Burden of Infectious Diseases in Europe and implications for estimating the burden of AMR

Mirjam Kretzschmar\textsuperscript{1,2}, Alessandro Cassini\textsuperscript{3}, Edoardo Colzani\textsuperscript{3}

\textsuperscript{1} University Medical Center Utrecht, The Netherlands
\textsuperscript{2} National Institute of Public Health and the Environment (RIVM), The Netherlands
\textsuperscript{3} European Center for Disease Control (ECDC)
Acknowledgements

- Alessandro Cassini (ECDC)
- Eduardo Colzani (ECDC)
- Diamantis Plachouras (ECDC)
- RKI team working on HAI

- BCoDE Consortium (RIVM, UMCU, ECDC, Bielefeld University, others)
- Marie-Josee Mangen, Dietrich Plass, Alies van Lier, Scott McDonald, Arie Havelaar (methodology)
- Juanita Haagsma (disability weights)
- Daniel Lewandowski (programming)
Estimating disease burden

- Disability-adjusted life years
- BCoDE project methodology
- BCoDE toolkit
- Estimates of DALYs for 32 infectious diseases
- Europe wide burden estimates hospital acquired infections

- Future steps in estimating burden of AMR
Summary measure of population health

Disability Adjusted Life Years (DALYs) to express the burden of disease

\[
\text{DALY} = \text{YLL} + \text{YLD}
\]

- **YLL** (Years of life lost due to mortality)
  \[
  \sum (d \times e)
  \]
  - \(d\) – sum of all fatal cases
  - \(e\) – remaining life expectancy at age of death

- **YLD** (Years of healthy life lost due to disability)
  \[
  \sum (n \times t \times w)
  \]
  - \(n\) – number of cases
  - \(t\) – duration of illness
  - \(w\) – disability weight

Introduced by Murray & Lopez 1997: Global Burden of Disease Study
Disability Adjusted Life Year

\[ \text{DALY} = \text{years of life lost (YLL)} + \text{years lived with disability (YLD)} \]

\[ = 20 \text{ years} + 16 \text{ years} = 36 \text{ years} \]
Burden of Communicable Diseases in Europe (BCoDE)

Collaboration ECDC with European Consortium led by RIVM

New Methodology for Estimating the Burden of Infectious Diseases in Europe

Mirjam Kretzschmar¹,²*, Marie-Josée J. Mangen², Paulo Pinheiro³, Beate Jahn⁴,⁵, Eric M. Fèvre⁶, Silvia Longhi⁷, Taavi Lai⁸,⁹, Arie H. Havelaar¹⁰,¹¹, Claudia Stein¹¹, Alessandro Cassini¹², Piotr Kramarz¹², for the BCoDE consortium

Incidence- and pathogen-based DALY approach

• Links sequelae to their infectious causes (pathogens) by means of outcome trees
• Based on incidence of infection per pathogen
• Burden attributed to time at infection
Outcome tree

Disease model including infection, acute disease and all sequelae

For a specific pathogen

- Define primary health outcome(s), possibly distinguish health states
- Define associated long term sequelae
- Quantify transition probabilities and durations including possible recovery and death
Incidence estimates

- Estimate population incidence of infection
- Based on notification data (*or other surveillance, hospitalization or mortality data*)
- Use multiplication factors to account for underreporting and underascertainment

Incidence of sequelae attributed to one infection is then computed using the outcome tree.
Underreporting

Disability weights were assessed in 4 European countries (project funded by ECDC and Institute for Health Metrics and Evaluation (IHME))
The BCoDE toolkit

ECDC BCoDE toolkit [software application]. Version 1.1
Stockholm: European Centre for Disease Prevention and Control; 2015.
Stepwise approach for burden calculation
Data input

- Incident cases by sex and age from surveillance system
- Multiplication factor to correct for underreporting
- Inclusion of asymptomatic cases if they contribute to burden
- Definition of time discount factor

Result output

- Estimated „true“ incidence of acute infections
- DALYs
  - Pathogen, age-group and sex specific
  - Per year, per 100,000 and per infected case
  - By YLL and YLD
  - By acute illness and sequelae
- Ranking of diseases according to DALYs
- Uncertainty bounds
Burden of Healthcare Associated Infections (HAI)

Implementation of 6 HAIs in toolkit:
- hospital acquired pneumonia (HAP),
- urinary tract infection (HA UTI),
- surgical site (HA SSI),
- *Clostridium difficile* (HA CDI),
- neonatal sepsis,
- primary blood-stream infections (HA primary BSI)

- Pathogen based approach is not feasible
- Syndrome based approach was chosen
- Use of BDoDE toolkit and results of Point Prevalence Survey
- Systematic reviews to define and quantify outcome trees
- Use of McCabe scores to deal with comorbidity

### Point-prevalence survey in acute care hospitals in Europe

**ECDC surveillance report 2011-2012**

Point prevalence survey of ECDC
250,000 pt, 947 hosp, 33 countries Europe
Found point prev of 6%, ranging from 2.3 in Latvia to 10.8 in Portugal.
Most freq encountered LRTI, SSI, UTI, BSI

