CRE Epidemiology:

Global & Israeli Perspectives

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Infection Control and Prevention
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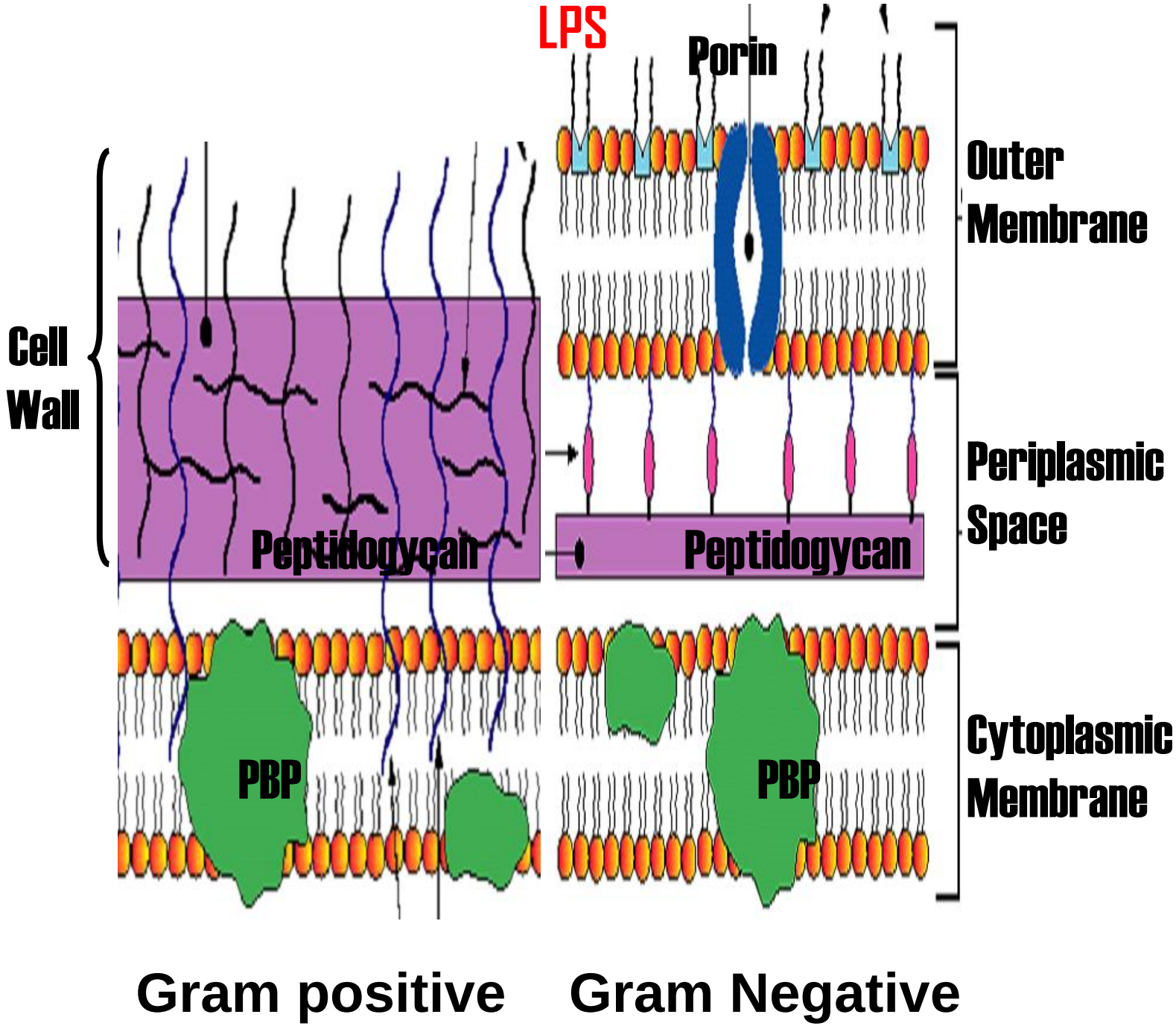

LPS
Porin
Outer Membrane
Cell Wall
Periplasmic Space
Peptidogycan
Peptidogycan
PBP
PBP
Cytoplasmic Membrane
Gram positive
Gram Negative

β-lactam Antibiotics Mechanism of Action

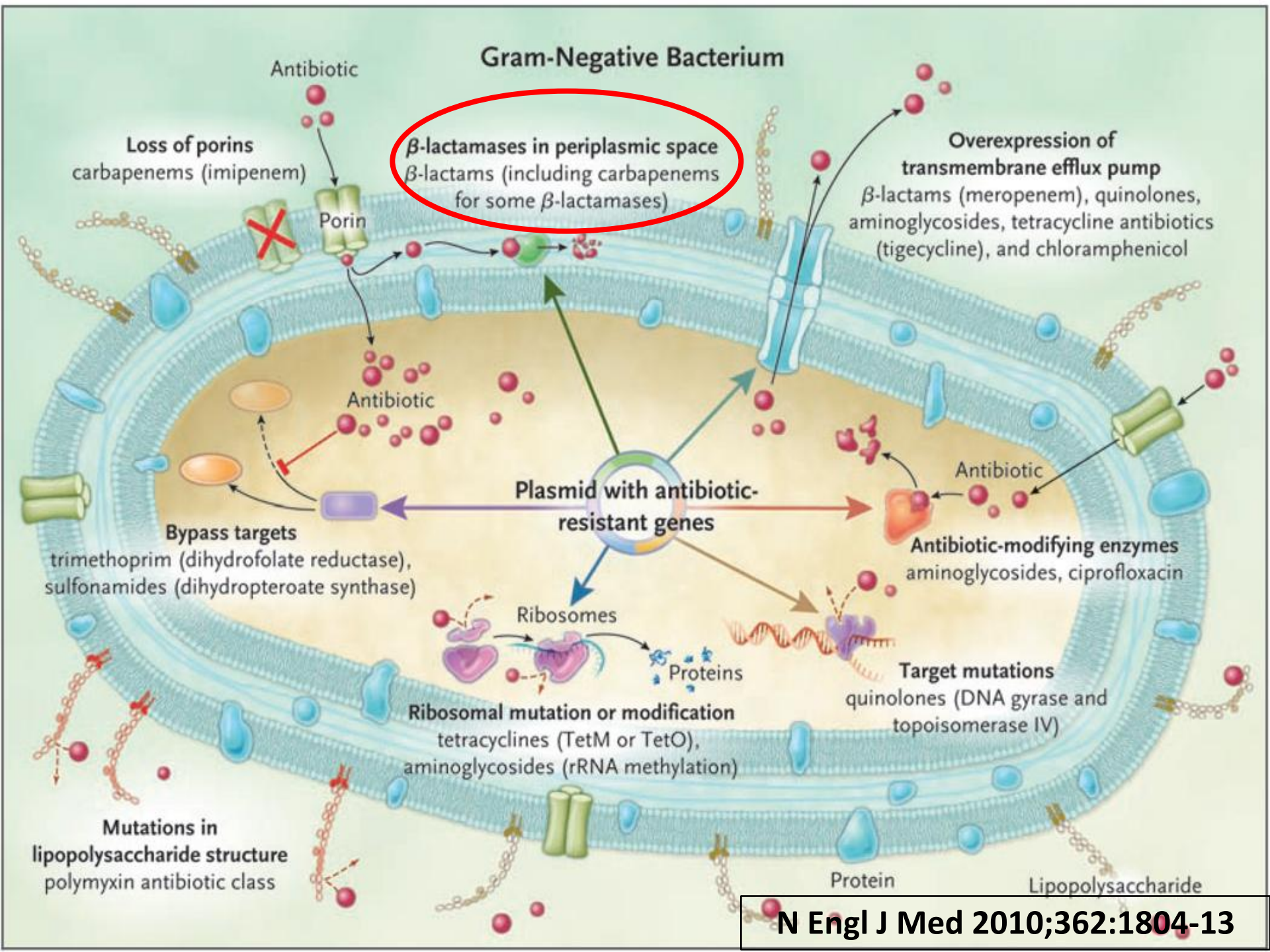
- **Inhibition of bacterial cell wall synthesis**
  - **Inhibition of the transpeptidation reaction of the peptidoglycan synthesis**

Mechanisms of β-lactam Resistance

- β-lactamases hydrolysis / destruction

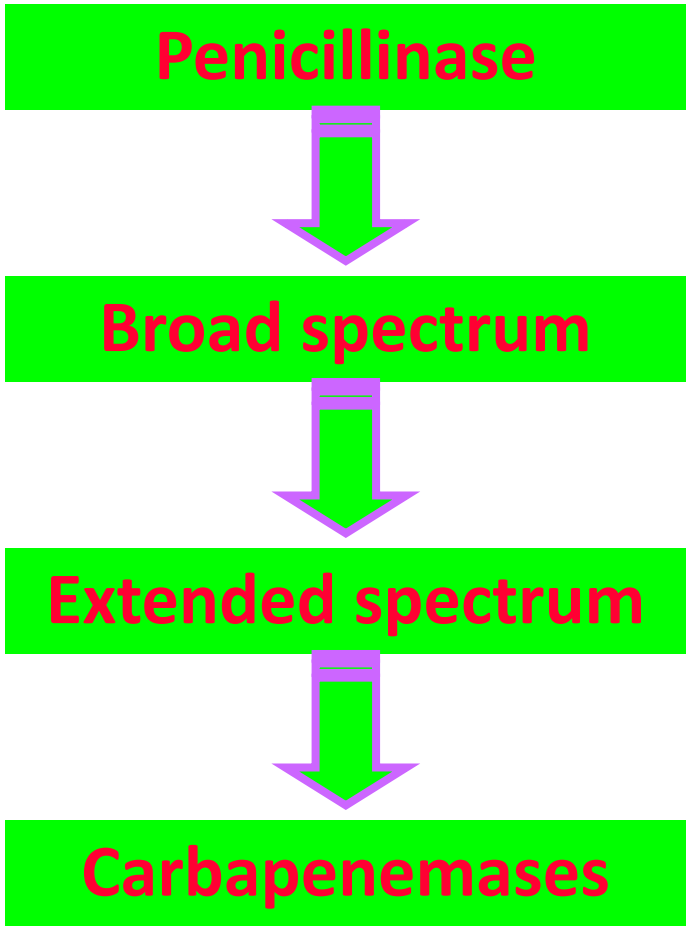
- **Low affinity binding to PBP's**
  - **Naturally occurring (*Enterococcus*)**
  - **Multiple mutations (P*neumococcus*)**

- **Failure to penetrate to PBP target**
  - **↓ penetration (loss of porins)**
  - **↑Efflux**



N Engl J Med 2010;362:1804-13

β-lactamases Spectrum >2000



Ambler Classification of β-lactamases

Class	Spectrum	Substrate
A (serine)	**Penicillinases**	
	Broad-spectrum	All penicillins, narrow-spectrum cephalosporins
	Extended-spectrum (ESBL)	Broad-spectrum + oxymino + aztreonam
	Carbapenemases	Extended-spectrum + cephamycins + carbapenems
B (Metallo-β-lactamases, Zn2+)	**Carbapenemases**	Extended-spectrum + cephamycins + carbapenems
C (serine)	**Cephalosporinases**	Extended-spectrum + cephamycins
D (Serine)	**Oxacillinases**	
	Broad-spectrum	All penicillins, ome narrow-spectrum cephalosporins
	Extended-spectrum	Broad-spectrum + oxymino + monobactam
	Carbapenemases	Extended-spectrum + cephamycins + carbapenems

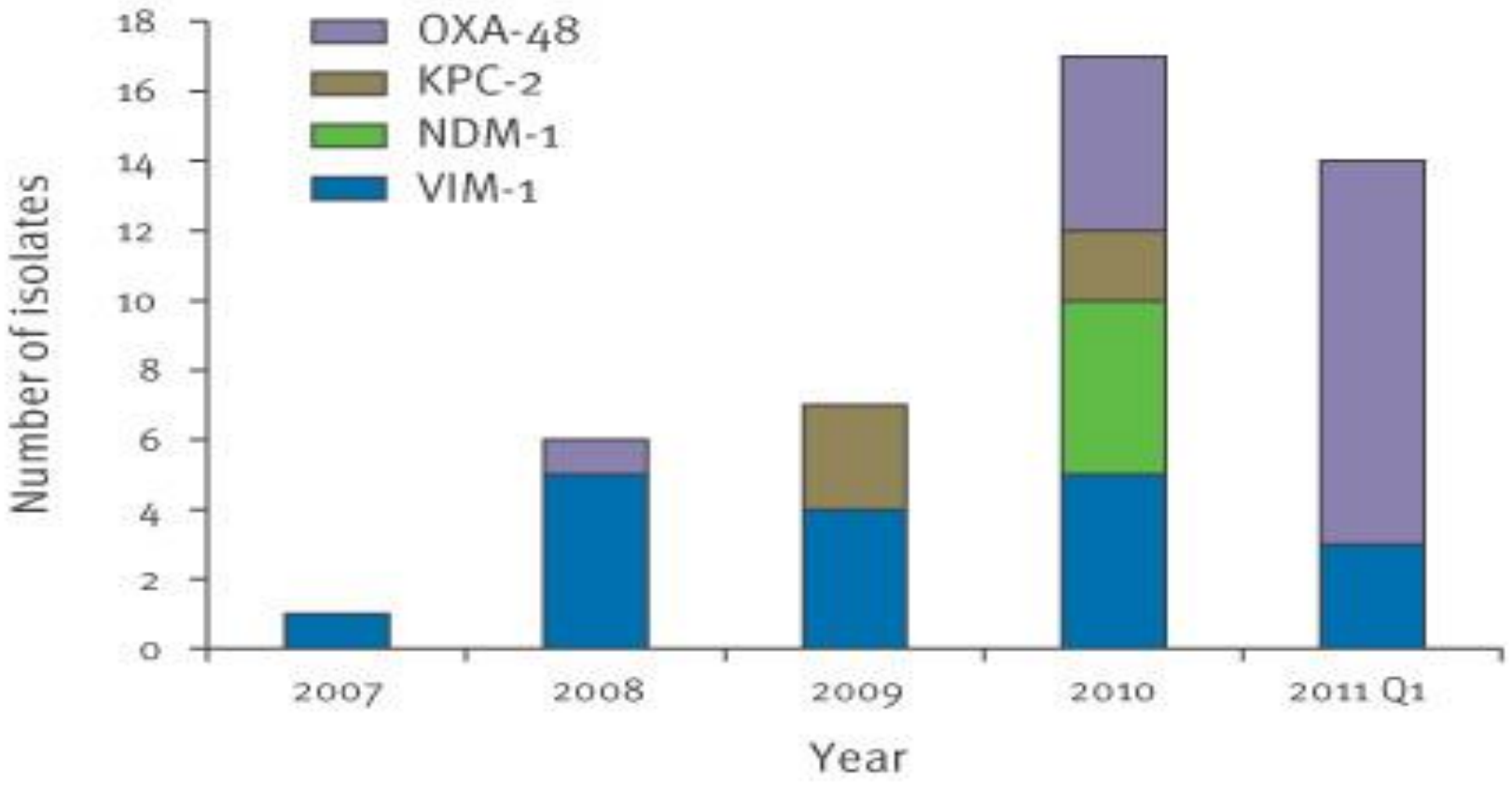
Ambler Classification of β-lactamases

- Class A: TEM, SHV, CTX-M, KPC
- Class B: NDM-1, VIM, IMP
- Class C: AmpC, CYM
- Class D: OXA

