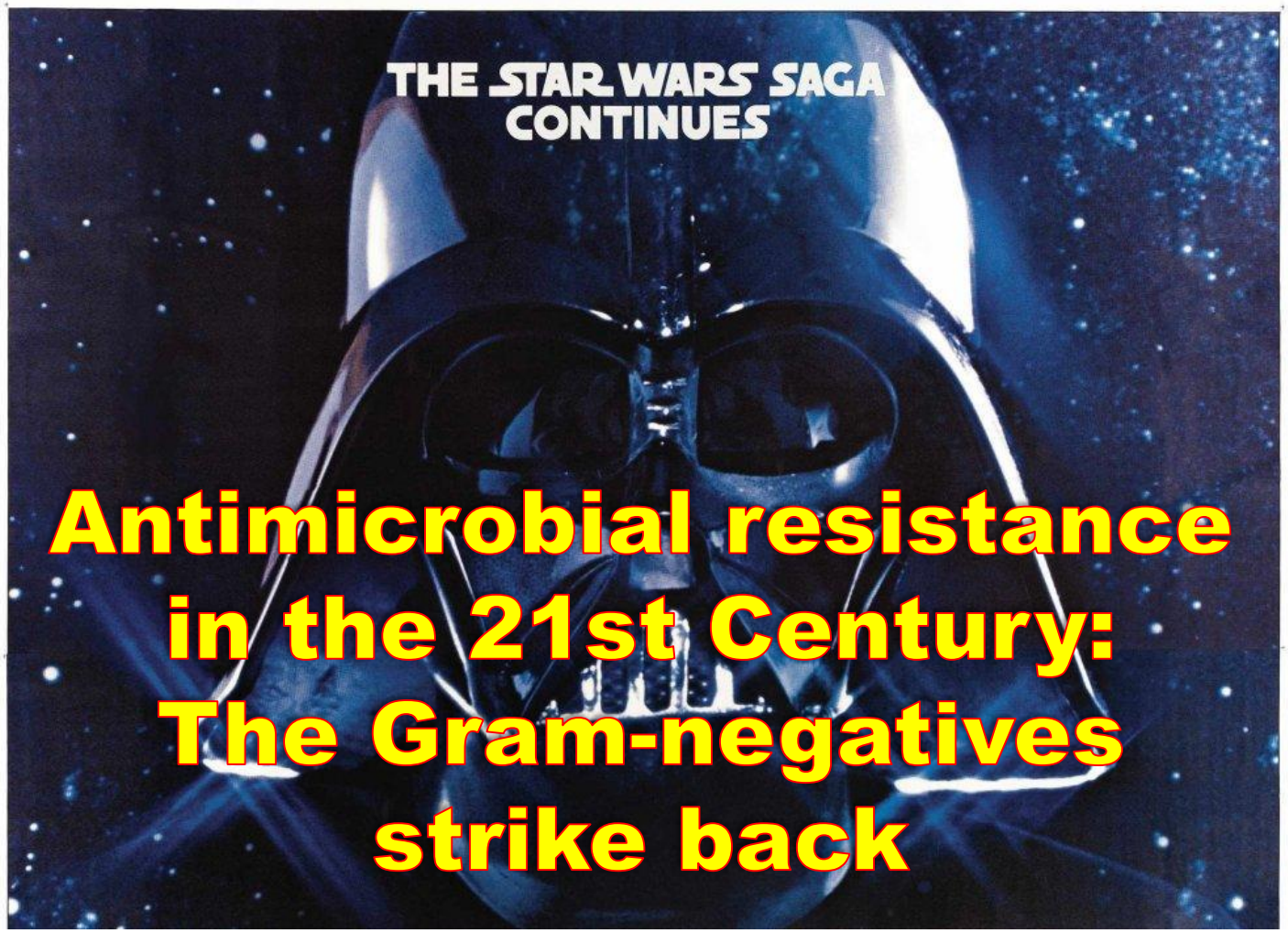
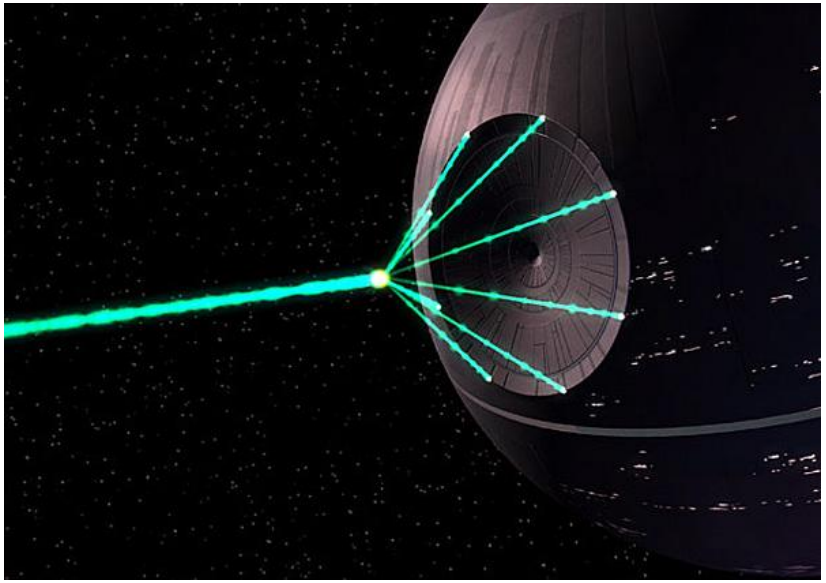
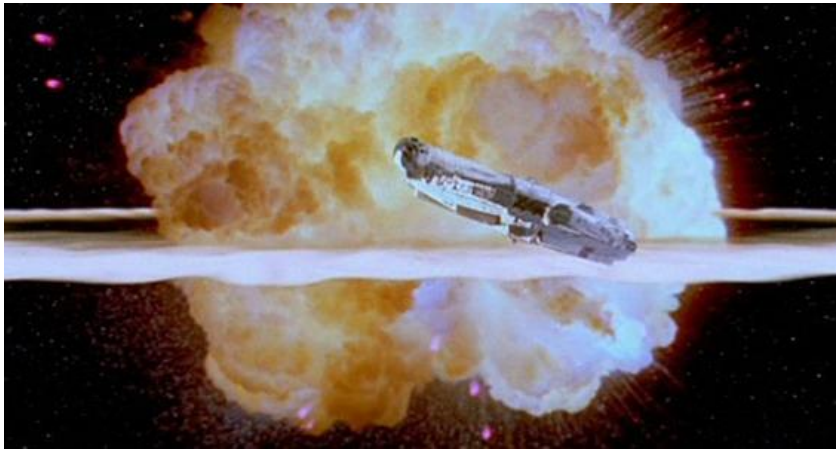


Antimicrobial resistance in the 21st Century: The Gram-negatives strike back

DR. MICHAEL A. BORG
DIRECTOR OF INFECTION PREVENTION & CONTROL
MATER DEI HOSPITAL - MALTA


STAR WARS
© 2011 Lucasfilm Ltd. & TM.





The good old days

"The dread (of) infections that used to rage through the whole communities is muted…

Their retreat has been rapid since the advent of antibiotics and new vaccines after World War II…"

New York Times report (July 1971)


THE EMPIRE STRIKES BACK
MARK HAMILL · HARRISON FORD · CARRIE FISHER
BILLY DEE WILLIAMS · ANTHONY DANIELS
DAVID PROWSE · KENNY BAKER · PETER MAYHEW · FRANK OZ
IRVIN KERSHNER · GARY KURTZ
LEIGH BRACKETT · LAWRENCE KASDAN · GEORGE LUCAS
GEORGE LUCAS · JOHN WILLIAMS
DOLBY STEREO

