RESEARCH ARTICLE

Feasibility of informing syndrome-level empiric antibiotic recommendations using publicly available antibiotic resistance datasets [version 1; peer review: 1 approved with reservations]

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Abstract

**Background:** Antibiotics are most often prescribed empirically, meaning that they are used to treat infection syndromes prior to identification of the causative bacteria and their susceptibility to antibiotics. The effectiveness of antibiotic therapies is now compromised by the emergence and spread of antibiotic-resistant bacteria. Guidelines on empiric antibiotic therapy are a key component of effective clinical care for infection syndromes, as treatment needs to be informed by knowledge of likely aetiology and bacterial resistance patterns.

**Methods:** We used open-access antimicrobial resistance (AMR) surveillance datasets, including the newly available ATLAS dataset from Pfizer, to derive a composite index of antibiotic resistance for common infection syndromes.

**Results:** We developed a framework that integrated data on antibiotic prescribing guidelines, aetiology of infections, access to and cost of antibiotics, with antibiotic susceptibilities from global AMR surveillance datasets to create an empirical prescribing index. The results are presented in an interactive web app to allow users to visualise underlying resistance rates to first-line empiric antibiotics for their infection syndromes and countries of interest.

**Conclusions:** We found that whilst an index for empiric antibiotic therapy based on resistance data can technically be created, the ATLAS dataset in its current form can only inform on a limited number of infection syndromes. Other open-access AMR surveillance datasets (ECDC Surveillance Atlas, CDDEP ResistanceMap and WHO GLASS datasets) are largely limited to bacteraemia-derived specimens and cannot directly inform treatment of other infection syndromes. With improving data availability on international rates of AMR and better understanding of infection aetiology, our approach
may prove useful for informing empiric prescribing decisions in settings with limited local AMR surveillance data. Syndrome-level resistance could be a more clinically relevant measure of resistance to inform on the appropriateness of empiric antibiotic therapies at the country-level.

**Keywords**
Antimicrobial resistance, empiric therapy, guidelines, online tool, data linkage

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Introduction

Worldwide, most bacterial infections are treated empirically, meaning that antibiotics are prescribed based on clinical judgement prior to the infectious agent and its susceptibilities to antibiotics being known. A point prevalence survey of antibiotic-prescribing in children showed that globally over 75% of antibiotics in neonatal treatment were given empirically. In low- and middle-income countries, the laboratory capacity that could inform appropriate empiric therapy choices is frequently lacking.

Empiric antibiotic prescribing guidelines contain recommendations on what antibiotics to use for specific infection syndrome. The use of prescribing guidelines has been associated with reductions in patient mortality, particularly among the most critically ill patients, though benefits vary by patient group and infection. Guidelines have also been shown to reduce levels of inappropriate prescribing, which leads to a reduction in the selective pressure for antimicrobial resistance (AMR). Empiric guidelines are even more crucial in low-income settings where microbiological confirmation rarely occurs due to infrastructural and resource constraints.

Guidelines for empiric antibiotic therapies are often set at the national level. For example, in England, Public Health England and the National Institute of Health and Care Excellence (NICE) produce national antimicrobial prescribing guidance. Creation of such guidelines requires an understanding of both the aetiology (typical causative bacteria) and the prevalence of relevant antibiotic susceptibilities. Each anatomic site of infection (e.g. respiratory tract, urinary tract, skin and soft tissue, gastrointestinal tract) has certain typical infecting microorganisms. The aetiology of some infection syndromes and associated antibiotic susceptibilities varies by setting, age and even season, but some broad generalizations can be made, especially with the broad-spectrum nature of some antibiotic agents.

Though it is recommended that prescribing guidelines should be adapted by healthcare institutions to take into account local patterns of AMR, in practice this is infrequently performed. This may be due to a lack of resources to develop appropriate guidelines or a lack of appreciation of the need – furthermore, the existence of guidelines is no guarantee that local prescribers will adhere to such recommendations. Providing readily available, easy-to-use, transparently created guidelines based on open-access international AMR surveillance data may help practitioners in resource constrained settings generate appropriately-tailored local prescribing guidelines.

Whilst antibiotic resistance levels and other clinical criteria form the basis for designing antibiotic prescribing guidelines, in practice, antibiotic use is also constrained by market factors, such as cost and access to antibiotics. This may be particularly true in the case of low- and middle-income countries, which have limited healthcare budgets and difficulties to access medicines. Two antibiotic market factors which can be informed through open-access data are those of antibiotic supplier prices and antibiotic placement on the World Health Organization’s (WHO’s) Essential Medicines List.

Currently, antibiotic resistance surveillance tools typically present resistance data for individual bacteria-antibiotic (“bug-drug”) combinations. We propose a more clinically-oriented presentation of resistance rates at the level of infection syndromes, which could be used to inform empiric antibiotic prescribing recommendations. We designed a syndrome-level composite resistance index that integrates information on syndrome aetiologies with antibiotic susceptibilities drawn from international AMR surveillance datasets. Additionally, we tested the feasibility and robustness of using open-access data sources to create a user-friendly, web-based application, AR.IA, that brings together all this information. This work was undertaken as part of the Wellcome Data Re-use Prize, motivated by the release of a new open-access dataset (ATLAS) from Pfizer that contained 633,820 bacterial clinical isolates collected from 77 countries over a 14-year period.

Methods

This work consists of three main objectives, where specific methods applied:

1. To compare the antibiotic resistance rates calculated using the ATLAS dataset with those estimated from other global AMR surveillance datasets.

2. To integrate data on antibiotic susceptibilities from the ATLAS dataset with the aetiology of infection syndromes to derive a syndrome-level composite resistance index; and combine such data with access to and cost of antibiotics.

