Estimating coverage of empiric treatment regimens for childhood bloodstream infection based on routine microbiological data

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Declaration

I, Julia Anna Bielicki, confirm that the work presented in this thesis is my own and that any contributions from other sources have been indicated in the thesis.

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Signed 

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I would like to thank my husband, parents and sister for supporting me through a period which, in combination with my other commitments, must at times have felt like several full time jobs. Last but not least, Paul and Jan, you are my rays of sunshine and make it all worthwhile.

Abstract

This research paper style thesis comprises six papers, each addressing a different aspect of the selection of empiric antibiotic regimens for the treatment of severe childhood infections, focussing on suspected bloodstream infection.

Antibiotics are a means to effectively manage life-threatening bacterial infections, such as bloodstream infections. Recommendations for life-saving empiric antibiotic treatment for bloodstream infection are traditionally based on knowledge of the epidemiology of the targeted infection, and are strongly influenced by knowledge about antibiotic resistance in causative pathogens. The underlying assumption is that the *in vitro* phenomenon of antimicrobial resistance relates to a poor response to antibiotics *in vivo*.

Bacteria causing bloodstream infection are increasingly found to be resistant to antibiotics and this can vary by region, hospital and patient group. It is therefore necessary to select and review best options for empiric treatment taking into account these trends. Details on the current approaches, data sources and the advantages and limitations of both are discussed in the first part of thesis (chapters 2-5).

The methods for selecting optimal empiric treatment from microbiological data, including information on antimicrobial resistance, are poorly defined. It is unclear which approach is most informative clinically and which can still use microbiology data generated as part of routine care and utilized for surveillance. Importantly, empiric regimens must be based on knowledge of the bacteria associated with a specific infection syndrome including their relative frequency as well as their resistance patterns. The probability that a given regimen will cover the next clinically identified episode of the infection in question can then be derived as guidance for regimen selection. In the second part of the thesis, a specific method for constructing a weighted-incidence syndromic combination antibiogram (or WISCA) to estimate coverage is therefore developed and presented.

The WISCA is derived from a Bayesian decision tree model, and has the advantages of explicitly combining relative incidence and resistance patterns for a given syndrome as well as accurately reflecting imprecision of coverage estimates. The Bayesian decision tree WISCA is used to investigate coverage of empiric antibiotic regimens at hospital level in Europe, including potential methods for dealing with heterogeneity between centres while still supporting data pooling to improve precision (Chapter 6). A further application is the estimation and comparison of coverage offered by recommended regimens for neonatal sepsis in Asian countries with data pooling at the level of country (Chapter 7).

Finally, the potential influence of patient characteristics on selection of antibiotics of last resort (i.e. those with a broad therapeutic spectrum but likely to be strong drivers for the selection of antimicrobial resistance and therefore to be used only when necessary) was investigated (Chapter 8). This demonstrates that certain patients or infection episodes are more likely to be treated with last resort antibiotics than others, and would seem to indicate expected heterogeneity among neonates and children with bloodstream infection. The Bayesian WISCA provides a useful approach to pooling information to guide empiric therapy and could increase confidence in the selection of specific regimens. In presented analyses, it provides evidence for the continued use of narrow-spectrum regimens in certain contexts, and could be further developed to address data pooling and allow the integration of local resistance data with surveillance data for data-based modification of high-level treatment recommendations (Chapter 9). Further work should focus on promoting the uniform reporting of coverage (and WISCA) to enable robust meta-analysis of antimicrobial resistance data and address best methods for dealing with small sample sizes expected at hospital-level and for stratified coverage estimates.

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Abbreviations

AMPGEN	Ampicillin plus gentamicin
AMR	Antimicrobial resistance
ARPEC	Antibiotic Research and Prescribing in European Children
ATC	Anatomical Therapeutic Chemical
CrI	Credible Interval
EARS-Net	European Antimicrobial Resistance Surveillance Network
ECDC	European Centre for Disease Prevention and Control
EUCAST	European Committee on Antimicrobial Susceptibility Testing
GAS	Group A Streptococcus
GBS	Group B Streptococcus
LSHTM	London School of Hygiene and Tropical Medicine
MEM	Meropenem
NRES	National Research Ethics Service
PIDRG	Paediatric Infectious Diseases Research Group
PPS	Point Prevalence Survey
SGUL	St George's University of London
TGC	Third generation cephalosporin (ceftriaxone or cefotaxime)
UK	United Kingdom
WHO	World Health Organization
WISCA	Weighted Incidence Syndromic Combination Antibiogram

1. Overview of thesis

This research paper style thesis comprises six papers, each addressing a different aspect of empiric antibiotic management of severe childhood infections, focussing on suspected bloodstream infection.

The overall aim of the research was to develop a new approach to the selection of empiric antibiotic regimens for the management of suspected bloodstream infection in neonates and children while confirmatory microbiological results are awaited. Relevant data that may inform the choice of empiric therapy are already available from blood cultures collected as part of the routine clinical work-up of children with bloodstream infection, and these data are currently used for surveillance of antimicrobial resistance trends. However, the numbers of neonatal and paediatric isolates contributed to hospital-level and surveillance databases are known to be small, and optimal use of these data are therefore paramount.

This overview chapter provides a summary of the thesis and its aims and objectives. Chapter 2 sets out the background to the thesis, providing details on the management of severe childhood infection, such as bloodstream infection, and outlining the limitations of current approaches to presenting routine microbiological data for clinical decision-making about empiric antibiotic treatment. Chapter 3 describes the data sources and provides details of the overall methodological approach.

The papers in chapters 4 and 5 identify and assess some limitations of the selection of empiric antibiotic regimens based on routine microbiology data available through surveillance programmes and at the individual hospital level. They identify important areas that need to be considered and addressed in the development of a novel methodology to support the selection of empiric antibiotic regimens for childhood bloodstream infection.

Chapter 6 describes the proposed method for selecting empiric antibiotic regimens for childhood bloodstream infection from routinely available blood culture data.

Chapter 7 demonstrates the application of this method to the evaluation of empiric antibiotic regimens for neonatal sepsis based on neonatal blood culture isolate data from several Asian countries.

The strong association between patient and infection-episode characteristics and prescribing of so-called last-resort antibiotics (i.e. those with a particularly broad spectrum that have also been identified as drivers of further selection of antimicrobial resistance) is examined in chapter 8. The results highlight how these characteristics affect antimicrobial resistance and highlights the need for further refinement of the methods developed in this thesis.

Finally, chapter 9 places the developed method into the context of current clinical practice and discusses its implications in different contexts as well as providing an outlook towards future work.

