Methods to demonstrate the link between consumption of antibiotics and change in resistance

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Conflicts of interest

Nothing to declare
Studying the link between antibiotic use and resistance

Outline

• Why it is important

• Why it is difficult

• How it can be done using
  – Individual-level data
  – Aggregate data
Studying the link between antibiotic use and resistance

Why prove the obvious?

• “As in all similar Darwinian selection systems, it is obvious that antibiotics generate resistance. It is also obvious to most that if more antibiotics are used, resistance will be more prevalent.”
• “So why prove the obvious?”
• “The answer is that the obvious correlation is not at all obvious when considered carefully.”
Studying the link between antibiotic use and resistance

Why it is important to understand it

The Economist – May 2016
Tackling, drug-resistant infections globally (O'Neill report) - Mai 2016
2012 policy statement on antimicrobial stewardship (SHEA, IDSA, PIDS)

- “Antimicrobial stewardship refers to coordinated interventions designed to improve and measure the appropriate use of antimicrobials by promoting the selection of the optimal antimicrobial drug regimen, dose, duration of therapy, and route of administration.”
WHO. Always finish your course of antibiotics - even if you feel better

https://www.youtube.com/watch?v=HHoZn27Ftt0
What do we really know?

50 year old patient with urosepsis with *E. coli* bacteremia
• R quinolones, R cotrimoxazole, R amoxicilline
• S co-amoxicilline, cefuroxime, ceftriaxone, piperacillin / tazobactam, carbapenems

• Optimal antimicrobial drug regimen?
• Optimal dose?
• Optimal duration of therapy?
• Optimal route of administration?
Studying the link between antibiotic use and resistance

Why it is difficult
Challenge: defining resistance

Ciprofloxacin/Escherichia coli
Antimicrobial wild-type distributions of microorganisms – reference database
EUCAST

MIC
Epidemiological cut-off: WT ≤ 0.064 mg/L
Clinical breakpoint: S ≤ 0.5 mg/L, R > 2 mg/L

4416 observations (6 materials)
Challenge: multiple germs, multiple antibiotics, multiple resistance mechanisms
ZOO

MRSA

C. diff

KPC

ESBL
Natural habitat

C. diff

Commensal microbiome

MRSA

KPC

ESBL

ESCMID Online Lecture Library © by author

110(K) Symposium

Understanding the Microbiome: The Next Big Breakthrough in Infection Control

Wednesday, 3:00 p.m. – 5:00 p.m. . . . . . . . Meeting Room 501

UAN: 0391-9999-13-158-L04-P

UNIVERSITÉ DE GENÈVE

HUG Hôpitaux Universitaires Genève

L'ESSENTIEL, C'EST VOUS.
Challenge: transmission
Challenge: veterinary antibiotic use

Estimated Annual Antibiotic Use in the United States (in kg/year)
The spread of antimicrobial resistance (AMR)

Introduction of resistant strains
Mutations
Gene transfer

Change in the prevalence of AMR

Adapté selon Bonten, Intensive Care Med 2003
Stepwise exposure to increasing levels of levofloxacin followed by selection of resistant mutants in *S. pyogenes* *in vitro*
Transfer of an *Escherichia coli* ST131 multiresistance cassette has created a *Klebsiella pneumoniae*-specific plasmid associated with a major nosocomial outbreak.

- May 2005
  - nosocomial outbreak of ESBL-producing *Klebsiella pneumoniae*
  - Swedish university hospital

- Single, multiresistant clone
  - CTX-M-15 ESBL enzyme

- Analysis of plasmid
  - 41 kbp resistance region
  - highly similar to the resistance regions of plasmids pEK499 and pC15-1a
  - previously isolated from *Escherichia coli* ST131
The spread of antimicrobial resistance (AMR)

Introduction of resistant strains
- Patient transfer
- Community reservoir
- Health care workers
- Environmental reservoir

Mutations
Gene transfer

Change in the prevalence of AMR

Adapted according to Bonten, Intensive Care Med 2003
Beta-lactamase
The role of travel in the worldwide spread of multiresistant *Enterobacteriaceae*