FIGURE 2

Evolution of the distribution of resistance mechanisms of carbapenemase-producing *Enterobacteriaceae* isolates, National Reference Centre, Belgium, January 2007–April 2011 (n=44)

Eurosurveillance June 2011



KPC: *Klebsiella pneumoniae* carbapenemase; NDM: New Delhi metallo-beta-lactamase; OXA: oxacillinase; Q1: first quarter; VIM: Verona integron-encoded metallo-beta-lactamase.

bla$_{KPC}$ first report… published in 2001…

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Apr. 2001, p. 1151–1161 Vol. 45, No. 4
0066-4804/01/$04.00+0 DOI: 10.1128/AAC.45.4.1151–1161.2001

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

HESNA YIGIT,[1] ANNE MARIE QUEENAN,[2] GREGORY J. ANDERSON,[1] ANTONIO DOMENECH-SANCHEZ,[3] JAMES W. BIDDLE,[1] CHRISTINE D. STEWARD,[1] SEBASTIAN ALBERTI,[4] KAREN BUSH,[2] AND FRED C. TENOVER[1]*

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Received 19 September 2000/Returned for modification 21 November 2000/Accepted 23 January 2001

A *Klebsiella pneumoniae* isolate showing moderate to high-level imipenem and meropenem resistance was investigated. The MICs of both drugs were 16 μg/ml. The β-lactamase activity against imipenem and meropenem was inhibited in the presence of clavulanic acid. The strain was also resistant to extended-spectrum cephalosporins and aztreonam. Isoelectric focusing studies demonstrated three β-lactamases, with pIs of 7.2 (SHV-29), 6.7 (KPC-1), and 5.4 (TEM-1). The presence of *bla*$_{SHV}$ and *bla*$_{TEM}$ genes was confirmed by specific PCRs and DNA sequence analysis. Transformation and conjugation studies with *Escherichia coli* showed that the β-lactamase with a pI of 6.7, KPC-1 (*K. pneumoniae* carbapenemase-1), was encoded on an approximately 50-kb nonconjugative plasmid. The gene, *bla*$_{KPC-1}$, was cloned in *E. coli* and shown to confer resistance to imipenem, meropenem, extended-spectrum cephalosporins, and aztreonam. The amino acid sequence of the novel carbapenem-hydrolyzing β-lactamase, KPC-1, showed 45% identity to the pI 9.7 carbapenem-hydrolyzing β-lactamase, Sme-1, from *Serratia marcescens* S6. Hydrolysis studies showed that purified KPC-1 hydrolyzed not only carbapenems but also penicillins, cephalosporins, and monobactams. KPC-1 had the highest affinity

First clinical reports… 2003-2006… mainly NYC…

ORIGINAL INVESTIGATION

Rapid Spread of Carbapenem-Resistant *Klebsiella pneumoniae* in New York City

A New Threat to Our Antibiotic Armamentarium

Simona Bratu, MD; David Landman, MD; Robin Haag, RN; Rose Recco, MD; Antonella Eramo, RN; Maqsood Alam, MD; John Quale, MD

MAJOR ART

Emergence of Carbapenem-Resistant *Klebsiella* Species Possessing the Class A Carbapenem-Hydrolyzing KPC-2 and Inhibitor-Resistant TEM-30 β-Lactamases in New York City

Patricia A. Bradford,[1] Simona Bratu,[2] Carl Urban,[4] Melissa Visalli,[1] Noriel Mariano,[4] David Landman,[2] James J. Rahal,[4] Steven Brooks,[3] Sanda Cebular,[2] and John Quale[2]

[1]Wyeth Research, Pearl River, [2]State University of New York–Downstate and [3]Kingsbrook Jewish Medical Center, Brooklyn, and [4]N Hospital Queens, Flushing, New York

Nineteen isolates of carbapenem-resistant *Klebsiella* species were recovered from 7 hospitals in Ne Most *K. pneumoniae* belonged to a single ribotype. Nucleotide sequencing identified KPC-2, a c hydrolyzing β-lactamase. In 3 strains, TEM-30, an inhibitor-resistant β-lactamase, was detected. C resistant *Klebsiella* species possessing KPC-2 are endemic in New York City. This study documen tification of an inhibitor-resistant TEM β-lactamase in the United States.

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ScienceDirect

Diagnostic Microbiology and Infectious Disease 56 (2006) 367–372

DIAGNOSTIC MICROBIOLOGY AND INFECTIOUS DISEASE

www.elsevier.com/locate/diagmicrobio

Emergence of serine carbapenemases (KPC and SME) among clinical strains of Enterobacteriaceae isolated in the United States Medical Centers: Report from the MYSTIC Program (1999–2005)

Lalitagauri M. Deshpande[a], Paul R. Rhomberg[a], Helio S. Sader[a,b], Ronald N. Jones[a,c,*]

[a]*JMI Laboratories, North Liberty, Iowa, USA,*
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[c]*Tufts University School of Medicine, Boston, Massachusetts, USA*

Received 6 June 2006; accepted 17 July 2006

Abstract

Among 8885 Enterobacteriaceae tested in the 1999 to 2005 period as part of the USA Meropenem Yearly Susceptibility Test Information Collection (MYSTIC) Program, 51 strains with increased imipenem and meropenem MIC values (≥2 μg/mL) were detected. bla_{KPC} was

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, July 2005, p. 3018–3020
0066-4804/05/$08.00+0 doi:10.1128/AAC.49.7.3018–3020.2005

Emergence of KPC-Possessing *Klebsiella pneumoniae* in Brooklyn, New York: Epidemiology and Recommendations for Detection

Simona Bratu,[1] Mohamad Mooty,[1] Satyen Nichani,[1] David Landman,[1] Carl Gullans,[2] Barbara Pettinato,[3] Usha Karumudi,[1] Pooja Tolaney,[1] and John Quale[1]*

Department of Medicine, SUNY-Downstate Medical Center,[1] Department of Microbiology, Kings County Hospital,[2] and Department of Pathology Services, Coney Island Hospital,[3] Brooklyn, New York

Received 14 February 2005/Returned for modification 24 March 2005/Accepted 3 April 2005

Among 257 isolates of *Klebsiella pneumoniae* collected in Brooklyn, NY, 24% were found to possess bla_{KPC}. Clinical microbiology laboratories that used automated broth microdilution systems reported 15% of the KPC-possessing isolates as susceptible to imipenem. The imipenem MIC was found to be markedly affected by the inoculum. For accurate detection of KPC-possessing *K. pneumoniae*, particular attention should be paid to proper inoculum preparation for broth-based susceptibility methods. In addition, using ertapenem or meropenem for class reporting of carbapenem susceptibility will improve detection.

ence and Characterization of Carbapenemase-Producing obacteriaceae: Report from the SENTRY Antimicrobial Surveillance Program (2000–2004)

LALITAGAURI M. DESHPANDE,[1] RONALD N. JONES,[1,2] THOMAS R. FRITSCHE,[1] and HELIO S. SADER[1,3]

ABSTRACT

nd dissemination of Enterobacteriaceae isolates harboring carbapenemases in various geographic resents a significant threat to the management of nosocomial infections. Enterobacteriaceae iso- e SENTRY Antimicrobial Surveillance Program (2000–2004) demonstrating decreased suscepti-

And in Israel… 2007-2009….

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Aug. 2007, p. 3026–3029 Vol. 51, No. 8
0066-4804/07/$08.00+0 doi:10.1128/AAC.00299-07

Emergence of KPC-2 and KPC-3 in Carbapenem-Resistant *Klebsiella pneumoniae* Strains in an Israeli Hospital[▽]

Azita Leavitt, Shiri Navon-Venezia, Inna Chmelnitsky, Mitchell J. Schwaber, and Yehuda Carmeli*

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Received 2 March 2007/Returned for modification 6 April 2007/Accepted 4 June 2007

Carbapenem resistance due to KPC has rarely been observed outside the United States. We noticed a sharp increase in carbapenem-resistant *Klebsiella pneumoniae* strains possessing KPC in Tel Aviv Medical Center from 2004 to 2006. Sixty percent of the isolates belonged to a single clone susceptible only to gentamicin and colistin and carried the bla_{KPC-3} gene, while almost all other clones carried the bla_{KPC-2} gene. This rapid dissemination of KPC outside the United States is worrisome.

Carbapenem resistance in *Klebsiella pneumoniae* does not occur naturally and is due mainly to the presence of acquired carbapenem-hydrolyzing β-lactamases (16). KPC-type en-

AST-GN09 card for the identification of gram-negative bacilli. Fifty-one isolates (1.2%) were carbapenem resistant, as defined by resistance to imipenem and/or meropenem. Sites of

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Apr. 2008, p. 1413–1418 Vol. 52, No. 4
0066-4804/08/$08.00+0 doi:10.1128/AAC.01103-07

Isolation of Imipenem-Resistant *Enterobacter* Species: Emergence of KPC-2 Carbapenemase, Molecular Characterization, Epidemiology, and Outcomes[▽]

Dror Marchaim,* Shiri Navon-Venezia, Mitchell J. Schwaber, and Yehuda Carmeli

Division of Epidemiology, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel

Received 22 August 2007/Returned for modification 31 December 2007/Accepted 16 January 2008

The prevalence of isolation of imipenem-resistant *Enterobacter* (IRE) strains is rising, with potential serious consequences in terms of patients' outcomes and general care. The study objective was to define the various epidemiological aspects of the isolation of these strains in comparison to cases of isolation of imipenem-susceptible *Enterobacter* (ISE) strains. Molecular analysis of IRE strains included genotyping and defining the presence of carbapenemases. We conducted a matched retrospective case-control study of patients hospitalized from April 2003 to December 2006. Each IRE case was matched with an ISE case by age and source of isolation. A multivariate analysis using conditional logistic regression was performed to compare the two patient groups. There were 33 cases of IRE isolations during the study period. Twenty isolates were analyzed and found to belong to three distinct pulsotypes. Cell extracts of all of these isolates hydrolyzed imipenem. PCR and sequencing revealed that these isolates harbored a KPC-2 gene. In multivariate analysis, a high invasive-device score ($P = 0.02$) remained a predictor of IRE isolation. The mortality in the IRE group was 33%, compared to

stant *Klebsiella pneumoniae* in
-Care Facilities in Israel

Shiri Navon-Venezia, PhD;[1] Hagit Mishali, MA;[1] Ilan Fridental, MD;[1]
n, MD;[1] Yehuda Carmeli, MD;[1] Mitchell J. Schwaber, MD[1];
ty Carbapenem-Resistant *Klebsiella pneumoniae*) Working Group[1]

rs for carbapenem-resistant *Klebsiella pneumoniae* (CRKP) carriage among patients

RIGINAL ARTICLE

ong *Klebsiella pneumoniae* Isolates: Risk
acteristics, and Susceptibility Patterns

PhD; Tania Mashiach, MA; Ilana Oren, MD; Imad Kassis, MD;
Renato Finkelstein, MD

fluids ($n = 10$), wounds
$n = 4$), and respiratory
stant isolates, resistance

penem resistance amo
ify risk factors for infe
ated with these infecti
case-control study.
ertiary care hospital.
ry 2006 through April
enem-susceptible *K. p*
ne use (odds ratio [OR
1.02–3.27]; $P = .042$
rug before isolation o
ely 90% of the tested i
all antibiotics, except

should be regarded
of their spread is cru

An effective intervention to limit the spread of an epidemic carbapenem-resistant Klebsiella pneumoniae **strain in an acute care setting: From theory to practice**

Pnina Ciobotaro, MD,[a] Maly Oved, MA,[a] Eyal Nadir, MD, MSc,[a] Rita Bardenstein, MSc,[b] and Oren Zimhony, MD[a]
Rehovot, Israel

Background: The highly transmissible and virulent carbapenem-resistant Klebsiella pneumoniae (CRKP) KPC-3 strain has been spreading in our medical center and in other centers in Israel since 2006. An intervention that aimed to diminish its prevalence was constructed and applied in our institute.
Methods: We analyzed the efficacy of the intervention during the years 2006-2010 using quasi-experimental methodology. The intervention included guidelines for patient isolation, cohorting, and environment cleaning; education of staff; and a computerized notification system that flags CRKP carriers and provides instructions. The efficacy of the program was evaluated through 3 quantifiable parameters: incidence of CRKP isolates from clinical samples, rate of cross-infections, and rate of screening for CRKP carriage in patients at risk identified by rectal samples.
Results: The incidence of CRKP decreased by 16-fold (P , .001), and this decrease was sustained for 30 months. The rate of cross-infection decreased from 6% during 2007-2008 to 2.7% in 2009-2010 (P , .05). This period saw an increased rate of active

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Feb. 2009, p. 818–820 Vol. 53, No. 2
0066-4804/09/$08.00+0 doi:10.1128/AAC.00987-08

First Report on a Hyperepidemic Clone of KPC-3-Producing *Klebsiella pneumoniae* in Israel Genetically Related to a Strain Causing Outbreaks in the United States▽

