World wide spread of antimicrobials

Herman Goossens
“If you cannot measure it, you cannot improve it”

Lord Kelvin, 1824-1907
First Part: Focus on Europe

- Develop methodology for monitoring antimicrobial use
- Antimicrobial use in Europe
- Conclusions and lessons learned
European Surveillance of Antimicrobial Consumption (ESAC): From a Project to an Infrastructure

- ESAC project was launched in November 2001 (during Belgian EU Presidency)
- ESAC was an international network of surveillance systems, aiming to maintain a continuous, comprehensive and comparable database on antimicrobial consumption for all Member States, candidate countries and EFTA-EEA countries
- Funding organisations: DG SANCO of the EC (2001-2007) and ECDC (2007-2011)
- Moved to ECDC in 2011 to become an infrastructure (ESAC-Net)
Surveillance of antimicrobials

- Which classification?
- Which indicators?
Anatomical Therapeutic Chemical (ATC) Classification

For example, amoxicillin = ATC  J  01  C  A  04

1\textsuperscript{st} level: Anatomical main group: J
= Anti-infectives for systemic use

2\textsuperscript{nd} level: Therapeutic subgroup: J01
= Anti-bacterials for systemic use (antibiotics)

3\textsuperscript{rd} level: Pharmacological subgroup: J01C
= Beta-lactam antibacterials, penicillins

4\textsuperscript{th} level: Chemical subgroup: J01CA
= Penicillins with extended spectrum

5\textsuperscript{th} level: Chemical substance: J01CA04
<table>
<thead>
<tr>
<th></th>
<th>Indicators of Outpatient Antibiotic use</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Defined Daily Doses per defined population</td>
</tr>
<tr>
<td>2</td>
<td>Defined Daily Doses per 100 person years</td>
</tr>
<tr>
<td>3</td>
<td>Defined Daily Doses per physician contacts</td>
</tr>
<tr>
<td>4</td>
<td>Defined Daily Doses per km²</td>
</tr>
<tr>
<td>5</td>
<td>Treatments/courses per defined population</td>
</tr>
<tr>
<td>6</td>
<td>Treatments/courses per physician contacts</td>
</tr>
<tr>
<td>7</td>
<td>Standard units per defined population</td>
</tr>
<tr>
<td>8</td>
<td>Packages per defined population</td>
</tr>
<tr>
<td>9</td>
<td>Packages per physician contacts</td>
</tr>
<tr>
<td>10</td>
<td>Prescriptions per defined population</td>
</tr>
<tr>
<td>11</td>
<td>Prescriptions per 100 person years</td>
</tr>
<tr>
<td>12</td>
<td>Prescriptions per physician contacts</td>
</tr>
<tr>
<td>13</td>
<td>Individuals treated with antibiotics per defined population</td>
</tr>
<tr>
<td>14</td>
<td>Individuals treated with antibiotics per 100 person years</td>
</tr>
<tr>
<td>15</td>
<td>Individuals treated with antibiotics per physician contacts</td>
</tr>
<tr>
<td>16</td>
<td>Kilograms per defined population</td>
</tr>
<tr>
<td>17</td>
<td>Antibiotic cost per defined population</td>
</tr>
<tr>
<td>18</td>
<td>Average Daily Quantities per defined population</td>
</tr>
<tr>
<td>19</td>
<td>Percentage of antibiotics per total drug use</td>
</tr>
<tr>
<td>20</td>
<td>Number of types of antibiotics prescribed in each patient-visit</td>
</tr>
</tbody>
</table>
Defined Daily Dose (DDD)

Definition: the assumed average maintenance dose per day for a drug used for its main indication in adults.