1.1 Contributions of the candidate

This PhD was undertaken alongside my work as a researcher with the Paediatric Infectious Diseases Research Group (PIDRG) at the Institute for Infection and Immunity, St George's University of London (SGUL). It builds on the Masters of Public Health (Health Services Research Stream) undertaken at the London School of Hygiene and Tropical Medicine prior to taking up my post at the Institute. The aim was to enable me to develop an area of academic expertise related to but not formally part of my work at SGUL.

The PhD was undertaken part-time while first being responsible for Antibiotic Resistance and Prescribing in European Children project (ARPEC, 2009-2013). The ARPEC project involved several European universities and Health Institutions, and aimed to develop and implement a method of surveillance of antimicrobial prescription and resistance in children attending hospitals and primary care across Europe. I was part of the project co-ordinating team at St George's University of London and in charge of the antimicrobial resistance surveillance work package.

The analyses and methodological approach presented in the thesis were designed and undertaken by me with appropriate guidance from my supervisors. My specific contributions and those of other authors are outlined at the start of each chapter, whenever collaborative work is included.

1.2 Funding

The PhD was funded by my employers, the PIDRG at SGUL. Prof. Mike Sharland from the PIDRG was my associate supervisor. Data from the ARPEC project were analysed to address some of the specific objectives of this PhD. However, this constituted secondary data use and the methods used for analysis were not part of the original ARPEC work plan.

1.3 Research aim and objectives

The overall aim of the research undertaken for my PhD thesis was to examine the utility and limitations of using routine bloodstream infection data for informing empirical prescribing, and develop a way in which these data could be used to give clinicians an estimate of coverage for different empiric treatment regimens. Regimen coverage describes the likelihood that the next microbiologically confirmed episode of bloodstream infection encountered will be adequately treated by the regimen.

The specific objectives were:

1. To critique common methods for presenting and using routine microbiological data for selecting empiric antibiotic regimens for the treatment of childhood bloodstream infections.
2. To assess how various characteristics of routine data affect their use in the selection of empiric antibiotic regimens, specifically:
    a. To investigate how variations in antimicrobial susceptibility testing approaches impact on the interpretation of routine microbiological data for the purpose of selecting empiric antibiotic regimens.

b. To determine how routine surveillance data from adults relates to data from children, and the potential impact of differences for population data use to guide decision-making about empiric antibiotic regimens for children.

3. To develop a method that addresses current weaknesses in utilisation of routine microbiological data for the selection of empiric antibiotic regimens, and in particular, which provides information on the estimated coverage of potential regimens with adequate reflection of statistical uncertainty around those estimates.
4. To demonstrate the potential for this new approach to inform clinical practice by using it to determine the estimated coverage of frequently used empiric antibiotic regimens.
5. To determine potential patient-related and disease-related factors that may be used by clinicians in decision-making about the choice of empiric antibiotic regimens to assess the need for stratified empiric antibiotic prescribing guidance.

1.4 Other outputs

During the period of research for the PhD, I also contributed to a number of research papers focusing on the epidemiology of bloodstream infection in children and the current pharmacoepidemiology of antibiotic use in paediatric bloodstream and other infections. These publications are not formally part of this thesis. However, some of this research work used the same datasets and explored related research questions and was to some extent shaped by the research undertaken for this thesis.

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g. Hsia Y, Sharland M, Jackson C, Wong ICK, Magrini N, Bielicki JA. Consumption of oral antibiotic formulations for young children according to the WHO AWaRe groups: an analysis of sales data from 70 middle and high-income countries. Lancet Infectious Diseases. Jan 2019; 19(1): 67-75

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classification to define patterns of hospital antibiotic use (AWaRe): an analysis of paediatric survey data from 56 countries. Lancet Glob Health. Jul 2019; 7(7): 861-71

2. Background

Bacterial infections can take several forms. Some of these are not generally life-threatening, for example, otitis media. Others are classified as serious, and can present an immediate danger to life, most importantly pneumonia, meningitis and bloodstream infections. In their most severe forms, these infections present as a severe inflammatory syndrome known as sepsis.

In 2013, 3.3 million children throughout the world were estimated to have died of infectious causes before the age of 5 years, accounting for 52% of all deaths in this age group (1). While the largest burden of mortality from infections is seen in lower and middle-income countries, severe infections remain a cause of death in high income countries with mortality from paediatric sepsis in high-income countries estimated to be up to 5%, increasing to up to 20% for the most severe cases and neonates (2-4).

Broadly speaking, sepsis represents a dysregulated inflammatory response to overwhelming infection (5). Severe inflammation can also have other causes and is not always confirmed to be due to bacterial infection. Differentiating between sepsis and other similar clinical entities is challenging, especially in neonates and young children in whom non-specific signs and symptoms often dominate (6).

The timely treatment of sepsis with antibiotics can be lifesaving. For this reason, the Surviving Sepsis Campaign, a global expert consortium produced evidence-based advice on the management of severe infections, and provided various recommendations on the use of early antibiotic treatment (7). More recently, similar recommendations have been made for neonates and children (8).

The need to administer antibiotics early in cases of severe infection means that confirmation of bacterial aetiology by microbiological culture is not available at the point of treatment initiation. In other words, treatment has to be administered empirically without knowledge of the causative bacteria. Empiric treatment regimens are traditionally selected to cover the

expected spectrum of bacteria according to age, patient characteristics and suspected site of infection (9). This ensures successive patients with suspected infections can be appropriately treated at an early stage of infection

Increasing antibiotic resistance has been observed among important bacteria commonly implicated in cases of childhood sepsis (9-12). This further complicates empiric antibiotic therapy as previously effective first-line and even second-line antibiotics may no longer work. The Surviving Sepsis Campaign, therefore, not only recommends early but also broad-spectrum antibiotic treatment taking into account the regional and local epidemiology of antibiotic resistance (7, 8). In line with this, an increasing empiric use of so-called last-resort very broad-spectrum antibiotics has been observed for childhood sepsis in regions with known high prevalence of antibiotic resistance (13).

Rising antibiotic resistance levels are creating a vicious circle for clinicians managing childhood sepsis as high use of broad-spectrum antibiotics has the potential to further drive selection of resistant bacteria (14). Thus, the need to treat severe bacterial infections early and broadly may jeopardize the continued effectiveness of these drugs (15).

International and national guidelines specify that treatment protocols for serious bacterial infections, including bloodstream infections, should be based on locally observed bacterial resistance patterns. Relevant information for severe childhood infections is available from blood cultures obtained as part of the routine work-up of children presenting with signs of sepsis. Such data are already locally presented in hospitals and collected as part of national and international antimicrobial resistance surveillance programmes (16-18). However, despite recommendations for the use of this data to inform the choice of empiric regimens, for example in the Surviving Sepsis Campaign guidelines, no guidance is provided for exactly how to analyse routine microbiological data and produce information to guide selection of empiric treatment regimens (7, 8).

