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Opinion

Forecasting antimicrobial resistance evolution

Jens Rolff [1,*] Sebastian Bonhoeffer,[2] Charlotte Kloft,[3] Rasmus Leistner,[4] Roland Regoes,[2] and Michael E. Hochberg [5,6]

Antimicrobial resistance (AMR) is a major global health issue. Current measures for tackling it comprise mainly the prudent use of drugs, the development of new drugs, and rapid diagnostics. Relatively little attention has been given to forecasting the evolution of resistance. Here, we argue that forecasting has the potential to be a great asset in our arsenal of measures to tackle AMR. We argue that, if successfully implemented, forecasting resistance will help to resolve the antibiotic crisis in three ways: it will (i) guide a more sustainable use (and therefore lifespan) of antibiotics and incentivize investment in drug development, (ii) reduce the spread of AMR genes and pathogenic microbes in the environment and between patients, and (iii) allow more efficient treatment of persistent infections, reducing the continued evolution of resistance. We identify two important challenges that need to be addressed for the successful establishment of forecasting: (i) the development of bespoke technology that allows stakeholders to empirically assess the risks of resistance evolving during the process of drug development and therapeutic/preventive use, and (ii) the transformative shift in mindset from the current praxis of mostly addressing the problem of antibiotic resistance *a posteriori* to a concept of *a priori* estimating, and acting on, the risks of resistance.

Highlights

The evolution of antimicrobial resistance (AMR), driven by the misuse of drugs – but also by the rationale with which antimicrobials are currently used – is a global health problem. The main measures against AMR are the prudent use of antimicrobials, rapid diagnostics, and the development of new drugs.

Forecasting the evolution of AMR, we argue, could add to the arsenal of measures to control and reduce the spread of AMR. While many examples of forecasting or prediction are scattered throughout the literature, it is not yet seriously considered for addressing AMR.

Forecasting, while challenging, will contribute to the sustainable use of antimicrobials and hence make them economically more viable. It will also inform the treatment of persistent infections.

Operationalizing the forecasting of evolving resistance will provide an additional tool to combat the spread of AMR; it will require the development of bespoke technology, adapted computational approaches, stakeholder involvement, and a shift in mindset from *a posteriori* to *a priori* measures.

Background and motivation

The evolution of AMR, driven by the use – and exacerbated by the misuse – of antimicrobials, continues to be one of the greatest challenges for public health [1–3]. Several strategies have been suggested to either delay or manage resistance [4]. These include the development of new drugs (including immunomodulatory compounds, antimicrobial peptides, and phages) and treatments such as antibiotic cycling and combinations, prudent use of antimicrobials, and rapid diagnostics, which can have a significant impact on treatment outcomes [5], ensure the appropriate selection of antimicrobials, and significantly reduce usage in animal husbandry. These are all important components of a global strategy. Yet, the inevitable emergence of resistance, even in countries with strict regulations and multiple measures in place [6], indicates that these measures are not always sufficiently effective. One approach to tackle the evolution of resistance, that could add to our current arsenal of measures, is forecasting the evolution of resistance; this should improve treatment outcomes and also result in a more sustainable use of antimicrobial drugs. The terms 'forecasting' and 'prediction' with regard to AMR are often used interchangeably in different scientific communities. Here, we use the term 'forecasting' as an instrument to describe and project complex phenomena into the future with sufficient accuracy and considering different scenarios.

In this perspective we argue that forecasting AMR – either once it has emerged (management of resistance) or before it has emerged (prevention) [7] – has the potential to be a promising additional tool to address the antimicrobial crisis. We see at least two goals for forecasting. First, the use of surveillance data from routine diagnostics to slow the rate of increase of existing

