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Abstract

Background: Increasing antibiotic resistance to WHO-recommended 1st and 2nd line treatments of paediatric sepsis requires adaptation of prescribing guidelines. We discuss the potential and limitations of a weighted-incidence syndromic combination antibiogram (WISCA) as a practical tool for incorporating local microbiology data when assessing empiric coverage of commonly used antibiotics.

Research design and methods: A brief questionnaire of 18 clinically-significant isolates from paediatric blood cultures (Jan-Dec 2018) was sent to a global network of paediatric hospitals in July 2019. Weighted coverage estimates of non-antipseudomonal third-generation cephalosporins (3GC) and meropenem were estimated using Monte Carlo simulation for each site reporting >100 isolates.

Results: 52 hospitals in 23 countries in 5 WHO regions responded to the questionnaire; 13 sites met the sample size requirement. The most common isolates were *S. aureus, Klebsiella* spp., *E. coli* and *Enterococcus spp.* Coverage of 3GC ranged from 39% [95%CrI: 34-43%] to 73% (two sites: [95%CrI: 65-80%]; [95%CrI: 68-86%]) and meropenem coverage ranged from 54% [95%CrI: 47-60%] to 88% [95%CrI:84-91%].

Conclusions: A WISCA is a data-driven, clinically intuitive tool that can be used to compare empiric antibiotic regimens for paediatric sepsis using existing large datasets. The estimates can be further refined using more complex meta-analytical methods, and patient characteristics.

Keywords

Antibiotic resistance, paediatric sepsis, empiric antibiotics, bloodstream infections, weighted incidence syndromic combination antibiogram (WISCA)

Article Highlights

- There is rising resistance to common empiric antibiotics and reported use of broad-spectrum antibiotics for paediatric bloodstream infections.
- Tools are needed to incorporate local resistance data into antibiotic prescribing guidelines for paediatric sepsis beyond traditional hospital cumulative antibiograms.
- A weighted-incidence syndromic combination antibiogram (WISCA) using basic microbiology data is a useful tool to assess coverage of common empiric antibiotics for paediatric sepsis in a robust and reproducible way.
- Key considerations for using microbiology data for a WISCA include: definition of clinically significant organisms (especially skin organisms, such as Coagulase-negative Staphylococci

(CoNS), bias in blood culturing processes, patient groups included in available data, sample size and precision of estimates

- Estimates can be refined through meta-analytic methods for pooled data, true Bayesian priors, and stratification by key patient features.
- Future possible data sources that could be used for WISCA calculations include resistome data such as colonisation surveillance data or pooled faecal samples; however, these methods require further research into the association between colonisation and infection.
- There is a balance to be found between relatively straightforward methods that could be undertaken in resource limited settings by infection prevention and control (IPC) professionals or microbiology teams using the methods demonstrated here, and increased precision and applicability of coverage estimates using more complex data sources or analytical methods.

1. Introduction:

Sepsis continues to be an important cause of global childhood mortality [1], and debate is ongoing about how antibiotic treatment could be optimised to reduce sepsis-attributable deaths in childhood. Current WHO guidelines for treatment of paediatric sepsis recommend adjustment of empiric antibiotic regimens to provide optimal coverage for the local pathogen and susceptibility profile [2]. However, the best methods by which to incorporate local antimicrobial resistance surveillance data into prescribing guidelines have not been clearly defined. Straightforward methods to adjust antimicrobial guidelines by local antimicrobial resistance (AMR) patterns are particularly important as there is an increase in resistance to 1st and 2nd line WHO-recommended treatments and a rise in empiric prescribing of broad spectrum antibiotics to neonates and children treated for sepsis presumed to be of bacterial origin [3–6]. Most antibiotic treatment in children with suspected bacterial sepsis is prescribed empirically due to limitations in cultures [7], non-specific presentation of infection, urgency of treatment needed particularly in young children and neonates, and due to

non-availability of laboratory capacity or financial barriers to blood cultures for some patients particularly in in low and middle income countries (LMIC). Appropriate (i.e. concordant) empiric therapy in children is thought to be an important factor for improving clinical outcomes [8,9]. In order to improve antibiotic treatment in children, prescribing must be based in part on infection epidemiology [7,10–12]. Traditional hospital cumulative antibiograms are limited in the amount of useful information they provide to clinicians, particularly linking the data to clinical infection syndromes, where guidance needs to be informed by both the relative proportions of isolates observed in each target syndrome as well as their resistance patterns [13,14]. Clinicians need a tool that can help select between alternative regimens based on likely coverage in their setting and support judicious decision making from an antimicrobial stewardship perspective.

Further concerns about traditional antibiograms are the scale at which these are applied. The recommendation to use local susceptibility patterns can be limited by small sample sizes of organisms (i.e. <30 isolates of one organism type) [15]; however, on the other side, pooled data (i.e. at a country level) may mask differing levels of resistance at different types of facilities (e.g. secondary vs. tertiary care hospitals) especially relating to the patient populations at risk and types of infections (e.g. hospital acquired vs. community acquired) [16]. Given the high levels of broad spectrum antibiotic prescribing currently being seen in paediatric sepsis [4], it is possible that clinician prescribing practices may be driven by the worst results they see in traditional antibiograms, which may be biased by a high percentage of resistance in a small number of isolates. Unlike a traditional antibiogram, a weighted incidence syndromic combination antibiogram (WISCA) incorporates known pathogen incidence and susceptibilities to the chosen antibiotics for a specific clinical syndrome with the potential to then apply Bayesian theory to calculate a weighted average of coverage of the chosen antibiotics [16]. This weighted average is a probability that the antibiotic of choice covers the most common organisms causing paediatric BSI at each hospital.

