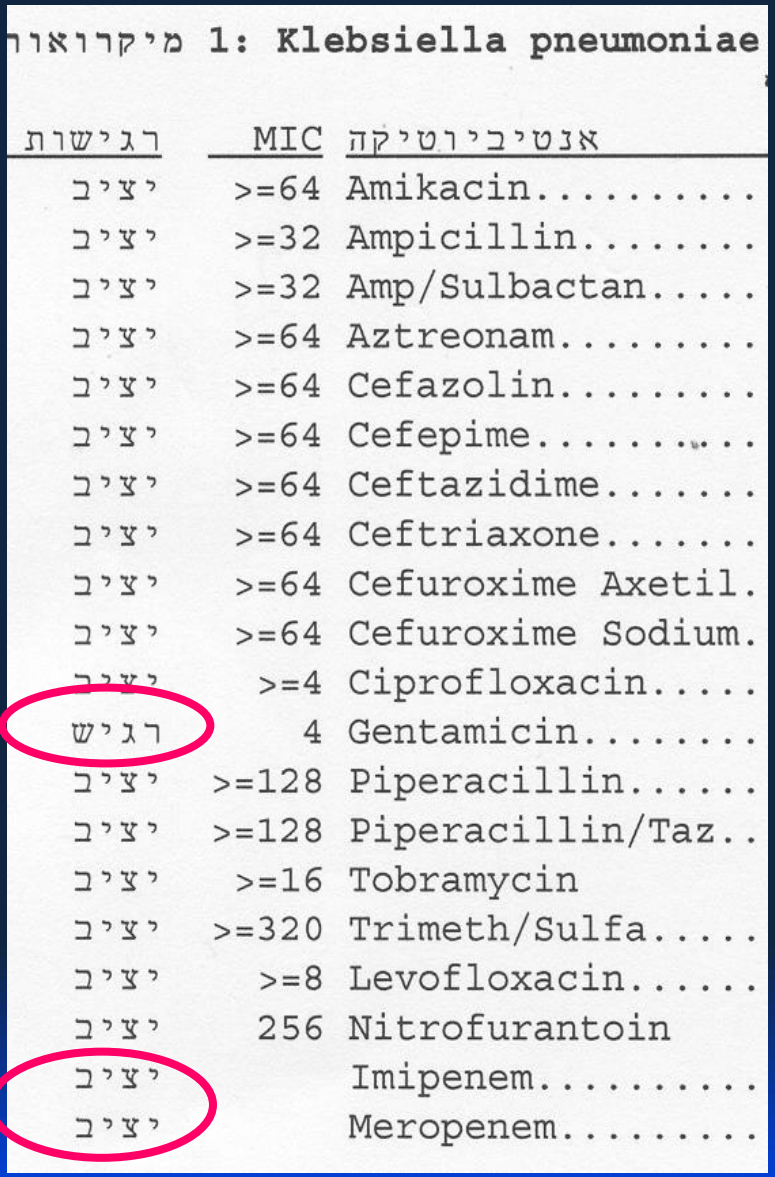
Natural history of CPE spread



EARSS DATA

Vatopoulus A. Eurosurveillance 2008

Israeli epidemic KPC-3 producing *Klebsiella*



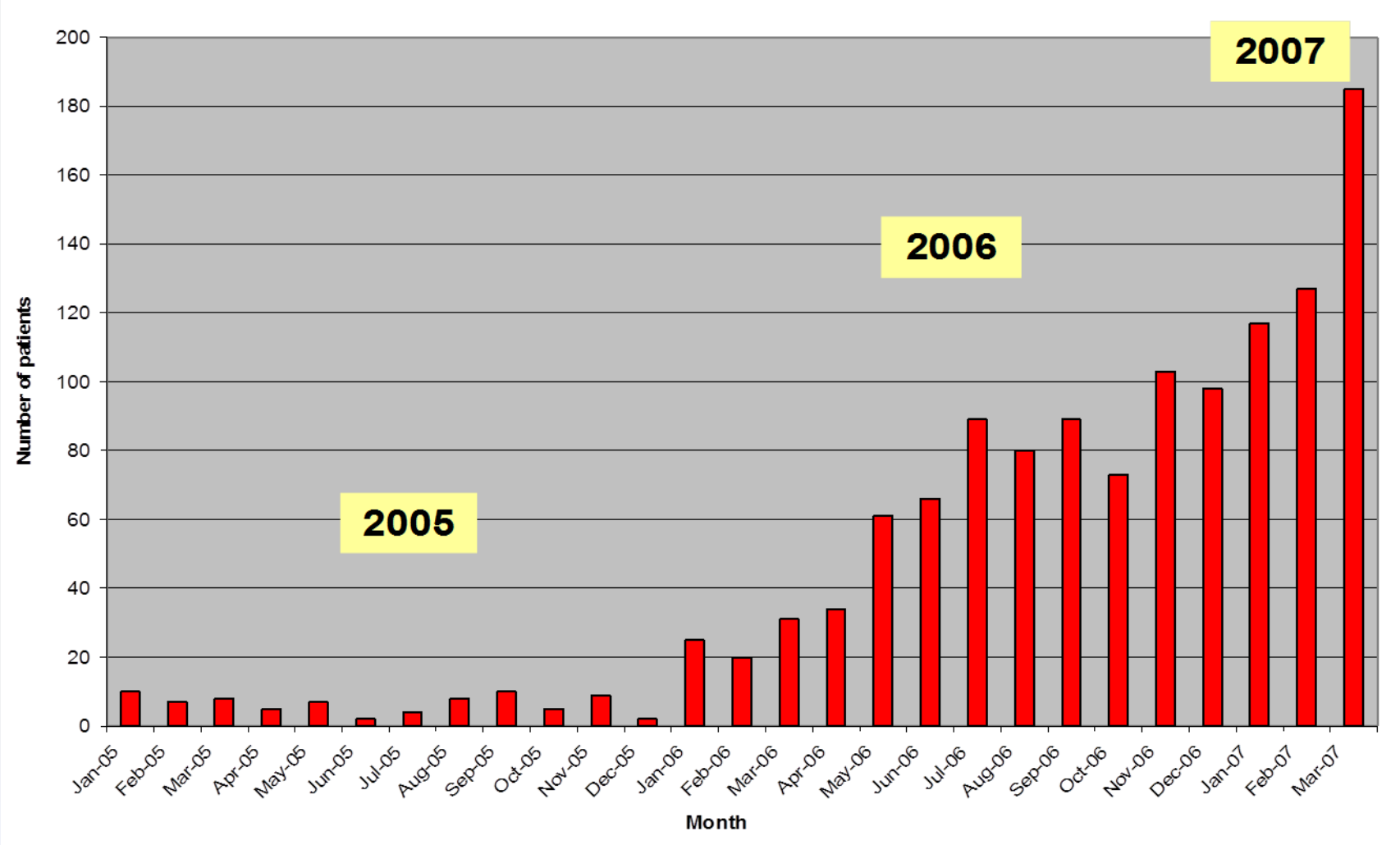
מיקרואורגניזם 1: Klebsiella pneumoniae

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

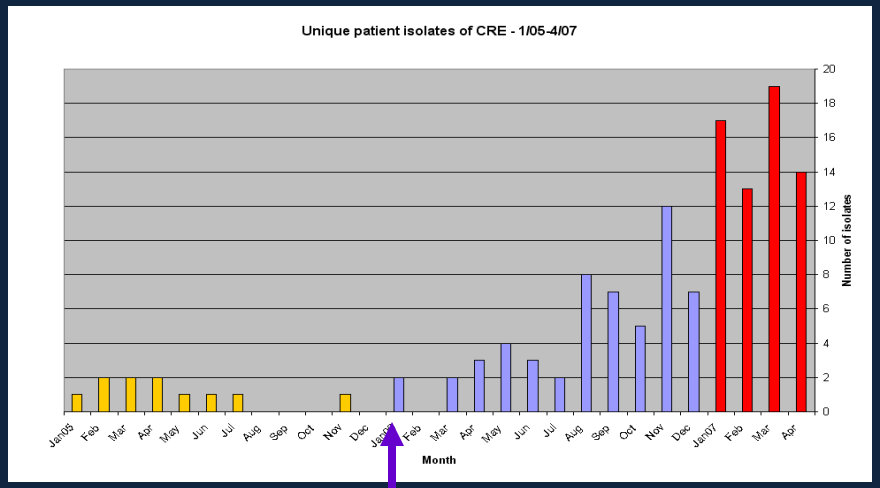
R

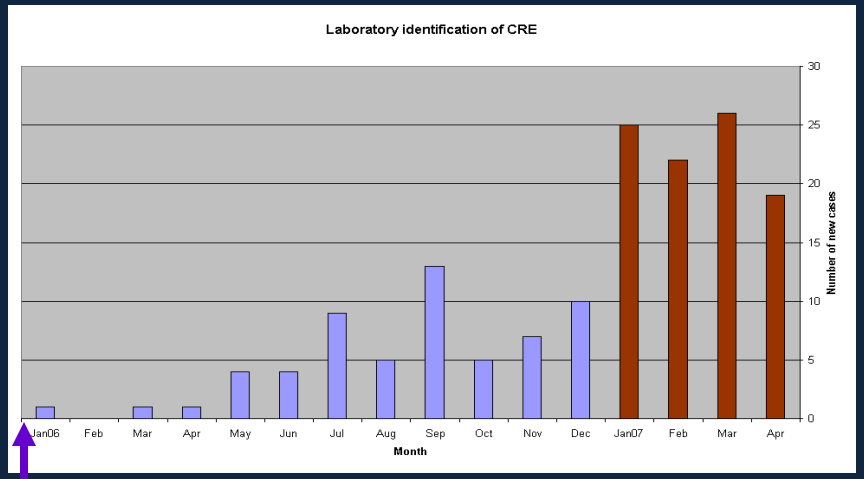
First-time CRE (carbapenem-resistant Enterobacteriaceae) isolations, clinical culture, Israeli general hospitals



Meeting of the IC society Early Feb 2007

data from several hospitals showing similar epidemic curve

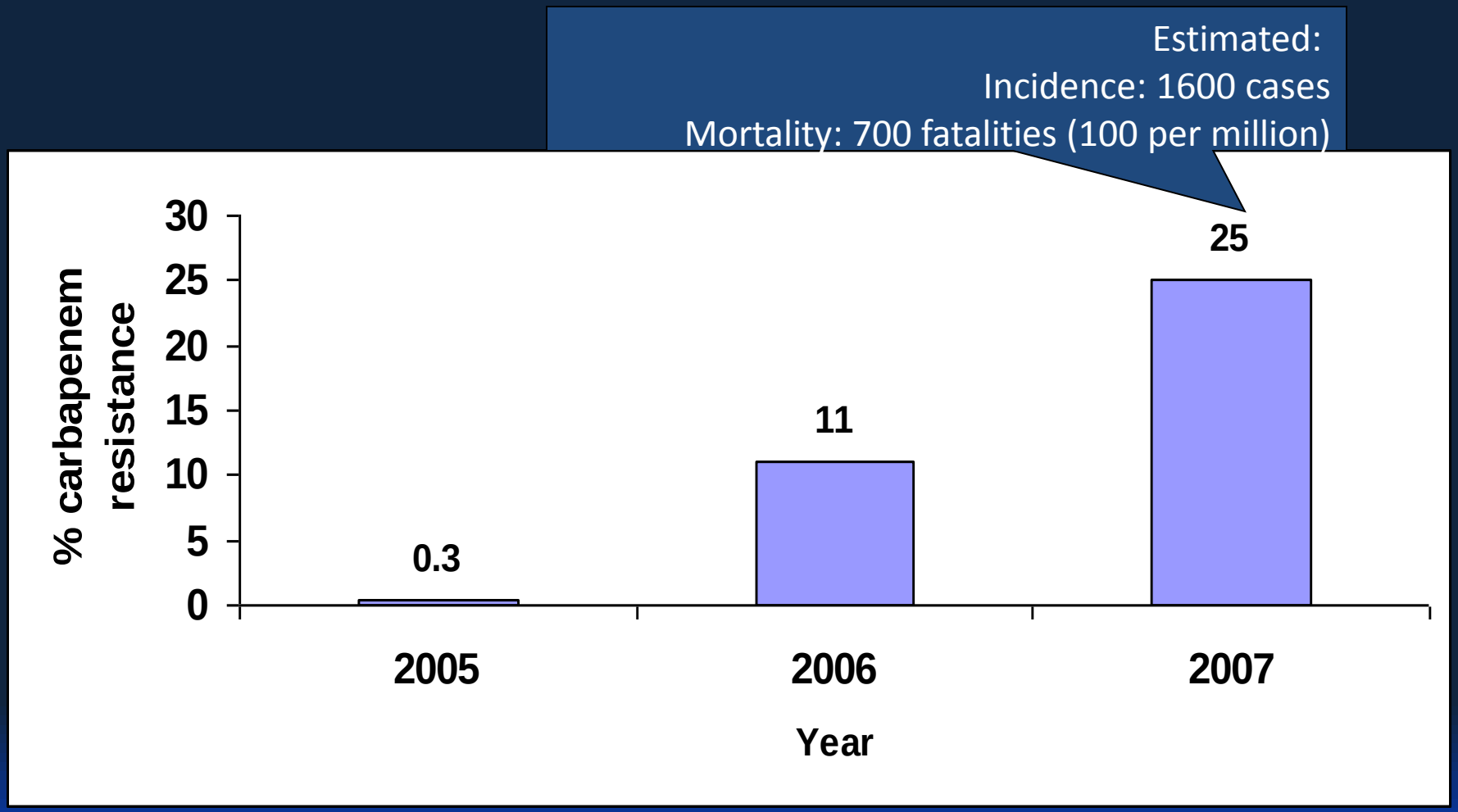




Jan 2006

Jan 2006

Carbapenem resistant Klebsiellae Pneumonia BSI - Israel



EARSS report
Schwaber M. AAC 2008


ידיעות אחרונות

בתי החולים אינם ערוכים למנוע החפשטות החיידק

נדבק

54%: המנכ"ל צודק

"אוהם פוחדים"


ידיעות אחרונות

חיידק אלים הרג עשרות מאושפזים

קרב הצרחות

"הגנרל האיראני ערק לארה"ב"

כל יום מחלוקת חדשה

8/3/07

7/3/07

- Surgeon General meets with all Hospital Directors, deputies and head nurses
  - informs them on the seriousness of the problem
  - Nominate a group of professionals as the task force to manage the outbreak
- Adopts the IC guidelines as regulations that goes into immediate effect

- Israeli government presented with the plan and decides to form the “National Institute for Antibiotic Resistance & Infection Control”
  - Regulatory and intervening center
  - Reference laboratory
  - Informatics Center

Mode of action

- CRE outbreak threaten the ability of the healthcare system to provide care
  - Elective surgery, Transplant, Chemotherapy
- Refer to the hospital CEO's as the responsible for control of CRE
  - All formal communications are with the CEO's
- Collaborative effort of the entire IC community
- Daily reports and feedbacks
- Laboratory capacity building
- Visits at all sites

