Antibiotics, resistance and hospital management

Why we should be worried and why we need a new approach

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Infectious Diseases & Microbiology Department, Austin Health
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Overview

• The view from Mars
• Basics of the problem
• 5 practical steps towards a solution in hospitals
• The impending tsunami
A brief summary of the problem

A view from Mars
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A view from Mars

• Pre-1940s – no Antibiotics
• Wonder drugs invented
• Within 70 years (2-3 human generations) – antibiotics misused
• Rapidly emerging multi-drug resistance
  – Gram+ves – MRSA, VISA, VRE, L-VRE
  – Gram-ves – MBLs, colistin-resistant, etc
  – XDR-TB
  – Hypervirulent C. difficile
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New Antibiotics?
Large US and European Pharmaceutical Companies Conducting Antibacterial Research

1980 (N=36)

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# Large US and European Pharmaceutical Companies Conducting Antibacterial Research

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<td>2010</td>
<td>AstraZeneca, Glaxo SmithKline, (Johnson &amp; Johnson), (Merck-Schering Plough), Novartis, Pfizer - Wyeth, Sanofi-Aventis</td>
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Antibiotic Discovery & Development

Historical Sources of Antibiotics

• Traditionally
  – Antibiotics collected and isolated from natural sources
  – Primarily from soil samples

• Synthetic medicinal chemistry used to improve drug-like properties
Anti-Infective Drug Discovery in the 1990’s

- De-emphasize natural products
- Bacterial genomes became available
  - Genomics used for target identification
- Genetic and microarray analyses identified essential genes
- Rapid screening of many targets using High Throughput Screening (HTS)
End Results of High-Throughput Screening

• HTS produced potent enzyme inhibitors
  – *But* - Outcomes were dependent on quality of compound libraries

• Same novel targets were identified by many groups in different companies

• No antibacterial compounds derived from HTS proceeded past Phase 2 clinical studies

• Antibacterial programs were shut down at many companies
Bad Bugs Need Drugs

Ten new ANTIBIOTICS by 2020
Figure 1. New systemic antibacterial agents approved by the US Food and Drug Administration per 5-year period, through 2012. Modified from Spellberg 2004 [23].
Houston, we have a problem!
Basics of controlling MDR pathogens
Pre-JETACAR (1999)

1. Limit emergence of new MDR pathogens
2. Limit transmission of existing MDR pathogens
Basics of controlling MDR pathogens
Pre-JETACAR (1999)

1. Limit emergence of new MDR pathogens
2. Limit transmission of existing MDR pathogens
Basics of controlling MDR pathogens

Now (2013 - )

1. Limit transmission of existing MDR pathogens
2. Limit emergence of new MDR pathogens
Basics of the solution

Key advances in human health and reductions in infectious diseases relate to:

1. Sanitation
2. Improved housing
   – Reduced overcrowding
   – Improved spatial separation
3. Clean food & water
Basics of the solution

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5 Practical Steps
Towards a solution in hospitals

1. Improved hand hygiene
2. Improved hospital cleaning
3. National standards for invasive device insertion and maintenance
4. Improved hospital design
5. Tighten antibiotic prescribing control
The solution:

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Reduce cross-transmission
The solution:

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Reduce cross-transmission:

Reduce emergence of “new” resistance & colonization pressure
5 Moments for HAND HYGIENE
Infection control

1. Palm to palm
2. Right palm over left back and left palm over right back
3. Palm to palm with fingers interlaced
4. Backs of fingers to opposing palms with fingers interlocked
5. Rotational rubbing of right thumb clasped in left palm and vice versa
6. Rotational rubbing backwards and forwards with clasped fingers of right hand in left palm and vice versa

Patients and staff in healthcare environments are vulnerable to infections, including methicillin-resistant Staphylococcus aureus (MRSA). Frequent and appropriate handwashing is a key principle to avoid contamination. Here is a guide to effective handwashing and some useful tips for avoiding the spread of infection:

