Using an index-based approach to assess the population-level appropriateness of empirical antibiotic therapy

M. Ciccolini1*, V. Spoorenberg2, S. E. Geerlings2, J. M. Prins2 and H. Grundmann1

1Department of Medical Microbiology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands; 2Division of Infectious Diseases, Department of Internal Medicine, Academic Medical Center, Amsterdam, The Netherlands

*Corresponding author. Tel: +31-503615169; Fax: +31-503619105; E-mail: m.ciccolini@umcg.nl

Received 11 March 2014; returned 27 May 2014; revised 15 July 2014; accepted 1 August 2014

Objectives: The population-level appropriateness of empirical antibiotic therapy can be conventionally measured by ascertainment of treatment coverage. This method involves a complex resource-intensive case-by-case assessment of the prescribed antibiotic treatment and the resistance of the causative microorganism. We aimed to develop an alternative approach based, instead, on the use of routinely available surveillance data.

Methods: We calculated a drug effectiveness index by combining three simple aggregated metrics: relative frequency of aetiological agents, level of resistance and relative frequency of antibiotic use. To evaluate the applicability of our approach, we used this metric to estimate the population-level appropriateness of guideline-compliant and non-guideline-compliant empirical treatment regimens in the context of the Dutch national guidelines for complicated urinary tract infections.

Results: The drug effectiveness index agrees within 5% with results obtained with the conventional approach based on a case-by-case ascertainment of treatment coverage. Additionally, we estimated that the appropriateness of 2008 antibiotic prescribing regimens would have declined by up to 4% by year 2011 in the Netherlands due to the emergence and expansion of antibiotic resistance.

Conclusions: The index-based framework can be an alternative approach to the estimation of point values and counterfactual trends in population-level empirical treatment appropriateness. In resource-constrained settings, where empirical prescribing is most prevalent and comprehensive studies to directly measure appropriateness may not be a practical proposition, an index-based approach could provide useful information to aid in the development and monitoring of antibiotic prescription guidelines.

Keywords: antimicrobial resistance, prescription guidelines, surveillance

Introduction

Worldwide, most infections are treated on empirical grounds. This is expected, as doctors aim to achieve rapid improvement and cannot or do not want to wait until laboratory results become available, or shun the extra cost and effort associated with aetiological investigations. More often, especially in low and middle income countries, microbiological diagnostic services that could inform appropriate therapy (i.e. identify agents to which the causative pathogen is susceptible) are simply not available. There has therefore been a growing appreciation of treatment guidelines that provide a rational basis for the choice of antibiotics for empirical therapy.1–7

But how rational can this basis be? With emerging and expanding antibiotic resistance, correct treatment choices are increasingly becoming a moving target. Thus, without an update, many of the treatment guidelines issued in the past have become obsolete. Consequently, guideline adherence drops whilst prescribing adapts to prevailing resistance. From a public-health perspective, it is then of utmost importance to assess whether recommended empirical treatment regimens match current susceptibility patterns. This involves estimating population-level appropriateness of empirical antibiotic prescribing and answering the following questions. What is the probability that a patient who will be treated empirically will actually receive the appropriate antibiotic? How will this probability change due to variations in prescribing practices or resistance patterns? Can the impact of adaptive prescribing on appropriateness be quantified?

Here we address these issues by proposing a novel approach to the evaluation of the population-level appropriateness of empirical treatment regimens. This approach is based on a drug resistance index, a concept recently introduced by Laxminarayan and
Klugman\textsuperscript{8} to communicate to non-specialist audiences trends in prevalence of antimicrobial resistance. The index-based method involves estimating empirical treatment appropriateness by employing three aggregated metrics: aetiological fractions of causative microorganisms, their level of resistance to the recommended antibiotic regimens, and relative frequency of antibiotic use. Most of these metrics can be estimated from data routinely collected by existing surveillance programmes.\textsuperscript{9–11} This is a clear advantage over the conventional method based on the ascertainment of treatment coverage (ATC), which involves resource-intensive case-by-case analysis of appropriateness of the prescribed antibiotic therapy.