Israeli Nationwide Intervention

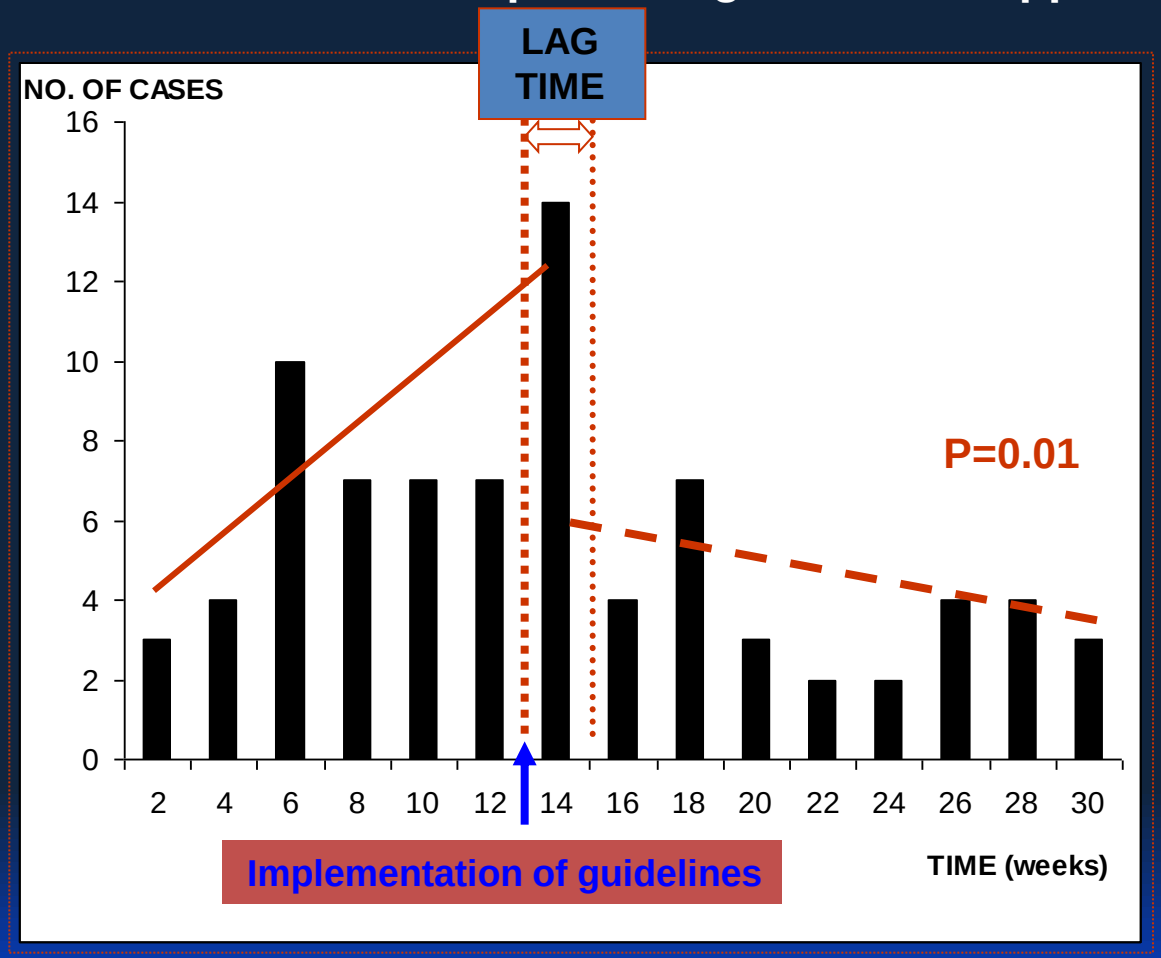
- To provide regional coordination and supervision
- National guidelines
- Strict isolation with dedicated staff
- Rapid identification of carriers
  - by flagging
  - information transfer
  - screening of high risk population
- Continuous root-cause analysis

IC guidelines of March 2007

- All carriers of CRE will be taken care in a stand alone isolation unit
- Dedicated nursing staff not allowed to take care of non-carriers on the same shift
- Other staff and visitors, require to change clothing on entry and exist of the unit
- Daily report to the task force on all the above

One hospital's experience –moving from single room contact isolation to cohorting with dedicated staff

Incidence of KPC-producing *Klebsiella* spp.



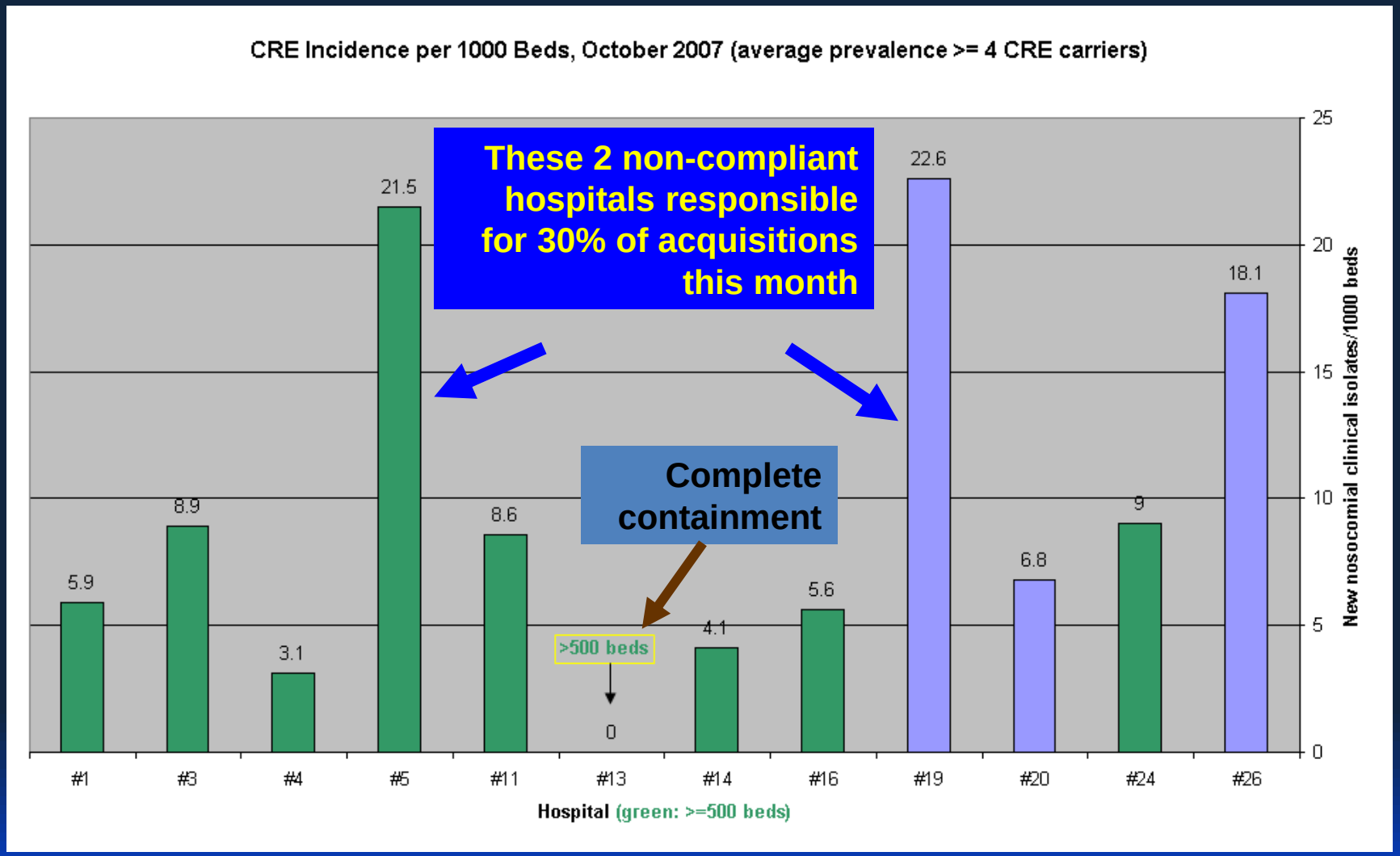
Schechner V, ICAAC 2007

Daily report by CEO's office

- Patients details
- New/or known carrier
  - Location of acquisition
- Ward
- Is marked as isolated
- Use of gowns
- Cohorting
- Dedicated nursing staff