- Hands should be washed with soap and water or alcohol hand-rub using the correct technique before and after procedures and contact with patients.
- Disposable gloves and aprons should be worn for contact with body fluids, lesions and contaminated materials (wash hands after use).
- If taking a uniform home to clean, a hot wash should be used and the washing machine should not be overloaded.
- Linen should be handled carefully (not shaken) and transported in correct colour-coded laundry bags. Soft furnishings, such as curtains, should be cleaned regularly.
- Patient areas should be uncluttered and cleaned regularly.
- Compliance with infection control policies should be monitored through audits.
Significant reduction in vancomycin-resistant enterococcus colonization and bacteraemia after introduction of a bleach-based cleaning–disinfection programme

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b Infectious Diseases Department, Austin Health, Heidelberg, Victoria, Australia
c Acute Operations Department, Austin Health, Heidelberg, Victoria, Australia
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f Department of Medicine, University of Melbourne, Parkville, Victoria, Australia
Universal approach to cleaning
No need to change for norovirus and C.diff. outbreaks
Assumes all patients are colonised with "Superbugs"
The solution:

5 Practical Steps
Towards a solution in hospitals

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Peripheral intravenous catheter-associated *Staphylococcus aureus* bacteraemia: more than 5 years of prospective data from two tertiary health services

Abstract

**Objectives:** To determine the incidence, risk factors for and outcomes of *Staphylococcus aureus* bacteraemia (SAB) associated with peripheral intravenous catheters (PIVCs).

**Design, setting and patients:** A review of prospectively collected data from two tertiary health services on all healthcare-associated SAB episodes occurring in adults aged >17 years from January 2007 to July 2012.

**Main outcome measures:** Numbers of healthcare-associated SAB episodes; device type, location of insertion, device dwell time and outcome at 7 and 30 days for all SAB episodes associated with use of a PIVC; rates of SAB per 10,000 occupied bed-days (OBDs).

**Results:** Overall, 137 of 583 health care-associated-SAB episodes (23.5%) were deemed to be PIVC associated, with an incidence of 0.26/10,000 OBD. The mean dwell time for PIVCs was 3.5 days (range, 0.25–9 days) and 45.2% of SABs occurred in PIVCs with a dwell time ≥4 days. Of the PIVC-associated SAB episodes, 39.6% involved PIVCs inserted in the ED, 39.6% involved PIVCs inserted on wards and 20.8% involved PIVCs inserted by the ambulance service. Of the PIVC-associated SABs occurring within 4 days of insertion, 61% were inserted by ED staff or the ambulance service. PIVC-associated SAB were associated with a 30-day all-cause mortality rate of 26.5%.

**Conclusion:** PIVC-associated SAB is an under-recognised complication. The high incidences of SAB associated with PIVCs inserted in emergency locations and with prolonged dwell times support recommendations in clinical guidelines for routine removal of PIVCs.
The solution:

Patient-to-Toilet ratio

1x bum
The solution:

Patient-to-Toilet ratio

1x bum
The solution:

Patient-to-Toilet ratio

1x bum per toilet
Patient-to-Toilet ratio

The solution:

The new mantra (standard) for hospital design:

“One bum per toilet”
5 Practical Steps
Towards a solution in hospitals

1. Improved hand hygiene
2. Improved hospital cleaning
3. National standards for invasive device insertion and maintenance
4. Improved hospital design
5. Tighten antibiotic prescribing control
How do we deal with Antibiotic Overload?
How often do we truly pay attention to these issues?

- The situation re. antibiotic resistance is now so serious
- ? Need for new accreditation rule for hospitals:

  Non-compliance with minimum standards of infection control, hand hygiene & antibiotic prescribing control =

  No ICU, neonatology, dialysis or transplantation
How often do we truly pay attention to these issues?

The situation re. antibiotic resistance is now so serious.

