Combining forecast probabilities with graphical visualization for improved reporting of antimicrobial susceptibility testing

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Sir,
Antimicrobial susceptibility testing (AST) reports are used by clinicians to guide antibiotic treatment of patients suffering from infectious diseases. AST reports, such as those based on the Kirby–Bauer disc diffusion test, in general do not include raw data, but an interpretation of the data in clinical categories (resistant, intermediate, susceptible), which reflect the likelihood of therapeutic success.[1] This practice is intended to provide clinicians with clear and unambiguous clinical information. However, it entails a major loss of data. In contrast to results from clinical chemistry or haematology, where methodological precision measurements and quantitative results are implemented in the reports, these are absent in AST reports, where a mere classification into clinical categories is performed on the basis of inhibition zone measurements or MIC determinations. As a consequence, AST reports do not allow estimation of the probabilities of miscategorization, especially for measurements close to the clinical breakpoints (CBPs), where the error probability is higher.[2,3]

Since 2014, AST categorization of most drug/species combinations has depended exclusively on MIC and/or inhibition zone measurements.[4] However, AST methods still suffer from a notable methodological variability, which can lead to miscategorization of a clinical isolate. Different miscategorization types are defined on the basis of the therapeutic implications. Erratic classifications of true-susceptible isolates as resistant are considered major errors (MEs), misclassifications of true-resistant isolates as susceptible are referred to as very major errors (vMEs) and false assignments of bacterial isolates to adjacent interpretative categories (S→I, I→S, I→R) are considered minor errors (mEs). The rates of MEs, vMEs and mEs depend on a number of factors: (i) presence and width of an intermediate zone; (ii) position of a population relative to the CBP; and (iii) methodological variation. The latter parameter includes both the methodological imprecision (inoculum size, agar composition, incubation time, disc content, inter- and intra-person variability in the reading) and the biological variation.[5]

Here we report on Antibiotrust, a software that visualizes the antibiogram and the reliability of the categorization. Antibiotrust was developed with the aim of conveying a graphic report displaying AST data from Kirby–Bauer disc diffusion testing. However, this approach can also be used for data based on MIC determination. As shown in Figure 1, Antibiotrust reports display the inhibition zone diameters of antibiotic panels used for the various bacterial groups (e.g. Enterobacteriaceae). The rectangular boxes correspond to the various antibiotics and are partitioned into the interpretative categories [resistant (r) in red, intermediate (i) in yellow and susceptible (s) in green]. Inhibition zone diameter distributions within the susceptible WT population appear in green shades, which become darker with higher prevalences. The distributions are based on local data and are updated each year. This feature is particularly relevant for susceptible clinical isolates, as it visualizes the position of the tested clinical isolate relative to the distribution of the WT population as derived from local epidemiological data. Black boxes and error bars indicate the inhibition zone diameter along with the methodological variation. The latter significantly influences the classification reliability and thereby the rate of MEs and vMEs.[3] The width of the error bars is continuously updated for each combination of antibiotic and species or bacterial group and is given by the 2-fold standard deviation of weekly repeated measurements of inhibition zones of a quality-control strain. The interpretative category is displayed on the left side of the antibiotic box and is accompanied by the reliability of the categorization, which is calculated separately for all antibiotics using a normal model.[2] Intrinsic antibiotic resistances are displayed in blue (e.g. ampicillin for *Klebsiella pneumoniae*). Monochromatic boxes display interpretative categorizations that are deduced from other antibiotics (i.e. ciprofloxacin and levofloxacin from norfloxacin) in agreement with EUCAST-derived in-house expert interpretation rules.[6] Reliabilities are not determined for intrinsic resistances, deduced interpretations and for antibiotic/species combinations classified as intermediate.
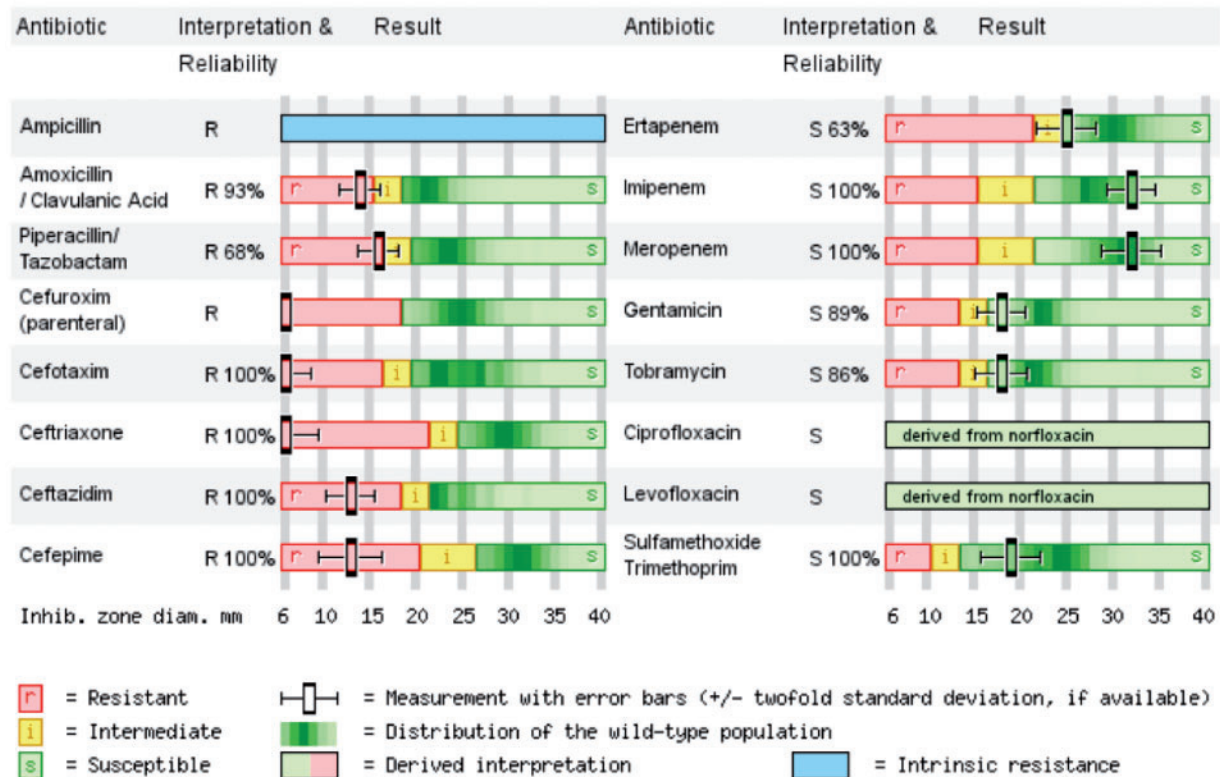
Several studies have shown a good correlation between MIC values and inhibition zone diameters in several bacterial species.[7,8] A prospective integration of MIC values inferred from disc diffusion assays by Antibiotrust may further advance the accuracy of the AST reports and allow a better estimate of the antimicrobial susceptibility patterns.