Example: Amoxicillin (DDD = 1000mg)

=> DDD per 1000 inhabitants per day (DID)
Total antibiotic use in 2011 in number of DDD per 1000 Inhabitants per Day in 12 European countries and Kosovo as compared to 29 ESAC-Net countries

Versporten et al, LID, 20 March 2014
Two problems

- DDD is a technical unit of measurement, not necessarily reflecting the prescribed daily dose;
- Increase of beta-lactam dose due to creeping MICs of pneumococci:
  - Several packages per treatment (e.g. France), or
  - Introduction of packages of higher substance (e.g. Belgium)
Changes of DDDs for molecules in ATC/DDD database

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Route of administration</th>
<th>Previous DDD (gm)^a</th>
<th>New DDD (gm)</th>
<th>Year of implementation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amoxicillin</td>
<td>Parenteral</td>
<td>1.00</td>
<td>3.00</td>
<td>2019</td>
</tr>
<tr>
<td>Amoxicillin</td>
<td>Oral</td>
<td>1.00</td>
<td>1.50</td>
<td>2019</td>
</tr>
<tr>
<td>Amoxicillin/Clavulanic Acid</td>
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<td>1.50</td>
<td>2019</td>
</tr>
<tr>
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<td>Parenteral</td>
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<td>6.00</td>
<td>2019</td>
</tr>
<tr>
<td>Cefepime</td>
<td>Parenteral</td>
<td>2.00</td>
<td>4.00</td>
<td>2019</td>
</tr>
<tr>
<td>Cefuroxidine*</td>
<td>Oral</td>
<td>2.10</td>
<td>2.10</td>
<td>2019</td>
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<tr>
<td>Cefteram Pivoxcil</td>
<td>Oral</td>
<td>0.60</td>
<td>0.40</td>
<td>2019</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>Parenteral</td>
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<td>0.80</td>
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<td>Parenteral</td>
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<td>Oral</td>
<td>0.24</td>
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<tr>
<td>Dalbavancin*</td>
<td>Parenteral</td>
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<td>1.50</td>
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<td>Garenoxacin*</td>
<td>Oral</td>
<td>0.40</td>
<td>0.40</td>
<td>2019</td>
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<td>Gemifloxacin*</td>
<td>Oral</td>
<td>0.32</td>
<td>0.32</td>
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<tr>
<td>Lomefloxacin</td>
<td>Oral</td>
<td>0.60</td>
<td>0.40</td>
<td>2019</td>
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<tr>
<td>Meropenem</td>
<td>Parenteral</td>
<td>2.00</td>
<td>3.00</td>
<td>2019</td>
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<td>Midecamycin</td>
<td>Oral</td>
<td>1.00</td>
<td>1.20</td>
<td>2019</td>
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<td>Tebipenem</td>
<td>Oral</td>
<td>0.84</td>
<td>0.56</td>
<td>2019</td>
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<tr>
<td>Tedzolid*</td>
<td>Parenteral</td>
<td>0.20</td>
<td>0.20</td>
<td>_b</td>
</tr>
<tr>
<td>Tedzolid*</td>
<td>Oral</td>
<td>0.20</td>
<td>0.20</td>
<td>_b</td>
</tr>
<tr>
<td>Temocillin</td>
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<td>4.00</td>
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<tr>
<td>Tosufloxacin</td>
<td>Oral</td>
<td>0.60</td>
<td>0.45</td>
<td>2019</td>
</tr>
</tbody>
</table>

* denotes molecules for which new DDDs for implementation in ATC/DDD index in 2019 were the same as those used in previous analysis

^a These are the values used in Klein et al. (5)

^b The DDDs will be reviewed at the March 2019 meeting (3-year revision)
Outpatient Antibiotic Use in Belgium 1997-2018 in DDD per 1,000 Inhabitants per Day (DID) – July-June
Outpatient Antibiotic Use in Belgium 1997-2018 in Adjusted DDD per 1,000 Inhabitants per Day (DID) – July-June
Outpatient Antibiotic Use in Belgium 1997-2018 in Packages per 1,000 Inhabitants per Day (PID) – July-June
Outpatient Antibiotic Use in Belgium
1997-2018 in Euros per 1,000 Inhabitants per Day (PID) – July-June

