How diagnostics reduce antibiotic resistance

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Conflicts of interest

Grants or consulting fees (payments to UMCU)

- Janssen Vaccines
- Pfizer
- Merck
- Astra Zeneca
- Pherecytes
- GSK
- Shionogi
The conventional wisdom

- Antibiotics select for antibiotic resistant bacteria
- Withholding antibiotics does not select for antibiotic resistant bacteria
- Targeted antibiotic therapy – usually - selects less for antibiotic resistant bacteria than untargeted broad-spectrum coverage
RAPID DIAGNOSTICS: STOPPING UNNECESSARY USE OF ANTIBIOTICS

THE REVIEW OF ANTIMICROBIAL RESISTANCE
CHAIRLED BY JIM O’NEILL

OCTOBER 2015

Rapid point-of-care diagnostic tests are a central part of the solution to this demand problem, which results currently in enormous unnecessary antibiotic use.
For lack of rapid diagnostics, the world vastly overuses antibiotics, in rich and poorer countries alike.

“This suggests it is possible that 27 million courses of antibiotics were wasted on patients who didn’t need them in one year in the United States alone, for respiratory symptoms only.”
5.

WE CAN IMPROVE OUR USE OF ANTIBIOTICS TODAY BASED ON EXISTING DIAGNOSTICS, COUPLED WITH PUBLIC EDUCATION

Solutions

- Fund and facilitate research
- Global innovation fund
- Diagnostic market stimulus
Community acquired acute respiratory tract infection (CA-ARTI)

• leading cause of morbidity and mortality
• common reason for consulting Emergency Department
• microbiological cause of infection mostly unknown at time of disease onset
• frequent cause of inadequate antibiotic prescription

Highly sensitive molecular assays increase detection of respiratory pathogens, but the impact in clinical decision making has not been properly evaluated.

**DIAGNOSTIC STEWARDSHIP**
- Right test
- Right patient
- Right time

**ANTIMICROBIAL STEWARDSHIP**
- Right interpretation
- Right antimicrobial
- Right time

**PATIENT**

**CLINICAL EVALUATION**
- Rapid diagnostic test performed

**HEALTH CARE PROVIDER**
- Rapid diagnostic result reported

**MICROBIOLOGY LABORATORY**
- Diagnosis & treatment
Objective of antimicrobial/diagnostic stewardship

Can we safely reduce hospital admissions and/or antibiotic use with rapid diagnostic testing?

The impact of rapid diagnostic testing of patients with CA-ARTI on:

- (1) hospital admission rates
- (2) antimicrobial prescriptions
- (3) clinical outcome

\[
\begin{align*}
\text{Superiority endpoints} & : \{1, 2\} \\
\text{Non-inferiority endpoint} & : 3
\end{align*}
\]
Systematic review

The quality of studies evaluating antimicrobial stewardship interventions: a systematic review

V.A. Schweitzer 1, *, I. van Heijl 2, C.H. van Werkhoven 1, J. Islam 3, K.D. Hendriks-Spool 2, J. Bielicki 4, M.J.M. Bonten 5, A.S. Walker 6, M.J. Llewelyn 3 on behalf of the Consensus on Antimicrobial Stewardship Evaluations (CASE) study group †
Table 3
Design quality features of the included studies stratified by studies performed in the community and the hospital setting

<table>
<thead>
<tr>
<th>Quality feature</th>
<th>Community (n = 205), n (%)</th>
<th>Hospital (n = 620), n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomized research design</td>
<td>95 (46)</td>
<td>55 (9)</td>
</tr>
<tr>
<td>External control group</td>
<td>129 (63)</td>
<td>99 (16)</td>
</tr>
<tr>
<td>Multicentre</td>
<td>148 (72)</td>
<td>101 (16)</td>
</tr>
<tr>
<td>Sample size calculation reported</td>
<td>77 (38)</td>
<td>96 (15)</td>
</tr>
<tr>
<td>Prospective data collection</td>
<td>144 (70)</td>
<td>288 (46)</td>
</tr>
<tr>
<td>Correction for confounding factors</td>
<td>113 (55)</td>
<td>157 (25)</td>
</tr>
<tr>
<td>Primary outcome defined</td>
<td>116 (57)</td>
<td>272 (44)</td>
</tr>
<tr>
<td>Clinical outcome reported</td>
<td>61 (30)</td>
<td>337 (54)</td>
</tr>
<tr>
<td>Microbiological outcome reported</td>
<td>17 (8)</td>
<td>173 (28)</td>
</tr>
<tr>
<td>Sustainability assessed (≥12 months)</td>
<td>115 (56)</td>
<td>347 (56)</td>
</tr>
</tbody>
</table>

Implications: Overall quality of antimicrobial stewardship studies is low and has not improved over time. Most studies do not report clinical and microbiological outcome data. Studies conducted in the community setting were associated with better quality. These limitations should inform the design of future stewardship evaluations so that a robust evidence base can be built to guide clinical practice.

