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Multi-drug resistant *Acinetobacter* (MDRA) Surveillance and Control

Alison Holmes

The National CIPM Centre for Infection Prevention & Management

- The organism and it's epidemiology
- Surveillance
- Control

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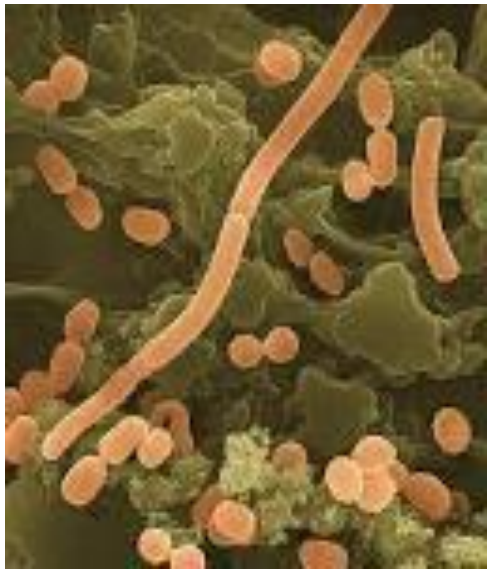
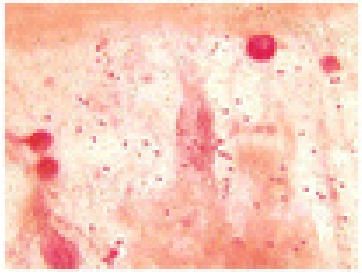
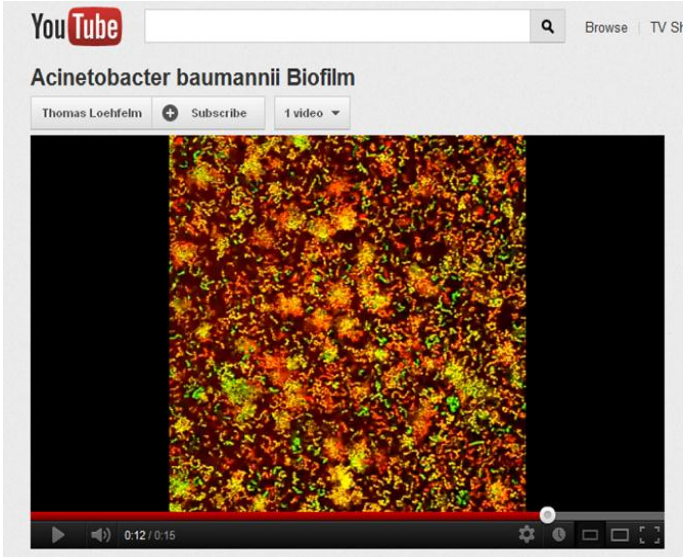
What is it?







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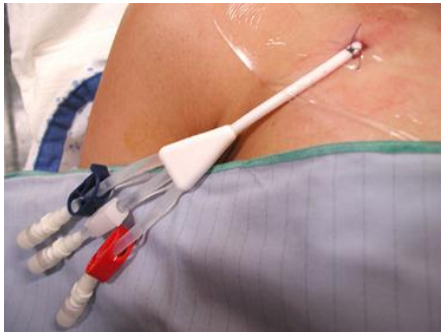

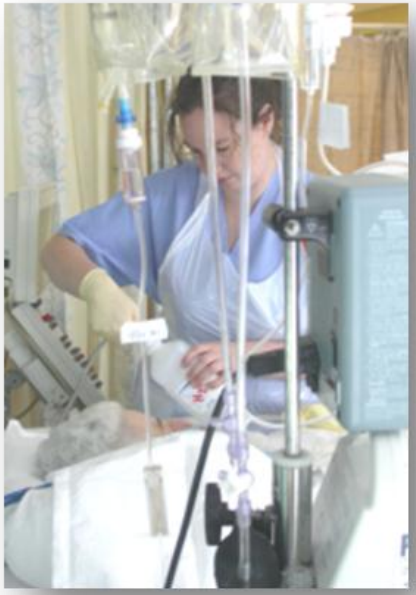

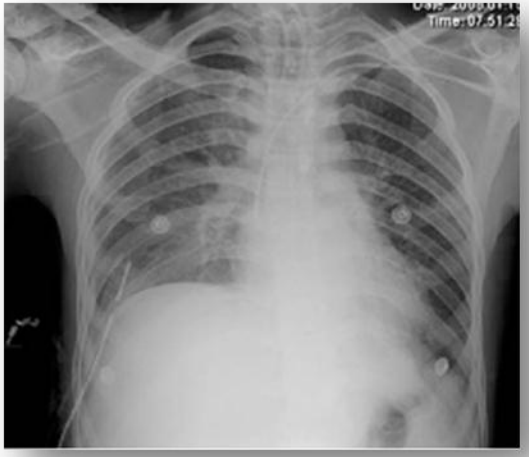

What is it?


NEWSTALK
DRUG-RESISTANT BACTERIA
INSURGENTS IN THE BLOODSTREAM
NEWS 8
CHANNEL

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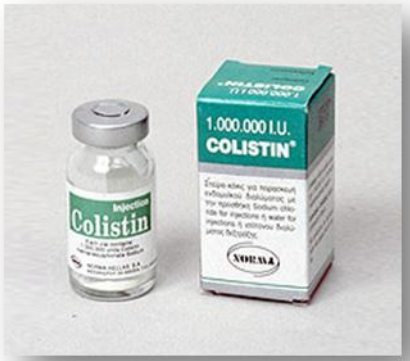
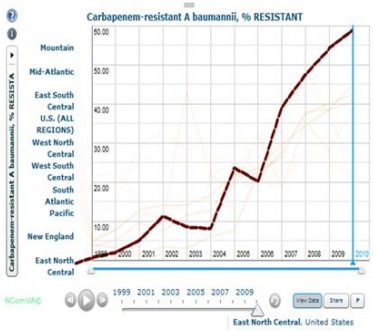
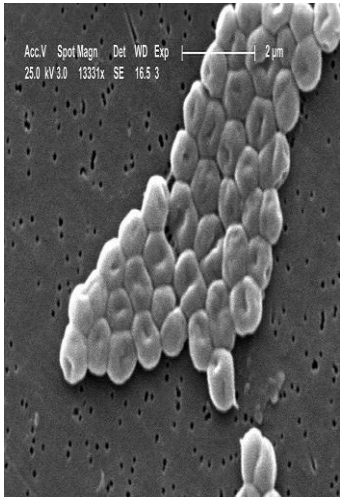
What is it?



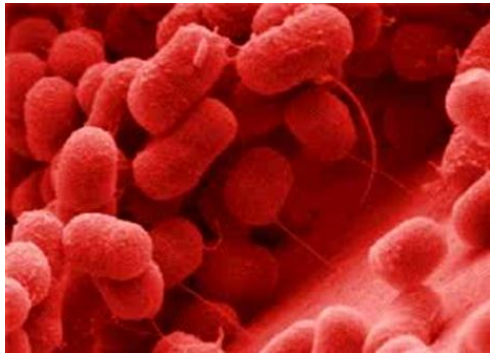


Acinetobacter : The organism

- Aerobic, Gram-negative bacterium, non motile, non fermenting, coccobacillus in stationary phase, rod shaped in rapid growth, forms biofilms and survives environmental dessication for weeks.
- Began to be recognised in 1970s as an opportunistic hospital pathogen, causing outbreaks
- A. baumanii >80% infections
- Infections in ICUs, ventilated patients, burns units
  - Pneumonia
  - Bacteraemia
  - Osteomyelitis (trauma/deep wound infection)
  - Can cause fatal infections in debilitated patients



- Historically, a pathogen of humid climates.
- Since the 1970s, an increasingly common nosocomial problem in temperate climates- where seasonal variation seen
- Years before a concern in ICUs in the US, it was cited as the cause of 17 % of cases of VAP in a Guatemalan ICU
- Most common cause of Nosocomial pneumonia in tertiary care hospitals in Thailand (Werarak P et al Feb 2012)
- Ability to accumulate diverse mechanisms of resistance and emergence of highly resistant strains
- Dramatic clonal outbreaks of MDRA have occurred across the world, some involving multiple hospitals



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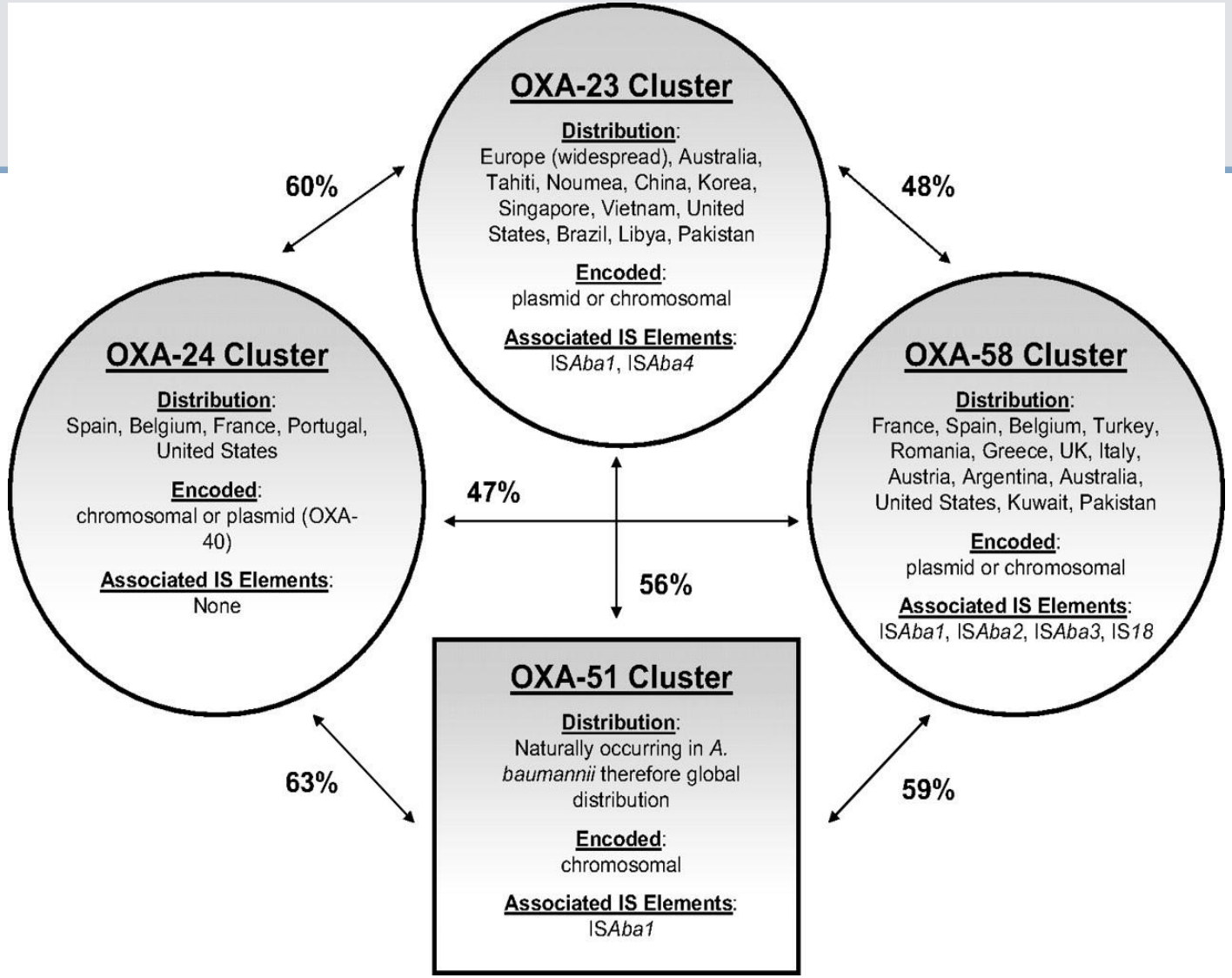
Multiple mechanisms of antibiotic resistance

