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NDM (New Delhi Metallo Betalcatamase)- A cause for concern?

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Carbapenemase resistant Enterobacteriaceae (CRE)

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- **Carbapenems** (Imipenem/Meropenem/Ertapenem) **often the "last line" antibiotics** against infections due to multi-drug resistant (MDR) Gram negative organisms, including ESBLs.
- **Carbapenemases are carbapenem-hydrolyzing beta-lactamases** that confer resistance to carbapenem antibiotics.
- Based on amino acid sequence homology, **betalactamases of Gram negative bacteria are classified into Ambler**:
  - **Class A** (TEM, SHV, CTX-M, KPC), C, and **D** (Oxa-type) beta-lactamases- **serine residue in active site**
  - **Class B betalactamases: have Zinc in active site → Metallo betalactamase (MBL)**
- **Species-to-species spread (Plasmid). Often multi- & some extra-drug resistant (MDR/XDR)**
- **Increasing problem** in the past few years.
- **Spectrum of infections as for other coliforms**, e.g. UTI, intra-abdominal infection, life threatening septicaemia, pneumonia & meningitis
- **Antibiotic treatment- according to sensitivity results**. However, **often no reliable treatment options- Colistin (Tigecycline)** but some strains already R!
- **Potentially devastating health & public health consequences- "return to pre-antibiotic era!"**

Class B beta-lactamases

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- **Metallo-beta-lactamases** (**MBLs)-Zinc dependent** for efficient hydrolysis of beta-lactams.
- **Inhibited by EDTA (an ion chelator) or Dipcolinic acid (DPA)** but not by beta-lactamase inhibitors tazobactam, clavulanate, and sulbactam.
- The **first MBL (IMP-1) described in Japan in 1991**. Subsequently, additional groups of acquired MBLs identified: IMP, VIM, GIM, SPM, and SIM.
- **A number of variants within each MBL group-** e.g. 19 IMP variants
- **Naturally occurring MBLs chromosomally encoded** and have been described in *Aeromonas hydrophilia*, *Chryseobacterium spp*, and *Stenotrophomonas maltophilia*.
- **Acquired MBLs** consist of **genes encoded on integrons** residing **on large plasmids that are transferable between both species and genera.**
- In a hospital outbreak involving 62 patients (including 40 in ICUs) an MBL gene (bla IMP-4) spread among seven different gram-negative genera (Serratia, Klebsiella, Pseudomonas, Escherichia, Acinetobacter, Citrobacter, and Enterobacter).

NDM (New Delhi Metallo-beta-lactamase)

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- Enterobacteriaceae isolates carrying **a novel MBL gene**, **NDM-1, first described in December 2009** in a patient hospitalized in India with an infection due to *Klebsiella pneumoniae* (Young, Tim Walsh et al. AAC 2009:53: 5046-54)
- Subsequent reports in **patients travelled to and or undergone procedures in India and Pakistan ("medical tourism"/imported infection). Additional risk factors- treatment with carbapenem**, indwelling urinary or intravascular catheters, dialysis, severe illness.
- Other cases reported elsewhere in Asia, Europe, and North America
- Isolates have also included *E. coli* and *Enterobacter cloacae*.
- Molecular epidemiology- **Diverse strain types** in UK. **Plasmid spread among strains & species more important than clonal spread among patients.** However **a few cases of cross-infection** have occurred in UK.
- **Now widespread in Enterobacteraceae** (especially *K.pneumoniae* & *E.coli*) **in the Indian subcontinent**.
- Probably **large environmental reservoir** in endemic countries- e.g. **water, food**.
- **Readily available over the counter antibiotics & poor sanitation** probably contributes to the problem by selecting for MDR organisms.

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41 year old Indian gentleman

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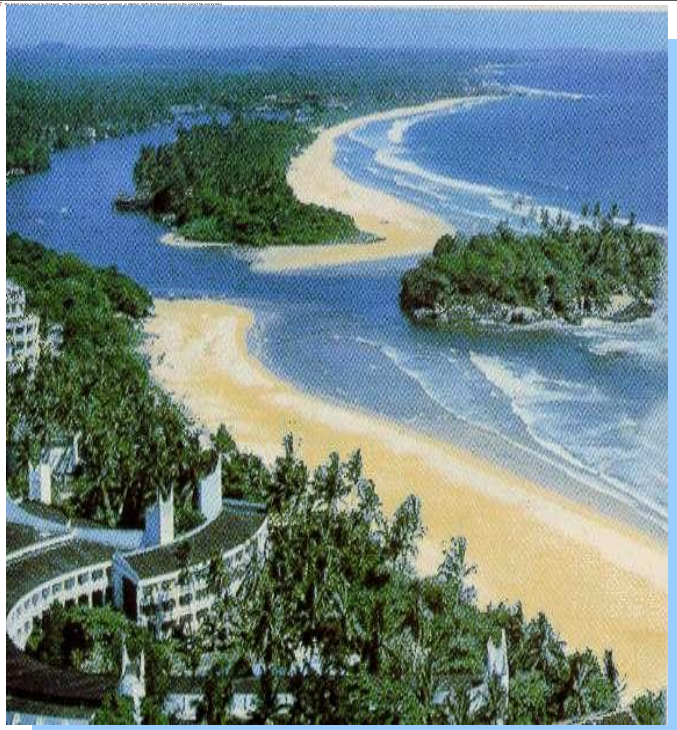
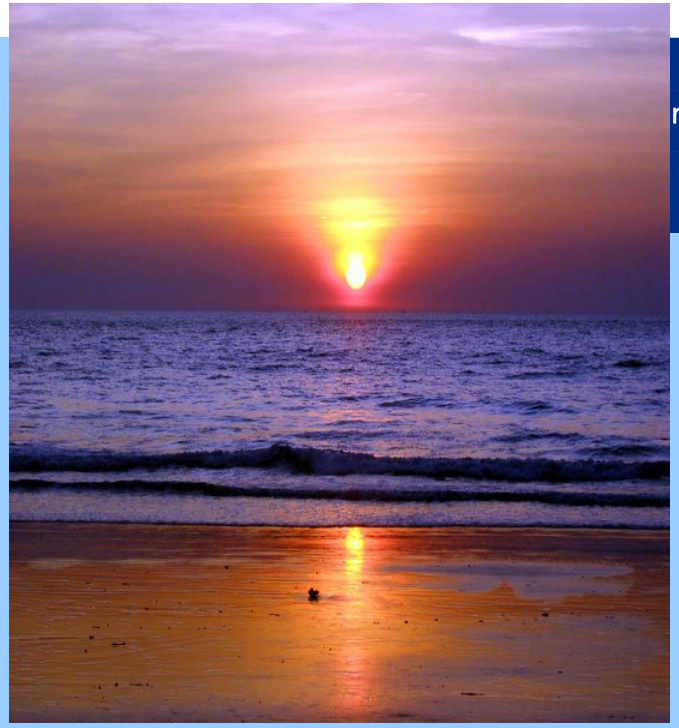
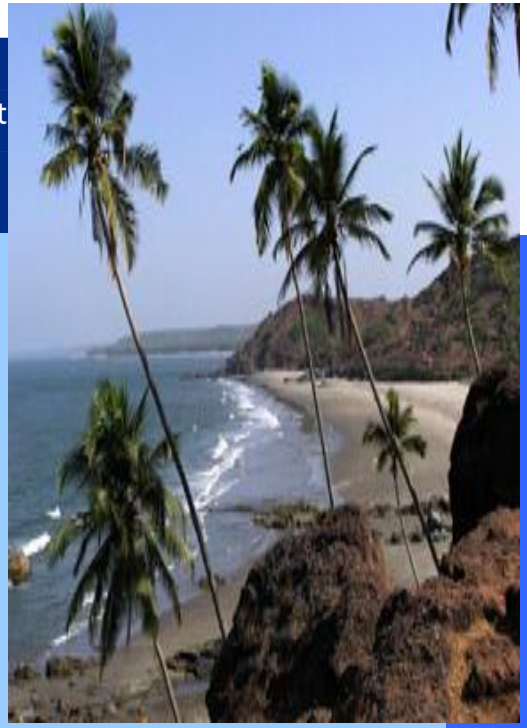
- **Born/lives in UK. Works as computer/IT analyst.**
- **Early Feb 2011-Travelled to Goa on holiday.**