[1]Evolutionary Biology, Institute of Biology, Freie Universität Berlin, Berlin, Germany
[2]Institute of Integrative Biology, ETH Zurich, 8092 Zurich, Switzerland
[3]Clinical Pharmacy and Biochemistry, Institute of Pharmacy, Freie Universität Berlin, Berlin, Germany
[4]Charité-Universitätsmedizin Berlin Medical Department, Division of Gastroenterology, Infectiology and Rheumatology, Berlin, Germany
[5]ISEM, Université de Montpellier, CNRS, IRD, EPHE, 34095 Montpellier, France
[6]Santa Fe Institute, Santa Fe, NM 87501, USA

resistance; this requires a data-driven approach. Second, to incorporate forecasting into antibiotic stewardship during the development of new drugs and the prudent use of currently available drugs (e.g., dosing regimens and drug combinations); the goal is to avoid or delay the evolution of resistance. This would also significantly benefit from experimental approaches testing bacteria–drug interactions *in vitro*. The ultimate goals of integrating forecasting into the prevention and management of AMR are to reduce disease morbidity and mortality, and the prevalence of AMR, and to extend the effective lifespans of antimicrobials.

Forecasting is successful in other scientific disciplines that deal with complex issues, such as epidemiology, albeit rarely combined with evolutionary dynamics [8], adaptation of species to climate change [9], and of course meteorology. Weather forecasting relies on station data and rapid processing using numerical models and requires effective collaboration. Even though the mechanisms associated with changes in the weather are fundamentally different from those influencing AMR, lessons can be learned from how meteorology platforms function and how they interact to form a successful forecasting network [10]. Despite clear limitations in translating forecasting methods from other disciplines to AMR, we believe that forecasting AMR is a feasible goal and one that merits concerted attention and action. It will be based on data that include bacterial resistance mechanisms, gene networks, and costs of resistance, prevalence, pathogenicity, and the intensity of antimicrobial use including pharmacokinetic and pharmacodynamic data [11,12], but also on expert opinion [11,12].

Forecasting will require not only a dedicated, operational scientific approach, but will also need to be transdisciplinary in satisfying considerable imagination and implementation challenges (*sensu* [13]). These include technological and computational improvements and innovations. Of equal importance are current regulations and traditions in antibiotic stewardship that would need to be reorganized to integrate forecasting as a new tool. Microbiology laboratories, too, will require significant structural changes to integrate forecasting with classical culture techniques.

We envisage forecasting based on clinical, veterinary, and environmental data, and spatial and temporal extrapolation through modeling to become a routine approach to address the antimicrobial crisis. Successful forecasting would increase effective AMR prevention and management, but would also hold the prospect of shifting measures from reactive, such as the development of new drugs to treat AMR or explicitly managing resistance. Explicit attempts to manage resistance include, for example, exploiting collateral sensitivity, whereby pairs of antimicrobials are given consecutively, if it is known that resistance to the first antibiotic increases susceptibility to the second, and vice versa [14,15]. Also the prevention of resistance evolution [7,16] has been tested for some combination therapies *in vitro* [17]. These strategies would make antimicrobial use more sustainable in both public health outcomes and economic costs. Forecasting could therefore be an integral component of antibiotic stewardship [18,19] for the benefit of society and part of One Health, the attempt to balance the health of humans, animals, and ecosystems [20]. Guidelines for antimicrobial stewardship currently do not contain procedures aimed at forecasting resistance evolution [21].

Data-driven forecasting

We briefly review and describe forecasting scenarios that provide estimates on the timing, probability, and rise of resistance evolution, which, if further developed, could be expressed as a composite resistance score (see later text). We currently have surveillance data on AMR that focuses on increases in the frequency of AMR at the population level [22]. By contrast, data on evolutionary rates – that is, the first appearance of resistance and the amount of time between the therapeutic use of a drug until resistance is discovered in human and veterinary situations – are scant [23].

*Correspondence:
jens.rolff@fu-berlin.de (J. Rolff).

Forecasting could be used for preventing the evolution of resistance [24] and also for managing existing resistance [25]. A variety of approaches on forecasting resistance are already available (Table 1). Most of them require sufficient patient and surveillance data as well as future extrapolations based on mechanistic and statistical models. Sampling and analysis are more hands-on: despite automation, they would still require detailed protocols, managed storage and analysis facilities, and data processing and relaying [26,27]. Although the spread of AMR can be slowed or stopped geographically, for example, through infection prevention, more usually the widespread use of antimicrobials will promote the spread of resistant strains [28].