Given the limited surveillance capacity for AMR in many settings, we aim to explore how basic microbiology data from paediatric BSI episodes can be used to address some of the limitations of the

traditional hospital antibiogram using data from a global network of paediatric hospitals. We discuss the potential and limitations of a weighted incidence syndromic combination antibiogram (WISCA) method as a practical and adaptable tool to assess coverage of common antibiotics on organisms isolated from paediatric bloodstream infections (BSI) [13]. We explore the WISCA methodology in this population for two commonly used antibiotic classes: non-antipseudomonal 3rd generation cephalosporins (e.g. ceftriaxone, cefotaxime) and carbapenems.

2. Patients and Methods:

2.1 Data Collection:

A simple microbiology questionnaire asking about significant blood culture isolates from paediatric patients (>30 days <18 years) identified between 1 January 2018 to 31 December 2018 was sent to hospitals in a global paediatric infection network in July 2019. Data requested included total number of paediatric blood cultures processed, total number of positive paediatric blood cultures, totals of a pre-defined list of organisms and specific resistance phenotypes. The organisms queried were: *Klebsiella spp., E. coli, Acinetobacter spp., Pseudomonas spp., Enterobacter spp., Salmonella* Typhi, non-typhoidal *Salmonella spp., Citrobacter spp., Serratia spp., Raoultella spp., Proteus spp., S. aureus, S. pneumoniae,* Group A Streptococcus (GAS), *Enterococcus spp., H. influenzae,* coagulase-negative Staphylococci (CoNS), and *Candida spp.*

Carbapenem resistance was reported for *Klebsiella spp., E. coli, Acinetobacter spp., Pseudomonas spp.,* and *Enterobacter spp.* Extended-spectrum beta-lactamase (ESBL) producers was reported for *Klebsiella spp., E. coli, and Enterobacter spp.*, methicillin resistance for *S. aureus*, vancomycin resistance for *Enterococcus spp*. and penicillin resistance for *S. pneumoniae* were also reported. Carbapenem resistant *Klebsiella spp.* includes any resistance (i.e. intermediate and resistant). ESBL for *Enterobacter spp.* was defined as *Enterobacter spp.* isolates resistant to non-antipseudomonal third generation cephalosporins. Penicillin resistance for *S. pneumoniae* was determined using the breakpoint for non-meningitis isolates.

To keep data collection feasible, sites were asked to report all blood culture sets including repeat cultures on consecutive days. Sites were asked to report isolates from polymicrobial cultures as individual isolates.

Data were collected voluntarily and sites received no financial incentive. Most sites did not require ethics approval as data were aggregated and included no patient information; any site that required approval received it prior to data collection.

2.2 Selecting clinically relevant bacteria:

Our analysis focuses on bacteria considered clinically relevant in pediatric sepsis thus *Candida spp.* was excluded from further analyses. In the interest of keeping the questionnaire simple we did not ask sites to provide data on the number of CoNS that were considered contaminants as this would have required clinical data. The treatment of CoNS as a pathogen or contaminant will vary greatly from site to site; however, patients with a high probability of having clinically significant CoNS can usually be identified with key clinical features (e.g. central lines, thrombophlebitis). Given high reported methicillin resistance in CoNS (up to 80% in some cases) [17], including non-clinically relevant CoNS in a WISCA can greatly reduce coverage estimates which may bias prescribing towards unnecessary empiric vancomycin. Adding vancomycin to regimens of patients meeting specific clinical criteria for potential CoNS infection essentially fully mitigates the impact of CoNS, therefore we have excluded CoNS from the WISCA analysis presented here.

In our questionnaire, we asked about 18 bacteria that could be considered clinically relevant in paediatric sepsis. Depending on the patient population and site, there may be other organisms that are considered clinically significant that were not accounted for in our questionnaire (18]. Selecting clinically relevant organisms at a site level can help account for local outbreaks or predominant organisms at one hospital that may not be as common at other hospitals in a country or region. While we selected organisms from a predefined list, a WISCA can be adapted to a local context to reduce this bias. Rather than using all organisms that were reported, we used the most commonly

reported isolates at each site that accounted for approximately 90% (range between 4 and 9 organisms per site) of the total reported bacterial isolates in the questionnaire from that site after excluding CoNS.

2.3 Site selection:

To minimize uncertainty of coverage estimates and maximise their discriminatory value when comparing estimates for different regimens, it is useful to define a minimal sample size (that is, number of isolates contributing to the WISCA). For the purpose of this manuscript, we estimated coverage only for sites reporting 100 or more total bacterial isolates (when excluding *Candida spp.* and CoNS*)*. We set a minimum cut off of 100 isolates as larger numbers of isolates provide improved precision and 100 isolates is when the 95% credible intervals start to be narrow enough to estimate and compare coverage of regimens or sites with sufficient precision [16,19].

Some sites reported a total number of these clinically significant organisms that was far less than the total number of reported positive blood cultures. Given that we are unsure what other organisms these sites were culturing in positive blood cultures, and it is likely to be a number of contaminants, we limited coverage estimation to sites with a total number of isolates reported equal to or greater than 65% of the total positive blood cultures reported. Since our questionnaire included most clinically significant bacteria, a lower percentage would indicate more contaminants or isolates that may be difficult to interpret; while 65% is slightly arbitrary it is high enough to allow for some quality check in site selection.