2.1 Clinical approach to treating severe bacterial infections: childhood bloodstream infection

The introduction outlined the general challenges clinicians face when selecting empiric antibiotic treatment for children with severe infections thought to be caused by bacteria. This section is based on a published paper outlining the clinical approach towards the selection of empiric antibiotic treatment in greater detail.

As noted, one of the most serious types of bacterial infections are bloodstream infections when bacteria can be grown from normally sterile blood cultures. Bloodstream infections can be primary or secondary, with translocation of bacteria into the blood occurs because of another focal infection, for example pneumonia or osteomyelitis. Both types of bloodstream infections can present as a severe inflammatory syndrome (sepsis). Signs resulting from inflammation may also be the result of other infections and non-infectious causes (19-21). This leads to empiric antibiotic treatment being started in more children than are finally confirmed to have bloodstream infection (22, 23).

An association between concordant empiric antibiotic treatment (that is, a regimen to which the subsequently identified causative bacteria are susceptible in antimicrobial susceptibility testing) and better clinical outcomes has been repeatedly described (24-27). Not all antibiotics are active against all bacteria, and agents covering many different types of bacteria are commonly referred to as having a broad spectrum. A regimen can consist of a single antibiotic or of multiple antibiotics given at the same time to cover a wider range of bacteria.

It is important that empiric antibiotic regimens for childhood bloodstream infections are informed by the current epidemiology and observed changes in the relative frequency of different species bacteria causing them and changes in their antimicrobial resistance. Balancing the need to capture episodes caused by bacteria resistant to narrower spectrum antibiotics and the need to use antibiotics judiciously is a particular challenge (28-30).

Generally, information from blood culture isolates is presented to clinicians at one of three levels:

1. Clinicians review the antimicrobial susceptibility profile (antibiogram) of individual bloodstream isolates during patient care (the patient perspective). At this point, they adapt empiric antibiotic therapy and define a targeted regimen as required. The data are applicable only to the specific patient and episode.
2. Hospitals often produce cumulative hospital antibiograms (31). These are summaries of the susceptibilities of different bacterial species identified from routine microbiological samples at the hospital (the hospital perspective). Of note, cumulative antibiograms are mostly focused on individual bacteria and their resistance profiles to specific antibiotics rather than providing an overall coverage estimate for potential antibiotic regimens (32).
3. In many countries, data on antimicrobial resistance in blood culture isolates are collected as part of surveillance (the public health surveillance perspective) (33, 34). These are then presented in reports to reflect the current state of and trends in antimicrobial resistance. Again, reporting focuses on individual bacteria and their resistance profiles. Furthermore, variation in bacterial incidence and resistance patterns between different patient groups as well as down to hospital and unit level means that it is unclear how such aggregate data can be used for local clinical decision-making.

All three formats present the same data in different ways. However, only the first format is directly clinically relevant. While the local and surveillance perspectives may contain relevant information about the bacteria expected to cause bloodstream infections in future patients, a focus on individual bacteria and their susceptibilities limits their clinical interpretation.

RESEARCH PAPER COVER SHEET

SECTION A – Student Details

Student ID Number	237152	**Title**	Dr
First Name(s)	Julia Anna		
Surname/Family Name	Bielicki		
Thesis Title	Estimating coverage of empiric treatment regimens for childhood bloodstream infection based on routine microbiological data		
Primary Supervisor	Prof. David Cromwell		

If the Research Paper has previously been published please complete Section B, if not please move to Section C.

SECTION B – Paper already published

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Date	17.08.2020	**Date**	31.08.2020

Fifteen-minute consultation: the complexities of empirical antibiotic selection for serious bacterial infections—a practical approach

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ABSTRACT

Potentially life-threatening infections require immediate antibiotic therapy. Most early stage antibiotic treatment for these infections is empirical, that is, covering a range of possible target bacteria while awaiting culture results. Empirical antibiotic regimens need to reflect the epidemiology of most likely causative bacteria, type of infection and patient risk factors. Summary data from relevant isolates in similar patients help to identify appropriate empirical regimens. At present, such data are mostly presented as hospital or other aggregate antibiograms, showing antimicrobial susceptibility testing results by bacterial species. However, a more suitable method is to calculate weighted incidence syndromic combination antibiograms for different types of infections and regimens, allowing head-to-head comparisons of empirical regimens. Once there is confirmatory or negative microbiological evidence of infection, empirical regimens should be adapted to the identified bacterial species and susceptibilities or discontinued.

THE CASE

A 3-year-old boy with cerebral palsy is admitted to the paediatric intensive care unit (PICU) with viral respiratory tract infection, intubated and invasively ventilated for 2 days because of respiratory failure. After extubation and in the absence of central venous catheters, he develops a fever without a clear focus. Clinically, the patient is stable from a respiratory point of view, but has signs of sepsis. He does not have any signs of meningitis. A urine sample is obtained without evidence of infection on dipstick. The child has not had any hospital admissions or antibiotic treatments in the last 15 months. The results from blood and urine cultures are pending.

SHOULD THIS PATIENT BE TREATED WITH ANTIBIOTICS IMMEDIATELY?

This largely depends on the clinical status of the patient and the confidence with which an immediate diagnosis can be made (figure 1). In this scenario, the assessment of the patient as having sepsis would indicate that immediate empirical antibiotic treatment within 1 hour is required.[1]

What is empirical antibiotic treatment?

This boy's treatment will have to be empirical to cover potential bloodstream infection. Empirical antibiotic treatment has several 'stages', depending on how much information is available from microbiological cultures (figure 2).[2] This in turn is influenced by the laboratory techniques in use and sample processing in specific laboratories.

