Antibiotic resistance in Gram negative bacteria

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What are the Gram negatives we need to worry about?

- E.coli
- ESCAPPM
- Pseudomonas
- Acinetobacter

- Genes are even more important
  - NDM New Delhi metalo betalactamase

Australia

Facing the challenge of multidrug-resistant gram-negative bacilli in Australia

Minimising the risk of MDR GNB becoming firmly established in Australian are will

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Antimicrobial resistance is a major challenge for current and future medical practice.[1,2] Yet the magnitude of the problem we face and its solutions are not obvious. It is estimated that at least 2 million people acquire infections with bacteria that are resistant to standard therapy each year in the United States alone.[3] The World Health Organization recently reported alarmingly high rates of bacterial resistance across all WHO regions.[2] This is not just a problem in hospitalised patients; community-acquired infections are now increasingly

Summary

- Multidrug-resistant (MDR) gram-negative bacilli (GNB) are now globally widespread and present a major challenge to modern medical practice.
- Resistance to common antibiotics such as ceftriaxone is becoming more frequent in Australia, primarily mediated by extended-spectrum β-lactamase enzymes in common organisms such as *Escherichia coli*, and may occur in both hospital- and community-acquired infections.

MJA 202 (5) · 16 March 2015

What antibiotics do we really have to worry about?

FOOD SAFETY INVITED ARTICLE

Frederick J. Angulo, Section Editor

World Health Organization Ranking of Antimicrobials According to Their Importance in Human Medicine: A Critical Step for Developing Risk Management Strategies for the Use of Antimicrobials in Food Production Animals

Peter Collignon,[1,2] John H. Powers,[3,4,5] Tom M. Chiller,[6] Awa Aidara-Kane,[7] and Frank M. Aarestrup[8]

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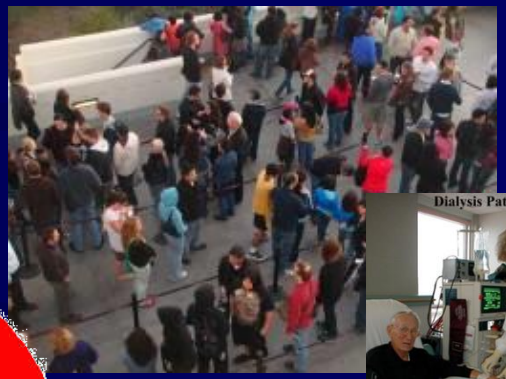
WHO list of Critically Important Antimicrobials, 4 editions (first in Canberra) (3 revisions). http://www.who.int/foodborne_disease/resistance/cia/en/

