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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

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Conflict of interest

The authors declare that they have no conflict of interest.

Ethical approval

Not applicable.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.jgar.2015.04.006.

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.

Keywords

Antimicrobial resistance; Computational modelling; Resistance monitoring

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.

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 (BARD-maps)’ 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, BARD-maps 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 (CLSI) 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.

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 tested. Each (β, δ) pair has a specific value of percentage

resistant isolates per country per year that is used in the subsequent steps of the model. An example of an equivalence class is (*E. coli*, carbapenems), which has specific values of percentage resistant isolates per country per year of *E. coli* tested against carbapenems.

After the assignment of equivalence classes, the structural analysis comprises the generation, visualisation and analysis of bacterial/antimicrobial resistance distribution (BARD) maps. These maps include differences in the percentage of resistant isolates of bacteria β to antimicrobial δ within each BAP (β, δ) that are calculated through automated differential analysis of 1-, 2-, 3-, 4- and 5-year differences for each BAP using a MATLAB script (MATLAB R2013a; MathWorks Inc., Natick, MA). The resistance difference used as an observation symbol for the hidden Markov model (HMM) is computed as the difference between the resistance percentage at the end year and the average resistance percentage across the previous years. The difference is taken against the average and not the first year to account for the dynamics of the resistance change across the previous years. Following the differential analysis, data are plotted as a BARD map, where nodes describe the resistance level at each year and edges describe the difference in resistance between connected years (an example is shown in Supplementary Fig. S1). Generated BARD maps are visualised through a Graphviz v.2.30.1 (<http://www.graphviz.org>) plug-in. Using an Intel Core-i7 processor with 8 GB RAM, an average of less than 5 s of CPU time is required to generate a desired graph for a BAP.

To detect abrupt changes in bacterial resistance for a given BAP, the resistance change within a given year was compared with a moving average of resistance changes of a random set of two consecutive years for the same BAP. When a change for a given year is more than two standard deviations away from the moving average, an abrupt change (increase or decrease) is reported and visualised as a discolouration of the node representing the corresponding year.

Standard graph theoretical algorithms [17] are employed to detect similarities in bacterial behaviour for different antimicrobials. For each graph structure corresponding to a BAP, topological sorting was used to find a topological signature of the BARD map by computing a sequence of resistance change signature vectors. Each such vector reflects the magnitude and direction of change of resistance between the corresponding 2 years. Distance metrics between the signature vectors of different BAPs were then used to compute similarities between those BAPs, and the final data are reported as a dendrogram (as illustrated in Fig. 3).

In the behavioural model, the same bacteria/antimicrobial resistance difference records were quantified and used as observations to train an HMM [18]. In brief, an HMM assumes that the modelled system is a Markov process with hidden states that produces a sequence of observations. Observations are used to train the system and to derive hidden states that are in turn used to predict progression of the system beyond the given observations. For our analysis, an HMM was trained using the available BARD maps and was used to answer questions of how likely the model will produce an observation ' θ_1 ' from a given state. The output of the HMM prediction for a given BAP in a following year includes scores for different candidate resistance levels. The HMM scores were used (i) to compute a predicted

resistance level for the upcoming year using a weighted average of all HMM scores and (ii) to provide data on the probability of an individual bacterial species exceeding a pre-set threshold of resistance. Using the same Intel Core-i7 system, a total of 30 h of CPU time was required to perform 1-year prediction for the entire data set. In addition, the same behavioural model was used to generate predictions using curve fitting based on linear regression, polynomial, logarithmic or exponential models for comparative purposes.

2.4. Model validation

To validate the behavioural model, the model was trained using observations of percentage resistant isolates, whilst eliminating either the last 1 year or 2 years from the training set of observations. One- and two-year predictions were obtained and compared with the actual reported levels of bacterial resistance for isolates from each country. To compare the model with standard methods, the same predictions were also performed using linear regression and other standard curve-fitting models. Inclusion or exclusion of percentage intermediate-resistant isolates from the model observations did not affect the outcome scores; therefore, data on intermediate-resistant isolates were not included in the model analysis to minimise computational time.