<table>
<thead>
<tr>
<th>Country (year of study)</th>
<th>Type of study</th>
<th>Infections</th>
<th>Travellers/patients</th>
<th>Country visited</th>
<th>Organisms</th>
<th>β-Lactamases</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>New Zealand (2004–06)</td>
<td>retrospective case study</td>
<td>UTIs</td>
<td>13</td>
<td>India (10/13 patients), China, USA</td>
<td><em>E. coli</em></td>
<td>CTX-M-1</td>
<td>29</td>
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<tr>
<td>Canada (2004–06)</td>
<td>prospective population-based survey</td>
<td>several, including community-onset UTIs</td>
<td>247</td>
<td>India, Middle East, Africa</td>
<td><em>E. coli</em></td>
<td>CTX-M-14, -15 and others</td>
<td>30</td>
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<tr>
<td>Switzerland (2005–07)</td>
<td>case-control</td>
<td>various</td>
<td>58</td>
<td>India, Middle East, Africa</td>
<td><em>E. coli</em></td>
<td>CTX-M-14, -15 and others</td>
<td>32</td>
</tr>
<tr>
<td>Sweden (2007–08)</td>
<td>colonization of travellers</td>
<td>travellers’ diarrhoea</td>
<td>242</td>
<td>various</td>
<td><em>E. coli</em></td>
<td>CTX-M-14 and others groups</td>
<td>33</td>
</tr>
<tr>
<td>LK (2006–08)</td>
<td>colonization of travellers</td>
<td>travellers’ diarrhoea</td>
<td>182</td>
<td>various, including India</td>
<td><em>E. coli</em></td>
<td>CTX-M-14 and others groups</td>
<td>34</td>
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<td>colonization of travellers</td>
<td>travellers’ diarrhoea</td>
<td>113</td>
<td>various, including India</td>
<td><em>E. coli</em></td>
<td>CTX-M-14 and others groups</td>
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<td>Sweden (2007–09)</td>
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<td>asymptomatic</td>
<td>100</td>
<td>various, including India, Japan</td>
<td><em>E. coli</em>, others</td>
<td>CTX-M-14 and others groups</td>
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<td>102</td>
<td>various, including India, Japan</td>
<td><em>E. coli</em>, others</td>
<td>CTX-M-14 and others groups</td>
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<td>France (2005)</td>
<td>case report</td>
<td>upper UTI</td>
<td>1</td>
<td>USA</td>
<td><em>K. pneumonia</em></td>
<td>KPC-2</td>
<td>43</td>
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<td>case report</td>
<td>upper UTI</td>
<td>1</td>
<td>USA</td>
<td><em>E. cloacae</em></td>
<td>KPC-3</td>
<td>44</td>
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<td>case report</td>
<td>characteristic colonization</td>
<td>100</td>
<td>USA</td>
<td><em>K. pneumonia</em></td>
<td>KPC-3</td>
<td>45</td>
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<td>Greece (2007)</td>
<td>case report</td>
<td>rectal colonization</td>
<td>1</td>
<td>USA</td>
<td><em>K. pneumonia</em></td>
<td>KPC-2</td>
<td>46</td>
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<tr>
<td>Colombia (2008)</td>
<td>case report</td>
<td>various</td>
<td>36 (22 infected)</td>
<td>Israel</td>
<td><em>K. pneumonia</em></td>
<td>KPC-8</td>
<td>47</td>
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<td>Norway and Sweden (2007–06)</td>
<td>case report</td>
<td>various</td>
<td>7</td>
<td>Greece, Israel</td>
<td><em>K. pneumonia</em></td>
<td>KPC-2 and -3</td>
<td>48</td>
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<td>The Netherlands (2009)</td>
<td>case report</td>
<td>various</td>
<td>1</td>
<td>Greece</td>
<td><em>K. pneumonia</em></td>
<td>KPC-2</td>
<td>49</td>
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<td>case report</td>
<td>various</td>
<td>4</td>
<td>Greece, Italy</td>
<td><em>K. pneumonia</em></td>
<td>KPC-2 and -3</td>
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<td>UTI</td>
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<td>USA</td>
<td><em>K. pneumonia</em></td>
<td>KPC-2</td>
<td>51</td>
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<td>Scandinavia (2005–06)</td>
<td>case report</td>
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<td>VIM-1</td>
<td>53</td>
<td></td>
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<td>case report</td>
<td>sepsis</td>
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<td>Greece</td>
<td><em>K. pneumonia</em></td>
<td>VIM-1</td>
<td>54</td>
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<td>Israel (2010)</td>
<td>case report</td>
<td>wound infection</td>
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<td>Greece</td>
<td><em>K. pneumonia</em></td>
<td>VIM-1</td>
<td>55</td>
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<tr>
<td>Sweden (2008)</td>
<td>case report</td>
<td>UTI</td>
<td>1</td>
<td>India</td>
<td><em>K. pneumonia</em></td>
<td>NDM-1</td>
<td>57</td>
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<tr>
<td>LK (2008–09)</td>
<td>case report</td>
<td>various, including UTI</td>
<td>37</td>
<td>India</td>
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<td>58</td>
</tr>
<tr>
<td>The Netherlands (2009)</td>
<td>case report</td>
<td>UTI</td>
<td>2</td>
<td>India</td>
<td><em>K. pneumonia</em></td>
<td>NDM-1</td>
<td>59</td>
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<tr>
<td>LK (2010)</td>
<td>case report</td>
<td>UTI</td>
<td>1</td>
<td>India</td>
<td><em>K. pneumonia</em></td>
<td>NDM-1</td>
<td>60</td>
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<tr>
<td>Australia (2010)</td>
<td>case report</td>
<td>pneumonia</td>
<td>1</td>
<td>Bangladesh</td>
<td><em>E. coli</em></td>
<td>NDM-1</td>
<td>61</td>
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<tr>
<td>France (2010)</td>
<td>case report</td>
<td>pneumonia</td>
<td>1</td>
<td>India</td>
<td><em>C. freundii</em></td>
<td>NDM-1</td>
<td>62</td>
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<tr>
<td>Japan (2009)</td>
<td>case report</td>
<td>pneumonia</td>
<td>1</td>
<td>India</td>
<td><em>E. coli</em></td>
<td>NDM-1</td>
<td>63</td>
</tr>
</tbody>
</table>
Patient Referral Patterns and the Spread of Hospital-Acquired Infections through National Health Care Networks