Clinical Infectious Diseases 2009; 49:132–41

One Health

It all goes around, and around, and around

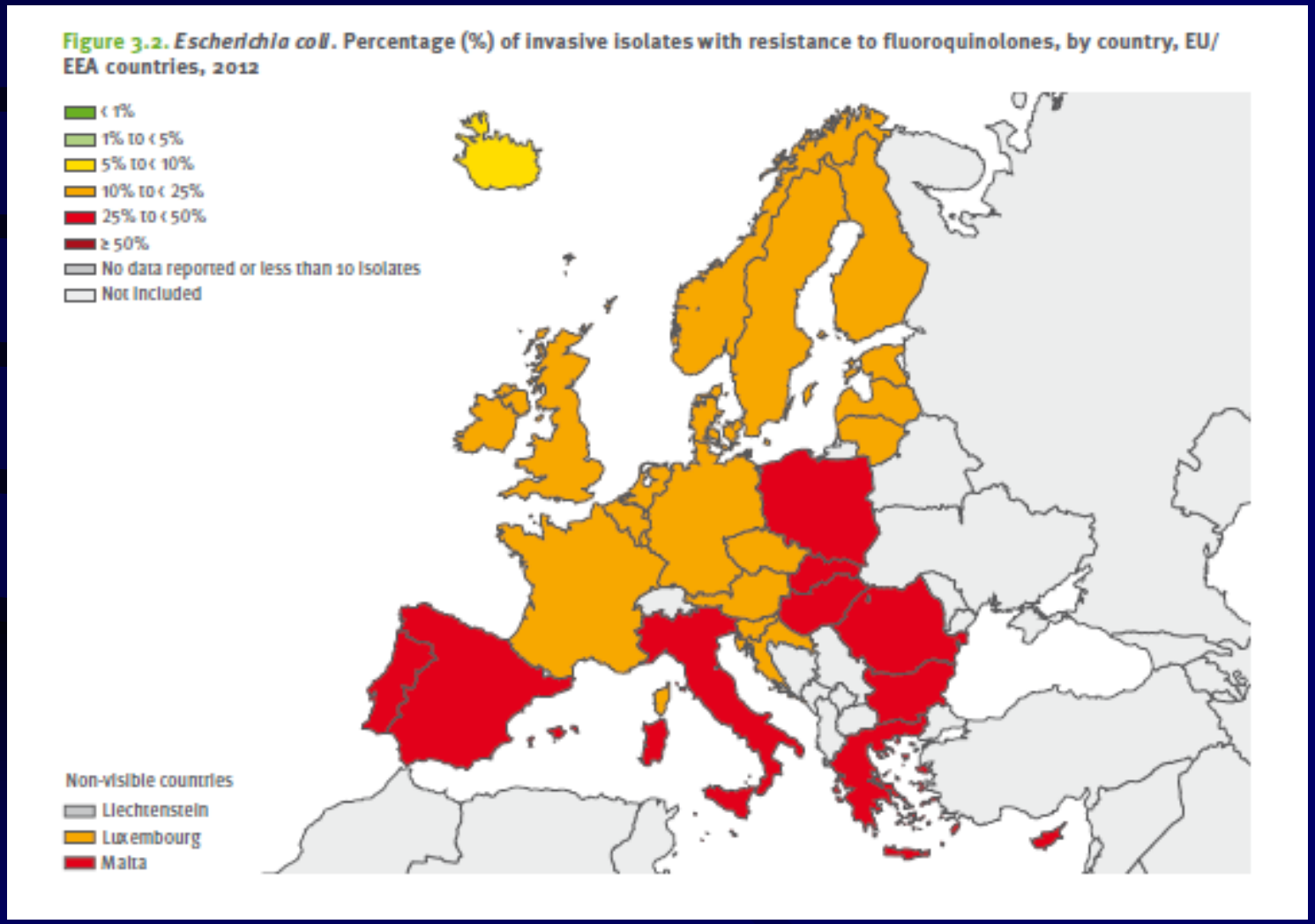


Resistance results in

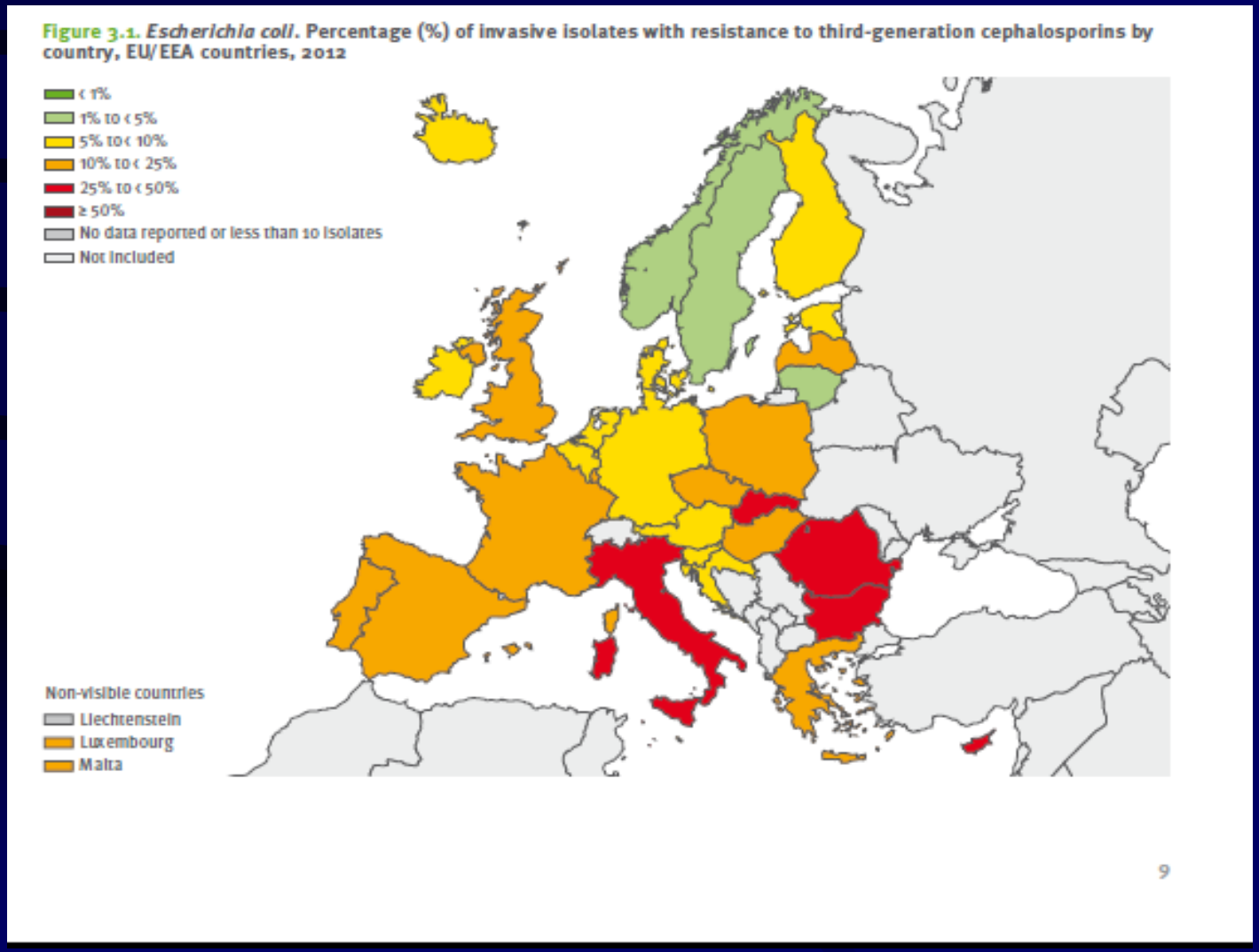
- increased deaths,
- increased complications,
- additional expenses,
- prolonged illness and hospital stays,
- additional toxicity and
- the need to have intravenous therapy rather being able to have oral therapy as a patient based in the community.

