Chewing it over: the clinical and public health relevance of antibiotic-resistant bacteria in food

Anna-Pelagia Magiorakos, MD
European Centre for Disease Prevention and Control
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1. Reservoirs of resistant food-borne pathogens
2. Emergence of resistance
3. Critically important antimicrobials
4. Public health and clinical consequences of infections with select resistant bacteria
   - *Enterobacteriaceae* producing ESBL
   - *Salmonella* spp.
   - MRSA ST 398
5. Strategies to control resistance in humans and animals
6. Perspectives
The ecological phenomenon of resistance

Dissemination of resistant bacteria and mobile genetic elements

Resistance in commensal and pathogenic organisms → reservoirs for resistant genes

Antibiotic use for growth promotion, prophylaxis, therapy

Food animals

Aquatic environments

Meat products

Hospitalized patients

Humans in the community

Faeces

Selective pressures

Main reservoir

Important environmental ecosystems

Horizontal transfer of mobile genetic elements to pathogenic bacteria in the animal and human gut

Emergence of antimicrobial resistance

1976 Levy et al. tet-feed to chickens
  • 36-48 hrs > 60% and 14 days: 90% intestinal flora R to tetracycline
  • 5-6 m 31.3 % faecal samples farm dwellers
  • Emergence of MDR E.coli in treated and untreated chickens

Success stories-Denmark
• 1995: ban of avoparcin; ↓ GRE 72.7%-5.8% in broilers, 1995-2000
• 1998: ban of virginiamycin; ↓ virginiamycin resistance 66.2% to 33.9%, 1998-2000

Selection Density
Amount of antibiotic per individual per geographic area

Levy et al. NEJM 1976 Sep;295(11):583-8
The route to the intestine

**Hummel et al.** nourseothricin replaced oxy-tetracycline in animal husbandry → plasmid-mediated R in *E. coli* of animals, farmers, humans in the community; *E.coli* in human UTIs and food-borne *Salmonella*

**Sørensen et al.** double-blind study; 18 volunteers
- 6 glycopeptide-resistant, 6 streptogramin-resistant, 6 sensitive *E. faecium*
- Stool samples 0, 7, 14, 35 d

**Corpet et al.** 6 volunteers ate usual diet for 21 d and sterile diet for 17 d
Control period: faecal concentration *E.coli* 10^8 per gram
Sterile diet: 24 hrs ↓ and 72 hrs → minimum concentrations

**Trobos et al.** volunteers ingested sulpha S (human) and sulpha R (pigs) strains of *E.coli*. Gene transfer of sul2 gene to human *E.coli*
Human susceptibility

- **Colonisation resistance** of human intestinal microflora - antimicrobial use

- **Attributable fraction** for resistant foodborne pathogens
  - “Excess cases” with “selective effect” of resistance
  - >3-fold increase in vulnerability to infection with resistant organisms

Antimicrobial use in animals

Amounts of veterinary antimicrobial agents sold in 2007 per kg biomass of animals. Substances vary per country

Adapted from: Grave et al. J Antimicrob Chemother 2010; 65: 2037-2040
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. Aarestrup8

Need

• Protect antimicrobials routinely used for human infections and used for animal husbandry

• Severe *Salmonella* infections: fluoroquinolones adults; extended-spectrum cephs children

• ESBL *Enterobacteriaceae*: R to 3rd and 4th gen cephs; overuse carbapenems
Enterobacteriaceae - producing ESBL

- Global increase of ESBL in commensal and pathogenic bacteria international clones (e.g. CTX-M-15)
- TEM, SHV and CTX-M ESBL-producing Enterobacteriaceae in food, food animals and humans (e.g. ESBL E.coli and Salmonella)
- Authorized use of cephalosporins in EU
- Increasing R in animals; e.g. The Netherlands
- ? Link to food producing animals/retail meats?
- Resistance first-line antimicrobial agents, failures critically important abx
- Appropriate and timely treatment
- Overuse of last line antimicrobials

Pitout and Laupland. Landet Infect Dis 2008; 8\;159-66
Population-weighted, average % resistant *E. coli* bacterial isolates from bloodstream infections, EU, Iceland and Norway, 2002-2008

**Excluding Belgium and Slovakia, which did not report data.**

## Evidence of food source of ESBL *E.coli* for human colonisation or infection

<table>
<thead>
<tr>
<th>Source</th>
<th>Description</th>
<th>Findings</th>
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</table>
| Lavilla *et al.* | 132 food-borne outbreaks with *E.coli*, cases and food handlers; retail meat and food from hospital kitchen | • Various ESBL: CTX-M-14, SHV-12 and TEM  
• 10 outbreaks, ≥ 2 had same ESBL-PB  
• 4 outbreaks, same strain in food handlers. |
| Leverstein- van Hall *et al.* | Retail chicken samples, clinical samples and prevalence survey in poultry | • 35% human isolates were “poultry associated”  
• 19% of these with ESBL genes/plasmids indistinguishable from meat  
• 86% of the ESBL genes CTX-M-1, TEM-52 also in 78% of poultry and 75% retail meat |
| Overdevest *et al.* | Retail meat, clinical cultures, faecal carriage | • ESBL in 79.8% of retail chicken meat  
• CTX-M-1: most frequent in meat (58.1%) and in rectal swabs (45.8%) and 2nd most in BSI- similar by MLST |

