Rhonda Stuart
Monash Health

Carbapenem Resistant Enterobacteriaceae

Outline

- A case
  - A reflection of a recent case
- Epidemiology
  - What is happening out there?
- Infection Control
  - Guidelines
  - Emphasis on
    - Governance, screening, cleaning

The Case

- It's a weekend and the IT system is down
- Old patient admitted
  - Placed in 4 bed room in MRSA precautions
  - Shared bathroom
- IC find patient 4 days later
  - Known CRE
- Screening of room contacts
  - 2 already discharged
  - Flagged for re-admission for a month
- Cohort - transmission based precautions

The Case

INFECTION CONTROL SCREEN

Specimen type Swab

Specimen site Rectal

Culture

1. Klebsiella pneumoniae

	ORGANISM 1
Amikacin	S
Amoxycillin	R
Augmentin	R
Cefazolin	R
Ceftriaxone	R
Ciprofloxacin	R
Cotrimoxazole	R
Ertapenem	R
Gentamicin	R
Meropenem	R
Piperacillin/Tazo	R
Tobramycin	R

Note: Carbapenem resistant Gram Negative Bacillus
This organism produced a Positive CarbaNP result indicating Carbapenemase production.

Screen Result – Contact 1

The Case

GENERAL MICROSCOPY AND CULTURE

Specimen type Swab

Specimen site Right malleolar wound

Gram Stain No polymorphs seen
+ Squamous epithelial cells
No organisms seen

Culture

1. ++ Klebsiella pneumoniae
2. ++ Pseudomonas aeruginosa
3. Skin flora

ORGANISM	1	2
Amikacin	R	
Amoxycillin	R	
Augmentin	R	
Cefazolin	R	
Cefepime	R	R
Ceftazidime	R	R
Ceftriaxone	R	R
Ciprofloxacin	R	S
Colistin	S	S
Cotrimoxazole	R	R
Gentamicin	R	S
Meropenem	R	S
[illegible]/Tazo	R	R
[illegible]	R	R
Tobramycin	R	

Klebsiella pneumoniae

Antimicrobial	MIC(ug/mL)	Interpretation
Colistin	1.0	Sensitive
Fosfomycin	3.0	Sensitive

Previous identified patient
Confirmed NDM 1

The Plot Thickens……

Current Data:Klebsiella pneumoniae

Amoxycillin|>=32|R
Augmentin|>=32|R
Timentin|>=128|R
Piperacillin/Tazo|>=128|R
Cephalexin|>=64|R
Cefazolin|>=64|R
Cefoxitin|>=64|R
Ceftazidime|>=64|R
Ceftriaxone|>=64|R
Cefepime|16|R
Meropenem|>=16|R
Amikacin|<=2|S
Gentamicin|<=1|S
Tobramycin|8|I
Ciprofloxacin|>=4|R

Isolates sent for WGS

Cleaning

- Fluorescent marker of room and ensuite

Area Marked	Cleaned
Shelf above hand basin	Yes
Hand basin taps	No
Hand towel dispens	Yes
Soap dispenser but	No
Hand basin taps	Yes
Shower taps	No
Shower hand rail	Yes
Shower chair	No
Over toilet commode chair push handle	No
Over toilet commode chair grab handle	No
Over toilet commode chair seat	Yes
Flush button	Yes
Nurse call button	No
Toilet hand rail	Yes
Toilet seat	Yes

53%

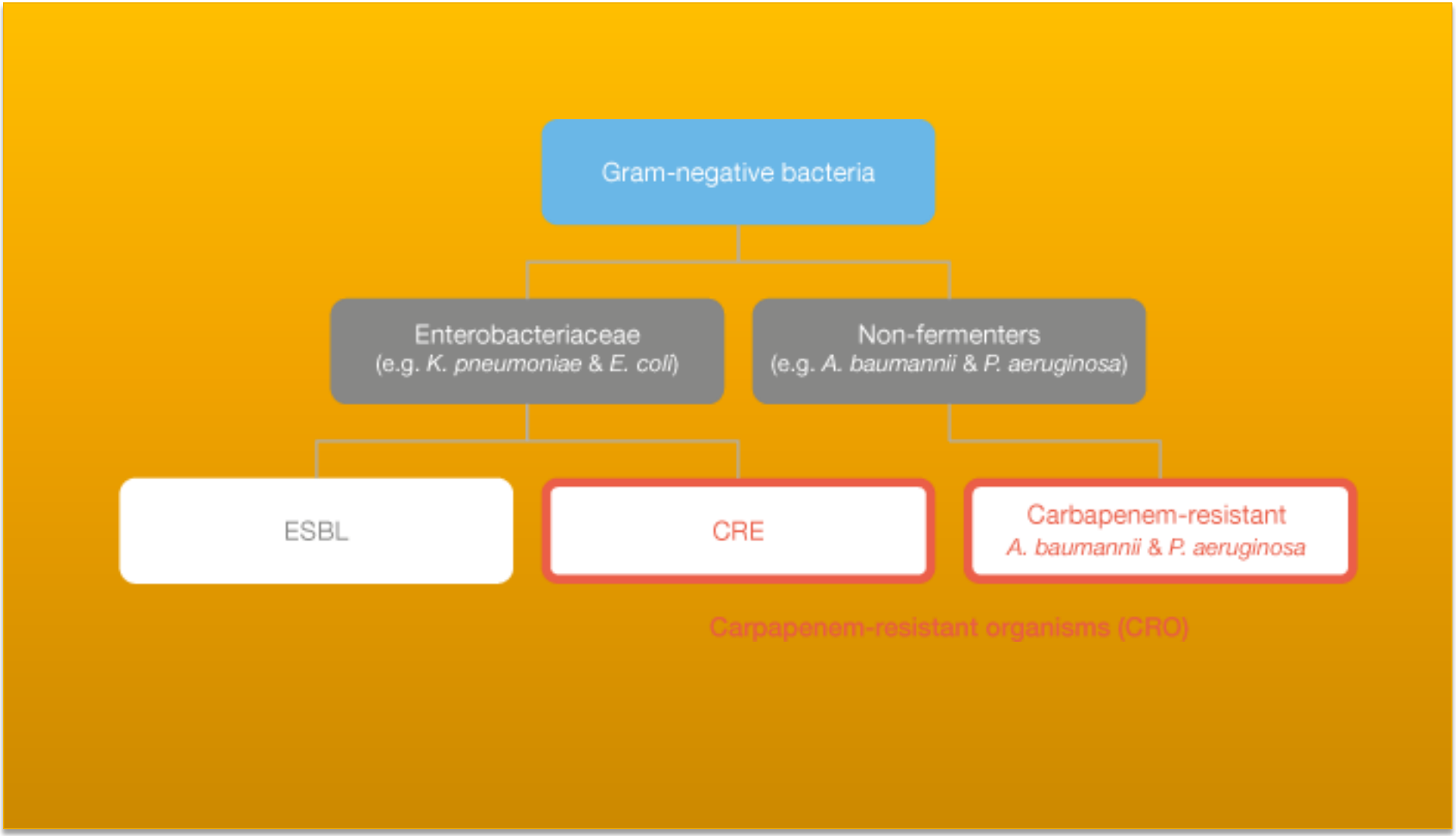
The Contacts

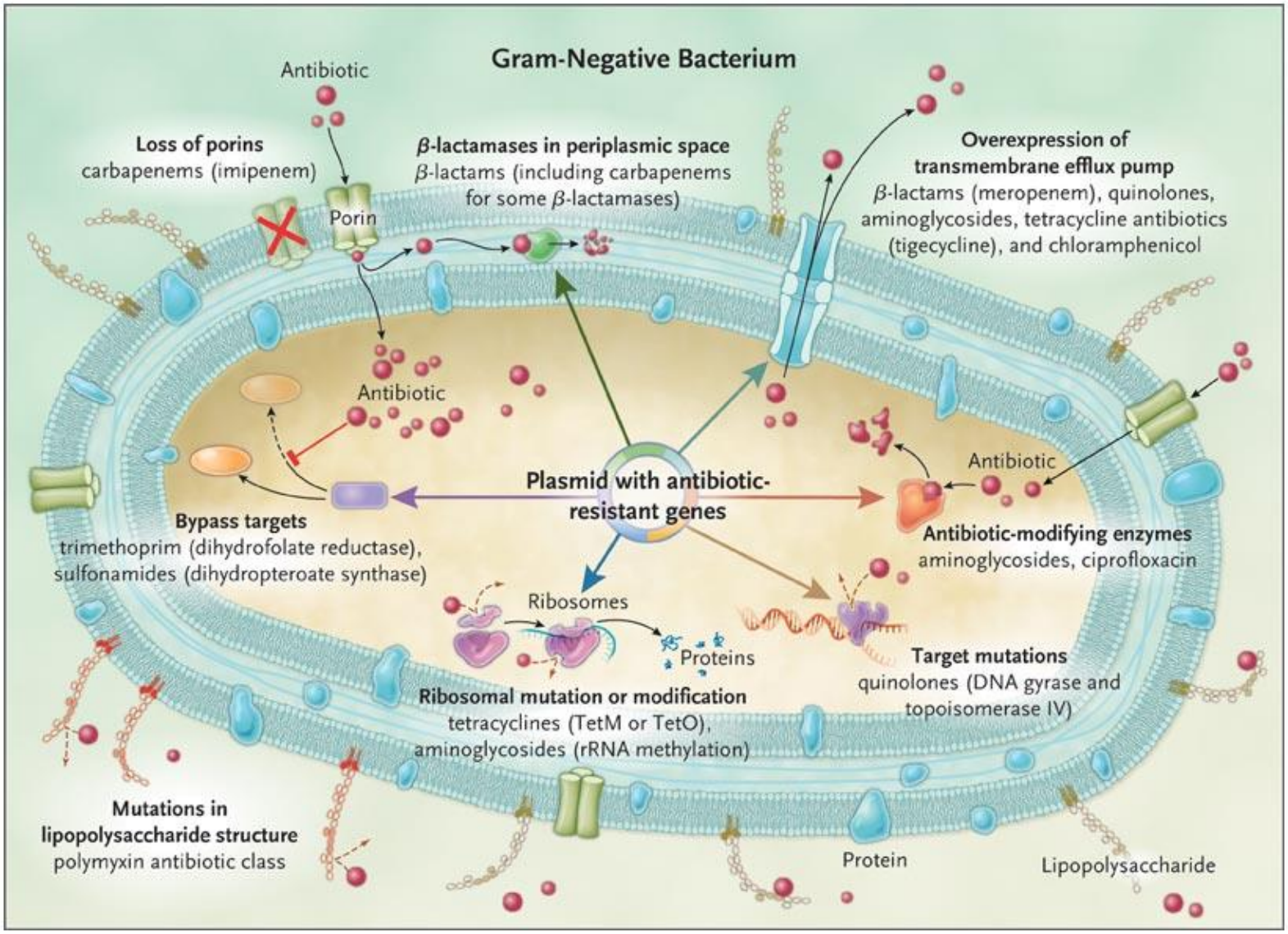
- Extended contact tracing to entire ward given likely transmission
- 21 additional screens completed
- All clear ……

Case Highlights

- Known cases require flagging on subsequent admissions
- Screening all close room contacts initially
- Extended once transmission obvious
- Cleaning – auditing important
- Benefits of markers system to monitor cleaning

What are CRE?