Data from the Dutch national medical register from 2004

Mathematic model

Health-care workers: source, vector, or victim of MRSA?

Werner C Albrich, Stephan Harbarth
169 publications originales (1980-2006) – 49 articles sans données de dénominateur

120 articles avec 127 investigations distinctes

33'318 soignants testés pour MRSA

1545 soignants MRSA+ (4.6 %)

942 soignants
Données cliniques disponibles concernant l’infection clinique

603 soignants
Impossibilité de distinguer entre portage, colonisation et infection

48 soignants (5.1%) symptomatiques,
- 34 infections cutanées à MRSA
- 14 autres infections

894 soignants (94.9 %) asymptomatiques

Community reservoir example ESBL-E

Environmental reservoir
Antibiotic timeline

- **S aureus** (1942)
- MRSA (1961)
- VRE (1987)
- ESBL (1983)
- KPC (1996)
- NDM-1 (2008)

When did the history of antibiotics start?

Sir Alexander Fleming (1881 – 1955)
Stromatolithe
Australie, 850 million d’années
The true antibiotic timeline

- **Homo sapiens**: 0.2 million years
- **Daptomycin**: 30 million years
- **Vancomycin**: 240 million years
- **Streptomycin**: 610 million years
- **Erythromycin**: 880 million years
- **Beta-lactamases**: > 2 billion years

Antibiotic resistance is ancient

“Here we report ... analyses of ... DNA from 30,000-year-old ... sediments and the identification of ... of genes encoding resistance to β-lactam, tetracycline and glycopeptide antibiotics”

“Structure and function studies on the complete vancomycin resistance element VanA confirmed its similarity to modern variants”
Antibiotic resistance is ancient

Completely isolated from the external environment for 3-7 million years

Antibiotic resistance is ubiquitous

The Shared Antibiotic Resistome of Soil Bacteria and Human Pathogens

Kevin J. Forsberg,1* Alejandro Reyes,1* Bin Wang,1,2 Elizabeth M. Selleck,3 Morten O. A. Sommer,4,5† Gautam Dantas1,2†

Soil microbiota represent one of the ancient evolutionary origins of antibiotic resistance and have been proposed as a reservoir of resistance genes available for exchange with clinical pathogens. Using a high-throughput functional metagenomic approach in conjunction with a pipeline for the de novo assembly of short-read sequence data from functional selections (termed PARFuMS), we provide evidence for recent exchange of antibiotic resistance genes between environmental bacteria and clinical pathogens. We describe multidrug-resistant soil bacteria containing resistance cassettes against five classes of antibiotics (β-lactams, aminoglycosides, amphenicols, sulfonamides, and tetracyclines) that have perfect nucleotide identity to genes from diverse human pathogens. This identity encompasses noncoding regions as well as multiple mobilization sequences, offering not only evidence of lateral exchange but also a mechanism by which antibiotic resistance disseminates.
Kluyvera spp.

Paenibacillus spp.