Our aim was to evaluate the applicability of the index-based approach as part of an actual guideline assessment exercise. We employed as a case study the Dutch national guidelines for complicated urinary tract infections (UTIs) developed by the Dutch Working Party on Antibiotic Policy (SWAB).\textsuperscript{12,13} We followed a two-step approach. Firstly, we calculated a drug effectiveness index (DEI) and determined its level of agreement with estimates of population-level empirical treatment appropriateness based on ATC. In this analysis we used the comprehensive dataset reported by Spoorenberg et al.\textsuperscript{14} Secondly, we illustrate the use of publicly available multi-year surveillance data for the calculation of the DEI and quantify the decline in appropriateness of empirical treatments for UTI in the Netherlands between 2008 and 2011, due to the emergence and expansion of antibiotic resistance. We performed these analyses in four different scenarios corresponding to all possible combinations of the two main UTI diagnostic groups, and two empirical treatment regimens, namely SWAB-guideline-compliant and non-SWAB-guideline-compliant prescribing.

In this article we focus on the methodological aspects and the applicability of the index-based approach. For a detailed analysis of the adequacy of Dutch UTI guideline recommendations the reader is referred to the work by Spoorenberg et al.\textsuperscript{15}

Methods

To consistently compare estimates of population-level empirical treatment appropriateness based on the DEI and ATC, we first used the same dataset to obtain both results. We begin this section with a description of these data, followed by a detailed explanation of the DEI and ATC calculations. We finish this section with an outline of the procedure to estimate DEI trends between 2008 and 2011 and a brief description of the antibiotic resistance surveillance data employed for this purpose.

UTI study dataset

We employed data collected retrospectively as part of a comprehensive study on the adequacy of empirical antibiotic therapy recommended by the Dutch national guidelines for the antimicrobial treatment of complicated UTI.\textsuperscript{14} These data consisted of 1219 records, each associated with a bacterial isolate obtained from one of 1073 patients diagnosed with a complicated UTI (one, two and three bacterial species were cultured from 945, 110 and 18 patients, respectively). Isolates were collected during the period 2007–08 from inpatients and outpatients at urology and internal medicine departments across 19 Dutch hospitals.

Each record contained information on clinical diagnosis (as defined by the SWAB guidelines), cultured bacteria and initial antibiotic therapy. We focused on the two most prevalent clinical presentations as defined by the SWAB guidelines: urosepsis/pyelonephritis/complicated UTI (diagnostic group 1) and complicated UTI associated with catheter use for >10 days (diagnostic group 2), which together represented 984 (92%) of the 1073 episodes in the study. We used records corresponding to the nine most frequently isolated bacterial species, namely Enterococcus spp., Staphylococcus spp., non-enterococcal Streptococcus spp., Escherichia coli, Klebsiella spp., Proteus spp., Pseudomonas spp., Enterobacter spp. and Citrobacter spp. Of all the isolates in the dataset, 96% belonged to one of these species.

The most common treatment choices were grouped into 20 different antibiotic regimens, listed in Table 1. Among all patients in the UTI study, 97% were initially prescribed one of these antibiotic regimens. Therapy was characterized as either empirical or adjusted. We used the same convention as Spoorenberg et al.,\textsuperscript{14} and defined empirical therapy as the first prescribed (combination of) antibiotics before identification of the causative uropathogen. If the initial therapy was adapted to a previous positive urine culture, this therapy was considered adjusted. For empirical therapy, compliance with the SWAB guidelines (i.e. whether guideline recommendations were followed) was recorded. Additionally, each record contained information on the ascertained susceptibility of the corresponding isolate to each of the 20 antibiotic regimens. Isolates were considered either fully susceptible or fully resistant based on the in vitro susceptibility test results and the comprehensive definitions and assumptions detailed by Spoorenberg et al.\textsuperscript{14}