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### Effect of inadequate antimicrobial therapy in critically ill patients

**Ibrahim et al.** prospective cohort study

- inadequate antimicrobial treatment: risk factor for hospital mortality (AOR, 6.86; 95% CI, 5.09 to 9.24; \( p < 0.001 \))

### Effect of inappropriate antimicrobial therapy in critically ill patients

**Kang et al.** retrospective study; GN BSI

- inappropriate initial antimicrobial \( \uparrow \) 30-d mortality (OR, 3.64; 95% CI, 1.13 to 11.72; \( P = 0.030 \)).

### Pathogens

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Inadequate Antimicrobial Treatment</th>
<th>Hospital Mortality</th>
</tr>
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<tbody>
<tr>
<td>OSSA</td>
<td></td>
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<tr>
<td>E. coli</td>
<td></td>
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<tr>
<td>Enterococcus spp.</td>
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<tr>
<td>Klebsiella spp.</td>
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<td>P. aeruginosa</td>
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<tr>
<td>CNS</td>
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<tr>
<td>ORSA</td>
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<tr>
<td>Candida spp.</td>
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<tr>
<td>VRE</td>
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</tbody>
</table>

Adapted from: Ibrahim et al. CHEST July 2000 vol. 118 no. 1 146-155
### Outcomes of infections with organisms resistant to antimicrobials

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients with infections</th>
<th>Outcomes</th>
</tr>
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</table>
| **Roberts et al.**     | 1391 patients            | - mortality OR=2.16  
                          |             | - attributable mortality rate 6.5%  
                          |             | - ↑ hospital and societal costs, ↑ LOS  |

#### Outcomes of infections with *E. coli* R to 3rd generation cephalosporins

<table>
<thead>
<tr>
<th>Study</th>
<th>Case-control during outbreak ESBL-producing <em>E. coli</em> or <em>K. pneumoniae</em></th>
<th>Outcomes</th>
</tr>
</thead>
</table>
| **Lautenbach et al.**  |                                                                         | - ↑ hospital cost; 2.90 times than control patients; (95% CI, 1.76–4.78; P < .001)  
                          |             | - ↑ LOS: 1.73 x than controls; 95% CI, 1.14–2.65; (P = .01)  |

<table>
<thead>
<tr>
<th>Study</th>
<th><em>E. coli</em> BSI R 3rd gen cephalosporins</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>de Kraker et al.</strong></td>
<td></td>
<td>- ↑ 30 d mortality (AOR 4.6), ↑ hospital mortality (AHR 4.6), ↑ LOS</td>
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Burden of invasive infections with resistant *Salmonella* spp.

- **Global burden of *Salmonella* infections**
  - 80.3 million foodborne cases; 155,000 deaths annually
  - NARMS: (1996-2007) 5.9% (1050) confirmed cases of NTS in U.S. were invasive
    - 22.4% invasive isolates R to ≥1 clinically important antimicrobials (amp/ceftriaxone/cipro/gent/TMP-SMX)
    - 2.5% R to ceftriaxone
    - 2.7% R to nalidixic acid

**Reported notification rates of zoonoses in confirmed human cases in EU, 2009**

**Causative agents in food-borne outbreaks in the EU, 2009**

- 103,400 clinical cases *Salmonella* annually

**Zoonoses**
- Campylobacteriosis
- Salmonellosis
- Yersiniosis
- VTEC
- Toxoplasmosis
- Q fever
- Listeriosis
- Echinococcosis
- Trichinellosis
- Brucellosis
- Tuberculosis caused by M. bovis*
- Rabies

**Notification rate per 100,000 population**

**Escherichia coli, pathogenic**

**Other causative agents**

**Unknown**

**Verified outbreaks**

**Possible outbreaks**

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Limitations in surveillance

- Inadequate testing and underreporting
- Incomparable data—different breakpoints, incomplete patient data
- Passive public health surveillance is not able to quantify size of resistance reservoirs in animals and humans

Cefotaxime resistance in *S. Enteritidis* from human samples, 2007-2009

Countries that use EUCAST ECOFF (>0.5 mg/L) or similar standard (1 mg/L).

Countries that use CLSI breakpoint (≥64 mg/L).

