Temporal effects of antibiotic use and Clostridium difficile infections

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Challenge of time series analysis

- Reinforce the evidence
- Real-world questions
- Real-world data
- Quantify an intervention
How does dynamic modeling fit into conventional health economics?
## Hierarchy of Evidence for Assessing Effectiveness

<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 <strong>ONE</strong> systematic review of well designed RCT</td>
<td>Meta-Analysis 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: <em>cohort study, time-series</em> or <em>matched case control studies</em></td>
<td>Articles published in peer-reviewed journals</td>
</tr>
<tr>
<td>IV</td>
<td>Evidence from well designed <em>non-experimental</em> 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>
Process of modeling

1) Economic Theory
2) Collect « real life data »
3) Time series analysis
4) Quantitative answer
5) New policy
6) Intervention
ARIMA models

\[ Y_t = a_0 + a_1 x_t + \varepsilon_t \]

H5: \( E(\varepsilon_t, \varepsilon_{t'}) = 0 \) errors are not correlated

Data: naturally correlated

AR: autoregressive
I: integrated
MA: moving average
1976: Box & Jenkins

Graph

? stationary
seasonal
effect
trend

Yes

Model identification
(ACF-PACF)
ARIMA

Validation:
(εt=white noise)

No

Yes

Log
y(t)-y(t-1)
y(t)-y(t-12)

forecasting

Box, G. E. P. and Jenkins, G. M. *Time Series Analysis, Forecasting and Control*, 1976
Design of the modeling

C Diff series

Antibiotic use

intervention (0,1)

ARIMA model

Transfer function model
Study design

- Study period: April 2004 to June 2008

- Outcomes of interest:
  - Ninewells (HA_CDIFF)
  - Ninewells (TOT_CDIFF)
  - Medicine & Cardiovasc (HA_CDIFF)
  - Medicine & Cardiovasc (TOT_CDIFF)

- Explanatory variables:
  - Antibiotic usage in DDD

\( C \text{ difficile infections} \)
Outcomes of interest

Ninewells (HA_CDIFF)
Ninewells (TOT_CDIFF)

<table>
<thead>
<tr>
<th>Year</th>
<th>HA_CDIFF</th>
<th>TOT_CDIFF</th>
</tr>
</thead>
<tbody>
<tr>
<td>2004</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2005</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2006</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2007</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- no trend Ninewells (HA_CDIFF)  p=0.0932
- trend Ninewells (TOT_CDIFF)  p=0.0309
- MA order 2

Medicine & Cardiovasc (HA_CDIFF)
Medicine & Cardiovasc (TOT_CDIFF)

<table>
<thead>
<tr>
<th>Year</th>
<th>CDIFF_HA</th>
<th>CDIFF_TOT</th>
</tr>
</thead>
<tbody>
<tr>
<td>2004</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2005</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2006</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2007</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- no trend Medicine & Cardiovasc (HA_CDIFF)  p=0.9054
- no trend Medicine & Cardiovasc (TOT_CDIFF)  p=0.5336
- MA order 2
Transfer function model

Ninewells (HA_CDIFF), $R^2=61\%$

Model 3: temporal relation between antibiotic use and HA_cdiff in the setting 2

Ninewells (tot_CDIFF), $R^2=48\%$

Model 4: temporal relation between antimicrobial use and tot_Cdiff in the setting 2

Medicine & Cardiovasc (HA_CDIFF), $R^2=53\%$

Model 1: temporal relation between antibiotic use and HA_cdiff in the setting 1

Medicine & Cardiovasc (tot_CDIFF), $R^2=56\%$

Model 2: temporal relation between antibiotic use and tot_Cdiff in the setting 1
## Quantitative answers for *C. difficile* infections

<table>
<thead>
<tr>
<th>Lag time</th>
<th>Ninewells HA_CDIF</th>
<th>Ninewells TOT_CDIF</th>
<th>Medicine &amp; Cardiovascular HA_CDIF</th>
<th>Medicine &amp; Cardiovascular TOT_CDIF</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>M&amp;C</td>
<td>M&amp;C</td>
</tr>
<tr>
<td>Tazocin</td>
<td>4</td>
<td>0.091559*</td>
<td>0.092976*</td>
<td>0.054005**</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Co-amoxiclav</td>
<td>0</td>
<td>0.002732*</td>
<td></td>
<td>0.005096**</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>0</td>
<td></td>
<td>0.007828</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>0.003976*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluoroquinolones</td>
<td>4</td>
<td></td>
<td>0.011412*</td>
<td>0.007004**</td>
</tr>
<tr>
<td>Cefuroxime</td>
<td>2</td>
<td>0.005655**</td>
<td>0.003399**</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>0.005535*</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>0.006130*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>2</td>
<td></td>
<td></td>
<td>0.014068**</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td></td>
<td></td>
<td>0.023926*</td>
</tr>
<tr>
<td>MA order 2</td>
<td></td>
<td>0.963635*</td>
<td>0.953730*</td>
<td>1.2379*</td>
</tr>
<tr>
<td>Overall fitting</td>
<td></td>
<td>61%</td>
<td>49%</td>
<td>53%</td>
</tr>
</tbody>
</table>

*statistical significant at p-value < 1%  
**statistical significant at p-value < 5%
Conclusion of the study

- strong relationship between variation in antibiotic use and variation in *C difficile* infections

- strong support for antibiotic policies that minimise the use of broad spectrum penicillins (*co-amoxiclav* and *Tazocin*), cephalosporins and fluoroquinolones
Strengths and limitations of time series analysis

- Appropriate
- Robust
- Time & effort
- Careful evaluation
- Learn methodology & Software
- 4 years retrospective data
“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