DEI calculation

We begin by calculating a drug resistance index (DRI) as described by Laxminarayan and Klugman.\textsuperscript{8} Briefly, for each bacterial species $i$, diagnostic group $D$ and guideline compliance $C$ (noted as either Y (SWAB compliant) or N (non-SWAB compliant) throughout) we estimated a pathogen-based drug resistance index $DRI(D, C)$ as a weighted average of resistance against the 20 antibiotic regimens. The weight associated with each regimen is equal to its relative frequency of prescription. In mathematical form:

$$DRI(D, C) = \sum_{j=1}^{20} p_j(D, C) R_{i, j},$$

where the sum is over all antibiotic regimens, $p_j(D, C)$ is the relative frequency of prescription of antibiotic regimen $j$.

Table 1. Antibiotic regimens: list of the 20 most frequently prescribed antibiotic regimens covered by the UTI dataset, together with abbreviations used throughout this work

<table>
<thead>
<tr>
<th>Antibiotic regimen</th>
<th>Abbreviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amoxicillin</td>
<td>AMX</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>GEN</td>
</tr>
<tr>
<td>Amoxicillin + gentamicin</td>
<td>AMX+GEN</td>
</tr>
<tr>
<td>Co-amoxiclav</td>
<td>AMC</td>
</tr>
<tr>
<td>Cephalosporin (second generation)</td>
<td>CE2</td>
</tr>
<tr>
<td>Cephalosporin (third generation)</td>
<td>CE3</td>
</tr>
<tr>
<td>Fluoroquinolone</td>
<td>FLQ</td>
</tr>
<tr>
<td>Ceftazidime</td>
<td>CAZ</td>
</tr>
<tr>
<td>Amoxicillin + fluoroquinolone</td>
<td>AMX+FLQ</td>
</tr>
<tr>
<td>Co-amoxiclav + gentamicin</td>
<td>AMC+GEN</td>
</tr>
<tr>
<td>Co-amoxiclav + fluoroquinolone</td>
<td>AMC+FLQ</td>
</tr>
<tr>
<td>Cephalosporin (second generation) + gentamicin</td>
<td>CE2+GEN</td>
</tr>
<tr>
<td>Cephalosporin (third generation) + gentamicin</td>
<td>CE3+GEN</td>
</tr>
<tr>
<td>Cephalosporin (second generation) + fluoroquinolone</td>
<td>CE2+FLQ</td>
</tr>
<tr>
<td>Cephalosporin (third generation) + fluoroquinolone</td>
<td>CE3+FLQ</td>
</tr>
<tr>
<td>Co-trimoxazole</td>
<td>SXT</td>
</tr>
<tr>
<td>Trimethoprim</td>
<td>TMP</td>
</tr>
<tr>
<td>Nitrofurantoin</td>
<td>NIT</td>
</tr>
<tr>
<td>Cephalosporin (first generation)</td>
<td>CE1</td>
</tr>
<tr>
<td>Cephalosporin (first generation) + fluoroquinolone</td>
<td>CE1+FLQ</td>
</tr>
</tbody>
</table>
frequency of prescription of antibiotic regimen \( j \) among patients in diagnostic group \( D \) that were prescribed a \( C \)-compliant therapy ([i.e. such that compliance was \( C \): either Y (SWAB compliant) or N (non-SWAB compliant)]), and \( R_{ij} \) is the prevalence of resistance to antibiotic regimen \( j \) among bacterial species \( i \). Next we obtained the integrated DRI as the weighted average of all probiotic-based DRIs. The weight associated with each bacterial species is equal to its aetiological fraction, i.e. the relative frequency of cases associated with that microorganism. In mathematical form:

\[
\text{DRI}(D, C) = \sum_{i=1}^{a} e_i(D) \text{DRI}(D, C).
\]

where the sum is over all species and \( e_i(D) \) is the relative frequency of cases in diagnostic group \( D \) caused by bacterial species \( i \) (i.e. the aetiological fraction).