Reimbursement from Class B to C on 1/5/2017
Consumption of antibiotics for systemic use (ATC group J01) in the community, EU/EEA, 2014

DDD per 1,000 Inhabitants and per Day

EU/EEA refers to the corresponding population-weighted mean consumption

(a) Cyprus and Romania provided total care data (i.e. including the hospital sector)
(b) Spain provided reimbursement data (i.e. not including consumption of antibiotics obtained without a prescription and other non-reimbursed courses)
Nutrition of antibiotics for systemic use (ATC group J01) in the community, EU/EEA, 2014

Packages per 1,000 Inhabitants and per Day

EU/EEA refers to the corresponding population-weighted mean consumption

(a) Spain provided reimbursement data (i.e. not including consumption of antibiotics obtained without a prescription and other non-reimbursed courses)

Source: ESAC-Net, 2015
Conclusion

- Surveillance of antibiotics in outpatients can be misleading, depending on the indicator used, healthcare structure, marketing of antibiotics, policy of prescribing, ...
- Collect information on several indicators (DDDs, packages...)
- Ultimately, antimicrobial use should be monitored in number of prescriptions
Why it matters!
Measures for antibiotic consumption in ambulatory care and level of targets set in different countries

<table>
<thead>
<tr>
<th>Measure</th>
<th>BE</th>
<th>DK</th>
<th>FR</th>
<th>IR</th>
<th>IT</th>
<th>JP</th>
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</thead>
<tbody>
<tr>
<td>Packages per 1000 inhabitants per year</td>
<td>600 by 2020</td>
<td>400 by 2025</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Prescriptions per 100 patients per year</td>
<td>-</td>
<td>-</td>
<td>-12% by 2016 (vs 2010)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Prescriptions per 1000 inhabitants per year</td>
<td>350 by 2020</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Prescriptions per 1000 inhabitants per day</td>
<td>-</td>
<td>-</td>
<td>-10% by 2021 (vs 2016)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Defined daily doses per 1000 inhabitants per day</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>≤ -10% by 2020 (vs 2016)</td>
<td>-33% by 2020 (vs 2013)</td>
<td>-</td>
</tr>
<tr>
<td>Defined daily doses per 1000 inhabitants per year</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Source: WHO, 2018
Measures for antibiotic consumption in ambulatory care and level of targets set in different countries

<table>
<thead>
<tr>
<th>Package per 1000 Inhabitants per year</th>
<th>NO</th>
<th>PT</th>
<th>KR</th>
<th>SE</th>
<th>TH</th>
<th>TU</th>
<th>UK</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prescriptions per 100 patients per year</td>
<td>250 by 2020</td>
<td>250 by 2014</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prescriptions per 1000 inhabitants per year</td>
<td>-30% by 2020 (versus 2012)</td>
<td>20% by 2020 (versus 2015)</td>
<td>-20% by 2021 (vs 2016)</td>
<td>-35% by 2017</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Source: WHO, 2018
Inpatients: Which indicator?

- **Numerator:**
  - Weight (g or kg or units of treatment)
  - Vials
  - Agent days
  - Courses
  - Treatment periods
  - Percentage of patients exposed to antimicrobials
  - Antibiotic days or Days of Treatment (DOT)
  - DDD (Defined Daily Dose)
  - PDD (Prescribed Daily Dose)

- **Denominator:**
  - Per month or year
  - Per 1000 inhabitants-days
  - Per 100 or 1,000 patient-days
  - Per 100 or 1,000 administrative bed-days
  - Per 100 or 1,000 occupied bed-days
  - Per 100 or 1,000 admissions
  - Per 100 or 1,000 discharges
  - Per month/occupied bed
  - Per Thousand Finished Consultant Episodes
Evaluation of Indicators: Methods

- **Objectives:**
  - Longitudinal survey validating two denominators

- **Duration:**
  - 6 years (Jan 2000- Jan 2006 as a monthly basis)

- **Numerator:**
  - Drug consumption for J01 antibacterials, converted to WHO (DDDs)