India
भारत
State or Union Territory
National Capital
State or Union Territory Capital
0 200 400 Kilometers
0 200 400 Miles
© Nations Online Project
Turkmenistan
Uzbek.
Tajikistan
Afghanistan
Kabul
Islamabad
Pakistani line of control
Chinese line of control
Jammu & Kashmir
Srinagar
Jammu
China
Himachal Pradesh
Shimla
Punjab
Chandigarh
Dehra Dun
Uttaranchal
Haryana
New Delhi
Delhi
Pakistan
Nepal
Kathmandu
Tibet
Sikkim
Gangtok
Bhutan
Thimphu
Arunachal Pradesh
Itanagar
Assam
Dispur
Nagaland
Kohima
Shillong
Meghalaya
Manipur
Imphal
Agartala
Tripura
Aizawl
Mizoram
Bangladesh
Dhaka
Jaipur
Rajasthan
Lucknow
Uttar Pradesh
Patna
Bihar
Jharkhand
Ranchi
West Bengal
Kolkata (Calcutta)
Myanmar
Gandhinagar
Gujarat
Bhopal
Madhya Pradesh
Chhattis-garh
Raipur
Orissa
Bhubaneswar
Daman
Diu
Dadra & Nagar Haveli
Daman
Silvassa
Maharashtra
Mumbai (Bombay)
Rangoon
Hyderabad
Arabian Sea
Pondicherry
Bay of Bengal
Panaji
Goa
Andhra Pradesh
Karnataka
Andaman Islands
Port Blair
Bangalore
Chennai (Madras)
Pondicherry
Pondicherry
Pondicherry
Tamil Nadu
Andaman and Nicobar Islands
Andaman Sea
Kavaratti
Lakshadweep
Kerala
Thiruvananthapuram
Nicobar Islands
Sri Lanka
Colombo
Laccadive Sea
Maldives
Indian Ocean







- **Beginning of March- Ill, developed fits/fevers, and multiorgan failure (MOF)**

- **4/3/11- Hospitalised in Goa- admitted to ITU** :

❖ **MRI scan brain- changes compatible with HSV encephalitis**

❖ CSF PCR negative across the board

❖ **Treated with IV Aciclovir** - just over 3 weeks.

- 26/3/11- Antivirals stopped.
- **Continued to spike temperature**
- *S.aureus* (likely **MRSA**) isolated from CVP catheter tip
- **'Carbapenem resistant Klebsiella'** from ETT aspirate.
- **Treated with Tazocin**

- **19/4/11**- ETT removed; **Medical repatriation to UK arranged**- to Royal London Hospital (**RLH**) as family unhappy with his care in Goa.

21.4.11

- **On admission to RLH HDU- No seizures, afebrile** but intermittent runs of tachy-arrhythmias.
- **Antibiotic treatment stopped-** reculture after 48h.
- **Advised isolation + barrier nursing**
- MRI - poor images. Persistence of signal changes in both temporal lobes.
- Inflammatory markers marginally raised.
- Most significant abnormality: very high Calcium level >> Thorough endocrinology investigation (NAD)
- CK now normalised, as has renal function.

22.4.11 (Good Friday)

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- Still in **HDU** (Medical High Dependency Unit), **not isolated and not barrier nursed**.

- **Screening swabs taken:**
  - ETT site, perineum, rectum
  - Plated on **CHROMagar KPC**

23.4.11

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- ***E coli* & *Klebsiella pneumoniae*** isolated from perineum & rectal swabs

- **PCR performed in house to detect antibiotic resistant genes in the above isolates** (by Dr David Wareham)

24.4.11 (Easter Sunday)

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- *K. pneumoniae*
  - CTXM-15 gene positive (i.e. ESBL producer)
  - Negative for NDM gene (initially contaminated with the *E.coli* below)

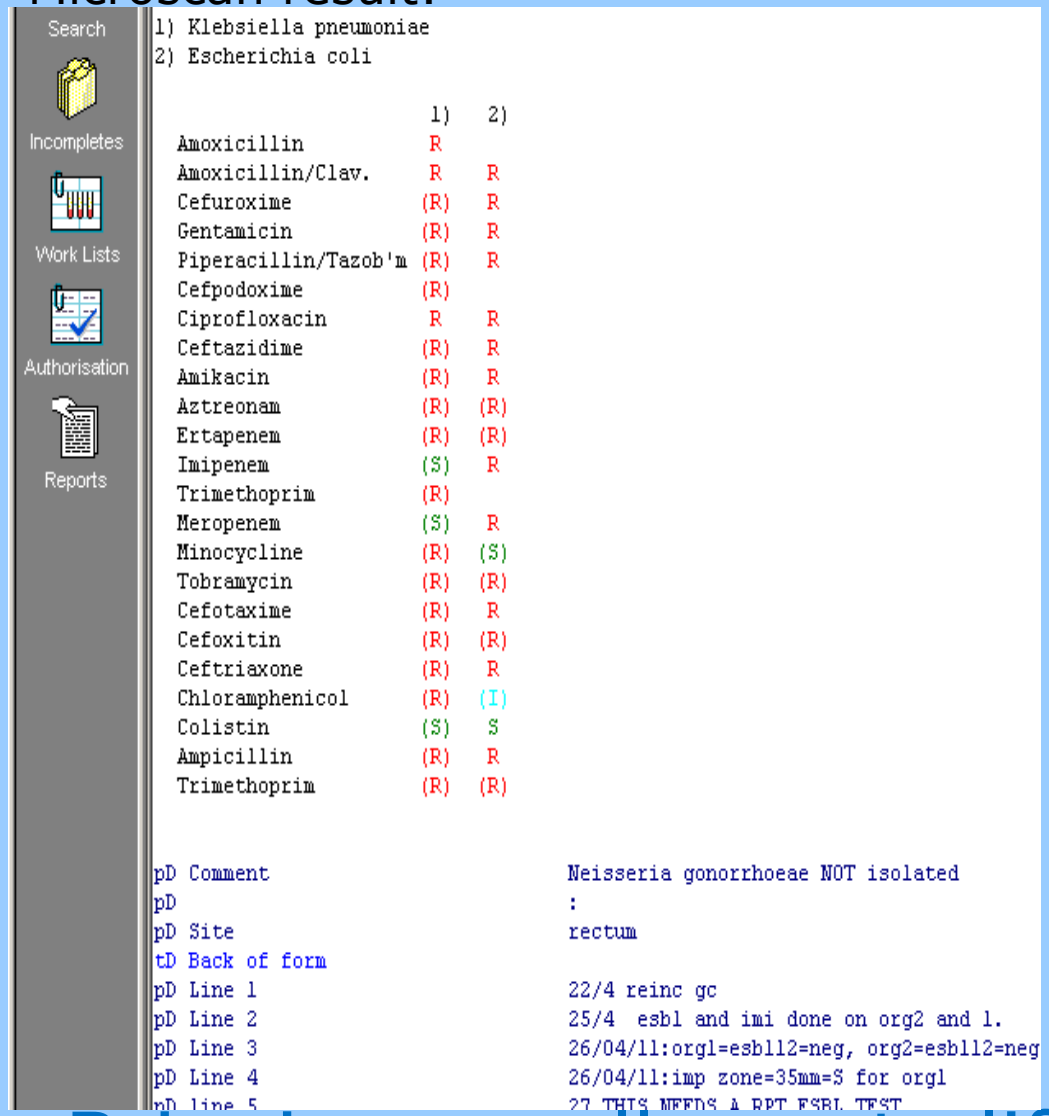
- ***E. coli***
  - PCR + ve for genes encoding for: NDM metallo-carbapenemase , TEM and CTX-M1 ESBLs, rmtB 16S methyltransferase, QnrB and S quinolone protection proteins
  - PCR -ve for SHV, plasmidic AmpC, OXA-1, VEB, PER, GES ESBLs; KPC, IMP, VIM, GIM, SPM, SIM carbapenemases, QnrA quinolone protection proteins