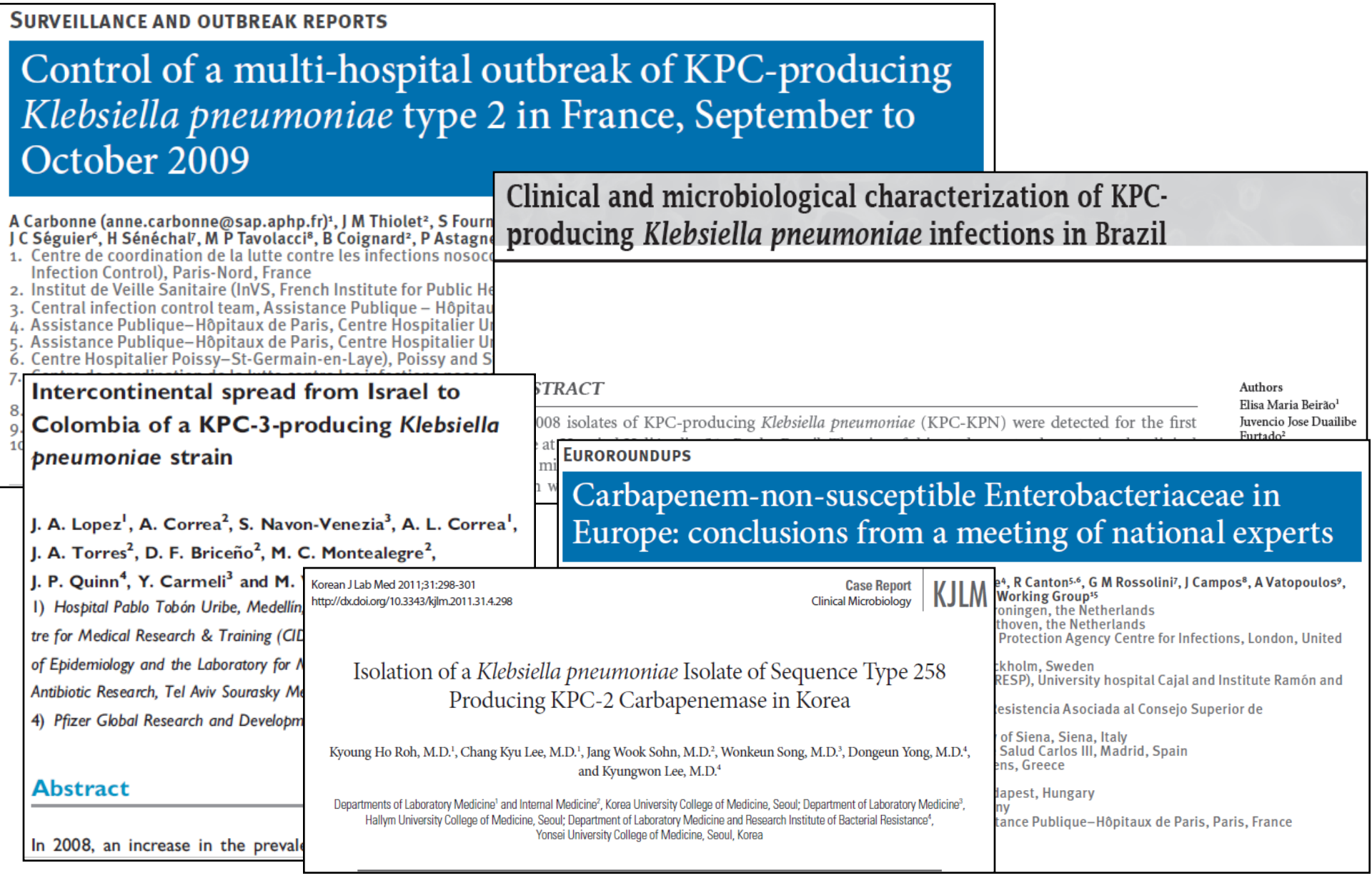
Shiri Navon-Venezia,[1]* Azita Leavitt,[1] Mitchell J. Schwaber,[1] J. Kamile Rasheed,[2] Arjun Srinivasan,[2] Jean B. Patel,[2] Yehuda Carmeli,[1] and the Israeli KPC Kpn Study Group†

Epidemiology Division, Tel Aviv Sourasky Medical Center, affiliated to the Sackler Faculty of Medicine, Tel Aviv, Israel,[1] and Centers for Disease Control and Prevention, Atlanta, Georgia[2]

Received 24 July 2008/Returned for modification 25 September 2008/Accepted 18 November 2008

A highly epidemic carbapenem-resistant clone of KPC-3-producing *Klebsiella pneumoniae* emerged in Israel in 2006, causing a nationwide outbreak. This clone was genetically related to outbreak strains from the United States isolated in 2000 but differed in KPC-carrying plasmids. The threat of the global spread of hyperepidemic, extensively drug-resistant bacterial strains should be recognized and confronted.

Worldwide dissemination



SURVEILLANCE AND OUTBREAK REPORTS

Control of a multi-hospital outbreak of KPC-producing *Klebsiella pneumoniae* type 2 in France, September to October 2009

A Carbonne (anne.carbonne@sap.aphp.fr)[1], J M Thiolet[2], S Fourn
J C Séguier[6], H Sénéchal[7], M P Tavolacci[8], B Coignard[2], P Astagne
1. Centre de coordination de la lutte contre les infections nosoc
Infection Control), Paris-Nord, France
2. Institut de Veille Sanitaire (InVS, French Institute for Public He
3. Central infection control team, Assistance Publique – Hôpitau
4. Assistance Publique–Hôpitaux de Paris, Centre Hospitalier Ur
5. Assistance Publique–Hôpitaux de Paris, Centre Hospitalier Ur
6. Centre Hospitalier Poissy–St-Germain-en-Laye), Poissy and S

Clinical and microbiological characterization of KPC-producing *Klebsiella pneumoniae* infections in Brazil

STRACT

008 isolates of KPC-producing *Klebsiella pneumoniae* (KPC-KPN) were detected for the first

Authors
Elisa Maria Beirão[1]
Juvencio Jose Duailibe Furtado[2]

Intercontinental spread from Israel to Colombia of a KPC-3-producing *Klebsiella pneumoniae* strain

J. A. Lopez[1], A. Correa[2], S. Navon-Venezia[3], A. L. Correa[1],
J. A. Torres[2], D. F. Briceño[2], M. C. Montealegre[2],
J. P. Quinn[4], Y. Carmeli[3] and M.
1) *Hospital Pablo Tobón Uribe, Medellín,*
tre for Medical Research & Training (CID
of Epidemiology and the Laboratory for M
Antibiotic Research, Tel Aviv Sourasky Me
4) *Pfizer Global Research and Developm*

Abstract

In 2008, an increase in the prevale

EUROROUNDUPS

Carbapenem-non-susceptible Enterobacteriaceae in Europe: conclusions from a meeting of national experts

e[4], R Canton[5,6], G M Rossolini[7], J Campos[8], A Vatopoulos[9],
Working Group[15]
oningen, the Netherlands
thoven, the Netherlands
Protection Agency Centre for Infections, London, United

ckholm, Sweden
RESP), University hospital Cajal and Institute Ramón and

esistencia Asociada al Consejo Superior de

of Siena, Siena, Italy
Salud Carlos III, Madrid, Spain
ens, Greece

dapest, Hungary
ny
tance Publique–Hôpitaux de Paris, Paris, France

Korean J Lab Med 2011;31:298-301
http://dx.doi.org/10.3343/kjlm.2011.31.4.298

Case Report
Clinical Microbiology

KJLM

Isolation of a *Klebsiella pneumoniae* Isolate of Sequence Type 258 Producing KPC-2 Carbapenemase in Korea

Kyoung Ho Roh, M.D.[1], Chang Kyu Lee, M.D.[1], Jang Wook Sohn, M.D.[2], Wonkeun Song, M.D.[3], Dongeun Yong, M.D.[4], and Kyungwon Lee, M.D.[4]

Departments of Laboratory Medicine[1] and Internal Medicine[2], Korea University College of Medicine, Seoul; Department of Laboratory Medicine[3], Hallym University College of Medicine, Seoul; Department of Laboratory Medicine and Research Institute of Bacterial Resistance[4], Yonsei University College of Medicine, Seoul, Korea

International dissemination of *Klebsiella pneumoniae* carbapenemase (KPC)–producing Enterobacteriaceae.

Gupta N et al. Clin Infect Dis. 2011;53:60-67

Clinical Infectious Diseases

U.S.A.

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Aug. 2009, p. 3365–3370 Vol. 53, No. 8
0066-4804/09/$08.00+0 doi:10.1128/AAC.00126-09

Molecular Epidemiology of KPC-Producing *Klebsiella pneumoniae* Isolates in the United States: Clonal Expansion of Multilocus Sequence Type 258[▽]

Brandon Kitchel,[1]* J. Kamile Rasheed,[1] Jean B. Patel,[1] Arjun Srinivasan,[1] Shiri Navon-Venezia,[2] Yehuda Carmeli,[2] Alma Brolund,[3] and Christian G. Giske[3]

Division of Healthcare Quality Promotion, Centers for Disease Control and Prevention, Atlanta, Georgia[1]; Division of Epidemiology, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel[2]; and Clinical Microbiology L2:02, Karolinska Institutet—MTC, Karolinska University Hospital Solna, SE-17176 Stockholm, Sweden[3]

Received 28 January 2009/Returned for modification 29 March 2009/Accepted 2 June 2009

Europe & Worldwide

Worldwide Diversity of *Klebsiella pneumoniae* That Produces β-Lactamase bla_{KPC-2} Gene[1]

Gaëlle Cuzon, Thierry Naas, HaVy Truong, Maria-Virginia Villegas, Karin T. Wisell, Yehuda Carmeli, Ana. C. Gales, Shiri Navon-Venezia, John P. Quinn, and Patrice Nordmann

Emerg Infect Dis 2010; 16:1349-56

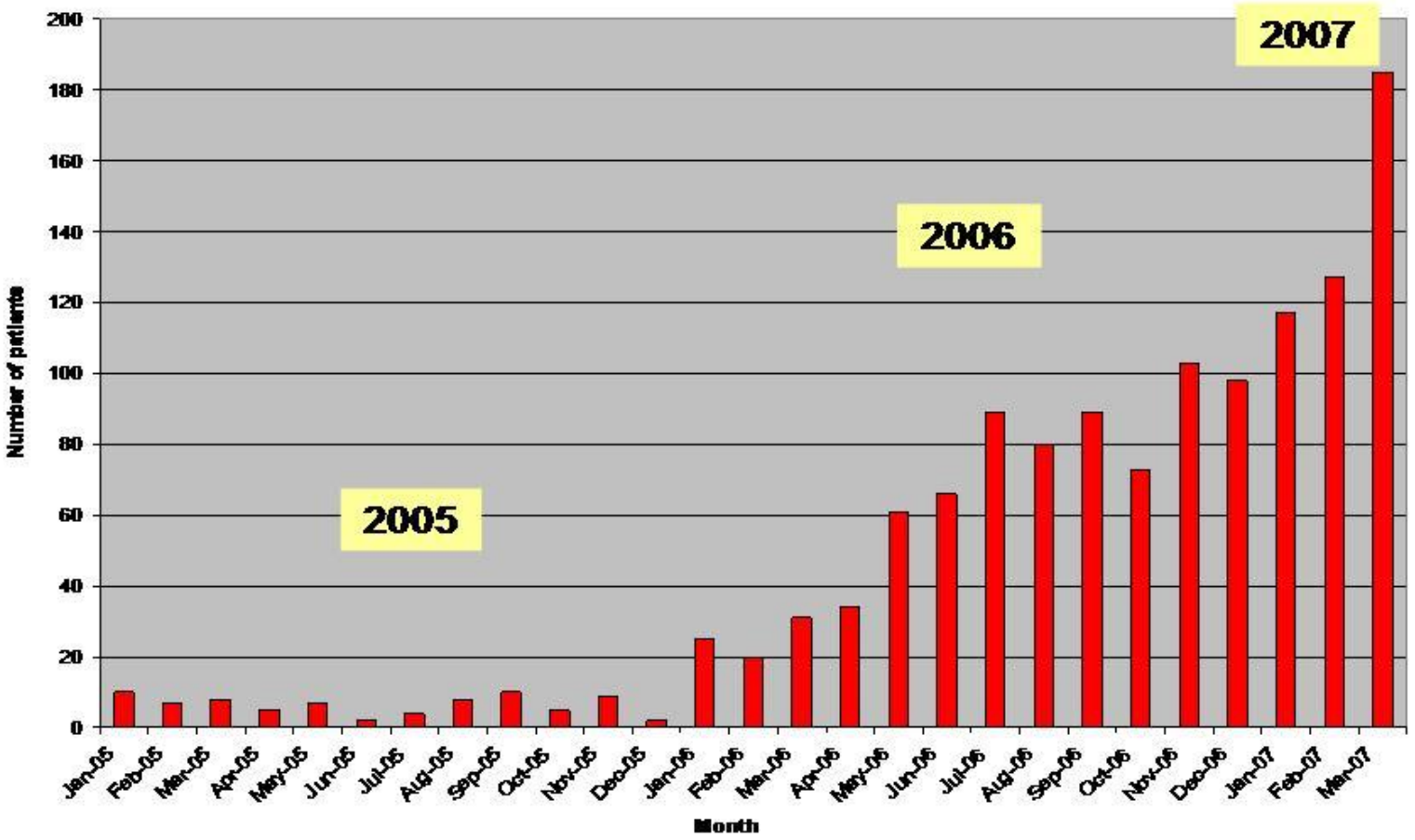
The Israeli Story

- **Late 2005 –KPC-producing *K. pneumoniae* ST-258 introduced to Israeli hospitals**
  - **2006 – outbreak began: ~700 cases**
  - **01/01/2007 - 04/30/2007: ~600 cases**
  - **Local attempts to contain: limited success**
  - **Crude mortality: ~40%**
  - **Attributable mortality of bacteremia: 50%** **(Borer et al, ICHE 2009)**
- **Since the start of the outbreak –**
  - **~17,000 patients identified with CRE**
  - **Vast majority of isolates tested (>90%): ST-258**