Resistance is rapidly rising

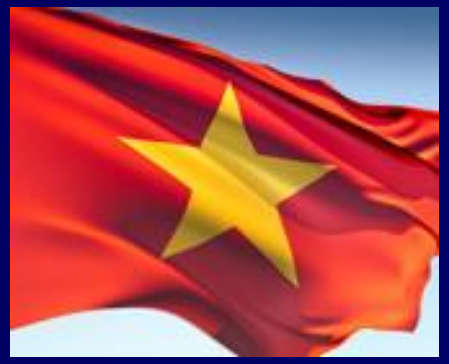
Europe 2012 E.coli Blood FQ resistance



EU 3rd Generation Cephalosporin resistance Bloodstream isolates 2012



Antibiotic resistance is worse in developing countries



Fluroquinolone resistance worldwide

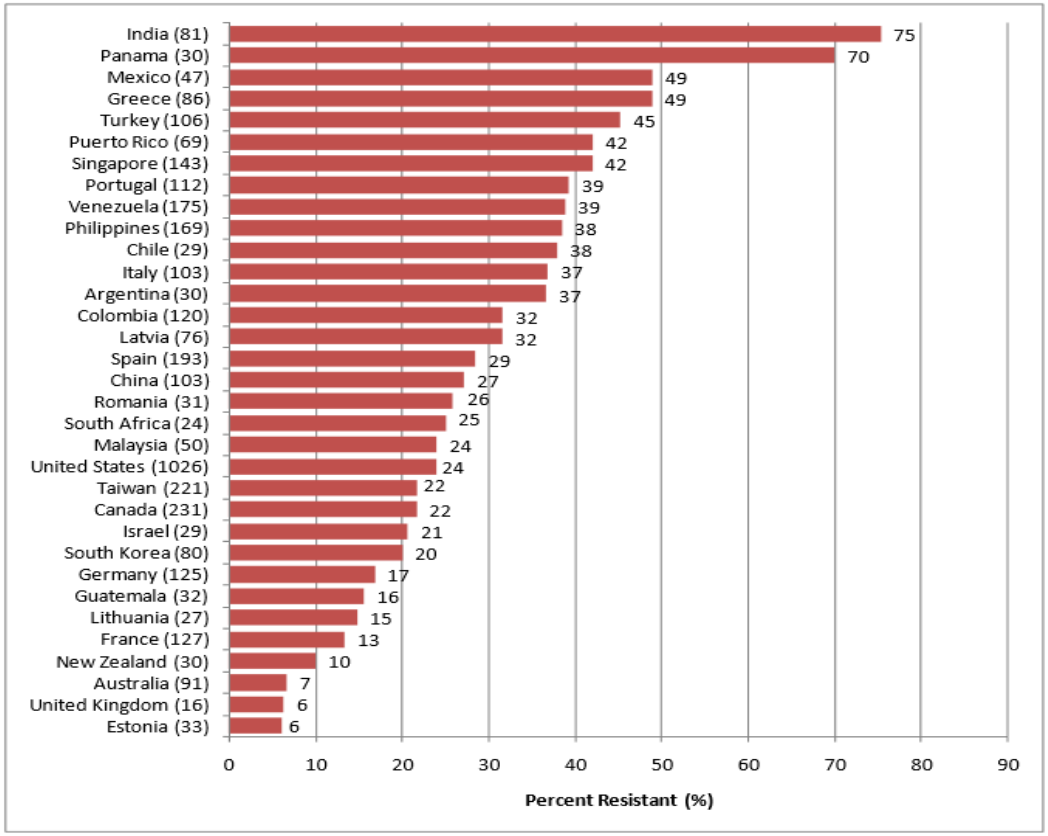


Fig. (1). Percent fluoroquinolone resistance* in 3,845 UTIs by country (n).

74 *The Open Microbiology Journal*, 2012, 6, 74-78

Open Access

Fluoroquinolone Resistance Among Gram-Negative Urinary Tract Pathogens: Global Smart Program Results, 2009-2010

Sam Bouchillon[1*], Daryl J. Hoban[1], Robert Badal[1], and Stephen Hawser[2]

Very High resistance rates in India with E.coli

For Fluoroquinolones
(e.g. Cipro - Resist is 73%)

Indian J Med Res 136, November 2012, pp 842-849

Antibiotic resistance pattern among common bacterial uropathogens with a special reference to ciprofloxacin resistant *Escherichia coli*

Jharna Mandal, N. Srinivas Acharya, D. Buddhapriya & Subhash Chandra Parija

Table II. Anti

Antibiotics	*E. coli* n=2671	*K. pneu-moniae* n=551	*P.*
Ceftriaxone	1618 (60.5)	327 (59.3)	
Ceftazidime	1526 (57.1)	311 (56.4)	
Gentamicin	1592 (59.6)	337 (61.1)	
Nitrofurantoin	720 (26.9)	323 (58.6)	
Meropenem	264 (9.8)	100 (18.15)	
Ciprofloxacin	1951 (73.04)	302 (54.8)	
Amikacin	621 (23.2)	158 (28.6)	
Ampicillin	2153 (80.6)	-	

Values in parentheses represent percent

Emergence of a new antibiotic resistance mechanism in India, Pakistan, and the UK: a molecular, biological, and epidemiological study

Karthikeyan K Kumarasamy, Mark A Toleman, Timothy R Walsh, Jay Bagaria, Fathana Butt, Ravikumar Balakrishnan, Uma Chaudhary, Michel Doumith, Christian G Giske, Seema Irfan, Padma Krishnan, Anil V Kumar, Sunil Maharjan, Shazad Mushtaq, Tabassum Noorie, David L Paterson, Andrew Pearson, Claire Perry, Rachel Pike, Bhargavi Rao, Ujjwayini Ray, Jayanta B Sarma, Madhu Sharma, Elizabeth Sheridan, Mandayam A Thirunarayan, Jane Turton, Supriya Upadhyay, Marina Warner, William Welfare, David M Livermore, Neil Woodford

Summary

Background Gram-negative Enterobacteriaceae with resistance to carbapenem conferred by New Delhi metallo-β-lactamase 1 (NDM-1) are potentially a major global health problem. We investigated the prevalence of NDM-1, in multidrug-resistant Enterobacteriaceae in India, Pakistan, and the UK.

Methods Enterobacteriaceae isolates were studied from two major centres in India—Chennai (south India), Haryana (north India)—and those referred to the UK's national reference laboratory. Antibiotic susceptibilities were assessed, and the presence of the carbapenem resistance gene bla_{NDM-1} was established by PCR. Isolates were typed by pulsed-field gel electrophoresis of XbaI-restricted genomic DNA. Plasmids were analysed by S1 nuclease digestion and PCR typing. Case data for UK patients were reviewed for evidence of travel and recent admission to hospitals in India or Pakistan.

Findings We identified 44 isolates with NDM-1 in Chennai, 26 in Haryana, 37 in the UK, and 73 in other sites in India and Pakistan. NDM-1 was mostly found among *Escherichia coli* (36) and *Klebsiella pneumoniae* (111), which were highly resistant to all antibiotics except to tigecycline and colistin. *K pneumoniae* isolates from Haryana were clonal but NDM-1 producers from the UK and Chennai were clonally diverse. Most isolates carried the NDM-1 gene on plasmids: those from UK and Chennai were readily transferable whereas those from Haryana were not conjugative. Many c
UK NDM-1 positive patients had travelled to India or Pakistan within the past year, or had links with these coun

Interpretation The potential of NDM-1 to be a worldwide public health problem is great, and co-ordinated internat
surveillance is needed.