NB NDM- characterised as NDM-5, a new variant of NDM

- Much more active than previously described NDM enzymes (i.e. even more resistant!)
- 2 amino acid substitutions in active site V. NDM-1 (one amino acid)

25.4.11 (Easter Monday):

Microscan result:



1) Klebsiella pneumoniae
2) Escherichia coli

	1)	2)
Amoxicillin	R	
Amoxicillin/Clav.	R	R
Cefuroxime	(R)	R
Gentamicin	(R)	R
Piperacillin/Tazob'm	(R)	R
Cefpodoxime	(R)	
Ciprofloxacin	R	R
Ceftazidime	(R)	R
Amikacin	(R)	R
Aztreonam	(R)	(R)
Ertapenem	(R)	(R)
Imipenem	(S)	R
Trimethoprim	(R)	
Meropenem	(S)	R
Minocycline	(R)	(S)
Tobramycin	(R)	(R)
Cefotaxime	(R)	R
Cefoxitin	(R)	(R)
Ceftriaxone	(R)	R
Chloramphenicol	(R)	(I)
Colistin	(S)	S
Ampicillin	(R)	R
Trimethoprim	(R)	(R)

pD Comment	Neisseria gonorrhoeae NOT isolated
pD	:
pD Site	rectum
tD Back of form	
pD Line 1	22/4 reinc gc
pD Line 2	25/4 esbl and imi done on org2 and 1.
pD Line 3	26/04/11:org1=esbl12=neg, org2=esbl12=neg
pD Line 4	26/04/11:imp zone=35mm=S for org1
pD Line 5	27 THIS NEEDS A RPT ESBL TEST

NDM *E.coli* MIC by Etest:

>32 mg/L (R):
All Beta-lactams,
Aminoglycosides
Quinolones

Tigecycline- 0.5 mg/L (S)
Colistin MIC 0.38 mg/L (S)

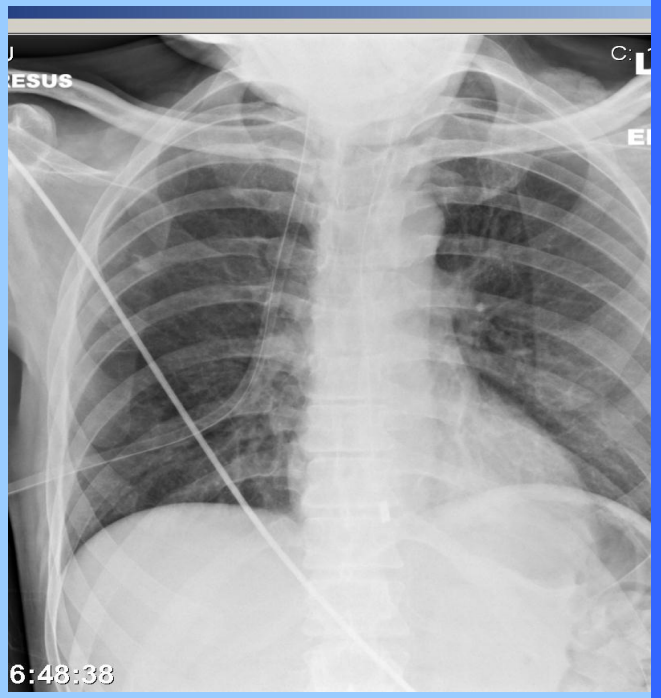
25.4.11

- Reviewed on medical ward round-
  spiking **high grade fever-** 40^0C.
- **Commenced on Meropenem + Vancomycin**
- CXR requested- normal

26.4.11

- Patient **Isolated**
- **1 to 1 nursing** agreed to

(NB Practical problems- staffing, cost, etc particularly for long term care)



30/4/11:

- WCC & CRP coming down slowly
- **Fever settling**

6/5/11:

- **Patient clinically better- Antibiotics stopped**
- Getting physiotherapy
- Unable to transfer patient to community hospital for rehabilitation

- Family (Brother in Basingstoke) unhappy to have patient home for rehab (also young children at home)
- **Weekly screens (rectal swabs) for NDM-** goal 3 negatives as in MRSA screening
- **Screens 16.06.11; 26.06.11; 4.07.11; 12.07.11- All positive for NDM *E.coli.*** Last screen also positive for *K.pneumoniae* (ESBL). Same sensitivity pattern as original isolates.
- But continued to make **good progress with Physiotherapy**
- **15/7/11- Discharged home (Basingstoke)**

NDM- What should we do?

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Infection Control meetings, Emails, Discussion with HPA/CCDC:

- **Strict infection control precautions to prevent further spread**:
- **Isolate** with **1:1 nursing. Limit healthcare worker contacts** with colonised patient
- **Restrict movement of colonised patient** unless absolutely necessary.
- Consider **separate toilet facilities** when the patient is ambulant.
- Step up **cleaning** and assure the quality of any **terminal cleaning**.
- **Screen other patients in the unit for NDM** to determine a) extent of transmission; b) actions to take to prevent further spread/outbreak (isolation/cohort nursing, closure of ward to new admissions) and c) whether change in antibiotic treatment required.
- **Flag NDM positive patient** so that infection control precautions can be implemented promptly on re-admission of patient.

NDM (2)- What should we do?

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- **Urgently review Trust antibiotic policy:**
  - Consider **Constraining use of carbapenems**
- Develop **Treatment protocol** for those presenting with suspected infection and a history of NDM colonisation.
- Develop a **Communication strategy** to explain what we are doing and why we are doing it (liaise with Trust Com Dept).
- Develop **Patient information sheet**.
- **Liaise with the local HPU** and agree policy for any **community implication**.
- Develop **Laboratory screening protocol** (see below)

Laboratory screening of NDM- important issues to consider (1)

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NB NDM is ultimately a gut organism- a coliform!