- Need for new accreditation rule for hospitals:
  - Non-compliance with minimum standards of infection control, hand hygiene & antibiotic prescribing control

  Non-ICU, neonatology, dialysis or transplantation

Should these MDR-risky activities only be allowed in hospitals that meet certain standards of infection and antibiotic control?
Health scare: Antibiotic-resistant bacteria on ascendency

Superbug reports spark concern

Julia Medew
Health Editor
The impending tsunami
The impending tsunami
The Scourge of Antibiotic Resistance: The Important Role of the Environment

Rita L. Finley,1 Peter Collignon,2 D. G. Joakim Larsson,3 Scott A. McEwen,4 Xian-Zhi Li,5 William H. Gaze,6 Richard Reid-Smith,7 Mohammed Timinouni,8 David W. Graham,9 and Edward Topp10

1Centre for Food-borne, Environmental and Zoonotic Infectious Diseases, Public Health Agency of Canada, Guelph, Ontario; 2Infectious Diseases Unit and Microbiology Department, The Canberra Hospital and Canberra Clinical School, Australian National University; 3Department of Infectious Diseases, Institute of Biomedicine, University of Gothenburg, Sweden; 4Department of Population Medicine, Ontario Veterinary College, University of Guelph, Canada; 5Veterinary Drugs Directorate, Health Canada, Ottawa, Ontario; 6European Centre for Environment and Human Health, Exeter University Medical School, Knowledge Spa, Royal Cornwall Hospital, Truro, United Kingdom; 7Laboratory for Foodborne Zoonoses, Public Health Agency of Canada, Guelph, Ontario; 8Molecular Bacteriology Laboratory, Pasteur Institute of Morocco, Casablanca; 9School of Civil Engineering and Geosciences, Newcastle University, United Kingdom; and 10Agriculture and Agri-Food Canada, London, Ontario

Antibiotic resistance and associated genes are ubiquitous and ancient, with most genes that encode resistance in human pathogens having originated in bacteria from the natural environment (eg, β-lactamases and fluoroquinolones resistance genes, such as qnr). The rapid evolution and spread of “new” antibiotic resistance genes has been enhanced by modern human activity and its influence on the environmental resistome. This highlights the importance of including the role of the environmental vectors, such as bacterial genetic diversity within soil and water, in resistance risk management. We need to take more steps to decrease the spread of resistance genes in environmental bacteria into human pathogens, to decrease the spread of resistant bacteria to people and animals via foodstuffs, wastes and water, and to minimize the levels of antibiotics and antibiotic-resistant bacteria introduced into the environment. Reducing this risk must include improved management of waste containing antibiotic residues and antibiotic-resistant microorganisms.
Diverse and abundant antibiotic resistance genes in Chinese swine farms

Yong-Guan Zhu, a,b,1,2 Timothy A. Johnson, c,d,1 Jian-Qiang Su, a Min Qiao, b Guang-Xia Guo, b Robert D. Stedtfeld, c,e Syed A. Hashsham, c,d,1 and James M. Tiedje a,d,2

a Key Lab of Urban Environment and Health, Institute of Urban Environment, Chinese Academy of Sciences, Xiamen 361021, China; b Research Center for Eco-Environmental Sciences, Chinese Academy of Sciences, Beijing 100085, China; and c Center for Microbial Ecology, Departments of Plant, Soil and Microbial Sciences, and Civil and Environmental Engineering, Michigan State University, East Lansing, MI 48824

Contributed by James M. Tiedje, December 31, 2012 (sent for review October 31, 2012)

Antibiotic resistance genes (ARGs) are emerging contaminants posing a potential worldwide human health risk. Intensive animal husbandry is believed to be a major contributor to the increased environmental burden of ARGs. Despite the volume of antibiotics used in China, little information is available regarding the corresponding ARGs associated with animal farms. We assessed type and concentrations of ARGs at three stages of manure processing to land disposal at three large-scale (10,000 animals per year) commercial swine farms in China. In-feed or therapeutic antibiotics used on these farms include all major classes of antibiotics except vancomycin. High-capacity quantitative PCR arrays detected 149 unique resistance genes among all of the farm samples, the top 63 ARGs being enriched 192-fold (median) up to 28,000-fold (maximum) compared with their respective antibiotic-free manure or soil controls. Antibiotics and heavy metals used as feed supplements were elevated in the manures, suggesting the potential for coselection of resistance traits. The potential for horizontal transfer of ARGs because of transposon-specific ARGs is implicated by the enrichment of transposases—the top six alleles being enriched 188-fold (median) up to 90,000-fold in manure—as well as the high correlation (r² = 0.95) between ARG and transposase abundance. In addition, abundance of ARGs correlated directly with antibiotic and metal concentrations, indicating their importance in selection of resistance genes. Diverse, abundant, and potentially mobile ARGs in farm samples suggest that unmonitored use of antibiotics and metals is causing the emergence and release of ARGs to the environment.