Although systems for direct detection of bacterial nucleic acid in blood are available, these systems are very expensive, and have not been shown to be reliable or useful enough to either replace or supplement blood cultures in most settings. Moreover, even these techniques are not fast enough to give a result before antibiotic treatment is started. Many microbiology laboratories do now use new technologies, such as using matrix-assisted laser desorption/ionisation time of flight, to give same-day species

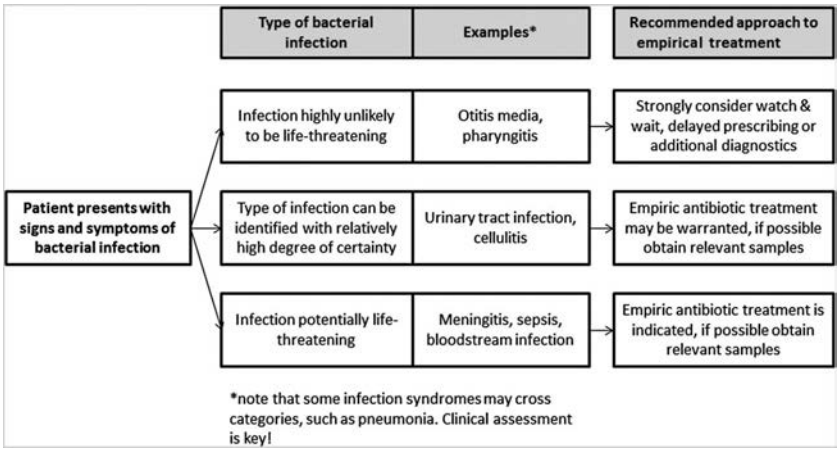

Figure 1 Bacterial infections for which empirical antibiotic treatment may be necessary.

identification of bacteria that have been isolated from blood cultures. This information can sometimes be useful in early review and de-escalation of ongoing empirical therapy.[3] However, antibiotic susceptibility testing will almost always have to be performed in the conventional manner, which requires a further overnight incubation. Thus there are at least two stages when empirical antibiotic therapy should be reviewed: when the blood culture signals positive and the identity of the isolate is established, and then on the following day when antibiotic susceptibilities become available. At each stage, microbiology staff can help with the interpretation of available data.

IF SO, WHICH ANTIBIOTIC(S) SHOULD BE GIVEN?

You may be working in a setting, in which hospital-level recommendations for empirical treatment are available. In such guidance, several options are often provided for children with sepsis, depending on age, the presence of comorbidities and the presence of central venous catheters. This demonstrates that there may be important information about the patient that needs to be considered before making a choice about empirical antibiotic treatment. At the hospital treating this patient, piperacillin/tazobactam would usually be used to empirically treat sepsis in children older than 1 month of age with underlying chronic comorbidities.

Your own hospital may not provide local guidance. In this case, the British National Formulary for Children suggests a number of possible regimens for treating community-acquired and hospital-acquired suspected bloodstream infections (table 1).[4]

Why is getting empirical antibiotic treatment right important?

When selecting the optimal empirical regimen, the principal aim is to cover the expected spectrum of the

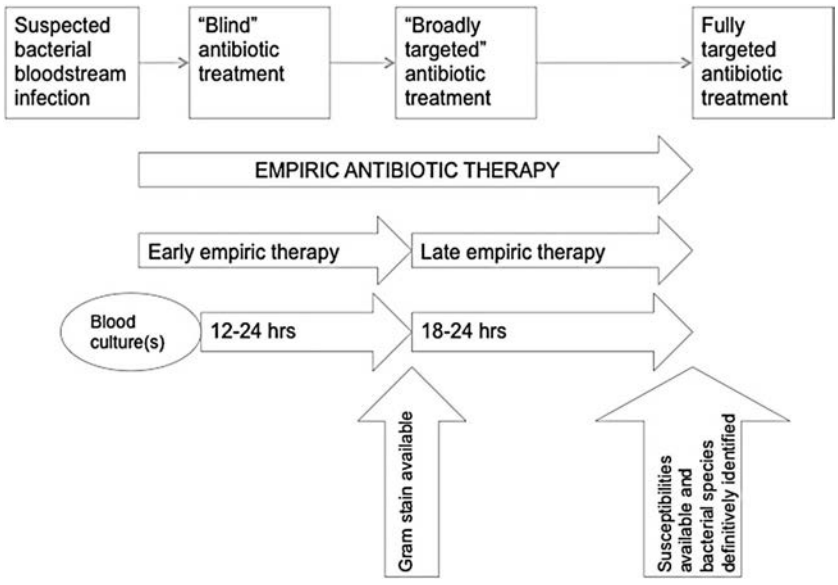

Figure 2 Different stages of empirical antibiotic treatment, depending on available information from microbiological samples.

Table 1 British National Formulary for Children 2015/2016 recommendations for empirical treatment of neonatal and paediatric septicaemia[4]

Infection	Antimicrobials
Septicaemia in neonate <72 hours old	Benzylpenicillin plus gentamicin If Gram-negative pathogen suspected: add cefotaxime, stop benzylpenicillin if Gram-negative infection confirmed
Septicaemia in neonate >72 hours old	Flucloxacillin plus gentamicin OR amoxicillin plus cefotaxime Suggested duration 7 days
Septicaemia in child 1 month to 18 years, community-acquired	Amoxicillin plus aminoglycoside OR cefotaxime alone If Pseudomonas spp or resistant organisms suspected: use broad-spectrum antipseudomonal β-lactam antibiotic If anaerobic infection suspected: add metronidazole If Gram-positive infection suspected: add flucloxacillin OR vancomycin Suggested duration at least 5 days
Septicaemia in child 1 month to 18 years, hospital-acquired	Broad-spectrum antipseudomonal β-lactam antibiotic, for example: piperacillin/tazobactam, imipenem/cilastin, meropenem If Pseudomonas spp or multiresistant organisms suspected or if severe sepsis: add aminoglycoside If methicillin-resistant Staphylococcus aureus (MRSA) suspected: add vancomycin If anaerobic infection suspected: add metronidazole to a broad-spectrum cephalosporin Suggested duration at least 5 days
Septicaemia in presence of central vascular catheter	Vancomycin If Gram-negative pathogens suspected: add broad-spectrum antipseudomonal β-lactam Consider line removal
Meningococcal septicaemia	Benzylpenicillin or cefotaxime, if allergic give chloramphenicol

Potentially to be used interchangeably: ampicillin and amoxicillin, ceftriaxone and cefotaxime, teicoplanin and vancomycin.

causative bacteria according to age, patient characteristics and suspected site of infection. This will ensure that patients, in whom bacterial infection is eventually proven, are appropriately treated at an early stage of infection. Treatment concordance or discordance, meaning antibiotic therapy to which the isolate is susceptible or non-susceptible in vitro, is assessed in relation to microbiological results rather than describing a clinical response to treatment. For life-threatening infections, such as bloodstream infections, there is some evidence, mainly from adult patients, that early concordant antibiotic treatment improves patient outcomes.[5]

SHOULD THIS PATIENT BE TREATED WITH A CARBAPENEM EMPIRICALLY?