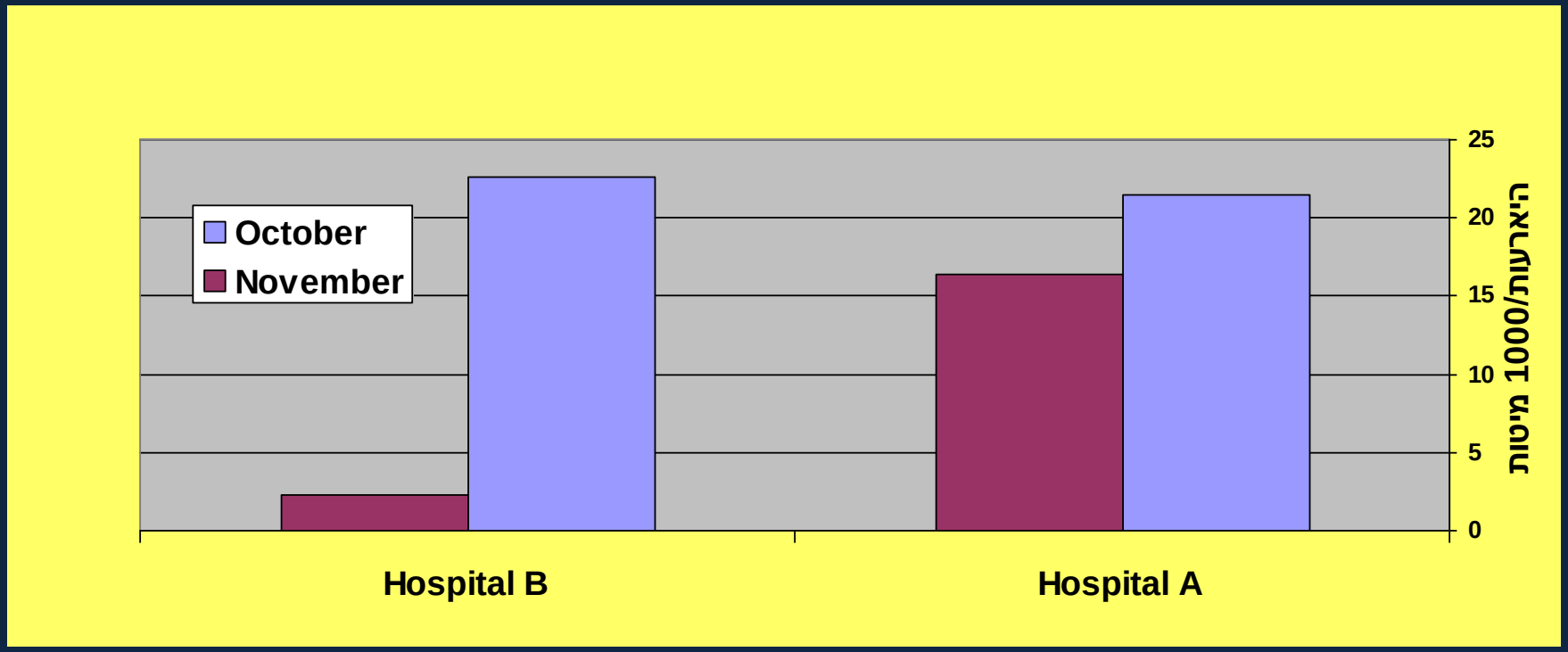
Admission and discharge data: Patient transfer

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

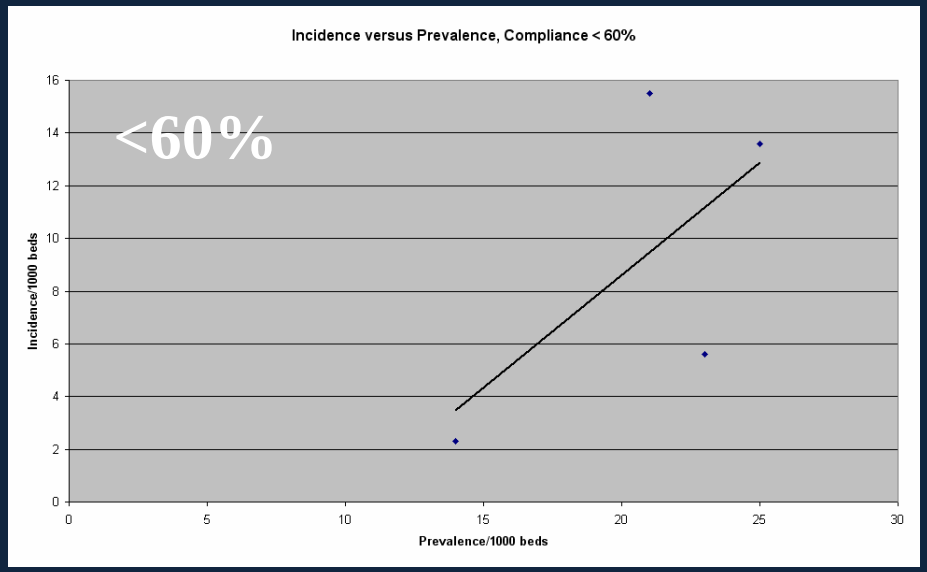


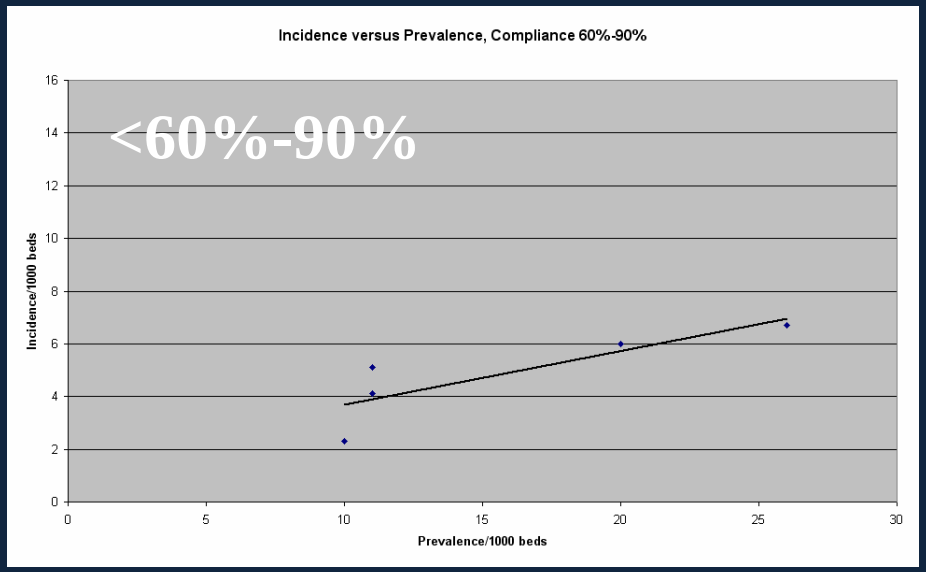
Differences in incidence patterns of CRE acquisitions in 2 hospitals:

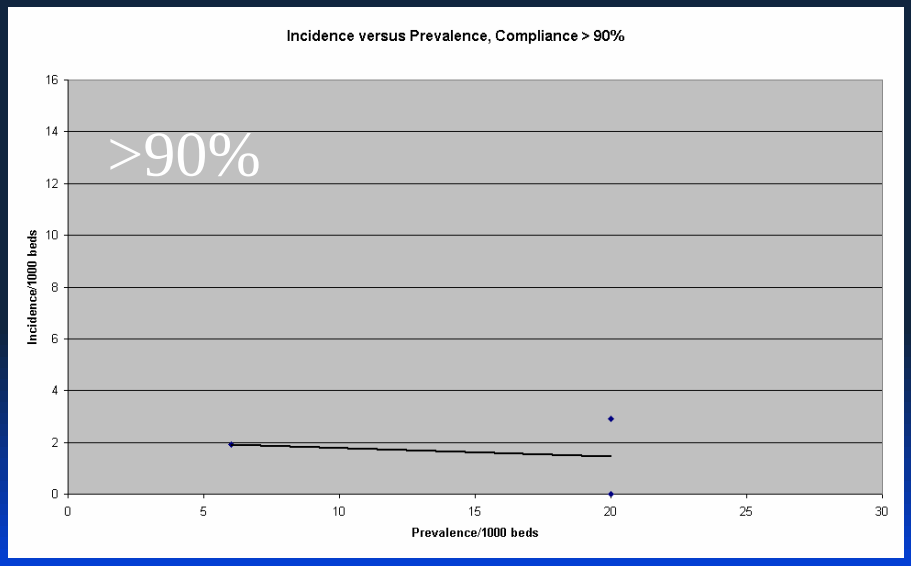
Both were non-compliant with guidelines in October;
in November Hospital A continued non-compliance while Hospital B became fully compliant



Incidence vs. colonization pressure

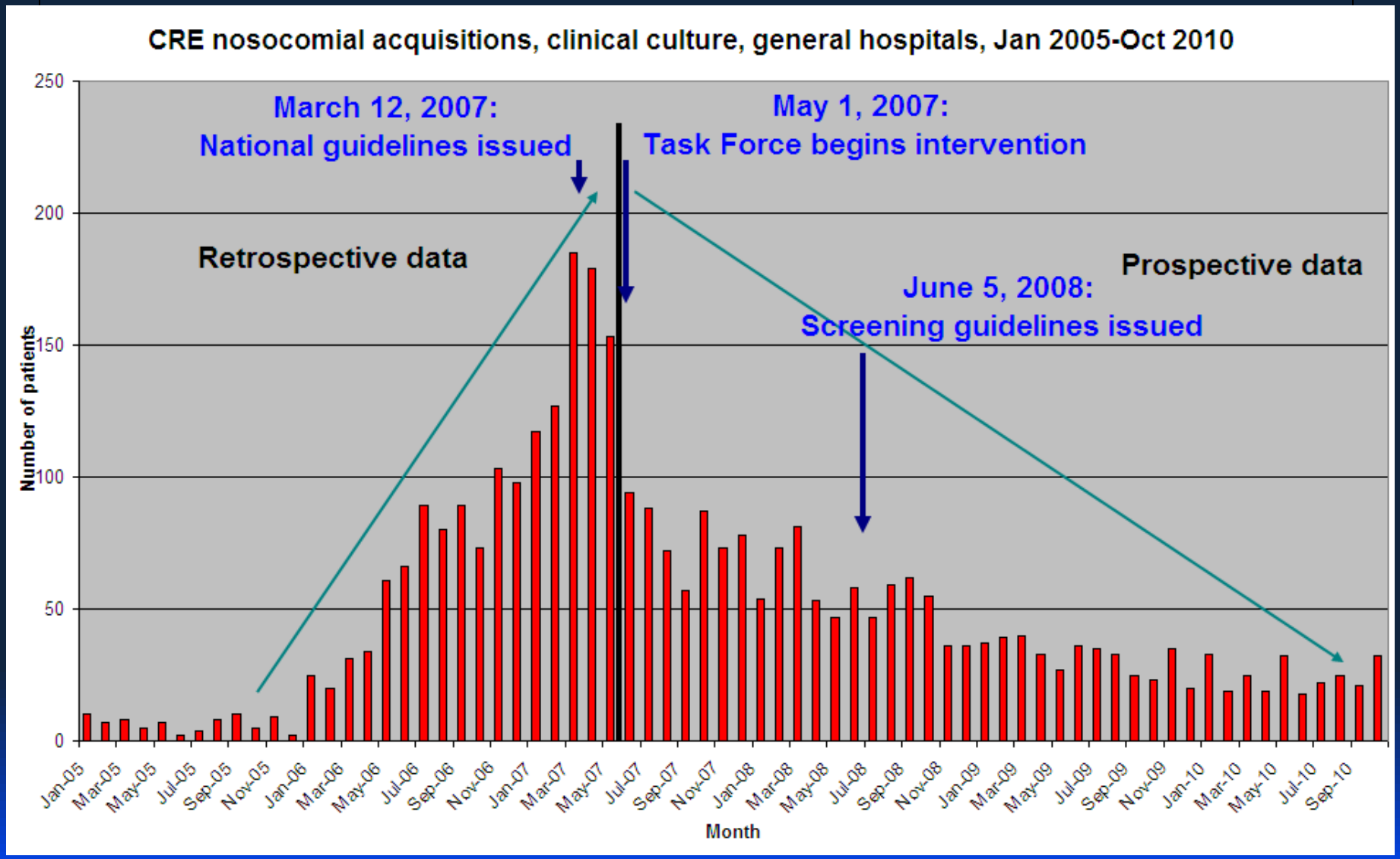




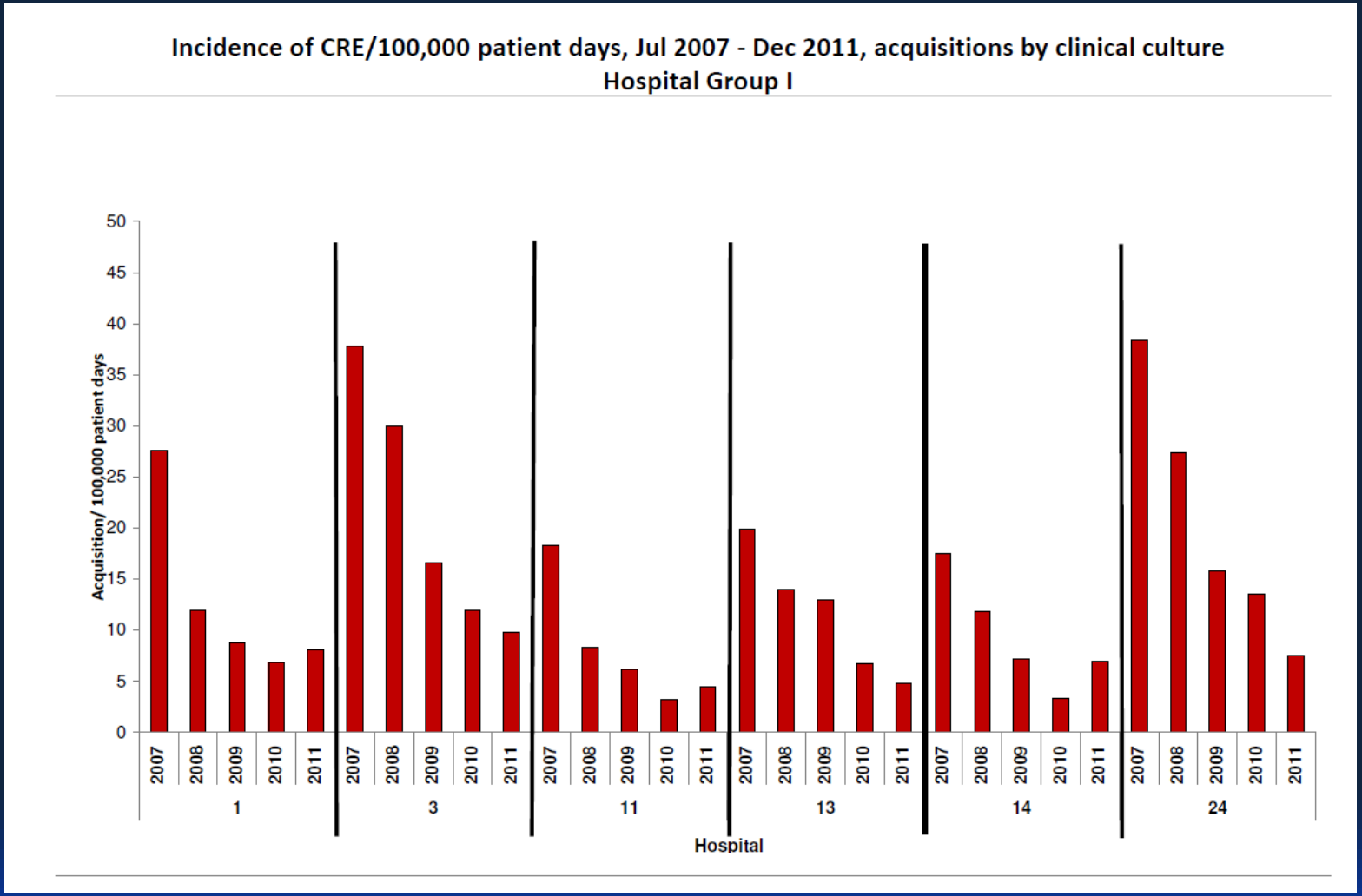


Compliance with cohorting and dedicated staff

Summary of intervention results 2010:



Similar effect in all hospitals

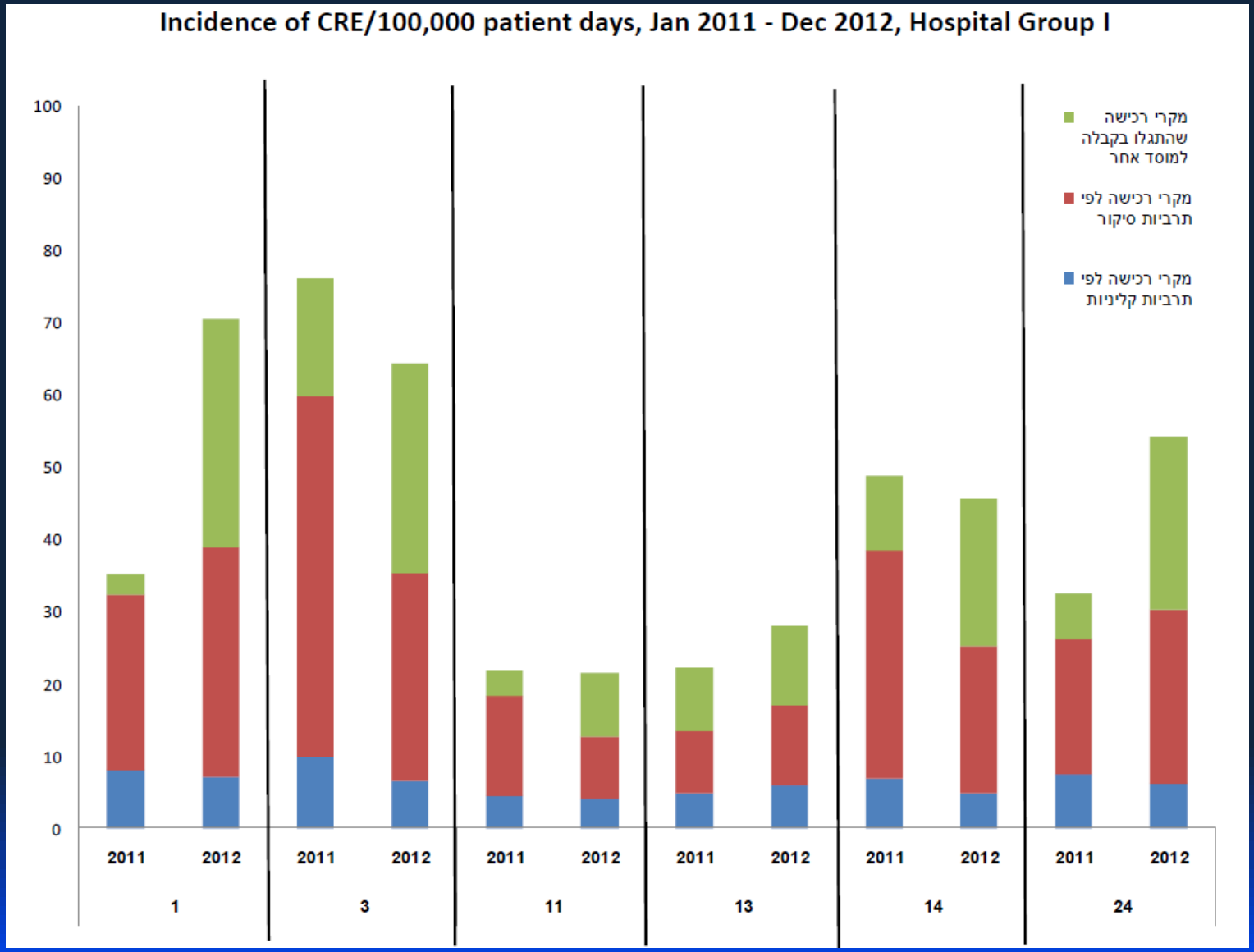


National intervention in post acute care facilities: 13 large LTCF

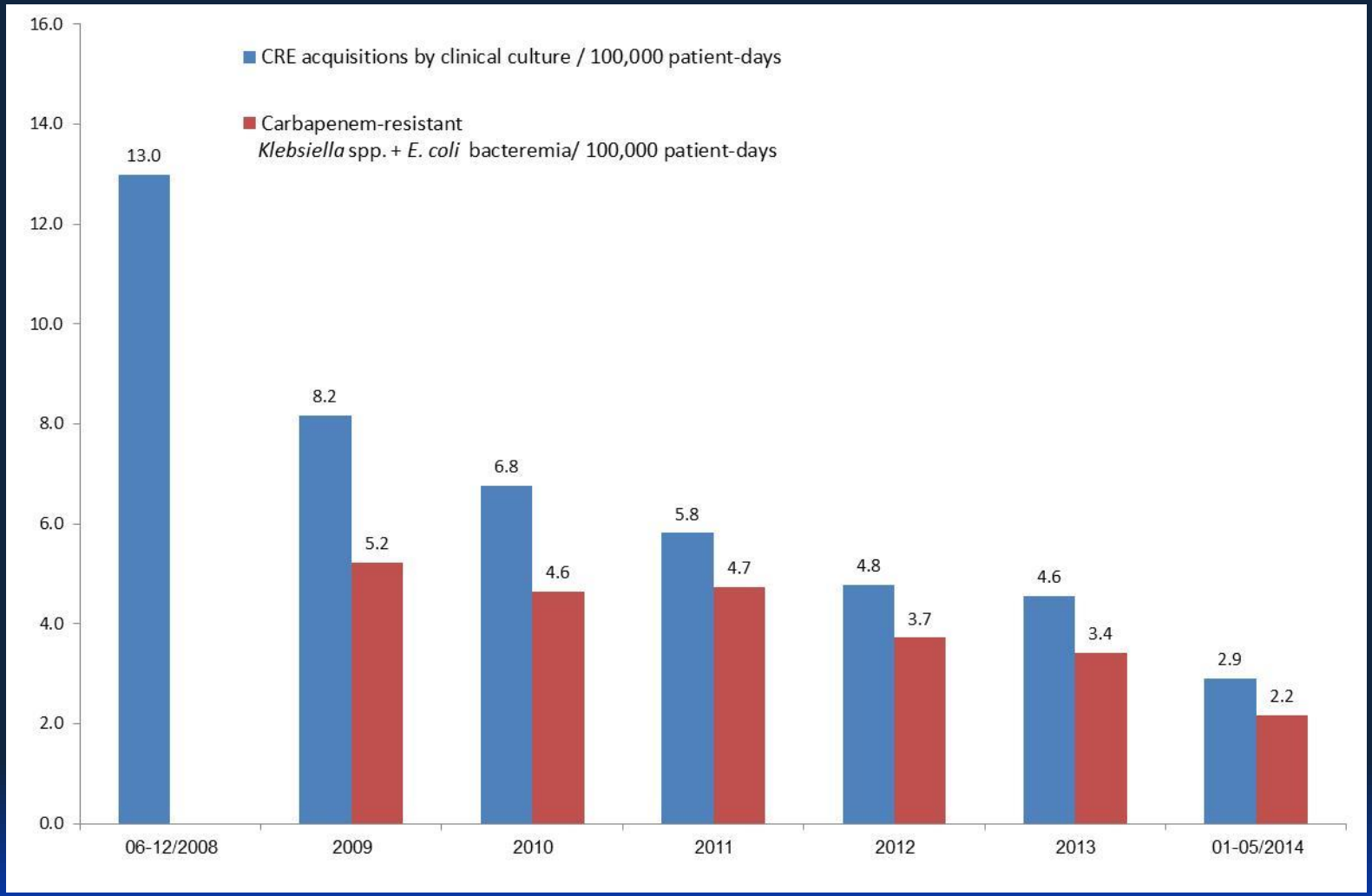
	2008	2010	2013
Infection control score	6.7	10.9	14
Strategies for prevention of CRKP			
cohorting patients	10	11	13
dedicated medical equipment	12	13	13
single-use gown	6	12	13
admissions screening	2	9	13
contact screening	5	10	13
Point prevalence carriage	12.5%	8.5%	3.9%

