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

Alison Holmes
• The organism and its epidemiology
• Surveillance
• Control
What is it?
What is it?
What is it?
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
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. baumannii* 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*.

OXA-23 Cluster
- **Distribution:** Europe (widespread), Australia, Tahiti, Noumea, China, Korea, Singapore, Vietnam, United States, Brazil, Libya, Pakistan
- **Encoded:** plasmid or chromosomal
- **Associated IS Elements:** ISAba1, ISAba4

OXA-24 Cluster
- **Distribution:** Spain, Belgium, France, Portugal, United States
- **Encoded:** chromosomal or plasmid (OXA-40)
- **Associated IS Elements:** None

OXA-51 Cluster
- **Distribution:** Naturally occurring in *A. baumannii* therefore global distribution
- **Encoded:** chromosomal
- **Associated IS Elements:** ISAba1

OXA-58 Cluster
- **Distribution:** France, Spain, Belgium, Turkey, Romania, Greece, UK, Italy, Austria, Argentina, Australia, United States, Kuwait, Pakistan
- **Encoded:** plasmid or chromosomal
- **Associated IS Elements:** ISAba1, ISAba2, ISAba3, IS18

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

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
Factors facilitating Spread

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

Towner KJ JHI 2009
A Review of *Acinetobacter baumannii* as a Highly Successful Pathogen in Times of War

Callie Camp, MS, MT(ASCP)CM, Owausha L. Tatsumi, PhD, MB(ASCP)CM, HCLD(ABB)
(Molecular Pathology Program, Texas Tech University Health Sciences Center, Lubbock, TX)

DOI: 10.1093/jnci/djx056
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
MDRA led to major focus of military on infection control, microbiology support, antibiotic programme ….. and MDRA control
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

• 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 year 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.
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.
Surveillance
Surveillance in UK

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

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

*Data extracted 29 October 2012.*
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.

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

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

Adapted from [http://www.hpa.org.uk/webc/HPAwebFile/HPAweb_C/1317131514188](http://www.hpa.org.uk/webc/HPAwebFile/HPAweb_C/1317131514188)
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
Need standardised definitions for surveillance and outbreak detection
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.

Definitions:

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


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

<table>
<thead>
<tr>
<th>Antimicrobial category</th>
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<th>Results of antimicrobial susceptibility testing</th>
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<tr>
<td>Aminoglycosides</td>
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<td>Ganciclovir</td>
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<td>Amikacin</td>
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<td></td>
<td>Natamycin</td>
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<td>Antipseudomonal carbapenems</td>
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<td></td>
<td>Imipenem</td>
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<td>Meropenem</td>
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<td></td>
<td>Doripenem</td>
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<td>Antipseudomonal fluoroquinolones</td>
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<td></td>
<td>Ciprofloxacin</td>
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<td></td>
<td>Levofloxacin</td>
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<tr>
<td>Antipseudomonal penicillins + β-lactamase inhibitors</td>
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<td></td>
<td>Piperacillin-tazobactam</td>
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<td></td>
<td>Tazobactam</td>
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<tr>
<td>Extended-spectrum cephalosporins</td>
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<td></td>
<td>Cefotaxime</td>
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<td></td>
<td>Ceftazidime</td>
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<td></td>
<td>Ceftriaxone</td>
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<tr>
<td>Folate pathway inhibitors</td>
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<tr>
<td></td>
<td>Trimethoprim-sulphamethoxazole</td>
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<tr>
<td>Penicillins + β-lactamase inhibitors</td>
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<td>Ampicillin-sulbactam</td>
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<td>Polymyxins</td>
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<td></td>
<td>Colistin</td>
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<td>Polymyxin B</td>
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<td>Tetracyclines</td>
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<td>Tetracycline</td>
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<td>Doxycycline</td>
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<td></td>
<td>Minocycline</td>
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</table>

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.


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**ORIGINAL ARTICLE**

**Multidrug-resistant, extensively drug-resistant bacteria: an international expert definitions for acquired resistance**


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10) Department of Medicine, Brigham and Women’s Hospital, Harvard Medical School, Boston, MA, USA
11) School of Public Health, Athens, Greece

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*Clin Microbiol Infect* 2012; 18: 268–281
### TABLE 5. Acinetobacter spp.; antimicrobial categories and agents used to define MDR, XDR and PDR (worksheet for categorizing isolates)

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<td>Tobramycin</td>
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<td>Amikacin</td>
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<td></td>
<td>Netilmicin</td>
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<td></td>
<td>Meropenem</td>
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### 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.
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
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
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
• 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.
Whole Genome Sequencing

- Genomic epidemiology
- Disruptive technology
- Several technologies on the market
- Determine chains of transmission
- Target intervention
- Pallen “JHI was a scoping study”
Active and Passive Immunization Protects against Lethal, Extreme Drug Resistant-*Acinetobacter baumannii* Infection

Guanping Shen Luo1, Lin Lin2,3, Ashraf S. Ibrahim1,2, Beverlie Baquir2, Paul Pantapalangkoor2, Robert A. Bonomo2, Yohei Doi5, Mark D. Adams6, Thomas A. Russo7, Brad Spellberg2,3

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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.


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Active and Passive Immunization Against Extreme Drug Resistant Infection

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Abstract

Extreme-drug-resistant (XDR) Acinetobacter baumannii infections are associated with high mortality rates due to inadequate available medical interventions. To conduct a rational, efficacious, humoral immune response after intravenous antibiotic therapy, a considerable number of patients with severe infections, including carbapenem-resistant strains, require additional interventions. This study aimed to assess the potential of a novel vaccine dose against Acinetobacter baumannii infection, using high-titered anti-OmpA antibody levels in sera from vaccinated mice.

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

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ABSTRACT

Background: The OmpA vaccine has been shown to protect mice from lethal infection caused by extreme-drug-resistant (XDR) Acinetobacter baumannii. The role of dose in immunogenicity of the OmpA vaccine was explored.

Methods: Mice were vaccinated with various doses of OmpA plus aluminum hydroxide (Al(OH)3) adjuvant. The impact of dose on antibody titers, cytokine production, and immunodominant epitopes was defined.

Results: Anti-OmpA IgG and IgG subtype titers were higher at larger vaccine doses (30 and 100 µg vs. 3 µg). The 3 µg dose induced an balanced IFN-γ-IL-17 immune response while the 100 µg dose induced a polarized IL-17-type response. Epitope mapping revealed distinct T-cell epitopes that activated IFN-γ, IL-14- 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 confirm the potential utility of the OmpA vaccine against A. baumannii, and also of great importance in that they indicate that immune polarization and epitope selectivity can be modulated by altering vaccine dose.
The Importance of closure

Needs adequate risk assessment and cost effectiveness analysis.

What are the health economic implications?
Termination of an Extreme-Drug Resistant Acinetobacter baumannii Outbreak in a Hospital After Flooding: Lessons Learned

Apisarnthanaraks, 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 (i.e., strict adherence to hand hygiene protocols before and after patient care and use of gowns and gloves for patient care of known cases), (2) obtaining active surveillance cultures (i.e., rectal cultures) for XDR-A. baumannii 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.
Lee Family Scholarship 2013-14

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 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.

Please rsvp to Rachel Wood; r.wood@imperial.ac.uk

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