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A computational model to monitor and predict trends in bacterial resistance

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ABSTRACT

Current concern over the emergence of multidrug-resistant superbugs has renewed interest in approaches that can monitor existing trends in bacterial resistance and make predictions of future trends. Recent advances in bacterial surveillance and the development of online repositories of susceptibility tests across wide geographical areas provide an important new resource, yet there are only limited computational tools for its exploitation. Here we propose a hybrid computational model called BARDmaps for automated analysis of antibacterial susceptibility tests from surveillance records and for performing future predictions. BARDmaps was designed to include a structural computational model that can detect patterns among bacterial resistance changes as well as a behavioural computational model that can use the detected patterns to predict future changes in bacterial resistance. Data from the European Antimicrobial Resistance Surveillance Network (EARS-Net) were used to validate and apply the model. BARDmaps was compared with standard curve-fitting approaches used in epidemiological research. Here we show that BARDmaps can reliably predict future trends in bacterial resistance across Europe. BARDmaps performed better than other curve-fitting approaches for predicting future resistance levels. In addition, BARDmaps was also able to detect abrupt changes in bacterial resistance in response to outbreaks and interventions as well as to compare bacterial behaviour across countries and drugs. In conclusion, BARDmaps is a reliable tool to automatically predict and analyse changes in bacterial resistance across Europe. We anticipate that BARDmaps will become an invaluable tool both for clinical providers and governmental agencies to help combat the threat posed by antibiotic-resistant bacteria.

1. Introduction

After decades of success in limiting the burden of bacterial infections, antimicrobial therapy is now facing an alarming lowering of efficacy owing to the ongoing increase in bacterial resistance to conventional and last-resort therapies [1,2]. This is amply illustrated by the emergence of so-called 'superbugs' that exhibit multidrug resistance and herald a new era in which bacterial infections will become increasingly untreatable [3–5].

The increased threat of antimicrobial resistance, coupled with reduced pharmaceutical interest in developing new antimicrobial agents, has driven healthcare authorities globally to develop resistance surveillance programmes [2,3,6–8]. Recently, the European Centre for Disease Prevention and Control (ECDC) launched a platform for collecting and reporting data on antimicrobial resistance annually across Europe [9,10]. The effort, co-ordinated through the European Antimicrobial Resistance Surveillance Network (EARS-Net), has amassed a large body of data on antimicrobial resistance patterns in countries across Europe [11]. The wealth of antimicrobial resistance data spanning more than a decade provides a unique opportunity to develop new computational tools and techniques that can model bacterial resistance trends.

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Traditionally, data in surveillance reports and databases are mainly analysed using epidemiological maps, manual standard curves and comparison of percentages [12–14], with limited exploitation of computational algorithms in automated handling of big data sets and performing secondary analyses. Here we present 'Bacterial and Antimicrobial Resistance Distribution maps (BARDmaps)' as a new tool for the analysis and prediction of bacterial resistance at the phenotypic level using data from surveillance databases, graph theory and machine-learning algorithms. Compared with manual analysis of resistance trends and the use of standard regression analyses to predict future resistance, BARDmaps employs a novel hybrid model to automate the analysis of massive data sets. Using data from the EARS-Net database, we demonstrate how BARDmaps can detect changes in response to bacterial disease outbreaks and interventions in a given country, and predict future resistance trends including identifying which countries will be nearly free of resistant superbugs. The proposed model is, to the best of our knowledge, the first epidemiological tool to perform such tasks and we anticipate that it will become a valuable asset for healthcare policy-makers.

2. Methods

2.1. Data description and collection

Data on European antimicrobial resistance surveillance were obtained from EARS-Net (http://www.ecdc.europa.eu/) [11,15]. These data were collected through The European Surveillance System (TESSy) as previously described [16]. In brief, EARS-Net reports antimicrobial susceptibility tests (ASTs) of invasive isolates obtained from blood or cerebrospinal fluid of patients from over 1400 hospitals in 30 European countries between 1999 and 2012 [16]. AST data are collected from laboratories through a national manager and, after filtering through TESSy to remove any duplicates, data are reported as the number of susceptible, intermediate-resistant and resistant isolates based on Clinical and Laboratory Standards Institute (CSLI) breakpoints. The exception to this is that EARS-Net requires PCR confirmation of meticillin resistance genes for an isolate to be considered meticillin-resistant *Staphylococcus aureus* (MRSA) (see Supplementary Table S1). Collected information includes AST results of seven bacterial species that are considered indicators for the development of antimicrobial resistance in Europe, including *Streptococcus pneumoniae*, *S. aureus*, *Escherichia coli*, *Enterococcus faecalis*, *Enterococcus faecium*, *Klebsiella pneumoniae* and *Pseudomonas aeruginosa*. Each is tested for resistance against 29 antimicrobials from 14 different classes, as shown in Supplementary Table S1. Results are reported as the proportion of isolates resistant to a given class of antibiotic.