The DRI can be interpreted as an overall measure of resistance or, similarly, as a measure of treatment failure rate. It is easy to see that DRI = 1 if there is complete resistance to all antibiotic regimens. Conversely, DRI = 0 if there is no resistance. As our interest lies in treatment appropriateness, we define and use throughout a DEI:

\[
\text{DEI}(D, C) = 1 - \text{DRI}(D, C).
\]

Prevalence of resistance, relative frequencies of prescription and aetiological fractions were all obtained from the UTI dataset.\(^{14}\) Resistance of bacterial species \( i \) to antibiotic regimen \( j \) \( (R_{ij}) \) was estimated as the fraction of isolates belonging to species \( i \) that were characterized as resistant to antibiotic regimen \( j \). Note that if bacterial species \( i \) was intrinsically resistant to antibiotic regimen \( k \), then \( R_{ik} = 1 \). Relative frequency of prescription \( P_{ij}(D, C) \) was estimated as the fraction of empirically treated patients prescribed antibiotic regimen \( j \) among patients in diagnostic group \( D \) and compliance \( C \). The aetiological fraction \( e_i(D) \) was estimated as the fraction of patients in diagnostic group \( D \) from whom an isolate belonging to bacterial species \( i \) was cultured. The aetiological fractions are properly defined only when infection is associated with a single bacterial species. Consequently, only patients with monobacterial cultures were considered in the \( e_i(D) \) calculation.

Antibiotic consumption surveillance systems aggregate data associated with empirical and adjusted therapy. To study the impact of using prescription data arising from adjusted therapy when assessing empirical treatment appropriateness, we repeated the calculation of the DEI and ATC by employing relative frequencies of prescription \( (P_j) \) obtained from all patients in the UTI dataset, irrespective of their being prescribed empirical or adjusted therapy. See Supplementary text (available as Supplementary data at JAC Online) for further details.

We include in Figure S1 a diagram further explaining the different datasets used in each of the above mentioned calculations.

**ATC calculation**

For patients in diagnostic group \( D \) who were prescribed a \( C \)-compliant therapy, we define \( \text{ATC}(D, C) \) as the fraction of patients for whom treatment provided adequate coverage, i.e. such that the cultured bacterial isolate was fully susceptible to the initially prescribed antibiotic regimen. In mathematical form:

\[
\text{ATC}(D, C) = \frac{1}{N(D, C)} \sum_{i=1}^{a} T_{ij}(D, C),
\]

where the sum is over all antibiotic regimens, \( N(D, C) \) is the total number of patients in diagnostic group \( D \) who were empirically prescribed \( C \)-compliant therapy and \( T_{ij}(D, C) \) is the number of patients in diagnostic group \( D \) prescribed \( C \)-compliant therapy who were empirically treated with antibiotic regimen \( i \) and from whom a bacterial isolate susceptible to \( i \) was collected. To consistently compare treatment coverage with results obtained in the index-based approach, we only considered patients with monobacterial cultures in this calculation.

We include in Figure S1 a diagram further explaining the different datasets used in each of the above mentioned calculations.

**Antibiotic resistance surveillance data**

To illustrate the flexibility of the index-based approach, we also calculated the DEI by estimating prevalence of resistance \( (R_{ij}) \) from Dutch resistance surveillance data published in NethMap 2010–2013.\(^{9}\) To match as closely as possible the patient population covered by the UTI study,\(^{14}\) we employed data from two different surveillance systems: data obtained in hospital urology departments as part of the Surveillance of Intramural Resistance in The Netherlands (SIRIN) programme and data obtained in unsolicited hospital departments as part of the Infectious Disease Surveillance Information System for Antibiotic Resistance (ISIS-AR).\(^{15}\)

In the NethMap reports, comprehensive data on prevalence of resistance are only available for four bacterial species relevant in UTI: *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus mirabilis* and *Pseudomonas aeruginosa*. In the UTI study these species were responsible for 89% of cases in diagnostic group 1, and 77% of cases in diagnostic group 2. We employed data covering two different timepoints: year 2008 (to match the UTI study) and year 2011 (the most up-to-date SIRIN data). To calculate the DEI we used the aetiological fractions (renormalized to the four relevant bacterial species) and relative prescription fractions already obtained from the UTI dataset (which covers the period 2007–08). We note that the use of prescribing data exclusively from the initial timepoint to assess trends in appropriateness corresponds to the calculation of a fixed DRI (see Lokmaninraray and Klugman\(^{14}\)). Further details on data extraction from the NethMap report are presented in the Supplementary text and Tables S5 and S6.