***Courtesy of Israel National Center for Infection Control; Schwaber , ICAAC 2012**

Nationwide epidemic curve prior to intervention

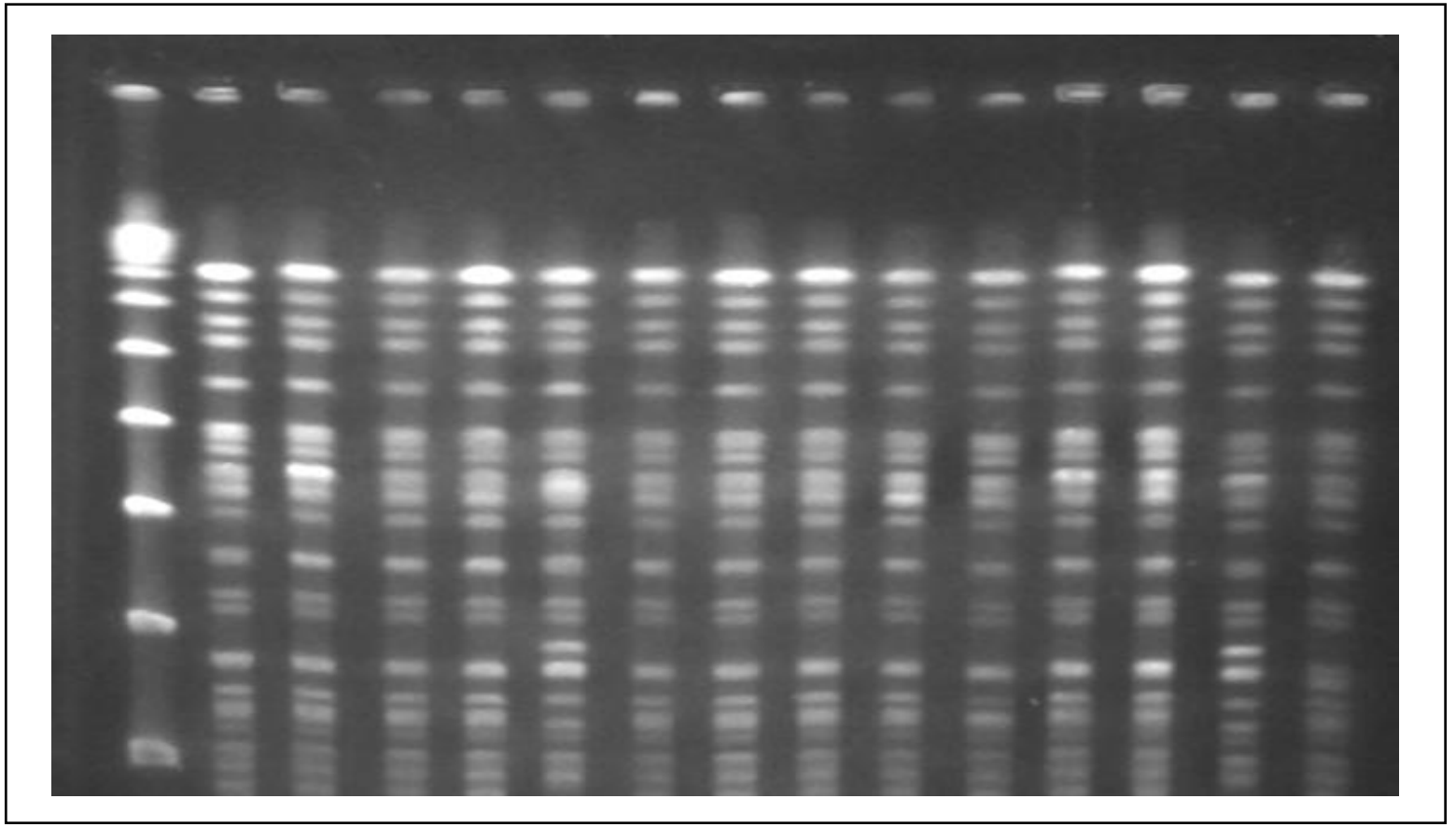
Acquisitions by clinical culture



Month

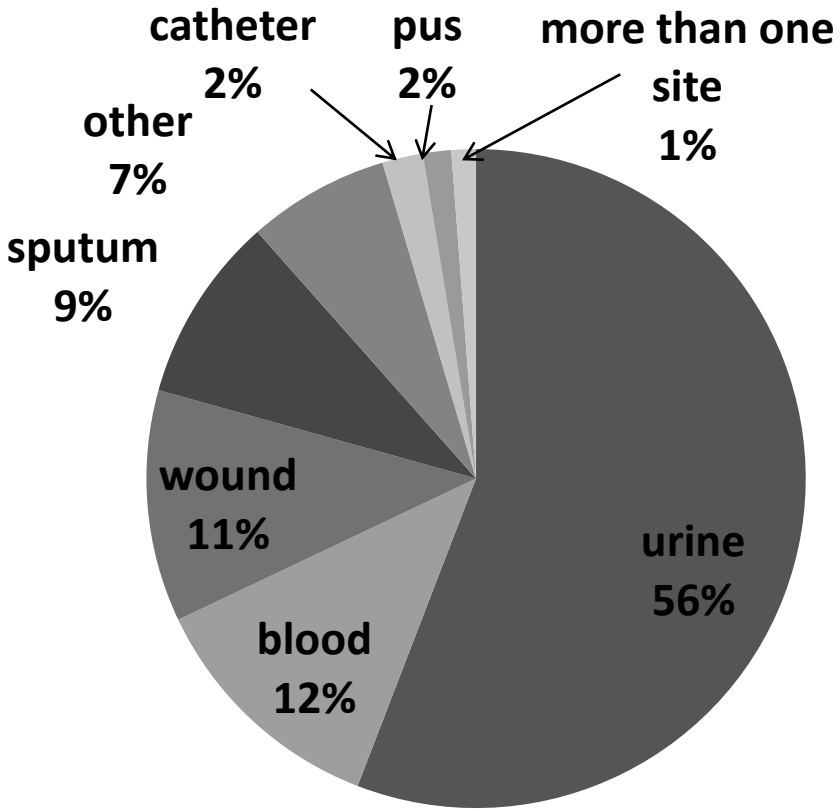
*Courtesy of Israel National Center for Infection Control; Schwaber , ICAAC 2012

A clonal outbreak, involving acute-care hospitals and long-term care facilities



Navon-Venezia et al, AAC 2009

Distribution of 1st-time CRE clinical cultures by site of isolation



*Courtesy of Israel National Center for Infection Control; Schwaber , ICAAC 2012

What was done?

- **March 2007**
  - **Isolation guidelines issued**
    - **Geographic separation of carriers**
    - **Dedicated nursing staffing**
  - **Task force created by the Ministry of Health**
    - **First assignment: contain the outbreak**

- **Daily census of all CRE carriers in acute-care hospitals required as of May 1, 2007**

***Courtesy of Israel National Center for Infection Control; Schwaber , ICAAC 2012**

MAJOR ARTICLE

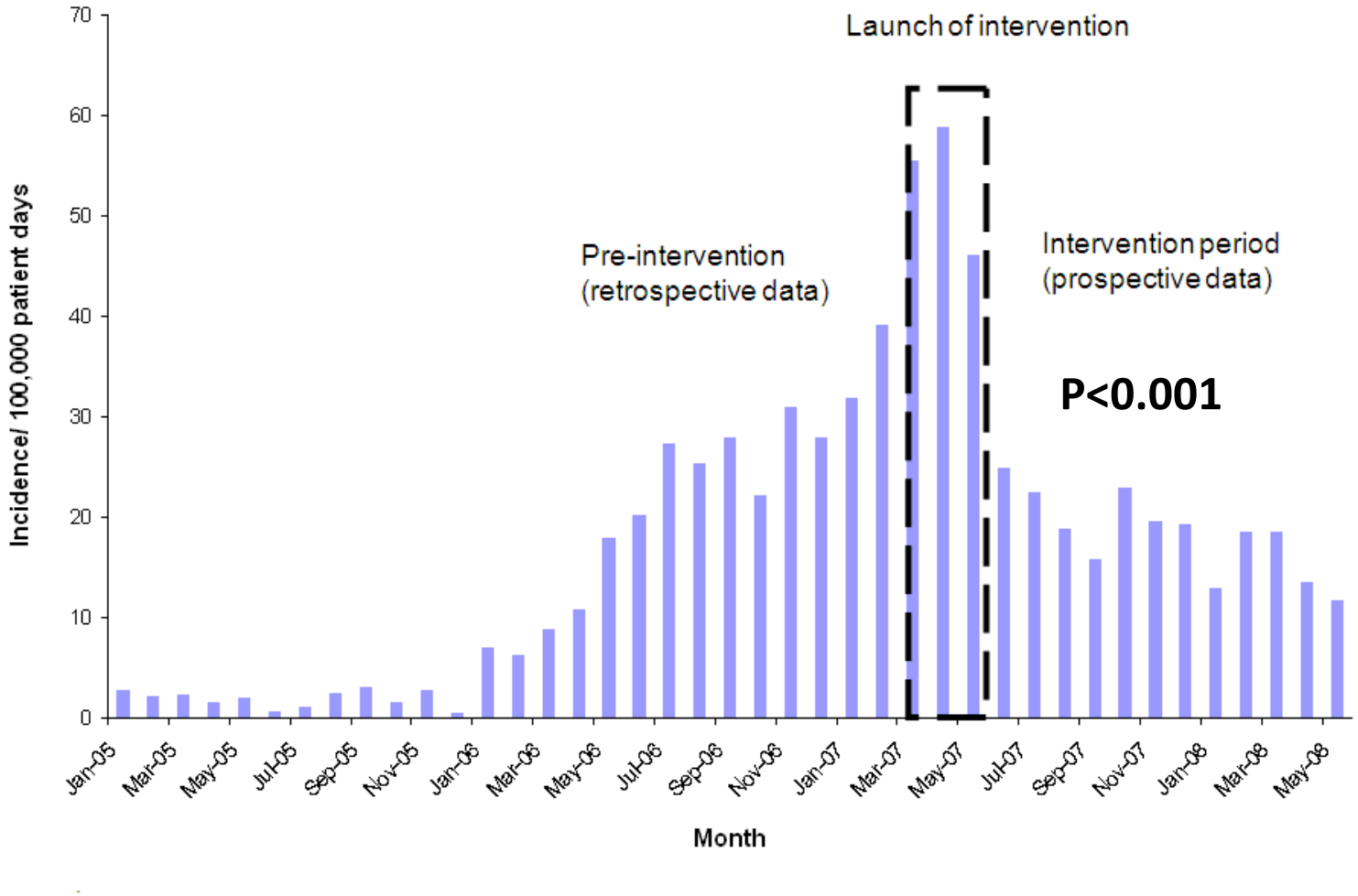
Containment of a Country-wide Outbreak of Carbapenem-Resistant *Klebsiella pneumoniae* in Israeli Hospitals via a Nationally Implemented Intervention

Mitchell J. Schwaber,[1] Boaz Lev,[2] Avi Israeli,[2] Ester Solter,[1] Gill Smollan,[1] Bina Rubinovitch,[1] Itamar Shalit,[1] Yehuda Carmeli,[1] and the Israel Carbapenem-Resistant Enterobacteriaceae Working Group[a]

[1]National Center for Infection Control, Israel Ministry of Health, Tel Aviv, and [2]Israel Ministry of Health, Jerusalem, Israel

Clinical Infectious Diseases 2011;52:848–855

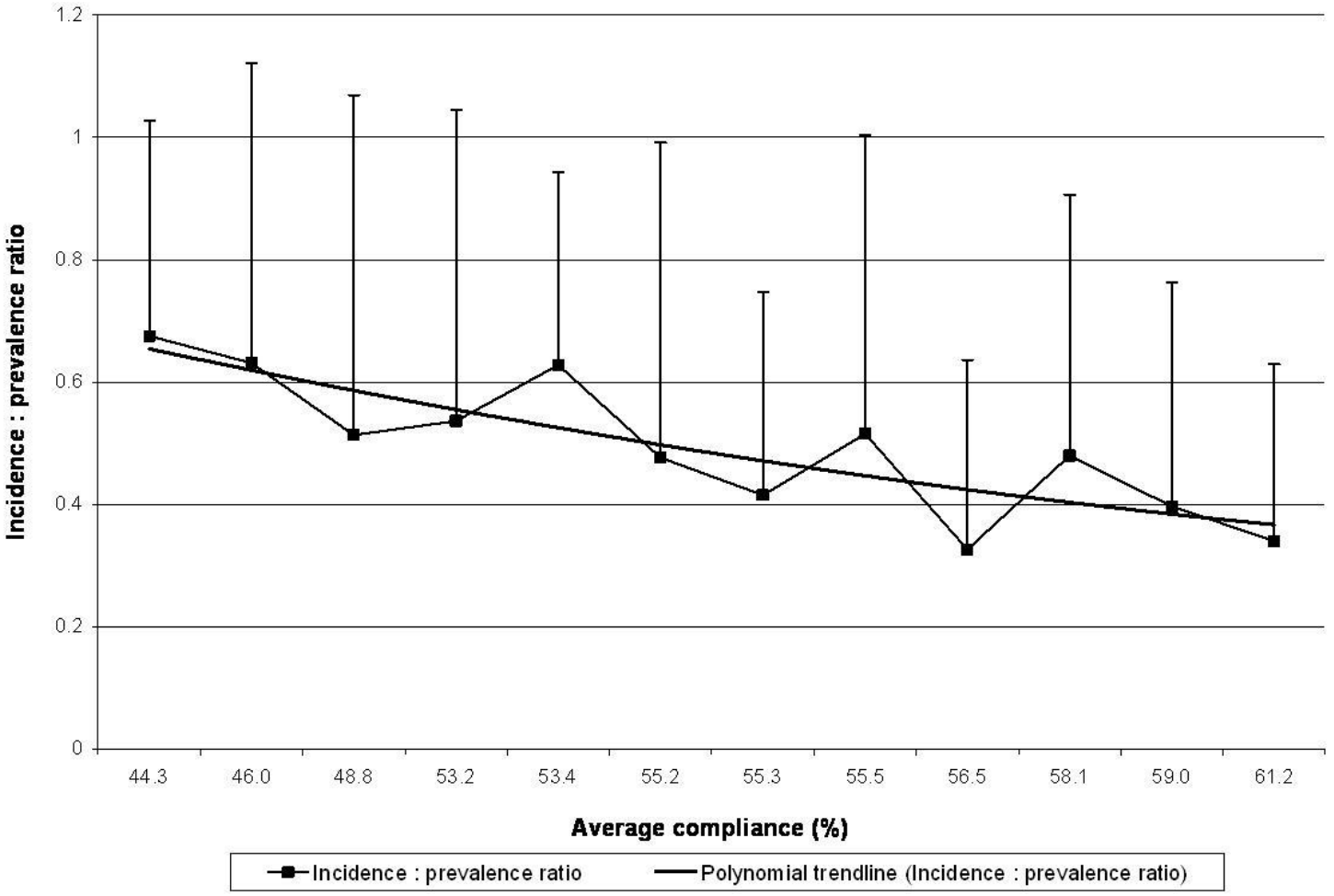
Outbreak contained



Clinical Infectious Diseases 2011;52:848–855

Compliance with isolation guidelines shown to work

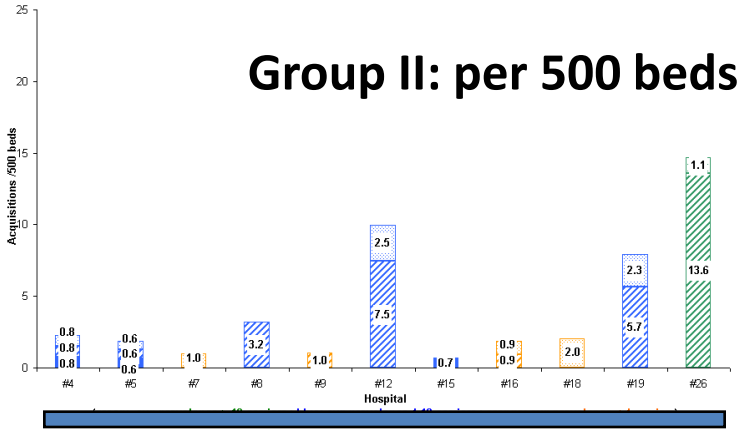
Effect of compliance on incidence: prevalence ratio