- **Who to screen**?
  - Routine?
  - **Targeted/high risk**: contacts of a +ve case, history of healthcare in the Indian subcontinent in the last year, household/community contacts?
  - Staff admitted to hospital and with a history of caring for a patient with NDM?

- **What specimens** to take & **how many** (rectal swab/faeces, urine, respiratory etc)?
- **When to screen** & **how frequently** (on- or pre-admission, post discharge)?

NDM Screening (2)

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- **Which media to use for screening?**
  - E.g. Maconkey with a carbapenem disc (+/- pre-enrichment in broth), Chromagar KPC agar (BD), Brilliance CRE agar (Oxoid/TFS)
  - **Sensitivity & Specificity** of available media (NB A double edged sword!); Also PPV & NPV. **Screening- sensitivity should be high**
- **What confirmatory tests to use?** (need **high specificity**!)- Disc diffusion/automated system >> (Hodge/Cloverleaf test) or Synergy test (Etest MBL- Imp v Imp +EDTA) >>Molecular identification of carbapenemase/NDM gene (by PCR).
- **Implication of a NDM positive screening result?** Being a gut organism, can not decolonise in the same way as for MRSA. **Ethical issues**
- **When to stop screening?** How many negative screens? What does a negative screen really mean? What is the threshold for detection (sensitivity)? How long GI carriage lasts? Effect of antibiotic treatment?
- **Who pays for the cost of screening?** Clinical Departments ? GP? Or does the lab absorb the cost?

Back to our NDM Patient
(Discharged home 15/7/11)

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- **Detail discussions with CCDC, GP, & Microbiologists/ICD** at Basingstoke Re Follow-ups, including **rectal swabs for NDM screening** + sending isolates to RLH for more detail testing & characterisation (including molecular)
- **How often to screen?**
  - **Initially monthly** (More practical- less disruptive to personal & family life & less hassle for the GP). Using same media as at RLH (Oxoid Brilliance CRE agar)
  - Once **3 negative screens**, then screen: yearly; after antibiotic treatment; if and when admitted to hospital.
  - **Patient has 2 negative screens so far post discharge**
- **Dilemma about screening family contacts at home**: What to do if positive……. And if admitted to hospital for other reasons?

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NDM *E.coli* screening 17 June 2011

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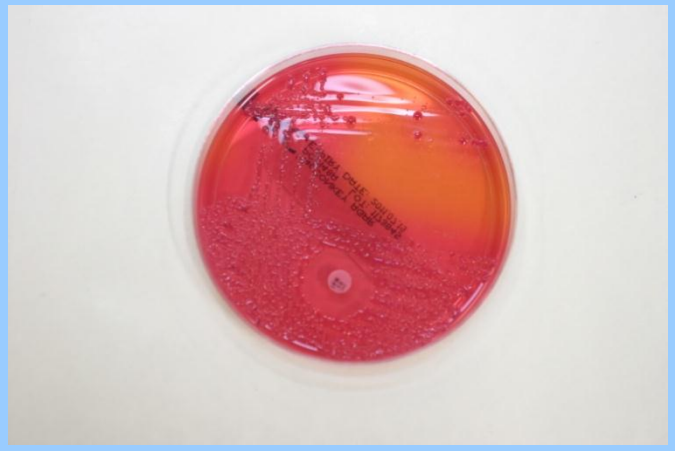
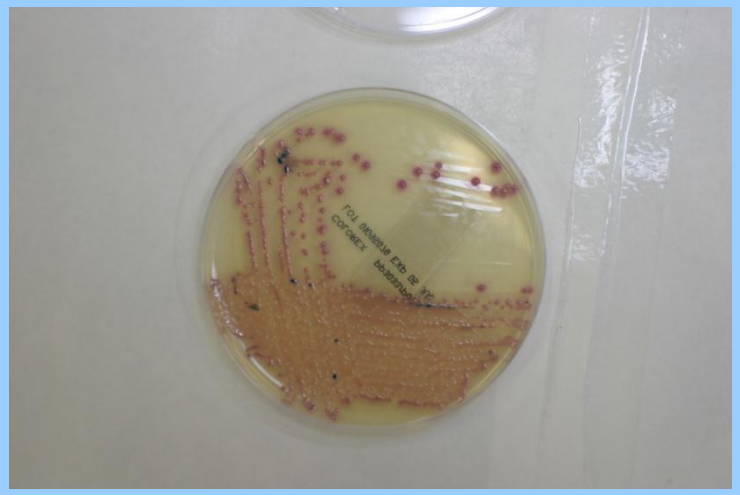
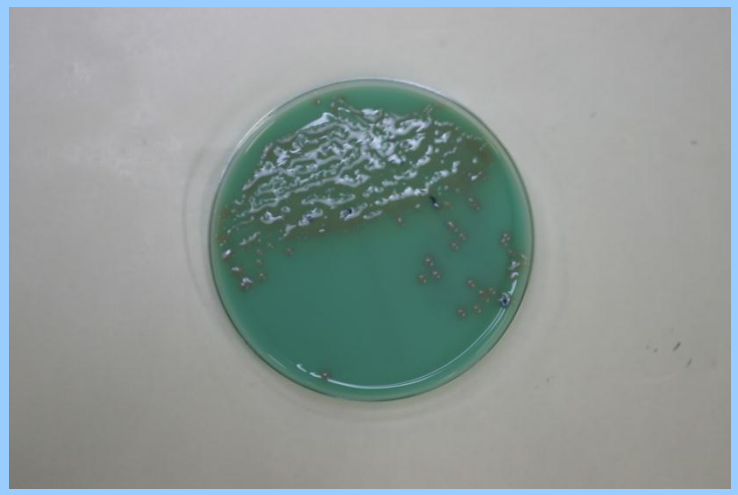
Maconkey + Imipenem disc (10mcg)



BBLChromagar
KPC agar (BD)



Oxoid Brilliance CRE agar



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Brilliance CRE Agar (Courtsey of Oxoid/TFS)

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E. coli- Pale- pink

KESC group- Blue

Non-CRE organisms -white or pigmented colonies

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Laboratory detection of MBL-producing organisms

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- **Can be especially difficult with routine susceptibility testing methods** (including Disc diffusion, Automated systems-Phoenix (BD), MicroScan (Siemens), Vitek-2 (bioMerieux))
- **MIC: Spectrum- low to very high**. Therefore can be missed sometimes (i.e. appear sensitive). Ertapenem better for screening carbapenem resistance in these strains (i.e. phenotypically: R to Ertapenem, S to Imipenem & Meropenem)
- Many were susceptible to carbapenems using CLSI susceptibility definitions in place prior to 2010.
- Additionally MBL E-test cannot consistently identify MBL-producing organisms.
- **Advice- If suspicious**/borderline on initial screening/testing, **send isolate to Ref Lab** (e.g. HPA Colindale) **for genotypic confirmation of MBL** (PCR using specific primers)