Ben-David D.

Improving further the report



An Ongoing National Intervention to Contain the Spread of Carbapenem-Resistant Enterobacteriaceae



Update on: Schwaber MJ. CID 2014

Explosive outbreaks reported upon admission of a colonized patient

- Admission of an unidentified carrier of KPC Klebsiella and 5 days delay until cohorting led to a difficult to control outbreak, involving 30 patients (6 clinical infections) in 4 wards[1]
- Transfer overseas of a known carrier, but failure to isolate immediately, resulted in 9 additional clinical cases
- Transfer of a colonized patient to NIH hospital led to 18 cases, 11 death

1 Schechner V. ICAAC/IDSA 2008, paper 3806
2 Morris M. ICAAC/IDSA 2008, paper 1015
3 Snitkin ES. Sci Trans Med 2012

Environmental Contamination by Carbapenem-Resistant *Enterobacteriaceae*

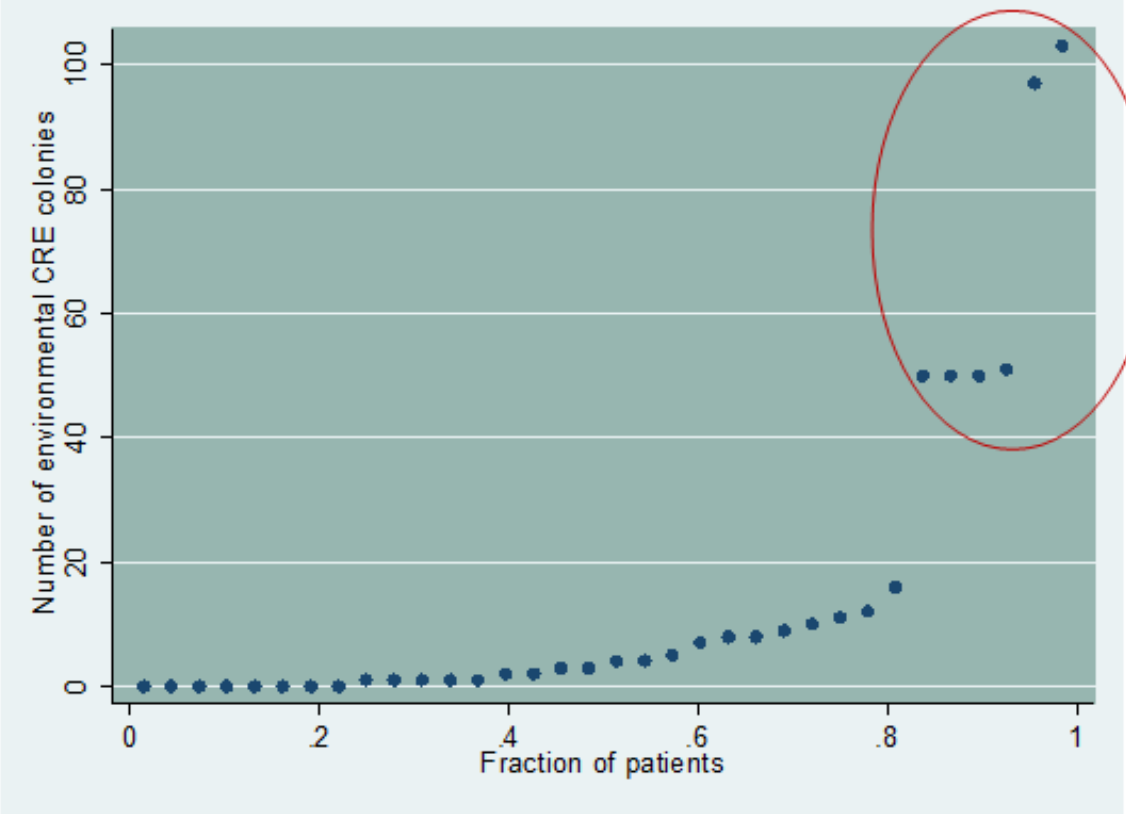
Activity	% contamination (gowns/gloves)
Wound care	36%
Touching catheter drain	37%
Touching infusion pump	20%
Touching bed rail	23%

HCW type	
Physician/nurse practitioner	3.9 (3/78)
Registered nurse	16.3 (15/92)
Other (physical, occupational, or respiratory therapist or patient care technician)	26 (13/50)

Lerner A. JCM 2013
Rock C. ICHE 2014

20% of the carriers:
80% of environmental contamination

Figure 1. The distribution of the number of CRE colonies detected in the carriers' vicinity. The vicinity of 6 super-spreaders (18% of the patients, circled in red) accounted for 80% of the environmental colonies.



Lerner A. in press CMI

Case detection

- Clinical isolates:
  - All *Enterobactriaceae* isolated in a clinical laboratory should be tested for carbapenem susceptibility.
    - Non-suseptibility to ertapenem is a sensitive (but not specific) marker for suspected CPE
    - Meropenem MIC >=0.5 is a good marker
  - All suspected CPE should be confirmed in real time
    - At early stages of the outbreak by a reference center
    - If endemicity is established
      - by local lab using validated methodology
      - unusual isolates (phenotype or setting) should be sent to reference center

Screening

- Rectal swabs containing stool.
  - Perirectal swabs have lower yield
- Validated sensitive methodology
- Results should be reported in 24 at least as: negative, suspected, or confirmed CPE, in order to not delay infection control activities
- Mechanisms to ensure that all high risk patients were screened should be placed by the infection control team

Culture based and Molecular methods should complement each other

- Culture based methods
  - Easily available
  - Processing start soon after specimen receipt
  - Relatively cheap
  - Provides information on phenotype
  - Isolate available for further testing
  - Slow result
  - Requires further testing to confirm CPE
- Molecular test
  - Rapid result from start of processing
  - Often more sensitive in detection lower load
  - Provide information on genotype
  - Processing time may be delayed
  - May not detect all carbapenamases
  - Often expensive

Laboratory algorithm – common language and definitions

Growth of CRE → MHT OR PCR

\+ -

CPE:
isolate and cohort

Non-CP-producing CRE:
isolate w/o cohorting

\+ -

CPE:
isolate and cohort

MHT

\+ -

Reference lab:
identification/confirmation

CPE
(not detected by local PCR):
isolate and cohort

Non-CP-producing CRE:
isolate w/o cohorting

Measures to prevent the spread of CPE

- Should be tailored to the local epidemiology
  - The stage of the problem
  - Reservoir: who are the patients at risk
  - What is the mode of spread
- Interventions
  - Early detection of carriers
  - Containment
  - Decolonization?
  - Formulary interventions?
- Regional coordination