3. To develop an interactive web app (AR.IA App) to access the above information and offer empiric therapy recommendations based on available data.

All of the above was conducted in R software, using the following packages: shiny 1.2.0, ggplot2 3.1.0, dplyr 0.7.8, rworldmap 1.3-18, RColorBrewer 1.0-50, reshape2 1.4.2, DT 0.5, magrittr 1.0.1, fuzzyjoiin 0.1.4. These are available at: https://cran.r-project.org/.

Surveillance data comparison

The ATLAS dataset is an open-access dataset on human AMR surveillance data generated by the commercial pharmaceutical company Pfizer that contains high-quality antibiotic susceptibility data, including ‘raw’ minimum inhibitory concentration (MIC) data, for 633,820 bacterial clinical isolates collected from 77 countries and spanning 14 years. This dataset was made public in 2017 to encourage reuse of AMR data shared by industry and to facilitate the development of common methodological and metadata standards.

We additionally used the European Centre for Disease Prevention and Control (ECDC) Surveillance Atlas, ResistanceMap by the Center for Disease Dynamics Economics and Policy (CDDEP) and the Global Antimicrobial Resistance Surveillance System (GLASS) database by the World Health Organization (WHO). The first holds AMR data collected in European countries whilst the second and third hold global data from national AMR surveillance programmes. Data between 2004 and 2017 were considered to match the ATLAS time coverage.
but only from 2017 for the GLASS dataset (the only year available for download at the time of our analysis). Missing susceptibility labels (i.e. “resistant”, “intermediate” or “susceptible”) in the ATLAS dataset (443,899/633,820) were assigned from available MIC data (see Further Methods in Extended Data for details)\(^9\).

We estimated the “accuracy” of the ATLAS dataset as the proportion of resistance rates for all bug-drug combinations with point estimates falling within the corresponding 95% confidence intervals in the ECDC Surveillance Atlas and ResistanceMap databases (see Further Methods in Extended Data for details)\(^9\). Sample sizes (i.e. number of isolates per country per year in each dataset) were compared using boxplots. We matched susceptibility labels across datasets by assigning isolates as “resistant” if they were non-susceptible (i.e. “intermediate” or “resistant”). Comparison between ECDC and ResistanceMap was not needed since they derive from the same source data.

**Data integration and Mapping**

Figure 1 shows the steps required to extract and integrate information from sources other than the ATLAS dataset to produce our composite resistance index. We focused on nine infection syndromes. Each infection syndrome was mapped to the corresponding causative bacteria (i.e. aetiology, informed by the scientific literature), antibiotics used to treat them empirically (informed by antibiotic prescribing guidelines and clinical consultation) and related specimen sources (informed by the ATLAS metadata and clinical consultation).

(a) **Common infection syndromes.** We first chose which infection syndromes to focus on. A comprehensive list of infection syndromes was extracted from NICE guideline\(^8\). We discarded viral and fungal infections and kept the nine most common bacterial ones. Clinically, these syndromes are all identifiable with simple clinical examination and/or basic radiology and occur worldwide.

(b) **Mapping isolate source to infection syndrome.** We linked isolates in the ATLAS dataset to the infection syndrome they most likely originated from informed by the clinical “source” description in the ATLAS metadata. Due to the diversity of sources, we kept sample types represented by at least 1,000 isolates. We discarded sample types not clearly linked to an infection syndrome (e.g. “wound”), as these samples might not necessarily represent infecting organisms, but rather colonizing bacterial flora.

(c) **Antibiotics used to treat infection syndrome empirically.** We extracted which antibiotics are used to treat empirically each of the nine infection syndromes from the NICE guidelines\(^8\) and as advised by clinical consultation. These empiric therapies represent typical current practice in the UK, though we attempted to make use of agents that were widely available at low cost internationally. For simplicity, we did not incorporate additional patient-level prescribing criteria (such as penicillin allergy status and pregnancy) when choosing these antibiotics.

(d) **Contributing pathogen distribution: syndrome aetiology.** To establish the distribution of causative pathogens for each infection syndrome, we identified reviews on the global aetiology for different syndromes and, if we could not find any, performed a rapid literature search for recent
publications. We used these findings to establish a suggested pathogen distribution for each syndrome.

(e) Combining antibiotic susceptibility data from four AMR surveillance datasets. We extracted the antibiotic susceptibility data from the ATLAS dataset as well as from three more AMR surveillance datasets: ECDC, ResistanceMap and GLASS, to allow the end-user of our AR.IA App to select the underlying antibiotic susceptibility data.

(f) Combining with drug information datasets. We extracted data on supplied cost (and cost unit) for antibiotics from the Management Sciences for Health (MSH) International Medical Products Price Guide which we inflated to the 2017 level using World Bank inflation data. We also included whether a recommended drug was on the WHO Essential Medicines List (EML) and on the AWaRE classification system, which builds on the EML to advise on what antibiotics to use for common infections (“access” category), for a small number of infections (“watch” category) and to be considered as last-resort options (“reserve” category) (Figure 2).

(g) Mapping data to recommendations for therapy. We multiplied the frequency of each syndrome’s contributing bacteria by their resistance rate to calculate a composite resistance index for empirically used antibiotics. As an example, an infection syndrome caused by two bacterial species contributing to 20% and 80% of infections, respectively, and with a resistance rate of 15% and 5%, respectively, for a particular antibiotic would result in a composite resistance index of 7% (= (20% x 15%) + (80% x 5%)) for that antibiotic. We designed a simple hierarchical decision workflow (Figure 3) to inform on the appropriateness of using first-line empiric antibiotic therapy by comparing the syndrome-level composite resistance index calculated for each country against the chosen resistance cut-off, defined as the resistance rate above which to escalate therapy, which is set to 15% by default in the AR.IA App.