2.5. Statistical analysis

Statistical analysis was performed using GraphPad Prism 6 (GraphPad Software Inc., La Jolla, CA). Paired *t*-tests were used to compare actual and predicted resistance levels with 95% confidence. Parametric Pearson's correlation coefficients and non-parametric Spearman correlation coefficients were used to assess the linear correlation between actual and predicted results.

3. Results and discussion

This paper presents BARDmaps, a new tool to model antimicrobial resistance surveillance data, together with its application to conduct an automated analysis of bacterial resistance trends in Europe using data derived from EARS-Net. Studies on antimicrobial resistance have traditionally focused on evaluating the burden of a specific infectious agent, comparing trends in bacterial resistance using standard curves and comparison of percentages, and studying the occurrence of a specific resistance-encoding gene in bacterial populations (see, e.g., [13,14,19]). By contrast, our approach adopts advanced computational modelling to enable automated analysis of over 4 million isolates across different European countries simultaneously and then to use the data to train the model to detect current trends and predict future trends. Such an approach has not been attempted previously, in part due to the limited availability of large and standardised databases of antimicrobial susceptibility data.

3.1. BARDmaps accurately predicts trends in bacterial resistance

To assess the ability of BARDmaps to predict future resistance, the extracted EARS-Net data were used to train the model without including the data on the final year, followed by comparison of the predicted and actual resistance levels. Results of comparison of actual and predicted percentages of resistant isolates for each of the BAP in each country show that there is no significant difference between actual and predicted resistance levels for the test

year (paired t -test, $P = 0.13$; $n = 640$ BAPs). Correlation analysis of actual and predicted resistance levels using parametric statistics showed a significant linear correlation with a slope of 0.95 (Pearson's coefficient, $R = 0.96$) (Fig. 4). A similar correlation was also observed when non-parametric measures were used (non-parametric Spearman coefficient, $R = 0.96$). We further assessed the ability of the model to predict 2 years in advance using a similar strategy. A correlation analysis of actual and predicted values for 2-year prediction also showed a significant linear correlation with a slope of 0.99 (Pearson's coefficient, $R = 0.97$; Spearman coefficient, $R = 0.94$) (Fig. 4). The analysis showed that a sequence of 4 years of data was the minimum needed to yield the three observations needed for 1-year prediction through the behavioural model. To further support the validity of our measures, a one-sample t -test was also performed comparing the difference between BARDmaps prediction and actual resistance to zero difference to check whether there is a significant difference between BARDmaps prediction and identical prediction. As shown in Fig. 5, there is no significant difference between BARDmaps predictions and identical predictions ($P = 0.1$) for 1-year and 2-year predictions, as well as across three ranges of resistances (0–30%, 30–60% and 60–100%). This further confirms the reliability of predictions performed through BARDmaps.

3.2. Comparison with linear regression-based prediction

To compare predictions made by BARDmaps with those derived from standard curve-fitting approaches, 1- and 2-year predictions were performed using linear regression, polynomial, logarithmic and exponential curve-fitting for the same BAPs used in the BARDmaps prediction. Linear regression-based fitting was found to be superior to all other curve-fitting approaches for 1- and 2-year predictions (data not shown) and is used hereafter for comparison with BARDmaps. Since standard linear regression returned negative values for BAPs fluctuating around zero, a boundary limit of zero was set to avoid negative values. Results of comparison between BARDmaps and linear regression are summarised in Table 1. For a 1-year prediction, BARDmaps and linear regression appear to have similar predictive capability, with linear regression performing slightly better. However, linear regression prediction returned the lower boundary (0%) for BAPs whose resistance percentage is highly fluctuating around zero, whereas BARDmaps had significantly better success for these predictions. For an interval of 2 years, BARDmaps was significantly superior to linear regression, both using parametric and non-parametric correlation measures (Table 1). Prediction reliabilities were further assessed by comparing correlation coefficients of each of the 25 BAPs between 1- and 2-year predictions using BARDmaps or linear regression. There was no significant difference in prediction reliability (measured through the Pearson's correlation coefficient) between 1- and 2-year predictions using BARDmaps (paired t -test = 0.43; $n = 25$ BAPs). Predictions via linear regression, however, showed a significant decrease in reliability for 2-year predictions compared with 1-year (paired t -test <0.0001; $n = 25$ BAPs). These results show that although BARDmaps may not be superior to current approaches for 1-year predictions, it performs significantly better for 2-year predictions, a period that is more relevant for policy-makers and healthcare authorities.