DNA directly from saliva and fecal samples from two unrelated healthy humans who had not been treated with antibiotics for at least 1 year.
MRSA is not the consequence of an accumulation of mutations.
Eradication of susceptible staphylococci increases the risk of acquiring MRSA (exogenously through transmission)
Antibiotics directly select for pre-existing MRSA and increase the likelihood of transmission
The spread of antimicrobial resistance (AMR)

Change in the prevalence of AMR

- Introduction of resistant strains
  - Patient transfer
  - Community reservoir
  - Health care workers
  - Environmental reservoir

- Dissemination of resistant strains
  - Failure of infection control

Adapté selon Bonten, Intensive Care Med 2003
Failure of infection control measures

• Outbreak de *K. pneumoniae* KPC
  – U.S. National Institutes of Health Clinical Center
• “... known to be colonized with carbapenem-resistant *K. pneumoniae* and was immediately placed in enhanced contact isolation in a private room in which staff and visitors are required to don gloves and gowns for entry”
• 18 patients (11 décès)
• Au moins trois épisodes différentes de transmission du patient index
  – Whole-genome sequencing + données épidémiologiques
The spread of antimicrobial resistance (AMR)

Introduction

- Introduction of resistant strains
  - Mutations
  - Gene transfer
- Patient transfer
- Community reservoir
- Health care workers
- Environmental reservoir

Dissemination of resistant strains
- Failure of infection control

Selection of resistant strains
- Traitement antibiotique

Change in the prevalence of AMR

Adapté selon Bonten, Intensive Care Med 2003
Studying the link between antibiotic use and resistance

How it can be done

Antimicrobial agent exposure and the emergence and spread of resistant microorganisms: issues associated with study design

C. Angebault • A. Andremont
Infectious disease epidemiology:
a special situation

John Snow (15 March 1813 – 16 June 1858)
Non-independence of outcomes

“...the traditional analytical approach in epidemiology ... assumes independence of outcomes. The assumption of independence means that the causal link between exposure and disease is made at the individual level. This model hinges on the conjecture that populations are simple collections of individuals, and the nature or arrangement of interactions between individuals does not alter patterns of risk”
Analyses de données individuelles

Effet
Randomized controlled trials (individual level)
Effect of macrolide treatment in the pharyngeal carriage of macrolide resistant streptococci

- Double-blind RCT
- Heathy volunteers
  - azithromycin 500 mg 1x/j 3j (n=74)
  - clarithromycin 500 mg 2x/j 7j (n=74)
  - placebo 2 groups (n=76)
- Pharyngeal swabs
  - d0, 48h after treatment, d8, d14, d28, d42, d180

Effect of macrolide treatment in the pharyngeal carriage of macrolide resistant streptococci

Selection of 2 different types of resistance mechanisms
- **azithromycin mef**: efflux pumps: low-level resistance
- **clarithromycineerm(B)**: methylase: high-level resistance

What is the impact of dosing on emergence of resistance?

- 48 healthy volunteers
- Randomized to 6 groups with different ciprofloxacin dosing (14 days)
  
<table>
<thead>
<tr>
<th>Dosage</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>250 mg</td>
<td>q12h</td>
</tr>
<tr>
<td>500 mg</td>
<td>q24h</td>
</tr>
<tr>
<td>500 mg</td>
<td>q12h</td>
</tr>
<tr>
<td>750 mg</td>
<td>q12h</td>
</tr>
<tr>
<td>750 mg</td>
<td>q24h</td>
</tr>
<tr>
<td>1000 mg</td>
<td>q24h</td>
</tr>
</tbody>
</table>
  
- Fecal and pharyngeal microbiology samples
  - Baseline, days 7, 14, and 42

- Quinolone susceptibility in dominant & subdominant flora
  - Viridans group streptococci (pharyngeal flora)
  - *Escherichia coli* (fecal flora)

- Serum, saliva and stool samples for ciprofloxacin concentrations

What is the impact of dosing on emergence of resistance?

- No significant difference in antibiotic exposure between subjects in whom resistance was selected and those in whom it was not
- Probability of emergence of resistance comparable regardless of ciprofloxacin regimen

Prevalence of resistance not different between days 7 and 14
Randomized controlled trials

• Advantages
  – Internal validity!
  – Control of measured / unmeasured and known / unknown confounders

• Disadvantages
  – Feasibility?
  – Ethics: is it ethical to expose healthy volunteers to antibiotics?
Case-control studies

Cases
- Exposed
- Unexposed

Controls
- Exposed
- Unexposed
Nosocomial Transmission of New Delhi Metallo-β-Lactamase-1-Producing *Klebsiella pneumoniae* in Toronto, Canada

At least one negative rectal swap for NDM-1 *K. pneumoniae*
And sufficient follow-up

<table>
<thead>
<tr>
<th>Exposed</th>
<th>Unexposed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Room contacts of patients with NDM-1 <em>K. pneumoniae</em> who acquired NDM-1</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Exposed</th>
<th>Unexposed</th>
</tr>
</thead>
<tbody>
<tr>
<td>38 contacts without NDM-1 <em>K. pneumoniae</em> acquisition</td>
<td></td>
</tr>
</tbody>
</table>