One option could be to simply administer the most 'broad spectrum' antibiotic available to this child, for example, meropenem. Unfortunately, there are several problems with this type of approach:

1. Empirical antibiotic therapy is supposed to be given for a short period of time. However, in reality once a broad-spectrum antibiotic, such as a carbapenem, is commenced empirically it can be very difficult to de-escalate treatment promptly. From a clinical decision-making point of view, a positive blood or other culture would enable us to tailor this patient's antibiotic therapy accordingly. However, his cultures may remain negative, while he may clinically still appear unwell. In this case, many clinicians would be worried about stopping or de-escalating empirical antibiotic treatment, a phenomenon that has been well described for neonatal intensive care patients, for example.[6] In such a situation, broad-spectrum antibiotics are likely to be continued or even escalated in the absence of proof of infection. Prolonged empirical use of broad-spectrum antibiotics is known to be associated with a number of negative outcomes, such as a higher risk of necrotising enterocolitis in neonates[7] and a higher risk of candida bloodstream infection in paediatric intensive care patients.[8]
2. Using the most broad-spectrum options for all children also drives antimicrobial resistance locally and globally. The local impact of a policy of broad-spectrum antibiotic use was demonstrated in a trial carried out in neonatal intensive care in the Netherlands:[9] an empirical regimen of amoxicillin and cefotaxime for the treatment of neonatal sepsis led to 18 times higher colonisation with resistant Gram-negative bacteria than when a more conservative regimen of penicillin plus tobramycin were used.
3. Our patient does not have any specific risk factors for bloodstream infection caused by multidrug resistant Gram-negative organisms. In patients with such risk factors (eg, known colonisation by extended-spectrum β-lactamase producing bacteria) the treating physician may feel that a very broad regimen, such as meropenem, is a safe bet. Even the broadest antibiotic regimens, however, have gaps in their cover: *K. pneumoniae* bloodstream isolate resistance to carbapenems is known to be around 7% in children across Europe.[10] This means that one would have to use ever more complicated combination regimens to ensure that all possible isolates, including carbapenem-resistant Enterobacteriaceae, are covered.

Thus, although we may feel that giving the broadest regimen will improve cover, this may not actually be the case, and this approach may be risky. Moreover, data are currently rarely available to support clinicians in daily practice that enable the cover of different regimens to be compared. However, clinicians could target empirical treatment better if this was available, and we address this issue in the next section.

How are empirical antibiotic treatments selected?

As mentioned above, patient-level knowledge of risk factors for a specific aetiology of sepsis is important in selecting empirical treatment. For example, if our patient had a central venous line, specific bacteria, such as *Staphylococcus aureus* or coagulase-negative staphylococci (CoNS), would be more likely to be causing the bloodstream infection, and we would need to consider the cover provided by regimens for these pathogens. Similarly, knowledge of whether an infection is nosocomial and information on any recent antibiotic treatments is important.

Local antibiotic guidelines are usually based on aggregate microbiological data gathered at a local/hospital level for many patients, based on the assumption that isolates from these patients are representative of isolates likely to be encountered at this hospital. Such data are frequently summarised in the form of a hospital antibiogram.[11] Table 2 is an example of a hospital antibiogram. These generally present resistance information by pathogen, summarising the results of individual isolates for the key bacterial species over a specified period of time, for example, 1 year. Of note, not all data in a hospital antibiogram may be of clinical relevance. For example, while Enterobacter or Serratia spp may appear susceptible to cephalosporins in vitro, these agents should not be used to treat Enterobacter or Serratia spp infection.

WHAT TOOLS CAN SUPPORT EMPIRICAL ANTIBIOTIC DECISIONS?

While hospital antibiograms provide useful summaries of the resistance of pathogens to various antibiotics, they have several limitations in the context of empirical treatment decision-making: although you may have a suspicion about the causative bacteria in a given patient, it is difficult to know for sure, and you would want to provide cover for less likely, but potentially dangerous candidates as well. It may be important to determine whether patients being treated for probable severe bacterial infection are colonised by multidrug resistant bacteria, for example, to provide appropriate empirical cover.

In our patient, there is a strong suspicion that the most likely type of infection is a primary bloodstream infection as he does not have any signs suggestive of urinary tract infection or meningitis and is stable from a respiratory point of view. We would therefore want to provide cover for bacteria that cause bloodstream infection in children seen at our centre.

One limitation is that many antibiograms will include isolates from all types of cultures, such as blood, urine and cerebrospinal fluid.[11] While this approach increases the sample size of isolates, and therefore improves confidence in estimates of cover provided by different antibiotics, the pathogen and resistance patterns can differ between different sites of infection. In order to improve concordance of an empirical regimen for a specific site of infection, it is preferable to limit an antibiogram to isolates from relevant cultures: for suspected bloodstream infection, these would be blood cultures; for urinary tract infections, it would be urine cultures, and so on.

Another limitation is that antibiograms are rarely age-specific, even though pathogen and resistance patterns for children and adults are not the same.[10 12] Consequently, to support empirical antibiotic prescribing, clinicians require a summary statistic that will describe the likely overall cover of different antibiotic regimens given the type of patient and infection.

Finally, you would want to know whether the cover provided by different regimens is in fact similar. As with any other type of data, any observed differences may be down to chance and, depending on sample size, one's confidence in the estimate of a regimen's cover may be low, as in the case when the 95% CI around the estimate is wide. Establishing the equivalence of regimens is important because guidelines such as 'Surviving Sepsis' recommend selecting a regimen that provides cover for the whole likely spectrum of causative bacteria guided by local microbiological results.[1]

The weighted incidence syndromic combination antibiogram

An alternative approach that overcomes the limitations of a hospital antibiogram is to present the microbiological data as a weighted incidence syndromic combination antibiogram (WISCA).[13–15] This describes the cover provided by different regimens, taking into account the distribution of pathogens and resistance patterns (weighted incidence) for a specific syndromic infection and can be calculated for both single and multiple (combination) antibiotic regimens. A further advantage is that it is possible to calculate 95% CIs for the cover estimates, which allows clinicians to consider whether different regimens are likely to provide truly different cover.[15] To select an appropriate regimen for our patient, we would want to review the WISCAs for candidate regimens, such as those listed in the British National Formulary for children (BNFc), based on bloodstream isolates only.