- **Denominator:**
  - Occupied Bed-days (OBD)
  - Admissions (AD)

- **Statistical method:**
  - Times Series Analysis

Ansari et al., J Antimicrob Chemother, 2010; 65: 2685- 91
Time series regression model

- $A =$ admissions
- $B =$ occupied bed days
- $R =$ discharges
- $L =$ estimated length of stay
- $\alpha_s, \beta_s, \gamma_s, \delta_s$ and $\phi_s$ are the coefficients which capture the impact of these variables with $s$ lags
- $t =$ time
- $Dm_i =$ seasonal dummies with coefficients $\Theta_i$ that capture the shift in month $i$ relative to month 1

$$Y_t = \sum_{s=0}^{S} (a_s Y_{t-s} + \beta_s A_{t-s} + \gamma_s B_{t-s} + \delta_s R_{t-s} + \phi_s L_{t-s}) + \sum_{j=0}^{J} \mu_j t^j + \sum_{i=2}^{12} \theta_i D M_{i,t} + \sum_{k=1}^{K} \lambda_k D I_{k,t} + \varepsilon_t$$
ESAC Longitudinal Survey: mean annual % change in DDD, DBD & DAD

Ansari et al., J Antimicrob Chemother, 2010
ESAC Point Prevalence Study: What We Achieved

- A web-based standardised PPS method was successfully developed
- Instant web-report per hospital
- Quantifiable outcome measures and targets for quality improvement:
  - Duration of surgical prophylaxis
  - Proportion of oral/parenteral use
  - Therapy for certain diseases (e.g. CAP) not including certain antibiotics (e.g. quinolones)
  - Indication documented
  - Compliance with guidelines
- Tool for assessing interventions to improve antibiotic prescribing in hospitals

Ansari et al., Clin Infect Dis, 2009; Zarb et al., J Antimicrob Chemother, 2010; Amadeo et al., J Antimicrob Chemother 2010
Prevalence of antimicrobial use in acute care hospitals, EU/EEA and Serbia, 2016-2017

1 in 3 patients in acute care hospitals in EU/EEA countries received at least one antimicrobial on any given day

* Bulgaria, the Netherlands: poor national representativeness of acute care hospital sample;
** Norway: national protocol.
Proportion of broad-spectrum antimicrobials in acute care hospitals, EU/EEA countries & Serbia, 2016–2017

Surgical antibiotic prophylaxis in acute care hospitals, by duration (single dose, one day, more than one day), EU/EEA countries and Serbia, 2016-2017

54% surgical antibiotic prophylaxis courses in EU/EEA countries were prescribed for more than one day

Duration of surgical prophylaxis in Belgian hospitals

Selection hospitals with ≥ 10 patients receiving surgical prophylaxis (n=31 hospitals)
Conclusions

• **Longitudinal surveillance is difficult:**
  Primary analysis should be done on DDD without adjustment for clinical activity
  Adjustment for clinical activity should be done with both admissions and occupied bed days
  A minority of hospitals can provide data

• **PPS methodology is easy and practical:**
  Stimulates local networking
  Allows identification of quantifiable outcome measures and high-impact targets for quality improvement (Antimicrobial Stewardship Programs)
  Tool for assessing interventions to improve antibiotic prescribing in hospitals
  But also several weaknesses
Why it matters!
National targets in the UK 2015 – 2019

- Total antibiotic consumption to be reduced by 1% per year 2015-2019 as measured by DDD per 1000 Admissions per Year.
- Total carbapenem consumption to be reduced to 2010 consumption levels as measured by DDD per 1000 Admissions per Year.
• Condition of participation in Medicare: every hospital, ASC and LTC facility, must have an antibiotic stewardship program by the end of 2017

• At least 95% of eligible hospitals will report antibiotic use data to the National Healthcare Safety Network (NHSN)

• Reduction of inappropriate antibiotic use by 20% in inpatient settings from 2014 levels by 2020
National targets in China

Changes in Chinese Policies to Promote the Rational Use of Antibiotics

Yonghong Xiao*, Jing Zhang, Beiwen Zheng, Lina Zhao, Sujuan Li, Lanjuan Li*

Collaborative Innovation Center for Diagnosis and Treatment of Infectious Diseases, State Key Laboratory for Diagnosis and Treatment of Infectious Diseases, The First Affiliated Hospital, College of Medicine, Zhejiang University, Hangzhou, China

Target for general hospitals: “antibiotic utilization in inpatients should be less than 40 DDD/100 Patient Days.”