Contact: shared room, ward or subsequent room occupant

**E.g. exposure**
- Any antibiotic
- Penicillin
- Cephalosporin
- First generation
- Second generation
- Third generation
- b-lactam/b-lactamase inhibitor
- Carbapenem
- Fluoroquinolone
- Aminoglycoside
- Trimethoprim-sulfamethoxazole
- Azithromycin
- Vancomycin

**Nosocomial Transmission of New Delhi Metallo-β-Lactamase-1-Producing Klebsiella pneumoniae in Toronto, Canada**

A retrospective case-cohort analysis of risk factors for acquisition in contacts of NDM1-Kp-positive patients

<table>
<thead>
<tr>
<th>ANALYSE UNIVARIE</th>
<th>NDM-1 pos (n=7)</th>
<th>NDM-1 neg (n=38)</th>
<th>OR</th>
<th>95%CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any antibiotic</td>
<td>7</td>
<td>31</td>
<td>∞</td>
<td>0.34–∞</td>
</tr>
<tr>
<td>Penicillin</td>
<td>6</td>
<td>10</td>
<td>16.8</td>
<td>1.61–799.3</td>
</tr>
<tr>
<td>1st gen Cephalosporin</td>
<td>3</td>
<td>11</td>
<td>2.1</td>
<td>0.26–14.7</td>
</tr>
<tr>
<td>2nd gen Cephalosporin</td>
<td>0</td>
<td>1</td>
<td>∞</td>
<td>0.01–∞</td>
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<td>4</td>
<td>19</td>
<td>1.33</td>
<td>0.19–10.3</td>
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<td>b-lactam/b-lactamase inhibitor</td>
<td>5</td>
<td>17</td>
<td>3.09</td>
<td>0.43–35.4</td>
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<td>Carbapenem</td>
<td>3</td>
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<td>8.75</td>
<td>1.30–58.8</td>
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<td>Fluoroquinolone</td>
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<td>10</td>
<td>16.8</td>
<td>1.79–157.3</td>
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<td>Aminoglycoside</td>
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<td>Trimethoprim-sulfamethoxazole</td>
<td>4</td>
<td>4</td>
<td>11.3</td>
<td>1.84–70.0</td>
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<tr>
<td>Azithromycin</td>
<td>4</td>
<td>2</td>
<td>24</td>
<td>3.04–189.4</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>4</td>
<td>7</td>
<td>5.9</td>
<td>1.07–32.5</td>
</tr>
</tbody>
</table>

Receipt of antibiotics within 3 months before a positive culture, the first negative carbapenem-resistant Enterobacteriaceae (CRE) screen for contacts, or the earliest exposure date for contacts discharged before being screened for CRE.
Problems with case-control studies

• **Outcome of interest**
  – Colonisation (surveillance cultures)
  – Infection (clinical cultures)

• **Polymicrobial resistance**
  – co-selection

• **Définition d’exposition aux antibiotiques (et définition de résistance)**

• **Selection fo control group**
  – Colonisation / infection avec germe susceptible
  – Absence de colonisation / infection

• **How to deal with different methods of « acquisition »**
  – Mutation de novo
  – Transmission (pression de colonisation!)
Problems with case-control studies

Infected (easy to detect)

COLONIZED
(difficult to detect)
Problem: definition of antibiotic exposure

Souvent: oui / non, mais....

- Ciprofloxacine 5d 2d
- Ciprofloxacine 5d
- Ciprofloxacine 5d 500mg 2x/j
- Ciprofloxacine 5d
- Ciprofloxacine 5d
- Co-Amoxicilline 5d
- Ciprofloxacine 5d 250mg 2x/j
- Ciprofloxacine 10d
- Ciprofloxacine 5d
- Ciprofloxacine 5d
- Ciprofloxacine 5d 2 months
- Ciprofloxacine 5d
- Ciprofloxacine 5d 2d
- Ciprofloxacine 5d 3d
Selection of control group

Controls: vancomycin susceptible enterococci

Controls: no VRE

Studies Using Controls With VRE
Boyle et al, 199321
Morris et al 3, 199526
Shay et al 1, 199529
Stosor et al, 199631
Tormieporth et al, 199632
Summary