2.4 Parameter estimation

The WISCA is conceptualised as a Bayesians decision tree model which incorporates relative incidence of pathogens and susceptibility to the antibiotics of interest for the given syndrome (e.g. paediatric BSI) (Figure 1). Essentially, most data are available directly from laboratory information management systems or require minimal additional cleaning or analysis: The relative incidence of

bacteria selected as contributing to the WISCA corresponds to the number of isolates reported for each included species, taking into account the impact of duplicate isolates if possible; in our dataset, repeat positive cultures for the same episode may have contributed to the WISCA.

Figure 1. Illustration of the WISCA as a decision tree model. Examples are different composition of pathogens contributing to 90% of total isolates at this site (isolates included in WISCA) A) Site UK2 with pathogens accounting for 90% of total isolates at this site. B) Site TH1 with pathogens accounting for 90% of total isolates at this site.

In our analysis we focus on two groups of antibiotics used as empiric treatment for paediatric BSI [3,4]: non-antipseudomonal third generation cephalosporins (referred to as 3GC] to account for the impact of increases in ESBL producing Gram-negative organisms, and meropenem due to observed wide-scale use as an empiric antibiotic [3,4].

Explicit informed assumptions regarding antimicrobial susceptibility can be incorporated into WISCAs, for example on intrinsic resistance of organisms, and inferring susceptibility to specific antibiotics of interest from antibiotics in the same class when susceptibility testing results are lacking [20]. Given how our questionnaire was structured, we used reported data and European Committee on Antimicrobial Susceptibility Testing (EUCAST) interpretive algorithms and expert rules, where applicable [21], to determine susceptibility of the clinically relevant bacteria to 3GC and meropenem for model parameters.. Where the number of resistant isolates to the antibiotic of interest was reported, the number susceptible was directly calculated using the total for that species. For organisms where no resistance data was reported, the following assumptions were used to determine the number of susceptible isolates. Note that for simplicity this approach assumes a direct and uniform link between in vitro susceptibility and in vivo efficacy for all included bacteria. Assumptions, particularly for Gram-positive organisms, are necessary for model parameters and do

not directly correspond to treatment recommendations (e.g. for methicillin-susceptible *Staphylococcus aureus (MSSA)*, beta-lactamase resistant penicillins are the treatment of choice regardless of their susceptibility to cephalosporins or carbapenems).

For susceptibility to 3GC (e.g. cefotaxime, ceftriaxone):

- Number of ESBL-producing isolates was used where reported (*Klebsiella spp., E. coli, and Enterobacter spp.*)
- 0% susceptibility due to intrinsic resistance in *Acinetobacter spp., Pseudomonas spp., Enterococcus spp.*
- Assumed 100% susceptibility for *Salmonella Typhi*, non-typhoidal Salmonella, GAS, *S. pneumoniae* and *H. influenzae*
- For *Citrobacter spp., Serratia spp., Proteus spp., Raoultella spp.* assumed same proportion susceptible as reported for *Klebsiella spp.*
- All reported methicillin-susceptible *S. aureus (*MSSA) were assumed susceptible.

For susceptibility to meropenem:

- Number of CRO was used where reported (*Klebsiella spp., E. coli, Acinetobacter spp., Pseudomonas spp., and Enterobacter spp.*)
- 0% susceptibility due to intrinsic resistance in *Enterococcus spp.* (as only EUCAST breakpoint is for imipenem)
- Assumed 100% susceptibility for *Salmonella Typhi*, non-typhoidal Salmonella, GAS, *S. pneumoniae* and *H. influenzae*
- For *Citrobacter spp., Serratia spp., Proteus spp., Raoultella spp.* assumed same proportion susceptible as reported for *Klebsiella spp.*
- All reported methicillin-susceptible *S. aureus (*MSSA) were assumed susceptible.

The full parameter tables can be found in Supplemental Material (Table S2 and Table S3).

We used non-informative priors for both relative incidence and susceptibility, meaning that coverage estimates are dominated heavily by the data. We assume that relative incidence comes from a multinomial Dirichlet distribution [19]. Susceptibility data is assumed to come from a binomial distribution. By restricting the model to the sites reporting 100 or more isolates we slightly mitigate the effects of priors on small sample sizes.

2.5 WISCA Model

We estimated coverage using Monte Carlo simulation with 1000 simulations which produced a weighted average of predicted coverage for the regimen of interest at that site with a 95% credible interval, a necessary measure of uncertainty of the point estimate of coverage that allows comparison of coverage point estimates between regimens at a site and between sites. All simulations were conducted in Microsoft Excel 2016 with basic programming.

This process was repeated for both 3GC and meropenem coverage at each site. For both regimens of interest, the clinically relevant pathogens stayed the same per site; however, the number susceptible varied by regimen (see parameter tables in supplemental material).

2.6 Pooled analysis

While we did not include individual sites with less than 100 isolates due to uncertainty associated with small sample sizes, it is possible to pool data to overcome this issue to improve the precision of the model. Here we use data from 7 hospitals in the UK to illustrate pooled data using meropenem coverage. First, we use pooled data from only the 3 sites that met the 100 isolate threshold without CoNS which provides improved precision reflected in the 95% credible interval compared to those three sites individually (also presented). We also present pooled data using 7 UK hospitals; while 4 sites had less than 100 isolates individually, the data were able to be pooled with other sites to increase sample size. For this example, with all 7 sites, we assume the sites are similar hospital types with organism distribution; however, that may not always be the case.