- Constitutive or acquired via plasmids, integrons, and transposons.
- Methods include:
    1. enzymatic inactivation of antibiotic
    2. modification of antibiotic target sites,
    3. expression of efflux pumps or down regulation porin channel expression.
- Resistance to β-lactams primarily caused by β-lactamase production, including extended spectrum β-lactamases, metallo- β-lactamases and most commonly, **oxacillinases (OXA)…which have carbapenemase activity**
- Antibiotic target site alterations confer resistance to fluoroquinolones (gyrA, parC) and aminoglycosides (arm, rmt), and to a much lesser extent, β-lactams.
- Efflux pumps contribute to resistance against β-lactams, tetracyclines, fluoroquinolones, and aminoglycosides.
- Porin channel deletion contribute to β-lactam resistance and may contribute to rarely seen polymyxin resistance.

- In UK - prior to 2000, virtually all *A. baumannii* isolates were susceptible to carbapenems and very few genotypes appeared to occur in multiple hospitals. These patterns changed with the multicentric isolation of the SE clone, with its variable resistance to imipenem and meropenem.
- The spread of two OXA-23-producing clones represent a further ratcheting of the problem, being more consistently resistant to carbapenems

- Emergence of *A. baumanii* related in part to survival ability and rapid development of resistance to all major antibiotic classes

Summary of the distribution and genetic context of the OXA-type enzymes in *Acinetobacter baumannii.*



Peleg A Y et al. Clin. Microbiol. Rev. 2008;21:538-582

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Common misconceptions…

- ‘ubiquitous in nature’
- ‘recovered easily from soil, water, animals’
- ‘frequent skin* and oro-pharyngeal coloniser’*


Journal of Hospital Infection (2009) 73, 355–363

Available online at www.sciencedirect.com

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REVIEW

Acinetobacter: an old friend, but a new enemy

K.J. Towner*

Department of Clinical Microbiology, Nottingham University Hospitals NHS Trust, Queen's Medical Centre, Nottingham NG7 2UH, UK

Available online 22 August 2009

This may apply to other members of the genus Acinetobacter ..

But not *A. baumanii* (and its close relatives of clinical importance)

*But the in tropics situation e.g. HK 53 % medical students hands carried *A. baumanni* in summer. Chu Y W et al ‘99 J Clin Micro 37,

Factors facilitating Spread

Increased length of hospital stay
Prior antibiotics
Mechanical ventilation
Exposure to patients colonised or infected with *A. baumannii*
Environmental contamination
Understaffing
Poor adherence of staff to hand hygiene

Towner KJ JHI 2009

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Towner KJ JHI 2009

Newsdesk

Reduced infection rates linked to better nurse staffing

Elderly intensive care unit (ICU) patients have lower rates of nosocomial infections in hospitals with better nurse staffing levels and where nurses work fewer overtime hours, say researchers from the Columbia University School of Nursing (New York, NY, USA).

Investigators examined data from the US Centers for Disease Control and Prevention's National Nosocomial Infection Surveillance system protocols and Medicare files on 15 846 elderly patients in 51 ICUs in 31 US hospitals. Additionally, 1095 nurses working at these ICUs were surveyed on working conditions, including measures of staffing (nurse hours per patient per day), overtime use, wages, and nurses' perceptions of working conditions.

"Patients admitted to an ICU with more registered nurse hours per patient day had significantly lower incidence of central-line-associated bloodstream infections, ventilator-associated pneumonia, 30-day mortality, and pressure ulcers", said Patricia Stone, lead author of the study. Increased overtime hours in ICUs were associated with higher rates of catheter-associated urinary tract infections and pressure ulcers, but slightly lower rates of central-line-associated bloodstream infections.

According to Stone, "Improving nurse working conditions using the systems approach is likely to help with nurse retention and recruitment, and this is very important given the magnitude of the nursing shortage we face and what is predicted".

"Several studies have shown that better staffing levels reduce infection. However, sometimes a high infection rate in a hospital or ICU is just a marker of other problems in management—eg, managing staff", said Alison Holmes (Imperial College London, UK). "What is new here is that this research particularly focuses on nurses' overtime in ICUs and the researchers provide some potential solutions", she added.

Stone said "The US Institute of Medicine has recommended a multi-pronged approach to keep patients safe, which includes improving management in the hospital, attention to adequate trained workforce and work processes, and improving the organisational culture. Results from this study support these recommendations."

In the UK, the Healthcare Commission said last month that it will carry out unannounced inspections at 120 National Health Service trusts over the coming year in its biggest ever programme of visits relating to health-care-associated infection. Cases of meticillin-resistant *Staphylococcus aureus* are falling, but there were 55 681 cases of *Clostridium difficile* infection reported in patients aged 65 years and above in England in 2006—an 8% increase on the year before. Assessment managers will look at the cleanliness of the hospital's environment as well as practices that are in place to prevent and manage infection—for example, procedures for isolating patients, hand-washing, and cleaning of equipment.

Jennifer Harwood

For more information on nurse working conditions and patient safety outcomes see MedCare 2007; 45: 571–78; DOI:10.1097/MLR.0b013e318038f617

For more information on the UK Healthcare Commission see http://www.healthcarecommission.org.uk

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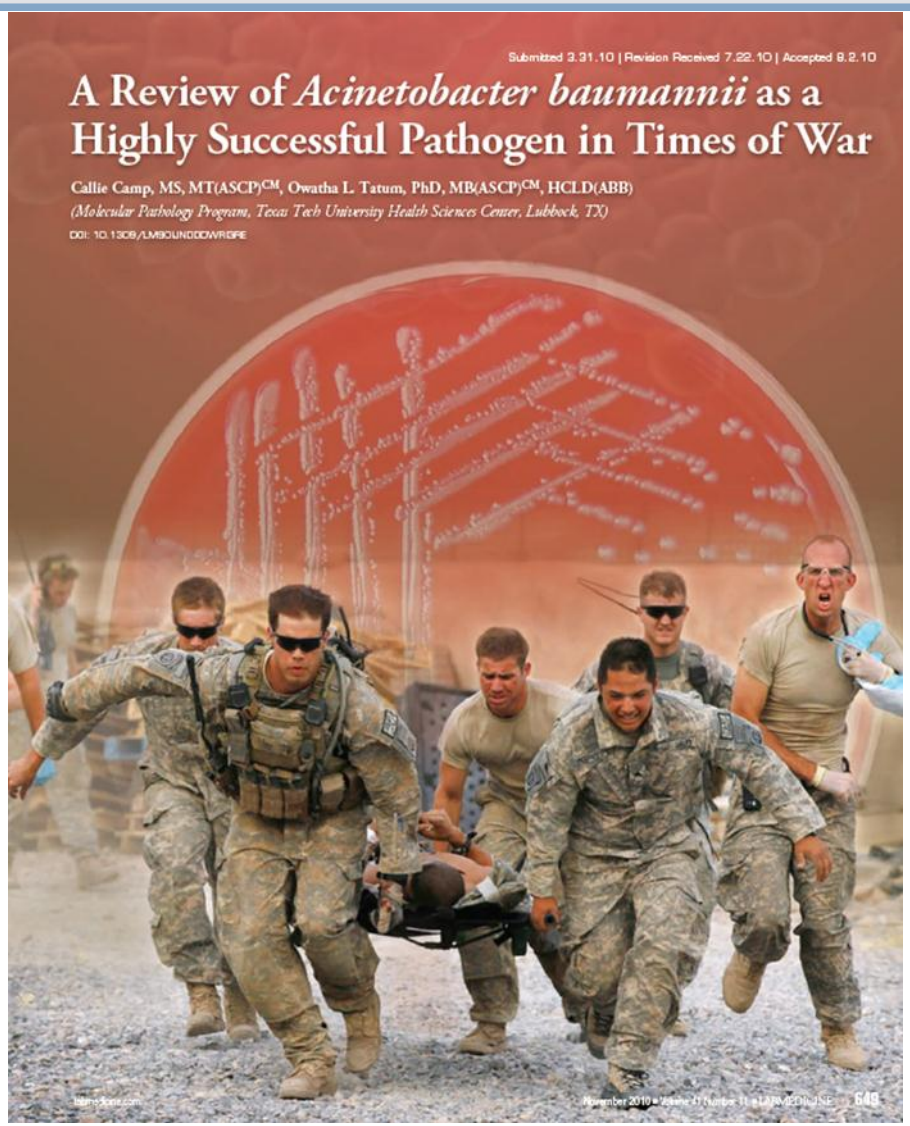
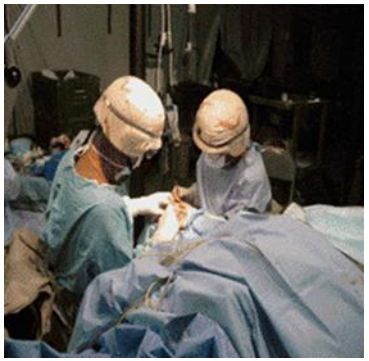