Cloverleaf ('Hodge') test

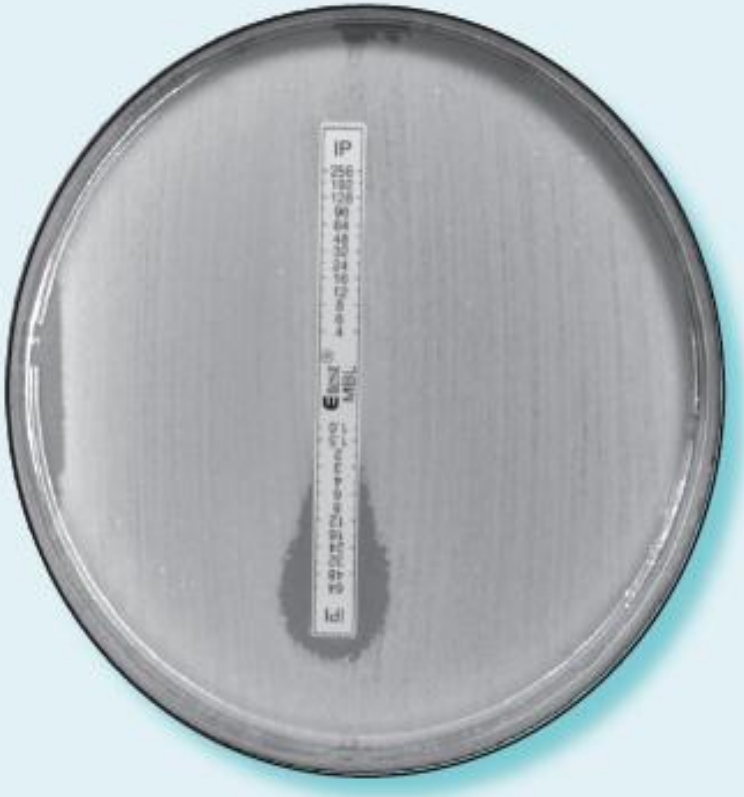
- Agar is spread with *E. coli* NCTC10418 (or ATCC25922), as for a disc test.
- The test strain is then inoculated, as 3 arms, 120° apart, cut into or streaked heavily on the agar from the plate centre.
- Imipenem, meropenem and ertapenem 10 µg discs are put at the end of these arms.
- Indentation of the inhibition zone(s) indicates that the test strain attacks carbapenems.

Caveats are that reading is subjective and that AmpC enzymes can give weak false positive results.

Synergy tests

- Metallo carbapenemases (IMP, NDM, VIM) are inhibited by EDTA or dipicolinic acid.
- Synergy between carbapenems and EDTA, indicating MBL production, can be detected with Etests (see below) or using double disc tests (with EDTA discs from e.g., Rosco).
- Caveats are that false-positive results are common with *P. aeruginosa* and *A. baumannii*, though rare with Enterobacteriaceae.

KPC carbapenemases are inhibited by boronic acids, and synergy between boronic acid discs (Rosco) and imipenem indicates their presence.



Carbapenem Resistant Enterobacteriaceae (CRE)- HPA data/figures

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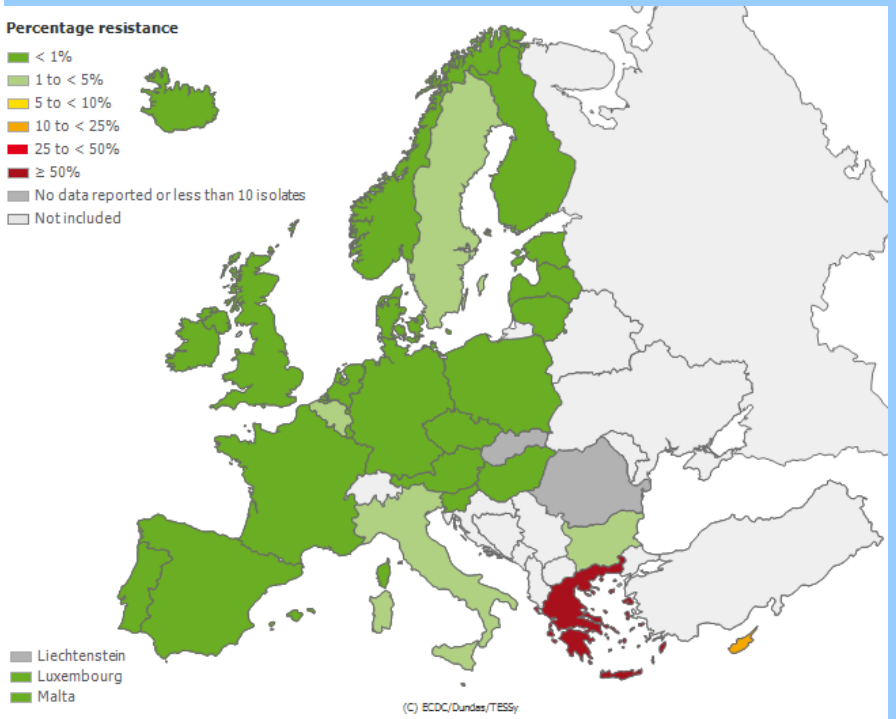