ecdc
EUROPEAN CENTRE FOR DISEASE PREVENTION AND CONTROL

PRESS RELEASE

Rates of carbapenem-resistant infections continue to increase in Europe

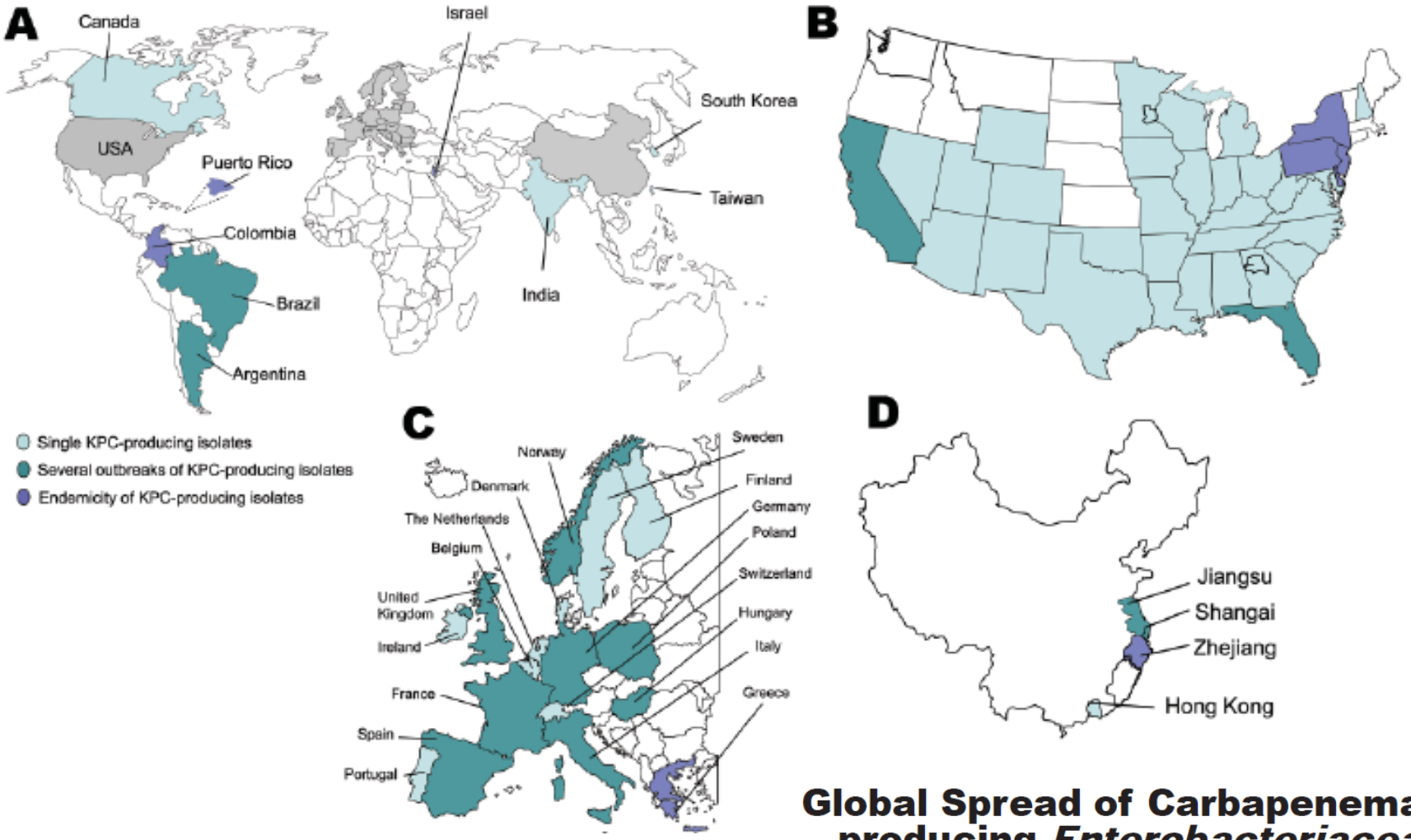
Stockholm, 15 November 2013

- ECDC Director, Dr. Marc Sprenger : *"The data show that carbapenem-resistant infections are increasing in numbers and geographic spread..."*
- The proportion of *Klebsiella pneumoniae* bloodstream infections that is resistant to the carbapenems has increased between 2009 and 2012.

Carbapenemase resistance in Enterobacteriaceae

- Enterobacteriaceae are common healthcare pathogens
- Cause life threatening infections especially in high risk patients within hospitals
  - Including transplant, oncology and intensive care patients
- Worldwide spread of extended spectrum beta-lactamase producing strains since 2000
- Carbapenems are essential for empiric and therapeutic treatment
  - Carbapenemase producing strains render treatment ineffective

Class A carbapenemases (KPC)



Global Spread of Carbapenemase-producing *Enterobacteriaceae*

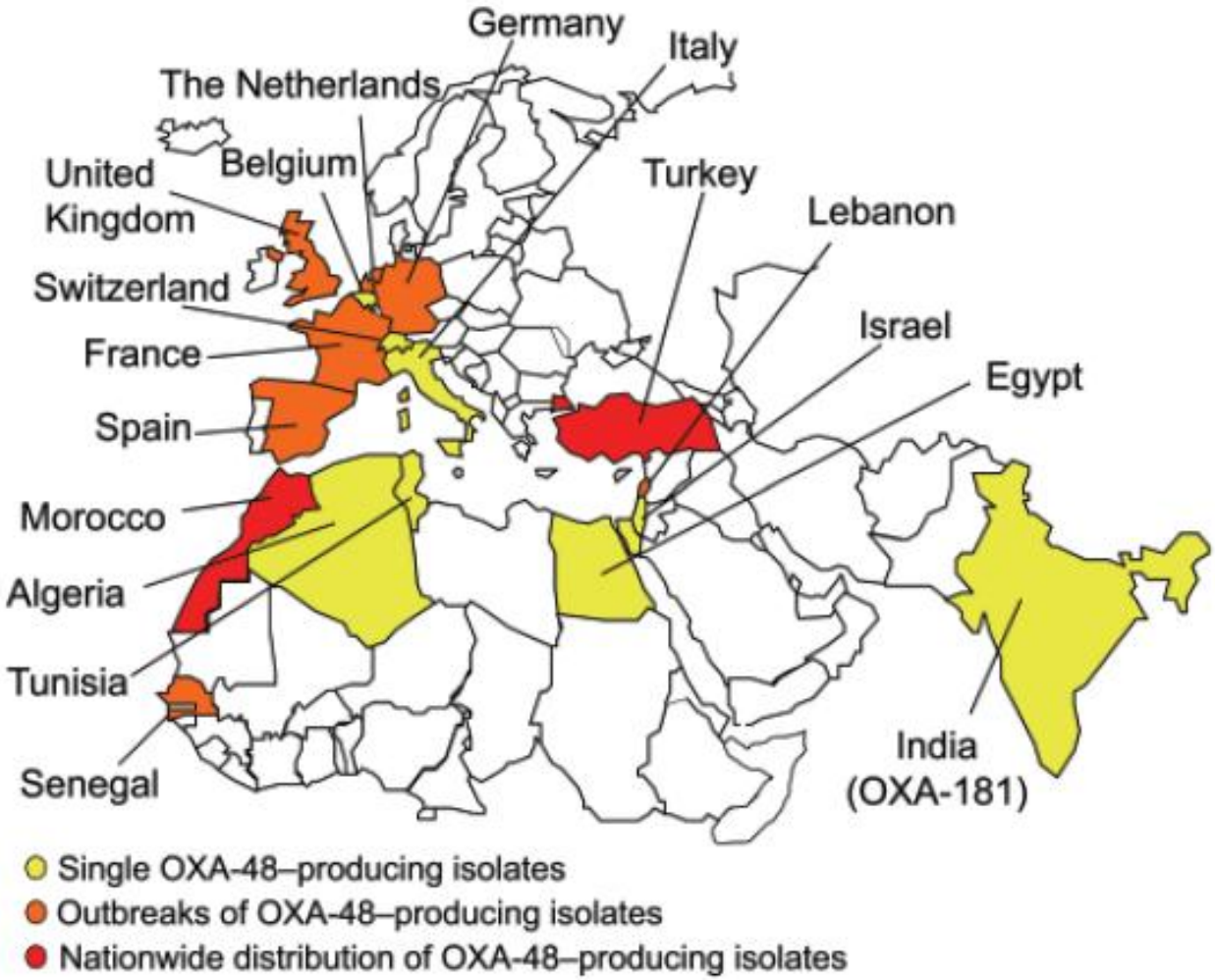
Patrice Nordmann, Thierry Naas, and Laurent Poirel

Emerging Infectious Diseases • www.cdc.gov/eid • Vol. 17, No. 10, October 2011

Class D carbapenemases

- Produce enzymes of the OXA-48 type
- Reported mainly from E. coli and Klebsiella pneumoniae
- Most difficult to identify and prevalence may be underestimated
  - Not inhibited by EDTA or clavulanic acid

OXA-48



Global Spread of Carbapenemase-producing *Enterobacteriaceae*

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Emerging Infectious Diseases • www.cdc.gov/eid • Vol. 17, No. 10, October 2011

J Antimicrob Chemother 2012
doi:10.1093/jac/dks167
Advance Access publication 10 May 2012

Importation of OXA-48-producing *Klebsiella pneumoniae* from Kuwait

Laurent Poirel[1], Etienne Carbonnelle[2], Sandrine Bernabeu[1], Laurent Gutmann[2], Vincent Rotimi[3] and Patrice Nordmann[1]*

[1]*Service de Bactériologie-Virologie, INSERM U914 'Emerging Resistance to Antibiotics', Hôpital de Bicêtre, Assistance Publique/ Hôpitaux de Paris, Faculté de Médecine et Université Paris-Sud, 78 rue de Général Leclerc, K.-Bicêtre, France;* [2]*Service de Bactériologie,*

23rd ECCMID

ESCMID EUROPEAN SOC MICROBIOLOGY

Home - 28.04.2013 - Carbapenemases type OXA, VIM and IMP

Carbapenemases type OXA, VIM and IMP

Sunday, April 28, 2013, 12:30 - 13:30

Emergence of OXA-48-producing enterobacterial isolates in Malta

L. Poirel*, N. Nestorova, E. Rondinaud, J. Haider, P. Caruana, P. Nordmann (Le Kremlin Bicetre, FR; M

International Journal of Infectious Diseases
Volume 17, Issue 12 , Pages e1130-e1133, December 2013