'Iraqibacter'



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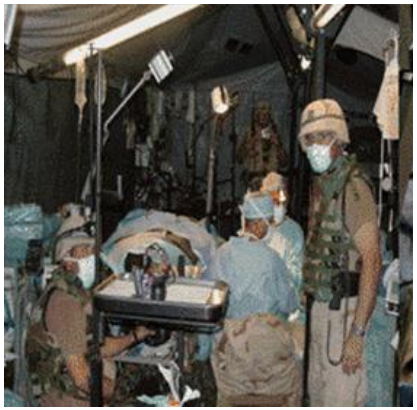
MDRA and Military



- Wounds and burns, bacteraemias
- High throughput, influx of trauma
- High levels broad spectrum antibiotics for trauma injuries
- Little de-escalation or microbiology support
- Antibiotic prescribing intense and without policy
- Much equipment, much contaminated
- Multiple transfers through different units in medical evacuation
- Many procedures along the routes
- MDRA isolated in every hospital on the aeromedical evacuation routes from Iraq and Afghanistan. Spread in units where repatriated
- High pressure lavage…aerosol generating

- Not pre-injury colonisation or inoculation at time of trauma
- Hospital unit is the habitat
- Periodic closures of units/tents for deep clean

International Journal of Antimicrobial Agents 39 (2012) 363–375

Contents lists available at SciVerse ScienceDirect

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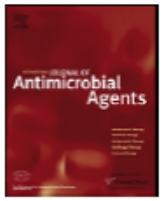

Review

Acinetobacter in modern warfare

M.K. O'Shea [a,b]

[a] Department of Military Medicine, Royal Centre for Defence Medicine, Birmingham, UK
[b] Department of Infectious Diseases & Tropical Medicine, Heartlands Hospital, Birmingham, UK

ARTICLE INFO

Keywords:
Acinetobacter baumannii
Acinetobacter calcoaceticus–A. baumannii (ACB) complex
Acinetobacter baumannii–A. calcoaceticus (ABC) complex
Military
Conflict
Afghanistan
Iraq

ABSTRACT

Increasing appreciation of the role of *Acinetobacter baumannii* in the aetiology of severe nosocomial infections, together with its ability to employ several mechanisms to rapidly develop resistance to multiple classes of antimicrobial agents, has led to growing interest in this organism over recent years. Recognition and subsequent investigation of the significance of pathogenic *Acinetobacter* infections in military personnel sustaining injuries during the conflicts in Afghanistan and Iraq has provided an important contribution to the epidemiology of infections with *Acinetobacter* spp. The following review examines this recent military experience.

- MDRA led to major focus of military on infection control, microbiology support, antibiotic programme …… and MDRA control

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The National CIPM Centre for Infection Prevention & Management

Multi-drug resistant *Acinetobacter* (MDRA)

- Over the past few decades, isolates of *Acinetobacter* spp. have successfully accumulated resistance to penicillins, cephalosporins, quinolones and aminoglycosides
- Between 2003 and 2006, two carbapenemase-resistant strains (SE clone and OXA-23) became prevalent in over 40 UK hospitals
  - OXA-23 clone susceptible only to colistin
  - SE clone susceptibility to carbapenems is variable
  - predominantly in the London area
  - isolates originated mainly from sputum and wound cultures
  - majority from patients in intensive care units

Coelho JM, *et al*. J Clin Microbiol. 2006; 44:3623-3627
Turton JF, *et al.* J Hosp Infect., 2004; 58: 170-179

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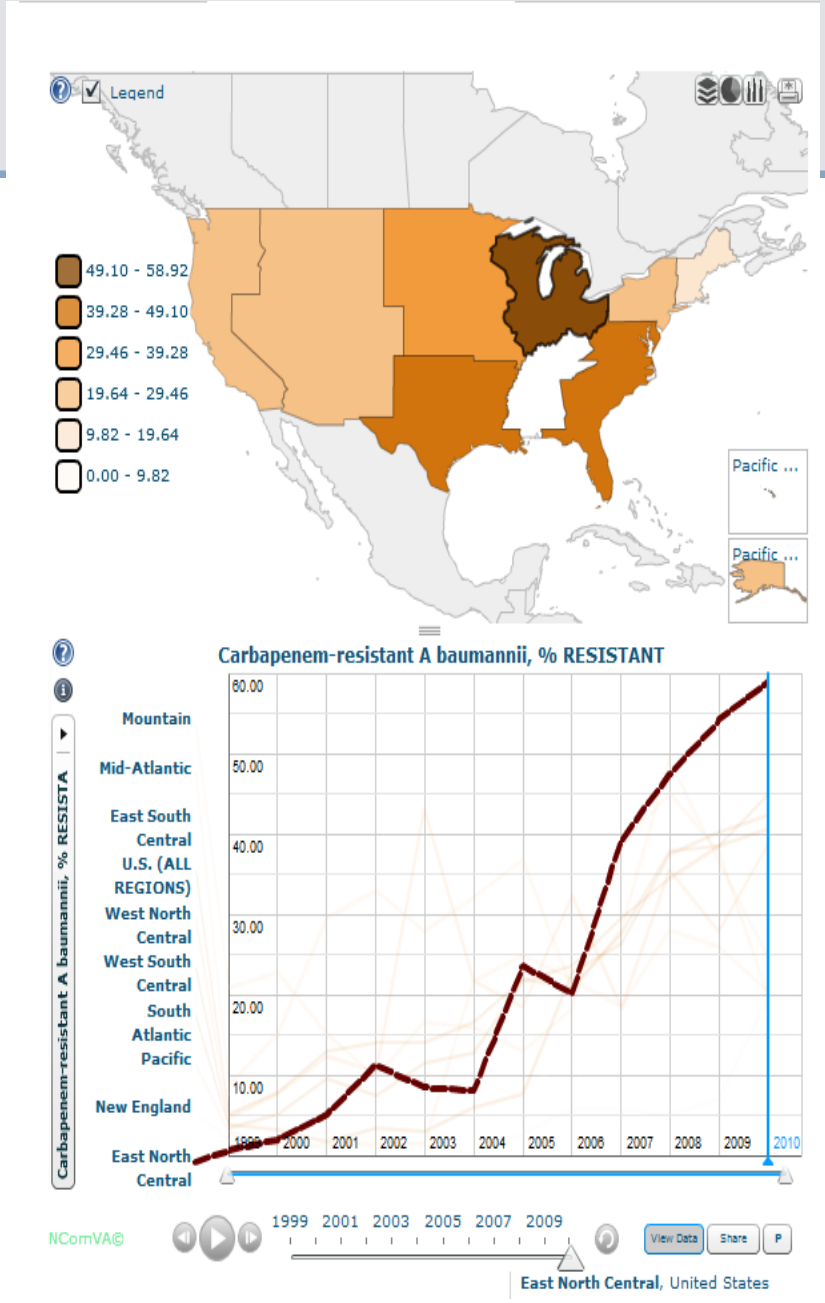
CDDEP THE CENTER FOR Disease Dynamics, Economics & Policy
WASHINGTON DC • NEW DELHI

- National-level *A. baumannii* resistance to carbapenems grew nearly eight times, going from 5.2% in 1999 to 40.8% in 2010 and increasing in all but one years during the period.

- The largest and most consistent increase came from the Midwest (East North and West South Central), followed by the South Atlantic and Pacific states.



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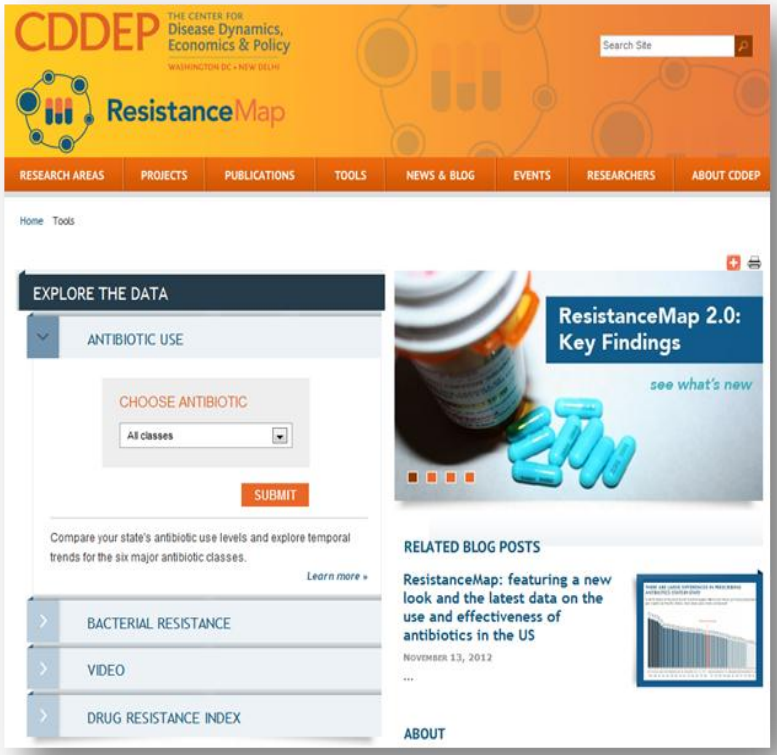

- Because of *Acinetobacter's* low virulence, few colonized patients develop a disease. However, when an infection does occur, it often results in hospital-wide outbreaks and relatively high rates of mortality. In the outpatient setting, the pathogen has been associated with wound infections among soldiers, earning it the name "Iraqibacter."

- The striking decline in carbapenem effectiveness points to two major conclusions: one is the urgent need to develop **new drugs** active against Gram-negative bacteria; second is the medical community's need to evaluate the benefits of **large-scale vaccination** of populations most affected by *A. baumannii,* such as military personnel and those in contact with them.