Agreement will also be necessary on the methods and types of data collected as well as centralization in data analysis and projections. Whereas simple mechanistic models can give useful insights into the basic process of resistance evolution, models of intermediate complexity are needed for more accurate projections that are amenable to the coarseness of input data

Table 1. Examples of how the prediction and/or forecasting of antimicrobial resistance have been studied[a]

Forecasting/prediction when resistance has already emerged		
Approach	Comments	Refs
Time series analysis	Prediction based on antibiotic use and prevalence of resistance in ceftazidime–Gram-negative bacilli and imipenem–*Pseudomonas aeruginosa* from a single hospital	[19]
Time series analysis	Prediction based on antibiotic consumption data and prevalence of carbapenem resistance in *Klebsiella pneumoniae*	[30]
Time series analysis	Evaluation of alternative forecasting models based on antibiotic use and incidence of methicillin-resistant *Staphylococcus aureus* (MRSA)	[57]
Time series analysis	Prediction based on MICs for five different bacterial species collected from farms in the USA	[58]
Transmission model for temporal trends	Studies of the intensity of selection on *Streptococcus pneumoniae*, double-resistant strains spread faster, predicting their frequency	[29]
Approaches based on genome data		
Prediction from Pan-Genome data	Prediction of *Escherichia coli* resistance from patient samples	[59]
Prediction of ARG[b] dissemination via horizontal gene transfer	Genomes from several bacterial taxa show spread of mobile genetic elements and allow forecasting resistance in 36% of cases	[33]
Statistical analysis of annual surveillance data	Sampling with sufficiently high spatial and temporal resolution necessary	[60]
Evolutionary modeling	Based on *S. pneumoniae*. Authors model seasonal fluctuations of described resistance	[61]
Machine learning	Predictions for individual patients using machine learning	[31]
Expert judgement compared with statistical modeling	Several genera of bacteria	[62]
Forecasting before resistance has emerged		
Approach	Comments	Refs
General population genetic models	Useful as proof of principle	[63,64]
Experimental evolution	Compares different treatment regimens in *E. coli* using pipetting robot, data on dynamics of resistance evolution	[17]
Pharmacodynamic and evolutionary model	Shows higher probability of resistance evolution against conventional antibiotics than against antimicrobial peptides. Useful as proof of principle	[65]

[a]The majority of studies deal with situations where some level of resistance has already evolved (management), but some also tackle the issue of prevention. Note that the use of the terms 'prediction' and 'forecasting' is not always clear in these examples. We have used the terminology employed in the references.
[b]Abbreviation: ARG, antibiotic-resistance genes.

expected from monitoring programs [11,12]. For example, McCormick and colleagues [29] developed a modified susceptible-infected model with five states incorporating sensitivity and resistance of *Streptococcus pneumoniae* to one or both of penicillin and erythromycin to show how the intensity of selection on resistance was key in accurately explaining geographical diversity and the dynamics of resistance. Mechanistic models will not always be appropriate for forecasting needs since important mechanisms might not be understood, or available data will be insufficient to estimate model parameters.

In these cases, nonmechanistic statistical models will serve as the basis for resistance forecasts. The utility of such approaches has been demonstrated using an autoregressive integrated moving average model based on antimicrobial consumption data for forecasting carbapenem resistance in a strain of *Klebsiella pneumoniae* [30] and ceftazidime resistance in Gram-negative bacilli and imipenem resistance in *Pseudomonas aeruginosa* [19]. Moreover, employing forecasting recommendations for stakeholders does not preclude the use of patient-level data for practitioners, for example, how treatment failure can be prevented based on information about existing resistant microbiota seeding new infections [31]. Often resistance is acquired through mobile genetic elements [32]. This has been extensively studied by Ellabaan *et al*. [33] who examined more than 400 k genomes of *Streptococcaceae, Staphylococcaceae,* and *Enterobacteriaceae* to predict the mobilization of AMR genes within and between species. The approaches discussed here, and cited in Table 1, are limited in not being part of integrated development and implementation frameworks. Aside from the studies discussed here, only a few AMR modeling studies take a proactive approach and explore future strategies to reduce resistance, as highlighted by a recent review [34]. Finally, whereas extensive modeling approaches used for epidemiological forecasts for coronavirus disease 2019 (COVID19) had variable success [35], longer epidemiological time scales, such as those of AMR spread, permit more accurate data estimates and more time to make robust forecasts (Figure 1).