**Evidence of transmission of MDR *Salmonella* spp. from outbreaks from food to humans**

<table>
<thead>
<tr>
<th>Food Item</th>
<th>References</th>
</tr>
</thead>
</table>
| Raw milk/raw milk cheese   | Bezanson et al. *S.* typhimurium in neonatal ward; outbreak and death of cattle, Canada.  
|                            | Cody et al. 2 outbreaks; MDR *S.* typhimurium DT104 in U.S.               |
| Raw, ground beef           | Dechet et al. *S.* typhimurium DT104; 9-state outbreak, U.S.               |
| Pork                       | Mølbak et al. 27 cases of *S.* typhimurium DT104 from pork from Denmark; 2 deaths in immunosuppressed patients with intestinal perforation |
## Patient outcomes in resistant *Salmonella* spp. infections

<table>
<thead>
<tr>
<th>Study</th>
<th>Outcome</th>
</tr>
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<tbody>
<tr>
<td><strong>Varma et al.</strong></td>
<td>▶ bloodstream infections (OR 1.6)</td>
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<tr>
<td></td>
<td>▶ hospitalisation (OR 3.1)</td>
</tr>
<tr>
<td><strong>Helms et al.</strong></td>
<td>▶ death by 2 years RR 10.3 (95% CI, 2.8-37.8; p= 0.02)</td>
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<tr>
<td></td>
<td>▶ invasive disease or death by 90 days RR 3.15 (95% CI, 1.39-7.10; p=0.0058)</td>
</tr>
<tr>
<td><strong>Martin et al.</strong></td>
<td>▶ hospitalization (p= 0.004)</td>
</tr>
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Risk from MRSA ST 398?

Nasal carriage

- **Van Loo et al.** case control, ↑ nasal carriage related to pig (OR 12.2) and cattle (OR 19.7) farming

What is prevalence in food? - many studies globally

- **De Boer et al.** MRSA strains were isolated from 264 (11.9%) of 2217 meat samples
  - 85% of the isolated strains belonged to ST398
- **Waters et al.** meat samples from 5 U.S. cities
  - *S. aureus* most common in turkey (77%)
  - 15 unique MLST sequences among isolates; 79% ST 398 in turkey, 4% chicken, 18% pork

Risk to humans

Infections in humans

- Ekkelenkamp et al. Endocarditis
- Wulf et al. Nosocomial outbreak
- Mammina C et al. Ventilator-associated pneumonia

Persistence in human carriers

Graveland H et al.

- Persistence associated with duration of animals contact; low during low exposure periods
- 58% intermittent carriers; 35% non-carriers; 7% persistent carriers

van Cleef et al.

- 8 of 15 countries in Europe reported MRSA ST 398 in humans
- ST 398 comprised only <2% in most countries in humans
- MRSA ST 398 was lower in BSI vs. “other MRSA” (1.8% vs 10.0% p= 0.004)
Public health significance- LA-MRSA

Joint scientific report of ECDC, EFSA and EMEA on meticillin resistant Staphylococcus aureus (MRSA) in livestock, companion animals and food\(^1\).

“there is no evidence for increased risk of colonisation or infection following contact of consumption of food contaminated with ST 398.”

- Evidence for successful colonisation and reports of infection
- Weak persistence of carriage, especially when low exposure
- Invasive disease rarely reported; less severe disease??
- Rare reports of MRSA from transmission from food
- Future monitoring necessary

EFSA Journal 2009; 7(11): 1376
Strategies to control resistance in humans and animals

➢ **Global strategies:** WHO, CDC

➢ **European Commission**
   - Community strategy against antimicrobial resistance

➢ Transatlantic task force on urgent antimicrobial resistance – **TATFAR**

➢ The European Surveillance of Veterinary Antimicrobial Consumption (**ESVAC**)

➢ **Joint EFSA, ECDC, EMA Opinions/Risk assessments**
   - Joint scientific report of ECDC, EFSA and EMEA on meticillin resistant Staphylococcus aureus (MRSA) in livestock, companion animals and food
   - Joint Opinion on antimicrobial resistance (AMR) focused on zoonotic infections
   - Scientific Opinion on Resistance caused by bacterial strains producing extended-spectrum β-lactamases and/or AmpC β-lactamases in food and food-producing animals (*in progress*)


Perspectives

Antimicrobial resistant bacteria from food growing public health threat

- ↑ morbidity, mortality, costs, inappropriate and delayed therapy
- Success stories of ↓ resistance with ↓ use of antimicrobials in animals

Necessary strategies

- Prudent use antimicrobials in animals and humans
- Strengthen surveillance networks
- Harmonise testing breakpoints in clinical isolates in EU Member States
- Strengthen reporting of patient data
- Harmonise susceptibility criteria in animals and humans
- Control options for misuse of antimicrobials in animal husbandry
Thank you