Published Online
August 11, 2010
DOI:10.1016/S1473-3099(10)70143-2

See Online/Reflection and Reaction
DOI:10.1016/S1473-3099(10)70168-7

Department of Microbiology, Dr ALM PG IBMS, University of Madras, Chennai, India (K K Kumarasamy MPhil, P Krishnan PhD); **Department of Infection, Immunity and Biochemistry, School of Medicine, Cardiff University, Cardiff, UK** (M A Toleman PhD, Prof T R Walsh PhD); **Health**

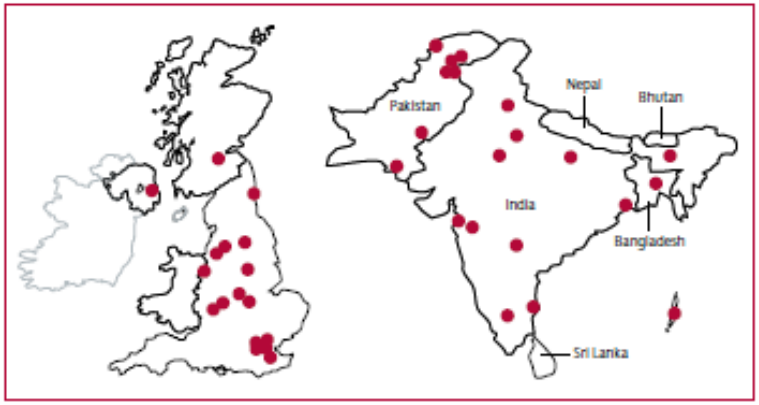


Figure 5: Distribution of NDM-1-producing Enterobacteriaceae strains in Bangladesh, Indian, Pakistan, and the UK

International travel major risk

Eur J Clin Microbiol Infect Dis
DOI 10.1007/s10096-010-1031-y

ARTICLE

Colonisation with *Escherichia coli* resistant to "critically important" antibiotics: a high risk for international travellers

K. Kennedy · P. Collignon

Colonisation with antibiotic-resistant *E. coli* increased significantly from 7.8% (95% confidence interval [CI] 3.8–14.9) pre-travel to 49% (95% CI 39.5–58.6) post-travel. Those colonised were more likely to have taken antibiotics whilst travelling; however, travel remained a risk independent of antibiotic use. Colonisation with resistant *E. coli* occurred most frequently following travel to Asia. While over half of those carrying resistant *E. coli* post-travel had no detectable resistant strains two months after their return, at least 18% remained colonised at six months.

Resistance is proportional to use

- When you use it, you loose it!

- The more you use then the more resistance
  - cross resistance an issue
  - low dose and topical lead to more resistance
  - Volumes are most important

- Need to maintain “last line” or “critically important” antibiotics

Antibiotic Resistance in E.coli the Wild kangaroos vs people

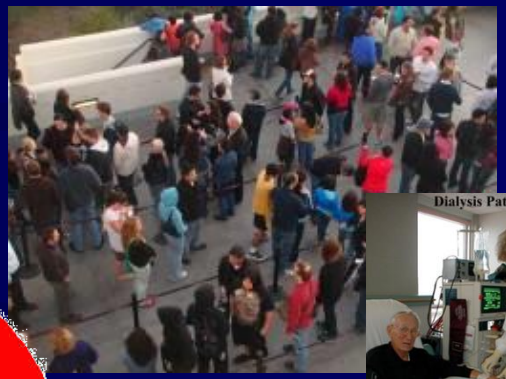
• ampicillin	2.9%	vs	46%
• tetracycline	0.2%		28%
• chloramphenicol	0.4%		14%
• trimethoprim	0.2%		15%

- in Australia in people low levels of resistance to “critically important” antibiotics
  - cefotaxime, meropenem, naladixic acid, ciproxin, gentamicin (many antibiotics have restricted use)

Sherley M, Gordon DM, Collignon PJ. Variations in antibiotic resistance profile in Enterobacteriaceae isolated from wild Australian mammals.Environ Microbiol. 2000 Dec;2(6):620-31.