Table 3 shows a WISCA that includes various regimens. These have been calculated from the data in table 2 using a method based on a decision tree.[15] You can see that amoxicillin plus gentamicin cover a

Table 2 Example of a hospital antibiogram

Paediatric annual hospital antibiogram for 2015	N	Ampicillin	Amoxicillin/clavulanate	Cefotaxime	Ceftazidime	Cefuroxime	Ciprofloxacin	Clindamycin	Erythromycin	Flucloxacillin	Fusidic acid	Gentamicin	Imipenem	Linezolid	Penicillin	Piperacillin/tazobactam	Rifampicin	Teicoplanin	Tetracycline	Tigecycline	Trimethoprim	Vancomycin
Escherichia coli	22	65	16	11	8	18	22					11	0			3				0		
Klebsiella spp	8		13	9	7	16	9					5	0			9				3		
Enterobacter spp	12			16	14		4					6	0			6				2		
Proteus. mirabilis	4	34	6	2	1	1	8					7				1						
Serratia spp	8			10	0		5					0	0			7				2		
Pseudomonas. aeruginosa	9						6					3	4			5						
Staphylococcus. aureus	28						16	3	16	11	12	3		0	83		1	1	6	0	12	0
Coagulase-negative staphylococci	32						51	14	59	68	54	59		0	93		8	28	46	4	64	0
Streptococcus. pneumoniae	12			0				7	9				0	0	0			0	8			0
Enterococcus. faecalis	3	0										35	0	0					3	0		3
Enterococcus. faecium	5	100										54	100	0				23		0		24

The number of isolates for 2015 is shown in the second column. Column headers are abbreviations for different antibiotics, for which susceptibilities may be tested. The numbers in the cells of the table represent the percentage of isolates found to be non-susceptible to the relevant antibiotic (these may be calculated by including isolates from the previous year as well, if sample size is low). Blank cells indicate that no relevant susceptibility testing results are available for this combination between bacterial species and antibiotic.

Table 3 Weighted incidence syndromic combination antibiograms (WISCAs) for specific empirical regimens when used for paediatric sepsis

Infection	Antimicrobial regimen	% of key isolates covered (95% CI)
Sepsis/bloodstream infection (based on blood culture isolates)	Amoxicillin plus gentamicin	76% (69% to 82%)
	Piperacillin/tazobactam	73% (66% to 79%)
	Ceftriaxone	65% (58% to 72%)
	Ceftriaxone or cefotaxime plus amoxicillin	66% (59% to 73%)
	Meropenem	74% (68% to 81%)

The cover estimates are based on data in table 2 and are presented with 95% CIs.

similar proportion of isolates as piperacillin/tazobactam or meropenem, and may therefore be as good an option for empirical treatment in this instance. This assumes that all isolates in table 2 were from blood cultures.

The low level of cover provided by broad-spectrum antibiotics, such as piperacillin/tazobactam and meropenem, is mainly due to the inclusion of pathogens with high levels of resistance to these agents, for example, CoNS. It may not be necessary to provide early cover for CoNS, especially for children without central venous access lines who will not have sepsis due to CoNS.

As several regimens are very similar in empirical cover, the selection of a specific regimen can be carbapenem-sparing and consider additional factors: piperacillin/tazobactam, for example, may have specific advantages in terms of renal toxicity compared with gentamicin in a combination treatment of amoxicillin and gentamicin and could be used to provide cover for specific bacteria of concern, such as *P. aeruginosa*. Our patient does not have risk factors for specific pathogens of concern, has normal renal function and could, on the basis of the WISCAs in table 3, perhaps have been empirically treated with amoxicillin plus gentamicin in the first instance.

MOVING ON FROM EMPIRICAL ANTIBIOTICS

It is very important to adapt empirical antibiotic regimens once additional information becomes available. This is also the reason why it is critical to take all relevant microbiological samples before starting antibiotics, if at all possible. In the UK, changes to empirical antibiotics should follow the 'Start Smart, Then Focus' approach.[16]

In our patient, you may want to stop any antibiotic therapy if he is improving at 48 hours, urine and blood cultures are negative at this stage, and clinically it appears that his deterioration was not due to infection. Equally, if his blood cultures grow a specific organism unlikely to be a contaminant, say *Escherichia coli*, you may want to adjust therapy to the most narrow-spectrum option compatible with the specific microbiological susceptibilities of the isolate. If you are unsure about how to de-escalate treatment safely, your microbiology colleagues will be able to help you. At the same time, you should think about how long you might need to treat (see table 1), and whether there will be an opportunity to switch from intravenous antibiotics to oral treatment. For example, if our patient had signs of urinary tract infection on dipstick, was improving clinically and his urine cultures grew *E. coli*, but his blood cultures remained negative, he may simply be suffering from a urinary tract infection and you could switch to oral treatment informed by the antibiogram of the urinary *E. coli* isolate.

SUMMARY

The selection of empirical antibiotic regimens for severe bacterial infections, when immediate treatment is required, needs to take into account the epidemiology of the targeted infection and key patient characteristics. This can be achieved by analysing available microbiological data, and presenting this in a clinically meaningful manner as a WISCA.

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Competing interests None declared.

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2.2 Challenges for deriving optimal empiric antibiotic regimen from routine microbiological data

There are several challenges of deriving relevant information from routine data when considering on-going large-scale surveillance of antimicrobial resistance. Such data are widely available in Europe and globally and could therefore potentially be made accessible to clinical decision-makers.

At present, microbiological cultures are the only widely available and used test to definitively confirm most severe bacterial infections, including bloodstream infections in children. Because of this, blood cultures are obtained for many children suspected of having a severe infection, but the rate of positive blood cultures is low (<3% in the UK, <7% in high-incidence settings, e.g. Kenya) (35, 36). Optimal sampling techniques can be difficult in busy clinical care with potential for false positive and false negative results (37). Therefore, in children it is often necessary to interpret blood culture results in a clinical context to guide definitive treatment.

Despite these concerns, information on bacteria isolated from a blood culture is considered one of the most robust sources of microbiological information (38-40) In addition to their clinical relevance, blood cultures are likely to have limited sampling bias (41). They examine a normally sterile site, making it easier to distinguish between merely colonizing and infecting isolates. Moreover, the majority of children with suspected bloodstream infection will be evaluated in the hospital setting, where appropriate samples can be taken. It is for these reasons that several established national and international surveillance programmes focus on bacteria isolated from blood culture (42, 43).

One limitation of using routine blood culture data is a lack of standardisation of laboratory procedures (44). Although there are several defined standards for the interpretation of susceptibility testing results, the selection of tested antibiotics is generally determined by the isolated bacterium, the type of infection, the antibiotics available for treatment at any given centre and the guidelines in use in the laboratory (43, 45). While this may seem justifiable on

the basis of clinical needs and patient characteristics, it is known that differences in the laboratory methods used to evaluate antimicrobial susceptibility can affect the observed resistance patterns (44, 46, 47). In particular so-called “reflex testing” can be problematic when certain bug-drug combinations are only evaluated based on the detection of resistance in a first line standardised antibiotic panel. Thus the denominator for these second line tests is constituted not of all isolates but only of those with some antimicrobial resistance, biasing resistance prevalence estimates.

