Modelling the impact of antibiotic use on antibiotic-resistant Escherichia coli using population-based data from a large hospital and its surrounding community

(Geneva, CH; Alicante, ES)

Efficacy and efficiency of a restrictive antibiotic policy on MRSA in the intensive care unit

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Challenge of time series models

- Reinforce the evidence
- Real-world questions
- Real-world data
- Methodological
Transfer function model

Outcomes of interest:
Incidence of non-duplicate clinical isolates

MRSA

E. coli resistant to
- ciprofloxacin
- cefepime (ESBL)

Explanatory variables:
antibiotic usage - interventions

antibiotic usage in ICU
Restriction antibiotic policy (0,1)

antibiotic usage
- surrounding community
- HUG (2,000 beds)

Efficacy and efficiency of a restrictive antibiotic policy

1) November 2003: withdrawing ampicillin/sulbactam prophylaxis
2) Mai 2004: targeting vancomycin therapy whenever indicated

on MRSA
in the intensive care unit

Study period: January 2002 to December 2007
MRSA model identification

\[ \text{MRSA} = 2.55 + 0.32 \text{MRSA}_{(t-2)} + \epsilon_t \]

Restrictive antibiotic policy efficacy

ampi-sulbactam, \( R^2 = 66\% \)

\[ \text{ampi-sulbactam} = 301 - 167 y - 0.267 \text{AR}(1) - 0.379 \text{MA}(7) + \epsilon_t \]
\[ y \begin{cases} 0 < \text{November 2003} \\ \geq \text{November 2003} \end{cases} \]

Vancomycin, \( R^2 = 39\% \)

\[ \text{vancomycin} = 34.9 - 23.5 y + 0.255 \text{AR}(3) + \epsilon_t \]
\[ y \begin{cases} 0 < \text{Mai 2004} \\ \geq \text{Mai 2004} \end{cases} \]
Transfer function on MRSA incidence: efficiency

<table>
<thead>
<tr>
<th>Variable</th>
<th>Lag</th>
<th>Coefficient</th>
<th>Std. Error</th>
<th>t-Statistic</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>intercept</td>
<td>month</td>
<td>1.628</td>
<td>0.673</td>
<td>2.420</td>
<td>0.019</td>
</tr>
<tr>
<td>ceftriaxone</td>
<td>2</td>
<td>0.021</td>
<td>0.008</td>
<td>2.531</td>
<td>0.014</td>
</tr>
<tr>
<td>ceftriaxone</td>
<td>3</td>
<td>0.023</td>
<td>0.008</td>
<td>2.990</td>
<td>0.004</td>
</tr>
<tr>
<td>levofloxacin</td>
<td>0</td>
<td>0.012</td>
<td>0.004</td>
<td>2.785</td>
<td>0.007</td>
</tr>
</tbody>
</table>

Useful tool for policy maker

• Modelling antibiotic usage and resistance is a useful tool for antimicrobial stewardship
  – to drive a more appropriate empirical and targeted antimicrobial therapy
  – to control and prevent the misuse of antimicrobials
  – to increase the level of evidence

• Time series analysis is a useful tool even at a ICU level
Questions?

Modeling the impact of antibiotic use on antibiotic-resistant *Escherichia coli* using population-based data from a large hospital and its surrounding community

Antibiotic prescribing quality indicator: outpatient fluoroquinolone use in 2003

![Box plot](image)

\[
\frac{\text{DDD (J01MA)} \times 100}{\text{DDD (J01)}}
\]

outside de Box plot: 18% at Geneva surrounding community

excess usage of fluoroquinolones can be associated with the development of resistance
Settings & Methods

- Incidence of non-duplicate clinical isolates of *E. coli* resistant to
  - ciprofloxacin; of community origin (= CA -Cipro-R)
  - ciprofloxacin; of hospital origin (= HA -Cipro-R)
  - cefepime (= surrogate of ESBL)
- Antibiotic usage:
  - Geneva surrounding community: 450’000 inhabitants
  - HUG: 2’000 beds
- Defined Daily Dose (DDD) normalised
  - per 100 patients-days
  - per 1’000 inhabitants
- Exclude Paediatric, Psychiatry, Rehabilitation wards
- Study period: Jan. 2000 to Dec. 2007

Non-duplicate, resistant *E. coli* isolates

![Graph showing incidence of non-duplicate, resistant *E. coli* isolates over time](image)
Total antibiotic usage surrounding community

Average antimicrobial use: 14.22 (8.6-19.77) DDD/1'000 inhabitants

Outpatient FQ usage
Antibiotic usage
Geneva Univ. Hospitals

Average antimicrobial use: 54.99 (45.63-62.17) DDD/100 patients-days

ESBL transformation

Null Hypothesis: R_ESBL has a unit root
Exogenous: None
Lag Length: 4 (Automatic - based on SIC, maxlag=11)

Augmented Dickey-Fuller test statistic  0.373541  0.7894
Test critical values: 1% level  -2.599934
5% level  -1.945745
10% level  -1.613633

ESBL

Y_t - Y_{t-1}^{*} D_ESBL

Null Hypothesis: D(R_ESBL) has a unit root
Exogenous: None
Lag Length: 3 (Automatic - based on SIC, maxlag=11)