The emergence of OXA-48- and NDM-1-positive *Klebsiella pneumoniae* in Riyadh, Saudi Arabia

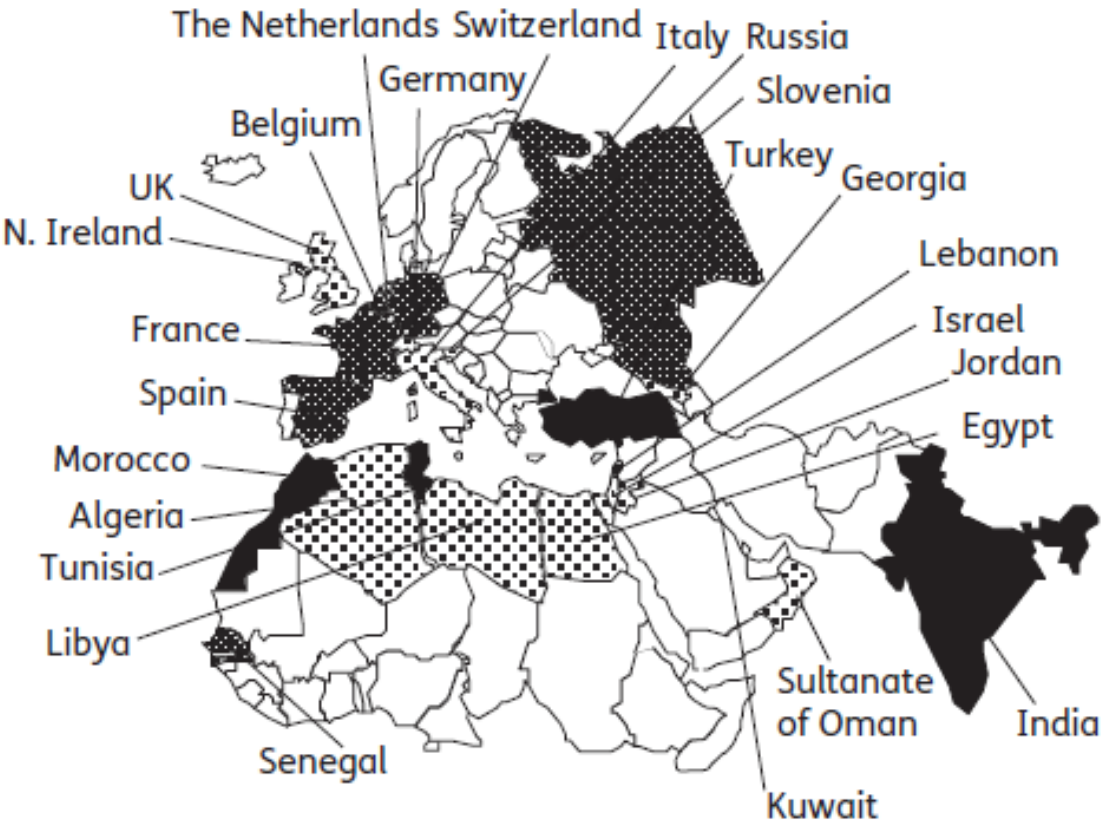
Atef Shibl, Mohamed Al-Agamy, Ziad Memish, Abiola Senok, Shamshad Abdul Khader, Abdullah Assiri

J Antimicrob Chemother 2012; **67**: 1597–1606
doi:10.1093/jac/dks121 Advance Access publication 11 April 2012

Journal of Antimicrobial Chemotherapy

OXA-48-like carbapenemases: the phantom menace

Laurent Poirel*, Anaïs Potron and Patrice Nordmann



OXA-48 management

- Hydrolise carbapenems weakly but may incorporate ESBL and permeability defects
- Efficacy of carbapenems to treat infections with Class D carbapenemases with low level resistance remains debatable
  - Treatment failure with imipenem reported
- Due to variable resistance, treatment usually needs to be done on case by case basis.

PRESS RELEASE

Rates of carbapenem-resistant infections continue to increase in Europe

Stockholm, 15 November 2012

- A new serious concern is the emergence and spread of carbapenem-resistant *Acinetobacter* species, which is above 25% in eight of 18 countries reporting data.
- This indicates even more seriously limited options for treatment of patients with *Acinetobacter* infections.

THE UNIVERSITY OF QUEENSLAND AUSTRALIA | UQCCR University of Queensland Centre for Clinical Research

Molecular Epidemiology of carbapenem non-susceptible *Acinetobacter baumannii* isolates from the Gulf Cooperation Council States

Zowawi HM[1,2*], Balkhy HH[2], AlJohani S[2], Al-Jindan RY[3], Dashti AA[4], Aljardani A[5], AlSalman J[6], Ebrahim E[7], Alfaresi M[8,9], Sidjabat H[1], Paterson DL[1]

JMM Journal of Medical Microbiology

JCM Journals.ASM.org

CASE REPORT

First Clinical Cases of OXA-48-Producing Carbapenem-Resistant *Klebsiella pneumoniae* in the United States: the "Menace" Arrives in the New World

Amy J. Mathers,[a,b] Kevin C. Hazen,[b,c] Joanne Carroll,[b] Anthony J. Yeh,[a] Heather L. Cox,[a] Robert A. Bonomo,[d] Costi D. Sifri[a,e]

Division of Infectious Diseases and International Health, Department of Medicine, University of Virginia Health System, Charlottesville, Virginia, USA[a]; Department of Pathology, University of Virginia Health System, Charlottesville, Virginia, USA[b]; Department of Pathology, Duke University Health System, Durham, North Carolina, USA[c]; Research Service and Infectious Diseases Section, Louis Stokes Cleveland Department of Veterans Affairs Medical Center, Cleveland, Ohio, USA[d]; Office of Hospital Epidemiology, University of Virginia Health System, Charlottesville, Virginia, USA[e]

Full Text

A. A. Alsultan, B. A. Evans, E. A. Elsayed, S. I. Al-Thawadi, A. Y. Al-Taher, S. G. B. Amyes, A. M. Al-Dughaym, and A. Hamouda

High frequency of carbapenem-resistant *Acinetobacter baumannii* in patients with diabetes mellitus in Saudi Arabia

J Med Microbiol June 2013 62:885–888;

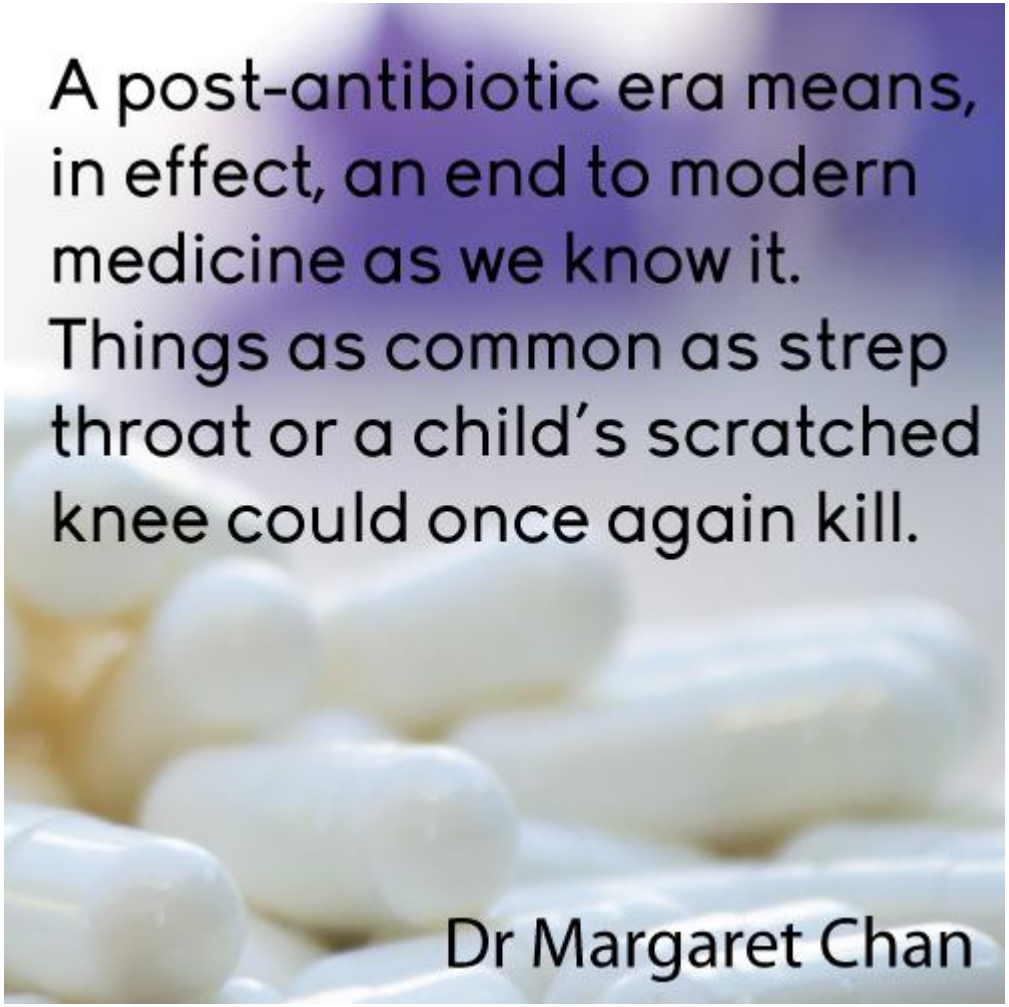
AAC Journals.ASM.org

Wide Dissemination of GES-Type Carbapenemases in *Acinetobacter baumannii* Isolates in Kuwait