Forecasting any complex process is prone to error. Obvious sources are patchy data, mis-specified models and insufficient implication of stakeholders, problems that might be of particular importance for low- and middle-income countries with limited funding for public health infrastructure [36], or, for example, erroneous forecasts resulting in needless modification to treatment strategies. Forecasting errors associated with uncertainties [37] or lack of expert oversight [36] generate health and economic costs and could result in a lack of confidence in antibiotic management and exacerbate existing nonadherence in certain treatment situations [38]. Should thresholds be insufficiently sensitive then they would likely not outperform the strategies that they were set to complement.

A resistance score

AMR is currently determined by the consensus of specialized committees such as European Committee on Antimicrobial Susceptibility Testing (EUCAST) and Clinical and Laboratory Standards Institute (CLSI) and their sentinel laboratories. A forecasting approach could be supported by a resistance score (Box 1), itself relying on influential factors, data networks, and mathematical and statistical models [39]. Given the global nature of AMR, additional support for existing monitoring centers, and the establishment of new monitoring cells in regions where they do not yet exist, will be necessary for effective forecasting. A resistance score, by providing an estimate of the probability of resistance evolution, will have the potential to translate the results of data collection, experimentation and modeling into recommendations for effective, sustainable antibiotic use.

Ideally, a resistance score would be attributed to each drug (or drug class)–bacterial species (or variant) pair, based on a single defining number (see Box 1 for discussion) on an agreed scale of sufficient precision. An easy-to-read output – such as a color scale from green (low threat)