3.3. Prediction reliability across multiple bacteria/antimicrobial pairs

A pertinent question to ask is whether certain bacterial pathogens exhibit resistance trends that are more difficult to predict than others. Fig. 6A shows the Pearson's correlation coefficients of 1- and 2-year predictions compared with actual values. A box-and-whisker plot of the correlation coefficients for the 2 years revealed a median correlation of 0.84 for a 1-year prediction and 0.83 for a 2-year prediction using BARDmaps (Fig. 6B). Three BAPs appeared as outliers with low prediction correlation: *E. coli* and carbapenems; *S. aureus* and rifampicin; and *E. faecalis* and vancomycin. The low prediction reliability for these BAPs is due to fluctuations in resistance levels and the type of statistical assessment used for prediction reliability. For instance, resistance values for *E. coli* and carbapenems fluctuate for the previous year between 0% and 8% and have a very low correlation coefficient for prediction using BARDmaps. However, the absolute average difference between predicted and actual resistance is only 0.4%, which indicates that the prediction is still more reliable than inferred from the correlation coefficient only (1-year $R = 0.2$; 2-year $R = 0.1$). The same was also true for another outlier, *E. faecalis* and vancomycin. Hence, correlation measures may not be the optimal assessments for BAPs with resistance <5%, and in these cases absolute differences may be a better indicator. An exception to this is the *S. aureus* and rifampicin outlier, whose low predictability is due to a high variability in resistance progression and an inability of the model to detect trending patterns. The exact reason behind this is unknown; however, a potential reason could be the relatively low number of overall isolates reported for this specific BAP. Notably, the BAPs with low prediction reliability had comparable correlation coefficients for BARDmaps and linear regression, but BARDmaps had a lower absolute difference in prediction. In addition, we have tested the potential of BARDmaps to predict resistance at individual country level and found that prediction reliability measured by Pearson's correlation coefficient was still high (>0.9) in the vast majority of tested countries (Supplementary Fig. S2). Exceptions include Malta and Estonia that had good prediction (Pearson's correlation coefficient between 0.70 and 0.85); however, BAPs from these countries have low sample numbers (average = 60–70 total isolate/BAP) and relatively lower number of years covered. These factors may have contributed to a lower prediction reliability for these countries.

3.4. BARDmaps allows for automated evaluation of past trends in bacterial resistance

Structural modelling implemented in BARDmaps allows for visualisation of the bacterial resistance progression against each antimicrobial in the form of a network of nodes showing the change in resistance between every 2 years (Fig. 7). Through this visualisation, the model automatically highlights abrupt changes in resistance patterns, i.e. increases and decreases in the percentage of resistant strains that may reveal outbreaks and interventions, respectively, and allow for a rapid epidemiological assessment of resistance trends. For instance, trends shown in Fig. 7 identify outbreaks that occurred in three different European countries. All of these outbreaks have been noted in the literature [20–24]. Two outbreaks of vancomycin-resistant *E. faecium* occurred in Germany in the years 2004–2007 that were associated with the spread of *vanA* gene clusters among different strain types of *E. faecium* (Fig. 7A) [20,21]. Similarly, an outbreak of penicillin-resistant *S. pneumoniae* in Spain in 2011 was rapidly contained in 2012 owing to the introduction of the 7-valent pneumococcal

conjugate vaccine (Fig. 7B) [22]. Finally, the significant reduction in the prevalence of MRSA in the UK in 2011 clearly matches the efforts in this country to improve surveillance and to combat MRSA bacteraemia (Fig. 7C) [23,24]. These examples illustrate how the BARDmaps approach can highlight abrupt changes in bacterial resistance trends, enabling focused and detailed investigation by health authorities.