Gram-negative bacteria
Enterobacteriaceae
(e.g. K. pneumoniae & E. coli)
Non-fermenters
(e.g. A. baumannii & P. aeruginosa)
ESBL
CRE
Carbapenem-resistant
A. baumannii & P. aeruginosa
Carpapenem-resistant organisms (CRO)

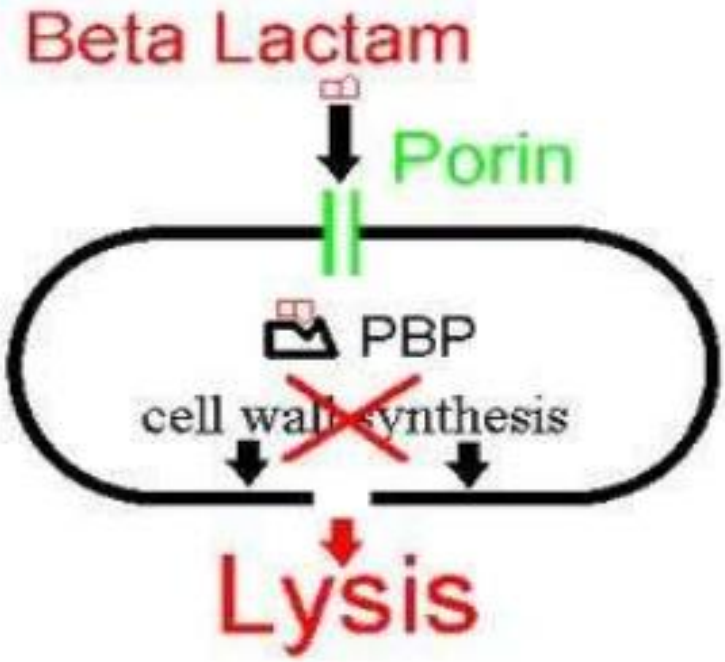


Peleg & Hooper . *N Engl J Med* 2010

CRE and CPE

Mechanisms of Carbapenem Resistance

- Carbapenemase hydrolyzing enzymes
- Porin loss "OprD"
- ESBL or AmpC + porin loss



Carbapenemase Producing Enterobacteriaceae

- Carbapenemases class A
  - K. pneumoniae carbapenemase (KPC)
  - GES, SME
- Carbapenemases class B
  - Metallo-β-Lacatamases: NCM-1, VIM, IMP
- Carbapenemases class D
  - Oxa-23, Oxa-24, Oxa-48, Oxa-58

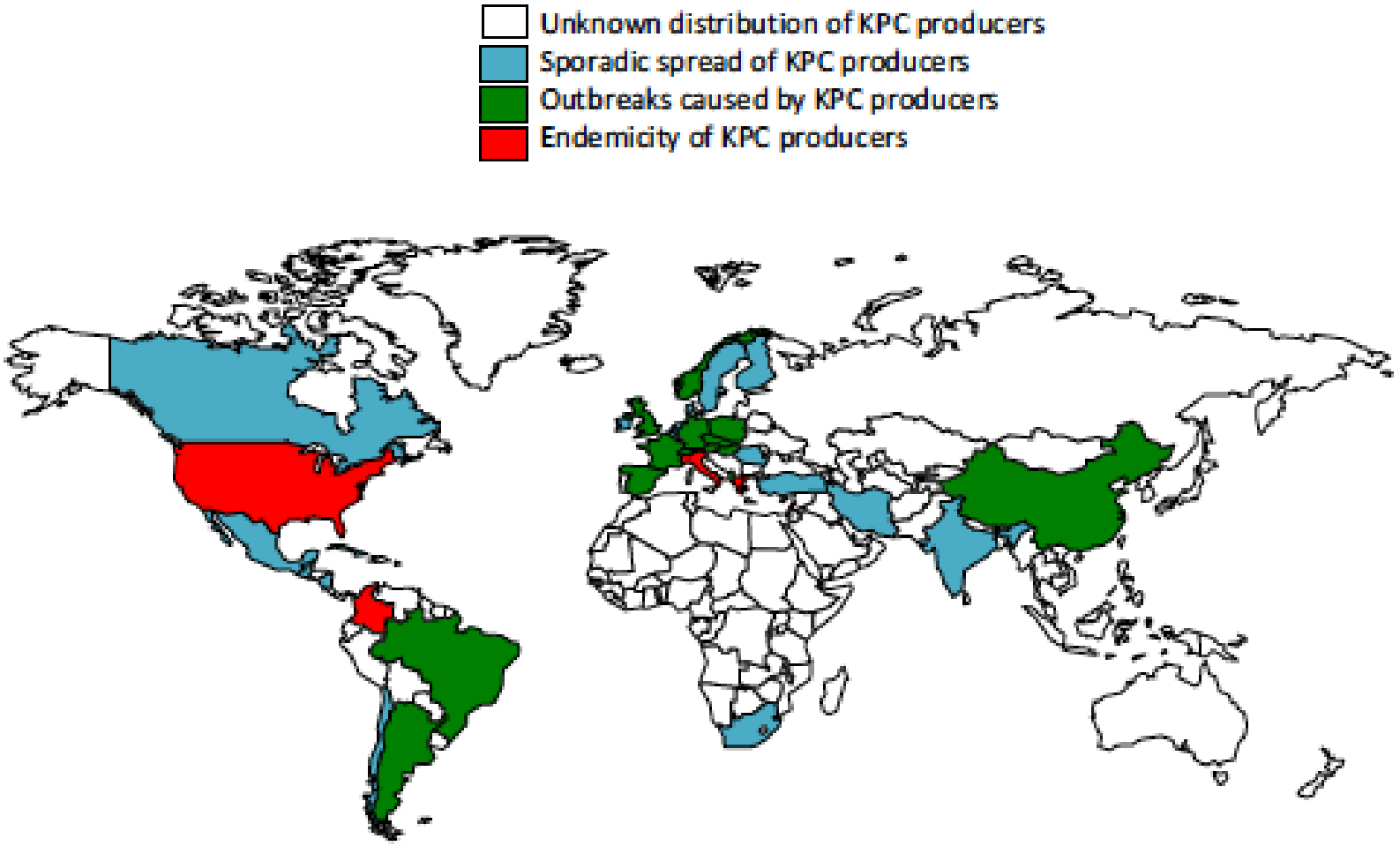
Confounding Issue:

Most of these genes are on mobile elements

CRE Epidemiology

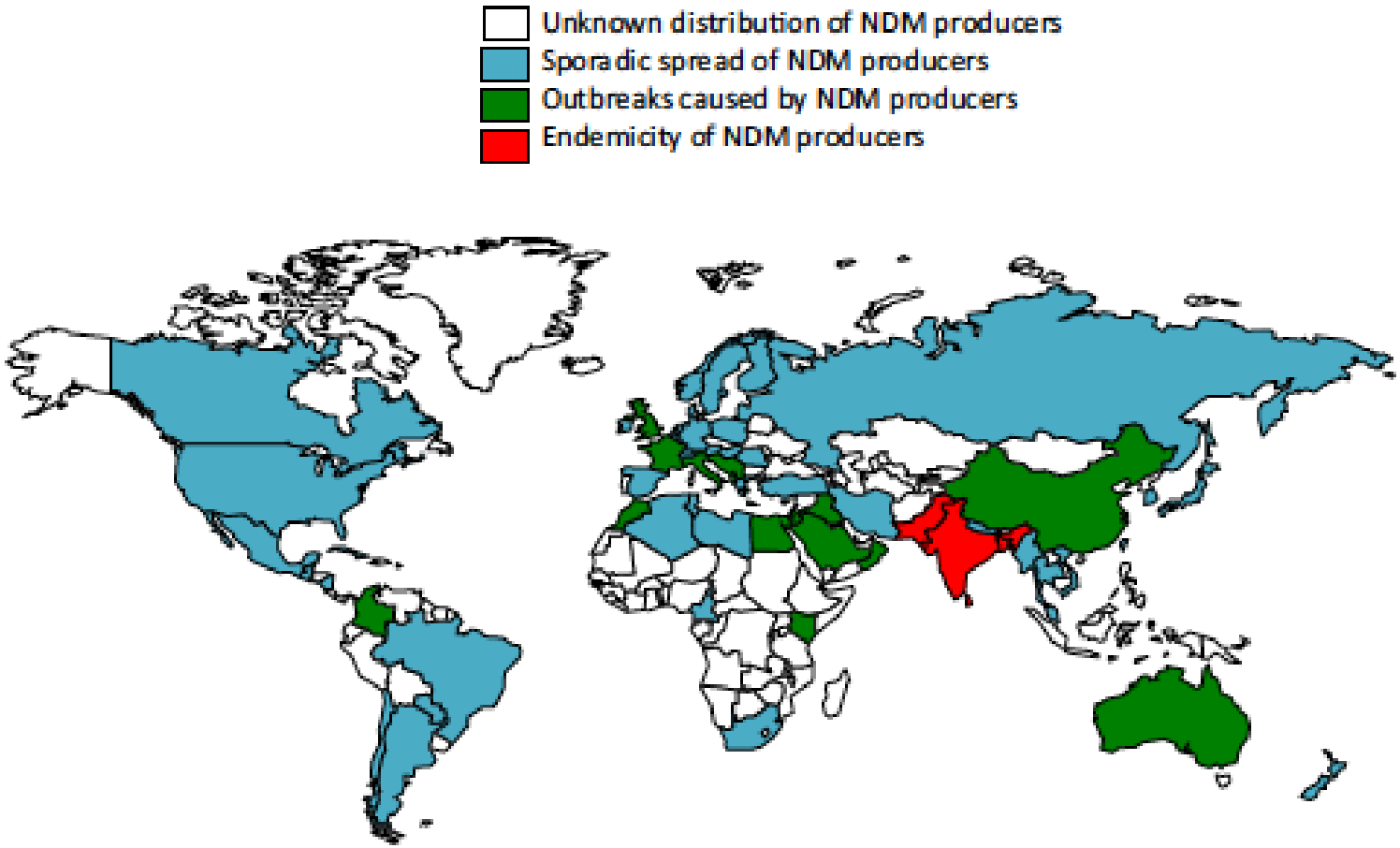
- 3 overlapping epidemics
  - Northeast United States
    - Epicentre of the *bla*$_{KPC}$ ST258 strains
    - Spread to Israel, Greece, Italy & Sth America
  - India and Pakistan
    - epicenter of the *bla*$_{NDM-1}$ epidemic
    - Spread to UK and Europe
  - Strains harboring *bla*$_{IMP}$ *bla*$_{VIM}$ and *bla*$_{OXA-48}$
    - commonly reported in Europe