2.2. Data processing and selection

For this analysis, data from EARS-Net were extracted in the form of records of bacterial species, antimicrobial agent tested, country of origin, number of isolates reported, and percentage of isolates that are either susceptible, intermediate-resistant or resistant. Data were then filtered as illustrated in Fig. 1. Records of a specific antimicrobial/organism combination per country were included only if (i) at least four years of ASTs were available and (ii) they had an average of more than 20 isolates reported annually (criteria set by ECDC) to provide enough input to the model and to exclude selection bias. For validation, a minimum of 5 years was required for a 1-year prediction and 6 years for a 2-year prediction. No country from EARS-Net was totally excluded from the analysis. Supplementary Table S2 shows the distribution of collected data among countries and bacteria/antimicrobial combinations.

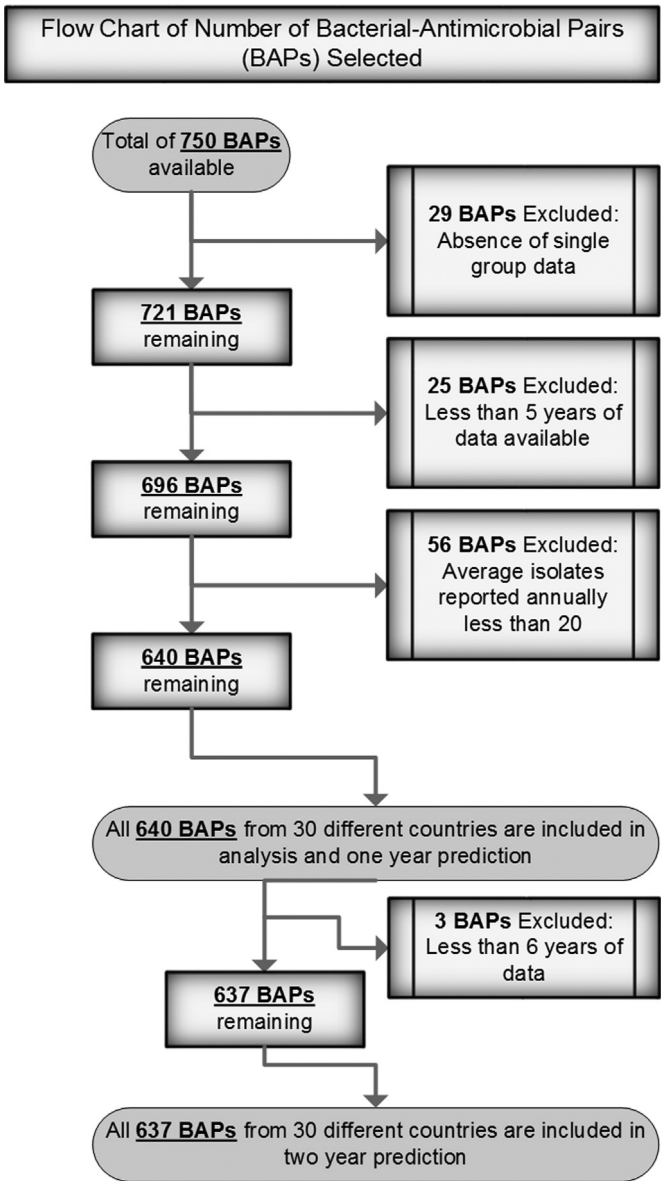

Fig. 1. Flow chart showing exclusion criteria and the total number of isolates included in the analysis. For a certain bacterial/antimicrobial/country combination to be included in the analysis, a minimum of 5 years of data was required (6 years in the case of 2-year predictions), based on the minimum requirements for running the prediction. In addition, an annual average of more than 20 isolates per year, based on European Antimicrobial Resistance Surveillance Network (EARS-Net) criteria, was needed to reduce selection bias. Data on multidrug-resistant *Klebsiella pneumoniae* were excluded since data are not available for single antimicrobial groups.

2.3. Model design and implementation

BARDmaps is a hybrid computational tool that employs both a structural model and a behavioural model. The structural model detects, compares and visualises patterns of resistance change across time, whereas the behavioural model uses patterns revealed by the structural model to predict future resistance. Fig. 2 outlines the overall design of the structural and behavioural models implemented in BARDmaps. In brief, records obtained from the database are assigned to features that define each bacterial isolate (bacterial genus, species, Gram stain, etc.) and antimicrobial drug tested (category and name), as well as the country of origin. A bacteria/antimicrobial pair (BAP) is defined as an equivalence class, comprising a bacteria 'β' with specific features (genus, species, group, etc.) and a specific antimicrobial 'δ' for which β was