Rémy A. Bonnin,[a] Vincent O. Rotimi,[b] Mona Al Hubail,[b] Elise Gasiorowski,[a] Noura Al Sweih,[b] Patrice Nordmann,[a] Laurent Poirel[a]

Service de Bactériologie-Virologie, INSERM U914, Emerging Resistance to Antibiotics, Hôpital de Bicêtre, Assistance Publique/Hôpitaux de Paris, Faculté de Médecine et Université Paris-Sud, Le Kremlin-Bicêtre, France[a]; Department of Microbiology, Faculty of Medicine, Kuwait University, Safat, Kuwait[b]

A return to the post-antibiotic era?



Acinetobacter baumanii

- ✓ Transmissible organism with prolonged environmental survival

JOURNAL OF CLINICAL MICROBIOLOGY, July 1998, p. 1938–1941 Vol. 36, No. 7
0095-1137/98/$04.00+0

Survival of *Acinetobacter baumannii* on Dry Surfaces: Comparison of Outbreak and Sporadic Isolates

A. JAWAD,[1] H. SEIFERT,[2] A. M. SNELLING,[1] J. HERITAGE,[1]* AND P. M. HAWKEY[1]

Strain no.	Site of isolation	Outbreak[a]	Mean survival time (days) ± SD[b]
St-284	Blood	G-III	22 ± 4.42
St-14733	Blood	G-III	31 ± 0.71
St-1650	Blood	G-X	25 ± 1.14
St-1954	Blood	G-X	27 ± 0.71
St-2312	Blood	G-VIII	27 ± 1.14
St-8195	Catheter	G-VIII	21 ± 3.53
St-11681	Blood	G-VIII	21 ± 1.14
St-7961	Blood	G-VIII	23 ± 4.42
St-14970	Catheter	G-V	28 ± 4.42
St-15598	Catheter	G-V	26 ± 2.12
St-16706	Blood	G-IV	26 ± 1.14
St-20820	Blood	G-IV	30 ± 2.82
St-21359	Catheter	G-IV	32 ± 1.14
St-17093	Blood	G-VI	27 ± 2.12
V-7459	Tracheal aspirate	G-VI	26 ± 0.71

Acinetobacter baumanii

- ✓ Transmissible organism with prolonged environmental survival
- ✓ Significant mortality & morbidity

Impact on mortality

- Systematic review of matched case-control and cohort studies.
- Six matched case-control studies included.
- **Attributable mortality** of patients with AB infection increased by:
  - **7.8% to 23%** in hospital wards
  - **10% to 43%,** in intensive care.
- "Although definitive statements about the mortality attributable to the acquisition of *A. baumannii* cannot be made from the available studies because of their methodological heterogeneity, the reviewed data suggest that **infection with or acquisition of *A. baumannii* seems to be associated with increased mortality"**

Falagas ME, Bliziotis IA, Siempos II. *Crit Care*. 2006

Acinetobacter baumanii

- ✓ Transmissible organism with prolonged environmental survival
- ✓ Significant mortality & morbidity
- ✓ Rapid development of resistance

OPEN ACCESS Freely available online PLoS GENETICS

Comparative Genomics of Multidrug Resistance in *Acinetobacter baumannii*

Pierre-Edouard Fournier[1¤*], David Vallenet[2], Valérie Barbe[2], Stéphane Audic[1], Hiroyuki Ogata[1], Laurent Poirel[3], Hervé Richet[4], Catherine Robert[4], Sophie Mangenot[2], Chantal Abergel[1], Patrice Nordmann[3], Jean Weissenbach[2], Didier Raoult[4], Jean-Michel Claverie[1*]

- Genome sequencing of the French epidemic strain AYE
- Identified 52 genes associated with resistance,
  - including 17 genes not previously described in A. baumannii.
- 86% of resistance genes were clustered in a “resistance island”
  - Built through the insertion of broad host-range mobile genetic elements originating from Pseudomonas, Salmonella, and Escherichia.
  - Similar structure in the genome of susceptible strain SDF, exhibiting mobility-associated genes but no resistance markers.
  - Specific hotspot of genomic instability in the A. baumannii genome

OPEN ACCESS Freely available online PLoS GENETICS

Comparative Genomics of Multidrug Resistance in *Acinetobacter baumannii*

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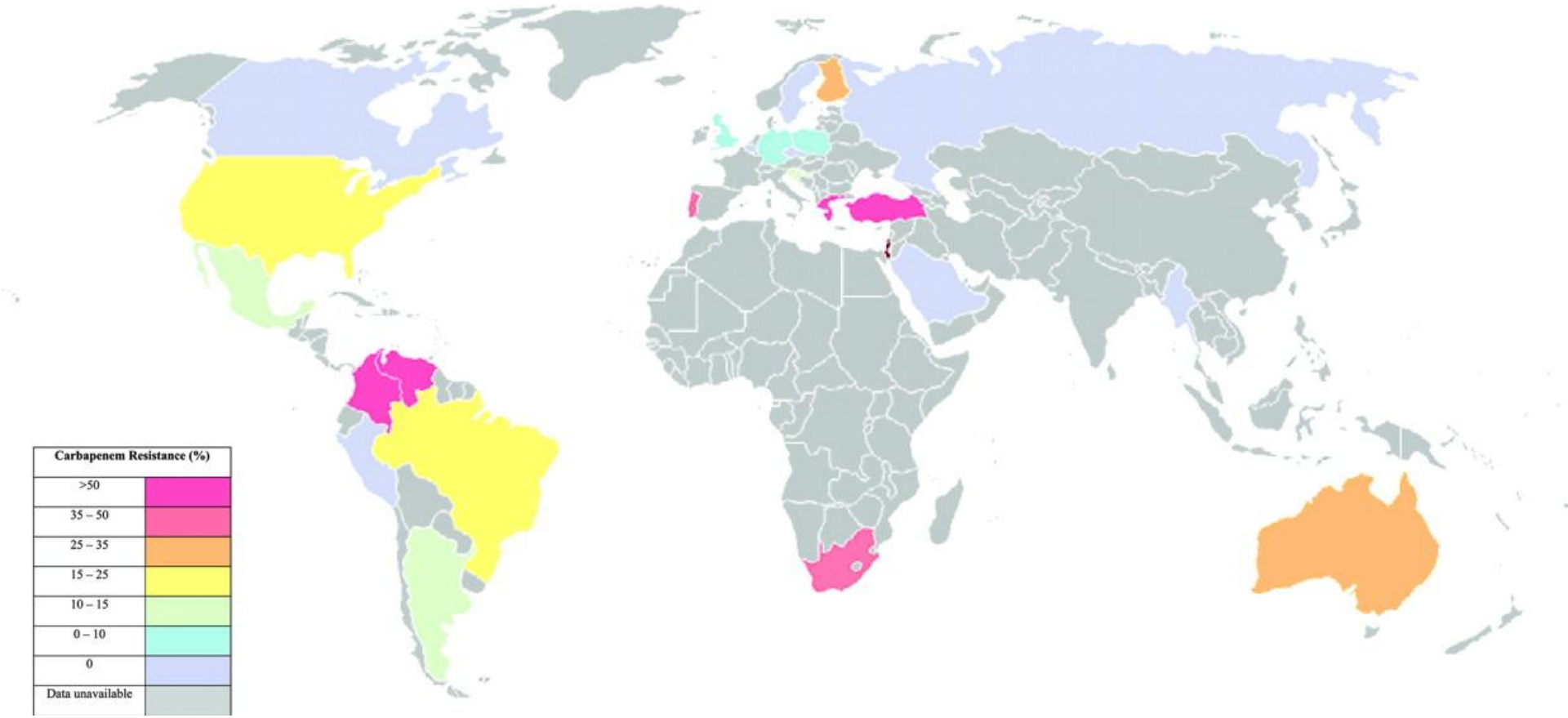
- Identification of several putative resistance genes despite not exhibiting the associated phenotype
  - maintenance of spare copies of ‘‘ready-to-optimize’’ resistance genes, perhaps selected by exposure to sub-inhibitory levels of the drug in the environment,
- Ability to ‘‘switch’’ its genomic structure when under antibacterial pressure,
  - such as in hospital intensive care units.