Initiation in May 2011 by vice-minster of China
Second Part: Global use

- Outpatient use (total use)
- Hospital use (PPS)
Global increase and geographic convergence in antibiotic consumption between 2000 and 2015

Eili Y. Klein\textsuperscript{a,b,c,1}, Thomas P. Van Boeckel\textsuperscript{d}, Elena M. Martinez\textsuperscript{a}, Suraj Pant\textsuperscript{a}, Sumanth Gandra\textsuperscript{a}, Simon A. Levin\textsuperscript{e,f,g,1}, Herman Goossens\textsuperscript{h}, and Ramanan Laxminarayan\textsuperscript{a,f,i}

PNAS 2018
Antibiotic consumption rate by country for 2015 in DID
Changes in the national antibiotic consumption rate between 2000 and 2015 in DIDs

Change in DDDs per 1000 inhabitants per day (2000–2015)

-20–15
-15–10
-10–5
-5–0
+0–5
+5–10
+10–15
+15–20
+20–25
+25–30
Global Point Prevalence Survey of Antimicrobial Consumption and Resistance in Hospitals (GLOBAL-PPS)
Antimicrobial consumption and resistance in adult hospital inpatients in 53 countries: results of an internet-based global point prevalence survey

Ann Versporten, Peter Zarb, Isabelle Caniaux, Marie-Françoise Gros, Nico Drapier, Mark Miller, Vincent Jarlier, Dilip Nathwani, Herman Goossens, on behalf of the Global-PPS network*

Summary
Background The Global Point Prevalence Survey (Global-PPS) established an international network of hospitals to measure antimicrobial prescribing and resistance worldwide. We aimed to assess antimicrobial prescribing and resistance in hospital inpatients.

Methods We used a standardised surveillance method to collect detailed data about antimicrobial prescribing and resistance from hospitals worldwide, which were grouped by UN region. The internet-based survey included all inpatients (adults, children, and neonates) receiving an antimicrobial who were on the ward at 0800 h on one specific day between January and September, 2015. Hospitals were classified as primary, secondary, tertiary (including infectious diseases hospitals), and paediatric hospitals. Five main ward types were defined: medical wards, surgical wards, intensive-care units, haematology oncology wards, and medical transplantation (bone marrow or solid transplants) wards. Data recorded included patient characteristics, antimicrobials received, diagnosis, therapeutic indication according to predefined lists, and markers of prescribing quality (eg, whether a stop or review date were recorded, and whether local prescribing guidelines existed and were adhered to). We report findings for adult inpatients.
Degree of participation or enrollment as of today

N = 96 countries
N ≈ 1000 hospitals
N ≈ 220,000 admitted patients
Antimicrobial use prevalence (%) by UN-region (country-ranges)

Worldwide AMU prevalence (%)

<table>
<thead>
<tr>
<th>Year</th>
<th>Mean (%; 95% CI)</th>
<th>Median (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2015</td>
<td>42.1 (26.3-57.9)</td>
<td>36.3</td>
</tr>
<tr>
<td>2017</td>
<td>43.6 (29.3-57.9)</td>
<td>39.5</td>
</tr>
</tbody>
</table>
### Antibiotic quality indicators for treatment of HAI IN 2015 & 2017