3. Results

3.1 Questionnaire response:

Overall, we received responses from 52 hospitals in 23 countries across 5 WHO regions (supplementary material 1). These responses reported a total of 19798 positive blood cultures. The total number of isolates reported from the questionnaire by all sites was 11611 when excluding *Candida spp* and 6701 when excluding *Candida spp.* and CoNS (n=4910). Overall, the most common organisms reported were *Klebsiella spp.* (n=1547), *S. aureus* (n=1309) and *E. coli* (n=788) (Table 1). The total number of reported bacterial isolates per site when excluding *Candida spp.* and CoNS ranged from 6 to 593.

3.2 Site selection:

13 sites met the inclusion criteria for the coverage calculation of ≥100 reported isolates and the reported isolates totalled ≥65% of the reported blood cultures. 23 sites were excluded because they did not meet the 100 isolate requirement, 10 sites were excluded because they did not meet the 65% requirement, and 6 sites were excluded meeting neither of the requirements. The 13 remaining sites for which WISCAs were calculated were from 10 countries and 5 WHO regions.

3.3 Clinically significant organisms and coverage estimation:

The most common isolates at sites were *S. aureus*, *Klebsiella spp*., *E. coli* and *Enterococcus spp*. (Table 1). Coverage of 3GC ranged from 39% [95%CrI: 34-43%] to 73% (two sites: [95%CrI: 65-80%]; [95%CrI: 68-86%]) and meropenem coverage ranged from 54% [95%CrI: 47-60%] to 88% [95%CrI:84-91%] (Figure 2).

Figure 2. Coverage estimates of non-antipseudomonal 3rd generation cephalosporin (3GC) and meropenem (Mero) when excluding Coagulase-negative Staphylococci (CoNS). Sites shown are those meeting the 100 isolate threshold when excluding CoNS.

3.4 Pooled analysis:

In the pooled analysis of 3 UK sites that met the 100-isolate threshold, the 95% credible interval reflects improved precision of the estimates compared to those three sites individually (Figure 3). In the analysis of all 7 UK sites, due to lower relative incidence of organisms at the 4 sites with less than 100 isolates, the pooled coverage estimate is weighted towards the larger sites contributing more isolates and precision is improved (Figure 3).

Figure 3. Meropenem coverage estimates illustrating pooled data from the UK when excluding CoNS. Estimates shown for pooled data from 3 sites that have >100 isolates without CoNS, estimates when pooling data from 7 UK hospitals and three sites individual coverage estimates without CoNS.

4. Discussion

To our knowledge this is one of the largest datasets of paediatric bloodstream isolates globally. Most studies reporting high levels of resistance in paediatric bloodstream infections have been single centre or single country [22–25]. Using these very basic data of key isolates and resistance phenotypes globally we were able to demonstrate the application of a WISCA to estimate the coverage of non-antipseudomonal 3rd generation cephalosporins and meropenem for paediatric BSI at sites around the world. While we used very basic microbiology data focussing on resistance to these two antibiotic classes, WISCAs can be expanded to include other antibiotics or combinations of interest [16,19]. With rising antimicrobial resistance to the WHO-recommended first line regimen for paediatric sepsis, estimating coverage from a WISCA can be a more effective way to use local resistance patterns to inform empiric antibiotic prescribing.

While our questionnaire had limited susceptibility data reported, prompting us to use broader assumptions of interpretive criteria, the WISCA can be improved with more reported susceptibility testing. Using EUCAST and other interpretive algorithms and expert rules allow sites and national antimicrobial resistance surveillance programs to maximise the utility of routine microbiology data in a clinically useful way. We only illustrated coverage for two antibiotics; however, a useful expansion of the WISCA methodology would be to consider common empiric antibiotic combinations to assess coverage. The number of regimens assessed can be expanded to include those most relevant at local sites.

There are a number of considerations when using the WISCA methodology to analyse antimicrobial resistance data collected during local or national surveillance. Bias must be reduced, including developing a sound understanding of the data being reported and the source population, including approaches to blood culturing [26]. In our study, the reporting hospitals are predominantly tertiary teaching facilities which could overrepresent severe infections, hospital-acquired BSI and higher resistance rates resulting in likely lower coverage estimates than hospitals with more community-acquired BSI. Thus, coverage estimates may not be generalisable between hospitals. Higher blood culturing rates in a patient population with limited prior antibiotic exposure are likely to result in less biased coverage estimates [27]. For some infection syndromes, particularly urinary tract infections, cultures may only be obtained from patients with an inadequate clinical response to first-line empiric treatment [28], resulting in potential underestimates of coverage for an unselected patient population. Furthermore, a high rate of on-going antibiotic treatment at the time of sampling may reduce the rate of positive culture and any detected isolates have a higher a priori probability of being resistant to first line empiric therapies [23].