Each infection syndrome was assumed to be caused entirely by bacterial species. We noted that not all bacterial species were included in the ATLAS database, nor were all species tested for the antibiotics included in empiric therapies. We thus define the “syndrome coverage” as the proportion of isolates from available species out of all syndrome-contributing species. The composite resistance index is then calculated using the resistance rates of available species and assuming missing bacteria to be totally susceptible, which may bias towards using first line therapies. We report the syndrome coverage as well as whether fewer than 10 isolates were available in the final recommendation table, but do not set a minimum threshold.

The AR.IA App creation
The Shiny R package was used to build an interactive web app (referred to as ‘the AR.IA App’) that hosts data from all four AMR surveillance datasets, integrated with external information, and the main output data used to recommend what antibiotics are appropriate to treat common infection syndromes in different regions of the world. Key parameters can be edited by the user including the underlying antibiotic susceptibility surveillance dataset used, the syndrome aetiology (proportion due to each included bacterial species) and the resistance cut-off for changing empiric therapy (see Usage of the AR.IA App in Extended Data for details). The underlying data manipulation and Shiny R code can be found on GitHub.

Results
Surveillance data comparison
We used four open-access datasets: ATLAS, ECDC, ResistanceMap and GLASS (Table 1).

Assigning susceptibility labels from MICs values in the ATLAS dataset reduced the number of missing isolates by 63% (to 164,918 isolates). The number of isolates per country and year was similar across datasets (Extended data, Supplementary Figure 1). The ATLAS dataset reports many more bacterial species and antibiotics tested than the other datasets (Table 1), resulting in smaller sample sizes for each country/year/species/antibiotic combination. The “accuracy” (agreement) of the ATLAS dataset by year as compared to the ECDC or ResistanceMap datasets ranged from 5–30% (Extended data, Supplementary Figure 2 in Further Results).

Figure 2. Flowchart of data linkage for further data. Orange boxes indicate additional datasets, blue boxes indicate ATLAS data and green boxes indicate resulting data utilised within this project.
Data integration and mapping

(a) **Common infection syndromes.** The nine chosen infection syndromes are shown in Table 2. These were chosen as they could be clearly linked to anatomic site or sample types, are common infections worldwide, and are caused by common bacterial species.

(b) **Mapping isolate source to infection syndrome.** We could map 366,001/633,820 isolates (58%) from the ATLAS data-set to the syndrome they likely originated from (Table 2). The major sources excluded were “INT: Wound” (n=96,306 isolates) and “Respiratory: Trachea” (n=19,278) as they could not be linked to a single syndrome and as they could represent colonizing flora. There was no accompanying clinical information available to help discriminate genuine infecting organisms from colonizers. The isolate “source” information was not sufficient to assign respiratory specimens (Table 2) to either community or hospital acquired pneumonia, thus we used the same pool of respiratory isolates for both syndromes, but with a different etiological make-up.

(c) **Antibiotics used to treat infection syndromes empirically.** The antibiotics used to treat the nine infection syndromes empirically are shown in Table 2 (Extended data, second line and third line presented in Supplementary Table 1 in Further Results). Some of the antibiotics recommended for treatment were not tested against in the ATLAS dataset and thus we mapped them to their equivalent tested antibiotic where possible (Extended data, Supplementary Table 2 in Further Results).

(d) **Contributing pathogen distribution: syndrome aetiology.** Except for bacterial meningitis, we could not find a consensus...
global aetiology for each infection syndrome. There are liable to be some regional differences in the aetiology of infections and also greater difficulty in obtaining reliable microbiological diagnosis in some parts of the world. We therefore relied on rapid literature reviews to find an approximate breakdown of the top bacterial species commonly isolated from each type of infection (see Further Results in Extended Data for details). However, the AR.IA App allows this aetiology to be changed by the user. Our syndrome aetiology from the literature included a total of 19 bacterial species. Of these, two were not present in the ATLAS dataset, including “Streptococcus, viridans group” and Neisseria gonorrhoeae, the latter responsible for the majority of purulent urethritis/cervicitis cases. Hence, we excluded this syndrome from the AR.IA App.

(e) Combining antibiotic susceptibility data from four AMR surveillance datasets. We aggregated antibiotic susceptibility data across the four AMR datasets (ATLAS, ECDC, ResistanceMap and GLASS) by keeping isolates from the most recent year available (2017) for all except ResistanceMap, which had very few data points for 2016 and 2017 (n=46 and n=197, respectively) and so we used 2015 instead (n=684); by standardizing the spelling of antibiotics, species and countries; and by mapping antibiotics in the ATLAS dataset to their corresponding antibiotic classes (reported in the rest of datasets). We mapped each isolate source to their relevant infection syndrome as done for the ATLAS dataset. Datasets included isolates from different infection syndromes (Table 1).

(f) Combining with drug information datasets. Approximately 75% of the antibiotics tested in the ATLAS database and used to treat the chosen syndromes were found on the 2015 EML list and over 80% in the AWaRE classification system (see Further Results in Extended Data for details). Only one of these antibiotics (fosfomycin) is classified on the AWaRe “reserve” group. As cost comparisons are difficult across different antibiotics that have different formulations, we allow the AR.IA App user to see exactly which formulation the available costs relate to by presenting the cost in “per specified unit.”
Summary of data integration and sub-setting. Following steps (a) - (f) above, we kept isolates in the ATLAS dataset that met the following criteria: were isolated from sources that could be mapped to infection syndromes (Table 2), belong to the list of bacterial species causing infection syndromes (Table 3), had assigned susceptibility status (susceptible/resistant) to at least one of the antibiotics used to treat infection syndromes, and were collected in 2017.