KPC



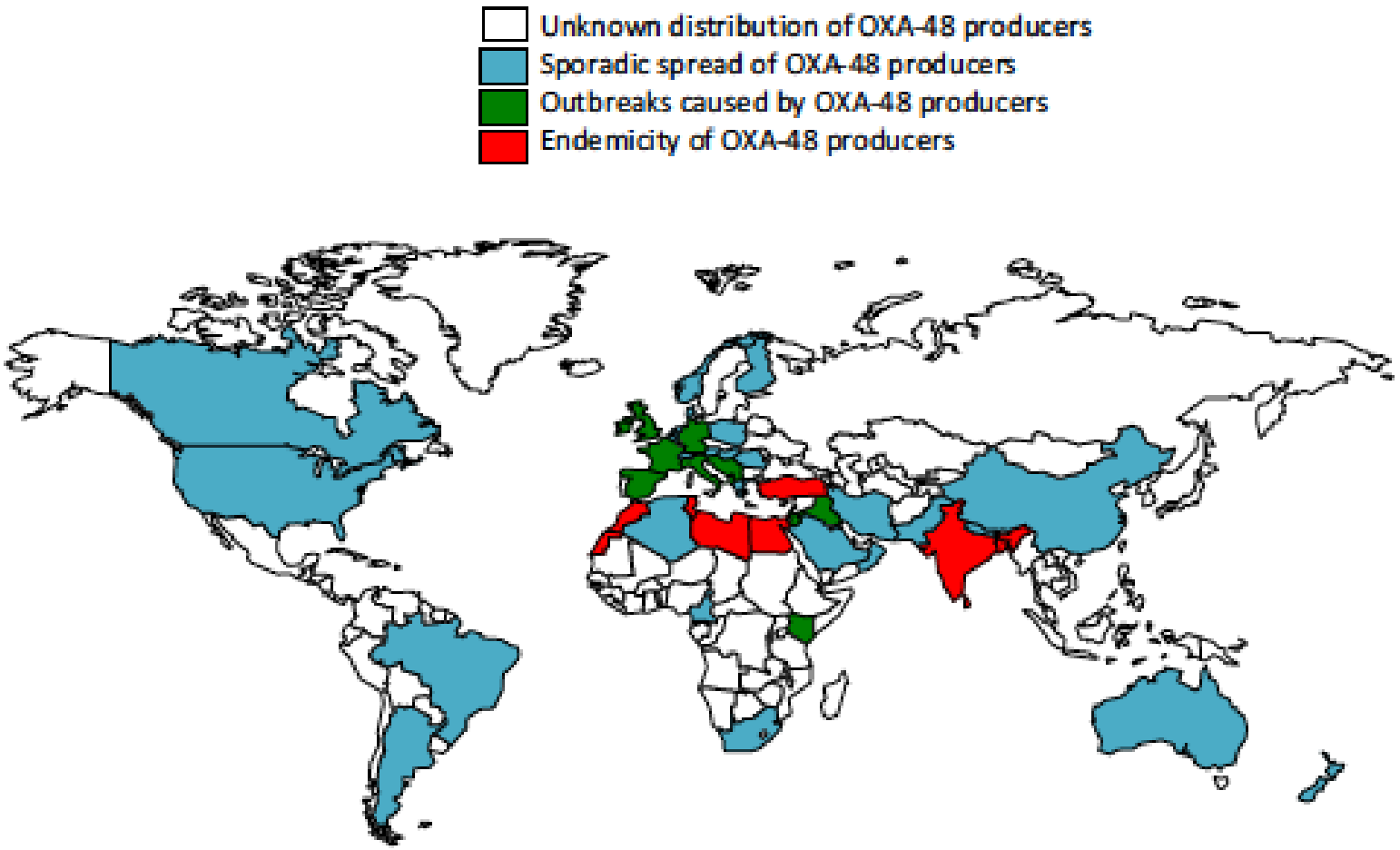
Nordman and Poirel *Clin Micro Infect* 2014

NDM



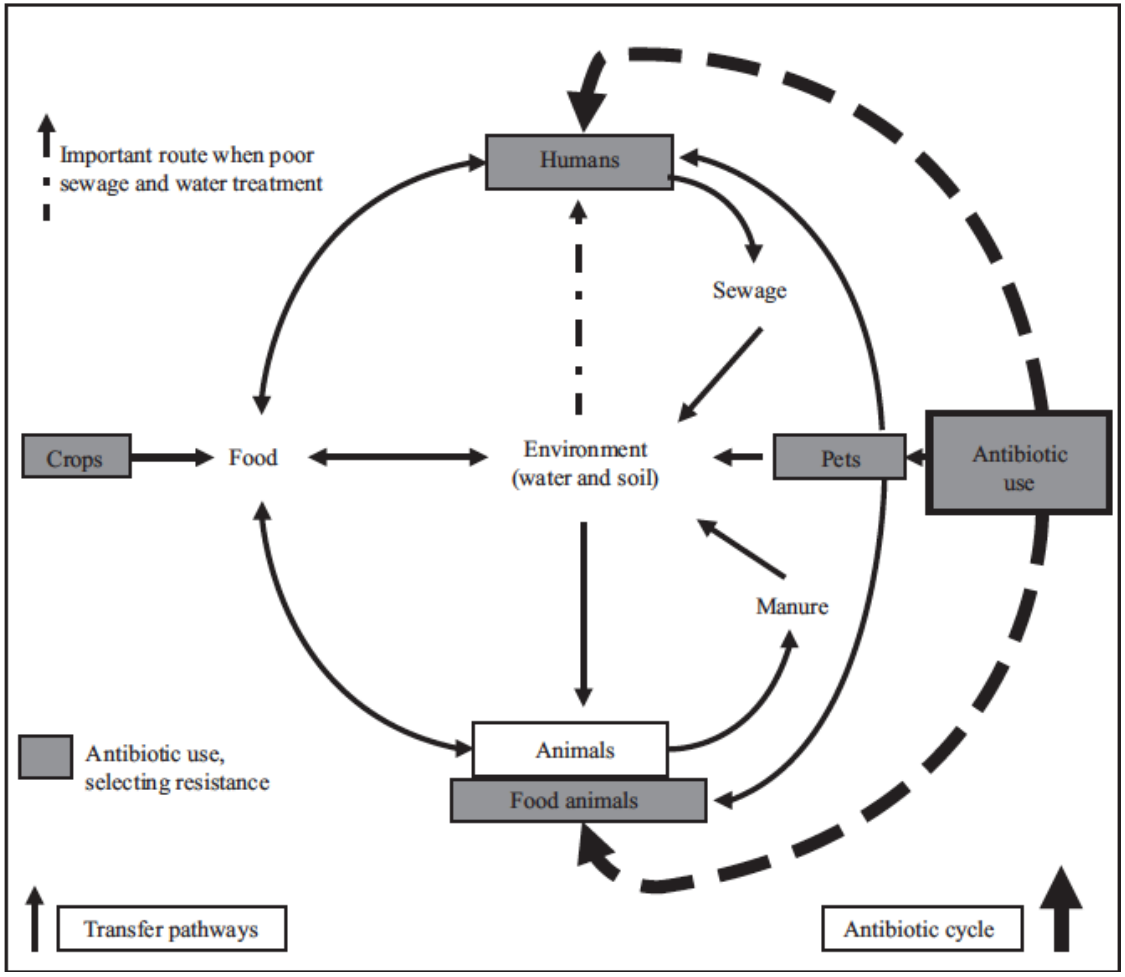
Nordman and Poirel *Clin Micro Infect* 2014