In some settings, including many LMICs, not all patients with suspected BSI may receive a blood culture due to financial and logistical constraints. The resulting bias means that estimates may apply to a small defined patient subgroup for whom a blood culture is typically obtained. Conversely, analysing data across a large age range can reduce the applicability of a WISCA to a specific subgroup [19]. A robust clinical algorithm to identify patients for whom cultures must be part of the routine work-up is critical [29,30] to reduce risk of bias. If the decision to culture is driven by other factors, such as availability of resources, coverage estimates based on a WISCA derived from routine data can become uninterpretable. Understanding practice of performing repeat cultures is also important (if repeat cultures are included in the sample such as here). In best practice, the first positive blood culture of an organism within an infection episode would be used to reduce bias compared to including all repeat cultures obtained from the same patient during a single infection episode[26,31]; however, a cut-off window (e.g. after 14 days) for repeat isolates within a BSI episode may be useful in hospitals or patients at risk of hospital-acquired infections (HAI).

In many settings selecting clinically relevant pathogens will be more complex than we have presented here. It would improve the local utility of the WISCA to better understand the differential impact of different causative pathogens on outcomes and to know how important concordance of early empiric antibiotics is for improving outcomes of BSI caused by each of these pathogens. Selecting a group of the organisms associated with the worst outcomes could allow a WISCA calculation to select regimens with expected maximum concordance and therefore greatest potential impact to alter early response to antibiotic therapy (e.g. a $WISCA_x$). There is some evidence that early concordance can improve outcomes in all children with BSI but it may be even more important in certain critically ill subgroups of children [9,32]. This $WISCA_x$ may need adapting to patient group (e.g. neonates or oncology patients). If sufficient isolates are available for WISCA calculations, it might be more informative to have a $WISCA_{10}$ for high-risk patients, and a different one for the general paediatric population – this requires robust data from paediatric populations to

inform the model. While bias can be addressed by acknowledging and where possible modifying blood culturing practices, sites will have a natural limit to sample size because the WISCA is driven by routine data. This means that further stratification to generate subgroup-specific WISCAs as clinically desirable can be particularly challenging. Stratification decreases heterogeneity of the patient population, which in turn increases the applicability of the WISCA to *that specific population* (potentially with a greater impact on outcome); however, the trade-off with precision due to smaller numbers of isolates in each subgroup has to be considered. Stratifying the WISCA based on local data may be an added complexity due to the potential bias in sampling and data collection as discussed.

Expanding on sample size considerations, basic pooling as we demonstrated is one way to improve precision that can be adapted to local contexts; however, for local adaptation, it is necessary to identify whether a site is an outlier in pathogen incidence or resistance patterns. Geography and other ecological factors will likely need to be considered when determining “similar patients” as patient groups from different countries or income settings may not be comparable (e.g. neonates in the UK vs. neonates in India). Rather than simplistic pooling, the estimates could be refined using meta-analytic methods to derive informative empiric priors for the model. This would allow for formal assessment of divergences between sites, and the model to account for these differences. Pooling data requires data access from multiple sites, ideally through a central data reporting system on a regional level that could perform the analyses for informative priors.

An advantage of using a WISCA approach and conceptualising it as a Bayesian decision tree model is that uncertainty about coverage estimates is adequately reflected. This is not generally the case in traditional hospital antibiograms. A 95% credible or uncertainty interval, comparable to a 95% confidence interval, around point estimates provides a measure of uncertainty associated with the point estimates of coverage. This is particularly relevant when using local data with a limited overall

sample size to estimate coverage. The disadvantage of estimating coverage of regimens in the described way is that it requires consideration of model behaviour and requirements that may not feel intuitive to microbiologists and clinicians.

While further data are needed to fully understand the impact of regimens with specific coverage estimates on outcomes, such estimates can immediately be used to aid clinicians deciding between multiple empiric regimens. It is possible that high carbapenem prescribing rates may be driven by clinicians acting on small numbers of highly resistant or difficult to treat pathogens presented on a traditional antibiogram [33,34]. However, by incorporating the relative incidence of pathogens as well as susceptibility, use of a WISCA could prevent clinicians from utilising such limited data to prescribe unnecessary broad-spectrum antimicrobials. This is particularly relevant in situations when coverage of most usable regimens available and affordable at a specific site is expected to fall short of the optimal. In such a case, clinicians are left with a number of suboptimal options and may wish to identify the regimen with the highest coverage among those options or clarify whether a broad-spectrum regimen truly provides better coverage compared to narrower-spectrum options (or WHO Watch vs. Access antimicrobials). If coverage is likely to be similar (overlapping 95% credible intervals), clinicians would have an evidence-base to choose the narrower-spectrum (or Access group) regimen which may be preferable from an antimicrobial stewardship, cost or side-effect profile perspective [35].

We currently assume that the higher coverage percent, the better, and in general clinicians have a strong preference for antibiotic regimens perceived to have a coverage of 90% or more [33]; however, in practice this is perhaps a bit more complex. The best coverage percentage for a specific syndrome will likely relate to the patient population of interest as outcome is likely to be strongly influenced by risk factors. For a patient population with a higher risk of poor outcome, concordant empiric treatment could be more important [8,9,36] than for lower risk patients. Further studies

assessing the use of WISCAs for empiric antibiotic selection on patient outcomes and antimicrobial stewardship outcomes and determination of optimal coverage percentage cut-offs will be needed. Despite its limitation, the WISCA is a useful practical tool that combines information for a specific syndrome and can aid clinicians in making empiric prescribing decisions in a more methodological approach than may be currently used particularly in resource limited settings. Machine learning techniques could be coupled with pooled incidence and resistance or resistome data to further improve coverage estimates [37–39]; however these approaches require large datasets not usually supported by basic data as we have used here. These types of complex algorithms can be difficult to understand which may limit their utility if there is low confidence in applying them.