**Results**

Figures 1–3 show estimates for the aggregated metrics needed to calculate the DEI, which were obtained using the UTI dataset. Aetiological fractions associated with each diagnostic group are presented in Figure 1. As expected, diagnostic group 2 (complicated UTI associated with catheter in place for \( \geq 10 \) days) was associated with a wider range of bacterial species: whereas 80% of diagnostic group 1 cases were associated with the two most frequently isolated bacteria (*Escherichia coli* and *Klebsiella spp.*), these species were responsible for only 66% of diagnostic group 2 cases. Moreover, diagnostic group 2 was also associated with a significantly larger fraction of polymicrobial infections \( [27\% (95\% \text{ CI 21\%–34\%} \text{ versus } 9\% (95\% \text{ CI 7\%–11\%}) \text{ in diagnostic group 1} \text{]}.\)

Figure 2 shows the prevalence of resistance to the 20 antibiotic regimens (estimated as the fraction of resistant isolates) among each of the nine indicator species included in the dataset. Relative frequencies of prescription of each antibiotic regimen are presented for all possible diagnostic group/SWAB-compliance combinations in Figure 3. Each panel in this figure corresponds to a cross-sectional description of the prevalent empirical prescribing practices among patients in the specified diagnostic class/SWAB-compliance group. We note that, to assess population-level treatment appropriateness, 180 pathogen–drug combinations needed to be taken into account.

Values of the DEI and ATC for each of the four scenarios determined by all the possible diagnostic group/SWAB-compliance combinations are shown in Table 2. These estimates of treatment effectiveness agree within 1%–2% for non-SWAB-compliant
prescribing and within 3%–5% for SWAB-compliant empirical therapy. The discrepancy between the DEI and ATC increased to 12% when relative frequencies of prescription were obtained from the UTI dataset by including patients who were prescribed adjusted therapy (see Supplementary text and Table S1).

Having confirmed the agreement between DEI- and ATC-based estimates of empirical treatment effectiveness, we now focus on the calculation of the DEI using resistance surveillance data. Results obtained with SIRIN data covering the years 2008 and 2011 are shown in Table 3. These results suggest that the effectiveness of both guideline-compliant and non-compliant treatments declined by 2%–4% during this 3 year period, assuming prescription practices had remained unchanged since 2008. The same analysis, but using an alternative method to manage missing multidrug resistance data, yielded similar results (see Supplementary text and Table S2). Additional DEI estimates based on ISIS-AR data suggest a decline in guideline effectiveness of 1%–2% (see Tables S3 and S4). The difference between these results reflects the different prevalence of resistance among uropathogens associated with the populations covered by the SIRIN and ISIS-AR surveillance schemes. We also note that, despite employing less comprehensive antimicrobial resistance data, which only cover four bacterial species, the values for the 2008 DEI inferred from SIRIN and ISIS-AR data agree within 1%–8% with the results obtained with the UTI dataset (Table 2).

**Discussion**

Throughout this work our focus has been firstly on quantifying the agreement between the DEI and ATC. Our second aim has been to assess the feasibility of calculating the DEI from routinely available surveillance data.

In our case study, the DEI agrees within 5% with ATC estimates of population-level empirical treatment appropriateness. This level of agreement reflects the fact that ATC and the DEI are two different estimates of the same probability, namely the likelihood that patients receive appropriate antibiotic therapy when treated empirically. Whereas ATC is a relative frequency estimate of this probability, the DEI is obtained by combining three different probabilities: the probability of infection being caused by a certain species, the probability of this microorganism being susceptible to an available antibiotic and the probability of the patient being prescribed a particular antibiotic regimen.