Augmented Dickey-Fuller test statistic -7.865141  0.0000
Test critical values: 1% level  -2.599934
5% level  -1.945745
10% level  -1.613633

t*: 0.37 > -1.94 non stationary

-7.89 < -1.94 stationary
## Transfer function model for *E. coli* resistant to cefepime (ESBL)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Lag (months)</th>
<th>Parameter (SE)</th>
<th>t-Statistic</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>d - ceftriaxone HUG</td>
<td>0</td>
<td>0.0041 (0.0017)</td>
<td>2.4047</td>
<td>0.0195</td>
</tr>
<tr>
<td>d - ciprofloxacin HUG</td>
<td>1, 5</td>
<td>0.0043 (0.0013), 0.0045 (0.0014)</td>
<td>3.2126, 3.2045</td>
<td>0.0022, 0.0022</td>
</tr>
<tr>
<td>d - cefepime HUG</td>
<td>3</td>
<td>0.0034 (0.0016)</td>
<td>2.1502</td>
<td>0.0358</td>
</tr>
<tr>
<td>d - piperacilline/tazobactam HUG</td>
<td>3</td>
<td>0.0099 (0.0042)</td>
<td>2.3073</td>
<td>0.0247</td>
</tr>
<tr>
<td>d - ciprofloxacin GE</td>
<td>4</td>
<td>0.0247 (0.0080)</td>
<td>3.0809</td>
<td>0.0032</td>
</tr>
<tr>
<td>Autoregressive term</td>
<td>1</td>
<td>-0.5877 (0.01084)</td>
<td>-5.4236</td>
<td>0.0000</td>
</tr>
</tbody>
</table>

Transfer function model on ESBL incidence explains 51% of ESBL variation over time.

## Transfer function model on *E. coli* resistant to ciprofloxacin

### ciprofloxacin, community origin (Cipro-R-CA, \( R^2 = 0.52 \))

<table>
<thead>
<tr>
<th>Variable</th>
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<th>Parameter (SE)</th>
<th>t-Statistic</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constant</td>
<td>-3.54 (0.24)</td>
<td>-14.76</td>
<td>0.0000</td>
<td></td>
</tr>
<tr>
<td>log ciprofloxacin GE</td>
<td>0</td>
<td>1.31 (0.49)</td>
<td>2.68</td>
<td>0.0089</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>1.01 (0.49)</td>
<td>2.08</td>
<td>0.0406</td>
</tr>
<tr>
<td>log moxifloxacin GE</td>
<td>4</td>
<td>0.44 (0.16)</td>
<td>2.72</td>
<td>0.0081</td>
</tr>
<tr>
<td>Autoregressive term</td>
<td>1</td>
<td>0.31 (0.11)</td>
<td>2.89</td>
<td>0.0050</td>
</tr>
<tr>
<td>Moving average term</td>
<td>8</td>
<td>0.36 (0.11)</td>
<td>3.24</td>
<td>0.0017</td>
</tr>
</tbody>
</table>

### ciprofloxacin, hospital origin (Cipro-R-HA, \( R^2=0.18 \))

<table>
<thead>
<tr>
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<th>Parameter (SE)</th>
<th>t-Statistic</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constant</td>
<td>-3.34 (0.01)</td>
<td>-42.86</td>
<td>0.0000</td>
<td></td>
</tr>
<tr>
<td>log ciprofloxacin GE</td>
<td>0</td>
<td>1.31 (0.49)</td>
<td>2.68</td>
<td>0.0089</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>1.01 (0.49)</td>
<td>2.08</td>
<td>0.0406</td>
</tr>
<tr>
<td>log moxifloxacin GE</td>
<td>4</td>
<td>0.44 (0.16)</td>
<td>2.72</td>
<td>0.0081</td>
</tr>
<tr>
<td>Autoregressive term</td>
<td>1</td>
<td>0.24 (0.10)</td>
<td>2.43</td>
<td>0.0170</td>
</tr>
<tr>
<td>Moving average term</td>
<td>8</td>
<td>0.36 (0.11)</td>
<td>3.24</td>
<td>0.0017</td>
</tr>
</tbody>
</table>
Conclusion

- Added value of time series analysis: to better understand the interaction between community and hospital antibiotic prescribing

- Temporal relationship between: outpatient fluoroquinolone use and incidence of
  - CA- Cipro-R- E Coli
  - HA- Cipro-R- E Coli
  - ESBL

- Support efforts to reduce prescriptions of fluoroquinolones

Useful tool for policy maker: hierarchy of evidence

<table>
<thead>
<tr>
<th>Level</th>
<th>Description</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Strong evidence from at least ONE systematic review of well designed RCT</td>
<td>Meta-Analysis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>The Cochrane Collaboration</td>
</tr>
<tr>
<td>II</td>
<td>Evidence from at least one properly designed RCT of appropriate size</td>
<td>Articles published in peer-reviewed journals</td>
</tr>
<tr>
<td>III</td>
<td>Evidence from well designed trials without randomization: cohort study, time-series or matched case control studies</td>
<td>Articles published in peer-reviewed journals</td>
</tr>
<tr>
<td>IV</td>
<td>Evidence from well designed non-experimental studies from more than one centre or research group</td>
<td>Articles published in peer-reviewed journals</td>
</tr>
<tr>
<td>V</td>
<td>Opinions from respected authorities, based on clinical evidence, descriptive studies or reports from committees</td>
<td>Evidence based local procedures and care pathways</td>
</tr>
<tr>
<td>VI</td>
<td>Views of colleagues / peers</td>
<td>Colleagues or members of the multidisciplinary team</td>
</tr>
</tbody>
</table>
“Remember that all models are wrong; the practical question is how wrong do they have to be to not be useful”

G. Box, N. Draper