<table>
<thead>
<tr>
<th>All HAI types</th>
<th>N of patients with HAI</th>
<th>HAI%</th>
<th>N of HAIs</th>
<th>Rel%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumonia</td>
<td>2902</td>
<td>1.3</td>
<td>2907</td>
<td>19.4</td>
</tr>
<tr>
<td>Other lower respiratory tract infections</td>
<td>607</td>
<td>0.3</td>
<td>609</td>
<td>4.1</td>
</tr>
<tr>
<td>Surgical site infections</td>
<td>2933</td>
<td>1.3</td>
<td>2941</td>
<td>19.6</td>
</tr>
<tr>
<td>Urinary tract infections</td>
<td>2848</td>
<td>1.2</td>
<td>2848</td>
<td>19.0</td>
</tr>
<tr>
<td>Bloodstream infections</td>
<td>1576</td>
<td>0.7</td>
<td>1585</td>
<td>10.6</td>
</tr>
<tr>
<td>Catheter-related infections without bloodstream infection</td>
<td>233</td>
<td>0.1</td>
<td>233</td>
<td>1.6</td>
</tr>
<tr>
<td>Cardiovascular system infections</td>
<td>203</td>
<td>0.1</td>
<td>204</td>
<td>1.4</td>
</tr>
<tr>
<td>Gastro-intestinal system infections(^a)</td>
<td>1130</td>
<td>0.5</td>
<td>1134</td>
<td>7.6</td>
</tr>
<tr>
<td>Skin and soft tissue infections</td>
<td>598</td>
<td>0.3</td>
<td>599</td>
<td>4.0</td>
</tr>
<tr>
<td>Bone and joint infections</td>
<td>243</td>
<td>0.1</td>
<td>245</td>
<td>1.6</td>
</tr>
<tr>
<td>Central nervous system infections</td>
<td>97</td>
<td>0.0</td>
<td>97</td>
<td>0.6</td>
</tr>
<tr>
<td>Eye, ear, nose or mouth infection</td>
<td>454</td>
<td>0.2</td>
<td>454</td>
<td>3.0</td>
</tr>
<tr>
<td>Reproductive tract infections</td>
<td>87</td>
<td>0.0</td>
<td>87</td>
<td>0.6</td>
</tr>
<tr>
<td>Systemic infections(^b)</td>
<td>933</td>
<td>0.4</td>
<td>934</td>
<td>6.2</td>
</tr>
<tr>
<td>Other/unknown</td>
<td>123</td>
<td>0.1</td>
<td>123</td>
<td>0.8</td>
</tr>
</tbody>
</table>

\(^a\) including *Clostridium difficile* infections 3.6%.
\(^b\) including clinical sepsis 5.4%.
23% of HAI are present at admission, often associated with previous hospital stay.
Next step: Burden of Antibiotic resistance

Figure 1: Percentage of resistant isolates among isolates from HAIs with known antimicrobial susceptibility testing (AST) results, by species and by country, ECDC PPS 2011–2012

a. Meticillin-resistant *Staphylococcus aureus* (MRSA)

b. Vancomycin-resistant *Enterococcus species* (VRE)

c. Third-generation cephalosporin-non-susceptible *Enterobacteriaceae*

d. Carbapenem-non-susceptible *Enterobacteriaceae*
Estimating burden of AMR

• Extend BCoDE methodology to estimate excess burden due to AMR
• How do we estimate incidence and/or prevalence?
• Attributable mortality?
• Impact on length of stay in hospital, mortality, other outcomes
• AMR correlated with co-morbidities?
• Disability weights available?
Differences in outcome for resistant pathogens?

Table 13  Overview of the findings addressing the question: Does the published scientific literature support that there is a difference in outcome for patients with infections caused by the selected bacteria if they are resistant or sensitive to the relevant specific antibacterial drugs?

<table>
<thead>
<tr>
<th></th>
<th><em>Escherichia coli</em></th>
<th><em>Klebsiella pneumoniae</em></th>
<th><em>Staphylococcus aureus</em></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antibacterial resistance</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3rd generation cephalosporins</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluoroquinolones</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3rd generation cephalosporins</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carbapenems</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MRSA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Outcome parameter</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bacterium-attributable mortality</td>
<td>Yes (n=4)</td>
<td>No (n=1)</td>
<td>Yes (n=4)</td>
</tr>
<tr>
<td>30-day mortality</td>
<td>Yes (n=11)</td>
<td>Yes (n=5)</td>
<td>Yes (n=7)</td>
</tr>
<tr>
<td>Hospital LOS</td>
<td>No (n=3)</td>
<td>No (n=3)</td>
<td>No (n=9)</td>
</tr>
<tr>
<td>Admission to ICU</td>
<td>No (n=1)</td>
<td>Yes (n=1)</td>
<td>Yes (n=3)</td>
</tr>
<tr>
<td>Post-infection LOS</td>
<td>No (n=3)</td>
<td>ND</td>
<td>Yes (n=4)</td>
</tr>
</tbody>
</table>

*ICU, intensive care unit; LOS, length of stay; MRSA, methicillin-resistant Staphylococcus aureus; n, evaluated number of studies; ND, no data.*
Ongoing work

• Project COMBACTE-MAGNET (WP3b)
  Evaluate the impact of HAP attributed to *P. aeruginosa* on DALYs

• ABC Project (Multicenter Study in the Netherlands):
  The attributable burden and costs of infections caused by antibiotic-resistant Gram-negative bacteria in Dutch hospitals

Thank you!