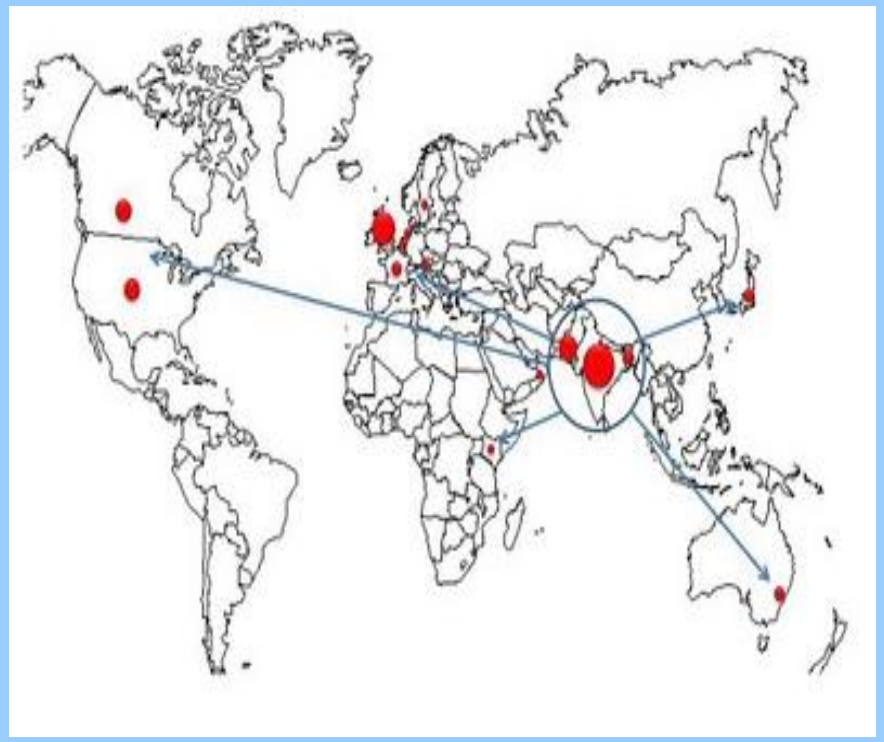

2009: CRE limited to Greece, India, Israel and US

Post 2009: NDM-1 spread

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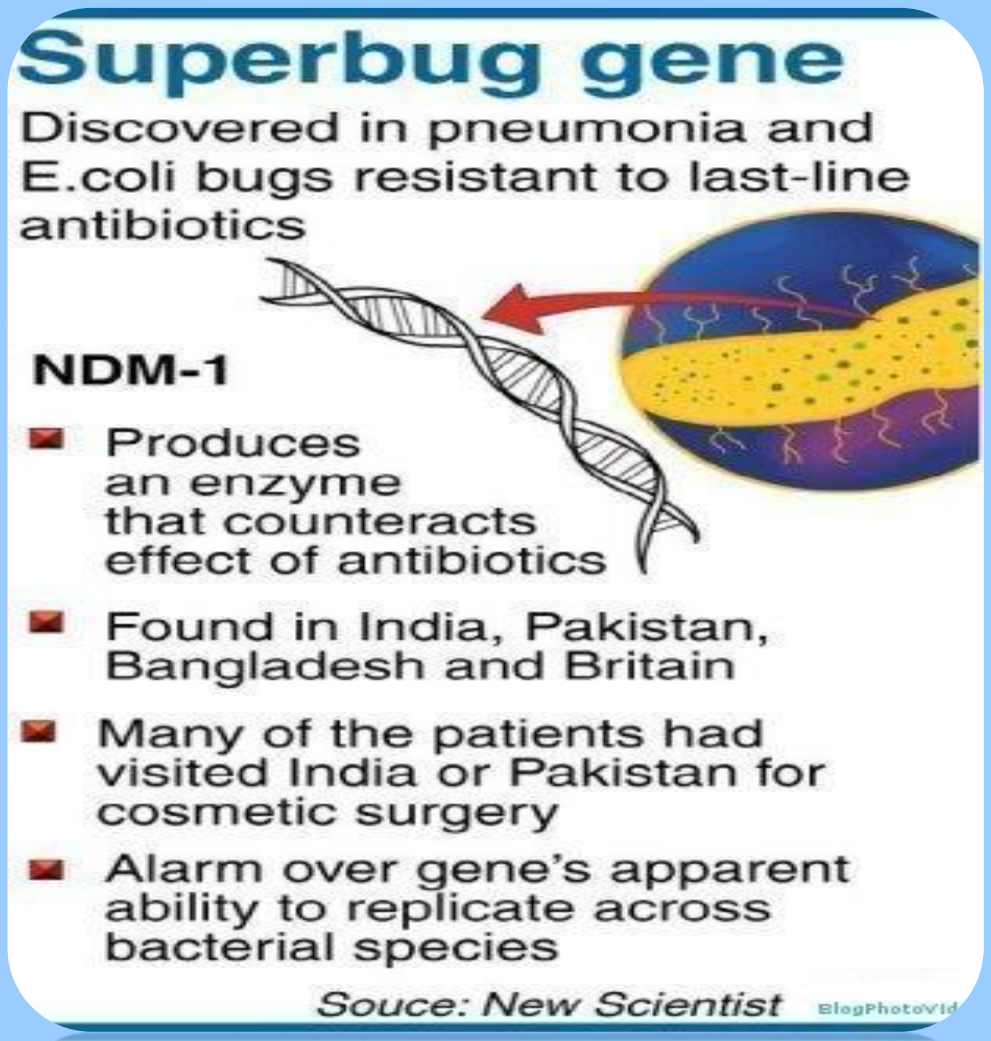
Travel makes patients vulnerable



- The superbug called New Delhi metallo-beta-lactamase, or NDM-1, was identified in 50 people who traveled to India or Pakistan for surgery and then returned to the United Kingdom, British scientists reported in the journal **Lancet Infectious Diseases** (Kumarasamy et al 2010; 10: 597-602)

ARHAI
Department of Health
*Advisory Committee on **A**ntimicrobial **R**esistance*
*and **H**ealthcare **A**ssociated **I**nfection*

Health Protection Agency

Advice on Carbapenemase Producers: Recognition, infection control and treatment

Carbapenems (imipenem, meropenem, ertapenem and doripenem) are invaluable for the treatment of infections due to multi-resistant gram-negative bacteria, including those with extended-spectrum β-lactamases. Carbapenem-resistant Enterobacteriaceae remain rare but are emerging. Their transmission characteristics and pathogenesis resemble those of more sensitive Enterobacteriaceae, but the infections are much more difficult to treat. For this reason, it is vital that NHS Trusts prevent their spread. Carbapenem resistance in Enterobacteriaceae can involve:

Combinations of ESBL or AmpC and porin loss: Porin loss is often unstable and may impose a fitness cost, meaning that these strains rarely spread. Ertapenem is particularly affected.

Acquired carbapenemases: These are the more serious risk and are beginning to spread in Enterobacteriaceae already resistant to multiple antibiotics. Several types occur, some with close geographic associations. They belong to three molecular classes: IMP, VIM and NDM types are metallo enzymes, with zinc at the active site; whereas KPC and OXA-48 belong to separate non-metallo families. Other carbapenemases (SME, IMI, SPM) occur, but are very rare.

Main Carbapenemases: distribution and molecular epidemiology

	Geographic distribution	Molecular epidemiology
NDM	Widespread in Enterobacteriaceae (esp. *K. pneumoniae* and *E. coli* in India and Pakistan. Imported to UK via patients with travel / hospitalisation / dialysis in India / Pakistan.	Diverse strain types in UK. Plasmid spread among strains and species is more important than clonal spread among patients. Nevertheless there have been a few cases of cross-infection in the UK.
VIM	Scattered globally, endemic in Greece; mostly *K. pneumoniae*. Sometimes imported to UK via patients previously hospitalised in Greece.	Plasmid spread among strains is more important than clonal spread of producer strains.
IMP	Scattered worldwide; no clear associations.	Mostly plasmid spread.
KPC	USA since 1999. Prevalent also Israel, and Greece; outbreaks elsewhere in Europe. Some UK cases imported via patient transfers, but local spread in NW England.	Some plasmid spread: mostly among *K. pneumoniae*, occasionally to other Entero-bacteriaceae. Also clonal spread, including global *K. pneumoniae* ST258 lineage.
OXA-48	Widespread *K. pneumoniae* in Turkey, Mid-East and N. Africa. Some import to UK and an outbreak in one London renal unit 2008-9.	Mixture of plasmid and clone spread.