Oxa-48 like



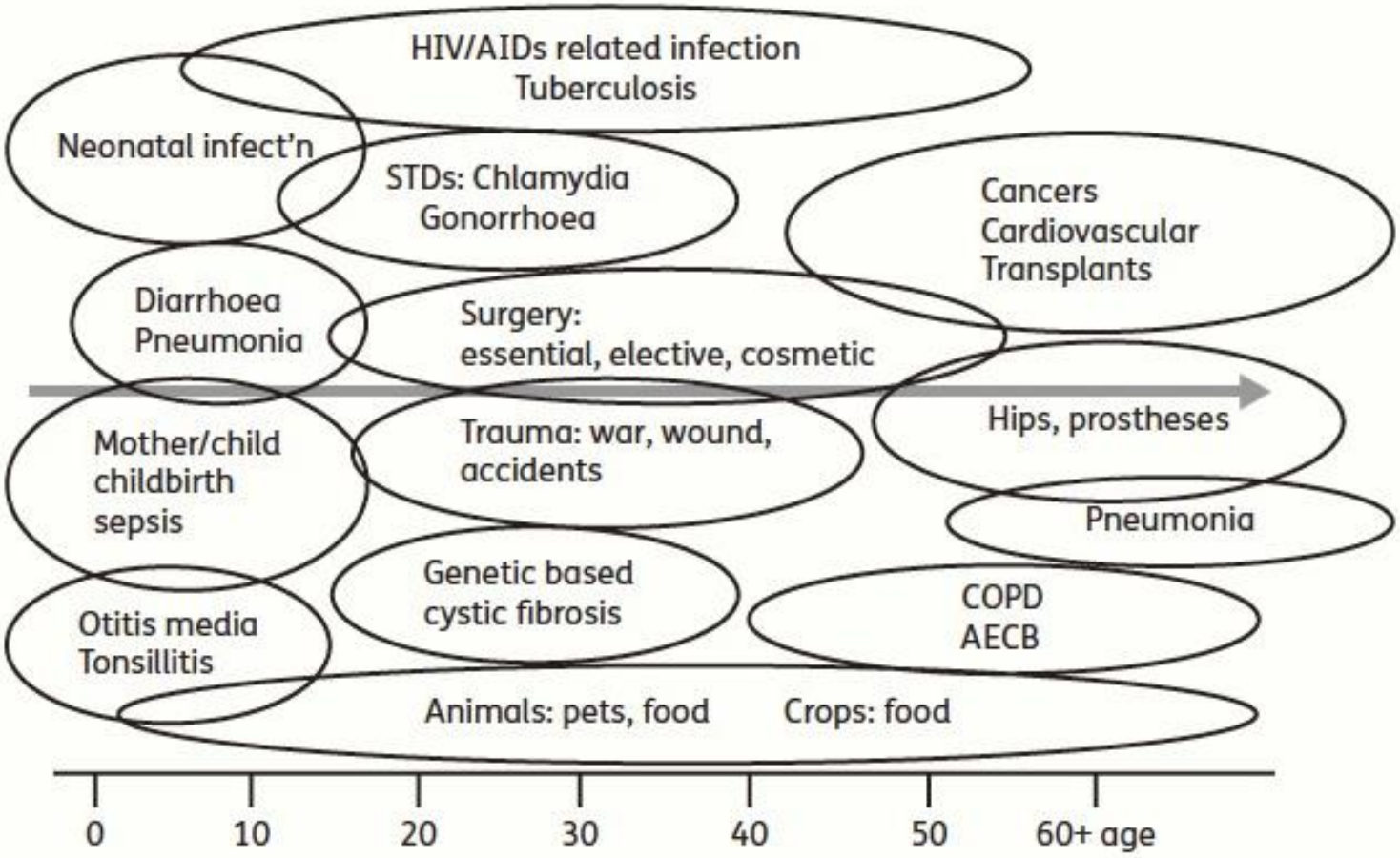
Nordman and Poirel *Clin Micro Infect* 2014

Humans, animals, food and environment



Hawkey *J Hosp Infect* 2015

Antimicrobials: From the cradle to the grave



White *JAC* 2011

Risk Factors

- Immunosuppression
- Mechanical ventilation/ICU stay
- Antimicrobial exposure
  - Carbapenems, cephalosporins, fluoroquinolones
- Poor functional status
- Long term care facilities
- Diabetes
- Overseas hospitalisation/travel

RESEARCH

Risk factors for acc… resistant Enteroba… tertiary care hospi…

Moi Lin Ling*, Yong Ming Tee, So… and Lai Chee Lee

…OBIAL RESISTANCE & …ION CONTROL

Table 2 Univariate analysis of risk factors associated with CRE carriage

Risk factors	CP-CRE patients (N = 203) n (%)	Control (N = 203) n (%)	X = value/Mann-Whitney U (p-value/Fisher Exact)	Odds Ratio [95 % CI]
Total length of stay ± SD (days) (mean days 95 % confidence interval)	48.0 ± 59.5 (39.8–56.3)	3.9 ± 3.8 (3.4–4.5)	U: 3223 (<0.001)	1.266 [1.197–1.340] (<0.001)
History of previous overseas hospitalisation	29 (14.3 %)	1 (0.5 %)	28.218 (<0.001)**	33.667 [4.539–259.700]
History of travelling in past 90 days	29 (14.3 %)	15 7.4 %)	4.996 (0.025)*	2.089 [1.083.4.028]
Ambulant on arrival	103 (50.7 %)	153 (75.4 %)	26.432 (<0.001)**	0.337 [0.221–0.513]
Admission to CU	54 (26.6 %)	6 (3.0 %)	45.059 (<0.001)**	11.899 [4.986–28.399]
Mean ICU stay ± SD, day (mean days 95 % confidence interval)	9.6 ± 12.2 (6.3—13.0)	1.2 ± 1.0 (0.1—2.2)	U: 46.0 (<0.004)**	-

Table 3 Multivariate analysis of risk factors

Risk factor (Multivariable model)	Adjusted Odds Ratio [95 % Confidence Interval] (Sig)
Exposure to antibiotics penicillin	4.640 [1.529–14.079] (0.007)*
Exposure to antibiotics glycopeptides	5.162 [1.377–19.346] (0.015)**
Presence of central line device	3.117 [1.167–8.330] (0.023)**

*$p < 0.01$; **$p < 0.05$ (Significance of association; 2-tailed)

Presence of urinary catheter device	86 (42.4 %)	30 (14.8 %)	37.842 (<0.001)**	4.239 [2.630–6.831]
Presence of ETT device	42 (20.7 %)	6 (3.0 %)	30.620 (<0.001)**	8.565 [3.55 1–20.658]
Presence of intra-arterial line device	24 (11.8 %)	5 (2.5 %)	13.406 (<0.001)**	5.309 [1.984–14.2 11]
Presence of drains device	31 (15.3 %)	11 (5.4 %)	10.623 (0.001)**	3.146 [1.534–6.450]
Presence of enteral feeding device	49 (24.1 %)	11 (5.4 %)	28.240 (<0.001)**	5.554 [2.793–11.044]
Presence of additional MRSA	47 (23.2 %)	26 (12.8 %)	7.365 (0.007)**	2.051 [1.213–3.468]
Presence of additional VRE	32 (15.8 %)	5 (2.5 %)	21.678 (<0.001)**	7.411 [2.825–19.441]
Exposure to bronchoscopy procedure	22 (10.8 %)	4 (2.0 %)	13.314 (<0.001)**	6.047 [2.045–17.881]
Exposure to gastroscopy procedure	18 (8.9 %)	10 (4.9 %)	2.455 (0.117)	1.878 [0.845–4.175]
Exposure to colonoscopy procedure	4 (2.0 %)	6 (3.0 %)	0.410 (0.522)	0.660 [0.183–2.375]
Exposure to angiogram procedure	9 (4.4 %)	6 (3.0 %)	0.623 (0.430)	1.523 [0.532–4.361]
Underwent surgery	141 (69.5 %)	146 (71.9 %)	0.297 (0.586)	1.126 [0.734–1.727]

*p <0.05 (Significance of association; 2-tailed), **p < 0.01 (Significance of association; 2-tailed)

fect Control 2015

Outcomes

- Rapid spread
  - Promiscuous – between and within species
  - Infection control "nightmare"
- Delayed time to diagnosis
  - Difficult laboratory issues
- Less available antimicrobials
  - Strains approaching pan-resistance
- Increased morbidity and mortality
  - ~ 50% mortality among transplant patients

Attributable mortality of carbapenem-resistant *Klebsiella pneumoniae* infections in a prospective matched cohort study in Italy, 2012–2013

A. Hoxha [a,*], T. Kärki [b,c], C. Giambi [b,c], C. Montano [b,c], A. Sisto [d], A. Bella [b], F. D'Ancona [b], the Study Working Group [†]

Table I
Characteristics of the patients with invasive CRKP and CSKP infection

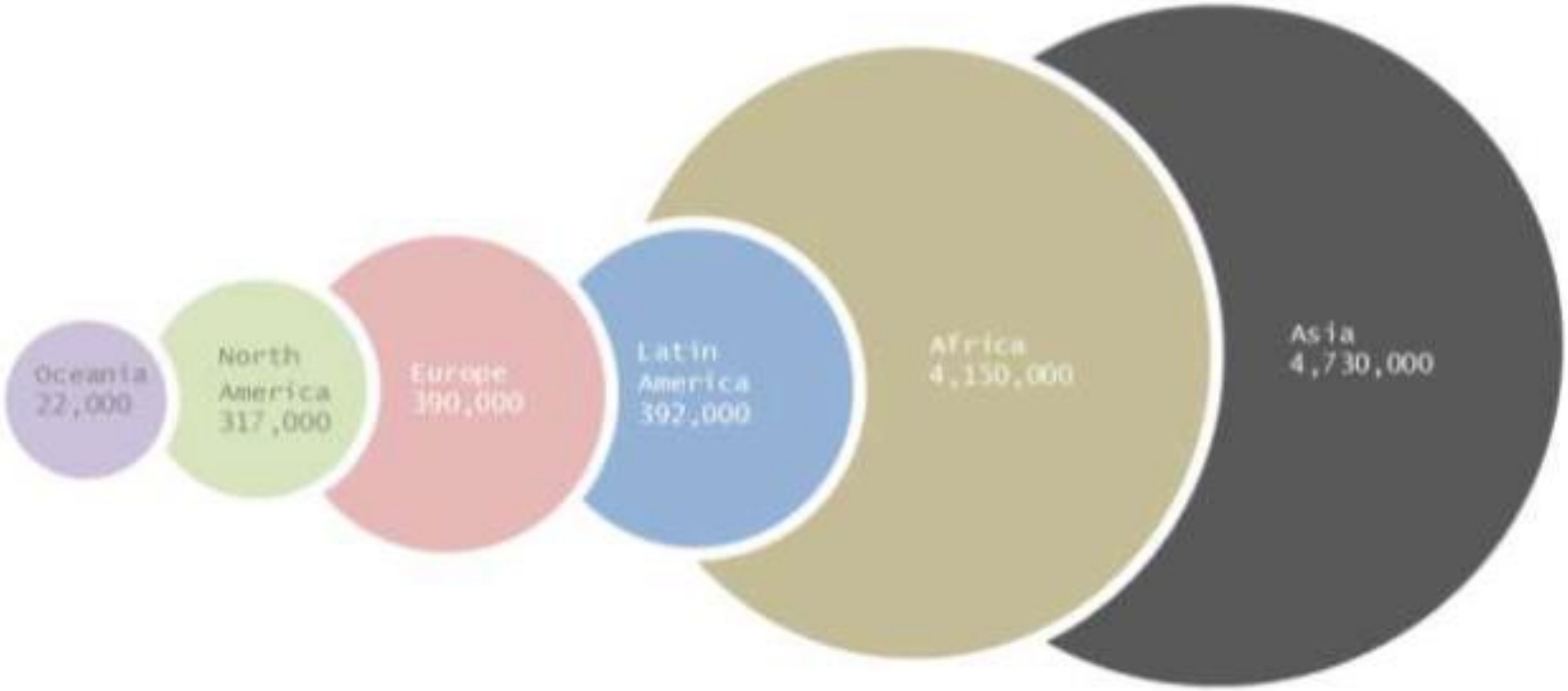
	CRKP patients	CSKP patients	*P*-value
Age >65 years	63% (31/49)	69% (34/49)	0.521
Sex (male)	65% (32/49)	65% (32/49)	1.000
ICU admission	50% (24/48)	49% (24/49)	0.920
Hospitalization in previous six months	50% (24/48)	53% (24/45)	0.748
SAPS II score			
<31	15% (7/47)	31% (14/45)	Ref.
31–61	72% (34/47)	62% (28/45)	0.088
≥62	13% (6/47)	7% (3/45)	0.099
Charlson comorbidity index ≥3	61% (30/49)	59% (29/49)	0.836
Immunodeficiency	43% (21/49)	29% (14/49)	0.140
Organ or blood transplant	0% (0/49)	2% (1/49)	1.000
Dialysis	20% (10/49)	12% (6/49)	0.274
Tracheotomy/gastrostomy/enterostomy carrier	35% (17/49)	22% (11/49)	0.180
Surgery[a]	49% (24/49)	49% (23/47)	0.997
Invasive procedure[b]	92% (45/49)	69% (34/49)	0.005

