

Selecting appropriate empirical antibiotic regimens for paediatric bloodstream infections: application of a Bayesian decision model to local and pooled antimicrobial resistance surveillance data

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Objectives: The objective of this study was to evaluate the ability of weighted-incidence syndromic combination antibiograms (WISCAs) to inform the selection of empirical antibiotic regimens for suspected paediatric bloodstream infections (BSIs) by comparing WISCAs derived using data from single hospitals and from a multicentre surveillance dataset.

Methods: WISCAs were developed by estimating the coverage of five empirical antibiotic regimens for childhood BSI using a Bayesian decision tree. The study used microbiological data on ~2000 bloodstream isolates collected over 2 years from 19 European hospitals. We evaluated the ability of a WISCA to show differences in regimen coverage at two exemplar hospitals. For each, a WISCA was first calculated using only their local data; a second WISCA was calculated using pooled data from all 19 hospitals.

Results: The estimated coverage of the five regimens was 72%–86% for Hospital 1 and 79%–94% for Hospital 2, based on their own data. In both cases, the best regimens could not be definitively identified because the differences in coverage were not statistically significant. For Hospital 1, coverage estimates derived using pooled data gave sufficient precision to reveal clinically important differences among regimens, including high coverage provided by a narrow-spectrum antibiotic combination. For Hospital 2, the hospital and pooled data showed signs of heterogeneity and the use of pooled data was judged not to be appropriate.

Conclusions: The Bayesian WISCA provides a useful approach to pooling information from different sources to guide empirical therapy and could increase confidence in the selection of narrow-spectrum regimens.

Introduction

Bloodstream infections (BSIs) are associated with significant mortality and morbidity^{1,2} and patients with suspected BSI should receive effective antibiotic treatment rapidly.³ At present, early therapeutic decisions for suspected BSI usually remain empirical as the causative pathogen and its resistance phenotype are unknown at the start of therapy.⁴ Consequently, broad-spectrum agents may be used preferentially in the assumption that this will ensure effective treatment.

Cumulative hospital antibiograms provide information on the locally observed *in vitro* susceptibility of individual species or genera of bacteria to particular antibiotics.⁵ During empirical treatment (ET), however, the causative pathogen is unknown as many different bacteria may cause the same clinical infection

syndrome.⁴ In contrast, syndromic metrics aim to give the expected coverage of an ET regimen defined as the probability that a regimen will be active against relevant potential causative pathogens.^{6–10} An important syndromic metric, the weighted-incidence syndromic combination antibiogram (WISCA), provides coverage estimates for a range of ET regimens as a weighted average of the pathogen susceptibilities, with the weights defined by the relative incidence of the pathogens. However, practical issues relating to the construction of a WISCA from routinely available antimicrobial resistance (AMR) data for use in day-to-day practice remain unexplored. For infections with a relatively low incidence, a major challenge is how to deal with uncertainty associated with small sample sizes. In this paper, we describe a Bayesian version of the WISCA, which helps to address various issues that arise because of the comparatively low incidence of childhood BSI.

Using AMR data for bloodstream isolates collected as part of the Antibiotic Resistance and Prescribing in European Children (ARPEC) project,¹¹ we focus on the potential benefit of pooling data from multiple centres and examine whether this improves clinicians' ability to select ET regimens with high coverage.

Methods

Development of a Bayesian WISCA

The WISCA was developed as a decision tree (Figure 1), with the first node (square) representing the clinical decision to initiate ET being linked to nodes (circles) that represent the regimen choices and subsequent branches describing chance events. These were the range of bacterial species causing paediatric BSI, their relative frequency and the proportions (as percentages) of each pathogen susceptible to each antibiotic regimen. The end branches (triangular nodes) correspond to concordant or discordant therapy. The expected coverage for each regimen is the combination of the probabilities along the regimen tree branches. A Bayesian perspective was then adopted in which the value of the pathogen incidence and pathogen-regimen susceptibility parameters for each regimen were

defined as a probability distribution that reflected the uncertainty in its value.^{12,13}

Data sources

First blood culture isolates of *Streptococcus pneumoniae*, *Staphylococcus aureus*, *Enterococcus faecalis*, *Enterococcus faecium*, *Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter* spp. and *Pseudomonas aeruginosa* from children aged 0–18 years reported to the ARPEC surveillance project (19 participating centres in 12 European countries from 1 January 2011 to 31 December 2012) were analysed.¹¹ Any blood cultures from a previously included patient and positive for the same organism within 4 weeks of the original reported isolate were excluded as duplicates. Participants were also asked to report counts of positive blood cultures of *Streptococcus pyogenes* (group A streptococci), *Streptococcus agalactiae* (group B streptococci), *Neisseria meningitidis*, *Haemophilus influenzae*, *Salmonella enterica* and *Acinetobacter baumannii*. Data on the AMR of these bacteria were not collected.