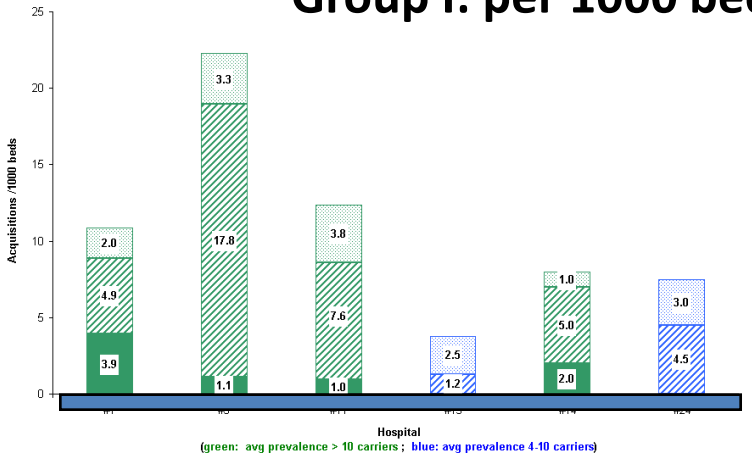
Clinical Infectious Diseases 2011;52:848–855

Feedback and intervention shown to make a difference

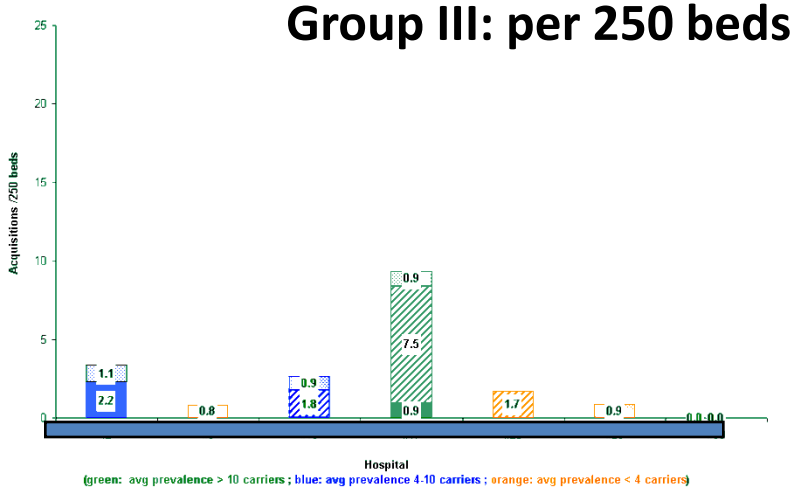
Group II: per 500 beds



Group I: per 1000 beds



Group III: per 250 beds



*Courtesy of Israel National Center for Infection Control; Schwaber , ICAAC 2012

After 15 months…

Monthly incidence reduced from high of

55.5 cases/100,000 pt-days to 11.7 cases/100,000 pt-days

- **79% reduction**
- **P<0.001**

Clinical Infectious Diseases 2011;52:848–855

After 15 months…

Monthly incidence reduced from high of

55.5 cases/100,000 pt-days to 11.7 cases/100,000 pt-days

- **79% reduction**
- **P<0.001**

BUT…….

Clinical Infectious Diseases 2011;52:848–855

Figured out along the way…

- **Adequate isolation of known carriers critical, but not sufficient for effective containment of spread**

- **Also required: adequate identification of unknown carriers, *meaning* -**
  - **Active surveillance**
  - **Intervention in long-term care, the *BLACK HOLE* of CRE carriage**

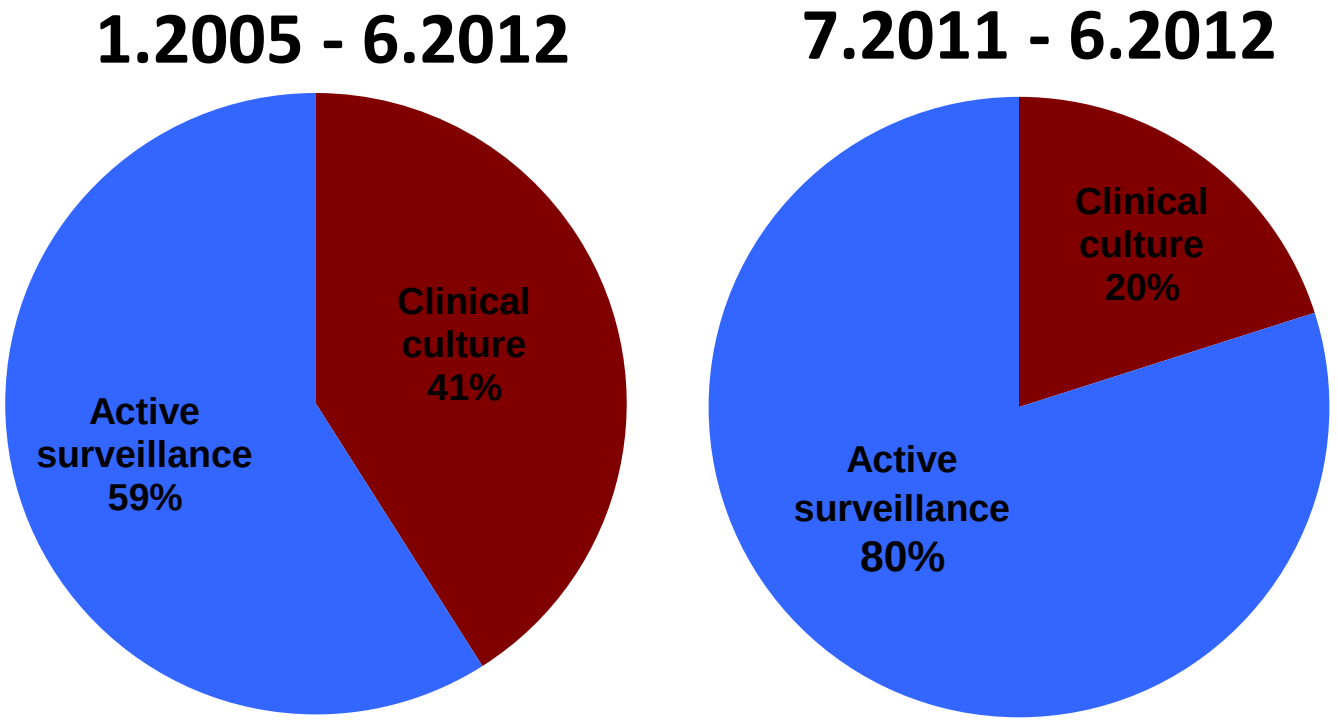
***Courtesy of Israel National Center for Infection Control; Schwaber , ICAAC 2012**

Guidelines for Active Surveillance

- **Issued June 2008**
  - **Required in 3 groups**
    - **Contacts of CRE carriers newly identified on wards**
      - **Based on local infection control (IC) team investigation**
      - **In ICU or "step-down" unit – entire unit**
    - **High-risk groups on admission**
      - **Practically speaking in 2012 – anyone with admission to hospital or LTCF in past year**
    - **High-risk wards in hospital – at hospital's discretion**

***Courtesy of Israel National Center for Infection Control; Schwaber , ICAAC 2012**

First isolation of CRE



*Courtesy of Israel National Center for Infection Control; Schwaber , ICAAC 2012

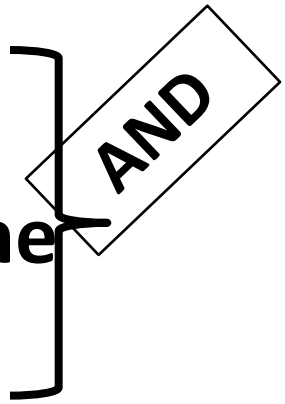
Requirement to check for carbapenemase

- **As of 2009 –**
  - **All isolates must undergo MHT or KPC PCR**
  - **If PCR negative, must undergo MHT**
- **95% of CRE isolates – carbapenemase producers**
- **Isolation policy:**
  - **carbapenemase-producing CRE – cohort, dedicated staff**
  - **Non-carbapenemase-producing CRE – "standard" contact isolation precautions**

***Courtesy of Israel National Center for Infection Control; Schwaber , ICAAC 2012**

Cessation of CRE carrier status

- 2 negative rectal swab cultures
- Negative rectal swab carbapenemase gene PCR



- Negative culture from original site of isolation
  - If a clinical site
  - If still relevant
- Performed at discretion of IC staff in acute care; required in long-term care, after 90 days

*Courtesy of Israel National Center for Infection Control; Schwaber , ICAAC 2012

Cessation of CRE carrier status

- **Number of carriers who have become non-carriers (September 2009 - June 2012): ~1300**
- **Recrudescence: ~ 7%**
  - **Reasons**
    - **Re-infection**
    - **Changed conditions – antibiotics, illness, etc. – allow organism to re-emerge above threshold of detection**

***Courtesy of Israel National Center for Infection Control; Schwaber , ICAAC 2012**

Intervention in long-term care

- **Israel demographics**
  - **Population: ~ 8 million**
  - **Density: ~ 960/mi^2 (CA: ~240/mi^2)**
  - **Acute-care beds: ~ 15,000 (=1.9 beds/1000 pop.)**
  - **Long-term-care beds: ~30,000**
    - **<u>3000 – post-acute care</u>**
    - **27,000 – chronic long-term nursing care**
  - **~ 20% of CRE carriers discharged from acute care - to PAC (~500/year)**

***Courtesy of Israel National Center for Infection Control; Schwaber , ICAAC 2012**

Intervention in long-term care

- **Focused on post-acute care (PAC) facilities**

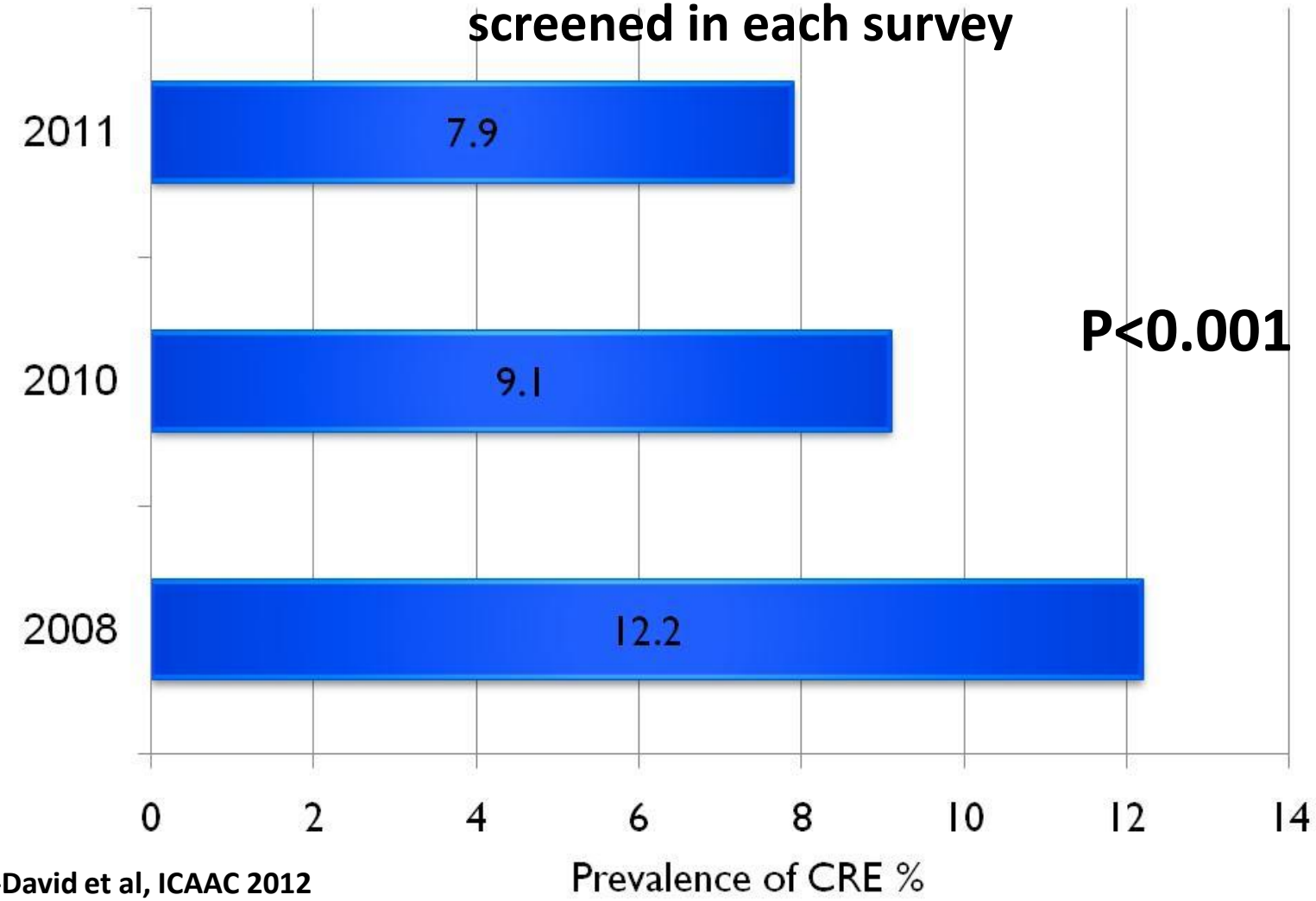
- **Elements of intervention**
  - **National staff established to conduct it – begun 2008**
    - **Physician**
    - **Nurse**
    - **Microbiologist**
  - **Data collection via email/fax**
  - **Regular site visits with written summaries**
  - **Evaluation based on 16-point Infection Control Score, including ward type-specific CRE isolation guidelines**
  - **3 CRE point prevalence surveys – 2008, 2010, 2011**