Concentrated animal feeding operations | horizontal gene transfer | growth-promoting antibiotics | tetracycline

The spread and aggregation of antibiotic-resistant genes into multidrug-resistant pathogens is challenging life-saving anti-Health, together with the US Food and Drug Administration and the World Health Organization, urge improved regulation of veterinary antibiotic use in over 100 developing countries (12).

China is the largest antibiotics producer and consumer in the world. In a 2007 survey, the estimated annual antibiotic production in China was 210 million kg, and 46.1% were used in livestock industries (13), at least four times the amount used in the US livestock industry in 1999 (14). In China, the use of antibiotics both for animal disease treatment and growth promotion is unmonitored, which often leads to high use, reflected by the high concentrations of antibiotic residues (hundreds of milligrams of tetracycline per kilogram) that are commonly detected in animal manures (15, 16). Manure is a major source of antibiotic pollution in the environment, and China produces an estimated 618 billion kg of swine manure annually (17). Most veterinary antibiotics are poorly absorbed by the animal and hence are excreted (18) and dispersed to soil when the manure is spread as fertilizer, the desired practice for recycling nutrients. Furthermore, the use of subtherapeutic levels of antibiotics in animal feeds causes an increase in antibiotic resistance traits in manure (19, 20), manure-amended soils (21), and downstream river waters and sediments (22). In addition, metals are added to swine feed for growth promotion and disease control and may provide a long-term coselective pressure for antibiotic resistance (23). The scale of the livestock industry in China and the volume of antibiotics use provide an opportunity to assess the impact of large-scale animal farm practices on antibiotic resistance genes in the environment. Previously, tetracycline resistance (tet) genes in soils adjacent to representative Chinese swine feedlots were positively correlated to concentrations of tetracycline residues (24), raising the question of whether the diversity and abundance of the antibiotic resistance reservoir extends beyond tetracycline...
Diverse and abundant antibiotic resistance genes in Chinese swine farms

Yong-Guan Zhu,a,b,1,2 Timothy A. Johnson,c Syed A. Hashsham,a,* and James M. Tiedje c

*aKey Lab of Urban Environment and Health, Institute of Urban Environment, Chinese Academy of Sciences, Hefei, Anhui, China, bCivil and Environmental Engineering, McGill University, Montreal, Quebec, Canada, and cCivil and Environmental Engineering, Montana State University, Bozeman, Montana, USA

Contributed by James M. Tiedje, December 31, 2012

Antibiotic resistance genes (ARGs) are emerging as a significant problem worldwide, posing a potential worldwide human health risk. In intensive swine operations, such as hog and other husbandry is believed to be a major contributor to the development of antibiotic resistance. The environmental burden of ARGs is globally significant and of concern, particularly in China, where it is estimated that as many as 10,000 animals are raised on a single farm. In this study, we present preliminary data on the concentration and distribution of ARGs at three stages of manure production: (1) manure application to soil; (2) manure disposal at three large-scale (10,000 animals) swine farms in China. In-feed or therapeutic antibiotics were used in all three of these farms include all major classes of antibiotics and have been documented as having been used in the production of pigs in China. High-capacity quantitative PCR arrays detected 273 distinct ARGs among all of the farm samples, with ARGs being enriched 192-fold (median) up to 28,000-fold (maximum) compared with their respective antibiotic-free manure controls. Antibiotics and heavy metals used as feed supplements or elevated in the manures, suggesting the potential to disrupt the development of resistance traits. The potential for horizontal gene transfer (HGT), which is expected because of transposon-specific ARGs is implicated in the spread of ARGs. The top six ARGs are enriched up to 90,000-fold in manure—amoxicillin, sulfadiazine, and tetracycline. The enrichment of ARGs correlated directly with antibiotic concentrations, indicating their importance in selection of resistance traits. Diverse, abundant, and potentially mobile ARGs suggest that unmonitored use of antibiotics and heavy metals in concentrated animal feeding operations is challenging. The spread and aggregation of antibiotic-resistant bacteria from swine facilities can lead to the emergence and release of ARGs to the environment. The results showed that pig manure samples were positively correlated to the concentrations of copper, zinc, arsenic, and total tetracycline. Environmental variables were chosen based on significance calculated from individual CCA results and variance inflation factors (VIFs) calculated during CCA. The percentage of variation explained by each axis is shown, and the relationship is significant (P = 0.005). CCA analyses were performed in R 2.13.0 with vegan package 1.17-9.