Crude and attributable mortality of CRKP at six and 30 days

Mortality	CRKP patients ($N = 49$)	CSKP patients ($N = 49$)	Attributable mortality[a]
At six days	12 (24%)	4 (8%)	16%
At 30 days	30 (61%)	10 (20%)	41%

Hoxha *et al J Hosp Infect* 2015

Number of deaths bu 2050 if AMR increases by 40%



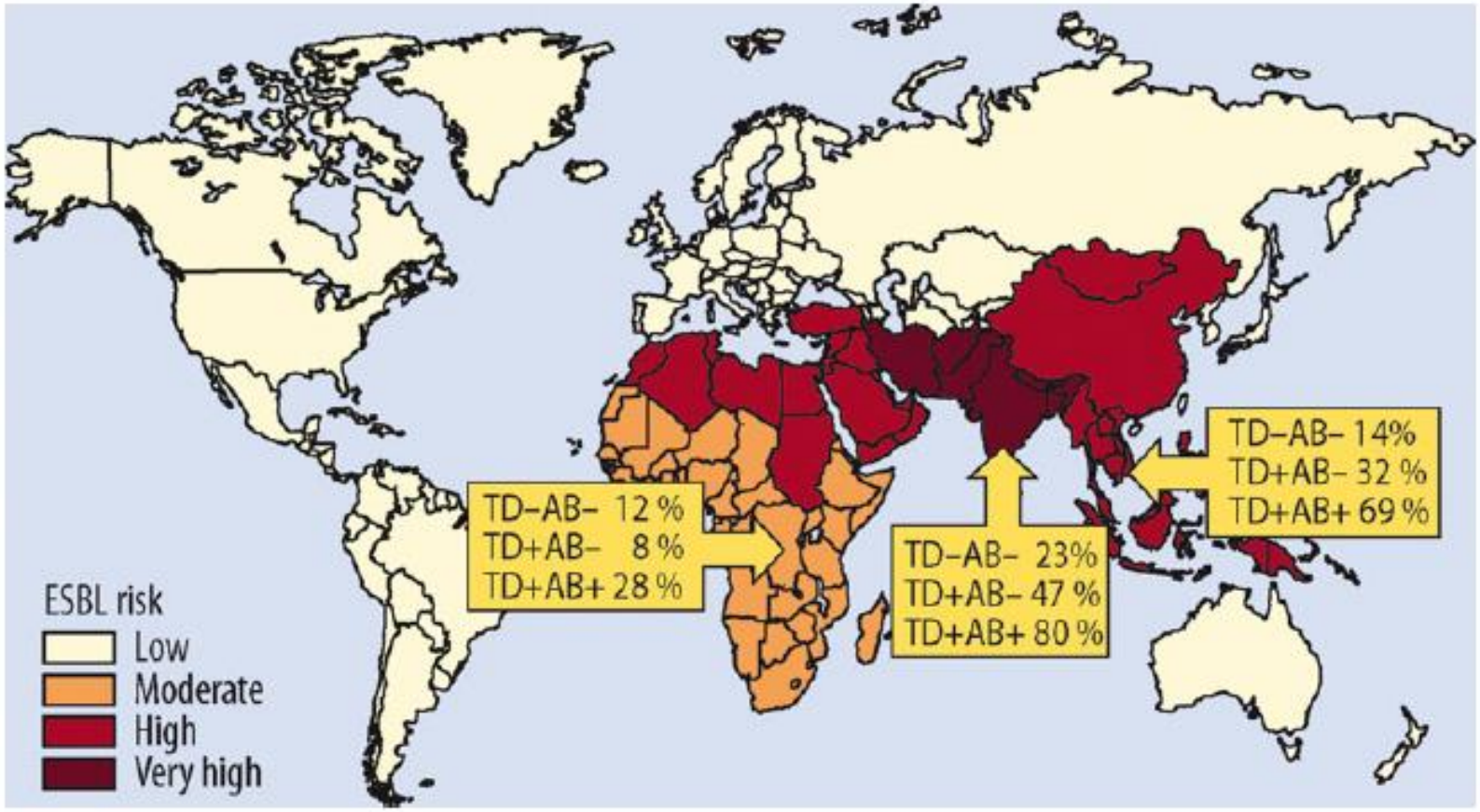
THE LAST RESORT

Health officials are watching in horror as bacteria become resistant to powerful carbapenem antibiotics — one of the last drugs on the shelf.