Applying these criteria resulted in a subset of 435,557 (69%) isolates from the ATLAS dataset that could be used to inform empiric guidelines. When grouped by country, species, syndrome and antibiotic, this resulted in 16,596 data points we could use in the AR.IA App. These data points represent resistance levels to individual antibiotics in our empiric guidelines in species isolated from a syndrome source in a single country. This subset of ATLAS isolates came from 46 countries only (Figure 4A), out of an original 73, limiting the number of countries we could generate recommendations for.

(g) Resulting recommendations on the appropriateness of empiric antibiotic therapies. Recommendations existed for

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Average syndrome coverage (S.D.)</th>
<th>Recommendation (as can be seen in the app)</th>
<th>Number of countries</th>
<th>Therapy</th>
<th>Key driver</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacteraemia</td>
<td>0.70 (0.14)</td>
<td>Use second line, as resistance to first (but no data on resistance to second)</td>
<td>2</td>
<td>Cefuroxime and Gentamicin</td>
<td>S. aureus resistance</td>
</tr>
<tr>
<td>Community acquired pneumonia</td>
<td>0.83 (0.18)</td>
<td>Use first line, but no data to inform – consider second or third if data</td>
<td>7</td>
<td>Amoxicillin and Clarithromycin</td>
<td>S. pneumoniae resistance</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Use second line, as resistance to first (but no data on resistance to second)</td>
<td>1</td>
<td>Co-Amoxiclav and Clarithromycin</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Use second line</td>
<td>10</td>
<td>Co-Amoxiclav and Clarithromycin</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Use third line (if exists)</td>
<td>24</td>
<td>Levofloxacin</td>
<td></td>
</tr>
<tr>
<td>Hospital acquired pneumonia</td>
<td>0.74 (0.16)</td>
<td>Use first line</td>
<td>2</td>
<td>Co-Amoxiclav</td>
<td>S. aureus and P. aeruginosa resistance</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Consider alternatives! Resistance to all recommended therapies seen</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cellulitis / skin abscess</td>
<td>0.55 (0.20)</td>
<td>Use first line, but no data to inform – consider second or third if data</td>
<td>6</td>
<td>Flucloxacillin</td>
<td>S. aureus resistance</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Use second line</td>
<td>2</td>
<td>Clindamycin</td>
<td></td>
</tr>
<tr>
<td>Bacterial meningitis</td>
<td>0.51 (0.32)</td>
<td>Use first line, but no data to inform – consider second or third if data</td>
<td>10</td>
<td>Penicillin and Gentamicin</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Use second line, as resistance to first (but no data on resistance to second)</td>
<td>4</td>
<td>Ceftriaxone and Gentamicin</td>
<td></td>
</tr>
<tr>
<td>Septic arthritis</td>
<td>0.57 (0.09)</td>
<td>Use first line but no data to inform – consider second or third if data</td>
<td>15</td>
<td>Oxacillin</td>
<td></td>
</tr>
</tbody>
</table>

S.D., standard deviation.

*There were little data to establish key drivers.
at least one of our eight syndromes for all 46 countries in the merged dataset. On average, each syndrome had recommendations for 32 countries ranging from 14 countries for bacterial meningitis to 44 countries for bacteraemia (Table 3). Most of these countries were in Europe, the Americas and Asia, and only two in Africa (South Africa and Morocco) (Figure 4A). This reflects the underlying availability of isolates in the ATLAS dataset.

First-line antibiotics were recommended if the composite resistance rate for the infection syndrome was lower than the resistance cut-off (15%). If susceptibility data to first line antibiotics was not available, we recommended first line therapy but clarified this as “Use first line, but no data to inform - consider second or third if data”.

Most syndromes had an average syndrome coverage, across all countries and antibiotics, of above 50% (Table 3), except for complicated urinary tract infection (UTI), upper respiratory tract infection and bacterial meningitis.

Empiric therapy recommendations by syndrome derived from the ATLAS dataset are given in Table 3. 42/44 countries had resistance to all recommended therapies for the treatment of bacteraemia. This was driven by high levels of amoxicillin (first-line therapy) resistance in *Staphylococcus aureus* (assumed to cause 25% of bacteraemia cases). In total, 48% of *S. aureus* bacteraemia isolates in the ATLAS database were resistant to oxacillin and hence phenotypically MRSA, which are also resistant to cefuroxime (2nd line agent). The high levels of resistance to first-line antibiotics seen in hospital-acquired pneumonia were driven by high rates of beta-lactam resistance (cefuroxime in this therapy) in *S. aureus* and *P. aeruginosa* contributing 35% and 28% to this syndrome, respectively. A similar pattern was seen in community-acquired pneumonia, in this case driven by *Streptococcus pneumoniae* resistance to amoxicillin. For cellulitis/skin abscess the opposite was true, with the majority (>75%) of countries being recommended to use the first line antibiotic (flucloxacillin).

*E. coli* causes around 70% of complicated UTI but was not commonly tested for trimethoprim susceptibility in the ATLAS dataset, which resulted in a mean syndrome coverage of only 2% across all countries. Low syndrome coverage for complicated UTI, respiratory tract infection, bacterial meningitis and septic arthritis, meant that recommendations could not be strongly supported for these syndromes.

In summary, we could make recommendations for a limited number of infection syndromes using the ATLAS dataset.
only for bacteraemia, pneumonia and cellulitis/skin abscess. These frequently recommended use of last-resort therapies due to high levels of resistance in \textit{S. aureus} and \textit{Pseudomonas aeruginosa}. This contrasts with the lower antibiotic resistance rates derived from ResistanceMap, ECDC and GLASS datasets, which suggest that first-line antibiotics are still appropriate to treat bacteraemia empirically in most regions of the world.