The study also used information on the distribution of pathogens from positive blood cultures from children 0–18 years of age in the PHE communicable diseases second-generation surveillance system (SGSS) database.

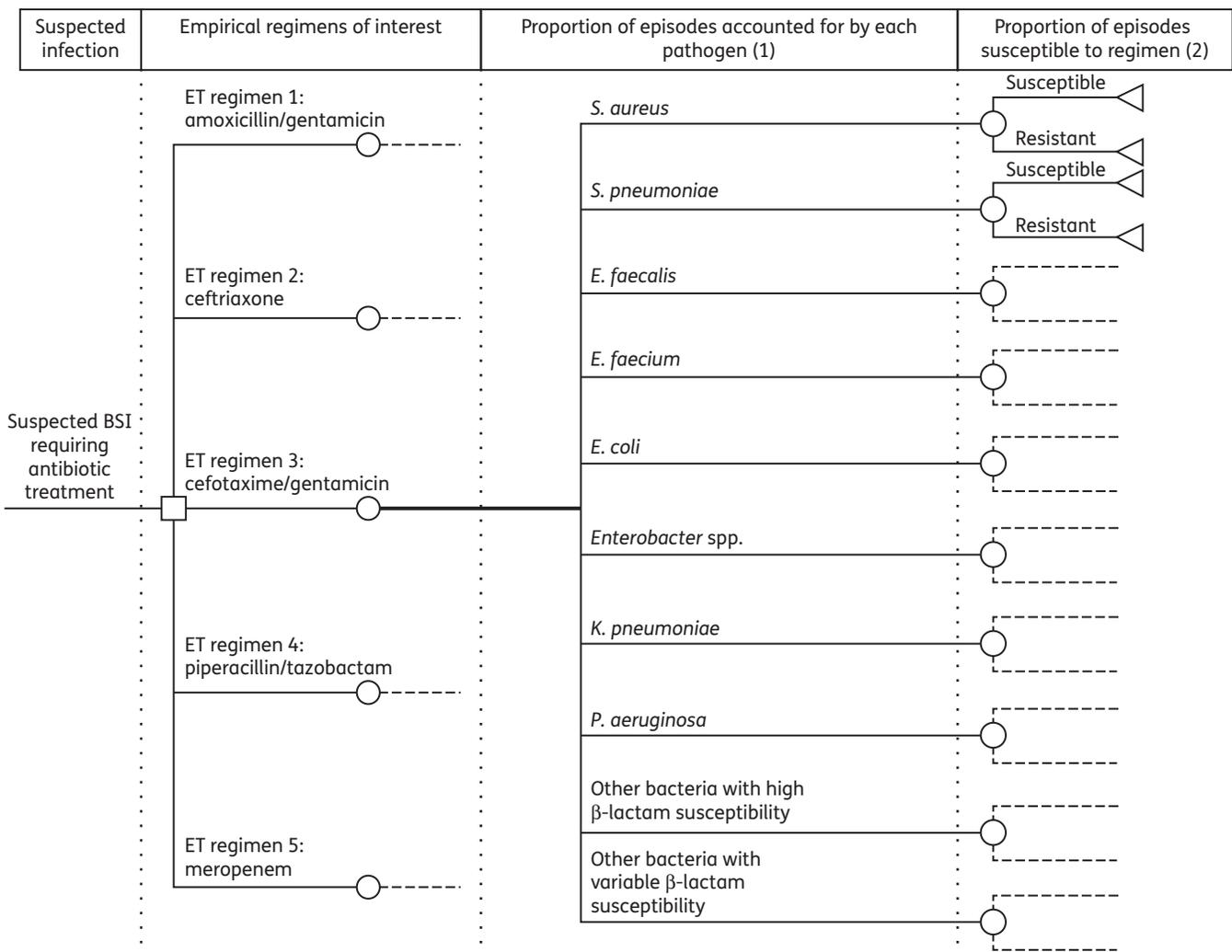


Figure 1. Decision tree for estimating ET regimen coverage.

This distribution was based on all relevant deduplicated isolates reported for 2014 from England, Wales and Northern Ireland and was compared with the pathogen distribution within the ARPEC data.