***Courtesy of Israel National Center for Infection Control; Schwaber , ICAAC 2012**

Comparison Between 3 Surveys

Prevalence of CRE

Approximately 1000 patients with no history of CRE were screened in each survey



P<0.001

Ben-David et al, ICAAC 2012

Intervention in community

מדינת ישראל – משרד הבריאות

החטיבה לעניני בריאות

מנהל רפואה

חוזר מס' : 44/2009

ירושלים, כ"ו כסלו, תש"ע
13 דצמבר, 2009

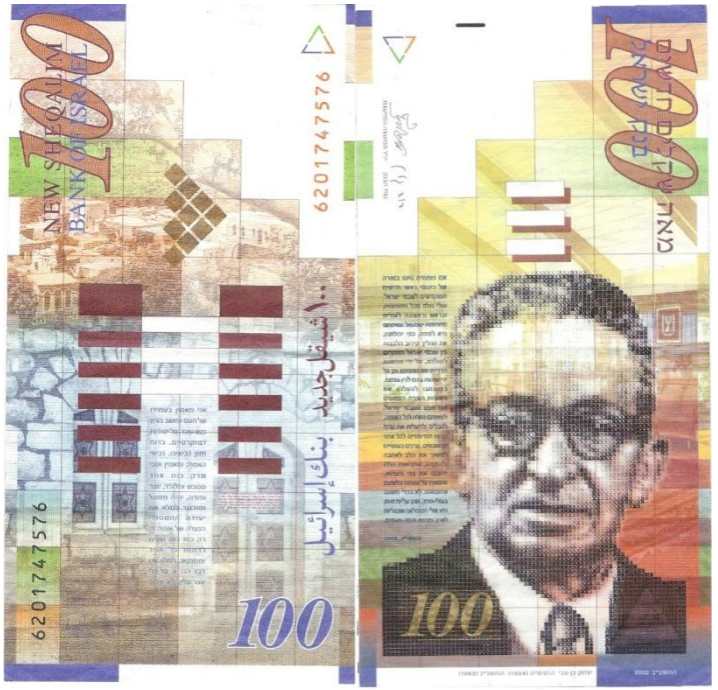
תיק מס' : 2/13 /יט א'

אל: מנהלי האגפים הרפואיים – קופות החולים
מנהלי בתי החולים הכלליים

הנדון: נהלי טיפול ודווח בנשא של חיידק יציב לאנטיביוטיקה CRE\VRE במערך האמבולטורי

- **2009: National mandatory guidelines issued for CRE isolation in ambulatory clinics**
- **Educational activities carried out by staff of National Center**

***Courtesy of Israel National Center for Infection Control; Schwaber , ICAAC 2012**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GEORGE WASHINGTON
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IN GOD WE TRUST
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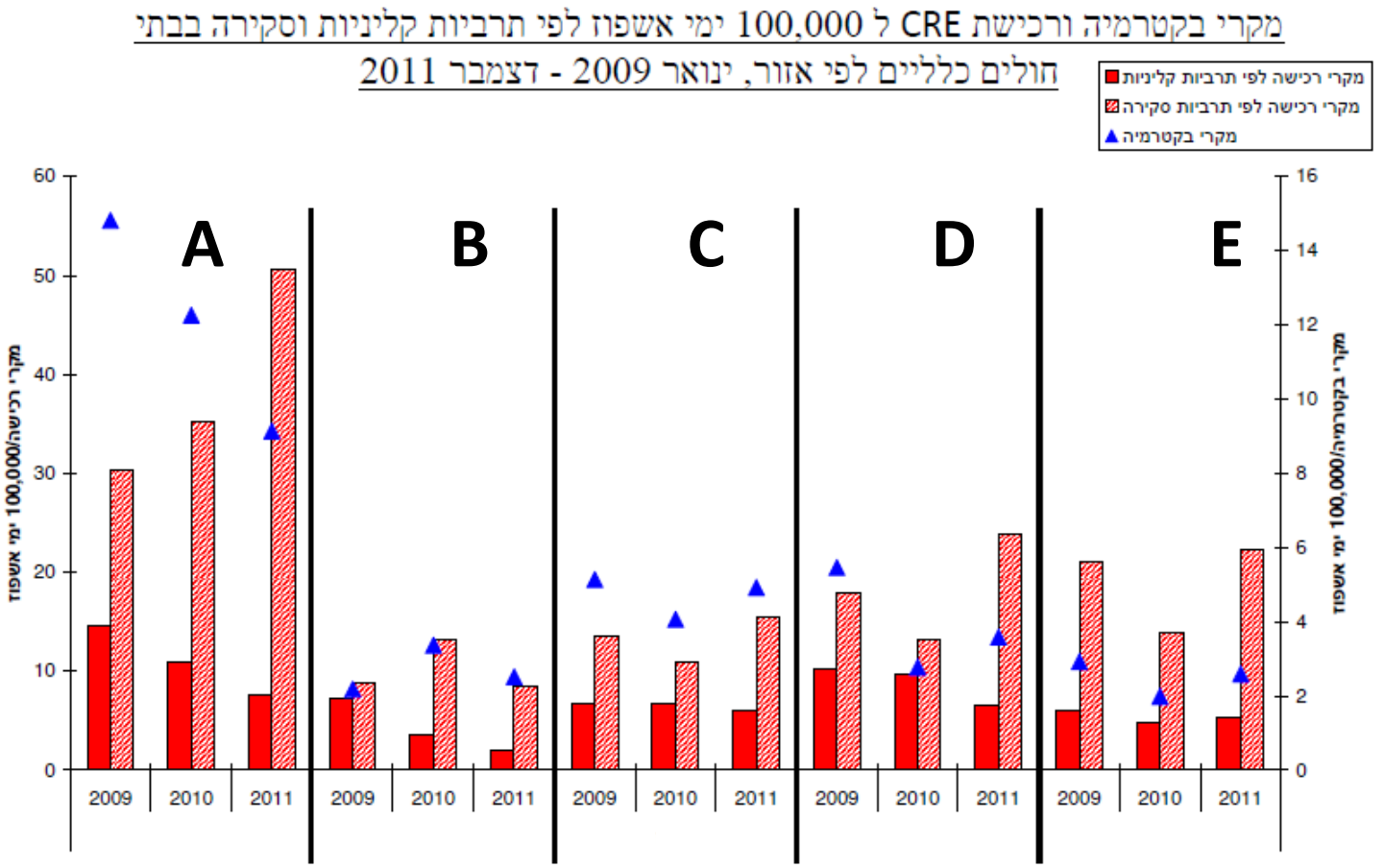
CRE incidence by region, 2009-11

Nosocomial incidence per clinical cultures and surveillance; bacteremia



*Courtesy of Israel National Center for Infection Control; Schwaber , ICAAC 2012

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Class action lawsuit over super bug being prepared

Relatives of deadly bug's victims to sue bodies that allegedly failed to prevent its outbreak; 'there was no h of hygienic regulations, standards onplace in hospitals all over the world,' says

, 11:28 / Israel News

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48 carriers of super bug still in hospitals

Dozens still hospitalized with antibiotic-resistant bacterial infection, which had killed at least 120 as of Tuesday; health ministry to go on high alert

Meital Yasur-Beit Or
Published: 03.08.07, 00:

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Super bug kills dozens in hospitals across country

Virulent stain of bacteria believed to be cause of death of 120-200 patients in hospitals. Experts explain most of those infected were already suffering from prior medical conditions. Health ministry says outbreak was kept secret to avoid mass panic

Meital Yasur-Beit Or
Published: 03.07.07, 09:53 / Israel News

Deadly Bacterium

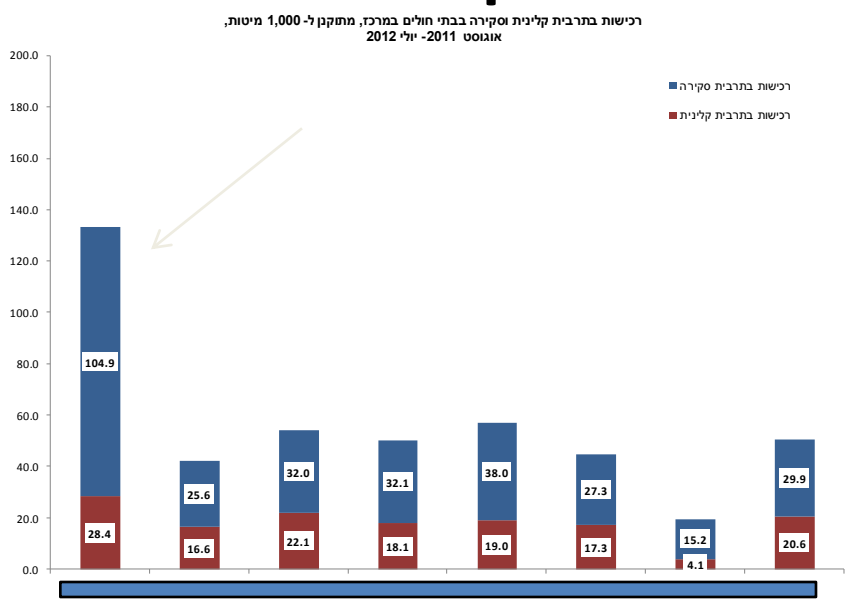
Super bug kills dozens in hospitals across country /
Meital Yasur-Beit Or

Virulent stain of bacteria believed to be cause of death of 120-200 patients in hospitals. Experts explain most of those infected were already suffering from prior medical conditions. Health ministry says outbreak was kept secret to avoid mass panic

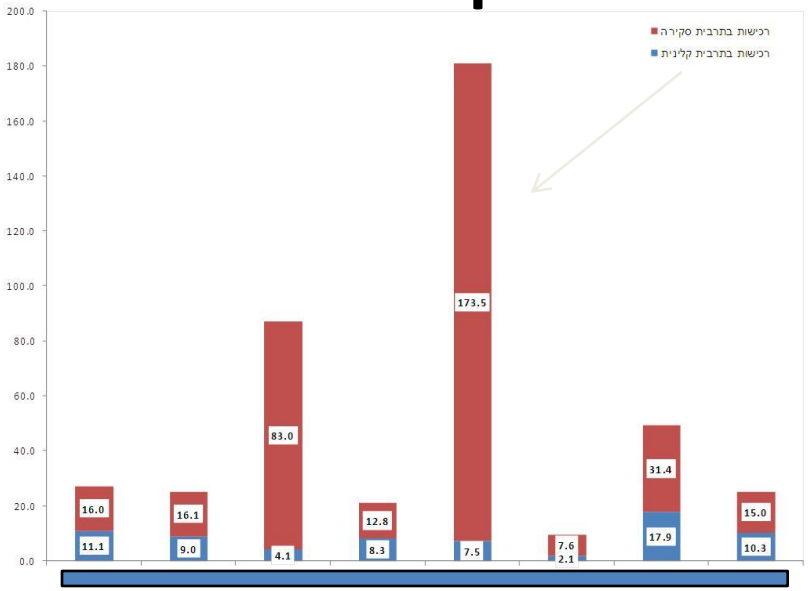
Full story

Targeted interventions using focused intra-regional comparisons

Acute care hospital



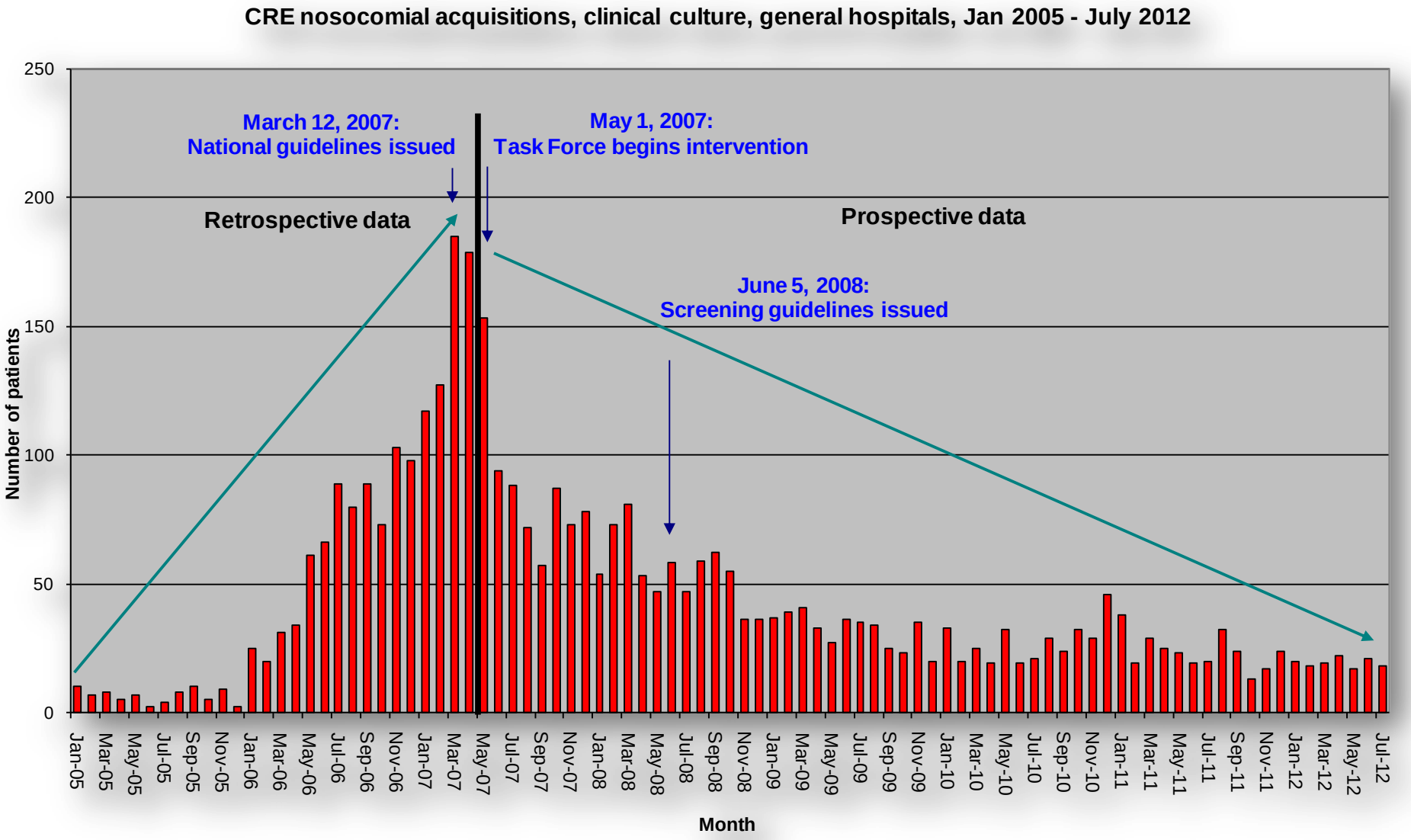
Acute care hospital



- **Multi-year intervention in problematic LTCF**
  - **Site visits, screening, strict isolation measures, periodic closures**
  - **Point prevalence among unknown carriers decreased from ~70% to 7%**