Actions to minimise risk of carbapenemase spread

Good practice actions	Number of cases		
Trust engagement	0	1	>1
Ensure the Board and Executive make it a high priority to mimimise carbapenemase spread, and are supportive of all prevention and eradication measures.	✓	✓	✓
Prepare a containment action plan (all trusts need to be prepared).	✓		
Laboratory			
Optimise and review laboratory methods to detect producers.	✓	✓	✓
Screen by plating faeces, rectal swabs and manipulated site swabs e.g. from skin breaks / catheter sites onto MacConkey or CLED agar with meropenem or ertapenem discs. Examine for colonies within the zone. Prior broth enrichment may be useful: use a rectal swab to inoculate 5-10 ml broth containing a 10 µg imipenem disc, then subculture as above.		✓	✓
Infection Prevention & Control			
Identify places for effective isolation, e.g. en-suite side rooms / cohort areas and prepare criteria for ward closure to new admissions / re-opening.	✓		
Develop an effective decontamination strategy for equipment. Employ dedicated or single use equipment where decontamination is impracticable.	✓		
Implement the containment action plan immediately, with meticulous adherence to standard and infection control precautions with patients isolated in a single room with en suite bathroom or dedicated commode.		✓	✓
Optimise care bundles and clinical practice for indwelling devices.	✓	✓	✓
Reinforce and optimise hand hygiene with soap and water.		✓	✓
Screen ALL index and secondary case contacts: case-find and isolate immediately, determining the extent of spread, flagging patient record.		✓	✓
Instigate weekly and discharge screening of all patients in affected units / wards until organism eliminated. Do not screen staff for carriage unless there is strong evidence to do so. Prolonged urine carriage has been noticed in some patients without faecal carriage. Screening of household contacts of patients is controversial, but could be considered.		✓	✓
Minimise spread by effective enhanced and terminal cleaning including of high contact and sanitary areas (consider increased frequency and use of a disinfectant).		✓	✓
Employ cohort staffing depending on risk assessment.		✓	✓
Review effective decontamination of equipment.		✓	✓
Ensure incident tracking, with epidemiological graphs and tables if transmission detected.		✓	✓
Prepare a readmission and transfer strategy for affected patients.		✓	✓
Ensure adequate communication to other healthcare providers.		✓	✓
Hospital-wide			
Run awareness and training campaign for medical and nursing staff.	✓	✓	✓
Screen high-risk patients on admission, e.g. known positives, those with previous hospitalisation /dialysis in countries where producers are prevalent.	✓	✓	✓
Hold regular incident management team meetings to review infection prevention and control strategies, including root cause analyses where applicable (if transmission detected).		✓	✓
Implement isolation strategy at triage / admission for high-risk patients.	✓		
Implement communication strategy. Report as SUI to SHA and HPU (DH letter PL/CMO/2003/4).			✓
Ensure that any transmission becomes a top Trust priority, with leadership from Board to Ward.			✓

Carbapenemase-mediated resistance in the UK

n = 1315- excludes *A. baumannii* with OXA-types

(ARMRL, Unpublished data – Courtesy of Prof Neil Woodford)

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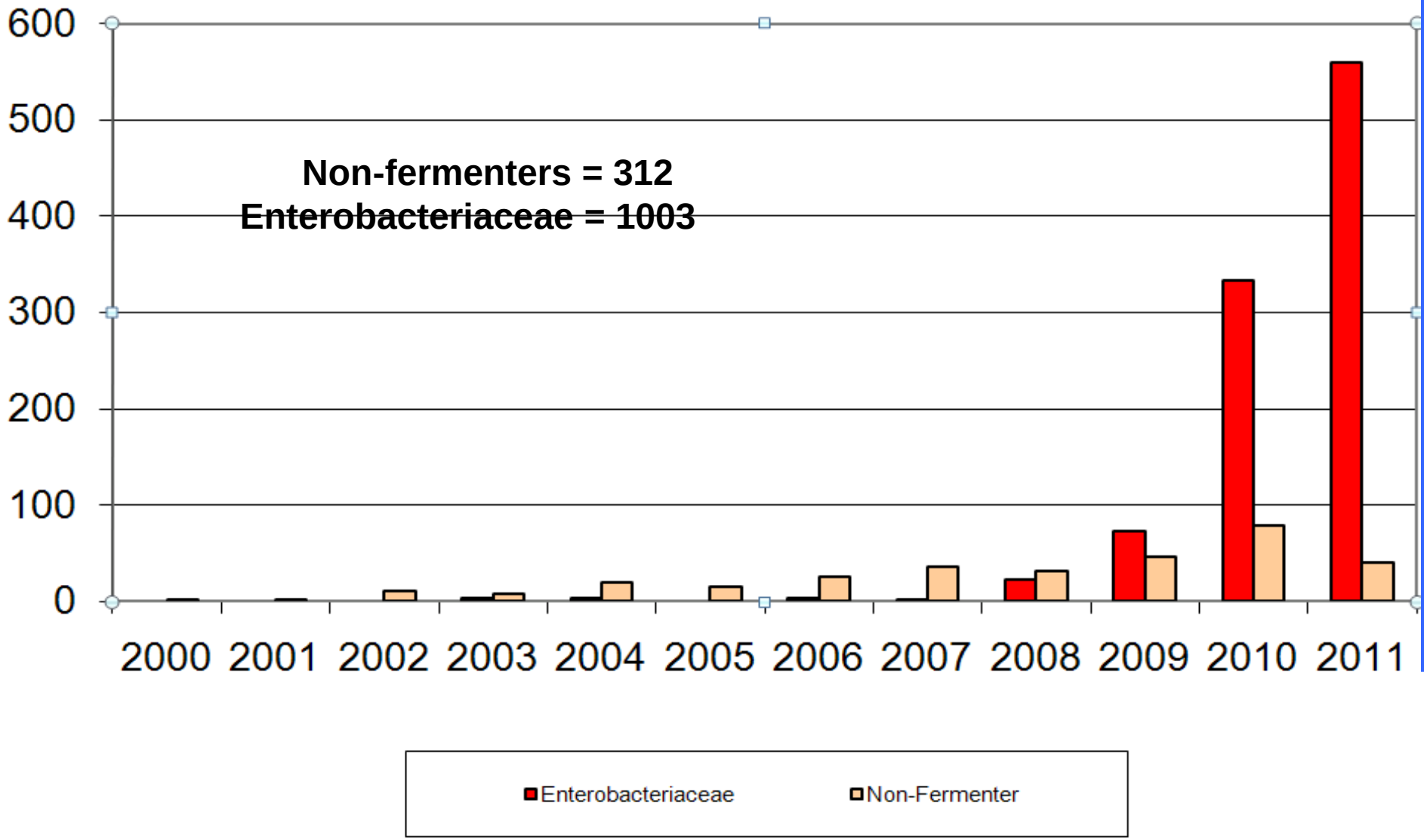

Carbapenemase-producing Enterobacteriaceae in the UK

n = 1003 (HPA ARMRL, Unpublished data)