<table>
<thead>
<tr>
<th>Reason in notes</th>
<th>2015 (%; range)</th>
<th>2017 (%; range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reason in notes</td>
<td>86.1 (75.5-94.5)</td>
<td>83.3 (68.1-95.0)</td>
</tr>
<tr>
<td>Stop/review date</td>
<td>41.5 (20.9-56.4)</td>
<td>38.9 (17.5-62.8)</td>
</tr>
<tr>
<td>Guidelines missing</td>
<td>15.8 (6.6-45.5)</td>
<td>17.1 (0.0-33.0)</td>
</tr>
<tr>
<td>Guideline compliance</td>
<td>82.8 (64.7-95.0)</td>
<td>80.3 (66.8-90.2)</td>
</tr>
</tbody>
</table>

Crude ranges (min-max) are calculated by region.
From the EU to the World

Legend

- Green: Data included
- Pink: Data submitted
- Dashed: Trained countries
- Dotted: Informed countries
- Gray: Not applicable

The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted and dashed lines on maps represent approximate border lines for which there may not yet be full agreement.

Data source: World Health Organization
Map production: Essential Medicines and Health Products Department
World Health Organization
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“When you can measure what you are speaking about and express it in numbers, you know something about it.”

Lord Kelvin, 1824-1907
Thank you!
Quaterly outpatient antibiotic use in PID in the UK and Belgium

Belgian media campaigns

Figure 4. Longitudinal trends and seasonal variation of total outpatient antibiotic use in four UK administrations and Belgium measured in PID.
Antimicrobial prevalence rates (%) in Belgian hospitals

Mean antimicrobial prevalence rate = 27.4%
## Antibiotic quality indicators

<table>
<thead>
<tr>
<th></th>
<th>Hosp 1</th>
<th></th>
<th>Hosp 2</th>
<th></th>
<th>Belgium</th>
<th></th>
<th>Europe</th>
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<tr>
<td></td>
<td>N</td>
<td>%</td>
<td>N</td>
<td>%</td>
<td>N</td>
<td>%</td>
<td>N</td>
<td>%</td>
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<tr>
<td><strong>Medical</strong></td>
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<td>6716</td>
<td>80.7</td>
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<td>36.9</td>
<td>1726</td>
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<td>4669</td>
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</tr>
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<td>1200</td>
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<td>3307</td>
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</tr>
<tr>
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<td>110</td>
<td>100.0</td>
<td>10</td>
<td>20.8</td>
<td>981</td>
<td>46.8</td>
<td>3357</td>
<td>46.7</td>
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<tr>
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</tr>
<tr>
<td>Reason in notes</td>
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<td>95.7</td>
<td>11</td>
<td>68.8</td>
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<td>89.6</td>
<td>2305</td>
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<tr>
<td>Guidelines missing</td>
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<td>8.7</td>
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<td>6.2</td>
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<td>93.9</td>
<td>8</td>
<td>80.0</td>
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<td>1417</td>
<td>84.1</td>
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<tr>
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<td>13.0</td>
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<td>301</td>
<td>34.6</td>
<td>1238</td>
<td>41.7</td>
</tr>
</tbody>
</table>

Antibiotic quality indicators by activity (medical, surgery, ICU) for all patients receiving antibacterials for systemic use (ATC J01).
- For reason in notes and stop/review date documented: Count at antibacterial level.
- For guidelines missing: Count on NA (= no local guidelines for the specific indication) at patient level and diagnosis over total scores for this indicator.
- For guideline compliance: Count at patient level and diagnosis for compliance= yes or no only. For combination therapy with >1 antibiotic: if 1 antibiotic by diagnosis is not compliant, this combination therapy as a whole for this diagnosis will be counted as non-compliant.
The Global-PPS database

**2015 (53 countries)**
- 100,777 admitted patients
- 34,747 treated patients (34.5%)
- 8644 patients with HAI (8.5%)
- 11768 antimicrobials to treat HAI

**2017 (50 countries)**
- 104,358 admitted patients
- 37,903 treated patients (36.3%)
- 8836 patients with HAI (8.6%)
- 12560 antimicrobials to treat HAI