3.5. BARDmaps detects similarities in bacterial resistance patterns

In addition to prediction of future trends in bacterial resistance by applying network analysis on our structural model, a novel aspect of our approach is its ability to detect similarity in evolution of resistance for certain bacteria across different antimicrobials. This provides insight into parallel trends that would be valuable to epidemiologists and infectious diseases specialists. The dendro-gram in Fig. 8 illustrates the results of topological graph comparison of the resistance trends for the different BAPs, showing pairs with high or low similarity in trending patterns. High similarity in topological patterns of different BAPs may reveal shared resistance mechanisms or a common environmental selection pressure driving the observed pattern of resistance changes. Many of the findings in Fig. 8 match our current understanding of respective resistance mechanisms. For instance, there is close agreement between the resistance of *E. coli* to aminoglycosides and extended-spectrum cephalosporins. Consistent with this, plasmids encoding extended spectrum β -lactamases usually also carry genes conferring aminoglycoside resistance [25,26]. Similarly, there is a strong similarity in the progression of aminopenicillin and vancomycin resistance in *E. faecium* isolates, which agrees with common finding that vancomycin-resistant enterococci are also resistant to aminopenicillins [27]. Interestingly, there appears to be a strong likelihood in the progression of carbapenem resistance in *E. coli* and vancomycin resistance in *E. faecium* (Fig. 8). Although these are two different BAPs, the similarity between them may be because carbapenems and vancomycin are both considered last-resort drugs for treatment of *E. coli* and *E. faecium*, respectively [19,28]. This finding provides quantitative evidence for the hypothesis that increased exposure to last-resort antimicrobial therapies is a major driving force for the progression of resistance against those therapies (see [29]) and therefore requires stricter countermeasures.

3.6. Prediction of upcoming trends in Europe

In order to predict trends for 2014, we took all available data up to and including 2012 and used it to train the model to generate a 2-year prediction for four representative BAPs. The species in these pairs are MRSA, carbapenem-resistant *E. coli*, vancomycin-resistant *E. faecalis* and piperacillin/tazobactam-resistant *P. aeruginosa*. Fig. 9 shows maps of predicted resistance percentage for the chosen isolates in Europe for 2014. This shows large variability in susceptibility to pathogens across different European countries. For instance, we predict that some countries will continue to be free from carbapenem-resistant *E. coli* (e.g. The Netherlands, Norway and Poland), but others (e.g. Bulgaria, Greece and Italy) can expect to observe carbapenem resistance in >50% of reported *E. coli* isolates. Variability was also noted within the same country for different pathogens. Poland, for example, is predicted to be free of carbapenem-resistant *E. coli* but is at high risk both of MRSA and piperacillin/tazobactam-resistant *P. aeruginosa* (Fig. 9). Such variability is likely due to differences in the practices of healthcare systems in different countries. For instance, The Netherlands

adopts a strategy to isolate patients at risk or known to be infected with MRSA to reduce the burden of this infection [30].

3.7. Graphical user interface (GUI) implementation of BARDmaps

By revealing patterns of current and future trends in antimicrobial resistance, BARDmaps can provide the information necessary to conjoin surveillance with antibiotic stewardship strategies by healthcare authorities. To enable this, we have implemented BARDmaps in a user-friendly GUI to perform trend analysis and prediction, as well as containing other features such as determining probabilities for a certain bacterial species to exceed a user-set threshold of percentage resistant isolates in the near future. Using the GUI available in the supplementary code, clinicians from a given country can choose a certain bacteria/antimicrobial combination and check for the predicted probability that the percentage resistant isolates for the given combination may exceed a threshold they assign. To illustrate, users can use the GUI to predict the probability that >10% of *E. coli* isolates will be resistant to carbapenems in a certain country. Such predictions can be used to inform treatment decisions as well as to prioritise antibiotic stewardship policies towards upcoming threats.