In the future coverage estimates may use different data sources beyond traditional routine microbiology data. For example, exploring hospital population level samples and next generation sequencing approaches could be one way of understanding resistance epidemiology in a hospital or paediatric unit [40]. One example is repeated regular surveillance of the resistome through nasopharynx and rectal swabbing in the target population(s) of interest. In the case of LMIC settings that lack full susceptibility testing capabilities, using colonisation data from intermittent surveys of colonising isolates could be used to populate the susceptibility assumptions for a WISCA. To use colonisation surveys, there needs to be a clearer understanding of the relationship between colonisation and infection isolates [41]. A recent novel approach using metagenomics of pooled faecal material to assess resistance potential was able to predict invasive infections of clinically relevant Gram-negative bacteria [42], which can also be further explored as a data source for coverage calculations.

6. Conclusion

The WISCA methodology demonstrated here using basic microbiology data highlights the ability to incorporate local data in a way to easily compare different antibiotic regimens for a specific clinical

syndrome (i.e. paediatric sepsis). At a local level, in the immediate future, basic computation tools (e.g. in Microsoft Excel) allow for microbiology data at a local level to be used to assess coverage of antibiotic regimens for a given syndrome. This can aid in clinical decision making, potentially improving outcomes and aiding antimicrobial stewardship efforts.

The use of WISCAs can be incorporated into national surveillance programs as a way to use basic surveillance data collected in many countries. Incorporating methodology such as this into a national surveillance program may be a way to facilitate pooling and provide enhanced analysis and model adjustments due to expertise beyond what may exist in a single site.

Future refinement of coverage estimates using novel data sources, such as discussed here, would require more complex analytical methods and potentially additional data (e.g. stratification by clinical factors, data from other sites for pooling) which may not always be possible due to resource limitations of IPC and microbiology professionals. This type of methodology will require verification and triangulation using different data sources and susceptibility assumptions to model coverage and compare the estimates to assess optimal ease and precision.

Finding the optimal balance between clinically intuitive simple approaches using highly accessible datasets, such as presented here, and the more complex refining methods that allow for better applicability to patient groups and sites can be difficult, but WISCAs provide a clinically relevant way of interpreting local resistance patterns and a set of data-driven tools to guide a more appropriate empiric antibiotic therapy selection in children.

Author contributions:

Conception and design: AC, MS, JB

Acquisition of data : YY, KG, JC, KC, DP, CHT, EB, CBS, IA, CV, CGC, CSS, PT, TM, LW, PJ, JD, HW, JF, YC, MJ, IL, SK, VK, SK, SD, UAO, ARAS, JH, MC, US, MH, BB, DD, VP, DG, FK, SM, EV, SS, AG, DD, RR, KS, VY, RNI, GAU, DR, LAH, HBZ, ML, PB, PP, SB, SE, YH, HH, MCC, LPV, EG, RP, SC, KC, TN, RB, AD, AW, AM, MO, FMT, ADU, LO, ML, KP, TR, SA, TC, SL, SM, WS, HB, PM, FS, AR, KF, WS, JH, AB, PM, CH, JM, LS, PM, EC, CA, AH, PA, ST, SP, DB, DT, NHTB

Statistical analyses and interpretations: Led by AC with input by JB and MS

Initial manuscript draft: AC, JB

Critical feedback and revisions: All authors provide critical feedback and revisions

All authors approved the final submitted draft and agree to be accountable for all aspects of work.

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****Resistome data for surveillance of antibiotic resistance**