Revisions to and variability between interpretive guidelines for antimicrobial susceptibility testing can add complexity to analyses of routine data for the identification of trends in antimicrobial resistance (45, 48, 49). This has to be borne in mind when using routine microbiological data to describe the epidemiology of bloodstream infections, especially when it is desirable to compare different hospitals or regions over time (50).

Nonetheless, the secondary use of routine data for selecting empiric regimens could be highly efficient: Hospitals may already be reporting these data internally or to surveillance databases; data may be in format that can easily be used for evaluation of coverage of different regimens of interest; despite limitations, such data are likely to provide a reflection of the current epidemiology. This is particularly true of surveillance data which are already widely available in Europe, North America and Australia (34). Defining methods for analysis and presentation of these data to support selection of empiric antibiotic regimens would mean that existing data could be used in a better way to inform clinical practice.

2.3 Rationale for thesis

Standard approaches towards determining empiric regimens from routine microbiological data at the hospital level, such as antibiograms, are unlikely to lead to clinically useful local adaptations of empiric treatment strategies. This is particularly true in a setting, where overall isolate numbers are low, like in neonatal and paediatric practice. Routine microbiological data are easily available in each hospital and are often already fed into large scale surveillance of epidemiological trends. However, surveillance data like hospital data are not generally presented in a clinically relevant fashion.

The optimal alternative approach would make use of such routinely available data routinely to

(i) allow the definition of infection-based rather than bacteria-based recommendations (e.g. for suspected bloodstream infection);

(ii) take into account the epidemiology of the infection of interest, that is both the prevalence of bacteria and their resistance patterns;

(iii) adequately handle low isolate numbers for any one of the bacteria of interest.

The benefits of such an approach would be a more efficient and clinically relevant use of routinely available data to ensure a high likelihood of concordant empiric treatment for children treated for bloodstream infections. At the same time, a robust method for selecting empiric antibiotic regimens could support the data-driven use of narrow-spectrum alternatives whenever appropriate and contribute to the conservation of broad-spectrum agents for use in patient groups most likely to benefit.

3. Thesis data sources and analytical approaches

3.1 Selection of empiric antibiotic regimens for bloodstream infections

The decision to prescribe empiric antibiotics is taken by an individual clinician for an individual patient but is usually informed by other sources of guidance. When selecting an empiric antibiotic regimen for inclusion in such guidance the following aspects need to be considered:

- The specific infection syndrome being targeted: In clinical practice, infection syndromes are variably characterised by a set of signs and symptoms, non-specific laboratory markers and radiological findings. Some bacteria can cause multiple infection syndromes (for example, *E. coli* is an important cause of urinary tract infection, but also primary bloodstream infection or meningitis).
- The relative incidence of different types of bacteria causing the target infection syndrome: Unless reliable point-of-care or rapid testing is available to identify causative bacteria at the time point of the treatment decision, a good understanding of the frequency with which different bacteria are isolated in a given infection syndrome will form the basis of selecting an empiric regimen.
- The antibiotic resistance patterns of causative bacteria: The prevalence of resistance to antibiotics available for use in a given location and for a given patient group in all bacteria commonly identified in the infection syndrome needs to be taken into account.
- Patient characteristics: The relative incidence and resistance patterns of bacteria may vary according to certain patient characteristics even within the same infection syndrome. For example, variation may be observed across age, according to the source of infection (community-acquired or hospital-acquired) or due to the presence of underlying chronic co-morbidities that lead to frequent healthcare contacts. Other patient characteristics, such as the presence of antibiotic allergies or impaired renal

or liver function, will also impact on whether a certain optimal empiric regimen is suitable for use in the individual patient.

Adaptations to the initial empiric regimen will occur as results from microbiological sampling become available. In most cases, this is still a sequential process relying on culturing the bacterium first, then subjecting that isolate to antimicrobial susceptibility testing (51). A summary of this process is presented in Figure a.

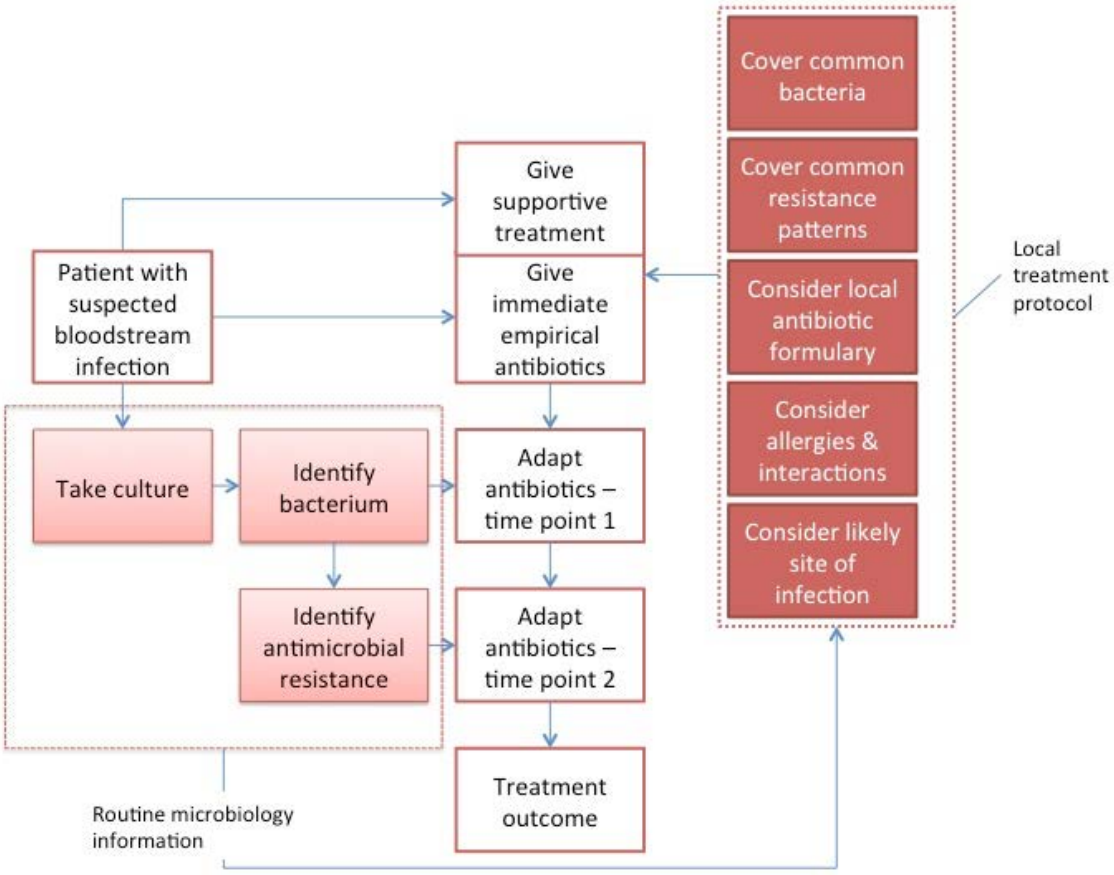

Figure a: Summary of the key steps for the selection of empiric antibiotic regimens at hospital level.