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Surveillance

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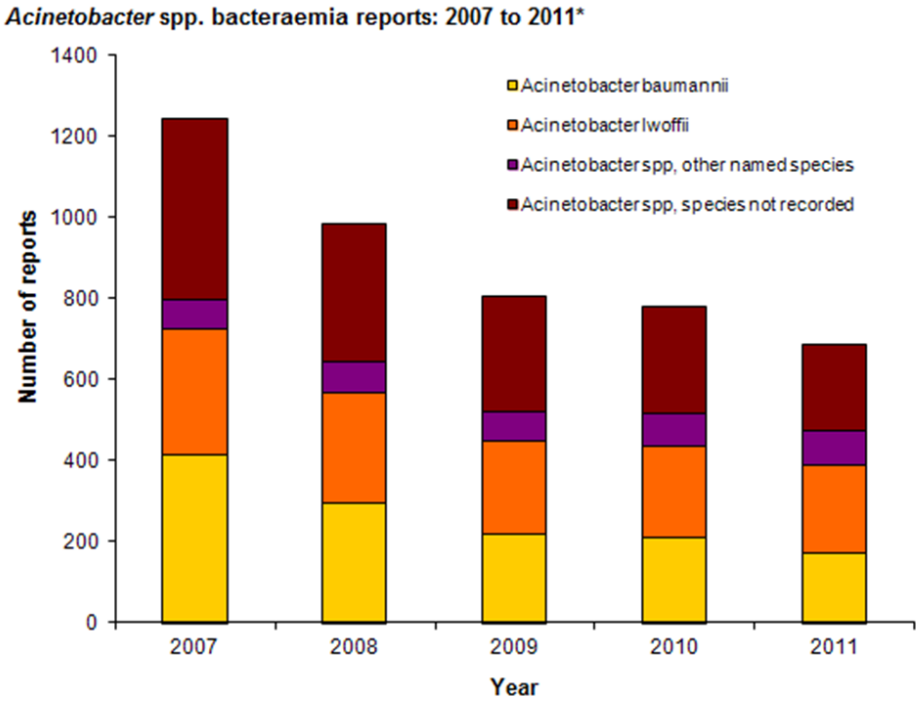
Surveillance in UK

Voluntary surveillance by diagnostic laboratories to the Health Protection Agency (HPA)

Health Protection Agency

- All *Acinetobacter* spp.
- Reporting of cases via electronic data transfer system to central database



* Data extracted 29 October 2012.

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HPA Voluntary Surveillance: Data Analysis

- For *A. baumannii*, there has been a significant rise in imipenem resistance from 21% in 2006 to 27% in 2010 ($p<0.05$)
- Only a small proportion of all isolates were tested.

- Between 2007 and 2011 there were no significant changes.

http://www.hpa.org.uk/webc/HPAwebFile/HPAweb_C/1317131514188

HPA Voluntary Surveillance: Data Analysis

- Antibiotic susceptibility data for reports of *A. baumannii* bacteraemia, England, Wales, and Northern Ireland: 2006 to 2010

		2006	2007	2008	2009	2010
	Total reports	413	415	295	219	212
Ciprofloxacin	**Non-susceptible**	**36%**	**31%**	**29%**	**27%**	**22%**
	Reports with susceptibility data	319	338	243	177	154
Imipenem	**Non-susceptible**	**21%**	**26%**	**30%**	**30%**	**27%**
	Reports with susceptibility data	126	183	108	91	56
Meropenem	**Non-susceptible**	**35%**	**24%**	**29%**	**14%**	**23%**
	Reports with susceptibility data	175	186	159	119	109
Ceftazidime	**Non-susceptible**	**70%**	**68%**	**72%**	**74%**	**75%**
	Reports with susceptibility data	233	272	186	155	134

Adapted from http://www.hpa.org.uk/webc/HPAwebFile/HPAweb_C/1317131514188

Surveillance cont…

British Society for Antimicrobial Chemotherapy (BSAC)

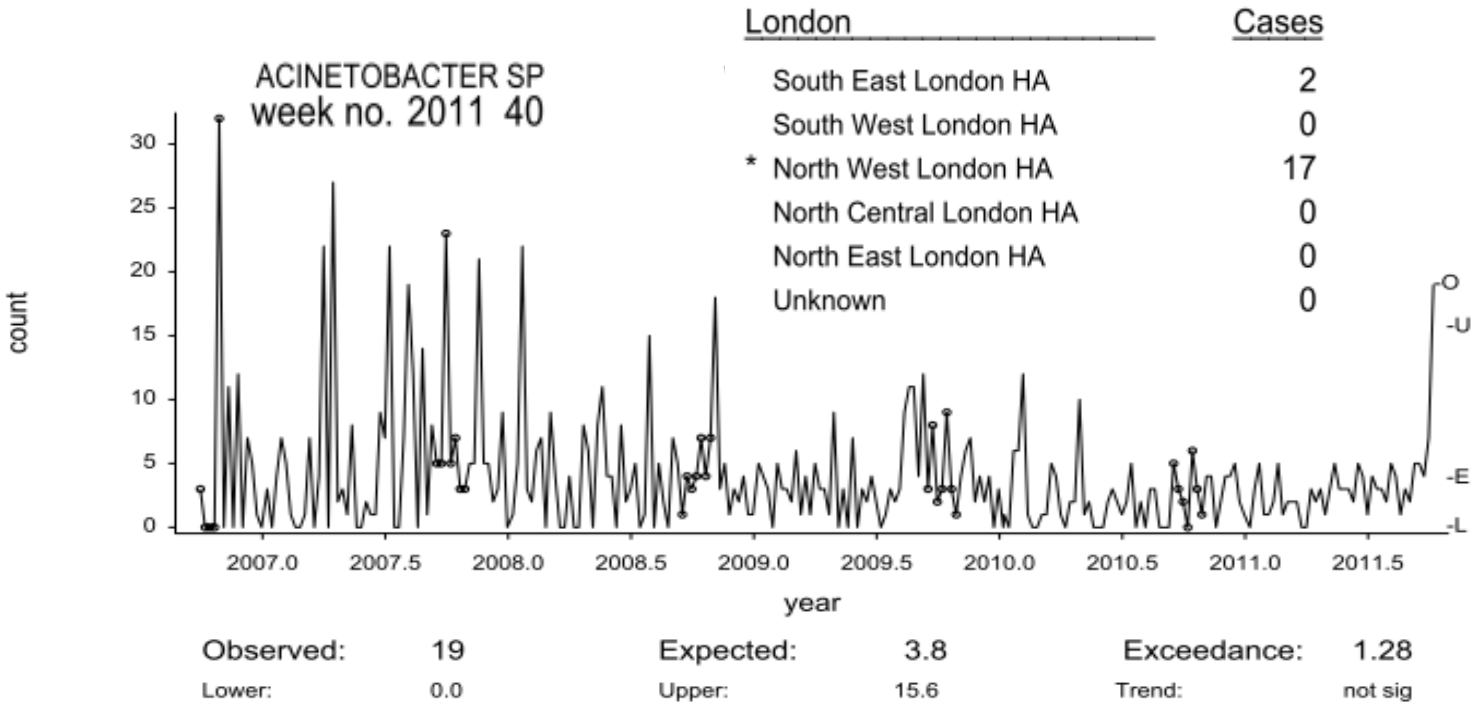
- Respiratory Resistance Surveillance Programme
- Sentinel surveillance
- All *Acinetobacter* spp., identified to species level
- Hospital-acquired infections
- Lower respiratory tract specimens, from patients with clinical infection
- Susceptibility testing against variety of antimicrobials

Antimicrobial Resistance and Healthcare Associated Infections Reference Unit (HPA)

- reference unit available for confirmation of “unusual” resistance patterns
- *Acinetobacter* spp. isolates can be sent if they exhibit resistance to carbapenems or colistin

Outbreak Detection

- At national and regional level, *Acinetobacter* spp. included in LabBase Exceedance Reporting performed weekly at the HPA
  - MDRA not distinguishable
  - Outbreak detection not available specifically, further investigation required



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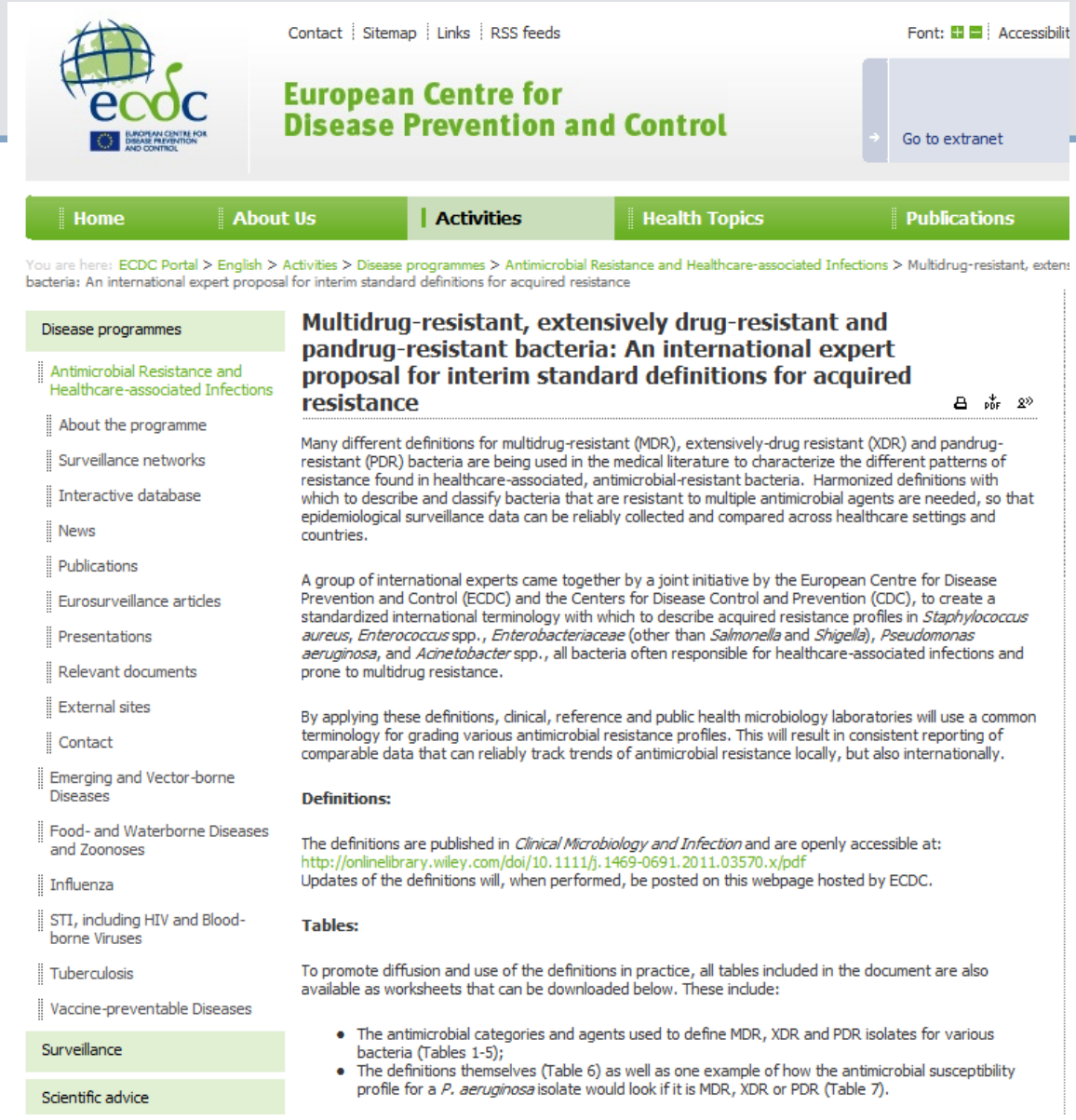
Need standardised definitions for surveillance and outbreak detection