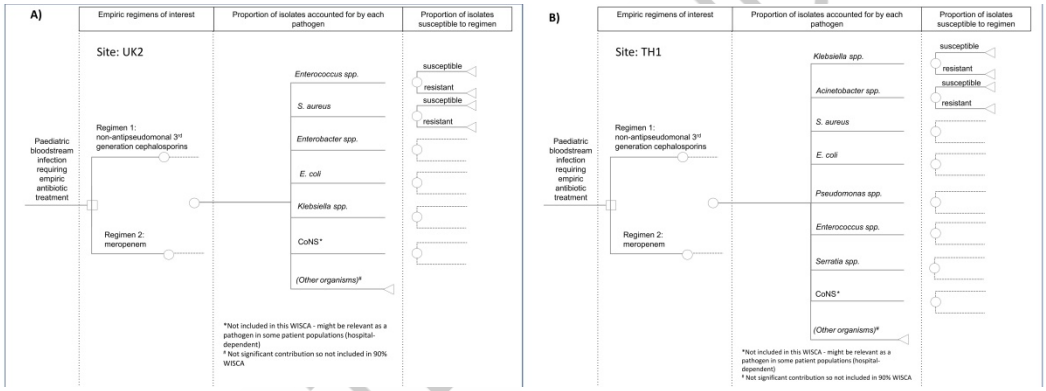

Fig 1

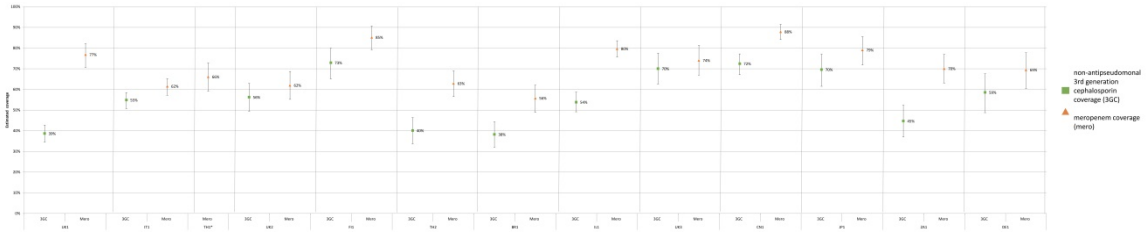

Fig 2

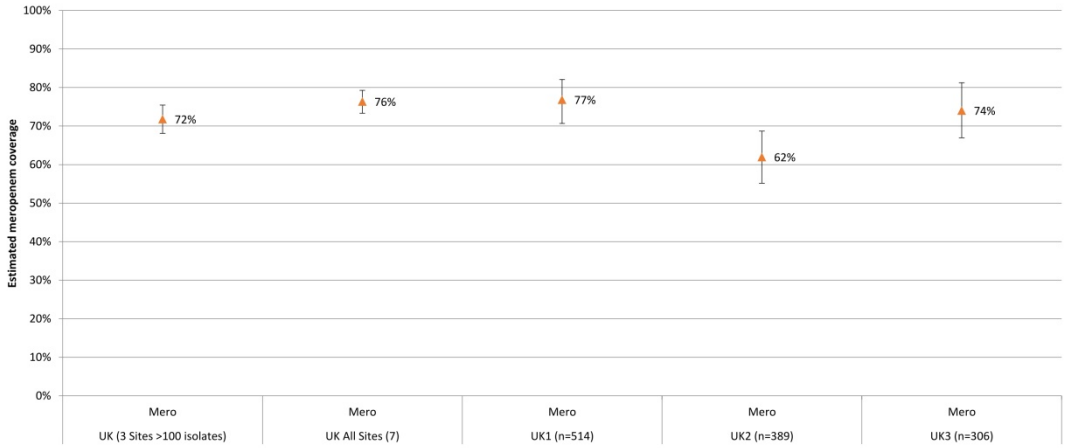

Fig 3

Table 1. Summary of reported bacterial isolates from all sites. Sites excluded from the weighted incidence syndromic combination antibiogram (WISCA) calculations are indicated with reason for exclusion.

Site	WHO Region	Total reported bacterial isolates	Total reported bacterial isolates w/o CoNS[#]	Klebsiella pneumoniae	Escherichia coli	Acinetobacter spp.	Pseudomonas spp.	Enterobacter spp.	Salmonella typhi	Salmonella spp. non-Typhi	Citrobacter spp.	Serratia spp.	Proteus spp.	Raoultella spp.	Staphylococcus aureus	Streptococcus pneumoniae	Group A Streptococcus	Enterococcus spp.	Haemophilus influenzae	CoNS[#]	Total isolates contributing to WISCA
IT1	EURO	1058	593	118	73	25	45	57	1	6	0	34	0	0	125	5	5	98	1	465	550
IL1	EURO	925	446	135	64	24	29	23	0	1	6	3	2	0	89	22	5	42	1	479	406
CN1	WPRO	609	313	44	43	12	12	95	17	1	1	1	0	0	37	35	1	14	0	296	313
UK1	EURO	571	232	20	38	12	15	13	2	0	4	7	2	1	67	7	6	35	3	339	214
BR1	PAHO	487	250	53	14	21	21	22	0	0	1	2	1	0	54	10	10	36	5	237	221
TH2	SEARO	440	234	61	14	58	15	4	1	18	4	1	0	0	22	11	3	15	7	206	214
UK1	EURO	430	214	18	19	1	16	38	0	0	1	2	0	0	55	2	0	61	1	216	191
UK3	EURO	332	143	13	19	3	5	8	0	0	1	6	1	0	25	20	11	29	2	189	131
TH1	SEARO	314	178	58	17	29	14	5	1	3	0	7	0	0	24	3	1	14	2	136	163
ZA1	AFRO	276	165	43	19	18	9	12	0	2	1	6	0	0	39	1	1	14	0	111	154
DE1	EURO	213	107	13	12	3	5	10	0	0	0	4	1	0	41	2	3	12	1	106	97
FI1	EURO	208	148	4	23	4	13	7	3	0	0	0	1	0	60	17	3	12	1	60	136
JP1	WPRO	183	132	28	14	0	1	1	0	0	0	12	0	0	60	7	3	5	1	51	121
UK6^	EURO	209	58	2	12	2	1	9	0	0	0	0	0	0	19	6	1	5	1	151	N/A
UK7^	EURO	207	94	12	10	4	5	10	0	0	0	2	0	0	17	10	5	18	1	113	N/A
DE2^	EURO	153	64	5	8	6	2	7	0	0	0	0	0	0	23	2	2	9	0	89	N/A
CN2^	WPRO	148	39	1	3	0	1	4	0	7	0	1	0	0	2	18	1	1	0	109	N/A
KH1^	WPRO	139	90	9	13	7	5	3	17	9	0	0	0	0	16	7	1	3	0	49	N/A
UK5^	EURO	134	30	1	5	3	0	1	2	1	0	0	0	0	9	5	2	1	0	104	N/A
UK4^	EURO	132	47	5	5	4	1	2	0	2	0	2	0	0	11	4	4	4	3	85	N/A
ES1^	EURO	120	40	7	10	1	0	1	0	1	0	2	0	0	5	6	1	5	1	80	N/A
SG1*,^	WPRO	75	57	5	20	0	6	7	1	4	0	0	1	0	8	3	0	2	0	18	N/A
BR2*,^	PAHO	62	52	9	1	8	5	5	0	1	0	3	2	0	6	2	1	9	0	10	N/A
GR1*,^	EURO	18	6	0	1	1	0	0	0	1	0	0	0	0	1	2	0	0	0	12	N/A