V.A. Schweitzer, Clin Microbiol Infect 2019;25:555
Routine molecular point-of-care testing for respiratory viruses in adults presenting to hospital with acute respiratory illness (ResPOC): a pragmatic, open-label, randomised controlled trial

Nathan J Brendish, Ahalya K Malachira, Lawrence Armstrong, Rebecca Houghton, Sandra Aitken, Esther Nyimbili, Sean Ewings, Patrick J Lillie, Tristan W Clark

Pragmatic, parallel-group, open-label, randomised controlled trial;

Adults (aged ≥18 years) within 24 h of presenting to the emergency department or acute medical unit of a large UK hospital with acute respiratory illness or fever (≤7 days duration), or both, over two winter seasons.

Patients were randomly assigned (1:1) to have a molecular POC test for respiratory viruses or routine clinical care.

The primary outcome was the proportion of patients who received antibiotics while hospitalised (up to 30 days).
<table>
<thead>
<tr>
<th></th>
<th>POCT (n=360)</th>
<th>Control (n=354)</th>
<th>Difference (95% CI)</th>
<th>Odds ratio (95% CI)</th>
<th>Number needed to test (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients tested for viruses</td>
<td>360 (100%)</td>
<td>158 (45%)</td>
<td>55.4% (50.1 to 60.0)</td>
<td>...</td>
<td>...</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Patients with any virus detected</td>
<td>161 (45%)</td>
<td>52 (15%)</td>
<td>30.0% (23.3 to 36.8)</td>
<td>4.70 (3.28 to 6.74)</td>
<td>4 (2.8 to 4.2)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Influenza A or B</td>
<td>61 (17%)</td>
<td>37 (10%)</td>
<td>6.5% (1.5 to 11.5)</td>
<td>1.75 (1.13 to 2.71)</td>
<td>15 (8 to 68)</td>
<td>0.0124</td>
</tr>
<tr>
<td>Rhinovirus or enterovirus (unspecified)*</td>
<td>55 (15%)</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Coronavirus*</td>
<td>18 (5%)</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Human metapneumovirus</td>
<td>14 (4%)</td>
<td>5 (1%)</td>
<td>2.5% (0.1 to 4.8)</td>
<td>...</td>
<td>...</td>
<td>0.060</td>
</tr>
<tr>
<td>Parainfluenza</td>
<td>11 (3%)</td>
<td>2 (-1%)</td>
<td>2.5% (0.6 to 4.4)</td>
<td>...</td>
<td>...</td>
<td>0.0214</td>
</tr>
<tr>
<td>RSV</td>
<td>9 (3%)</td>
<td>6 (2%)</td>
<td>0.8% (-1.3 to 2.9)</td>
<td>...</td>
<td>...</td>
<td>0.60</td>
</tr>
<tr>
<td>Adenovirus</td>
<td>1 (&lt;1%)</td>
<td>2 (&lt;1%)</td>
<td>-0.3% (-1.2 to 0.7)</td>
<td>...</td>
<td>...</td>
<td>0.62</td>
</tr>
<tr>
<td>Viral co-detection</td>
<td>8 (2%)</td>
<td>0</td>
<td>2.2% (0.7 to 3.7)</td>
<td>...</td>
<td>...</td>
<td>0.0075</td>
</tr>
<tr>
<td>Turnaround time (h)</td>
<td>2.3 (1.4)‡</td>
<td>37.1 (21.5)</td>
<td>-34.7 (-38.1 to -31.4)</td>
<td>...</td>
<td>...</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Data are n (%) or mean (SD). Medians are presented in the appendix for completeness. POCT=point-of-care testing. RSV=respiratory syncytial virus. *Not tested for by laboratory PCR. ‡Assessed in 356 patients.

Table 2: Patients tested for viruses, rate of detection, and turnaround time
<table>
<thead>
<tr>
<th></th>
<th>POCT (n=360)</th>
<th>Control (n=354)</th>
<th>Risk difference (95% CI)</th>
<th>Unadjusted odds ratio (95% CI)</th>
<th>Adjusted odds ratio (95% CI)</th>
<th>Number needed to test (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All antibiotics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antibiotics given</td>
<td>301 (84%)</td>
<td>294 (83%)</td>
<td>0.6% (-4.9 to 6.0)</td>
<td>1.04 (0.70 to 1.54)</td>
<td>0.99 (0.57 to 1.70)</td>
<td></td>
<td>0.96*</td>
</tr>
<tr>
<td>Single dose only</td>
<td>31/301 (10%)</td>
<td>10/294 (3%)</td>
<td>6.9% (2.9 to 11.0)</td>
<td>3.26 (1.59 to 6.68)</td>
<td>15 (9 to 35)†</td>
<td>0.0010</td>
<td></td>
</tr>
<tr>
<td>Given for &lt;48 h</td>
<td>50/301 (17%)</td>
<td>25/294 (9%)</td>
<td>7.8% (2.5 to 13.1)</td>
<td>2.05 (1.40 to 3.39)</td>
<td>13 (8 to 43)‡</td>
<td>0.0047</td>
<td></td>
</tr>
<tr>
<td>Duration (days)</td>
<td>7.2 (5.1)</td>
<td>7.7 (4.9)</td>
<td>-0.4 (-1.2 to 0.4)§</td>
<td>0.95 (0.85 to 1.05)¶</td>
<td>0.91 (0.80 to 1.04)¶</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Intravenous antibiotics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intravenous antibiotics given</td>
<td>196 (54%)</td>
<td>183 (52%)</td>
<td>2.7% (-4.6 to 10.0)</td>
<td>1.15 (0.83 to 1.50)</td>
<td></td>
<td></td>
<td>0.46</td>
</tr>
<tr>
<td>Single dose only</td>
<td>50/196 (26%)</td>
<td>37/183 (20%)</td>
<td>5.3% (-3.1 to 14.0)</td>
<td>1.35 (0.84 to 2.19)</td>
<td></td>
<td></td>
<td>0.22</td>
</tr>
<tr>
<td>Given for &lt;48 h</td>
<td>106/195 (54%)</td>
<td>100/183 (55%)</td>
<td>-0.5% (-11.0 to 9.5)</td>
<td>0.98 (0.65 to 1.46)</td>
<td></td>
<td></td>
<td>0.91</td>
</tr>
<tr>
<td>Duration (days)</td>
<td>3.1 (4.6)</td>
<td>2.9 (3.7)</td>
<td>0.3 (-0.6 to 1.1)§</td>
<td>1.09 (0.86 to 1.40)¶†</td>
<td></td>
<td></td>
<td>0.48</td>
</tr>
</tbody>
</table>