Parameter estimation

Five ET regimens (amoxicillin/gentamicin, ceftriaxone, cefotaxime/gentamicin, piperacillin/tazobactam and meropenem) reported as in use for suspected BSI in the hospitals participating in ARPEC were selected for evaluation of coverage estimated based on the decision tree described above.¹⁴

The WISCA distinguished between 10 categories of bacteria that could lead to a paediatric BSI. These consisted of the eight core ARPEC bacterial species and two additional groups of bacterial species for which AMR information was not collected as part of ARPEC surveillance. For these latter two groups, pathogens were grouped according to likely β -lactam susceptibility, because all five regimens contained a β -lactam. CoNS and non-pyogenic streptococci were not included in this analysis, as identification of clinically relevant bloodstream isolates would require application of additional algorithms as BSI caused by these pathogens is unlikely to be life-threatening in a great majority of cases (therefore not needing coverage during early ET).^{15,16}

The estimated susceptibility of the eight ARPEC organisms to each regimen was determined directly from ARPEC AMR surveillance data. For monotherapy regimens, isolates reported as intermediate or resistant to any antibiotic representative of the antibiotic class were classified as resistant. Standard algorithms were applied to infer susceptibility from testing results as appropriate, e.g. when different antibiotics were considered equivalent or when interpretive algorithms were available.^{17,18} Isolates were classified as susceptible to a combination when they were reported as susceptible to at least one of the antibiotics in the combination.

In addition, for bacteria that would be expected to have intrinsic resistance [and for which there was selective (non-)testing], we assumed expected susceptibility values of 0%, regardless of the availability of antimicrobial susceptibility testing (AST) information.^{17,18} Where AMR data were not available in the ARPEC database, susceptibility for grouped bacteria was estimated based on surveillance data from the bacteraemia surveillance programme sponsored by the BSAC for 2012.¹⁹

In the framework of the Bayesian decision tree, the observed pathogen data were assumed to be drawn from a multinomial distribution with 10 possible outcomes. We selected a non-informative uniform prior, specified as the Dirichlet(1, 1, ..., 1) distribution. The Dirichlet distribution is the conjugate prior for data from a multinomial distribution and results in a posterior distribution of the form Dirichlet(1+n₁, 1+n₂, ..., 1+n₁₀) where n_i are the observed number of each type of pathogen.^{12,13} Using a non-informative prior meant the posterior distribution was predominately determined by the data.

Susceptibility percentages were assumed to be drawn from a binomial distribution. The prior distributions for the susceptibility parameters were defined using the conjugate beta distribution, thus resulting in the posterior being a beta distribution.^{12,13} For most regimens, we had no strong prior beliefs about resistance patterns and used a non-informative prior, the beta(0.5, 0.5) distribution. For bacteria that would be expected to have intrinsic resistance, we specified the prior as a beta(1, 9999), which gave a 99.8% coverage interval for susceptibility of 0%–0.1%, dominating any AST results. All modelling was undertaken using Microsoft Excel® 2010.

Scenario analysis

We developed a series of scenarios to examine the difference in coverage estimates produced using data from single hospitals and from all 19 ARPEC centres and how this affected clinicians' ability to select ET regimens with high coverage.

Single hospital data scenario

The first scenarios examined the usefulness of a WISCA derived using data from single hospitals. Two hospitals were selected from the 19 ARPEC participants based on their number of reported bloodstream isolates being near to the median number of isolates reported across all participating hospitals. Using their local data, we estimated the expected coverage of the five regimens applying the decision tree model.

Surveillance data scenario

The second scenario evaluated the extent to which using data from all 19 hospitals increased the precision of the coverage estimates at the two hospitals and hence the usefulness of the resulting WISCA. To determine whether the single centre could be regarded as being representative of the group of hospitals, we adopted a technique that could be used when both single hospital and pooled results were available. We first examined whether the patterns of AMR at the single hospital were substantially different from the pattern of AMR in the pooled data using a funnel plot technique.²⁰ This corresponds to testing whether AMR patterns at a hospital differed from the average across all hospitals only by an amount consistent with the influence of random variation alone. We considered it acceptable to substitute the overall average for the hospital average if the estimate from the single hospital fell within the 95% inner and outer control limits of the funnel displayed as a bullet graph. For the incidence estimates, we used a χ^2 test to evaluate whether the incidence estimates of bacteria at the single hospital data differed markedly from the other ARPEC hospitals, and considered it acceptable to use the incidence estimates from all hospitals if the *P* value was >0.05.

Results

The full ARPEC dataset contained 1704 isolates with complete susceptibility testing information and 232 isolates for which no AMR data were recorded. As specified above, the likely AMR patterns for the latter 232 isolates were simulated based on BSAC surveillance data.¹⁹

Parameter table for WISCA estimation

Table 1 shows the parameter estimates for the Bayesian WISCA needed to estimate coverage for the ET regimen combining amoxicillin and gentamicin for the two single hospitals and the full dataset. Table 1 also includes the 95% credible interval from the posterior distributions to illustrate the uncertainty associated with each parameter estimate. For the data from the single hospitals, the 95% credible interval widths for the susceptibility parameters varied from 11% to 85%, reflecting the small numbers of some pathogens identified and/or subjected to susceptibility testing. Table 1 also illustrates that the number of isolates tested was often less than the number of pathogens recorded.