Fig. 4. Canonical correspondence analysis (CCA) compares the abundance of detected resistance genes (symbols) and the concentration of heavy metals and antibiotics (arrows). The results showed that pig manure samples were positively correlated to the concentrations of copper, zinc, arsenic, and total tetracycline. Environmental variables were chosen based on significance calculated from individual CCA results and variance inflation factors (VIFs) calculated during CCA. The percentage of variation explained by each axis is shown, and the relationship is significant (P = 0.005). CCA analyses were performed in R 2.13.0 with vegan package 1.17-9.
Extended-Spectrum β-Lactamase–Producing *Escherichia coli* From Retail Chicken Meat and Humans: Comparison of Strains, Plasmids, Resistance Genes, and Virulence Factors


Laboratory for Medical Microbiology and Infection Control, Amphia Hospital, Breda, Laboratory for Medical Microbiology and Immunology, St Elisabeth Hospital, Tilburg, Laboratory for Medical Microbiology and Infection Control, VU University Medical Centre, Amsterdam, and National Institute for Public Health and the Environment, RIVM, Bilthoven, The Netherlands; Veterans Affairs Medical Center, University of Minnesota, Minneapolis; and The Australian National University, Canberra

**Background.** The worldwide prevalence of extended-spectrum β-lactamase (ESBL)-producing Enterobacteriaceae is increasing rapidly both in hospitals and in the community. A connection between ESBL-producing bacteria in food animals, retail meat, and humans has been suggested. We previously reported on the genetic composition of a collection of ESBL-producing *Escherichia coli* (ESBL-EC) from chicken meat and humans from a restricted geographic area. Now, we have extended the analysis with plasmid replications, virulence factors, and highly discriminatory genomic profiling methods.

**Methods.** One hundred forty-five ESBL-EC isolates from retail chicken meat, human rectal carriers, and blood cultures were analyzed using multilocus sequence typing, phylotyping, ESBL genes, plasmid replications, virulence genes, amplified fragment length polymorphism (AFLP), and pulsed-field gel electrophoresis (PFGE).

**Results.** Three source groups overlapped substantially when their genetic composition was compared. A combined analysis using all variables yielded the highest resolution (Wilks lambda [A]: 0.08). Still, a prediction model based on the combined data classified 40% of the human isolates as chicken meat isolates. AFLP and PFGE showed that the isolates from humans and chicken meat could not be segregated and identified 1 perfect match between humans and chicken meat.

**Conclusions.** We found significant genetic similarities among ESBL-EC isolates from chicken meat and humans according to mobile resistance elements, virulence genes, and genomic backbone. Therefore, chicken meat is a likely contributor to the recent emergence of ESBL-EC in human infections in the study region. This raises serious food safety questions regarding the abundant presence of ESBL-EC in chicken meat.

**Keywords.** ESBL-producing *Escherichia coli*; chicken meat; molecular typing; resistance genes; plasmids.
Human Deaths and Third-Generation Cephalosporin use in Poultry, Europe

To the Editor: Globally, antimicrobial drug resistance is rapidly rising, with resultant increased illness and death. Of particular concern is *Escherichia coli*, the most common bacterium to cause invasive disease in humans (1). In Europe, increasing proportions of bloodstream infections caused by *E. coli* are resistant to third-generation cephalosporins (1,2).