Most of our final recommendations included therapies that were in the WHO Essential Medicines List and none were on the AWaRE reserve list. This means that theoretically most of the recommended antibiotics should be available on the market, even in resource constrained settings.

The AR.IA App

The AR.IA App (available here: https://gwenknight.shinyapps.io/empirc_prescribing/)\textsuperscript{13} presents the underlying data and recommendations described above. User instructions on how to use the App are presented in the section AR.IA App Documentation in Extended Data\textsuperscript{13}. The AR.IA App allows the user to choose and combine multiple AMR surveillance datasets when calculating the syndrome-level composite resistance index. It allows the user to change multiple parameters, including syndrome type, resistance cut-off and aetiology. It can produce visual aids like the maps showed above (see Figure 4B, showing a global map of the proportion of syndromes for each available country for which we still recommended to use first-line therapy).

Discussion

We aimed to determine whether open-access AMR surveillance datasets, such as the newly available ATLAS dataset, could be used to inform on the appropriateness of empiric antibiotic therapies to treat common infection syndromes. We integrated data on which antibiotics are commonly prescribed as empiric therapy, the bacterial aetiology of each syndrome and the antibiotic susceptibilities of syndrome-contributing bacteria to produce a syndrome-level composite resistance index. We presented our results on an interactive web app, the AR.IA App\textsuperscript{13}, to allow users to explore the impact of resistance rates on prescribing decisions. Our code is available in an open-access format and broken down into discrete sections that can be re-used and modified by any user. To our knowledge, this is the first time that antibiotic resistance estimates have been compared between multiple global AMR surveillance datasets and linked to the MSH International prices dataset to present a coalition of resistance, proxy cost and proxy access indicators.

We report antibiotic resistance aggregated at the syndrome level which we believe has greater clinical relevance and could directly inform policy. Similar “indices” have been previously proposed\textsuperscript{13}. The Drug Resistance Index was developed to quantify resistance to multiple antibiotics for individual bacterial species\textsuperscript{5} and communicate to policymakers and non-experts the impact resistance has on the antibiotics available for treatment. Here we extended this concept to take into account the aetiology of infectious syndromes to inform on antibiotic availability and clinical treatment guidelines. This idea was explored by Ciccolini \textit{et al.}\textsuperscript{7} where the relative frequency of causative agents and frequency of resistance was combined with antibiotic usage data to assess the population-level appropriateness of empiric treatment regimens for complicated UTI in the Netherlands. A study in a Canadian intensive care unit explored the likely efficacy of empiric treatment for three device-associated infections by creating a composite syndrome level resistance\textsuperscript{38}. A “basket” of bacterial agents causing each infection was used similarly to how economists measure the average price of a standard basket of consumer goods weighted by the relative importance of each good\textsuperscript{39}.

Despite the variety of antibiotics tested, clinical sources, bacterial species and countries represented in the ATLAS dataset, we often found there were not enough isolates—from syndrome-causing bacteria, syndrome-relevant sources and tested for the antibiotic of interest—to calculate composite resistance indices for most syndromes. As a result, we could only derive country recommendations for relatively few infections (bacteraemia, pneumonia and cellulitis/skin abscesses). We also noted what appeared to be an over-representation of antibiotic-resistant isolates in the ATLAS dataset, as compared to the ECDC and ResistanceMap datasets. This may reflect a sampling bias to test for non-susceptible isolates or particular types of infections with higher rates of resistance. We are therefore more likely to observe resistance to first-line therapies in the ATLAS dataset, which leads to frequent recommendation of last-line therapies.

Our analysis has several limitations. We only included a limited set of infection syndromes and hence used only part of all available ATLAS entries. Future work should include other syndromes, such as purulent urethritis (typically caused by \textit{Neisseria gonorrhoeae}), and sub-classify broad syndromes into narrower types of infections. Syndrome aetiology was informed only by basic literature reviews and will need to be supported by in-depth systematic reviews and account for regional, seasonal and host population differences. At this stage, we allow AR.IA App users to change the aetiological distributions. The choice of antibiotics used as empiric therapies could also be inputted by the user. The level of recommendations (i.e. country-level) was dictated by the type of sampling available from global AMR surveillance datasets. Increased granularity will be needed to tailor antibiotic prescribing guidelines to local settings (e.g. hospital-level). Alternatively, resistance data could be pooled across multiple neighbouring countries with sparse availability of resistance information.

AMR surveillance datasets do not report the susceptibilities of antibiotics that bacteria are commonly sensitive or intrinsically resistant to. For example, \textit{Pseudomonas aeruginosa} is intrinsically resistant to many beta-lactams and thus it is never tested against these agents. AMR surveillance datasets will need to systematically incorporate these rules. Datasets other than ATLAS reported susceptibility to antibiotic classes (e.g. cephalosporins), instead of that to individual drugs (e.g. ceftriaxone), which was not helpful for empiric therapy design as resistance is not always common to all antibiotics belonging to the same class. Identifying such an “optimum arrangement for recording and reporting of AMR data” is indeed one of the objectives of the UK Five-Year Antimicrobial Resistance Strategy\textsuperscript{39}. This includes using point prevalence surveys as the
gold standard (as opposed to convenience sampling of isolates from clinical specimens that may be biased towards resistant strains) to estimate the total burden of antimicrobial resistance, determine the aetiology of common infection syndromes and ultimately inform empiric antibiotic guidelines.