Single hospital coverage

Figures 2 and 3 present the BSI coverage estimates for the five antibiotic regimens using data from the two selected single hospitals with estimates based on the full surveillance dataset shown for comparison. For Hospital 1, the coverage estimates ranged from 72% (for ceftriaxone) to 86% (for amoxicillin/gentamicin). For Hospital 2, the estimates ranged from 79% (for piperacillin/tazobactam) to 94% (for meropenem). For both hospitals, there was a marked degree of overlap of the 95% credible intervals

Table 1. Parameter table for surveillance simulation with data sources indicated; see the Methods section for further information on parameter definition and pathogen grouping

Incidence	Hospital 1			Hospital 2			Full ARPEC dataset		
	<i>n</i>	%	95% CrI ^a	<i>n</i>	%	95% CrI ^a	<i>n</i>	%	95% CrI ^a
<i>S. aureus</i>	20	22%	14%–31%	23	18%	12%–25%	449	23%	21%–25%
<i>S. pneumoniae</i>	5	6%	2%–12%	13	11%	6%–17%	163	9%	7%–10%
<i>E. faecalis</i>	10	11%	6%–18%	3	3%	1%–6%	175	9%	8%–10%
<i>E. faecium</i>	3	4%	1%–9%	1	2%	<1%–4%	95	5%	5%–6%
<i>E. coli</i>	18	20%	12%–28%	24	19%	13%–26%	380	20%	18%–21%
<i>Enterobacter</i> spp.	3	4%	1%–9%	3	3%	1%–7%	122	6%	5%–8%
<i>K. pneumoniae</i>	7	8%	4%–14%	14	11%	7%–17%	183	10%	8%–11%
<i>P. aeruginosa</i>	2	3%	1%–7%	0	0%	0%–3%	137	7%	6%–8%
Other bacteria with high susceptibility	17	19%	12%–27%	35	28%	21%–35%	175	9%	8%–10%
Other bacteria with variable susceptibility	2	3%	1%–7%	5	5%	2%–9%	57	3%	2%–4%
Total	87	100%		148	100%		1936	100%	

Amoxicillin/gentamicin resistance	Hospital 1			Hospital 2			Full ARPEC dataset		
	<i>n</i>	% susceptible	95% CrI ^b	<i>n</i>	% susceptible	95% CrI ^b	<i>n</i>	% susceptible	95% CrI ^b
<i>S. aureus</i>	14	90%	71%–99%	22	98%	89%–100%	421	97%	94%–98%
<i>S. pneumoniae</i>	5	92%	62%–100%	8	94%	73%–100%	152	97%	93%–99%
<i>E. faecalis</i>	10	95%	78%–100%	3	63%	17%–97%	160	93%	89%–97%
<i>E. faecium</i>	3	37%	4%–82%	1	24%	0%–85%	86	15%	8%–23%
<i>E. coli</i>	18	82%	63%–95%	24	82%	66%–94%	378	88%	85%–91%
<i>Enterobacter</i> spp.	3	88%	47%–100%	3	63%	18%–97%	121	90%	85%–95%
<i>K. pneumoniae</i>	7	81%	50%–98%	14	23%	7%–46%	183	75%	68%–80%
<i>P. aeruginosa</i>	2	83%	32%–100%	—	—	—	137	76%	69%–82%
Other bacteria with high susceptibility	9	91%	74%–99%	33	96%	87%–100%	164	96%	92%–98%
Other bacteria with variable susceptibility	2	84%	37%–100%	5	92%	65%–100%	56	98%	94%–100%

CrI, credible interval.

^aBased on a Dirichlet posterior distribution that combines the observed data with a non-informative prior, Dirichlet(1, 1, 1, ..., 1).

^bBased on a beta posterior distribution that combines the observed data with a non-informative prior, beta(0.5, 0.5).