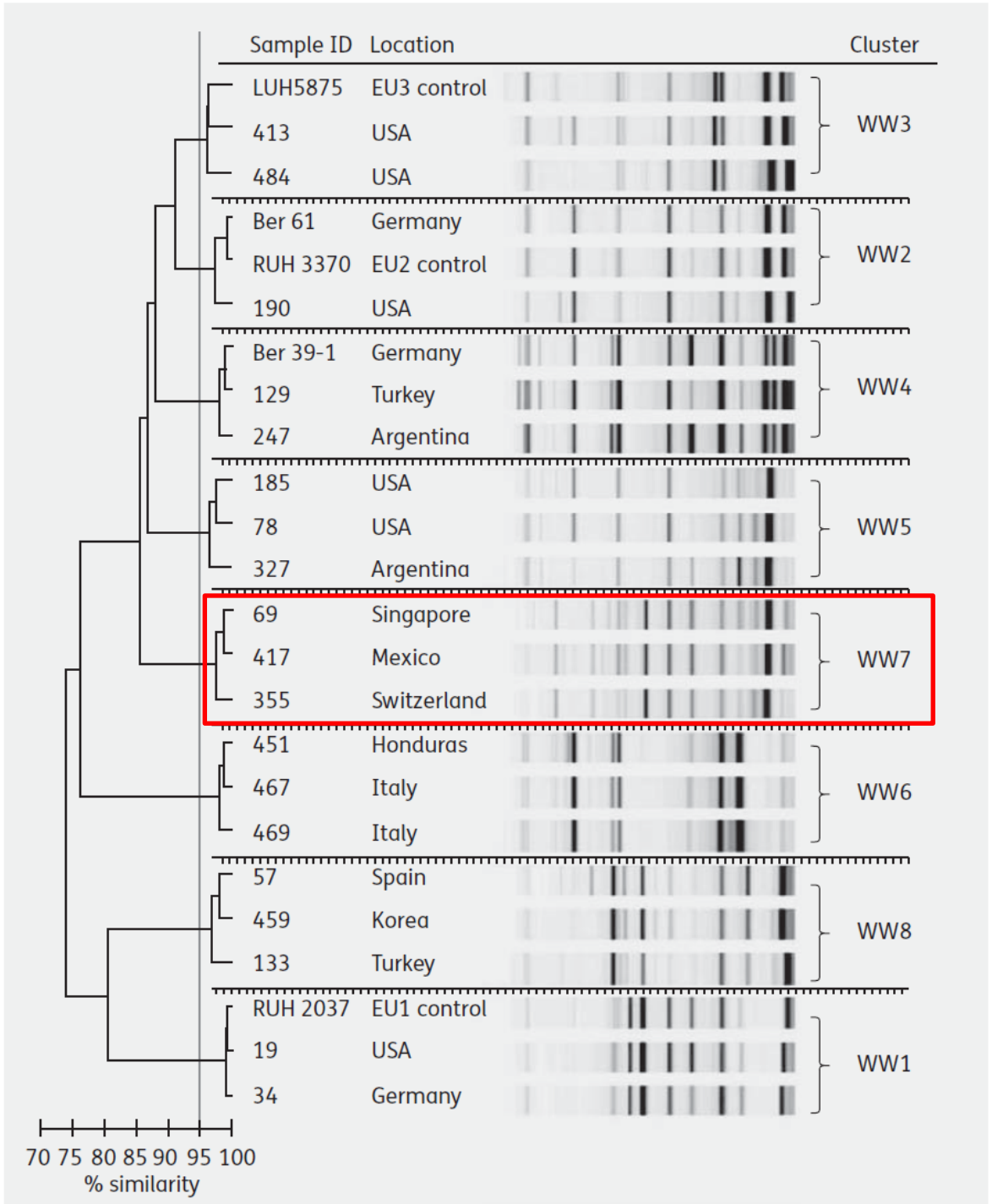
Acinetobacter baumanii

- ✓ Transmissible organism with prolonged environmental survival
- ✓ Significant mortality & morbidity
- ✓ Rapid development of resistance
- ✓ Increasing global epidemiology

Carbapenem resistance in A. baumanii (MYSTIC study 2004)



Perez F et al. Antimicrob. Agents Chemother. 2007;51:3471-3484



J Antimicrob Chemother 2010; **65**: 233–238
doi:10.1093/jac/dkp428 Advance publication 8 December 2009

Journal of Antimicrobial Chemotherapy

Global spread of carbapenem-resistant *Acinetobacter baumannii*

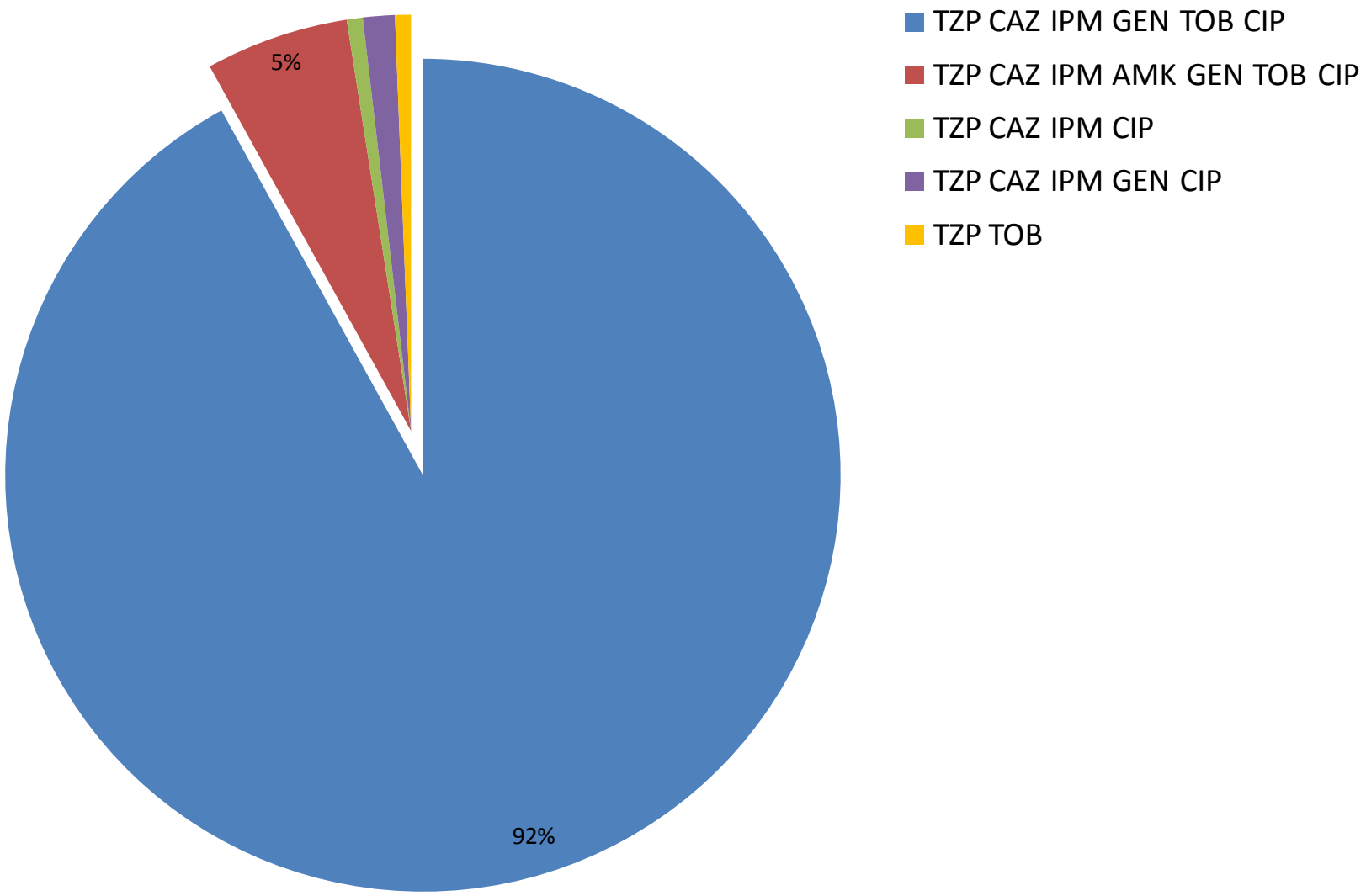
Paul G. Higgins[1]*, Cathrin Dammhayn[1], Meredith Hackel[2] and Harald Seifert[1]

- Effective spread of clones between different countries and often widely distant regions

Acinetobacter baumanii

- ✓ Transmissible organism with prolonged environmental survival
- ✓ Significant mortality & morbidity
- ✓ Rapid development of resistance
- ✓ Increasing global epidemiology
- ✓ Challenges in instituting effective treatment
  - – extensive multi-resistance
  - – toxicity of therapeutic options