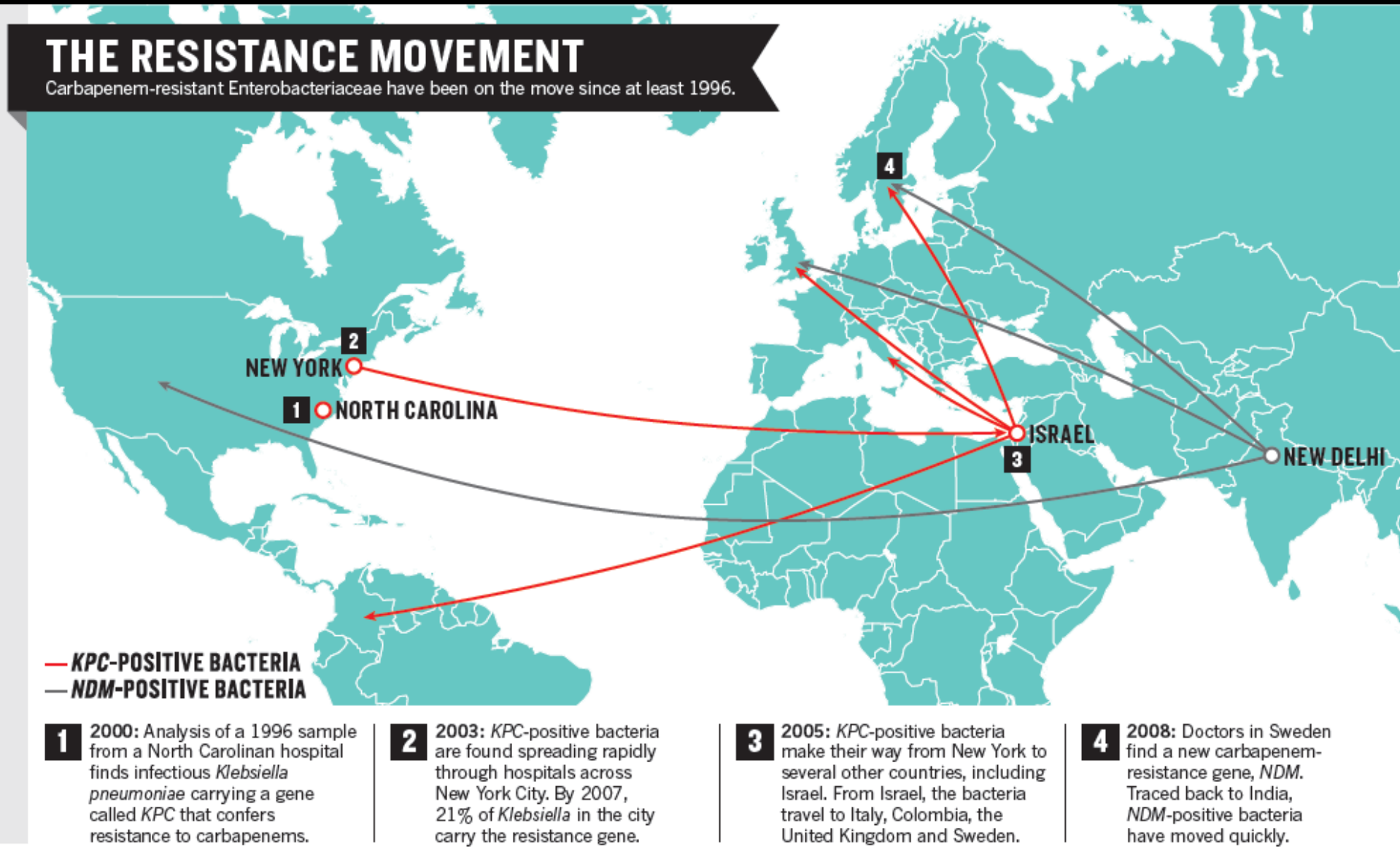
BY MARYN MCKENNA

McKenna *Nature* 2013

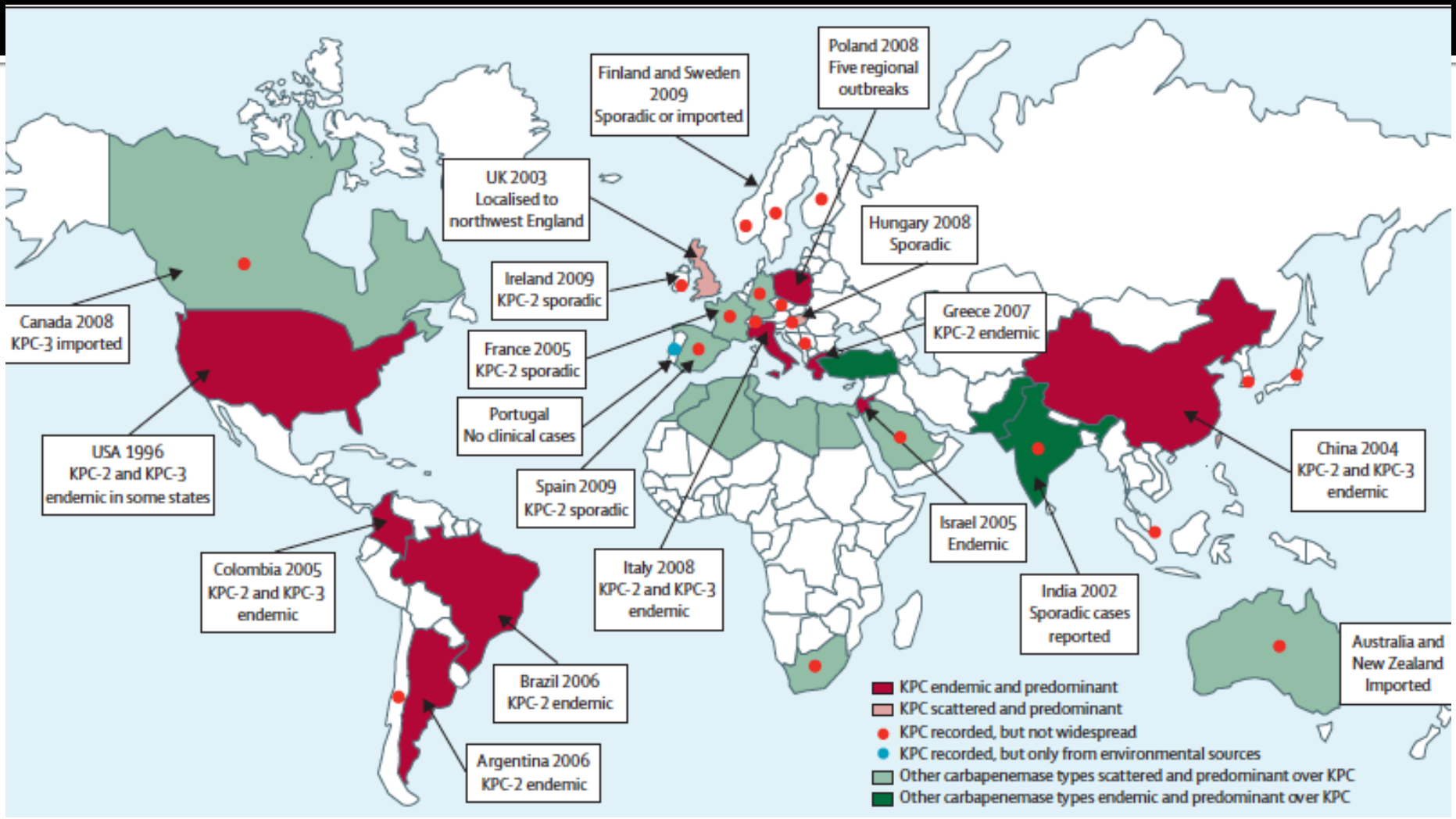
Travellers and MRO acquisition



Kantele *et al. Clin Infect Dis* 2015



McKenna *Nature* 2013



Munoz *et al. Lancet Infect Dis* 2013

"THEY WERE FLYING UNDER THE RADAR. AND AT ABOUT THE TIME WE PICKED THEM UP, THEY JUST EXPLODED."

McKenna *Nature* 2013

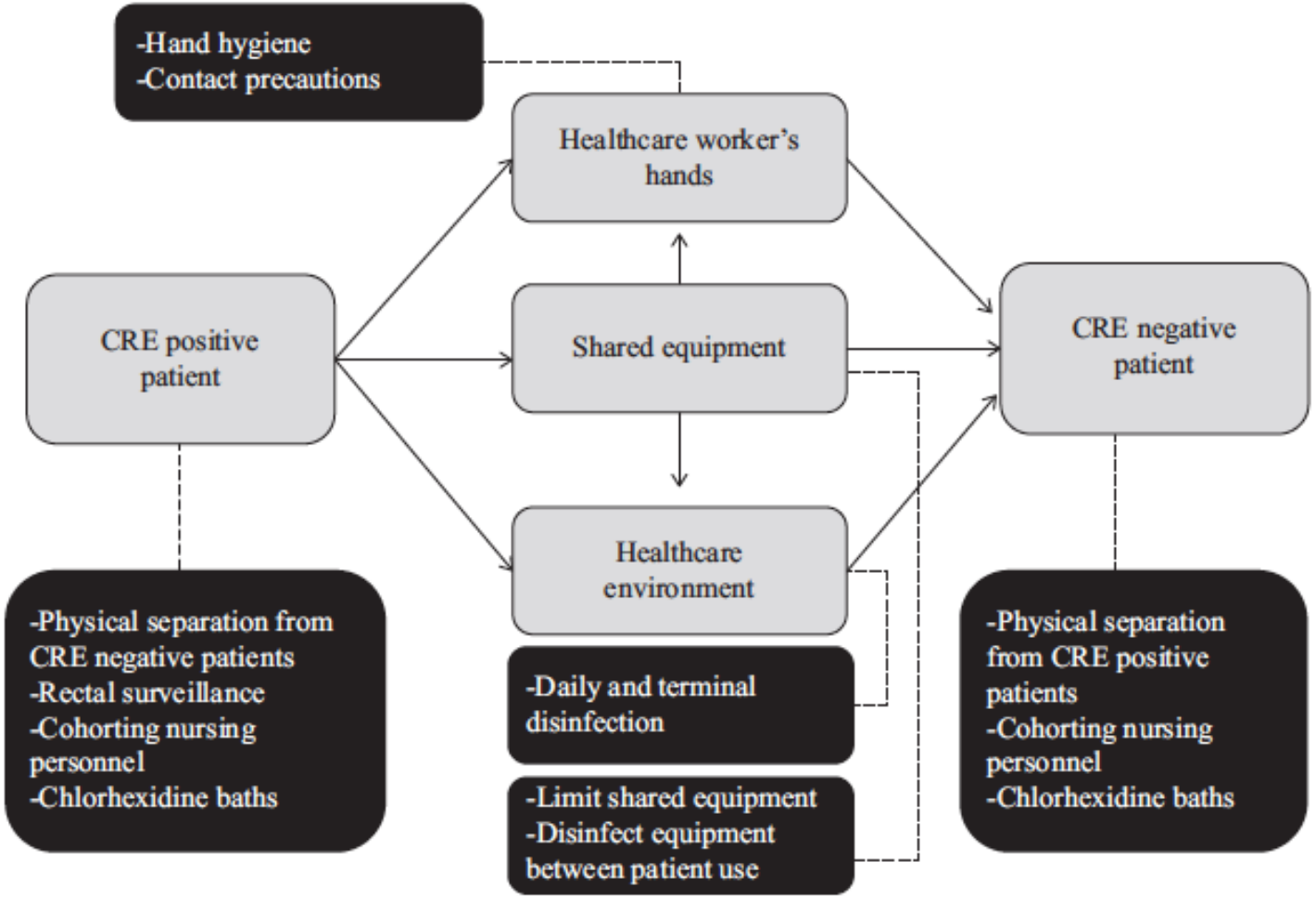
The fight against resistance

- Antimicrobial Stewardship
  - Acute and primary care
  - Residential aged care
  - Companion animals, Livestock
- Improved surveillance
  - Improved laboratory methods
  - Reporting and data handling
- Infection control
- Fostering Research and Development

Quality of evidence low
Evidence from outbreak settings unreliable
Low quality intervention studies

Infection Control

- Evidence-free zone
  - Shrouded in expert opinion
  - Short on evidence
  - No specific randomised-controlled trials
- Heterogeneity
  - Different to MRSA, VRE or C diff
  - A family of loosely related bacteria
- Hand hygiene and contact precautions
  - Recommended by all guidelines for all organisms in all settings