One Health

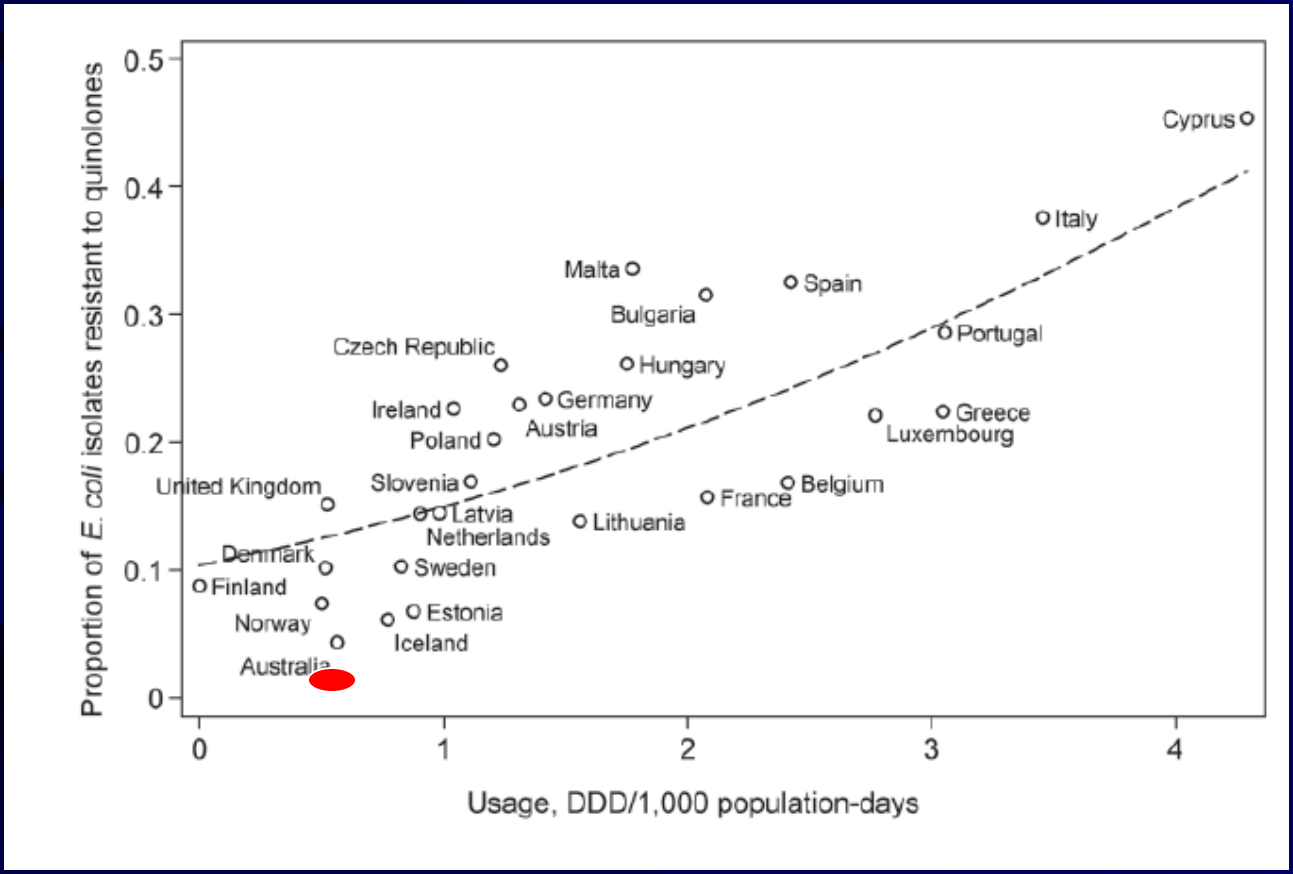
It all goes around, and around, and around



Australia the lucky country

- Low levels of resistant bacteria in people to “critically important” antimicrobials
- And also currently Low levels in food animals and domestic foods

Australia 2010
FQ resistance 4.1% to 5.2%



Control of Fluoroquinolone Resistance through Successful Regulation, Australia

Allen C. Cheng, John Turnidge, Peter Collignon, David Looke, Mary Barton, and Thomas Gottlieb

Emerging Infectious Diseases • www.cdc.gov/eid • Vol. 18, No. 9, September 2012 1453

E.coli - Quinolone resistance

E.coli is the most common human bacterial pathogen

- In Australia fluoroquinolones NOT approved for livestock use
  - Low resistance in human E.coli
  - Negligible resistance levels in food animals
  - nil in food isolates (2007)
- In Spain
  - in children, 22% ciprofloxacin resistant
  - in chickens, 90% resistant

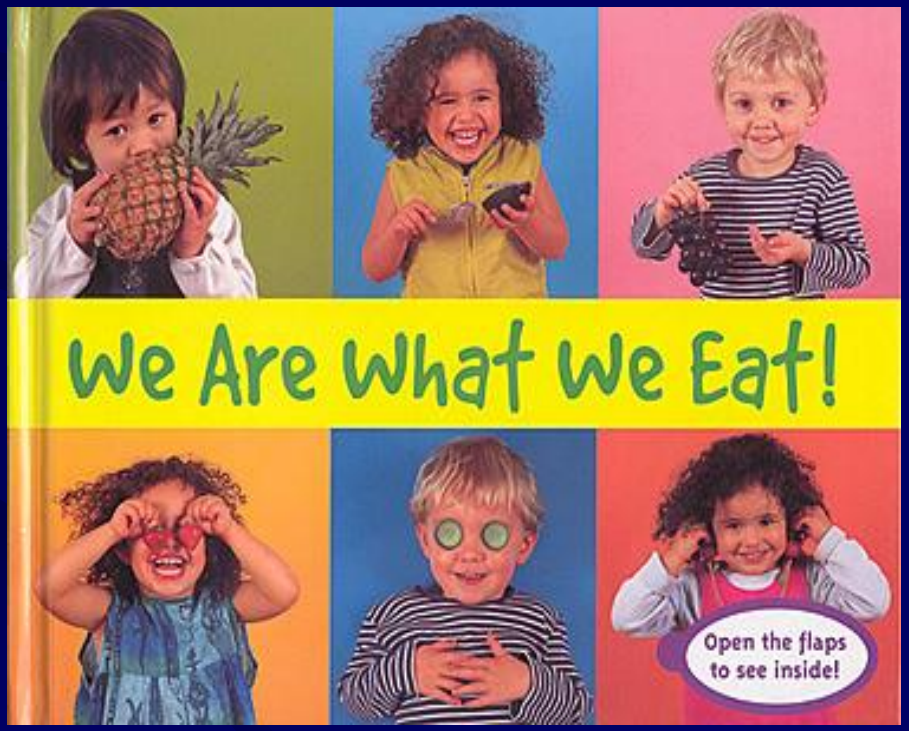
We are what we eat

Resistant *Escherichia coli*—We Are What We Eat

Peter Collignon

Infectious Diseases Unit and Microbiology Department, The Canberra Hospital, and School of Clinical Medicine, Australian National University, Canberra, Australia

Clinical Infectious Diseases 2009; 49:202–4



You can get just driving a car!