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Surveillance

Scientific advice

Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: An international expert proposal for interim standard definitions for acquired resistance

Many different definitions for multidrug-resistant (MDR), extensively-drug resistant (XDR) and pandrug-resistant (PDR) bacteria are being used in the medical literature to characterize the different patterns of resistance found in healthcare-associated, antimicrobial-resistant bacteria. Harmonized definitions with which to describe and classify bacteria that are resistant to multiple antimicrobial agents are needed, so that epidemiological surveillance data can be reliably collected and compared across healthcare settings and countries.

A group of international experts came together by a joint initiative by the European Centre for Disease Prevention and Control (ECDC) and the Centers for Disease Control and Prevention (CDC), to create a standardized international terminology with which to describe acquired resistance profiles in *Staphylococcus aureus*, *Enterococcus* spp., *Enterobacteriaceae* (other than *Salmonella* and *Shigella*), *Pseudomonas aeruginosa*, and *Acinetobacter* spp., all bacteria often responsible for healthcare-associated infections and prone to multidrug resistance.

By applying these definitions, clinical, reference and public health microbiology laboratories will use a common terminology for grading various antimicrobial resistance profiles. This will result in consistent reporting of comparable data that can reliably track trends of antimicrobial resistance locally, but also internationally.

Definitions:

The definitions are published in *Clinical Microbiology and Infection* and are openly accessible at:
http://onlinelibrary.wiley.com/doi/10.1111/j.1469-0691.2011.03570.x/pdf
Updates of the definitions will, when performed, be posted on this webpage hosted by ECDC.

Tables:

To promote diffusion and use of the definitions in practice, all tables included in the document are also available as worksheets that can be downloaded below. These include:

- The antimicrobial categories and agents used to define MDR, XDR and PDR isolates for various bacteria (Tables 1-5);
- The definitions themselves (Table 6) as well as one example of how the antimicrobial susceptibility profile for a *P. aeruginosa* isolate would look if it is MDR, XDR or PDR (Table 7).

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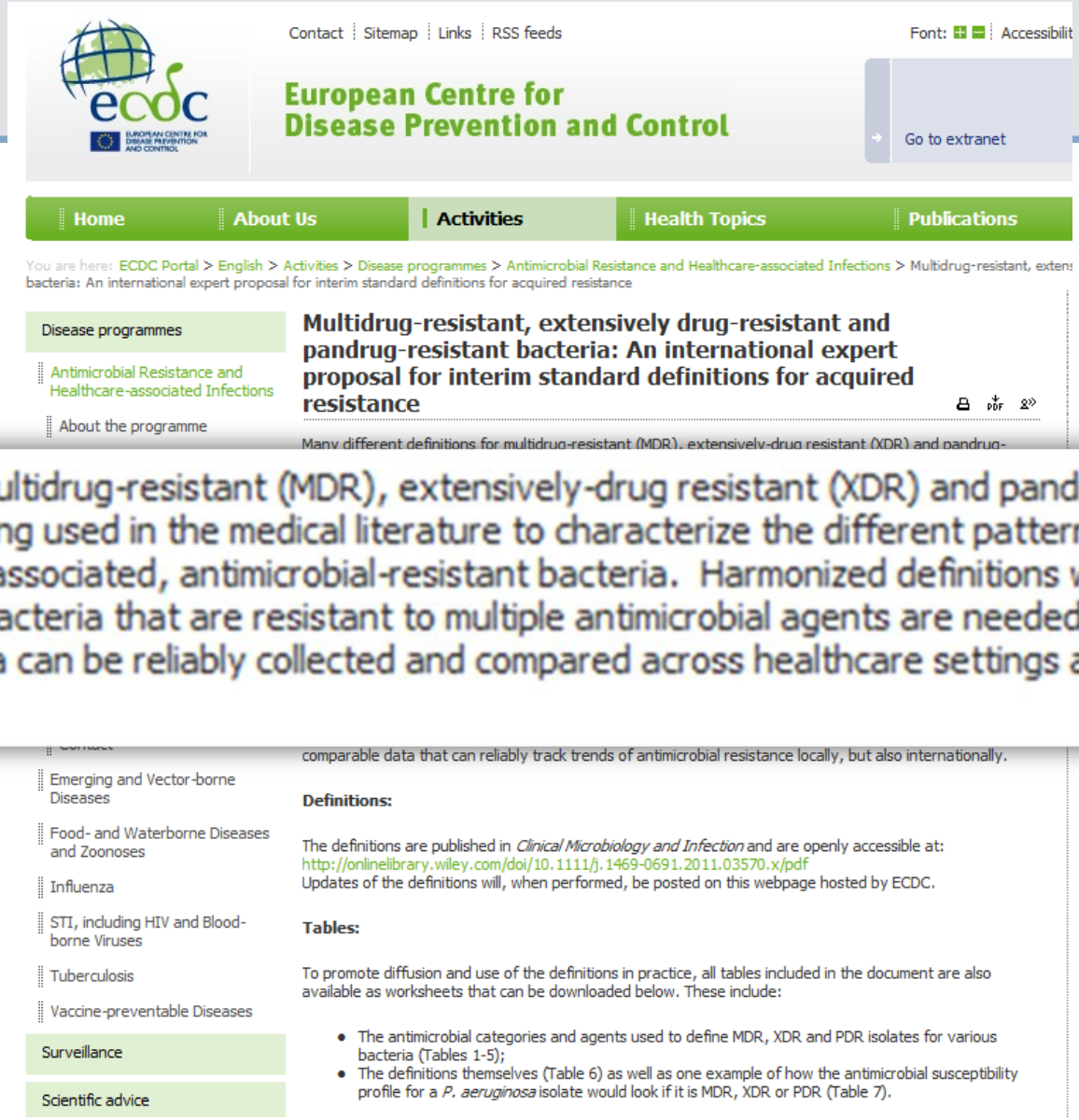

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Need for Standard Definitions

Clin Microbiol Infect 2012; 18: 268–281

ORIGINAL ARTICLE BACTERIOLOGY

Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: an international expert proposal for interim standard definitions for acquired resistance

A.-P. Magiorakos[1], A. Srinivasan[2], R. B. Carey[2], Y. Carmeli[3], M. E. Falagas[4,5], C. G. Giske[6], S. Harbarth[7], J. F. Hindler[8], G. Kahlmeter[9], B. Olsson-Liljequist[10], D. L. Paterson[11], L. B. Rice[12], J. Stelling[13], M. J. Struelens[1], A. Vatopoulos[14], J. T. Weber[2] and D. L. Monnet[1]

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Clin Microbiol Infect 2

ORIGINAL ARTICLE

Multidrug-resistant, extensively bacteria: an international exper definitions for acquired resistan

A.-P. Magiorakos[1], A. Srinivasan[2], R. B. Carey[2], Y. Carn Kahlmeter[9], B. Olsson-Liljequist[10], D. L. Paterson[11], L. E and D. L. Monnet[1]

1) *European Centre for Disease Prevention and Control, Stockholm, S Centers for Disease Control and Prevention, Atlanta, GA, USA, 3) Div of Biomedical Sciences (AIBS), Athens, Greece, 5) Department of Me Microbiology, Karolinska University Hospital, Stockholm, Sweden, 7) I Department of Pathology and Laboratory Medicine, University of Cali Microbiology, Central Hospital, Växjö, 10) Department of Bacteriolog Queensland Centre for Clinical Research, Royal Brisbane and Women's University, Providence, RI, 13) Department of Medicine, Brigham and School of Public Health, Athens, Greece*

TABLE 5. ***Acinetobacter*** **spp.; antimicrobial categories and agents used to define MDR, XDR and PDR (worksheet for categorizing isolates)**

Antimicrobial category	Antimicrobial agent	Results of antimicrobial susceptibility testing (S or NS)
Aminoglycosides	Gentamicin	
	Tobramycin	
	Amikacin	
	Netilmicin	
Antipseudomonal carbapenems	Imipenem	
	Meropenem	
	Doripenem	
Antipseudomonal fluoroquinolones	Ciprofloxacin	
	Levofloxacin	
Antipseudomonal penicillins + β-lactamase inhibitors	Piperacillin-tazobactam	
	Ticarcillin-clavulanic acid	
Extended-spectrum cephalosporins	Cefotaxime	
	Ceftriaxone	
	Ceftazidime	
	Cefepime	
Folate pathway inhibitors	Trimethoprim-sulphamethoxazole	
Penicillins + β-lactamase inhibitors	Ampicillin-sulbactam	
Polymyxins	Colistin	
	Polymyxin B	
Tetracyclines	Tetracycline	
	Doxycycline	
	Minocycline	

Criteria for defining MDR, XDR and PDR in *Acinetobacter* spp.
MDR: non-susceptible to ≥1 agent in ≥3 antimicrobial categories.
XDR: non-susceptible to ≥1 agent in all but ≤2 categories.
PDR: non-susceptible to all antimicrobial agents listed.
http://www.ecdc.europa.eu/en/activities/diseaseprogrammes/ARHAI/Pages/public_consultation_clinical_microbiology_infection_article.aspx.