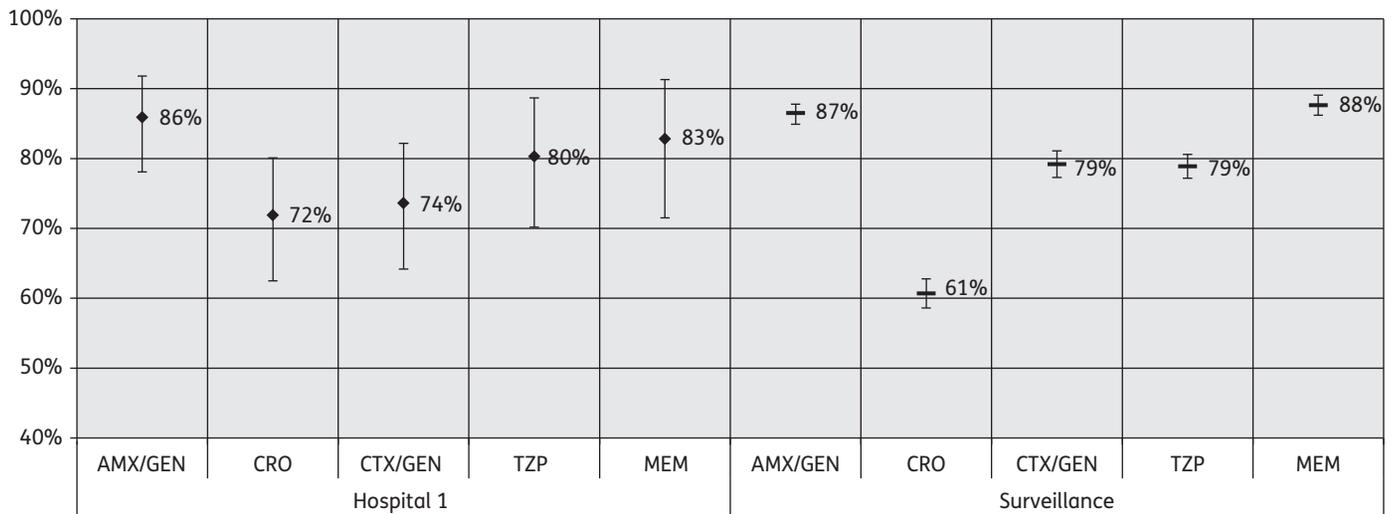


Figure 2. BSI coverage estimates for different ET regimens based on single centre data for Hospital 1 or on the pooled surveillance data. The 95% credible intervals are shown as bars. AMX/GEN, amoxicillin/gentamicin; CRO, ceftriaxone; CTX/GEN, cefotaxime/gentamicin; TZP, piperacillin/tazobactam; MEM, meropenem.

for coverage estimates, indicating that the estimates derived from a single hospital's data could not generally provide robust information on the relative performance of the regimens.

Using pooled surveillance data to improve coverage estimates

The impact of using the pooled data from all 19 hospitals to estimate coverage is shown in Figures 2 and 3. As a result of the much larger sample, coverage estimates were more precise and this revealed clear differences between the regimens. The right-hand column of Table 1 gives the parameter values for the amoxicillin/gentamicin regimen based on the pooled ARPEC data, with the

improved precision being reflected by the smaller 95% credible intervals of the parameter values.

Establishing whether pooled surveillance data are applicable to a specific hospital

For Hospital 1, we found no evidence that this hospital had a different pattern of pathogen incidence ($P=0.57$) compared with the remaining 18 centres or that the regimen susceptibility differed significantly from that of the overall cohort of all 19 hospitals. This indicated that the hospital was unlikely to be an outlier and using the pooled data was appropriate. Figure 4 shows how the values of the susceptibility parameters for individual

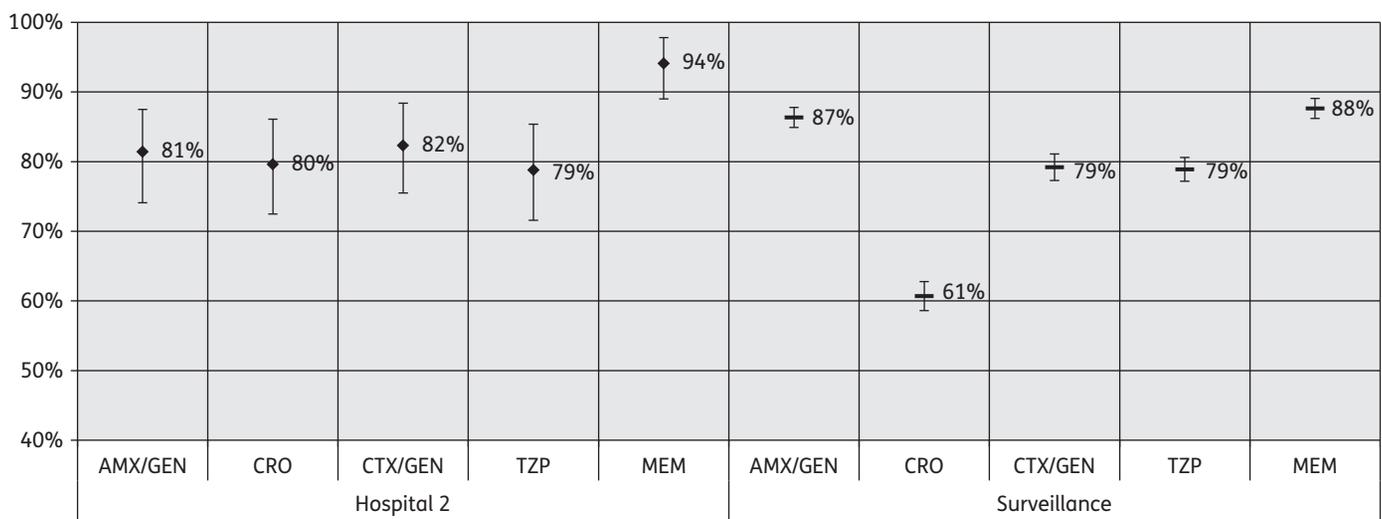


Figure 3. BSI coverage estimates for different ET regimens based on single centre data for Hospital 2 or on the pooled surveillance data. The 95% credible intervals are shown as bars. AMX/GEN, amoxicillin/gentamicin; CRO, ceftriaxone; CTX/GEN, cefotaxime/gentamicin; TZP, piperacillin/tazobactam; MEM, meropenem.