This work focuses on improving guidelines for empiric treatment of infection, but there are several fundamental limitations to the usefulness of this approach. Firstly, patients identified by laboratory investigation to have antibiotic-susceptible infections can still be effectively treated with agents showing extensive resistance rates at the population level. Secondly, empiric guidelines typically favour the use of broad-spectrum antibiotics to achieve the highest chance of treatment success, but this may not always be in the individual or population’s best overall interest in terms of minimizing side-effects (such as Clostridium difficile infection) or conserving effectiveness of treatments. Thirdly, some drugs with low-levels of resistance but multiple other sub-optimal properties (such as vancomycin) may be recommended in later lines of empiric therapy at high levels of resistance. And fourthly, the assumption is made that infection syndromes are caused entirely by bacterial pathogens requiring antibiotic treatment, when in reality many infections are caused by viruses and would recover without needing antibiotics. Whilst future advances on rapid and cheap point-of-care diagnostics for AMR bacteria might remove the need for empiric therapy, these will continue to widely be used in many settings, especially in low-income countries.

Conclusion
We have shown how independent sources of data can be combined with AMR surveillance information, such as the ATLAS dataset, to add clinical and policy-making value. Our results suggest that whilst the creation of a composite resistance index is technically feasible, the data needed to make robust prescribing recommendations for most infectious syndromes is currently lacking. In line with the WHO calls for “evidence-based prescribing”, we believe this approach could be used to monitor the effectiveness of antibiotic empiric therapies, the cornerstone of current antibiotic prescribing practices. Such an approach can be applied to more robust data as these become available.

Data availability
Underlying data
Table 4 contains the underlying data used in this study; Table 5 contains these data compiled for use in the AR.IA App.

Table 4. Source of the underlying data used in this study.

<table>
<thead>
<tr>
<th>Title</th>
<th>Use</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATLAS</td>
<td>Source of laboratory data</td>
<td><a href="https://atlas-surveillance.com/#/login">https://atlas-surveillance.com/#/login</a></td>
</tr>
<tr>
<td>GLASS</td>
<td>Used in comparison of datasets</td>
<td>Dataset provided by the World Health Organization. <a href="https://www.who.int/glass/en/">https://www.who.int/glass/en/</a></td>
</tr>
</tbody>
</table>
Table 5. Data from Table 4 compiled for use in the final running of the AR.IA App.

<table>
<thead>
<tr>
<th>Title</th>
<th>DOI</th>
<th>Use</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>AR.IA App all datasets</td>
<td><a href="https://doi.org/10.6084/m9.figshare.9821996">https://doi.org/10.6084/m9.figshare.9821996</a></td>
<td>Data from the ATLAS dataset, the ECDC Surveillance Atlas, ResistanceMap, and GLASS aggregated by species and drugs of interest in our analysis</td>
<td>41</td>
</tr>
<tr>
<td>AR.IA App drug breakdown</td>
<td><a href="https://doi.org/10.6084/m9.figshare.9822077">https://doi.org/10.6084/m9.figshare.9822077</a></td>
<td>Baseline empiric therapy recommendations</td>
<td>42</td>
</tr>
<tr>
<td>AR.IA App drug breakdown (groups)</td>
<td><a href="https://doi.org/10.6084/m9.figshare.9822104">https://doi.org/10.6084/m9.figshare.9822104</a></td>
<td>Baseline empiric therapy recommendations with drug groupings instead of individual drugs</td>
<td>43</td>
</tr>
<tr>
<td>AR.IA App species breakdown</td>
<td><a href="https://doi.org/10.6084/m9.figshare.9822179">https://doi.org/10.6084/m9.figshare.9822179</a></td>
<td>Baseline contributing bacteria distributions</td>
<td>44</td>
</tr>
<tr>
<td>AR.IA App all species</td>
<td><a href="https://doi.org/10.6084/m9.figshare.9822146">https://doi.org/10.6084/m9.figshare.9822146</a></td>
<td>List of species to include</td>
<td>45</td>
</tr>
<tr>
<td>AR.IA App economic data</td>
<td><a href="https://doi.org/10.6084/m9.figshare.9822122">https://doi.org/10.6084/m9.figshare.9822122</a></td>
<td>Cost, WHO EML and AWaRe</td>
<td>46</td>
</tr>
</tbody>
</table>

Extended data

This project contains further information on the manipulation of the ATLAS dataset, the comparison of the ATLAS dataset with ECDC Surveillance Atlas and ResistanceMap, the creation of our drug-resistance index, and details on other drug information datasets used in our analysis.


This project contains further information on the comparison of the ATLAS dataset with ECDC Surveillance Atlas and ResistanceMap, the antibiotics used in our analysis, the summary of our review for the aetiology of the infection syndromes, the process to combine the antimicrobial resistance datasets, and to combine the drug information datasets. Also contained are Supplementary Figures 1-3, and Supplementary Tables 1-6.


This project contains instructions regarding the usage of the App developed as part of this project. Also contained is Supplementary Figure 4.

Extended data are available under the terms of the Creative Commons Attribution 4.0 International license (CC-BY 4.0).

Software availability
The AR.IA App is available at: https://gwenknight.shinyapps.io/empiric_prescribing/.


Archived source code at time of publication: https://doi.org/10.5281/zenodo.3418998.

Licence: GNU General Public License v3.0.

Acknowledgments
The authors would like to acknowledge Dr Lisa Knight for consultation relating to clinical input.

References
6. Fernández González F, Detrés J, Torrellas P, et al.: Comparison of the...