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Clin Microbiol Infect 20

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A.-P. M
Kahlme
and D. L. Monnet[1]

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of Biomedical Sciences (AIBS), Athens, Greece, 5) Department of Medicine,
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Queensland Centre for Clinical Research, Royal Brisbane and Women's Hosp
University, Providence, RI, 13) Department of Medicine, Brigham and Wom
School of Public Health, Athens, Greece

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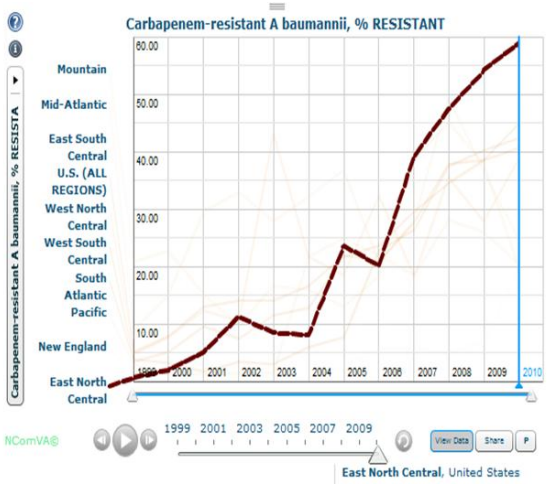
However……outside the lab…..

- Need pragmatic definitions for surveillance and for clinicians…
- Carbapenem resistance ?
- What about ‘CRAB’ ?
- See CDDEP (→)
- Drug/Bug surveillance
- Useful as a definition....?
- Can be CRAB without being MDRA...
- Addresses importance of OXA type carbapenemase
- And clinical significance ‘resistance to critically important drug class’



The Control

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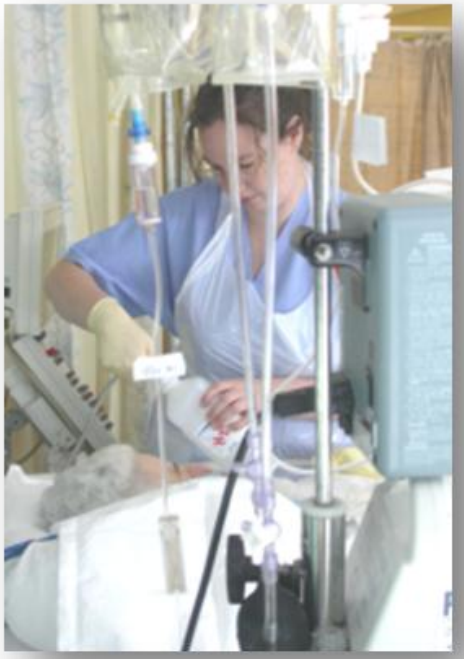
Potential Sources in Hospital Environment

- Hands of staff
- Ventilators and tubing
- Oxygen analysers
- Bronchoscopes
- Bed frames
- Sinks
- Jugs
- Soap
- Plastic screens
- Bed linen, pillows and mattresses
- Resuscitation bags
- Blood pressure cuffs
- Parenteral nutrition solution
- Gloves
- Humidifiers
- Patients
- Respirometers
- Lotion dispensers
- Rubbish bins
- Air supply
- Bowls
- Hand cream
- Bedside charts
- Service ducts/dust
- Computer keyboards
- Cell phones



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The National CIPM Centre for Infection Prevention & Management

Infection Control

Key measures include:

- Patient contact-isolated in side-room
- Careful review of practice
- More than one case, outbreak management
- Typing
- Cohorting patients, nursing staff.
- Antimicrobial prescribing reviewed
- Strict hand hygiene practices
- Implementation of “deep clean” strategies;
- Close attention to environment and all equipment

Infection Control

- Ward closures often required
- Followed by terminal clean before re-open
- Most significant source in an outbreak situation are patients already infected/colonised with MDRA
- The importance of adequate staffing needs to be addressed

- Once endemic in a healthcare setting, MDRA is difficult to eradicate

Detailed guidelines on how to deal with MDRA outbreaks prepared by a Working Party of the HPA
http://www.hpa.org.uk/webc/HPAwebFile/HPAweb_C/1194947325341

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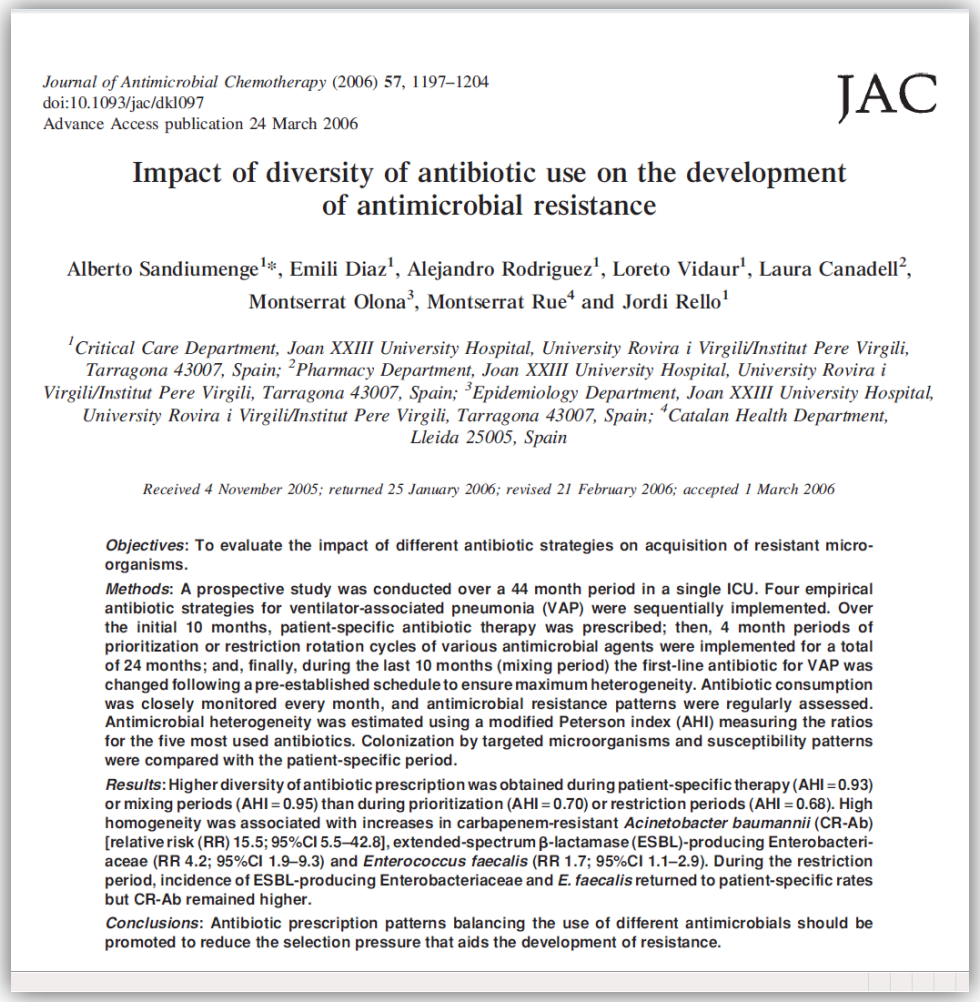

Journal of Antimicrobial Chemotherapy (2006) **57**, 1197–1204
doi:10.1093/jac/dkl097
Advance Access publication 24 March 2006

JAC

Impact of diversity of antibiotic use on the development of antimicrobial resistance

Alberto Sandiumenge[1]*, Emili Diaz[1], Alejandro Rodriguez[1], Loreto Vidaur[1], Laura Canadell[2], Montserrat Olona[3], Montserrat Rue[4] and Jordi Rello[1]

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Received 4 November 2005; returned 25 January 2006; revised 21 February 2006; accepted 1 March 2006

Objectives: To evaluate the impact of different antibiotic strategies on acquisition of resistant micro-organisms.

Methods: A prospective study was conducted over a 44 month period in a single ICU. Four empirical antibiotic strategies for ventilator-associated pneumonia (VAP) were sequentially implemented. Over the initial 10 months, patient-specific antibiotic therapy was prescribed; then, 4 month periods of prioritization or restriction rotation cycles of various antimicrobial agents were implemented for a total of 24 months; and, finally, during the last 10 months (mixing period) the first-line antibiotic for VAP was changed following a pre-established schedule to ensure maximum heterogeneity. Antibiotic consumption was closely monitored every month, and antimicrobial resistance patterns were regularly assessed. Antimicrobial heterogeneity was estimated using a modified Peterson index (AHI) measuring the ratios for the five most used antibiotics. Colonization by targeted microorganisms and susceptibility patterns were compared with the patient-specific period.

Results: Higher diversity of antibiotic prescription was obtained during patient-specific therapy (AHI = 0.93) or mixing periods (AHI = 0.95) than during prioritization (AHI = 0.70) or restriction periods (AHI = 0.68). High homogeneity was associated with increases in carbapenem-resistant *Acinetobacter baumannii* (CR-Ab) [relative risk (RR) 15.5; 95%CI 5.5–42.8], extended-spectrum β-lactamase (ESBL)-producing Enterobacteriaceae (RR 4.2; 95%CI 1.9–9.3) and *Enterococcus faecalis* (RR 1.7; 95%CI 1.1–2.9). During the restriction period, incidence of ESBL-producing Enterobacteriaceae and *E. faecalis* returned to patient-specific rates but CR-Ab remained higher.

Conclusions: Antibiotic prescription patterns balancing the use of different antimicrobials should be promoted to reduce the selection pressure that aids the development of resistance.

- Avoid homogeneity of prescribing
- Minimise carbapenem use

Novel Strategies needed

- *A. baumannii* poses a particular challenge due to the intrinsic drug resistance imparted by its impermeable outer membrane and its rapid acquisition of resistance to new antibiotics
- Given these characteristics, small molecule antibiotics will unlikely prove to be a lasting solution to *A. baumannii* infections.
- Novel strategies for the treatment and prevention of these infections are therefore desperately needed.