The local epidemiology

- Should be examined periodically by each hospital and by regional authorities
  - Surveillance of clinical specimens results
  - Screening of high risk patients data
  - Targeted periodic point prevalence studies
  - Investigation of each positive case
- Determine the stage of the outbreak
  - No cases or sporadic cases
  - Ongoing outbreak
  - Established endemicity in healthcare setting (regional/inter-regional spread)
  - Community as a major source of CPE
- Have a preparedness plan

Adapted from: Carmeli Y. CMI 2010, and Grundmann H. Eurosurviellance 2010

Epidemiological investigation after case detection

- Determine the likely site and time of acquisition
  - Examine all likely sites in your institution
- Contact tracing and screening
  - For case detected within 2-3 days in hospital we typically screen 8-10 contacts
  - In high risk units (ICU, BMT): all patients in the unit at the "time at risk" are considered contacts
  - Contacts should be traced wherever they were transferred to, or if d/c on readmission
- In case of positive contact: wider circle of screening, and repeated screening of negative contacts ("incubation")

Epidemiological investigation of the event

- Lessons to be learned to
  - facilitate early detection of future cases
    - Missed screen: improve identification and confirmation
    - Delayed result: discuss with lab
    - New regional “risk factor”
  - prevent future cases
    - Establish preemptive isolation
    - Failure of isolation
- Regional authorities should be updated to enable regional response

Communication is essential for successful control

- Within an institution:
  - Between infection control – wards – lab: to ensure that high risk population are screened ASAP, micro-lab is able to process the samples – receive preliminary reports and act upon them
  - Hospital administration
  - Across admissions “flags” of carrier status, or “exposed to be screened”
- Between institutions
  - Reports on outbreaks or endemic institutions
  - History of carriage regarding transferred patients

Why it is not succeeding everywhere? Why it does not disappear?

- Human factors
  - Cohorting with dedicated staff, is a difficult intervention which requires hospital management involvement
    - Clinicians often object to it as the immediate benefit is often not seen
  - It is difficult to reach high compliance with screening on admission of high risk population
  - Regional collaboration is unusual in medicine
  - Lack of response to failures

- Microbiological obstacles to success
  - Variants which are missed by testing methods
    - Low MICs
    - Carbapenamases which are not targeted by our tests
    - Variation in stool concentration which results in false negative screening
- Lack of leadership
  - Health authority level
  - Hospital administration level
  - Infection control professional level
- Overcoming the obstacles
  - Regulation and supervision of adherence
  - Health authorities coordinated regional collaboration
  - Expert team to analyze failures at the local and the regional level and provide new plans

Summary

- CPE are here to stay
  - Once introduced have the potential for rapid spread within institutions and between institutions
- The pillars of successful prevention are understanding the concurrent epidemiology, and tailoring the local plan:
  - Early reliable detection of carriers
  - Containment
    - in most settings cohorting with dedicated staff
  - Communication
  - Regional coordination
- God is in the details: written protocols, education, ensuring compliance, root cause analysis of failures
- Open questions:
  - Control where spread in the community is common
  - The role of formulary interventions

Formulary interventions/antibiotic stewardship?

Trends in Antibacterial Use in US Academic Health Centers

2002 to 2006

Amy L. Pakyz, PharmD, MS; Conan MacDougall, PharmD; Michael Oinonen, PharmD, MPH; Ronald E. Polk, PharmD

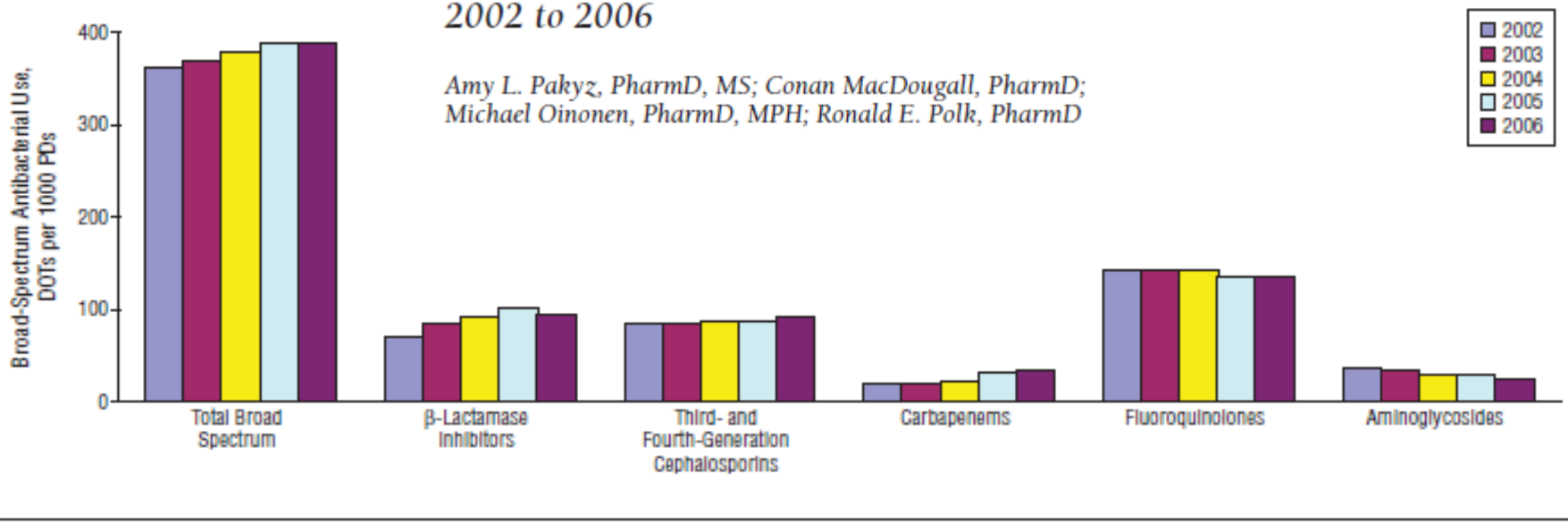


Figure 2. Trends in broad-spectrum antibacterial drug use (in days of therapy [DOTs] per 1000 patient days [PDs]) at 22 US academic health centers from 2002 to 2006. There is a statistically significant increase in total broad-spectrum antibacterial use. Increases in carbapenem and piperacillin-tazobactam use were statistically significant, as was the decline in aminoglycoside use. There was no significant change in fluoroquinolone or cephalosporin use.

Arch Intern Med. 2008;168(20):2254-2260

The role of antimicrobial stewardship in curbing carbapenem resistance

Christopher Bogan[1] & Dror Marchaim*[2,3]

Table 1. Univariate analyses of certain exposures to antibiotics as potential risk factors for isolation of *Enterobacteriaceae* with various levels of antimicrobial resistance (Detroit Medical Center, MI, USA, September 2008–September 2009).

Parameter	CRE, n (%)	ESBL, n (%)	Susceptibles†, n (%)	Controls, n (%)	CRE versus controls		CRE versus susceptibles†	
					OR (95% CI)	*p-value*	*OR (95% CI)*	*p-value*
Cephalosporin in past 3 months	60 (85.7)	58 (69)	23 (26.7)	18 (20.9)	23 (10–53)	$p < 0.001$	16.4 (7.2–37)	$p < 0.001$
Carbapenem in past 3 months	15 (21.7)	8 (9.5)	2 (2.3)	2 (2.3)	11.7 (2.6–53)	$p < 0.001$	11.7 (2.6–53)	$p < 0.001$

The percentages displayed in the table are calculated out of the patients for whom data were available, for example excluding the missing cases.
†*Non-ESBL and non-CRE-susceptible* Enterobacteriaceae.
CRE: Carbapenem-resistant Enterobacteriaceae; *ESBL: Extended-spectrum β-lactamase-producing* Enterobacteriaceae; *OR: Odds ratio.*

- In multivariate analyses CRE is :
  - no correlated with carbapenemse use.
  - Moderately correlated (OR 1.8-4.7) with cephalosporins