We have shown that it is possible to evaluate population-level appropriateness by employing the index-based formalism together with antibiotic resistance surveillance data. This has allowed us to estimate the decline in UTI treatment effectiveness in the Netherlands between 2008 and 2011. Because we used prescribing data for the 2007–08, these estimates are conditional on prescribing practices having remained unchanged since 2008 (fixed index). In other words, these results are an objective measure of antibiotic effectiveness decline as they do not include the potential effect of the treating physician’s adaptive prescribing practices motivated by the increase in antibiotic resistance. We expect that calculating the DEI with 2011 prescribing data (i.e. the adaptive index) would, as a result of adaptive prescribing, yield higher values than those reported in Table 3. We stress that the index-based formalism particularly lends itself to this type of counterfactual analysis as well as to similar extrapolations of results to other theoretical scenarios.
Although the index-based formalism is a promising alternative to current approaches to the estimation of treatment appropriateness, there are some difficulties that should be noted, namely obtaining antibiotic prescription patterns from consumption data, assessing DEI CIs and the impact of polymicrobial infections.

Whereas surveillance systems for antibiotic usage generally report data in terms of DDDs, the DEI calculation requires relative numbers of patients prescribed each antibiotic regimen. Conversion between these two quantities remains an important challenge. Although the index-based approach is ideal for assessing the effectiveness of empirical treatment, antibiotic usage data collection systems do not discriminate between therapy initiated before (empirical) or after laboratory confirmation of \textit{in vitro} susceptibility (adjusted). Even in case-by-case ATC studies, assessing this distinction retrospectively is an extremely time-consuming and error-prone task. We have evaluated the impact of including patients that were prescribed adjusted therapy in the DEI and ATC analysis, and found that a bias is introduced in both calculations (see Supplementary text). This bias depends on how the treating physicians modify their prescribing after obtaining the antibiotic susceptibility test results. In our case, ATC increases due to the prescription of more adequate treatment based on susceptibility testing. Conversely, DEI decreases due to a shift towards the prescription of antibiotic regimens against which there are higher levels of resistance. This conservative approach to prescribing skews prescription patterns employed in the DEI calculation such that, in the weighted average of resistance (Equation 1), higher weights are given to antibiotic regimens associated with higher levels of resistance. This results in a decrease in the observed DEI (or, similarly, an increase in the DRI). The overall effect is an increase in the relative difference between the two metrics. In resource-limited settings, where aetiological investigations are rarely performed and empirical prescribing is the norm, we expect the size of this bias to be extremely low.

To obtain more detailed antibiotic prescribing data, as well as the required aetiological fractions, comprehensive laboratory and pharmacy databases in large tertiary hospitals could be used.
Table 2. Integrated DEI and ATC associated with all diagnostic group/SWAB guideline compliance combinations

<table>
<thead>
<tr>
<th>Diagnostic group</th>
<th>SWAB compliance</th>
<th>DEI</th>
<th>ATC</th>
<th>Difference (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>N</td>
<td>0.873 (0.791 – 0.906)</td>
<td>0.891 (0.827 – 0.938)</td>
<td>−2.02</td>
</tr>
<tr>
<td>2</td>
<td>N</td>
<td>0.791 (0.640 – 0.896)</td>
<td>0.800 (0.687 – 0.886)</td>
<td>−1.12</td>
</tr>
<tr>
<td>1</td>
<td>Y</td>
<td>0.837 (0.753 – 0.879)</td>
<td>0.880 (0.844 – 0.909)</td>
<td>−4.89</td>
</tr>
<tr>
<td>2</td>
<td>Y</td>
<td>0.899 (0.720 – 0.905)</td>
<td>0.875 (0.676 – 0.973)</td>
<td>2.74</td>
</tr>
</tbody>
</table>