Resistant *E. coli* can be transmitted to humans from animals. A large proportion of resistant isolates causing human infections are derived from food animals (3-6). However, lack of data has made it difficult to quantify the proportion of antimicrobial drug resistant *E. coli* infecting persons through food sources and the associated effects on human health. Recent data from the Netherlands now make such estimates possible (2,4). The additional illness and death among humans resulting from bloodstream infections caused by third-generation cephalosporin-resistant *E. coli* (G3CREC) has been calculated for Europe (2). In the Netherlands, there were 205 G3CREC cases during 2007 (4% of all *E. coli* bloodstream infections) (2). Another study in the Netherlands revealed that 56% of the resistance genes in G3CREC in humans were identical to genes derived from *E. coli* isolated from retail chicken samples (6). Using the findings of Overdevest et al. (6) and de Kraker et al. (2), we calculated that, in the Netherlands, infections in humans with G3CREC derived from poultry sources were associated with 21 additional deaths. G3CREC-related illness also resulted in 908 hospital bed-days needed to treat persons with these antimicrobial drug resistant bloodstream infections. If these values were extrapolated to all of Europe (i.e., if 56% of G3CREC were derived from poultry), 1,518 additional deaths and an associated increase of 67,266 days of hospital admissions would be counted as a result of cephalosporin and other antimicrobial drug use in poultry.

To more accurately estimate the associated increased deaths among persons resulting from third-generation cephalosporin use in poultry, detailed data from more countries is essential. Needed data include records of antimicrobial drug use and resistant bacterial strains found in food animals and domestic and imported foods. However, we already know that G3CREC is rapidly rising in many countries, and in Europe, the infection rate is likely to have tripled from 2007 to 2012 (2). Globally, billions of chickens receive third-generation cephalosporins in ovo or as day-old chicks to treat *E. coli* infection, a practice that has resulted in large reservoirs of resistant bacteria (7). In Canada, this practice has been associated with substantial increases in resistance to third-generation cephalosporins in *Salmonella enterica* serovar Heidelberg isolates detected in humans (7). The United States Food and Drug Administration recently prohibited the off-label use of cephalosporins, including prophylactic uses, in major food animal species, including poultry (8).

The number of avoidable deaths and the costs of health care potentially caused by third-generation cephalosporin use in food animals is staggering. Considering those factors, the ongoing use of these antimicrobial drugs in mass therapy and prophylaxis should be urgently examined and stopped, particularly in poultry, not only in Europe, but worldwide.

References

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Resistant *E. coli* can be transmitted to humans from animals. A large proportion of resistant isolates causing human infections are derived from food animals (3–6). However, lack of data has made it difficult to quantify the proportion of antimicrobial drug resistant *E. coli* infecting persons through food sources and the resultant effects on human health. Recent data from the Netherlands now make such estimates possible (2,6). The additional illness and death among humans resulting from bloodstream infections caused by third-generation cephalosporin-resistant *E. coli* (G3REC) has been calculated for Europe (2). In the Netherlands, there were 205 G3REC cases during 2007 (4% of all *E. coli* bloodstream infections) (2). Another study in the Netherlands revealed that 56% of the resistance genes in G3REC in humans were identical to genes derived from *E. coli* isolated from retail chicken samples (6). Using the findings of Overdevest et al. (6) and de Kraker et al. (2), we calculated that, in the Netherlands, infections in humans with G3REC derived from poultry sources were associated with 21 additional deaths. G3REC-related illness also resulted in 908 hospital bed-days needed to treat persons with these antimicrobial drug resistant bloodstream infections. If these were extrapolated to all of Europe (i.e., if 50% of G3REC were derived from poultry), 1,518 additional deaths and an associated increase of 67,236 days of hospital admissions would be counted as a result of cephalosporin and other antimicrobial drug use in poultry.

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The impending tsunami

Contamination of the food chain
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Ban resistant strains from food chain

No reliable treatment is available for humans infected with carbapenem-resistant Enterobacteriaceae (CREs; see *Nature* 499, 394–396; 2013). Because these antibiotic-resistant bacterial pathogens are already entering the food chain (J. Fisher et al. *J. Antimicrob. Chemoth.* 68, 478–480; 2013) and can be transmitted through oral consumption (A. R. Manges and J. R. Johnson *Clin. Infect. Dis.* 55, 712–719; 2012), we call for a zero-tolerance ruling on CREs in retail food to stop the situation getting out of control.

By 2007, it was estimated that more than 1,500 people in Europe had died from an
Finance and Public Administration References Committee

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June 2013
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