Malta isolates: resistance profiles



Therapeutic options

- Colistin
  - Often the only realistic therapeutic option
  - Highly active against *A. baumannii*
    - including carbapenem resistant strains.
  - However, heteroresistance has been described and has been associated with clinical failure.
    - Patients who had prior receipt of colistin were more likely to have heteroresistant strains
  - Biggest limitation is nephrotoxicity

Incidence of and Risk Factors for Colistin-Associated Nephrotoxicity in a Large Academic Health System

Clinical Infectious Diseases 2011;53(9):879–884

Jason M. Pogue,[1,2] Jiha Lee,[2] Dror Marchaim,[2,3] Victoria Yee,[2] Jing J. Zhao,[4] Teena Chopra,[2,3] Paul Lephart,[5] and Keith S. Kaye[2,3]

- 43% patients developed nephrotoxicity
  - RIFLE criteria: Risk (13%), Injury (17%), or Failure (13%)
- Independent predictors for nephrotoxicity
  - colistin dose of ≥5.0 mg/kg per day of IBW (OR = 23.41)
  - receipt of concomitant rifampin (OR = 3.81)
  - coadministration of ≥3 concomitant nephrotoxins (OR = 6.80)

Acinetobacter baumanii

- ✓ Transmissible organism with prolonged environmental survival
- ✓ Significant mortality & morbidity
- ✓ Rapid development of resistance
- ✓ Increasing global epidemiology
- ✓ Challenges in instituting effective treatment
  - – extensive multi-resistance
  - – toxicity of therapeutic options

Post-antibiotic era

Prevention of MDR-AB

ESCMID EUROPEAN SOCIETY OF CLINICAL MICROBIOLOGY AND INFECTIOUS DISEASES

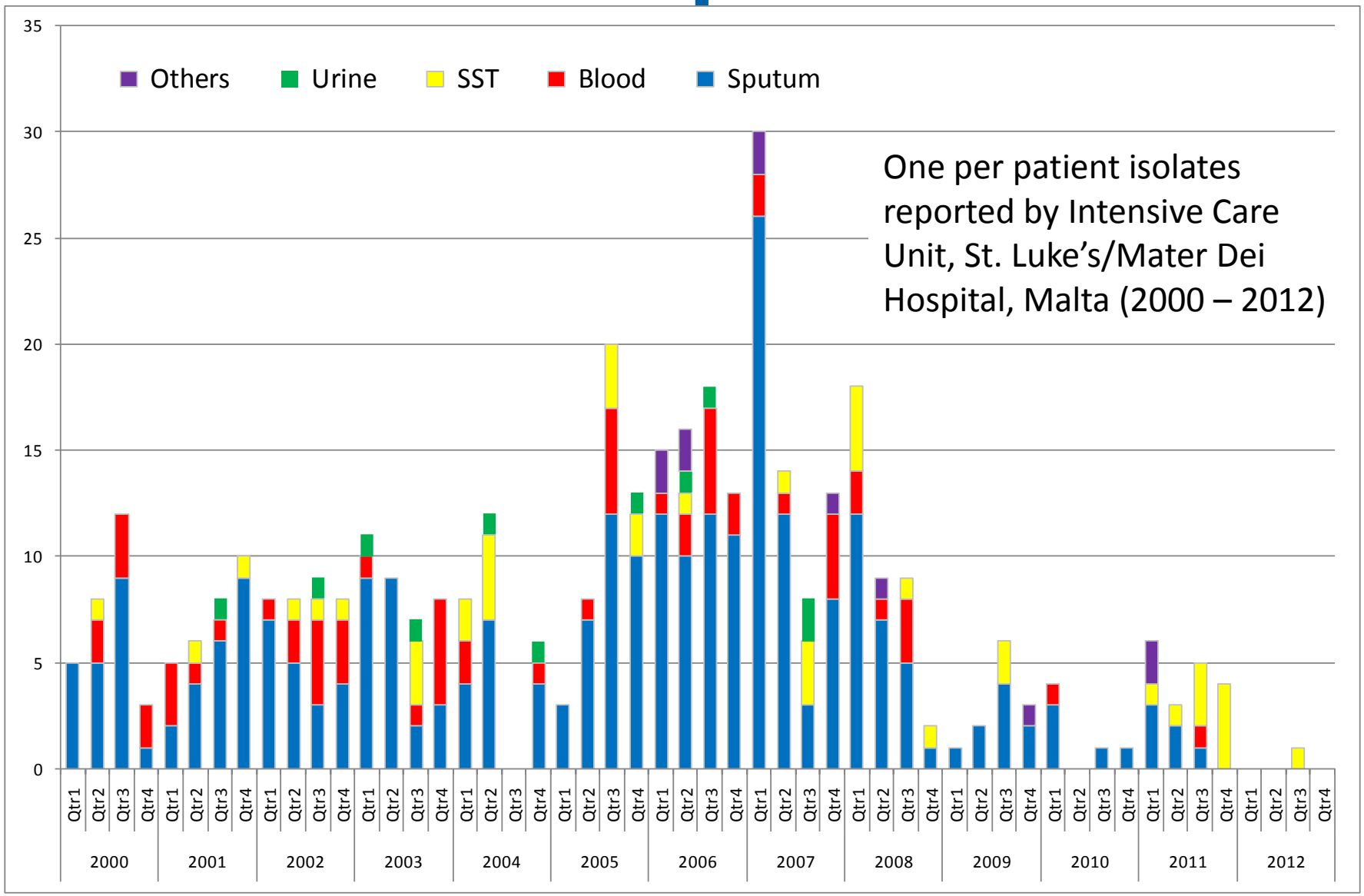
ENDEMIC SETTINGS:

- Implementation of hand hygiene programme and contact precaution;
- Implementation of education programme and antibiotic stewardship should be added in a multifaceted approach.

EPIDEMIC SETTINGS:

- Implementation of hand hygiene programme, contact precaution, and isolation room;
- Implementation of environmental cleaning should be added in a multifaceted approach.