The relative difference between DEI and ATC is shown in the rightmost column. Diagnostic group 1 corresponds to urosepsis/pyelonephritis/complicated UTI and diagnostic group 2 corresponds to complicated UTI associated with catheter use for >10 days. SWAB compliance is noted as either Y (SWAB-compliant therapy) or N (non-SWAB-compliant therapy). Results were obtained employing exclusively the UTI study dataset. Values in parentheses are 95% CIs (see Supplementary text for a detailed explanation of the CI calculation).
The relative difference between DEI2008 and DEI2011 (i.e. the trend in DEI) is shown in the rightmost column. Diagnostic group 1 corresponds to urosepsis/pyelonephritis/complicated UTI and diagnostic group 2 corresponds to complicated UTI associated with catheter use for >10 days. SWAB compliance is noted as either Y (SWAB-compliant therapy) or N (non-SWAB-compliant therapy). Results were obtained by employing prevalence of resistance data from the SIRIN programme, with the lower estimates for missing multidrug resistance data (see the Supplementary text). Prescription patterns and aetiological fractions were obtained from the UTI study.14

These hospital information systems would also open the possibility of employing the index-based approach as part of antibiotic stewardship programmes in order to monitor, with a single metric, within-hospital prescribing appropriateness. Care should be taken when employing these data to estimate population-level appropriateness of empirical therapy, however, as results would become biased towards the population of hospitalized individuals. Evaluating the uncertainty of DEI calculations is significantly more involved than in the case of direct estimates of treatment coverage. Whereas for ATC this involves calculating the uncertainty associated with a single proportion, for the DEI it involves combining the uncertainties associated with three different relative frequency distributions. This approach can yield larger CIs than in the case of ATC, as observed in our results, which could reduce the statistical significance of the observed trends in appropriateness. Further analysis is required to define an easier-to-obtain representative metric of uncertainty associated with DEI-based estimates of treatment appropriateness.

Due to the complexity of defining aetiological fractions in the presence of polybacterial cultures, we consistently restricted all our calculations to patients for whom a single bacterial species was identified in culture. Comparing ATC-based estimates of treatment effectiveness obtained with and without consideration of polybacterial cultures yields a difference of 4%–11%. Extending the DEI formalism to allow for the inclusion of data from confections by multiple causative pathogens would be a useful addition to the index-based approach.

Supplementary data

Supplementary text, Figure S1 and Tables S1 to S6 are available as Supplementary data at JAC Online (http://jac.oxfordjournals.org/).

Acknowledgements

We thank the two anonymous referees for helpful suggestions. M. C. acknowledges the editors of the NethMap 2013 report, J. Mouton and S. de Greeff, for promptly providing an updated figure on K. pneumoniae multidrug resistance trends.

Funding

This work was supported by The Netherlands Organisation for Health Research and Development (grant number 80-82315-98-09004) and by the United Kingdom Clinical Research Collaboration—Translational Infection Research Initiative supported by the Medical Research Council, with contributions to the Grant from the Biotechnology and Biological Sciences Research Council, the National Institute for Health Research on behalf of the Department of Health, the Chief Scientist Office of the Scottish Government Health Directorates and the Wellcome Trust (grant number G1000803 to M. C. and H. G.).

Supplementary data

None to declare.

References


Table 3. Integrated DEI calculated employing data from the SIRIN programme for years 2008 (DEI2008) and 2011 (DEI2011) associated with all possible diagnostic group/SWAB guideline compliance combinations

<table>
<thead>
<tr>
<th>Diagnostic group</th>
<th>SWAB compliance</th>
<th>DEI2008</th>
<th>DEI2011</th>
<th>Trend (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>N</td>
<td>0.896</td>
<td>0.880</td>
<td>−1.74</td>
</tr>
<tr>
<td>2</td>
<td>N</td>
<td>0.848</td>
<td>0.817</td>
<td>−3.60</td>
</tr>
<tr>
<td>1</td>
<td>Y</td>
<td>0.881</td>
<td>0.846</td>
<td>−3.96</td>
</tr>
<tr>
<td>2</td>
<td>Y</td>
<td>0.942</td>
<td>0.927</td>
<td>−1.63</td>
</tr>
</tbody>
</table>