Site	WHO Region	Total reported bacterial isolates	Total reported bacterial isolates w/o CoNS[#]	Klebsiella pneumoniae	Escherichia coli	Acinetobacter spp.	Pseudomonas spp.	Enterobacter spp.	Salmonella typhi	Salmonella spp. non-Typhi	Citrobacter spp.	Serratia spp.	Proteus spp.	Raoultella spp.	Staphylococcus aureus	Streptococcus pneumoniae	Group A Streptococcus	Enterococcus spp.	Haemophilus influenzae	CoNS[#]	Total isolates contributing to WISCA
UK8[*]	EURO	384	362	56	37	6	8	27	2	0	1	9	0	4	90	10	5	99	8	22	N/A
AU1[*]	WPRO	122	73	10	16	0	1	6	3	3	1	0	0	1	17	9	5	1	0	49	N/A
DE3[*,^]	EURO	93	40	5	15	0	1	4	0	0	1	1	2		2	0	0	7	2	53	N/A
IN1[*]	SEARO	300	294	74	26	27	21	13	35	3	0	6	0	1	45	22	5	14	2	6	N/A
IN2[*]	SEARO	116	89	31	1	5	8	0	15	12	0	0	0	0	4	0	6	7	0	27	N/A
ZA2[*]	AFRO	417	191	41	13	19	4	21	0	2	2	3	2	0	52	11	0	19	2	226	N/A
IN3[*]	SEARO	246	135	13	14	20	10	3	29	6	1	1	0	0	9	16	2	10	1	111	N/A
RU1[*]	EURO	126	116	36	22	4	21	7	0	1	2	1	1	0	13	0	0	8	0	10	N/A
TH3[*,^]	SEARO	92	92	10	12	12	6	4							0	26	4	14	4		N/A
UG1[*]	AFRO	646	495	400	18	11	1	0	0	11	4	0	0	0	27	5	0	17	1	151	N/A
MX1[*]	PAHO	329	274	70	50	8	42	10	0	12	1	6	1	0	37	10	1	26	0	55	N/A
VN1[*]	WPRO	345	324	55	31	44	35	19	0	0	0	13	0	0	97	19	0	10	1	21	N/A
GR2[^]	EURO	42	11	4	1	0	0	2	0	0	0	0	0	0	0	1	0	3	0	31	N/A
IN4[^]	SEARO	11	6	0	1	1	0	0	2	0	0	0	0	0	2	0	0	0	0	5	N/A
PL1[^]	EURO	70	22	0	10	0	0	0	0	0	0	0	0	0	10	1	1	0	0	48	N/A
GR3[^]	EURO	49	25	5	3	4	4	3	0	0	0	0	0	0	1	3	0	1	1	24	N/A
EE1[^]	EURO	66	20	0	4	1	1	1	0	0	0	0	0	0	6	4	1	2	0	46	N/A
IN5[^]	SEARO	36	36	1	0	0	1	0	29	0	0	0	0	0	1	4	0	0	0	0	N/A
BR3[^]	PAHO	67	31	9	0	1	2	3	0	0	0	2	0	0	14	0	0	0	0	36	N/A
UK9[^]	EURO	50	15	0	7	1	0	0	0	1	0	0	0	0	3	1	2	0	0	35	N/A
IN6[^]	SEARO	96	85	32	10	13	13	2	0	0	0	1	1	0	6	5	0	2	0	11	N/A
EE2[^]	EURO	73	41	7	9	1	2	1	0	0	0	0	1	0	16	1	1	2	0	32	N/A
ES2[^]	EURO	81	29	3	1	0	2	3	1	2	0	1	0	0	13	1	1	1	0	52	N/A
GM1[^]	AFRO	92	32	1	5	0	0	1	0	6	0	0	0	0	13	3	0	2	1	60	N/A
AU2[^]	WPRO	91	46	1	13	1	1	1	0	6	0	0	1	0	12	5	4	1	0	45	N/A
IT2[^]	EURO	99	68	18	10	0	7	30	0	0	0	0	0	0	2	1	0	0	0	31	N/A

Site	WHO Region	Total reported bacterial isolates	Total reported bacterial isolates w/o CoNS[#]	Klebsiella pneumoniae	Escherichia coli	Acinetobacter spp.	Pseudomonas spp.	Enterobacter spp.	Salmonella typhi	Salmonella spp. non-Typhi	Citrobacter spp.	Serratia spp.	Proteus spp.	Raoultella spp.	Staphylococcus aureus	Streptococcus pneumoniae	Group A Streptococcus	Enterococcus spp.	Haemophilus influenzae	CoNS[#]	Total isolates contributing to WISCA
BR4^	PAHO	23	11	1	1	0	1	5	0	0	0	0	0	0	1	1	1	0	0	12	N/A
UK10*,^	EURO	6	6	0	1	1	0	0	0	0	0	0	0	0	1	2	0	0	1	0	N/A

CoNS = Coagulase-negative Staphylococci; CoNS was excluded in final WISCA calculations as data on contamination was not available.

^excluded because total number of reported bacterial isolates (excluding CoNS) was <100.

*excluded because total reported isolates (including Candida spp.) accounted for <65% of total reported positive blood cultures.