Studies Using Controls Without VRE
Anglim et al, 199618
Bonten et al, 199619
Boyce et al, 199420
Henning et al, 199625
Dembry et al, 199622
Edmond et al, 199523
Handwerger et al, 199324
Morris et al 1, 199526
Morris et al 2, 199526
Morris et al 4, 199629
Ostrowski et al, 199727
Ostrowski et al 2, 199727
Rubin et al, 199228
Shay et al 2, 199529
Slaughter et al, 199630
Summary

TRANSMISSION CHANGES EVERYTHING!
The Role of “Colonization pressure” in the Spread of Vancomycin-Resistant Enterococci

Medical ICU Chicago (1994-1995), Cox regression analysis
Analysis of aggregated data

Antibiotic exposure → Effect → Resistance
Association between antibiotic use and antimicrobial resistance

Association between antibiotic use and antimicrobial resistance

Fluoroquinolone resistant *E. coli*

Penicillin non susceptible *S. pneumoniae*

Ciprofloxacin sales and ciprofloxacin resistance in *E. coli* in Switzerland

Stopping all antibiotics

CONTROL OF INFECTION DUE TO KLEBSIELLA AEROGENES IN A NEUROSURGICAL UNIT BY WITHDRAWAL OF ALL ANTIBIOTICS

D. J. E. Price J. D. Sleigh
Division of Neurosurgery, Institute of Neurological Sciences, and Department of Bacteriology, Killearn Hospital, Glasgow

Summary Klebsiella aerogenes infection became epidemic in a neurosurgical intensive-care ward. 1 patient in 4 had chest infections, 1 in 8 had urinary infections, and 8 patients died with klebsiella meningitis. Even isolation of infected cases and treatment with massive doses of colistin failed to control the outbreak. Once antibiotics, both prophylactic and therapeutic, were discontinued in the unit, the incidence of klebsiella infection fell dramatically with no obvious ill-effects on the outcome of infections due to this or other organism. In fact, the infection-rate from all organisms was considerably reduced.

Link between ciprofloxacin use and resistance in Israel

Ciprofloxacine use

Ciprofloxacin resistance (E. coli urine)

Interrupted time series analysis

CIPROFLOXACIN
87 DDD/1000PD

Ciprofloxacin susceptibility not reported

AMOXICILLIN / CLAV

MOXIFLOXACINE

Squeezing the balloon
For *E. coli* the slope of susceptibility changed from declining to stable after the intervention (P 0.036).
“There was no statistically significant change to the slope or level of *P. aeruginosa* susceptibility to ciprofloxacin.”
Interventions to control MRSA: high time for time-series analysis?

S. Harbarth\textsuperscript{1} and M. H. Samore\textsuperscript{2,3}

\textsuperscript{1}Infection Control Program, University of Geneva Hospitals and Medical School, CH-1211 Geneva 14, Switzerland; \textsuperscript{2}VA Salt Lake City Health Care System, Salt Lake City, UT 84148, USA; \textsuperscript{3}Division of Epidemiology, University of Utah School of Medicine, Salt Lake City, UT 84108, USA

Time-series methods are useful in quasi-experimental study designs in which rates of antibiotic-resistant infections are ascertained before and after an intervention. However, uncertainties remain regarding the use of time-series analysis as an appropriate research methodology for analysing the effect of infection control interventions and antibiotic policies on the epidemiology of methicillin-resistant \textit{Staphylococcus aureus} (MRSA). In particular, there is still a substantial gap in our understanding of what actually happens to MRSA incidence when a planned intervention is made on use of one or more antibiotic drug classes.
Time-series analysis

Investigate a potential link

- Aggregated use of certain antibiotics
- Hand hygiene campaign
- Bed occupancy

MRSA incidence

Time-series analysis

• Series of observed variables
  – Over time
  – With regular intervals
  – During a long period (≥ 50 observations)

• Characterized by the presence of an auto-correlation
  (⇒ monthly incidence of MRSA)
Modelisation
### Temporal effects of antibiotic use and hand rub consumption on the incidence of MRSA

<table>
<thead>
<tr>
<th>Variable</th>
<th>Lag time (months)</th>
<th>Parameter (SE)</th>
<th>P</th>
<th>Effect MRSA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autocorrelation</td>
<td>1</td>
<td>0.546 (0.168)</td>
<td>0.002</td>
<td>↑</td>
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<tr>
<td>Quinolones</td>
<td>1</td>
<td>0.010 (0.004)</td>
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<td>↑</td>
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<tr>
<td>Macrolides</td>
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<td>0.014 (0.004)</td>
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<tr>
<td>Broad-spectrum Cephalosporins</td>
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<tr>
<td>Piperacillin/tazobactam</td>
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<td>0.004</td>
<td>↑</td>
</tr>
<tr>
<td>Hand hygiene campaign 2005</td>
<td>0</td>
<td>-0.032 (0.005)</td>
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**Multivariate transfer function (R² = 57%)**