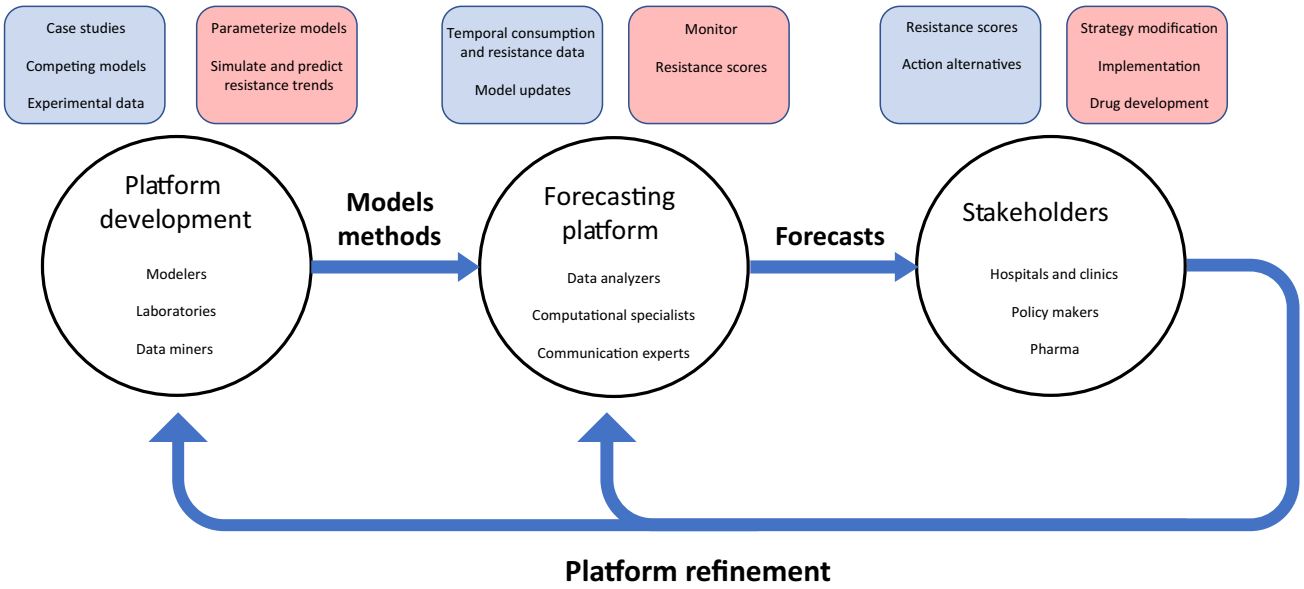

Figure 1. Flow diagram of main transdisciplinary features in an antimicrobial resistance forecasting platform. Stakeholders and the forecasting platform, together with developers, provide input in the establishment of the development platform. The forecasting platform is the operational center and it depends on foundation from developers and subsequent refinements from stakeholders. A network of monitoring stations/centers and perhaps even data collection with citizen science approaches (patients, farmers etc.) would produce a periodically updated dataset, headlined by local and regional resistance scores. This would, in turn, provide the contexts for evaluation committees. Expert committees would bring together scientists, physicians, pharmacists, policy makers, and stakeholders to evaluate, develop, and communicate recommendations to administrative bodies in a first step. When forecasting using resistance scores is established in selected treatments, similar procedures will be communicated to infectious disease practitioners, antibiotic stewardship teams in hospitals for prudent antimicrobial use. These would include the choices of the antimicrobial drug or drug combinations, of treatment doses and dosing schedules. These choices and their implementation can be challenging, given possible specificities and idiosyncrasies associated with particular drug–bug pairs, infection sites, and clinical conditions [39,66].

to red (high threat) – would make this practical. We have summarized the possible elements of such a score in Box 1. Using a resistance score could provide additional valuable information for antibiotic stewardship plans since it is a very simple way to make an informed assessment about future resistance evolution. While red and green result in very clear recommendations accompanied by scientific justification, yellow would necessitate looking more carefully into the details of the composition of the resistance score. For example, if the resistance score is driven primarily by a high risk of spread, this could be addressed with increased containment measures at appropriate scales.

A three-point resistance score is necessarily a simplification, but this is also the case for the current best practice use of minimal inhibitory concentrations (MICs) and clinical breakpoints, neither of which consider the risk of evolving resistance. These latter approaches have other significant shortcomings [40–42], yet they are widely employed because they are simple. We believe that adding an easy-to-use resistance score to inform stewardship plans and downstream treatment decisions would be a useful step forward.

Determining thresholds and forecasting horizons based on data quality and specific requirements of bacteria–antibiotic pairs will ultimately come down to whether limitations in forecasting resistance results in inferior health and economic parameters compared with the default strategy of replacing or adding alternative antibiotics only once a drug in current use has limited efficacy. Such a question can be addressed through simulation scenarios of previous cases of antibiotic resistance. This would require fitting statistical models to past time series data from several data-rich sources in order to determine the key variables to be incorporated in the resistance

Box 1. Towards a resistance score

Developing a single or a small number of combined resistance scores poses a significant challenge. Laxminarayan and Klugman proposed antibiotic resistance score based on drug usage and proportion of resistant bacteria [67]. This resistance index shows, at least for high-income countries, a high correlation with daily dosage [68]. Resistance scores and predictions based on more complex data such as genome-wide association studies, combined with physiological and behavioral data, are currently under development for diseases including Alzheimer's or diabetes mellitus [69]. Given opportunities to collect rich and diverse data on AMR, a score would be calculated based on a stakeholder-agreed formula. To calculate an AMR score, parameters that can be obtained from existing data sources include the MICs, pharmacodynamics and pharmacokinetics, pathogen identification, disease site(s), fraction of samples positive, cross-resistance, risk of spread of AMR from other pathogens, AMR genes (sequencing), likelihood of spread (cost of resistance), prescriptions, incidence trends in time and in space (monitoring cell networks) and experimental resistance evolution data (Box 2). Starting from available data (see, e.g., Table 1 in the main text), the first step is to see how combining different data into both numerical and mechanistic models can be collapsed into a few risk estimates that can be translated into an accessible traffic light system (Figure I), for example, based on thresholds [19].