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Whole Genome Sequencing

Journal of Hospital Infection 75 (2010) 37–41

Available online at www.sciencedirect.com

Journal of Hospital Infection

journal homepage: www.elsevierhealth.com/journals/jhin

High-throughput whole-genome sequencing to dissect the epidemiology of *Acinetobacter baumannii* isolates from a hospital outbreak

T. Lewis[a,1], N.J. Loman[b,1], L. Bingle[b], P. Jumaa[a], G.M. Weinstock[c], D. Mortiboy[a], M.J. Pallen[b,*]

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ARTICLE INFO

Article history:
Received 13 November 2009
Accepted 21 January 2010
Available online 17 March 2010

Keywords:
Acinetobacter baumannii
Epidemiology
Multidrug resistance
Single nucleotide polymorphism
Whole-genome sequencing
454 pyrosequencing

SUMMARY

Shared care of military and civilian patients has resulted in transmission of multidrug-resistant *Acinetobacter baumannii* (MDR-Aci) from military casualties to civilians. Current typing technologies have been useful in revealing relationships between isolates of *A. baumannii* but they are unable to resolve differences between closely related isolates from small-scale outbreaks, where chains of transmission are often unclear. In a recent hospital outbreak in Birmingham, six patients were colonised with MDR-Aci isolates indistinguishable using standard techniques. We used whole-genome sequencing to identify single nucleotide polymorphisms in these isolates, allowing us to discriminate between alternative epidemiological hypotheses in this setting.

- Genomic epidemiology
- Disruptive technology
- Several technologies on the market
- Determine chains of transmission
- Target intervention
- Pallen ‘’JHI was a scoping study’’

OPEN ACCESS Freely available online

PLoS one

Active and Passive Immunization Protects against Lethal, Extreme Drug Resistant-*Acinetobacter baumannii* Infection

Guanpingshen Luo[1], Lin Lin[2,3], Ashraf S. Ibrahim[1,3], Beverlie Baquir[2], Paul Pantapalangkoor[2], Robert A. Bonomo[4], Yohei Doi[5], Mark D. Adams[6], Thomas A. Russo[7], Brad Spellberg[2,3]*

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Abstract

Extreme-drug-resistant (XDR) *Acinetobacter baumannii* is a rapidly emerging pathogen causing infections with unacceptably high mortality rates due to inadequate available treatment. New methods to prevent and treat such infections are a critical unmet medical need. To conduct a rational vaccine discovery program, OmpA was identified as the primary target of humoral immune response after intravenous infection by *A. baumannii* in mice. OmpA was >99% conserved at the amino acid level across clinical isolates harvested between 1951 and 2009 from cerebrospinal fluid, blood, lung, and wound infections, including carbapenem-resistant isolates, and was ≥89% conserved among other sequenced strains, but had minimal homology to the human proteome. Vaccination of diabetic mice with recombinant OmpA (rOmpA) with aluminum hydroxide adjuvant markedly improved survival and reduced tissue bacterial burden in mice infected intravenously. Vaccination induced high titers of anti-OmpA antibodies, the levels of which correlated with survival in mice. Passive transfer with immune sera recapitulated protection. Immune sera did not enhance complement-mediated killing but did enhance opsonophagocytic killing of *A. baumannii*. These results define active and passive immunization strategies to prevent and treat highly lethal, XDR *A. baumannii* infections.

Citation: Luo G, Lin L, Ibrahim AS, Baquir B, Pantapalangkoor P, et al. (2012) Active and Passive Immunization Protects against Lethal, Extreme Drug Resistant-*Acinetobacter baumannii* Infection. PLoS ONE 7(1): e29446. doi:10.1371/journal.pone.0029446

Editor: Lionel G. Filion, University of Ottawa, Canada

Received October 5, 2011; **Accepted** November 28, 2011; **Published** January 10, 2012

Funding: Financial support was provided by Public Health Services/National Institute of Allergy and Infectious Diseases R01 AI081719, AI077681, and AI072052. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing Interests: The authors have declared that no competing interests exist.

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Active and Passive In
Extreme Drug Resist
Infection

**Guanpingshen Luo[1], Lin Lin[2,3], Ashraf
Bonomo[4], Yohei Doi[5], Mark D. Adams**

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States of America, **4** Departments of Medicine, Pharmacology
Center, Case Western Reserve University, Cleveland, Ohio, Uni
Pennsylvania, United States of America, **6** Department of Gene
States of America, **7** Veterans Administration Western New Yor
States of America

Abstract

Extreme-drug-resistant (XDR) *Acinetobacter*
high mortality rates due to inadequate avail
unmet medical need. To conduct a rationa
humoral immune response after intravenou
acid level across clinical isolates harvested
infections, including carbapenem-resistant
minimal homology to the human proteome.
hydroxide adjuvant markedly improved su
Vaccination induced high titers of anti-Om
transfer with immune sera recapitulated pr
enhance opsonophagocytic killing of *A. ba*
prevent and treat highly lethal, XDR *A. bau*

Citation: Luo G, Lin L, Ibrahim AS, Baquir B, Pantapalangk
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Funding: Financial support was provided by Public Health
The funders had no role in study design, data collection a

Competing Interests: The authors have declared that n

* E-mail: bspellberg@labiomed.org

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JVAC-13740; No. of Pages 6

ARTICLE IN PRESS

Vaccine xxx (2012) xxx–xxx

Contents lists available at SciVerse ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Acinetobacter baumannii rOmpA vaccine dose alters immune polarization and immunodominant epitopes

Lin Lin[a,b], Brandon Tan[b], Paul Pantapalangkoor[b], Tiffany Ho[b], Andrea M. Hujer[c,g], Magdalena A. Taracila[c], Robert A. Bonomo[c,d,e,f,g], Brad Spellberg[a,b,*]

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ARTICLE INFO

Article history:
Received 9 August 2012
Received in revised form 3 October 2012
Accepted 4 November 2012
Available online xxx

Keywords:
Acinetobacter baumannii
OmpA
Vaccine
Type 1/Type 2 immunity
Epitope spreading

ABSTRACT

Background: The rOmpA vaccine has been shown to protect mice from lethal infection caused by extreme-drug-resistant (XDR) *Acinetobacter baumannii*. The role of dose in immunology of the rOmpA vaccine was explored.
Methods: Mice were vaccinated with various doses of rOmpA plus aluminum hydroxide ($Al(OH)_3$) adjuvant. The impact of dose on antibody titers, cytokine production, and immunodominant epitopes was defined.
Results: Anti-rOmpA IgG and IgG subtype titers were higher at larger vaccine doses (30 and 100 μg vs. 3 μg). The 3 μg dose induced a balanced IFN-γ–IL-4 immune response while the 100 μg dose induced a polarized IL-4/Type 2 response. Epitope mapping revealed distinct T cell epitopes that activated IFN-γ-, IL-4-, and IL-17-producing splenocytes. Vaccination with the 100 μg dose caused epitope spreading among IL-4-producing splenocytes, while it induced fewer reactive epitopes among IFN-γ-producing splenocytes.
Conclusions: Vaccine dose escalation resulted in an enhanced Type 2 immune response, accompanied by substantial IL-4-inducing T cell epitope spreading and restricted IFN-γ-inducing epitopes. These results inform continued development of the rOmpA vaccine against *A. baumannii*, and also are of general importance in that they indicate that immune polarization and epitope selectivity can be modulated by altering vaccine dose.

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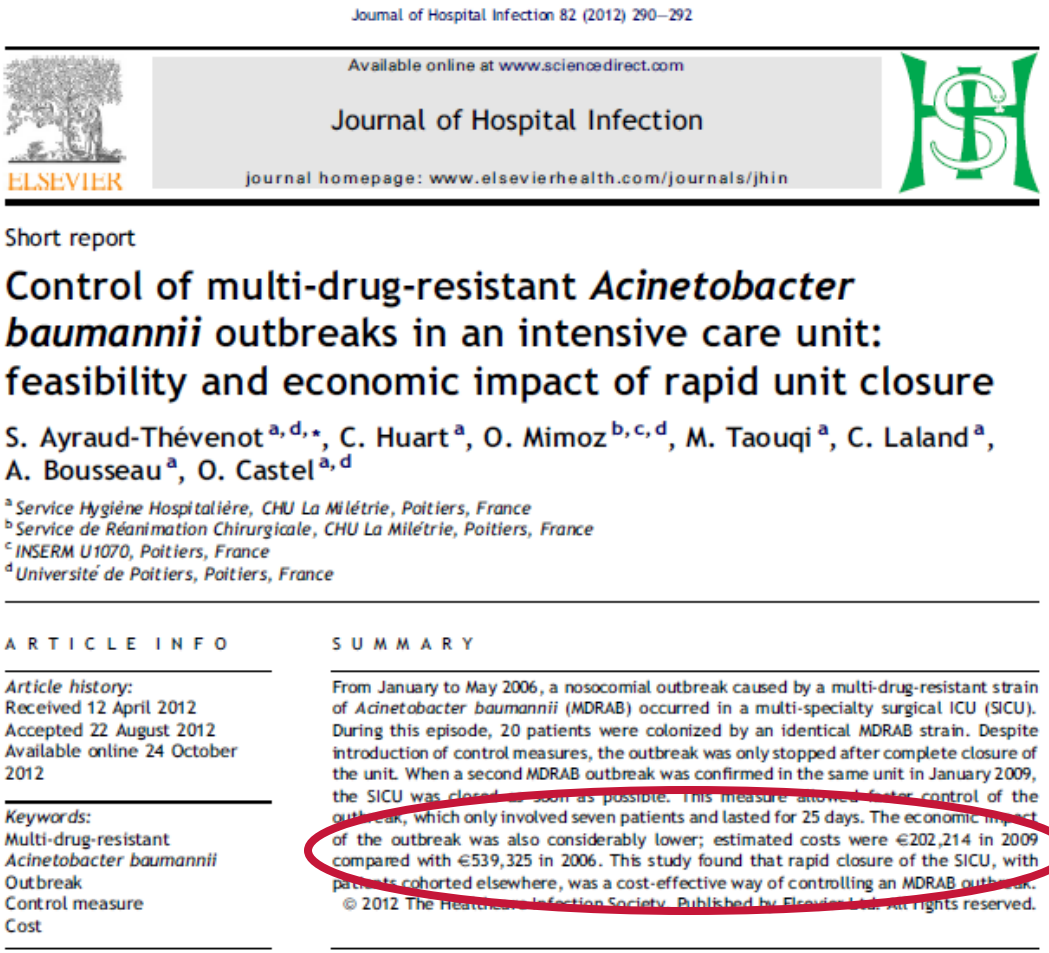
The Importance of closure



Journal of Hospital Infection 82 (2012) 290–292

Available online at www.sciencedirect.com

Journal of Hospital Infection

journal homepage: www.elsevierhealth.com/journals/jhin

Short report

Control of multi-drug-resistant *Acinetobacter baumannii* outbreaks in an intensive care unit: feasibility and economic impact of rapid unit closure

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ARTICLE INFO

Article history:
Received 12 April 2012
Accepted 22 August 2012
Available online 24 October 2012

Keywords:
Multi-drug-resistant
Acinetobacter baumannii
Outbreak
Control measure
Cost

SUMMARY

From January to May 2006, a nosocomial outbreak caused by a multi-drug-resistant strain of *Acinetobacter baumannii* (MDRAB) occurred in a multi-specialty surgical ICU (SICU). During this episode, 20 patients were colonized by an identical MDRAB strain. Despite introduction of control measures, the outbreak was only stopped after complete closure of the unit. When a second MDRAB outbreak was confirmed in the same unit in January 2009, the SICU was closed as soon as possible. This measure allowed faster control of the outbreak, which only involved seven patients and lasted for 25 days. The economic impact of the outbreak was also considerably lower; estimated costs were €202,214 in 2009 compared with €539,325 in 2006. This study found that rapid closure of the SICU, with patients cohorted elsewhere, was a cost-effective way of controlling an MDRAB outbreak.