***Courtesy of Israel National Center for Infection Control; Schwaber , ICAAC 2012**

Updated epidemic curve



*Courtesy of Israel National Center for Infection Control; Schwaber , ICAAC 2012

Real-time communication network

- **CRE status: permanent part of medical record**
- **At all times, the staff of the National Center is aware of the location of every CRE carrier hospitalized in the acute care and post-acute-care settings (and others)**
- **All movement of these carriers between facilities and into the outpatient setting is tracked**
- **The receiving institution (acute, LTCF, HMO) is notified in real time to ensure proper isolation in each setting**

*Courtesy of Israel National Center for Infection Control; Schwaber , ICAAC 2012

CRE acquisitions in hospitals

- **Some MDRO acquisitions, particularly CRE, should be perceived as a violation of patient safety**

- **As with HAIs, the responsibility for prevention is that of every employee in the institution – up to the CEO**

- **CRE acquisition is preventable, should be perceived as a "system failure" → strictly follow specific facility-driven SOP for every episode**
  - **Goal: getting to 0, staying at 0**

***Courtesy of Israel National Center for Infection Control; Schwaber , ICAAC 2012**

- **Withholding reimbursements of CRE-related complications?**
  - **Would increase surveillances and resources allocation for preventive measures**

Summary

- **CRE is endemic in Israeli healthcare facilities**
  - **No significant transmission detected in community**
  - **Large and persistent reservoir in LTCFs**
  - **Frequent and continuous movement of carriers between LTCFs and acute care**

- **Primary goal of national intervention:**
  - **to contain CRE spread in acute care setting**

- **Pillars of approach (carrier isolation/dedicated staffing/identification of silent carriers) remain effective**

- **Continued success requires recruitment and continued vigilance at <u>every level</u> of healthcare system**

- **No end in sight**

***Courtesy of Israel National Center for Infection Control; Schwaber , ICAAC 2012**

The “consumer side”

- **Benchmark establishment**
- **Standardization:**
  - **Infection Control practices**
  - **Laboratory processing**
- **Monthly and Annual reports**
- **Direct notifications of carriers admitted**
- **Post-discharge follow-ups**
- **Molecular testing upon request on special circumstances (e.g. suspected SME in *Serratia*)**
- **Administrators are forced into the loop**

what's the "real" modifiable risk factor?

INFECTION CONTROL AND HOSPITAL EPIDEMIOLOGY AUGUST 2012, VOL. 33, NO. 8

ORIGINAL ARTICLE

Recent Exposure to Antimicrobials and Carbapenem-Resistant Enterobacteriaceae: The Role of Antimicrobial Stewardship

Dror Marchaim, MD;[1] Teena Chopra, MD;[1] Ashish Bhargava, MD;[1] Christopher Bogan, BS;[1] Sorabh Dhar, MD;[1] Kayoko Hayakawa, MD, PhD;[1] Jason M. Pogue, PharmD;[2] Suchitha Bheemreddy, MD;[1] Christopher Blunden, BS;[1] Maryann Shango, MD;[1] Jessie Swan, BS;[1] Paul R. Lephart, PhD;[3] Federico Perez, MD;[4,5] Robert A. Bonomo, MD;[4,5,6,7,8] Keith S. Kaye, MD, MPH[1]

BACKGROUND. Carbapenem-resistant Enterobacteriaceae (CRE) are rapidly emerging worldwide. Control group selection is critically important when analyzing predictors of antimicrobial resistance. Focusing on modifiable risk factors can optimize prevention and resource expenditures. To identify specific predictors of CRE, patients with CRE were compared with 3 control groups: (1) patients with extended-spectrum β-lactamase (ESBL)–producing Enterobacteriaceae, (2) patients with non-ESBL-containing Enterobacteriaceae, and (3) uninfected controls.

DESIGN. Matched multivariable analyses.

- **3 “control” groups:**
  - **ESBLs**
  - **Susceptible Enterobacteriaceae**
  - **“un-infected”**

- **Matching criteria:**
  - **Time at risk**
  - **Hospital**
  - **Unit**
  - **Calendar year**

- **Matched analysis**

CRE Predictors Multivariate Analysis

TABLE 2. Multivariable Models of Risk Factors for Enterobacteriaceae Isolation, Detroit Medical Center, September 1, 2008, to August 31, 2009

	CRE vs uninfected[b]		ESBL vs uninfected[b]		Susceptible vs uninfected[b]		CRE vs ESBL		CRE vs susceptible		CRE vs all controls combined	
Variable[a]	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
Any antibiotic exposure in previous 3 months	11.4 (2–64.3)	.006	1.7 (0.7–4.1)	.24			5.2 (1.4–19.4)	.015	12.3 (3.3–45)	<.001	7.1 (1.9–25.8)	.003
Permanent residency in institution	1.04 (0.2–4.5)	.96	1.3 (0.5–3.6)	.56	0.15 (0.05–0.5)	.002	2.1 (1–4.2)	.05	5.3 (2.1–12.9)	<.001	2.6 (1.3–5.3)	.01
Isolation of resistant bacteria in previous 6 months[c]	15.3 (4.2–55.6)	<.001	8.25 (2.7–25.7)	<.001	6.6 (1.9–23.3)	.003	1.7 (0.76–3.7)	.2	1.8 (0.7–4.7)	.23	2.9 (1.4–5.7)	.003
Dependent functional status in background	1.4 (0.5–4.4)	.55	5.6 (2.1–14.7)	.001	2.6 (1.1–6.4)	.03			2.0 (0.7–6.2)	.2	1.6 (0.6–4)	.33
ICU stay in recent 3 months	3.9 (1.3–12.4)	.02	5.2 (2.1–13.2)	.001	3.0 (1.2–7.2)	.02			1.6 (0.6–4)	.34	1.36 (0.7–2.7)	.37
Recent (6 months) invasive procedure	4.2 (1.2–15)	.03	1.2 (0.4–3.4)	.76	3.2 (1.3–8)	.01	2.8 (1.1–7.6)	.04			2.7 (1.1–7.1)	.04
Charlson weighted index comorbidity ≥3	3.1 (0.8–11.8)	.1	1.1 (0.4–2.7)	.87	2.2 (0.94–5)	.07	2.4 (1.03–5.6)	.04	4.8 (1.9–12.5)	.001	3.1 (1.4–7)	.006

NOTE. CI, confidence interval; CRE, carbapenem-resistant Enterobacteriaceae; ESBL, extended-spectrum β-lactamase–producing Enterobacteriaceae; ICU, intensive care unit; OR, odds ratio.

[a] If a variable was not significant in bivariate analysis, it was not forced into the multivariable model.

[b] Part of the case-case-control analysis.

[c] Includes methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant *Enterococcus*, ESBL-producing Enterobacteriaceae, *Acinetobacter baumannii*, and *Pseudomonas aeruginosa*.

CRE Predictors Multivariate Analysis

Variable	CRE vs. uninfected		ESBL vs. uninfected		Susceptible vs. uninfected		CRE vs. ESBL		CRE vs. susceptible		CRE vs. all controls combined	
	OR (CI-95%)	P	OR (CI-95%)	P	OR (CI-95%)	P	OR (CI-95%)	P	OR (CI-95%)	P	OR (CI-95%)	P
Any antibiotic exposure in previous 3 months	**11.4 (2-64.3)**	**0.006**	**1.7 (0.7-4.1)**	**0.24**			**5.2 (1.4-19.4)**	**0.015**	**12.3 (3.3-45)**	**<0.001**	**7.1 (1.9-25.8)**	**0.003**
Permanent residency in institution	1.04 (0.2-4.5)	0.96	1.3 (0.5-3.6)	0.56	0.15 (0.05-0.5)	0.002	2.1 (1-4.2)	0.05	5.3 (2.1-12.9)	<0.001	2.6 (1.3-5.3)	0.01
Isolation of resistant bacteria in previous 6 months	15.3 (4.2-55.6)	<0.001	8.25 (2.7-25.7)	<0.001	6.6 (1.9-23.3)	0.003	1.7 (0.76-3.7)	0.2	1.8 (0.7-4.7)	0.23	2.9 (1.4-5.7)	0.003
Dependent functional status in background	1.4 (0.5-4.4)	0.55	5.6 (2.1-14.7)	0.001	2.6 (1.1-6.4)	0.03			2.0 (0.7-6.2)	0.2	1.6 (0.6-4)	0.33
ICU stay in recent 3 months	3.9 (1.3-12.4)	0.02	5.2 (2.1-13.2)	0.001	3.0 (1.2-7.2)	0.02			1.6 (0.6-4)	0.34	1.36 (0.7-2.7)	0.37
Recent (6 months) invasive procedure	4.2 (1.2-15)	0.03	1.2 (0.4-3.4)	0.76	3.2 (1.3-8)	0.01	2.8 (1.1-7.6)	0.04			2.7 (1.1-7.1)	0.04
Charlson's weighted Index Comorbidity ≥ 3	3.1 (0.8-11.8)	0.1	1.1 (0.4-2.7)	0.87	2.2 (0.94-5)	0.07	2.4 (1.03-5.6)	0.04	4.8 (1.9-12.5)	0.001	3.1 (1.4-7)	0.006

Univariate Outcomes Analysis

Parameter	Died in hospital	Died within 3 months	Functional status deterioration	Discharged to LTCF	Additional hospitalizations within 6 months	Invasive procedure/surgery within 3 months	LOS after culture excluding dead
CRE vs. controls	3.2 (1.4-7.2), 0.006	3.6 (1.6-7.9), 0.001	6.8 (3.1-15.3), p<0.001	11.9 (5.0-28.1), p<0.001	1.2 (0.6-2.2), 0.64	2.0 (1.1-3.9), 0.05	P<0.001
CRE vs. susceptible	3.3 (1.5-7.5), 0.004	4.5 (1.9-10.3), p<0.001	5.0 (2.3-10.8), p<0.001	7.1 (3.1-16.3), p<0.001	1.0 (0.5-1.8), 1.00	1.0 (0.6-1.9), 1.00	P=0.61
CRE vs. ESBL	1.8 (0.9-3.6), 0.15	1.7 (0.8-3.3), 0.17	5.1 (2.3-11.0), p<0.001	5.6 (2.4-13.2), p<0.001	1.2 (0.6-2.2), 0.75	1.1 (0.6-2.0), 0.87	P=0.42
CRE vs. all 3 non- CRE groups combined	2.6 (1.4-4.7), 0.003	2.8 (1.6-5.0), p=0.001	5.5 (2.9-10.6), p<0.001	7.9 (3.9-16.0), p<0.001	1.1 (0.7-1.8), 0.70	1.3 (0.8-2.2), 0.35	P=0.48
ESBL vs. controls	1.8 (0.8-4.2), 0.21	2.2 (1.0-4.9), 0.07	1.4 (0.6-2.9), 0.56	2.1 (0.9-4.9), 0.09	1.0 (0.5-1.9), 1.00	1.9 (1.0-3.5), 0.07	P=0.005
Susceptibles vs. controls	1.0 (0.4-2.4), 1.00	0.8 (0.3-2.1), 0.81	1.4 (0.6-2.9), 0.45	1.7 (0.7-3.8), 0.30	1.2 (0.7-2.2), 0.64	2.0 (1.0-3.7), 0.06	P=0.058

In-Hospital Mortality Multivariate Analysis

Variable	CRE vs. all 3 non-CRE groups combined		CRE vs. controls		CRE vs. susceptible controls	
	OR (CI-95%)	P	OR (CI-95%)	P	OR (CI-95%)	P
CRE infection	1.43 (0.72-2.86)	0.308	1.18 (0.41-3.42)	0.766	2.2 (0.82-5.92)	0.118
Age > 65 years	1.28 (0.63-2.60)	0.50	2.04 (0.64-6.5)	0.226	1.16 (0.42-3.18)	0.78
ICU stay in past 3 months	1.76 (0.91-3.40)	0.094	2.04 (0.74-5.66)	0.17	1.95 (0.70-5.49)	0.204
Charlson's combined condition score	5.11 (1.39-18.87)	0.014	4.37 (0.45-42.9)	0.205	5.72 (0.65-50.8)	0.117
Dependent functional status	2.55 (1.0-6.48)	0.05	3.76 (0.94-14.97)	0.06	2.10 (0.52-8.51)	0.301
Rapidly fatal McCabe score	2.49 (1.10-5.62)	0.029	1.51 (0.45-5.07)	0.506	1.57 (0.48-5.09)	0.45
Body site of isolation: Blood					3.35 (1.21-9.28)	0.02
Constant	0.013	<0.001	0.009	<0.001	0.008	<0.001