Horizontal vs Verticle

Munoz-Price *J Hosp Infect* 2015

Variations in MRGN infection control

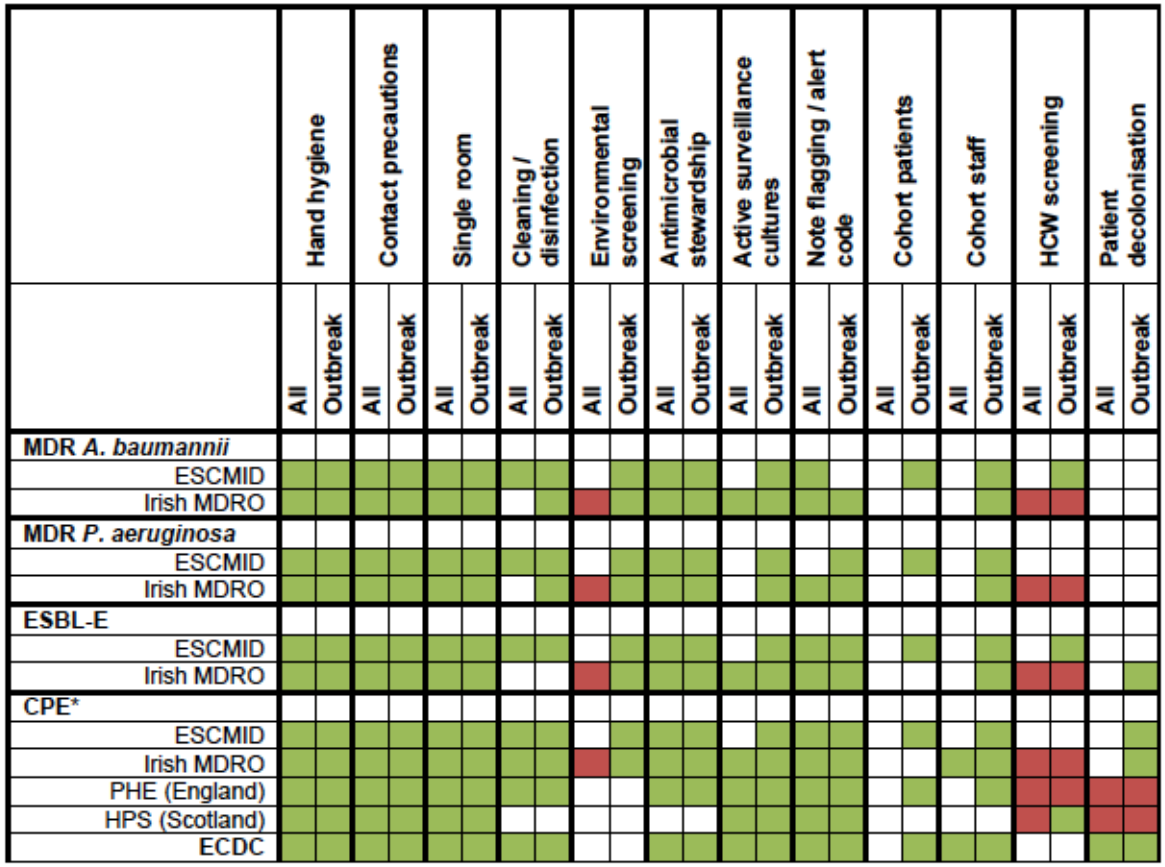


FIG. 1. Overview of recommendations by guideline, setting and organism. *Multidrug-resistant *Klebsiella pneumoniae* in the European Society of Clinical Microbiology and Infectious Diseases guidelines; green squares = recommended; red squares = not recommended; white squares = not mentioned or no recommendation.

Otter *et al Clin Micro Infect* 2015

Being Prepared

- National
  - Standardised methods for detection and reporting
  - National reference centre for confirmation, harmonised molecular testing & central data collection
- Facility governance and management
  - Systems to implement/monitor measures for CRE control including staffing capacity and capacity for increased cleaning
  - Laboratories-protocols for identification, reporting to infection control and flagging of significant isolates
  - Systems to detect and manage clusters and outbreaks including screening

Being Prepared

- Standard precautions
  - High levels of hand hygiene compliance
  - Daily cleaning
  - Protocols on re-usable equipment
- Antimicrobial Stewardship
  - AMS programs implemented including GP, RACF
  - Measures of antimicrobial use
  - Audit and feedback
  - Monitoring of antimicrobial resistance

Screening

- Why?
  - Early identification vital
- Who?
  - Strategy based on current epidemiology and resources
    - Overseas stay in hospital or RACF in previous 12 months
    - Room/ward contact of positive patients
    - Consider at risk patients
    - Consider at risk units/wards
    - Opportunistic – eg faecal specimens sent to lab
- How?
  - Faecal/rectal specimen plus/- wound swabs, IDC urine
  - Presumptive isolation based on risk-assessment & where resources permit

Controversies

- Who should have active surveillance culture?
- Should these have pre-emptive isolation?
- How far (time and place) to contact trace?
- Decolonisation
  - Chlorhexidine bathing
  - Selective digestive decontamination

"Down the drain": carbapenem-resistant bacteria in intensive care unit patients and handwashing sinks

Despina Kotsanas
BSc(Hons), MClinEpi, Scientist[1]

WRPLI Wijesooriya
MB BS, MD, MPhil, Medical Microbiologist[1]

Tony M Korman
MB BS, FRACP, FRCPA, Director[1]

Elizabeth E Gillespie
BN, MPubHlth, Nursing Director[2]

Louise Wright
BN, Infection Control Consultant[2]

Kylie Snook
BN, Infection Control Consultant[2]

Natalie Williams
BN, Infection Control Consultant[2]

Jan M Bell
BSc, Scientist[3]

Hua Y Li
MMed, Research Fellow[4]

Rhonda L Stuart
MB BS, PhD, FRACP, Infectious Diseases Physician,[1] and Adjunct Clinical Associate Professor[5]

Abstract

Objectives: Clinical utility of carbapenem antibiotics is under threat because of the emergence of acquired metallo-β-lactamase (MBL) genes. We describe an outbreak in an intensive care unit (ICU) possibly associated with contaminated

m-negative bacteria
ICU at Dandenong Hospital
cal investigations were
. During September 2012,
environmental swabs
lected. Samples were
acteriaceae (CRE) agar.
ng the modified Hodge test
ion and sequencing of MBL
yped by pulsed-field gel

e of CRE (consisting of
terobacter cloacae [1] and
e over the 30-month period.
g and drain of eight central
ironmental isolates were
mpts to clean and
cleaning proved

dentification of potential
utbreaks of environmentally
hardy multiresistant organisms.

One of the most concerning emerging resistance traits among gram-negative bacteria is the ability of these organisms to produ
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We
the pr
mase gene bla_{IMP-4} in an intensive care unit (ICU) associated with contaminated sinks. This report highlights the key role of bacterial environmental contamination and sink design and usage in the propagation of CRE outbreaks.

(including 11 sinks and taps, as well as water fountains and ice machines) was performed. Samples were recollected from CRE positive locations

Guidelines on ICU handwashing sink styles were reviewed to establish whether sinks met clinical design standards.[8]

Prolonged carriage

- Duration of carriage unknown
  - Our case = > 18 months
- Two negative cultures often accompanied by subsequent positive culture
  - Kim *et al. Infect Control Hosp Epidemiol* 2015
- Require at least 3 negatives
  - Role of subsequent antimicrobials
- "Flagged for life"
  - Decolonisation – not an option …..yet

Transmission based precautions

- Single room, long sleeved gowns, gloves
- Own toilet
- Cohort if required
- Notify receiving facilities on transfer
- Avoid unnecessary bed movements
- Audit compliance

Cleaning

- Cleaned and disinfected daily
- Thorough discharge cleaning
- Guidelines go against changing service practice
- Monitor cleaning process
  - Fluorescent marker
  - ATP
  - Feedback

Hydrogen Peroxide Vapor

Bug buster: Jan Steele, an enrolled nurse at the National Burns Centre at Middlemore Hospital, with the Bioquell machine.

Photo: Peter Meecham/Fairfax

We will exterminate superbugs

By MARIKA HILL

THE SPAWN of an evil Dalek and affectionate R2-D2 is exterminating superbugs in hospital wards and potentially saving lives.

It may not shoot fire like a Dalek,

superbugs and norovirus outbreaks.

"It basically kills every bug known to man, including the little spores of the nastiest bugs," Dr Seddon said.

just started seeing in New Zealand. That has spores that can sit in the environment and make people very, very sick."

Washing hands and scrubbing the wards can reduce the risk, but

Middlemore Hospital in Octob and November.

The Bioquell would have helpe hospital staff limit the outbreak b disinfecting wards of the high contagious bug that causes nause vomiting and diarrhoea, she sai

- HPV: used in outbreak settings and has been associated with reductions in colonization or infection with pathogens.
- Issues: prolonged time required and recontamination

An Evaluation of Environmental Decontamination With Hydrogen Peroxide Vapor for Reducing the Risk of Patient Acquisition of Multidrug-Resistant Organisms

Clinical Infectious Diseases 2013;56(1):27–35

Catherine L. Passaretti,[1,2,3] Jonathan A. Otter,[4] Nicholas G. Reich,[5,6] Jessica Myers,[5] John Shepard,[1] Tracy Ross,[7] Karen C. Carroll,[7] Pam Lipsett,[8] and Trish M. Perl[1,2,5]

- HPV decontamination associated with 45% reduction in room contamination
- 80% reduction in VRE acquisition but decrease in MRGN not significant
- No mention of adequacy of cleaning in non-HPV rooms

Table 2. Summary of the Incidence of Acquisition, by Multidrug Resistant Organism (MDRO) and Cohort, and for all MDROs Combined

MDRO/Cohort	No.	Acquisitions, No.	Patient-Days, No.	Acquired, %	Crude IR per 1000 Patient-Days	Adj IRR[a]	95% CI	*P* Value
VRE	6936	333						
MDRO-standard	654	53	4566	8.1	11.6	…	…	…
No MDRO-standard	5808	272	37 973	4.7	7.2	0.85	(.61–1.18)	.32
MDRO-HPV	474	8	3267	1.7	2.4	0.25	(.10–.60)	<.01
MRSA	7514	121						
MDRO-standard	494	14	3736	2.8	3.7	…	…	…
No MDRO-standard	6463	102	44 931	1.6	2.3	0.62	(.33–1.17)	.13
MDRO-HPV	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
MDR-GNR	8117	111						
MDRO-standard	1298	23	9928	1.8	2.3	…	…	…
No MDRO-standard	6235	81	43 092	1.3	1.9	0.81	(.48–1.34)	.40
MDRO-HPV	584	7	4225	1.2	1.7	0.55	(.20–1.57)	.26
Clostridium difficile	[illegible]	[illegible]						
MDRO-standard	1253	26	9676	2.1	2.7	…	…	…
No MDRO-standard	6118	100	42 328	1.6	2.4	0.95	(.60–1.51)	.83
MDRO-HPV	557	4	4029	0.7	1.0	0.49	(.16–1.47)	.19
Combined	6350	497						
MDRO-standard	927	98	6228	10.6	15.7	…	…	…
No MDRO-standard	4986	381	30 119	7.6	12.6	0.9	(.70–1.16)	.40
MDRO-HPV	437	18	2904	4.1	6.2	0.36	(.19–.70)	<.01