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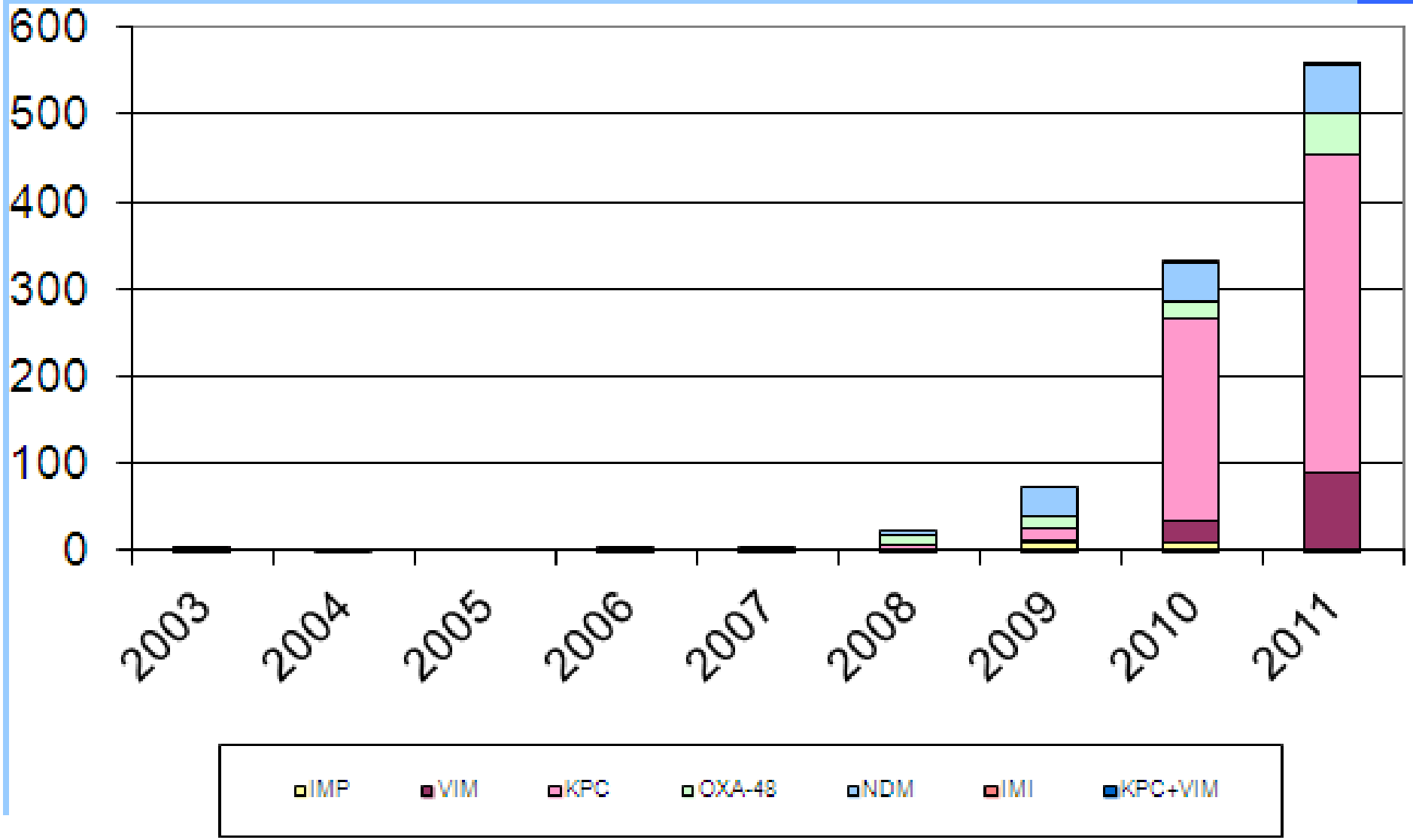

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***Enterobacteriaceae* producing carbapenemases in the UK (2003-11) HPA data**

Genus	Carbapenemase type							Total (%)
	IMI	IMP	KPC	KPC+VIM	NDM	OXA-48	VIM	
Citrobacter spp.	–	–	1	–	3	–	1	5 (1)
Enterobacter spp.	2	8	29	–	11	1	7	58 (9)
Escherichia coli	–	2	26	–	22	10	1	61 (9)
Klebsiella spp.	–	13	325	1	71	46	71	527 (80)
Morganella morganii	–	–	–	–	1	–	–	1 (0.2)
Providencia stuartii	–	–	–	–	1	–	–	1 (0.2)
Raoultella spp.	–	–	2	–	–	–	1	3 (0.5)
Serratia spp.	–	–	1	–	–	–	–	1 (0.2)
Total	2	23	384	1	109	57	81	657 (100)

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Antibiotic susceptibilities of carbapenemase-producing *Enterobacteriaceae* from the UK 2003-2011 (HPR, 2011; 5: issue 24 -17/06/11; Woodford & Livermore)

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Antibiotic	% Susceptibility [a]					
	Metallo-enzyme Producers (IMP, NDM or VIM)			Non-metallo-enzyme Producers (KPC or OXA-48-like)		
	E. coli	*Klebsiella*	*Enterobacter / Citrobacter*	*E. coli*	*Klebsiella*	*Enterobacter / Citrobacter*
Imipenem	**9%**	**1%**	3%	10%	5%	18%
IPM+EDTA [b]	**100%**	**99%**	100%	27%	8%	27%
Meropenem	**9%**	**5%**	3%	47%	8%	27%
Ertapenem	**0%**	**0%**	0%	0%	0%	0%
Ampicillin	**0%**	**0%**	0%	0%	0%	0%
Co-amoxiclav	**0%**	**0%**	0%	0%	0%	0%
Piperacillin	**0%**	**0%**	3%	0%	0%	0%
PIP + tazobactam	**4%**	**0%**	7%	0%	0%	0%
Cefotaxime	**0%**	**0%**	0%	3%	2%	0%
Ceftazidime	**0%**	**0%**	0%	17%	6%	0%
Aztreonam	**4%**	**18%**	13%	13%	6%	0%
Ciprofloxacin	**9%**	**10%**	17%	53%	49%	50%
Gentamicin	**0%**	**12%**	27%	70%	65%	41%
Tobramycin	**0%**	**1%**	0%	50%	58%	50%
Amikacin	**17%**	**32%**	50%	90%	85%	91%
Colistin	**100%**	**97%**	93%	100%	92%	100%
Tigecycline	**100%**	**47%**	47%	100%	74%	68%

a. Susceptibility defined using BSAC v. 10.1 breakpoints [7].

b. Diagnostic test to distinguish metallo- from non-metallo- enzymes; not for therapeutic use.

Multi-resistance is the norm

Active *vs.* ≥90% producers	Active *vs.* >75-89% producers
Active *vs.* 50-74% producers	Active *vs.* <50% producers

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Drug	Potential	Limitations
Polymyxin B and E (colistin) (i.v.)	Active vs. >90% of producers. Case reports of successful use in a range of infections due to carbapenemase producers.	Significant nephro- and neuro-toxicity and poor lung penetration. Use high dose, with possible addition of nebulised colistin in pneumonia.
Tigecycline (i.v.)	Active in vitro vs. most carbapenem-resistant *E. coli*. Licensed for skin and soft tissue and complicated intra-abdominal infections. Case reports of success in various infections with carbapenemase producers.	Low blood concentrations; off-label use should be cautious; unsuitable in urinary infections as only 22% excreted in urine. Excess deaths in some trials, esp. ventilator pneumonia (not a licensed indication). Many *Klebsiella* only intermediately susceptible (MIC, 2 mg/L); some resistant.
Fosfomycin (oral and i.v.)	Active against most *E. coli* with carbapenemases, including NDM-1. Effective in urinary infections.	Borderline susceptibility common in *Klebsiella* spp. Risk of mutational resistance. Not marketed in the UK, but pharmacists can import.

NDMs a cause for concern because:

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- **Extremely limited therapeutic option due to XDR**
- **Promiscuous- Plasmid spread across species barrier**
- **IC implications- Eradication difficult** (Gut organism!), **prevention & control costly**
- **Maintain high index of clinical & lab suspicion- Risk factors, reduced susceptibility to carbapenems**
- **Rapid & reliable testing & screening methods** (for the detection of CRE/NDM) **essential** to prevention & control as well as for optimsing antimicrobial therapy !

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Any Question?

THANK YOU!

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