4. Conclusions

We have developed a new, automated approach to analyse bacterial resistance trends and applied it to data from European surveillance databases. It enables better tracking of resistance trends as well as accurate prediction of future trends that will be of tremendous value to healthcare authorities who seek to address outbreaks of resistance as swiftly as possible. One potential limitation of this model is that it does not take into account data on antimicrobial use, population migration or healthcare system practices that may influence the progression of antimicrobial resistance. Using only bacterial resistance levels as an input provides both advantages and limitations. One advantage is the lack of availability of standardised data on antimicrobial use and population metrics; therefore, limiting the model to one data source may allow expansion of the application to settings where antimicrobial use data are not available. Moreover, using only bacterial resistance percentage as input to the model helps focus the aim of the model to predict changes in bacterial resistance regardless of the underlying cause that can be subsequently inferred by comparing data from different sources. However, the disadvantage of this approach is that it is possible that adding more variables (such as antimicrobial use) in the model will help improve the quality of prediction. Therefore, future work will aim at collecting data on antimicrobial use in Europe from different resources and incorporating the data into a new model to be compared with BARDmaps for prediction quality. In addition, another follow-up goal is to extend the implementation of this model to include surveillance data from other regions.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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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.

Fig. 2.

An overview schematic of the model design. The colour coding is as follows: blue for user input; pink for output of the method; and white for intermediary output and processes. First, equivalence filters use the bacteria resistance records from pre-processed data with optional bacteria and antimicrobial features, and produce equivalence classes [bacteria/antimicrobial pairs (BAPs)] based on the features. Then, differential analysis takes (i) the equivalence classes and (ii) a scope parameter that designates the number of periods of time that should be covered by the differential analysis for each BAP. Differential analysis will produce a set of bacterial/antimicrobial resistance distribution tuples (BARDs) that are used through structural analysis to produce the resistance difference maps. Graph analysis takes those maps with a similarity threshold and detects similar behaviours across BAPs. Meanwhile, the differences between BARDs are quantified to the nearest 2% difference interval, producing two sets: (i) a set of observations of interval differences; and (ii) a set of sequences of observations that form a training base for the hidden Markov model (HMM). Both sets are fed to the HMM training process to produce the HMM. The sequence generation process takes a short-term resistance difference query from the user, adds it as a suffix to existing sequences, and generates prediction evaluation sequences used for future predication. The prediction evaluation sequences can also be fed with a threshold to the HMM evaluation process to produce bacteria/antimicrobial short-term therapeutic value predictions. (For interpretation of reference to colour in this figure legend, the reader is referred to the web version of this article.)

Fig. 3.

Distance between resistance change signature vectors of two bacteria/antimicrobial pairs (BAPs) compared with *Escherichia coli* & carbapenems. (A) Shows the close similarity between *Enterococcus faecalis* & vancomycin and *E. coli* & carbapenems compared with *Pseudomonas aeruginosa* & fluoroquinolones. For each BAP, the resistance change signature vectors represent the changes in resistance between years ordered according to their topological sequence. At each point of topological order, the distance between the signature vectors of the two pairs relative to *E. coli* & carbapenems is shown. The horizontal axis represents the signature vectors of *E. coli* & carbapenems. The bars represent the distance relative to *E. coli* & carbapenems of signature vectors of *E. faecalis* & vancomycin (black) or *P. aeruginosa* & fluoroquinolones (grey). (B) Dendrogram representing the results of (A) on a relative similarity scale.

Fig. 4.

Correlation between actual resistance and predicted resistance for the test years using BARDmaps and linear regression predictions. Each dot designates a bacteria/antimicrobial pair (BAP) in a specific country. Solid line = identity line. R shown on the graph is the Pearson's coefficient. (A) Correlation between actual resistance and resistance predicted by BARDmaps for 1-year (left panel) and 2-year predictions (right panel). Prediction for 1 future year: slope = 0.93; significant correlation ($P < 0.0001$); Pearson's coefficient, $R = 0.96$; $N = 644$. Prediction for 2 future years: slope = 0.99; significant correlation ($P < 0.0001$); Pearson's coefficient, $R = 0.97$. (B) The correlation graphs for predictions based on linear regression for 1 year (Pearson's coefficient, $R = 0.98$; $N = 644$) and 2 years (Pearson's coefficient, $R = 0.88$; $N = 644$). (C) Expansion of the region between 0% and 50% resistance for the graphs of panel (A) showing that high correlation also exist between BARDmaps predictions and actual resistances for BAPs at the lower end of resistance levels ($R = 0.90$ for 1-year prediction and $R = 0.91$ for 2-year prediction). A detailed comparison between BARDmaps and linear regression predictions is shown in Table 1.