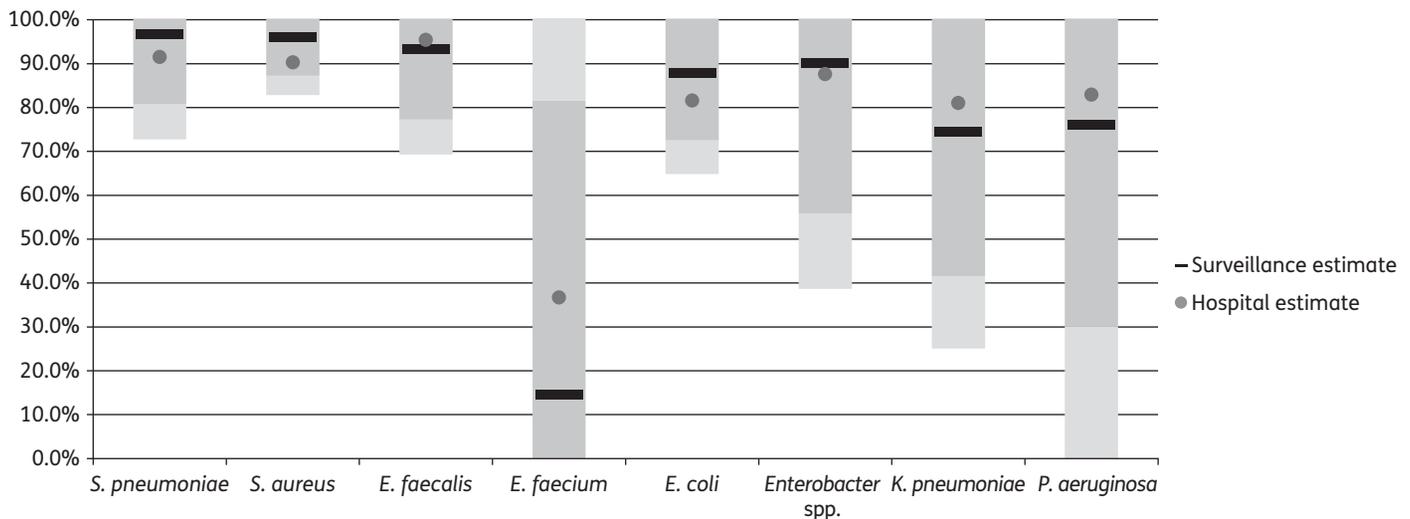


Figure 4. Susceptibility parameters (%) for the amoxicillin/gentamicin regimen for individual pathogens from Hospital 1 and the overall ARPEC cohort of 19 hospitals. The graph shows bullet plots derived from the individual funnel plots. The grey bars indicate the standard inner and outer control limits (dark grey, 95% control limits; light grey, 99.8% control limits) around the overall ARPEC cohort value.

pathogens from Hospital 1 compared with the values of the pooled data for the amoxicillin/gentamicin regimen. In the bullet plots, the bars indicate the position of the 95% and 99.8% control limits and reveal that each value falls within the 95% limits.

For Hospital 2, however, patterns for both pathogen incidence ($P=0.001$) and regimen susceptibility (Figure 5 for amoxicillin/gentamicin) differed from the overall cohort. This would indicate that coverage estimates from pooled surveillance data should not be regarded as representative for Hospital 2 and it would not be appropriate to substitute the values from the pooled data for the hospital values.

Discussion

The critical question when initiating empirical antibiotic treatment for any infection is which regimens provide the highest coverage.⁴ This paper focuses on whether coverage provided by different regimens can be reliably estimated using a WISCA derived from local data when the incidence of the infection being studied is low. While our study used data from the ARPEC paediatric BSI project, this general approach is pertinent not only to neonates and children, but also to a range of other defined patient populations especially if further stratification, such as by age or ward, is desirable.^{11,21}

This study clearly demonstrates the value of data pooling to improve confidence in the selection of an optimal regimen for ET of low-incidence infections. In the single hospital scenarios (Figures 2 and 3), true differences in ET regimen coverage for paediatric BSI were undetectable due to the small sample size. Estimating coverage using local data, as widely recommended, may therefore not result in clinically useful information.²² Pooling microbiological information over a longer period is one potential solution, but both pathogen incidence and AMR levels

are known to change over time.²³ An alternative strategy is to combine data from multiple hospitals often available as pooled AMR estimates, e.g. from surveillance programmes.