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http://www.doj.org/10.6084/m9.figshare.9852029.v2


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http://www.doj.org/10.6084/m9.figshare.9821995.v1


http://www.doj.org/10.6084/m9.figshare.9822077.v1


http://www.doj.org/10.6084/m9.figshare.9822104.v1


http://www.doj.org/10.6084/m9.figshare.9822179.v1


http://www.doj.org/10.6084/m9.figshare.9822146.v1


http://www.doj.org/10.6084/m9.figshare.9822122.v1
This is an important proof-of-concept study. The aim is to provide a "clinically-oriented presentation of resistance rates" from available AMR surveillance datasets. The main conclusion is that while this is technically possible for some syndromes, the datasets are not yet adequate.

I enjoyed reading the manuscript and anticipate that it will be read with interest by other researchers interested in this general approach. Thanks to the authors for carrying out this work!

Positive points:

- An impressive integration with existing datasets beyond the central dataset (ATLAS).
- A range of sources of data have been synthesised – not just resistance rates but also information on syndromes, guidelines, etc.
- Clear presentation of methodology and results.
- Online interactive app so readers can experiment themselves and get a feel for the approach.
- Reproducibility: I could successfully clone the github repository and run the app myself in under a minute.

I have selected “Approved with reservations” as I do have some suggestions for improvement, which I hope the authors will consider.

Major points

1. Infection syndromes:
   I think a strict definition of what is meant by “infection syndrome” should be given, as readers may not be that familiar with the term (I admit I wasn’t totally clear what was meant without looking at the examples). With the caveat that I am not a clinician, I think it is underplayed that the infection syndromes looked at are often not known to be due to bacteria. For example, upper respiratory
tract infections – the majority are viral (the Further Methods state 90%). And for bacteraemia, patients can present only with fever, at which point a decision has to be made about treatment. It seems to me it would be less common to have a scenario where a patient has a known bacterial infection syndrome but nothing is known beyond that. This may be my own ignorance; I'd welcome any supporting evidence about how often this is the case in practice.

I know the authors are aware of this problem, but I think it should be stated explicitly that the problem considered here is: “an ideal world where one was confident that an infection was bacterial but did not know the species or the resistance profile” (I think that’s a reasonable formulation?). The effect of including the proportion expected to be non-bacterial and therefore unaffected by antibiotics would be to reduce the likelihood of prescribing antibiotics. The high proportion of recommendations to treat with antibiotics beyond first-line antibiotics is driven by this exclusively bacterial assumption (and the resistance datasets used). This should be emphasised.

To be clear, I’m not suggesting redoing all this work taking into account the proportion of patients presenting with symptoms X/Y/Z who have a bacterial vs. viral infection. The work here stands in its own right. However, the major problem in antibiotic prescribing is the decision to prescribe antibiotics *at all* rather than deciding whether to prescribe first/second/third-line antibiotics. I think this needs to be mentioned up front; at present it comes very late as the fourth limitation in the discussion. In practice this is what most readers will think of when thinking about antibiotic stewardship and how prescribing apps might help.

2. Accuracy

I appreciate this is always put in quotes to emphasise the restricted sense of “accurate” that is meant, but I still think this is the wrong term. I suggest changing all uses of it and avoiding the word entirely. “Accurate” suggests that the ground truth or right answer can be derived from the ResistanceMap or ECDC dataset, and that because the ATLAS point estimate lies outside the 95% confidence interval from these datasets it is “inaccurate”, which I think is misleading. The right answer for the ‘true’ prevalence of resistance isn’t known in this circumstance, and in fact resistance prevalence is context-dependent on the sampling (community vs. hospital etc.). I’d suspect variation in sampling is the driver, as suggested, and also that the ATLAS dataset for some countries might include only a few sites. What is being defined is not accuracy, but agreement between datasets. So, “concordance” or “agreement” would be a better term.

I would also be interested to see a plot using data presented in Supplementary Figure 1, but adding the agreement against the number of samples that went into producing the ATLAS point estimate. If the problem driving low agreement is not enough samples in the ATLAS dataset, then more samples would produce more agreement with ECDC. If the problem is differences in sampling (e.g. bias towards resistant organisms in ATLAS due to specific clinical setting) then more samples in ATLAS would produce less agreement with ECDC. It might not be as clear-cut as I'm assuming, but at the moment this isn't clear. It seems like an important distinction to shed light on.

3. Comparison with other datasets

I agree that ECDC data is merged into ResistanceMap and the resistance rates for those countries are therefore the same. Therefore, I'm a bit confused why a comparison is made of ATLAS vs. ECDC and ATLAS vs. ResistanceMap without apparently removing ECDC as far as I could tell? Fundamentally the ECDC data is inside ResistanceMap. It seems to me that the important comparisons would be ATLAS vs. ECDC and ATLAS vs. (ResistanceMap – ECDC). I think for this
reason there’s currently double-counting going on in Supplementary Figure 1, 2, 3 which could be rectified. If I misunderstood and this has already been removed, apologies!

Minor points

I have ordered these by section.

Introduction

- Para 1: First sentence, suggest replacing “being known” by “determined by tests” (as highlights that this can only be really known by some sort of test/procedure outside normal clinical assessment, and also that sometimes tests are inconclusive).

- Para 2: “infection syndrome” --> “infection syndromes”.

- Para 3: suggest providing example(s) of a bacterial infection syndrome where the aetiology varies by season.

- Para 4: think the usual phrase is “resource-limited” rather than “resource constrained” (I could be wrong)

- Para 5: “which have limited healthcare budgets and difficulties to access medicines” --> “which can have limited healthcare budgets and access to medicines”

- Para 6: “infection syndromes” need to be defined earlier. Suggest in Para 2.

Methods

- Para 2: “This dataset was made public in 2017” – I accept this was when the ATLAS website went live, but the dataset was made browsable, not downloadable. Worth explaining that the whole dataset as csv was actually released in 2018 to participants in Data Reuse Prize.