- Air and surface samples from cars driving
  2-3 car lengths behind poultry trucks
  → ↑concentrations of antibiotic-resistant bacteria

Ana M et al. J Infect Publ Health, 2008; 1

Ceftiofur (3rd gen cephalosporin)

Major producers moving against "antibiotics and Superbugs"

Globally, water is the major risk for spread of resistant bacteria

PHARMACEUTICALS

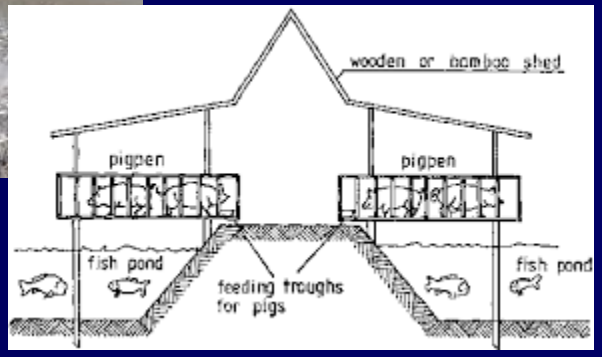
China's lakes of pig manure spawn antibiotic resistance

Researchers begin to size up a public health threat from burgeoning pork production

By **Christina Larson**, *in Tongxiang and Xiamen, China*

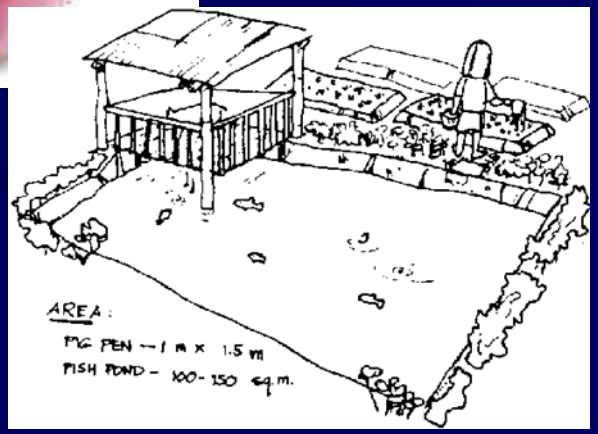
ment into action. In a 2013 study published in the *Proceedings of the National Academy of Sciences* (*PNAS*), he and his colleagues

Aquaculture



One Health
Not just superbugs

vegetables



PLOS | ONE

RESEARCH ARTICLE

Antimicrobial Resistance: The Major Contribution of Poor Governance and Corruption to This Growing Problem

Peter Collignon[1,2]*, Prema-chandra Athukorala[3,4], Sanjaya Senanayake[5,6], Fahad Khan[3]

1 ACT Pathology, Canberra Hospital, Australian National University, Garran, Australia, 2 Canberra Clinical School, Australian National University, Garran, Australia, 3 Arndt-Corden Department of Economics, Australian National University, Acton, Australia, 4 School of Environment and Development, University of Manchester, Manchester, England, 5 Australian National University, Garran, Australia, 6 Canberra Hospital, Garran, Australia