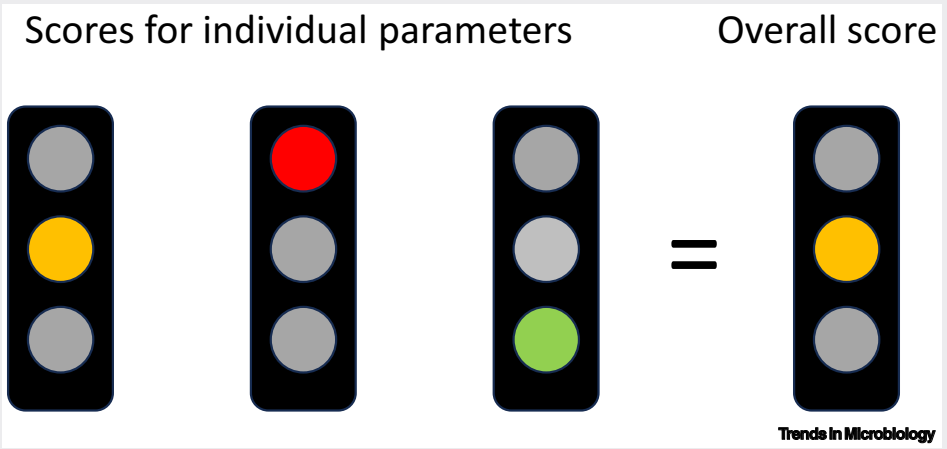

Figure I. A traffic light system would reflect forecasting platform model predictions of statistically key resistance score components and their integration to produce an overall score.

The development of a resistance score would need to be pioneered in geographical areas with the availability of high-quality data. First tests could, in principle, be carried out in veterinary settings, including companion animals [70], the area where most antimicrobials are used [71] and for which reducing resistance evolution would also contribute greatly to reducing resistance in human medicine [72]. The organization of animal farming could provide an opportunity for testing a resistance score, because of the controlled environment and populations, and known geographic distribution of farms. The development of resistance scores depends on tests in real situations, which in turn hinges on the willingness of stakeholders (farmers, veterinarians, agricultural industry) to provide the opportunity for testing.

score (Box 1) and how they are predictive on different time scales by testing the simulation model with independent data sets. Thus, the resistance score would be time sensitive and have a confidence level associated with it for each future time point, similar to weather forecasts.

Box 2. Experimental devices for forecasting

A technology to be used in a laboratory setting that simulates resistance evolution *in vitro* should ideally fulfill a number of criteria. Progress in microfluidics [5] – such as lab-on-a-chip [5] and automated susceptibility tests [73] – promises to provide ample technological foundations. First and foremost, a forecasting device needs to be easy to employ, especially if it were to be integrated into routine workflows in clinical surveillance schemes, diagnostic laboratories, and perhaps even hospital laboratories to support treatment decisions. It would also need to have the flexibility to allow for defined population sizes and investigation of resistance from standing genetic variation, horizontal gene transfer, or *de novo* mutation.

To simulate *in vivo* conditions – taking into account the evolutionary biology of the studied bacterial strain or species – the technology would need to generate different concentration–time profiles. Ideally, this results in highly repeatable evolutionary outcomes that can be simplified into a resistance score (see Box 1). Such experimental approaches allow defining the starting population and hence allow investigation of the role of pre-existing AMR and *de novo* evolution. The resulting strains would need to be genome-sequenced to identify mechanisms providing drug resistance. Harvesting of resistant mutants and genome sequencing could ultimately be automated.