- Para 5, Surveillance data comparison: see major point about changing “accuracy” (and change elsewhere as well).

- (a) “Common infection syndromes”: I’m not sure if all these syndromes are identifiable with simple clinical examination and/or radiology, so just want to check this point i.e. what’s meant by “clinical examination”. As I mentioned, as far as I’m aware patients can present only with fever for bacteraemia, so I’m not sure how it can be easily identified. Also, the syndromes are assumed to be independent of each other i.e. patients present with only one. This is a limitation as in practice they can be linked e.g. bacterial meningitis develops from initial bacteraemia. Or e.g. NICE guidelines highlight link between hospital-acquired pneumonia and bacteraemia.

- “NICE guideline” --> “NICE guidelines”. Also, the link to the NICE guidelines (reference 8) is wrong. It takes me to PHE’s 119-page document “Summary of antimicrobial prescribing guidance – managing common infections”. I think the correct link should be: [https://www.nice.org.uk/Media/Default/About/what-we-do/NICE-guidance/antimicrobial%20guidance/antimicrobial-prescribing-guidance.pdf](https://www.nice.org.uk/Media/Default/About/what-we-do/NICE-guidance/antimicrobial%20guidance/antimicrobial-prescribing-guidance.pdf). Is this correct? Assuming these are the correct guidelines, I became slightly confused about how the syndromes were identified. For example, upper respiratory tract infection as defined in Table 2 doesn’t include “acute otitis media”, which is included in this syndrome in the NICE guidelines. The first-choice treatment for acute otitis media is amoxicillin, rather than penicillin V. I have not
investigated all the other syndromes but I just want to check why this was excluded? Apologies if I missed this somewhere.

- On this point, I couldn’t find the guidelines for bacteraemia in that NICE link. “Bacteraemia” is the presence of bacteria in the blood; “sepsis” is probably a better term for the infection syndrome. I noticed that the app uses “sepsis”, but the main paper uses “bacteraemia”, suggest to make them consistent.

- (d) “Contributing pathogen distribution: syndrome aetiology”: on “rapid literature search”, it would be good to know how this review worked in practice e.g. searching PubMed / Google Scholar / the wider web? One author assigned to a syndrome? One author doing all syndromes? How were results integrated? There’s no problem at all with it being rapid and informal, but a little more info on the process would be great.

Results

- Table 3: the summary table of the recommendations for therapy is based on the arbitrary 15% cut-off. This should be stated in the caption of the table. I think it would be good to present the actual distributions in a supplementary figure (i.e. the percentages for the index), but this isn’t essential. I would also state that only those syndromes with an average above 50% were included (which I infer from the associated text). Column stating “Average syndrome coverage” – presume “Mean syndrome coverage” is meant instead.

- (g) “Resulting recommendations on the appropriateness of empiric antibiotic therapies” Para 3: bacterial meningitis has an “average syndrome coverage” of 0.51 in Table 3, so why does a sentence here state it has lower than 50%? Also, suggest stating the syndrome coverages for these syndromes that are not listed in Table 3.

- Figures: in general, please check the resolution of the figures. For example, Figure 3 seems quite low-res to me. For Figure 1: the arrows on the left-hand side aren’t clear, I got a bit confused with the arrows pointing to other arrows. Suggest using a colour key for these arrows instead.

- Table 2: “Infectious syndrome” --> “Infection syndrome” (first column)

Discussion

- Para 3: “over-representation of antibiotic-resistant isolates in the ATLAS datasets” – see previous comment about a plot of ATLAS sample size against agreement with ECDC which might provide some more support for the hypothesis causing this.

- Para 5: “antimicrobial resistance” --> AMR

Conclusion

- “the WHO calls for” --> “the WHO’s call for”. Also provide a reference for this call for “evidence-based prescribing”. I wasn’t sure what was being referred to.

Further methods

- Section 1: no new MIC thresholds were included, which is acknowledged as a limitation. These would not in principle be difficult to include from EUCAST and could bump up the dataset. For example, *E. coli* and ceftaroline-avibactam: there are 13,203 isolates with a reported MIC. The EUCAST breakpoint is 0.5 mg/L. So using my version of the ATLAS dataset, 139/13,202 isolates
(1.05%) are resistant. I accept compiling bug/drug combinations for breakpoints (and considering both EUCAST and CLSI) would be tedious, and so much data integration has already been done! I’d be happy to approve the paper without this extra work. But it would be good to have some idea of how much doing this would increase sample sizes, which could be done without external data integration.

- Section 3: This paragraph is quite dense and a brief overview in the main paper would be useful, because the index is a key concept. In a talk based on this work by Francesc Coll at a SEDRIC meeting on October 9th 2019, I saw a great diagram, I think of the example given here. I would strongly suggest including this as a figure in the main paper, as it quickly conveys the idea of the index visually.

Further results
- Section 3: Upper respiratory tract infection has a reference (49) which is missing from the references at the end of this document.

Is the work clearly and accurately presented and does it cite the current literature?
Partly

Is the study design appropriate and is the work technically sound?
Yes

Are sufficient details of methods and analysis provided to allow replication by others?
Yes

If applicable, is the statistical analysis and its interpretation appropriate?
Yes

Are all the source data underlying the results available to ensure full reproducibility?
Yes

Are the conclusions drawn adequately supported by the results?
Yes

Competing Interests: I entered the same competition as the authors (Wellcome AMR Data Reuse Prize) and received a runner-up award. I also did a short masters project supervised by Gwen Knight in 2014. I do not feel this has unduly biased my review.

Reviewer Expertise: My main research area is bacterial genetics, including antimicrobial resistance. I also have direct experience of analysing the ATLAS dataset used in this work.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.