Fig. 5.

Comparison of the difference between BARDmaps predictions and actual resistance to that of identical prediction where difference is zero. One-sample *t*-test was used to compare the difference between BARDmaps prediction and actual resistance to zero showing that there is no significant difference between BARDmaps predictions and identical prediction. Comparison was performed for 1- and 2-year predictions as well as for subsets of resistance ranges (0–30%, 30–60% and 60–100%). Markers represent mean $\pm$ S.D. #*P* < 0.1.

Fig. 6.

Difference in prediction reliability across the different bacteria/antimicrobial pairs (BAPs).

(A) Pearson's correlation coefficients for prediction reliability of BARDmaps across the different BAPs. CBP, carbapenems; FQ, fluoroquinolones; MRSA, methicillin-resistant *Staphylococcus aureus*; VNC, vancomycin; AG, aminoglycosides; 3GC, third-generation cephalosporins; AMP, aminopenicillins; MAC, macrolides; PEN, penicillin; GEN, gentamicin; AK, amikacin; CFT, ceftriaxone; PPT, piperacillin/tazobactam; RF, rifampicin.

(B) Box-and-whiskers plot to detect outlier BAPs in prediction reliability. Three outliers were present in the 2-year prediction identified to be *Escherichia coli* and carbapenems, *S. aureus* and rifampicin, and *Enterococcus faecalis* and vancomycin. These outliers had a relatively low prediction reliability compared with the remaining BAPs and they exhibited a prominent change in prediction reliability between 1- and 2-year predictions. (C) The distribution of different BAPs across categories of correlation coefficients. Only four BAPs in 1-year predictions and five BAPs in 2-year predictions had a Pearson's correlation coefficient <0.6.

Fig. 7.

Snapshots of output graphs with automated detection of abrupt changes. (A) Trends in vancomycin-resistant *Enterococcus faecium* occurring in Germany between the years 2004 and 2008. (B) Trends in penicillin-resistant *Streptococcus pneumoniae* occurring in Spain between 2010 and 2012. (C) Trends in methicillin-resistant *Staphylococcus aureus* (MRSA) occurring in the UK between 2009 and 2011. Green nodes indicate a significant decrease in resistance; red nodes indicate a significant increase in resistance; and white nodes indicate nodes with no significant change in resistance compared with the entire graph. (For interpretation of reference to colour in this figure legend, the reader is referred to the web version of this article.)

Fig. 8.

Dendrogram representing the similarity in progression of resistance across different bacterial/antimicrobial pairs (BAPs). The longer the segment length, the less similar are the pairs. For instance, *Escherichia coli* & carbapenems and *Enterococcus faecium* & vancomycin BAPs are more similar compared with *Pseudomonas aeruginosa* & carbapenems and *E. coli* & carbapenem BAPs. MRSA, methicillin-resistant *Staphylococcus aureus*; 3rd G, third-generation.

Fig. 9.

Epidemiological maps showing the predicted resistance of four bacterial/antimicrobial pairs (BAPs) in Europe for the year 2014: (A) carbapenem-resistant *Escherichia coli*; (B) vancomycin-resistant *Enterococcus faecalis*; (C) methicillin-resistant *Staphylococcus aureus* (MRSA); and (D) piperacillin/tazobactam-resistant *Pseudomonas aeruginosa*. NA, not available (refers to countries whose predictions are not available due to lack of enough training data).

Table 1

Comparison of BARDmaps model prediction with linear regression.

Prediction length	Model	Prediction	
		BARDmaps	Linear regression
1 year	Correlation	0.96	0.98
	Slope	0.95	1.03
	Spearman	0.96	0.98
2 years	Correlation	0.97	0.88
	Slope	0.99	0.97
	Spearman	0.94	0.89