The additional information provided by Antibiotrust will help in choosing the most appropriate antibiotic, as clinicians will be in the

Patient:
Patient Name
Date of birth / 10753643.5551876

Graphic Report

Klebsiella pneumoniae

r	= Resistant	⊢▭⊣	= Measurement with error bars (+/− twofold standard deviation, if available)				
i	= Intermediate	▬	= Distribution of the wild-type population				
s	= Susceptible	▬	= Derived interpretation	▬	= Intrinsic resistance		

Comments:

Resistance mechanisms predicted: Extended-Spectrum-Beta-Lactamase, type AmpC Beta-Lactamase.
Infection control and prevention measures are recommended.
Further analyses are required for the characterization of the resistance mechanisms.

Figure 1. Antibiogram visualized with Antibiotrust. The graphic report of a Kirby–Bauer antibiotic testing of a *K. pneumoniae* strain isolated from an in-patient at the University Hospital of Zürich is depicted.

position to select the drug with the highest reliability of categorization and thus likelihood of therapeutic success.

In conclusion, we describe an automated visualization software that includes indicators of interpretation reliability in AST reports based on the local epidemiological situation and methodological variation. The integration of reliabilities of misclassifications together with a graphic visualization will allow improved therapeutic decision making based on AST reports.

Transparency declarations

None to declare.

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Prevalence of resistance to antibiotics in children's urinary *Escherichia coli* isolates estimated using national surveillance data

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Sir,

Recently, Bryce *et al.*[1] showed in a prospective study that the prevalence of resistance to antibiotics in urinary *Escherichia coli* isolates obtained from children <5 years of age was high. For example, the prevalences of resistance to amoxicillin and trimethoprim, two antibiotics recommended for the treatment of lower urinary tract infection (UTI) in children,[2] were approximately 50% and 28%, respectively (Table 1).[1,3] In contrast, all isolates were susceptible to nitrofurantoin.[1,2] To improve the certainty on the actual prevalence of resistance in England, a larger sample size is needed. In response to the relatively high prevalence of trimethoprim resistance in isolates from adults, guidelines have been revised recently and now recommend nitrofurantoin be used over trimethoprim as a first-line treatment for uncomplicated UTIs in adults.[2,4] However, Bryce *et al.*[1] speculated that the same recommendation has not been made for children due to the absence of resistance data for this age group in the UK. NICE are currently reviewing the antibiotic treatment recommendations for children and adults.[5]

PHE's national laboratory surveillance system, Second Generation Surveillance System (SGSS), captures data supplied electronically by ~98% of hospital microbiology laboratories in England. SGSS records contain results for all antimicrobials tested (including results suppressed from clinical reports) for isolates from all clinical specimen types as well as demographic patient information such as age and gender.[6] A limitation of using urine specimens recorded in SGSS is that samples may be more likely to be tested if a patient has risk factors for antibiotic resistance, potentially leading to overestimation of resistance prevalence. However, among infants and children <3 years of age the prevalence should not be systematically overestimated as national guidance recommends to always send a sample in case of symptoms suggestive of UTI.[2] For children aged ≥3 years, the prevalence might be overestimated to a certain extent as current NICE guidance recommends sending a sample for culture only if the patient is at risk of serious illness and/or has a history of recurrent UTI, if both leucocyte esterase and nitrite are positive.[2]

Here we evaluated whether, when using these national data, the estimated prevalence of resistance to antibiotics in urinary *E. coli* isolates obtained from children <5 years of age was concordant with the results of Bryce *et al.*[1] We restricted our analysis to one financial year (April 2014 to March 2015) (as compared with 2010 to 2013 in Bryce *et al.*[1]) and only included samples received from general practices (as compared with primary care and emergency department presentations in Bryce *et al.*[1]). Repeat specimen reports received from the same patient with matching causative agents were excluded if the specimen dates were within 90 days. We focused on antibiotics recommended for treatment of UTI in children and for which at least 75% of the urinary *E. coli* samples included susceptibility test results: trimethoprim (99%), nitrofurantoin (99%), co-amoxiclav (93%), ciprofloxacin (82%), cefalexin (82%) and amoxicillin (77%). We observed similar prevalences of resistance to Bryce