Nonetheless, this approach involves a number of steps that require careful consideration. First, it is necessary to ensure the local patterns of AMR and pathogen incidence are not significantly different from the figures derived from pooled data. We demonstrated a simple method for doing this that can be applied when local and overall figures are available. If information is available from multiple sources, alternative methods of evidence synthesis could be used to assess the degree of heterogeneity across the different data.²⁴

Second, the results will be sensitive to the choice of prior distributions.¹³ We chose non-informative priors (except for pathogens with inherent resistance), but alternatives could have been selected. For example, if susceptibility was expected to be between 60% and 80%, a weakly informative prior such as a beta(50, 20) distribution could have been used. Information to support these decisions might be drawn from various sources (expert opinion, research studies and results from different regions) and the best source of evidence will depend on the particular circumstances of each application. We recommend that the sensitivity of the results in relation to the choice of prior distributions is always assessed.

Achieving a high degree of certainty about difference and equivalence in ET regimen coverage is an important consideration in clinical decision-making. Clinicians require tools to reject ET regimens that are clearly inferior and to enable them to select amongst regimens with equivalent coverage, after which a decision might be guided by additional clinical considerations (such as potential toxicity or pharmacokinetic/pharmacodynamic considerations for specific infections).²⁵ In particular, there is a need to identify when narrow-spectrum single or combination therapy regimens can be used safely in order to conserve critically important antimicrobials.

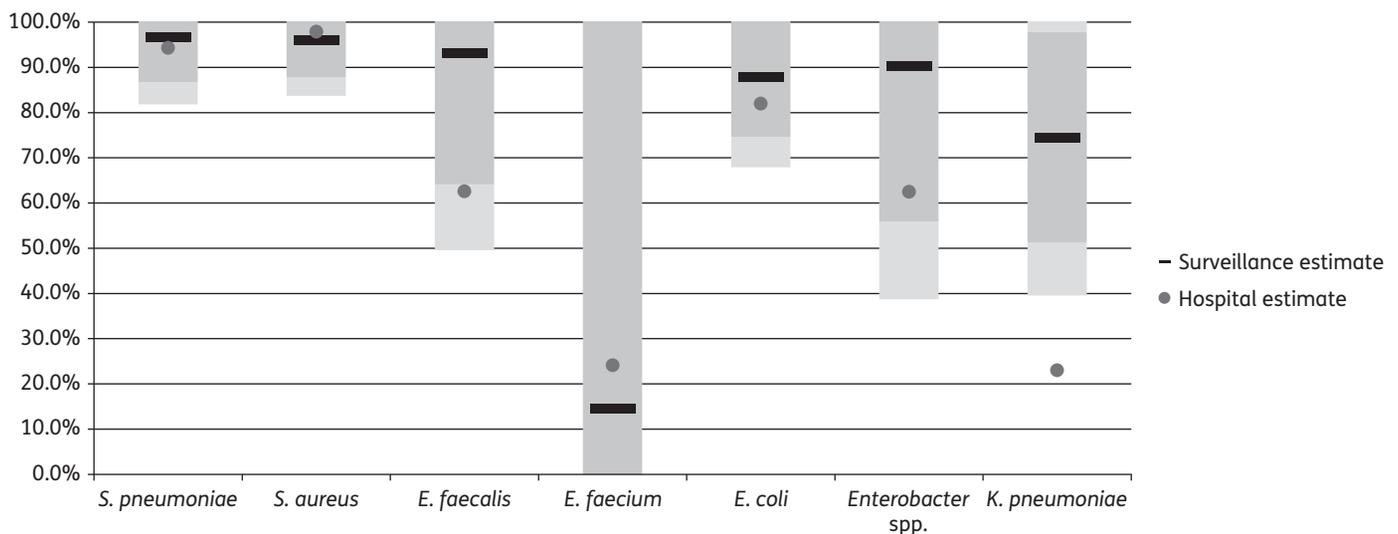


Figure 5. Susceptibility parameters (%) for the amoxicillin/gentamicin regimen for individual pathogens from Hospital 2 and the overall ARPEC cohort of 19 hospitals. The graph shows bullet plots derived from the individual funnel plots. The grey bars indicate the standard inner and outer control limits (dark grey, 95% control limits; light grey, 99.8% control limits) around the overall ARPEC cohort value.