Visualisation of the model

Modèle R2 = 55.6 %

## Temporal effects of antibiotic use and hand rub consumption on the incidence of MRSA


Multivariate transfer function ($R^2 = 57\%$)

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<tr>
<td>Broad-spectrum Cephalosporins</td>
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<td>Is this plausible?</td>
<td>0.03</td>
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Problems with aggregated data

- Insufficient number of time points
- Multiple comparisons
- Incorrect statistical analyses
- Ecologic bias
Multiple comparisons

- Increased probability to find spurious correlations
- Need to adapt significance level of p-value

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<table>
<thead>
<tr>
<th>Change (in Vancomycin doses)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>t test</strong></td>
<td>-31 per 1000 pd</td>
</tr>
<tr>
<td><strong>Slope</strong></td>
<td>+ 6 per month</td>
</tr>
</tbody>
</table>

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 Courtesy: Peter Davey, Dundee (UK)
Control of extended-spectrum β-lactamase-producing *Klebsiella pneumoniae* using a computer-assisted management program to restrict third-generation cephalosporin use

Jeong Yeon Kim¹, Jang Wook Sohn¹,², Dae Won Park¹,², Young Kyung Yoon¹, Young Mi Kim³ and Min Ja Kim¹,²,⁸

Ecologic fallacy
Ecologic fallacy

Did Nobel Prize Winners really eat more chocolate?

Will I win eat a Nobel Prize if I eat more chocolate?

Probably not
Linking antibiotic exposure to antibiotic resistance depends on the type of analysis used.

Parallel Analysis of Individual and Aggregated Data on Antibiotic Exposure and Resistance in Gram-Negative Bacilli

Stephan Harbarth,1 Anthony D. Harris,2 Yehuda Carmeli,4 and Matthew H. Samore3

1Harvard Medical School, Boston; 2University of Maryland, Baltimore; 3University Hospital of Utah, Salt Lake City; and 4Sourasky Medical Center, Tel Aviv, Israel
Individual level or aggregated data?

- Availability (+)
- Needs several time points
- Assesses patient exposure
- Does not take into account the effect on other patients

- Availability ++
- Continuous surveillance
- Takes into account colonization pressure
Multi-level approach

Individual effect?

Group-level effect?
MRSA prevalence ↔ FQ use

Number of MRSA isolates per 100 pt-days

- Weak consumer HU
- High consumer HU

Non-exposed patients
Exposed patients
MRSA prevalence ↔ Penicillin use

Distribution of patient-days with MRSA isolation among total patient-days, comparison of individual and collective exposure to antibiotics

Muller A et al. JAC 2006; 58: 878-81
Multivariate analysis

<table>
<thead>
<tr>
<th>Antibiotique</th>
<th>Individual OR($p$)</th>
<th>Group level OR($p$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penicillins</td>
<td>0.89 (0.79)</td>
<td>2.52 (0.03)</td>
</tr>
<tr>
<td>Fluoroquinolones</td>
<td>2.63 (0.01)</td>
<td>0.85 (0.64)</td>
</tr>
</tbody>
</table>

Model adjusted for age, year, colonization pressure, type of service

Courtesy: X. Bertrand  Muller A et al. JAC 2006; 58: 878-81
Mathematical modelling

yearly proportion of antibiotic resistance modelling publications
Modeling antibiotic resistance in hospitals: the impact of minimizing treatment duration.

\[
\begin{align*}
\frac{dP_U(t)}{dt} &= (v_N P^N(t) + v_R P^R(t)) - v_V \beta_V P_I(H_N(t) + H_{NR}(t) + H_R(t)) P^U(t), \\
\left(\frac{\partial}{\partial t} + \frac{\partial}{\partial a}\right)p^N(t,a) &= -(v_N + v_V \beta_V P_I(H_R(t) + H_{NR}(t))p^N(t,a), \\
p^N(t,0) &= v_V \beta_V P_I H_N(t) P^U(t), \\
\left(\frac{\partial}{\partial t} + \frac{\partial}{\partial a}\right)p^{RS}(t,a) &= -v_R P^{RS}(t,a), \\
p^{RS}(t,0) &= v_V \beta_V P_I H_R(t) + H_{NR}(t) P^N(t), \\
\left(\frac{\partial}{\partial t} + \frac{\partial}{\partial a}\right)p^{RR}(t,a) &= -v_R P^{RR}(t,a), \\
p^{RR}(t,0) &= v_V \beta_V P_I H_R(t) P^U(t), \\
\left(\frac{\partial}{\partial t} + \frac{\partial}{\partial a}\right)p^{NR}(t,a) &= -v_R P^{NR}(t,a), \\
p^{NR}(t,0) &= v_V \beta_V P_I H_{NR}(t) P^U(t),
\end{align*}
\]

individual-based model (IBM)

Un début de thérapie précoce et une minimisation de la durée atténuent des épidémies de résistance dans des hôpitaux.