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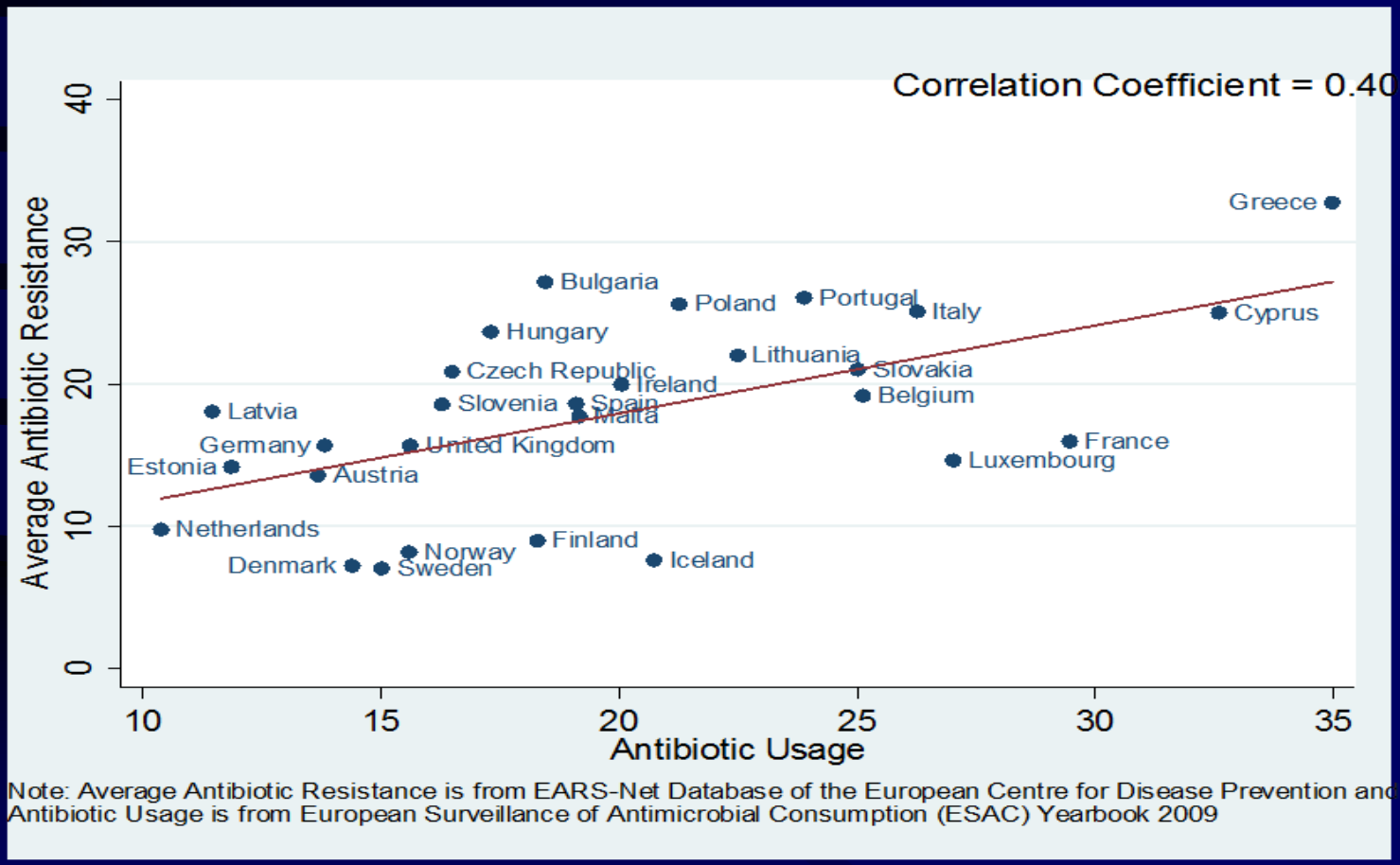
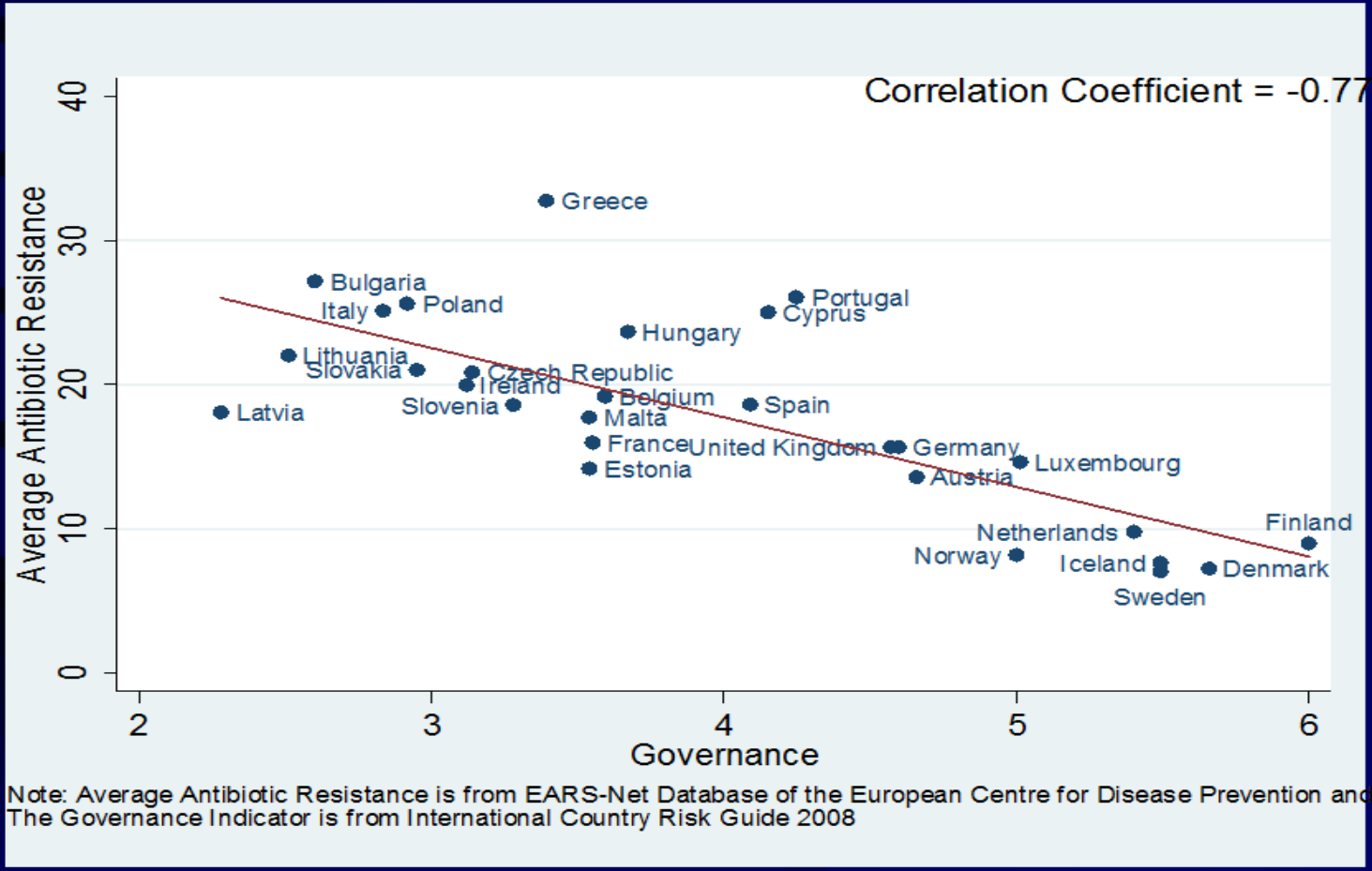
PLOS ONE | DOI:10.1371/journal.pone.0116746 March 18, 2015

Resistance versus usage EU 2009



Note: Average Antibiotic Resistance is from EARS-Net Database of the European Centre for Disease Prevention and Control
Antibiotic Usage is from European Surveillance of Antimicrobial Consumption (ESAC) Yearbook 2009

Resistance versus corruption in EU



Note: Average Antibiotic Resistance is from EARS-Net Database of the European Centre for Disease Prevention and Control
The Governance Indicator is from International Country Risk Guide 2008

Colistin resistance

Colistin resistance: a major breach in our last line of defence

In hospital practice, clinicians have been buoyed by the recent development of new antibiotics active against multidrug resistant Gram-negative bacilli. However, recently approved antibiotics like ceftazidime-avibactam or ceftolozane-tazobactam do not provide activity against all Gram-negative bacilli, with notable gaps in their coverage, including the notorious New Delhi metallo-β-lactamase 1-producing organisms and many strains of carbapenem resistant *Acinetobacter baumannii*. For this reason, the polymyxins (colistin and polymyxin B) remain the last line of defence against many Gram-negative bacilli. Colistin-resistant and

Liu and colleagues[4] present data from China showing that *E coli* from pigs at slaughter and from retail chicken and pork have high rates of plasmid-mediated colistin resistance. The same mechanism was found in *E coli* and *K pneumoniae* isolates from Chinese patients in hospital. These findings suggest that the links between agricultural use of colistin, colistin resistance in slaughtered animals, colistin resistance in food, and colistin resistance in human beings are now complete. One of the few solutions to uncoupling these connections is limitation or cessation of colistin use in agriculture. This will require substantial political