A forecasting package

Constructing a robust forecasting framework will be challenging (Figure 1). In a first phase, mechanistic and statistical models of resistance evolution and spread will be developed from examples in the literature (Table 1). These would need to accommodate the types and richness of data collected at clinics, but should also be sufficiently flexible to cope with missing or discarded data, data supplementary to what is expected, and new types of data. Given uncertainties in the detailed processes influencing resistance evolution, a range of mechanistic and statistical models would be evaluated under different data-input scenarios [43] to determine the operational temporal and spatial windows that provide the most accurate forecasts. These tests will also explore how they accord with the time frames for the implementation of modified or alternative strategies.

In a second phase, those models retained will be confronted with retrospective data on the evolution of AMR. This necessitates that datasets are sufficiently information-rich for given bacterium–antimicrobial pairs [19,30]. They will then be compared and contrasted with model predictive performance on documented resistance trends, for example, as has been done with machine learning using molecular sequences [25]. Simulations would employ subsets of the full time and/or spatial data to make forecasts that could be checked with the unused data. In this way, model structure and prescriptions for necessary levels of monitoring/data accuracy would be made so that forecasting packages can be operational. This will require, in parallel, assays estimating probabilities of resistance (see next section) of target bacterial pathogens for existing and prospective antimicrobials.

Standardized resistance probability scores for bacteria–drug pairs require adaptive data-driven forecasting platforms. First, pairs with a high propensity to acquire resistance require finer data in terms of collection frequency and spatial resolution. These pairs also need heightened forecasting alert levels, that is, identifying and reacting to a potential resistance threat on a faster time scale. Second, adapted variations in forecasting packages will be necessary given possible differences in data collection capacities between regions and nations. Third, forecasting packages will begin with pathogen–antibiotic pairs providing the richest data and most amenable to alternative strategies. Once packages are operational, retroactive assessments (sensitivity analysis) of forecasting performance will be conducted as well as how future forecasts and deployment of alternatives can be improved. Due to the variable dynamics of resistance evolution [39], monitoring on a continuous basis (frequency depending on the forecast/resistance score) is vital for possible accounting in reporting resistance scores.

Given increasing risks of resistant bacterial infections in hospitals and nursing homes [44], we believe that forecasting priorities should be given to nosocomial pathogens. This will require modifications to standard transmission and infection models [45] and careful monitoring of hospital infections and regional trends in resistance.

The need for new technologies

One development that would make forecasting an integral part of antibiotic stewardship and drug development is technology that allows empirical estimation of resistance risks. This is especially important for the prevention of resistance when new drugs or new treatment combinations are introduced. Experimental simulation of resistance evolution should also allow for testing different treatment regimens [i.e., which drug(s) and which dosing regimen(s)] in relation to resistance evolution.

Basic tools to accomplish this already exist. For example, serial passage of bacteria to increasing concentrations of antibiotics have long been used to assess limits of resistance evolution and associated genetic changes. A study by Barlow and Hall, published in 2001, revealed that TEM β-lactamase mutations from experimental evolution reproduced natural resistance evolution

[46]. While mostly focused on *de novo* mutations, serial passage has also been successfully applied to plasmid-borne AMR [47]. These experimental assays allow for assessing resistance evolution within days or weeks. Although yielding useful background information, such assays greatly oversimplify *in vivo* resistance evolution, which will be influenced by drug concentration gradients, complex physiological conditions, and immune responses [48–50]. Nevertheless, the technology to go beyond simple *in vitro* analysis exists. A study with an automated pipetting robot system tested different treatment regimens (mono-therapy, mixing, cycling, and combinations) in parallel evolution experiments [17]. While such an approach is very powerful in the initial assessments of resistance evolution, the complexity and time required for such experiments limit their feasibility for all but the most developed platforms.

A possible scenario integrating existing technology would be a device that allows the quantification of resistance evolution (Box 2) in a highly automated set-up. For example, for a new drug under development, such a device would incorporate concentration gradients predicted or obtained from (pre-)clinical studies and could be closer to the physiological and pharmacokinetic conditions inside a host [48]. The resulting strains from this test could then be genome sequenced for ground-truthing to determine whether resulting mutations match resistance mutations known from patient strains, or rather if the resistance providing mutations or plasmids is new, which arguably would require additional experimental work. An additional benefit that experimental resistance evolution *in vitro* could yield is the identification of mutations that have not been recorded from clinical or environmental strains [51].