Data are n (%) or mean (SD). POCT=point-of-care testing. * Applies to adjusted effect sizes. † Number needed to test to change a standard course to a single dose. ‡ Number needed to test to change a standard course to a brief course. § Mean difference. ¶ Unadjusted rate ratio. || Adjusted rate ratio.

*Table 3: Comparison of antibiotic use*
... we investigated whether an antibiotic stewardship intervention would reduce the use of broad-spectrum antibiotics in patients with moderately severe community-acquired pneumonia without compromising their safety.

Aiming for benzylpenicillin, amoxicillin or doxycycline instead of amoxicillin-clavulanic acid, cephalosporins, macrolides or fluoroquinolones
A stepped-wedge cluster-randomized design

Assuming an all-cause 90-day mortality of 10%, a non-inferiority margin of 3%, a one-sided alpha of 0.05, and taking into account the stepped-wedge design, a total of 4464 patients were required for 80% power to detect non-inferiority.
Antibiotic stewardship intervention

Educational activities were targeted at physicians in pulmonary and internal medicine departments and consisted of:
- clinical lessons,
- electronic (e)-learning,
- educational attributes.

Clinical lessons, in which national community-acquired pneumonia guidelines were addressed by use of case-based discussions and feedback, with antibiotic prescribing data of the respective hospitals anonymously benchmarked against other participating hospitals, were given at month 0 of the intervention period and then every 6 months until study completion.
Results: antibiotic use

Narrow-spectrum:
- Benzylpenicillin
- Amoxicillin
- Doxycycline

The median total days of therapy per patient were 8 days (IQR 7–10) in the control and 8 days (7–11) in the intervention period.

The adjusted mean broad-spectrum days of therapy per patient was reduced from 6.5 days in the control period to 4.8 days in the intervention period, with an adjusted absolute difference of −1.7 days (95% CI −2.4 to −1.1) and an adjusted relative reduction of 26.6% (95% CI 18.0–35.3).
Results: safety

90-day all-cause mortality was 10.9% (242 of 2228 patients died) in the control period and 10.8% (199 of 1841 patients died) in the intervention period.
Improving antibiotic prescribing for UTIs in frail older adults

Summary
Implementation of the intervention resulted in a clinically relevant reduction in antibiotic prescribing for suspected urinary tract infections (UTIs) without evidence for increased adverse outcomes.

Study design
Cluster randomised controlled trial
38 clusters consisting of general practices and older adult care organisations
Located in Poland, the Netherlands, Norway, and Sweden

Population
1041 frail older adults aged 70 years or older
Mean age: 86 years
Sex: 71% women
Dementia: 44% incidence

Comparison
Intervention: Multifaceted antibiotic stewardship intervention
Decision tool
Educational toolbox
Educational and evaluation sessions

Control: Usual care

Outcomes
Intervention vs control, per person year
Adjusted rate ratio 95% CI
Antibiotic prescriptions for suspected UTIs: 0.27 0.42 0.26 to 0.68 0.58
Complications within 21 days after suspected UTIs: <0.01 No important difference 0.05
All cause mortality: 0.26 No important difference 0.26

Conclusions

- Empiric treatment of infections remains challenging, mostly because a documented causative pathogen hardly ever informs treatment decisions.

- Demonstrating safe reductions of unnecessary antibiotic use requires well-designed pragmatic clinical trials demonstrating the safety/non-inferiority of using less broad-spectrum antibiotics.

- Antimicrobial and diagnostic stewardship are suitable interventions to change practices, but the impact on reducing antibiotic resistance remains to be determined.

- The complexities of integrating diagnostics into the care path should not be underestimated.