Acinetobacter baumanii control is not impossible

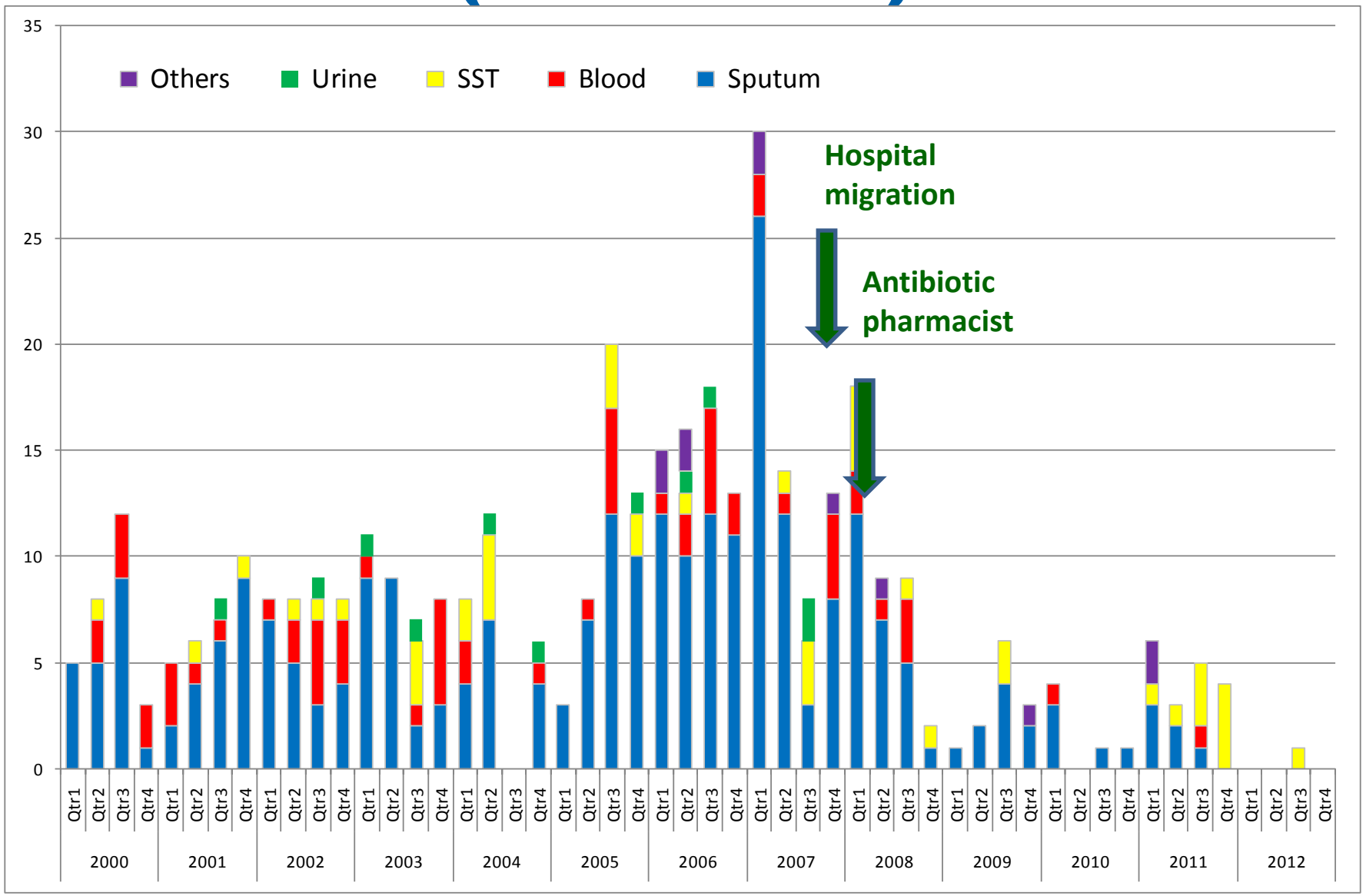


St. Luke's Hospital

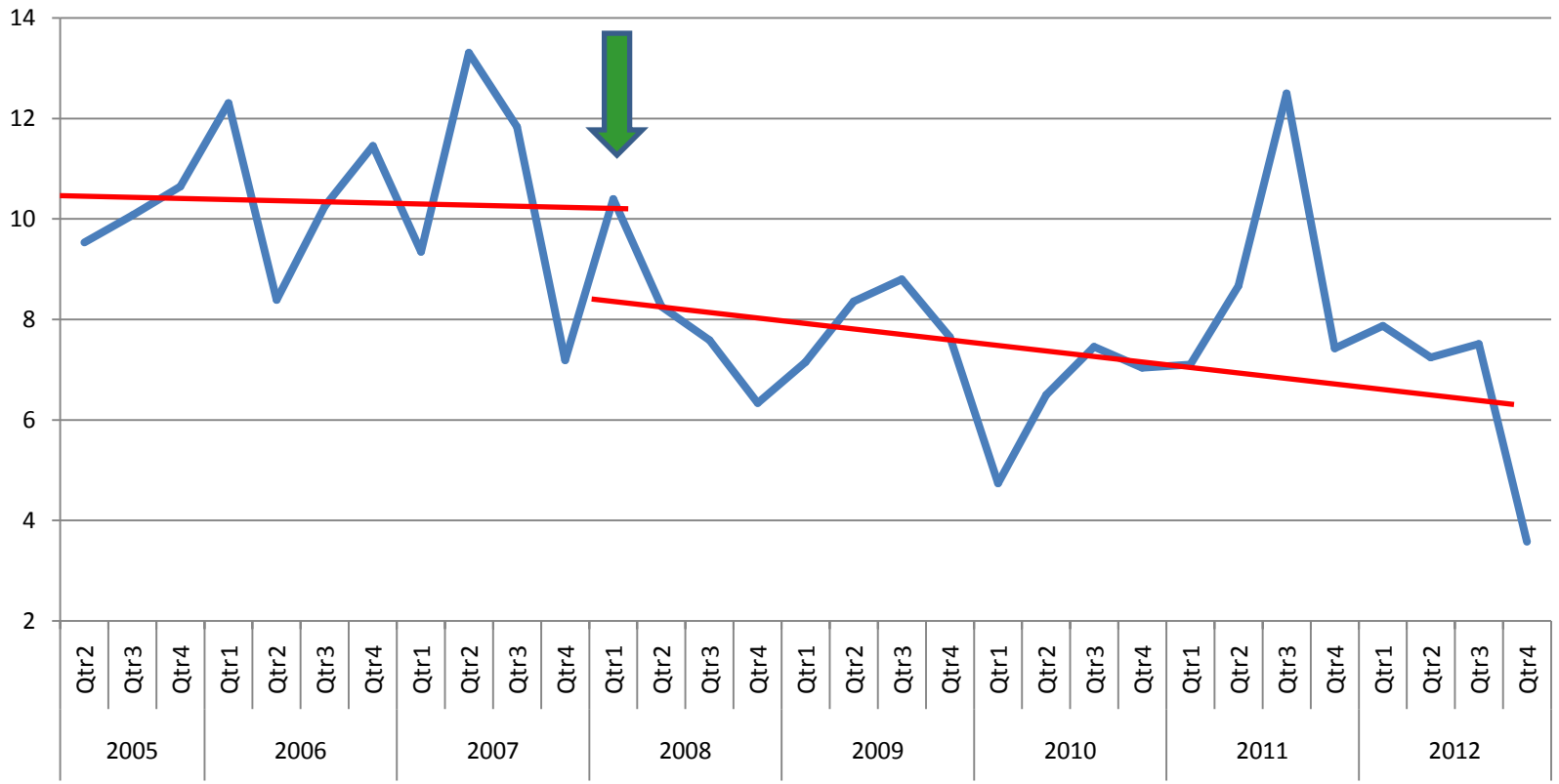
November 2007 →

Mater Dei Hospital

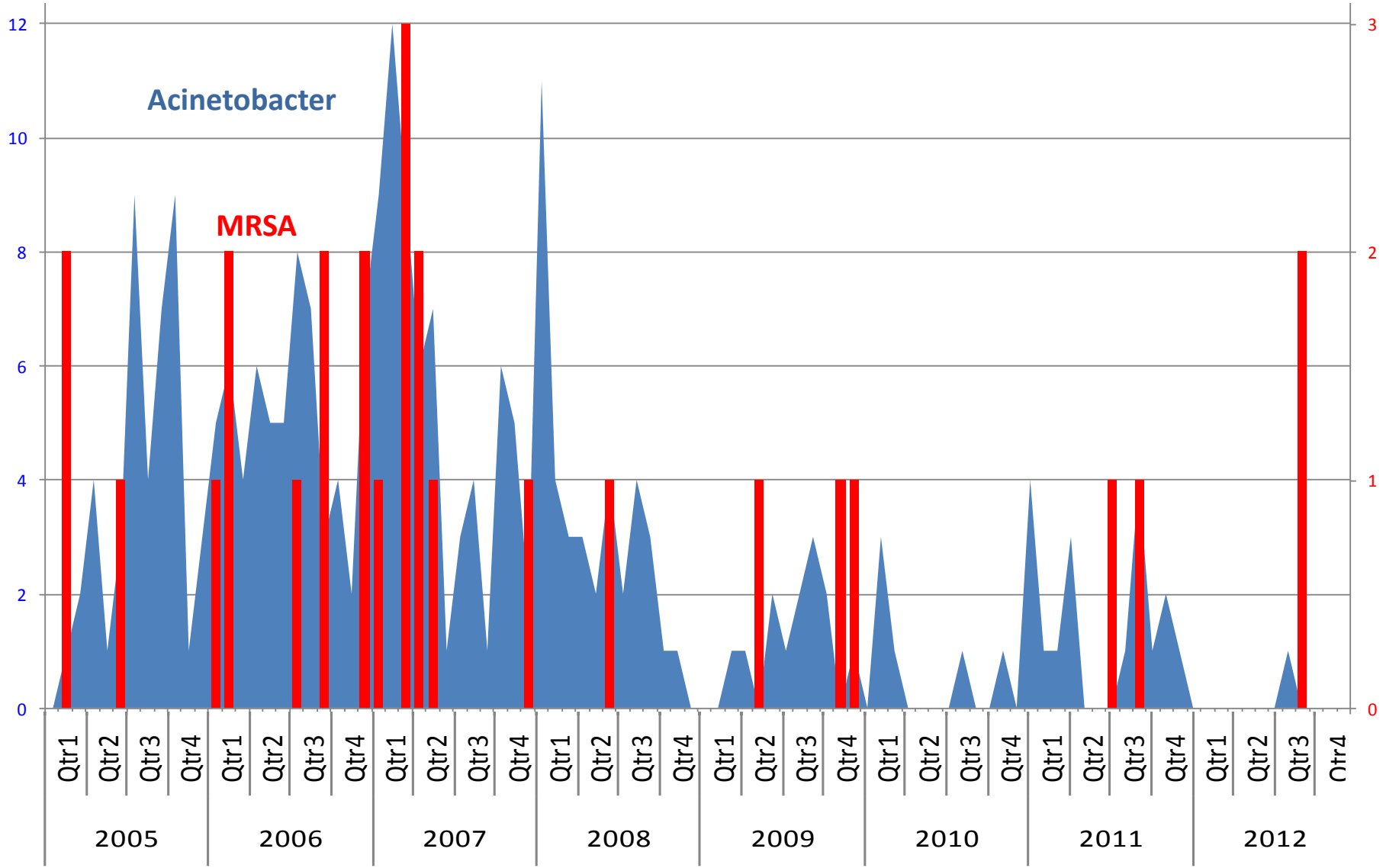
Acinetobacter baumanii ICU cases: (2000 – 12)