We used data from multiple hospitals across Europe, which may be expected to differ in incidence of pathogens (e.g. due to differences in vaccine programmes) and AMR prevalence. Other sources could be considered, including isolates cultured from samples other than blood or isolates from other age groups. Resistance patterns differ between different sample types, e.g. for *S. pneumoniae* isolated from sputum and blood or for Gram-negative bacteria isolated from complicated versus uncomplicated urinary tract infections.^{26,27} Similarly, the epidemiology of BSI differs between adults and children in terms of both bacterial incidence and antibiotic resistance.^{11,28–32} While each of these alternative sources may be appropriate in a specific context, a thorough assessment of heterogeneity is therefore required, which could take a similar approach to that presented here for data pooling between geographically disparate hospitals. When surveillance data are used, pooling between hospitals within a specified region or between hospitals whose case mix is broadly similar will likely reduce the risk of identifying heterogeneity.

Adopting a decision analysis framework and Bayesian modelling to explicitly consider whether pooled data can in some cases be substituted for local data has various benefits. First, it allows for the integration of evidence from multiple sources when the local sample size is small, but there is other information available to augment it. This can be modelled by combining prior beliefs about parameter values with observed data. The use of priors also enables a Bayesian WISCA to explicitly incorporate knowledge about intrinsic resistance, maximizing the amount of data that is available to inform the selection of ET regimens. Similarly, a Bayesian WISCA can handle differentially missing data, e.g. when laboratories operate a selective susceptibility testing approach for specific antibiotics. Additional benefits arise from the separate consideration of incidence and susceptibility parameters, as uncertainty about the estimates of both can be incorporated into the model. Importantly, the proposed WISCA framework can be further extended to cover clinical outcomes, e.g. mortality, by expanding the decision tree to include a further branch that captures the outcome of treatment in patients with infection caused by susceptible and resistant bacteria.

There are various limitations in our analysis of coverage that arise from the ARPEC dataset. We included information on all reported bacteria causing BSI in our scenarios to demonstrate the structure of the model. Overall, excluding likely contaminants, the bacterial species surveyed by ARPEC account for ~82% of bloodstream isolates reported in the UK (Table 2). AMR patterns were unavailable for two groups of bacteria for which they would be expected to vary across the different hospitals. ARPEC centres used EUCAST, CLSI, BSAC and other national interpretive guidelines to determine susceptibility, which could result in inconsistent breakpoints. Further work is necessary to evaluate the utility of the Bayesian WISCA for informing clinical practice using an independent dataset with more complete and homogeneous pathogen incidence, resistance prevalence and clinical outcome data. Finally, we did not incorporate stratification by key patient characteristics (such as age) or episode characteristics (e.g. community- and hospital-acquired BSI) in our analysis. These could be incorporated into the Bayesian WISCA as additional decision tree branches, but stratification has the disadvantage of further decreasing sample size.

In conclusion, the WISCA has the potential to support clinical decision-making by clearly identifying differences or equivalence

Table 2. Distribution of pathogens in the ARPEC dataset and in 2014 routine surveillance data for children 0–18 years of age in England, Wales and Northern Ireland

	ARPEC		SGSS		
	n	%	n	% ^a	% ^b
<i>S. aureus</i>	449	23	771	15	21
<i>E. coli</i>	380	20	739	15	20
<i>K. pneumoniae</i>	183	9	179	4	5
<i>E. faecalis</i>	175	9	234	5	6
<i>S. pneumoniae</i>	163	8	303	6	8
<i>P. aeruginosa</i>	137	7	132	3	4
<i>Enterobacter</i> spp.	122	6	165	3	4
Group B <i>Streptococcus</i>	98	5	481	10	13
<i>E. faecium</i>	95	5	78	2	2
<i>N. meningitidis</i>	41	2	198	4	5
Group A <i>Streptococcus</i>	36	2	242	5	7
<i>A. baumannii</i>	19	1	23	<1	1
<i>H. influenzae</i>	19	1	98	2	3
<i>S. enterica</i>	19	1	35	1	1
Other—non-speciated (<i>Acinetobacter</i> spp., <i>Klebsiella</i> spp., <i>Pseudomonas</i> spp., <i>Enterococcus</i> spp., <i>Salmonella</i> spp. and <i>Neisseria</i> spp.)	—	—	464	9	—
Other—unusual pathogens (without CoNS, non-pyogenic streptococci, <i>Micrococcus</i> spp. and diphtheroids)	—	—	895	18	—
Total	1936	100	5037	100	—

^aProportion calculated on total of 5037 isolates including unusual pathogens.

^bProportion calculated on total of 3678, excluding non-speciated pathogens and unusual pathogens.

of potential empirical regimens for childhood BSI through data-driven estimation of coverage presented with a measure of precision. When this method is applied, it becomes apparent that the limitations imposed by small sample sizes in single hospitals or for special patient groups must be overcome to support evidence-based regimen selection. A Bayesian WISCA achieves this by transparently handling missing data and combining data from different sources. The Bayesian WISCA and its potential extensions therefore provide a way to maximize the clinical utility of AMR surveillance data to inform the selection of empirical antibiotic treatment for critically ill patients while helping to conserve critically important antibiotics.

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Transparency declarations

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