In conjunction with improvements and innovations in data collection and analysis, forecasting platform updates in, for example, model structure, routine experimental tests will contribute to maintaining the platform as a state-of-the-art tool. A useful starting point for the implementation of experimental forecasting could be a database that provides a comparison of *in vitro* studies on the dynamics of resistance evolution and comparative data for the same bacterial species and its resistance patterns collected from patients and the environment. Bacterial resistance evolution is constrained, as shown in a classic study on *Escherichia coli* and β-lactamase evolution: only 18 trajectories to high resistance out of 120 mutational trajectories were accessible [52]. This lends support to the utility of preventive forecasting.

The need for transformative shifts

A main challenge to new approaches is their application and implementation, both of which will depend on awareness, attitude, and trust of stakeholders, but ultimately on improved patient outcome. An example of a transformation in antibiotic use is the shortening of antibiotic treatment courses [53]. The evidence of superior outcomes for a strict course of fixed length is very limited, yet many physicians still adhere to this practice [54].

Cooperation and coordination through the network of stakeholders will be required to monitor and forecast resistance evolution. Then solutions based on current antimicrobial use and the development and deployment of new drugs can be devised. Mutual dependence and no strict overarching authority mean, for example, that risks of resistance evolution of currently used antimicrobials do not elicit research and development by big pharma. This is because of the high cost of drug development, clinical trials and marketing, and the uncertainty of economic profitability for drugs with limited lifetimes or those considered as a 'last resort' only. Forecasting and more rational use could constitute an economic incentive for developing new antimicrobials since the new drugs would not be rapidly lost to emerging resistance [23].

Concluding remarks and future perspectives

Integrating forecasting into AMR prevention and management will be a stepwise process, starting with selected examples where data, facilities, and knowledge are most developed. ESKAPE (*Enterococcus faecium*, *Staphylococcus aureus*, *K. pneumoniae*, *Acinetobacter baumannii*, *P. aeruginosa*, and *Enterobacter* spp.) pathogens, in particular, are closely monitored in a number of countries, and such data would provide good case studies. A growing understanding of the environmental factors influencing the spread and evolution of AMR [55] will yield additional valuable information. Insights would also be provided by comparisons between AMR recorded from culture-based or molecular methods. Preventive forecasting can be applied to the increasing number of antimicrobial combinations such as those currently undergoing clinical trials and listed by the World Health Organization (WHO) as new drugs (https://www.who.int/activities/coordinating-r-and-d-on-antimicrobial-resistance).

Implementing forecasting of AMR would add a new tool to the reactive and preventive measures that are currently available. Forecasting will be useful for antimicrobial drug development and antibiotic stewardship planning as well as antimicrobial treatment guidelines provided by learned societies or regulations for drug approval by regulatory bodies. Forecasting will add to the current arsenal of rapid diagnostics [5] drug decisions, drug development (WHO), and prudent antibiotic use (also see Outstanding questions). Experimental forecasting could also be applied in personalized medicine, especially in long-lasting or chronic infections. Examples include *Pseudomonas* infections in cystic fibrosis patients and tuberculosis. The rationale proposed here is also almost certainly applicable to the use of biocides and antifungals [56].

Outstanding questions

Can a resistance score be developed that is applicable across drug–bacteria pairs and concentrations that will form a viable instrument in antibiotic stewardship?

What are the key biological and epidemiological parameters that will significantly contribute to the resistance score?

What is a feasible device that allows experimental simulation of resistance evolution at-scale to inform antimicrobial usage in a way that minimizes resistance evolution?

What challenges need to be addressed, building on existing AMR surveillance schemes, to generate data that allow statistical analyses and modeling on a larger scale to forecast the probability of resistance evolution?

Once developed, how can forecasting – as an additional tool against the evolution of AMR – be implemented?

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Declaration of interests

No interests are declared.

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