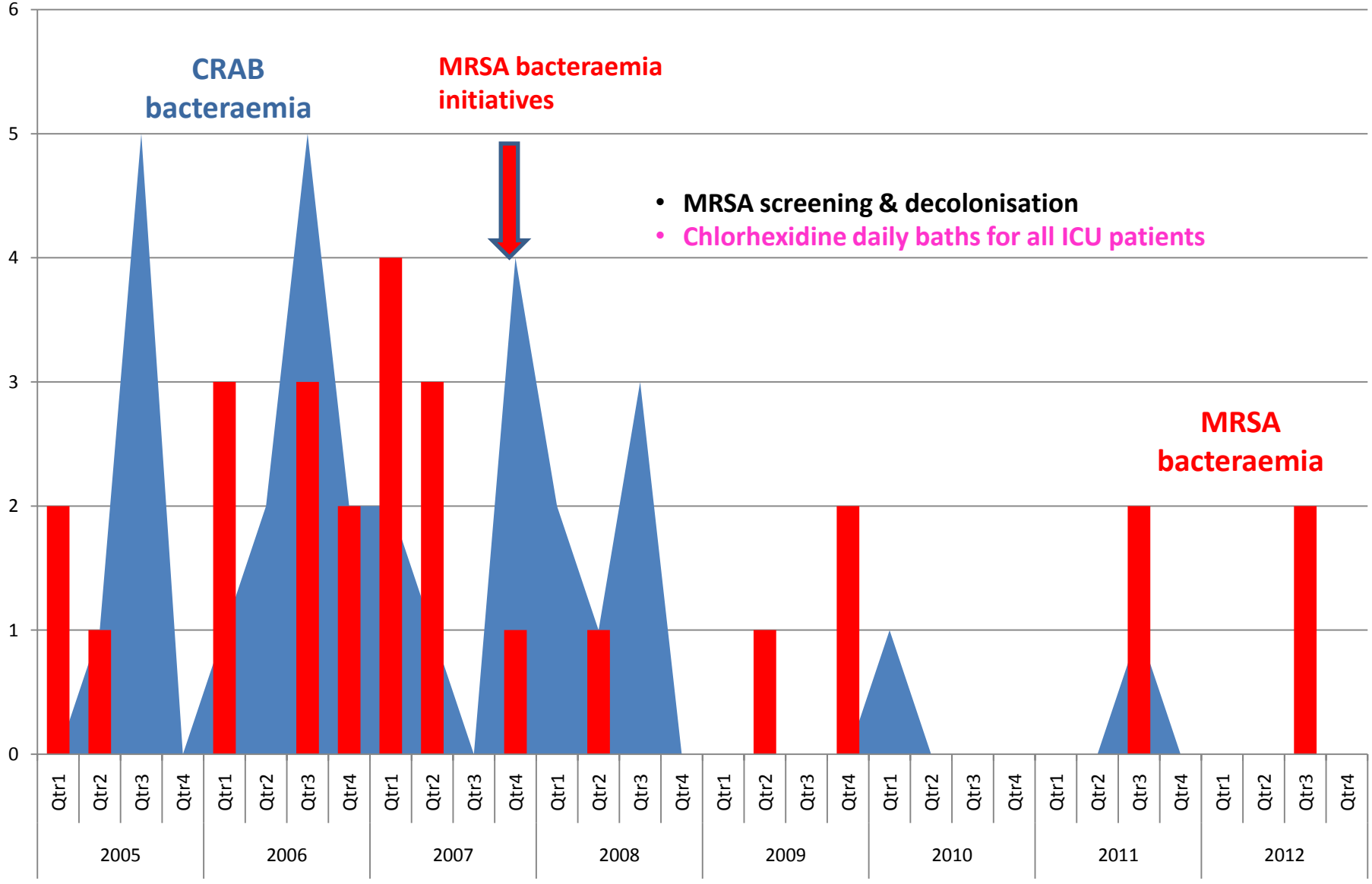
Carbapenem consumption DDD/100BD



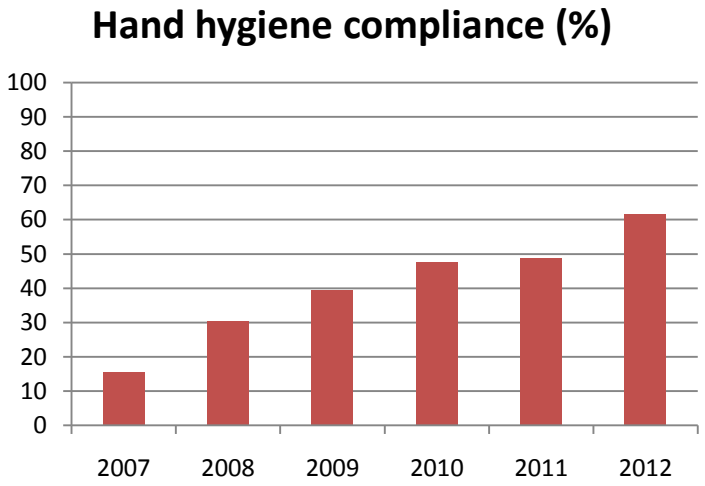
Acinetobacter baumanii & MRSA bacteraemia epidemiology (ICU MDH)

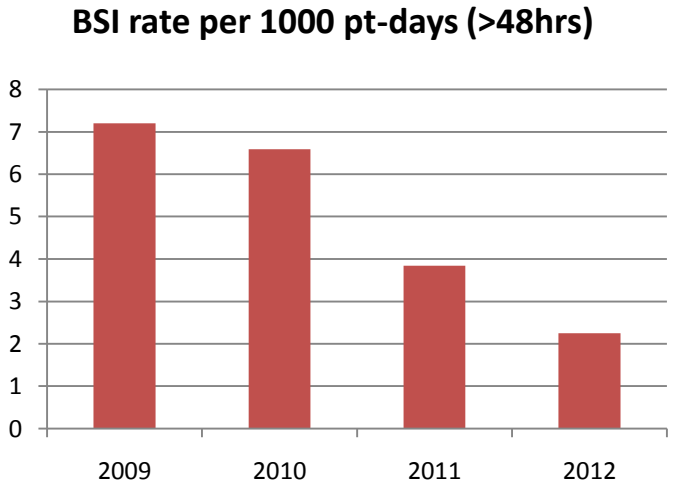


CRAB & MRSA bacteraemia epidemiology (ICU MDH)



Possible confounders





Journal of Hospital Infection (2007) 67, 149–155

Available online at www.sciencedirect.com

ScienceDirect

www.elsevierhealth.com/journals/jhin

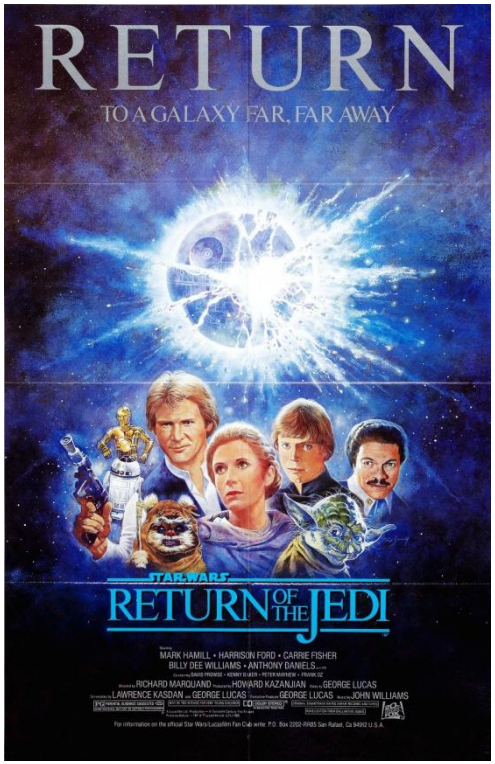
Impact of 4% chlorhexidine whole-body washing on multidrug-resistant *Acinetobacter baumannii* skin colonisation among patients in a medical intensive care unit

A. Borer [a,*], J. Gilad [a], N. Porat [b], R. Megrelesvilli [c], L. Saidel-Odes [a], N. Peled [d], S. Eskira [a], F. Schlaeffer [e], Y. Almog [c]

- Prevalence of ACBA-BSIs decreased from 4.6% to 0.6% (P<0.001; OR: 7.6)
- Incidence of ACBA-BSIs decreased from 7.8 to 1.25 per 100 admissions (85% reduction)

Conclusions

- Multiresistant Gram negatives genuinely threaten to take us back to the pre-antibiotic era
  - Especially in nosocomial Klebsiella pneumoniae and Acinetobacter baumanii
- Few new antibiotics on the horizon
  - B-lactamase inhibitor NXL104 shows some promise
- The key is infection prevention & control
  - You don’t need to be perfect to get success


RETURN
TO A GALAXY FAR, FAR AWAY
STAR WARS
RETURN OF THE JEDI
MARK HAMILL • HARRISON FORD • CARRIE FISHER
BILLY DEE WILLIAMS • ANTHONY DANIELS
RICHARD MARQUAND
HOWARD KAZANJIAN
GEORGE LUCAS
LAWRENCE KASDAN
GEORGE LUCAS
GEORGE LUCAS
JOHN WILLIAMS

Thank you