Benefits of enhanced terminal cleaning disinfection study (BETR)

- 9 hospitals over 28 months
  - Compared 4 strategies
  - 7 month study arms, 1 month wash-in
    - Quaternary ammonium
    - Quaternary ammonium plus UV-C
    - Bleach
    - Bleach plus UV-C
- Primary outcome
  - Clinical incidence of MROs
    - VRE, MDR Acinetobacter, MRSA, *C. difficle*

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Benefits of enhanced terminal cleaning disinfection study (BETR)

Figure 1. Patient enrollment and eligibility for BETR-Disinfection study outcomes

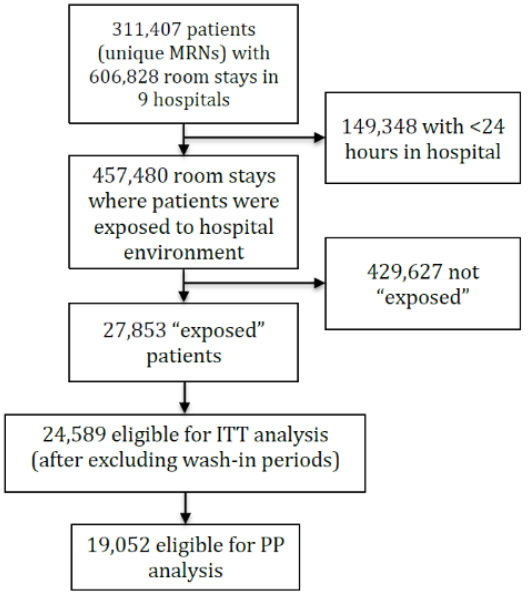
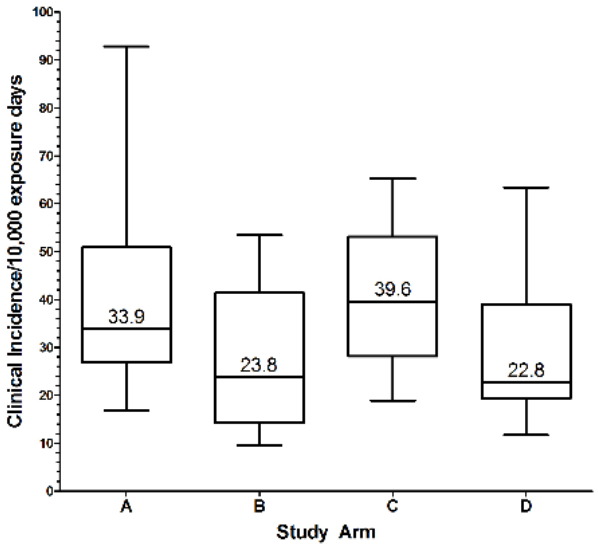
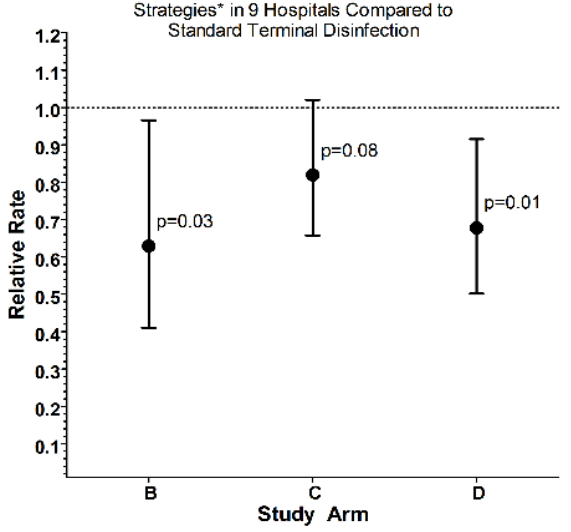


Figure 2. ITT Analysis - Clinical Incidence of All Target MDROs following 4 Terminal Room Disinfection Strategies in 9 Hospitals



Study Arm Description: A-quaternary ammonium (reference); B-quaternary ammonium+UV-C emitter; C-bleach; D-bleach+UV-C emitter

Figure 3. ITT Analysis - Relative Clinical Incidence of All Target MDROs following Enhanced Terminal Room Disinfection Strategies* in 9 Hospitals Compared to Standard Terminal Disinfection



*Study Arms B (quaternary ammonium+UV-C emitter), C (bleach), and D (bleach+UV-C emitter) were compared to Study Arm A (quaternary ammonium). Model controlled for time period, hospital, and correlation between different study phases within the same hospital

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Issues in outbreak management

Epidemiological scale	Description	Stage
No cases reported	No cases reported	0
Sporadic occurrence	Single cases, epidemiologically unrelated	1
Single hospital outbreak	Outbreak defined as two or more epidemiologically related cases in a single institution	2a
Sporadic hospital outbreaks	Unrelated hospital outbreaks with independent, i.e. epidemiologically unrelated introduction or different strains, no autochthonous inter-institutional transmission reported	2b
Regional spread	More than one epidemiologically related outbreak confined to hospitals that are part of a regional referral network, suggestive of regional autochthonous inter-institutional transmission	3
Inter-regional spread	Multiple epidemiologically related outbreaks occurring in different health districts, suggesting inter-regional autochthonous inter-institutional transmission	4
Endemic situation	Most hospitals in a country are repeatedly seeing cases admitted from autochthonous sources	5

Grundmann *et al Eurosurveillance* 2010

Issues in outbreak management

- Incident Management Teams
  - Established when there is a declared outbreak
    - Executive
    - Nurse unit / medical unit lead
    - Infectious diseases / infection prevention /microbiology
    - Environmental services
  - Jurisdictional Management Team
    - Support and oversea the response
    - Chief health officer or delegate
    - Expertise in microbiology, infectious diseases, infection control, communications, quality

Outbreak management

- Resources
- Staff and patient education
- Staff and patient cohorting
- Ongoing screening
- Ward closures
- When to call the outbreak over
  - 4 weeks of negative screens in the unit/ward

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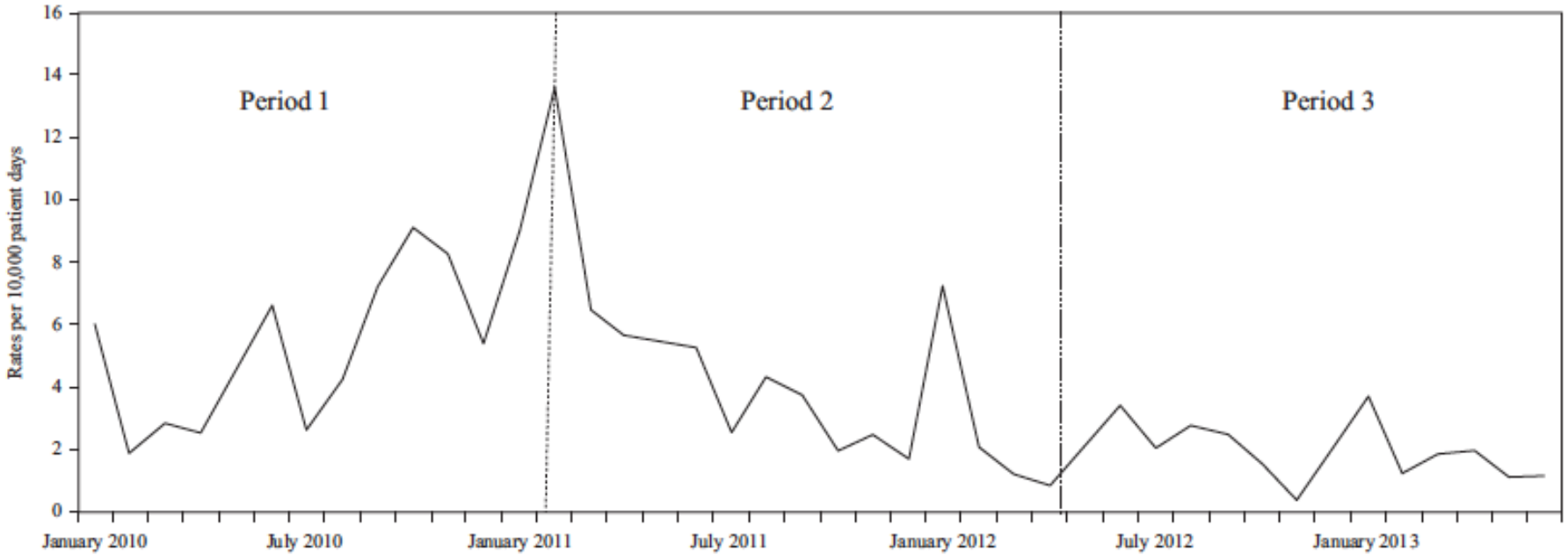
Controlling multidrug-resistant Gram-negative bacilli in your hospital: a transformational journey

L.S. Munoz-Price*

Institute for Health and Society and Department of Medicine, Medical College of Wisconsin, Milwaukee, WI, USA



Driving CRE down

- Changing culture
  - Communications to executive and managers
  - Ranking of wards and new MRGN
  - Case reports to transform data to a personal level
- Evaluating environmental cleaning
  - UV powder marker
  - Rates published widely in the hospital
  - Gaming of marker results
  - Surveillance cultures

Driving CRE down

- Hand Hygiene Culture
  - Education on environment and hands role in spread
  - Hand plating
  - "Faecal patina"
- Equipment use and cleaning
  - Scissors, stethoscopes, trays etc
  - Orthopedic rounds and equipment
- Transformation
  - Occurred when nurses adopted CRE as **their** problem to tackle and not purely an Infection Control drive

Draft Vi
Carbap
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For Health S

November 20

Updated Guidelines
Due SOON

Recommendations
for the control of
Multi-drug resistant
Gram-negatives:
carbapenem resistant
Enterobacteriaceae

August 2013

AUSTRALIAN COMMISSION
ON SAFETY AND QUALITY IN HEALTH CARE

Guidance:
ntion and Control
re Workers in All
lthcare Settings

penem-resistant
-negative Bacilli

Canada

"Now, here, you see, it takes all the running you can do just to keep in the same place. If you want to get somewhere else, you must run at least twice as fast!“

- Red Queen from *Through the Looking Glass*