Needs adequate risk assessment and cost effectiveness analysis.

What are the health economic implications?

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Termination of an Extreme-Drug Resistant–*Acinetobacter baumannii* Outbreak in a Hospital After Flooding: Lessons Learned

CID 2012:55 (11): 1589-90
Apisarnthanarak, Li Yang, Warren

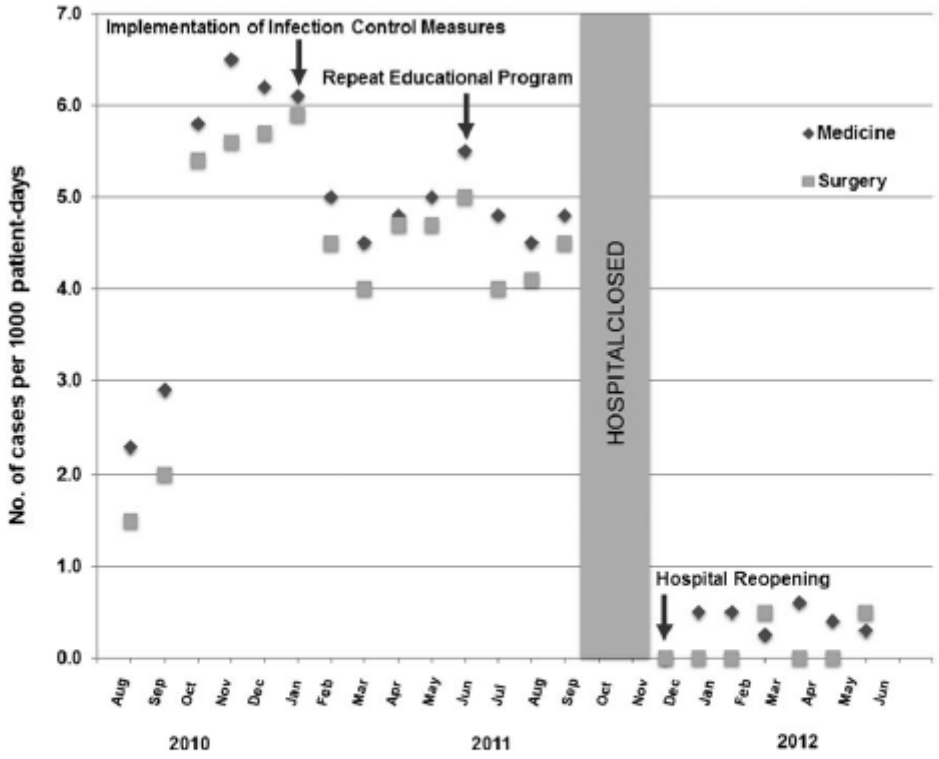

Figure 1. Extreme-drug resistant (XDR)–*Acinetobacter baumannii* incidence among general medical units (n = 6) and surgical units (n = 4) in relation to infection control measures implemented between October 2011 and December 2012. Infection Control measures include (1) enhanced contact isolation precautions (ie, strict adherence to hand hygiene protocols before and after patient care and use of gowns and gloves for patient care of known cases), (2) obtained active surveillance cultures (ie, rectal cultures) for XDR–*A. baumanii* from all patients in the index units, (3) environmental cleaning with detergents, and with phenolic agents for surfaces contaminated with body fluids and/or blood, (4) implemented staff educational programs and (5) provided unit-specific feedback on adherence to infection prevention measures. If there are ≥2 cases at a time in a unit, a cohort area was created.

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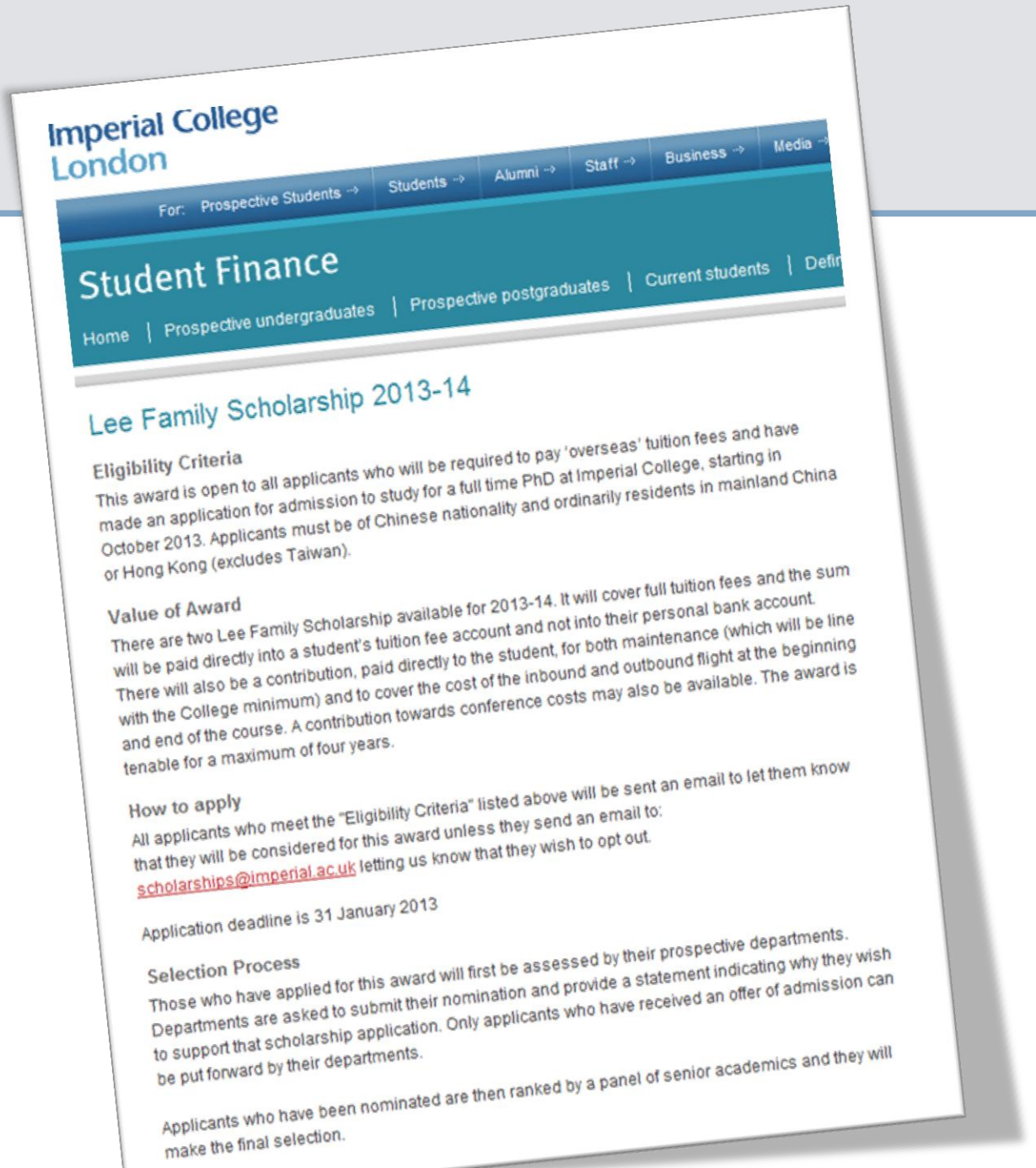

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Eligibility Criteria

This award is open to all applicants who will be required to pay 'overseas' tuition fees and have made an application for admission to study for a full time PhD at Imperial College, starting in October 2013. Applicants must be of Chinese nationality and ordinarily residents in mainland China or Hong Kong (excludes Taiwan).

Value of Award

There are two Lee Family Scholarship available for 2013-14. It will cover full tuition fees and the sum will be paid directly into a student's tuition fee account and not into their personal bank account. There will also be a contribution, paid directly to the student, for both maintenance (which will be line with the College minimum) and to cover the cost of the inbound and outbound flight at the beginning and end of the course. A contribution towards conference costs may also be available. The award is tenable for a maximum of four years.

How to apply

All applicants who meet the "Eligibility Criteria" listed above will be sent an email to let them know that they will be considered for this award unless they send an email to: scholarships@imperial.ac.uk letting us know that they wish to opt out.

Application deadline is 31 January 2013

Selection Process

Those who have applied for this award will first be assessed by their prospective departments. Departments are asked to submit their nomination and provide a statement indicating why they wish to support that scholarship application. Only applicants who have received an offer of admission can be put forward by their departments.

Applicants who have been nominated are then ranked by a panel of senior academics and they will make the final selection.

The National

CIPM

Centre for Infection Prevention & Management

Wednesday 3 July 2013

Annual Scientific Research Meeting

The National Centre for Infection Prevention & Management will be holding its annual meeting at the Hammersmith Campus.

If you are a researcher, clinician, medical staff, NHS manager or student and have an interest in infection and its prevention, please join us for our annual meeting. This will be a valuable opportunity to hear the Centre's researchers and collaborators talk about their work to date.

The event will be followed by a drinks reception.

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