Shortening Time to Appropriate Therapy

The CRE bed-side score

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Brief report

The carbapenem-resistant *Enterobacteriaceae* score: A bedside score to rule out infection with carbapenem-resistant *Enterobacteriaceae* among hospitalized patients

Emily T. Martin MPH, PhD [a,*], Ryan Tansek BS [b], Vicki Collins MD [b], Kayoko Hayakawa MD, PhD [b], Odaliz Abreu-Lanfranco MD [b], Teena Chopra MD [b], Paul R. Lephart PhD [c], Jason M. Pogue PharmD [d], Keith S. Kaye MD, MPH [b], Dror Marchaim MD [b]

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Resistance issues

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Major article

"Swimming in resistance": Co-colonization with carbapenem-resistant Enterobacteriaceae and *Acinetobacter baumannii* or *Pseudomonas aeruginosa*

Dror Marchaim MD[a,*], Federico Perez MD[b,c], Jiha Lee MD[a], Suchitha Bheemreddy MD[a], Andrea M. Hujer BA[b], Susan Rudin BA[b], Kayoko Hayakawa MD, PhD[a], Paul R. Lephart PhD[d], Christopher Blunden BS[a], Maryann Shango MD[a], Michelle L. Campbell BA[a], Jastin Varkey BA[a], Palaniappan Mani
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ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Feb. 2011, p. 593–599 Vol. 55, No. 2
0066-4804/11/$12.00 doi:10.1128/AAC.01020-10

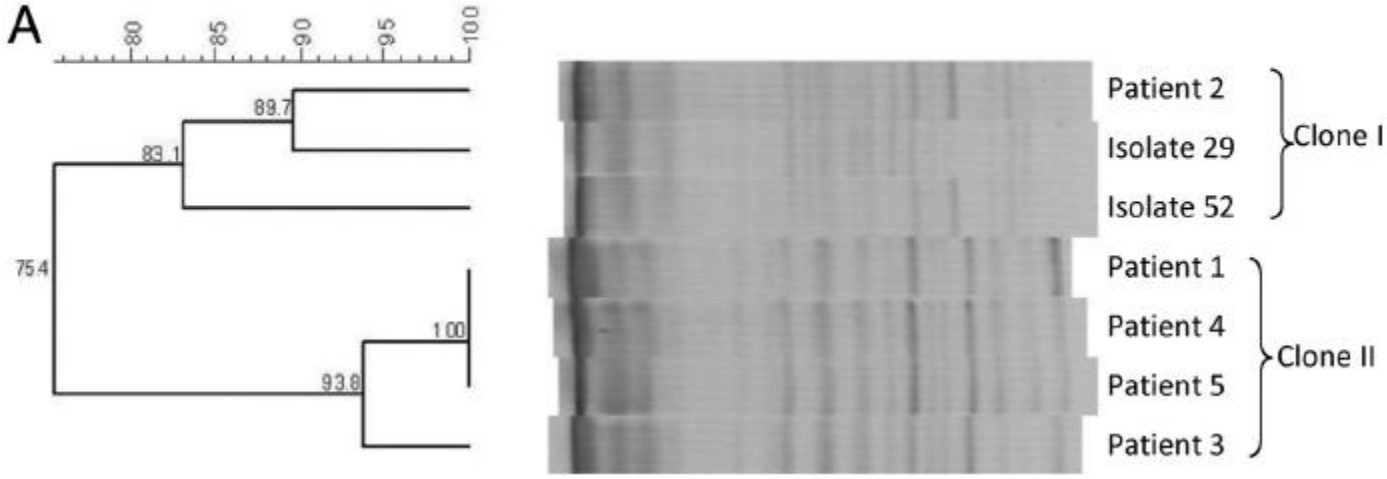
Outbreak of Colistin-Resistant, Carbapenem-Resistant *Klebsiella pneumoniae* in Metropolitan Detroit, Michigan▽

Dror Marchaim,[1]* Teena Chopra,[1] Jason M. Pogue,[2] Federico Perez,[3] Andrea M. Hujer,[3] Susan Rudin,[3] Andrea Endimiani,[3] Shiri Navon-Venezia,[4] Jatinder Hothi,[1] Jessica Slim,[1] Christopher Blunden,[1] Maryann Shango,[1] Paul R. Lephart,[5] Hossein Salimnia,[5] Deborah Reid,[1] Judy Moshos,[1] Wasif Hafeez,[1] Suchitha Bheemreddy,[1] Ting-Yi Chen,[1] Sorabh Dhar,[1] Robert A. Bonomo,[3,6] and Keith S. Kaye[1]

Division of Infectious Diseases,[1] Department of Pharmacy Services,[2] and Department of Clinical Microbiology,[5] Detroit Medical Center, Wayne State University, Detroit, Michigan; Research Service, Louis Stokes Cleveland Department of Veterans Affairs Medical Center,[3] and VISN 10 Geriatric Research, Education, and Clinical Centers (GRECC) at Veterans Affairs Medical Center,[6] Cleveland, Ohio; and Division of Epidemiology, Tel-Aviv Sourasky Medical Center, Sackler School of Medicine, Tel-Aviv University, Tel-Aviv, Israel[4]

Received 24 July 2010/Returned for modification 17 September 2010/Accepted 19 November 2010

1 pediatric patient


A
80
85
90
95
100
89.7
83.1
75.4
100
93.8
Patient 2
Isolate 29
Isolate 52
Clone I
Patient 1
Patient 4
Patient 5
Patient 3
Clone II

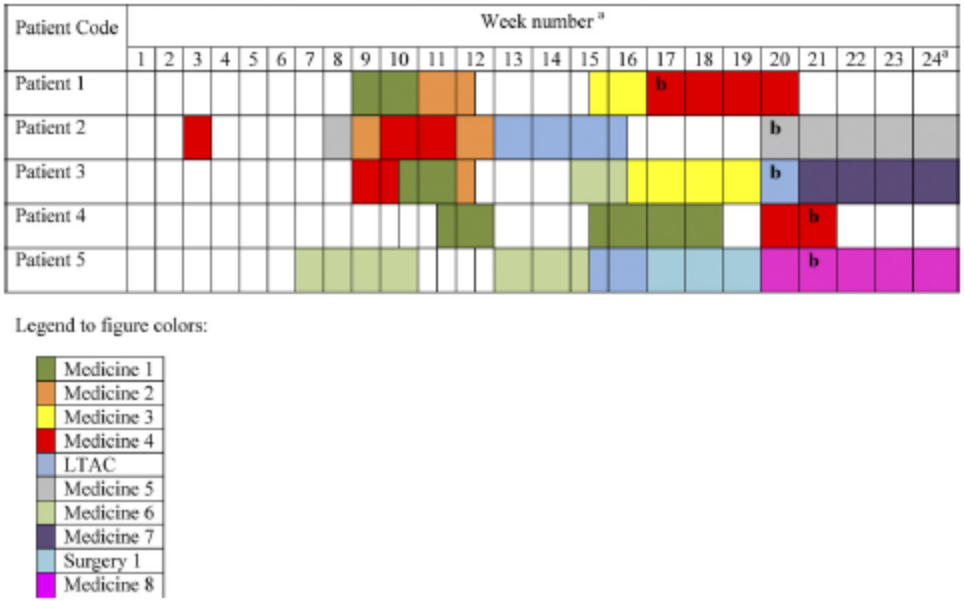


FIG. 1. Time line and transmission opportunities among patients during the outbreak. Each row represents a patient, and each column represents a week. The colors represent the different units/wards as presented in the legend at the bottom. A transmission opportunity was deemed to have occurred if two patients were in the same ward during the same time period. For example, patients 1 and 2 had a transmission opportunity during week 12 in the Medicine 2 ward. Superscript a: week1, 29 March to 4 April 2009; week 24, 5 to 11 September 2009. Superscript b: date of clinical culture.

Colistin resistant CRE

- In case-control analysis:
  - The strongest independent predictor was co-colonization with a carbapenem-resistant non-fermenter (*P. aeruginosa* or *A. baumannii*)

- Confounder?
- Mobile genetic element crossing the inter-species barrier ? i.e. VRSA scenario?

And story keeps evolve….

Articles

Emergence of a new antibiotic resistance mechanism in India, Pakistan, and the UK: a molecular, biological, and epidemiological study

Karthikeyan K Kumarasamy, Mark A Toleman, Timothy R Walsh, Jay Bagaria, Fafhana Butt, Ravikumar Balakrishnan, Uma Chaudhary, Michel Doumith, Christian G Giske, Seema Irfan, Padma Krishnan, Anil V Kumar, Sunil Maharjan, Shazad Mushtaq, Tabassum Noorie, David L Paterson, Andrew Pearson, Claire Perry, Rachel Pike, Bhargavi Rao, Ujjwayini Ray, Jayanta B Sarma, Madhu Sharma, Elizabeth Sheridan, Mandayam A Thirunarayan, Jane Turton, Supriya Upadhyay, Marina Warner, William Welfare, David M Livermore, Neil Woodford

Summary

Background Gram-negative Enterobacteriaceae with resistance to carbapenem conferred by New Delhi metallo-β-lactamase 1 (NDM-1) are potentially a major global health problem. We investigated the prevalence of NDM-1, in multidrug-resistant Enterobacteriaceae in India, Pakistan, and the UK.

Lancet Infect Dis 2010; 10: 597–602

Published Online August 11, 2010

The NEW ENGLAND JOURNAL of MEDICINE

Perspective

DECEMBER 16, 2010

NDM-1 — A Cause for Worldwide Concern

Robert C. Moellering, Jr., M.D.

have occurred since the original isolate was discovered in 2008.[5] In addition, isolates of Enterobacteriaceae-containing NDM-1 have now been characterized in the United States, Israel, Turkey, found in increasing numbers in isolates of Enterobacteriaceae obtained from outpatients throughout the world and, at the very least, will compromise our ability to use beta-lactam antibiotics

resistant *Staphylococcus aureus*. Clin Infect Dis 2010;50:821-5.

5. Kumarasamy KK, Toleman MA, Walsh TR, et al. Emergence of a new antibiotic resistance mechanism in India, Pakistan, and the UK: a molecular, biological, and epidemiological study. Lancet Infect Dis 2010;10:597-602.

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International Journal of Antimicrobial Agents

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Letter to the Editor

Emergence of New Delhi metallo-β-lactamase in Jerusalem, Israel

Sir,

New Delhi metallo-β-lactamase-1 (NDM-1) was first reported in *Klebsiella pneumoniae* and *Escherichia coli* in a Swedish patient returning from India [1]. After this seminal case, sporadic cases

PCR. No other NDM carriers were found
tigation.

2. Patient 2

In May 2011, a 74-year-old male v
Zedek Medical Center for rehabilitatio
included uncontrolled diabetes, hyperte

JOURNAL OF CLINICAL MICROBIOLOGY, Apr. 2009, p. 969–974 Vol. 47, No. 4
0095-1137/09/$08.00+0 doi:10.1128/JCM.00651-08

Ertapenem Resistance among Extended-Spectrum-β-Lactamase-Producing *Klebsiella pneumoniae* Isolates▽

Azita Leavitt,[1] Inna Chmelnitsky,[1] Raul Colodner,[2] Itzhak Ofek,[3] Yehuda Carmeli,[1] and Shiri Navon-Venezia[1]*

The Laboratory for Molecular Epidemiology and Antibiotic Research, Division of Epidemiology, Tel Aviv Sourasky Medical Center—Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel[1]; Clinical Microbiology Laboratory, Ha'Emek Medical Center, Afula, Israel[2]; and Department of Clinical Microbiology and Immunology, Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel[3]

Received 7 April 2008/Returned for modification 19 September 2008/Accepted 3 February 2009

Ertapenem resistance in *Klebsiella pneumoniae* is rare. We report on an ertapenem-nonsusceptible phenotype among 25 out of 663 (3.77%) extended-spectrum-β-lactamase (ESBL)-producing *K. pneumoniae* isolates in a multicenter Israeli study. These isolates originated from six different hospitals and were multiclonal, belonging to 12 different genetic clones. Repeat testing using Etest and agar dilution confirmed ertapenem nonsusceptibility in only 15/663 (2.3%) of the isolates. The molecular mechanisms of ertapenem resistance in seven single-clone resistant isolates was due to the presence of ESBL genes (CTX-M-2 in four isolates, CTX-M-10 and OXA-4 in one isolat

OMPK36. Seven of 10 is

J Antimicrob Chemother. 2011 Dec;66(12):2763-6.

Introduction of OXA-48-producing Enterobacteriaceae to Israeli hospitals by medical tourism.

Adler A, Shklyar M, Schwaber MJ, Navon-Venezia S, Dhaher Y, Edgar R, Solter E, Benenson S, Masarwa S, Carmeli Y.

National Center for Infection Control, Israel Ministry of Health, Tel-Aviv, Israel. amosa@tasmc.health.gov.il

Abstract

OBJECTIVES: The carbapenemase OXA-48 has been reported from different Mediterranean countries. It is mostly encoded on a single plasmid in various Enterobacteriaceae species. We characterized the epidemiological and molecular features of OXA-48-producing Enterobacteriaceae (OPE) in Israel.

METHODS: Epidemiological investigation was conducted by the National Center for Infection Control. Genotyping was performed using multilocus sequence typing. The bla(OXA-48)-carrying plasmids were investigated using S1 endonuclease and restriction fragment length polymorphism (RFLP). Conjugation efficiency of the bla(OXA-48)-carrying plasmids was studied in a filter mating experiment.

- **Non-ST-258 KPC-producing *K. pneumoniae***
  - **(Warburg et al, JAC 2012; Benenson et al, JAC 2012)**

- **NDM-1-producing CRE**
  - **27 cases to date**
  - **Though some clearly acquired in hospital, no documented carriage among contacts, despite extensive screening**

- **OXA-48-producing CRE**
  - **72 cases to date**
  - **Originally introduced by medical tourism (Adler et al, JAC 2011)**
  - **48 cases due to single-NICU outbreak (primarily *Klebsiella*)**

***Courtesy of Israel National Center for Infection Control**

Thanks!!!

- **Mitchell J. Schwaber** 
- **Yehuda Carmeli** 
- **Keith S. Kaye** 


Questions?