AP Photo

Lancet Infect Dis 2015

Published Online
November 18, 2015

Spread from agriculture is a major factor

Emergence of plasmid-mediated colistin resistance mechanism MCR-1 in animals and human beings in China: a microbiological and molecular biological study

Yi-Yun Liu, Yang Wang*, Timothy R Walsh, Ling-Xian Yi, Rong Zhang, James Spencer, Yohei Doi, Guobao Tian, Baolei Dong, Xianhui Huang, Lin-Feng Yu, Danxia Gu, Hongwei Ren, Xiaojie Chen, Luchao Lv, Dandan He, Hongwei Zhou, Zisen Liang, Jian-Hua Liu, Jianzhong Shen*

Lancet Infect Dis 2015
Published Online
November 18, 2015
http://dx.doi.org/10.1016/

Summary

Background Until now, polymyxin resistance has involved chromosomal mutations but has never been reported via horizontal gene transfer. During a routine surveillance project on antimicrobial resistance in commensal *Escherichia coli* from food animals in China, a major increase of colistin resistance was observed. When an *E coli* strain, SHP45,

Pets are a risk (bidirectional)

J Antimicrob Chemother 2014; **69**: 1155–1157
doi:10.1093/jac/dkt518 Advance Access publication 6 January 2014

Journal of Antimicrobial Chemotherapy

Carbapenemase-producing bacteria in companion animals: a public health concern on the horizon

Sam Abraham[1*], Hui San Wong[1], John Turnidge[2,3], James R. Johnson[4] and Darren J. Trott[1]

Infection control and prevention is essential

1 Strategies for managing infections caused by multidrug-resistant gram-negative bacilli

	Third-generation cephalosporin-resistant Enterobacteriaceae	Carbapenem-resistant Enterobacteriaceae (CRE)
Treatment		
Severe illness and/or requiring intravenous therapy (includes pyelonephritis)	Discuss with an infectious diseases physician or clinical microbiologist. Typically treated with a carbapenem (eg, meropenem). Occasionally aminoglycosides or fluoroquinolones are a suitable alternative if susceptible. Piperacillin–tazobactam may be effective but clinical experience is limited.	Highly specialised therapy required. Always discuss with an infectious diseases physician or clinical microbiologist. Often requires combination therapy.
Non-severe illness (eg, cystitis)	Fluoroquinolone or trimethoprim–sulfamethoxazole can be used if susceptible. For cystitis, amoxicillin–clavulanate or nitrofurantoin can be used if susceptible. Fosfomycin and pivmecillinam are commonly available overseas but not easily obtained in Australia. Agents that test resistant in vitro using minimum inhibitory concentration break points calibrated for systemic infection may still be effective in uncomplicated urinary infection. Even for non-severe infection outside of the urinary tract, intravenous therapy may be required owing to a lack of suitable oral therapies.	Always discuss with an infectious diseases physician or clinical microbiologist. Frequently no oral options are available for therapy. In non-severe and potentially self-limiting illnesses, occasional observation without treatment is appropriate.
Infection control[22,23]		
Universal	Practices aimed at preventing patient infection including: • minimising the use of invasive devices (eg, urinary catheters, short-term intravenous catheters and long-term vascular access devices such as peripherally inserted central catheters or central venous catheters) and their rapid removal when not required • antimicrobial stewardship • hand hygiene • care with environmental cleaning • surveillance of infection rates and antimicrobial resistance patterns (these should be tailored to the clinical setting and resources available and may range from a simple audit to a broad-based integrated program) • education of health care workers, patients and the public about multidrug-resistant bacteria.	
Acute care hospitals	Current National Health and Medical Research Council guidelines recommend use of contact precautions (although with consideration given to local circumstances). Data suggest a low risk of transmission of extended-spectrum β-lactamase *Escherichia coli* in an acute care setting. Practice among Australian hospitals varies widely from full contact precautions to use of only standard precautions.	Covered by Australian Commission on Safety and Quality in Health Care guidelines, which recommend active case finding with screening of high-risk patients and contact precautions for all patients harbouring CRE.
Nursing homes and subacute settings	Transmission may be higher in these settings owing to longer cohabitation and greater sharing of facilities. However, contact precaution use is very problematic due to staff levels, cost and impact on patients, hence it is used infrequently. Careful attention should be paid to the universal measures above.	Guidelines suggest risk-based stratification dependent on factors such as patient continence and clinical site of CRE. Use of contact precautions in high-risk patients is recommended.
Outpatient and clinic settings	Risk of transmission likely low; no precautions recommended.	No specific recommendations from guidelines. Gloves for examination and cleaning of examination bed recommended by some authorities overseas. ◆

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REVIEW 10.1111/1469-0691.12748

Combating the spread of carbapenemases in *Enterobacteriaceae*: a battle that infection prevention should not lose

P. Savard[1,2] and T. M. Perl[3,4]

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Abstract

The emergence of carbapenemases in *Enterobacteriaceae* has raised global concern among the scientific, medical and public health communities. Both the CDC and the WHO consider carbapenem-resistant *Enterobacteriaceae* (CRE) to constitute a significant threat that necessitates immediate action. In this article, we review the challenges faced by laboratory workers, infection prevention specialists and clinicians who are confronted with this emerging infection control issue.

Keywords: Carbapenemase, carbapenem-resistant, *Enterobacteriaceae*, infection prevention, review
Article published online: 01 July 2014
Clin Microbiol Infect 2014; **20**: 854–861

Table 1 The two fundamentals to control antimicrobial resistance

Decrease antimicrobial use and control what is used
Dramatically lower antibiotic volumes currently used (human and non-human)
Restrict broad spectrum and critically important antibiotics in people
Ban the use of critically important antibiotics in food animals
Do not use antibiotics to spray plants
Prevent infections
Do not dump antibiotics into the environment
Stop the presence of antibiotic residues in foods and water
Stop the spread of resistant bacteria and genes and exposure to them
Control spread into the environment
Hygiene
Infection control
Agriculture sector
Aquaculture
No superbugs in foods and water

One Health

It all goes around, and around, and around