Une durée plus courte et une interruption précoce de la thérapie antibiotique représentent un avantage pour les souches résistantes.
Agent-based models

• From the individual to the population effect

Separation

Cohesion

Alignment

http://www.red3d.com/cwr/boids/
Impact of Antibiotic Exposure Patterns on Selection of Community-Associated Methicillin-Resistant *Staphylococcus aureus* in Hospital Settings

- Agent-based model of a hypothetical 20-bed hospital ward
- Patients: spatial location, LOS, colonization status, and exposure to abx
- HCWs: daily schedule, colonization status

<table>
<thead>
<tr>
<th>ATC4 Code</th>
<th>Antibiotic class</th>
<th>Sensitive</th>
<th>Resistant</th>
<th>Intermediate</th>
<th>Resistance</th>
</tr>
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<tbody>
<tr>
<td>C00AA</td>
<td>Tetracyclines</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>A</td>
</tr>
<tr>
<td>C01CA</td>
<td>Ampicillins</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
</tr>
<tr>
<td>C01CA</td>
<td>Ampicillin with extended spectrum</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>A</td>
</tr>
<tr>
<td>C01CE</td>
<td>Beta-lactamase-sensitive penicillins</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>A</td>
</tr>
<tr>
<td>C01CF</td>
<td>Beta-lactamase-resistant penicillins</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>B</td>
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<tr>
<td>C01CR</td>
<td>Combination of penicillins, incl. beta-lactamase inhibitors</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>B</td>
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<tr>
<td>C01CE</td>
<td>First-generation cephalosporins</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>B</td>
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<tr>
<td>C01CD</td>
<td>Second-generation cephalosporins</td>
<td>R</td>
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<tr>
<td>C01DD</td>
<td>Third-generation cephalosporins</td>
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<tr>
<td>C01DE</td>
<td>Fourth-generation cephalosporins</td>
<td>R</td>
<td>R</td>
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<tr>
<td>C01DF</td>
<td>Monobactams</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>B</td>
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<tr>
<td>C01DH</td>
<td>Carbapenems</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>B</td>
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<tr>
<td>C01EE</td>
<td>Combination of sulphonamides and trimethoprim, incl. derivatives</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>OD</td>
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<tr>
<td>C01FA</td>
<td>Macrolides</td>
<td>S</td>
<td>R</td>
<td>R</td>
<td>B</td>
</tr>
<tr>
<td>C01FF</td>
<td>Lincosamides</td>
<td>S</td>
<td>R</td>
<td>R</td>
<td>B</td>
</tr>
<tr>
<td>C01FC</td>
<td>Streptogramins</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>D</td>
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<td>C01FA</td>
<td>Streptogramins</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>D</td>
</tr>
<tr>
<td>C01EE</td>
<td>Other aminoglycosides</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>B</td>
</tr>
<tr>
<td>C01MA</td>
<td>Fluoroquinolones</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>B</td>
</tr>
<tr>
<td>C01MB</td>
<td>Other quinolones</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>B</td>
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<tr>
<td>C01MA</td>
<td>Glycopeptide antibiotics</td>
<td>S</td>
<td>S</td>
<td>B</td>
<td>D</td>
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<tr>
<td>C01MD</td>
<td>Lincosamid derivatives</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>A</td>
</tr>
<tr>
<td>C01XX</td>
<td>Other antibiotics</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>B</td>
</tr>
</tbody>
</table>

S = susceptible, R = resistant
Problems with simulations

• Output depends a lot on the parameters used in the model
  – Eg the probability of transmission of MRSA from patient A to B if a certain antibiotic is used
• These parameters are often based on assumptions
• => Your (biased) assumptions will influence the outcome of the model
• But: mathematical models help to better understand what we do not know
Conclusions

• The link between antimicrobial use and resistance is complicated
  – Transmission
  – Many different bacteria, resistance mechanisms, antibiotics...
  – A lot fo the basic science is unknown

• There are many different analytic methods
  – None is perfect
  – A lot depends on data availability
  – Mathematical models can be useful but need to be interpreted with caution
Thank you!
RESERVE
Evolution de la résistance aux glycopeptides de *E. faecium* chez la volaille

Evolution de la résistance aux sulfonamides en Angleterre