3.2 The role of the cumulative antibiogram: how hospitals summarize routine data

The usual tool for informing the selection of empiric treatment regimens at the hospital is a hospital antibiogram (31). The hospital antibiogram is the most basic cumulative summary reflecting the local microbiology of bacterial infections. It is based on summarizing the antibiograms of individual isolates of the key bacterial species. This is usually constructed by including all isolates of the bacteria of interest over a specified period of time, for example

one year. As such, hospital antibiograms often do not apply to an infection syndrome of interest as included isolates will come from different sources and types of patients.

Hospital antibiograms list pathogens individually and focus on key bacteria, often those for which extensive susceptibility testing is relevant. Bacteria for which resistance is not considered a substantial problem, such as *Streptococcus pyogenes* or *Streptococcus agalactiae,* are unlikely to be included, and the relative frequency of these in specific infection syndromes therefore cannot be estimated from a hospital antibiogram. Finally, hospital antibiograms can be subject to bias resulting from local laboratory practices, such as the selection of antibiotics for susceptibility testing, and the inclusion or exclusion of repeat isolates from an individual patient. Patients with the same pathogen being repeatedly isolated are often the most complex patients and therefore most at risk of at some point carrying or being infected by resistant isolates. This could lead to overestimations of resistance.

Low numbers of neonatal and paediatric isolates (compared with isolates from adults) are one reason why hospitals may choose not to present childhood data separately (18). An additional limitation for informing empiric treatment is the focus on reporting susceptibility results for specific bacteria-antibiotic pairs, since the causative pathogen is generally unknown at the time of treatment initiation. The relevance of the hospital antibiogram for guiding empiric antibiotic regimen selection is therefore unclear.

3.3 The desirable characteristics of a metric for selecting empiric antibiotic regimens for childhood bloodstream infections

Current guidance on defining empiric treatment approaches for childhood bloodstream infection may be confusing for clinicians. Although relatively robust data on which to base recommendations are available, these are generally summarized in terms of bacterial susceptibility rather than being presented in a clinically meaningful manner. Standard cumulative antibiograms are therefore unlikely to lead to clinically useful adaptations of

empiric treatment strategies. This is particularly true in settings, where overall isolate numbers are low, like in neonatal and paediatric practice.

The optimal approach would make use of routinely available data to

(i) allow the definition of clinical infection-based rather than bacteria-based recommendations (e.g. for suspected bloodstream infection) (52),

(ii) take into account the epidemiology of the infection of interest, that is both the prevalence of bacteria and their resistance patterns (53),

(iii) adequately handle low isolate numbers for any one of the bacteria of interest (53).

It is therefore desirable to have a syndromic metric that provides information about the expected coverage of an empiric antibiotic regimen. This is defined as the percentage of isolates, in this case causing childhood bloodstream infections, against which the regimen of interest was active in microbiological testing (also defined as concordance) (54). In essence, the expected coverage can be derived as a weighted average of the susceptibilities of relevance bacteria with the weights defined by their relative incidence (55). At the same time, coverage reflects the probability that a regimen will be active against all relevant potential causative bacteria for the next child presenting with bloodstream infection.

Refinement of the classical cumulative antibiogram has led to alternative approaches being proposed that address some of the challenges above while still using widely available data from routine microbiological samples and generating an estimate of coverage. One method is the weighted incidence syndromic combination antibiogram or WISCA (55). This approach has been used to evaluate coverage of antibiotic regimens for bloodstream infection in neonates and children based on population data (16, 53, 56). However, the original description of the WISCA did not address the potential impact and handling of low isolate numbers including quantification of uncertainty.

3.4 Interpretive algorithms to derive antibiotic concordance from antimicrobial susceptibility testing data

Hospital antibiogram and surveillance data are generally used for reporting on specific pathogen-antibiotic combinations. However, results for antimicrobial susceptibility testing involving some pathogen-antibiotic combinations can be used to make inferences about susceptibility for related agents or even antibiotic groups (57, 58). The application of interpretive rules is important in clinical decision-making when individuals are treated to determine whether a specific causative bacterium is covered by current antibiotic therapy or not. For example, susceptibility to benzylpenicillin for Streptococcus pneumoniae is indicative of the isolate being susceptible to all beta-lactams without further testing (57). This can then guide escalation or de-escalation decisions when moving from empiric to definitive therapy. Similarly, the application of interpretive rules could improve the use of routine data for aggregate analyses, such as a WISCA. For this thesis, interpretive rules were based on EUCAST algorithms (59).

For monotherapy regimens, EUCAST standard algorithms were applied to infer susceptibility from other testing results when different antibiotics were considered equivalent (for example, oxacillin and cefoxitin for methicillin-resistance in *S. aureus*). Isolates reported as intermediate or resistant to an antibiotic representative of a monotherapy regimen, such as ceftriaxone, were classified as resistant. Very recently, the intermediate category has been reclassified by EUCAST to indicate susceptible if treated with an increased dose and eliminated where this is not the case (60). For combination regimens, isolates were classified as susceptible to the regimen if they were reported as susceptible to at least one of the antibiotics in the combination. The antibiotic with higher susceptibility levels in a combination regimen determined the estimate of susceptibility to the regimen (for example *E. coli* amoxicillin susceptibility reported to be 20%, gentamicin susceptibility reported to be 90%, overall susceptibility of *E. coli* to amoxicillin and gentamicin is 90%).

One reason for missing data from antimicrobial susceptibility testing is that a certain pathogen has intrinsic resistance to a given antibiotic. This pathogen-antibiotic combination

would then not be tested as a result indicating susceptibility would be uninterpretable and would not indicate that the antibiotic could be suitable for treatment. An example for such a situation is the susceptibility of enterococci to cephalosporins (61). Similarly, there are bacteria for which a resistant phenotype would be considered highly unusual and assumptions can be made about being generally susceptible to certain antibiotic groups regardless of the availability of susceptibility testing. An example would be susceptibility of Group B streptococcus to cephalosporins or carbapenems (59).

3.5 Data sources

3.5.1 ARPEC antimicrobial resistance database

Using established methodology from the European Antimicrobial Resistance Surveillance Network (EARS-Net), information on bacteraemia rates and antimicrobial susceptibilities for key bacteria was collected as part of the ARPEC project (62).

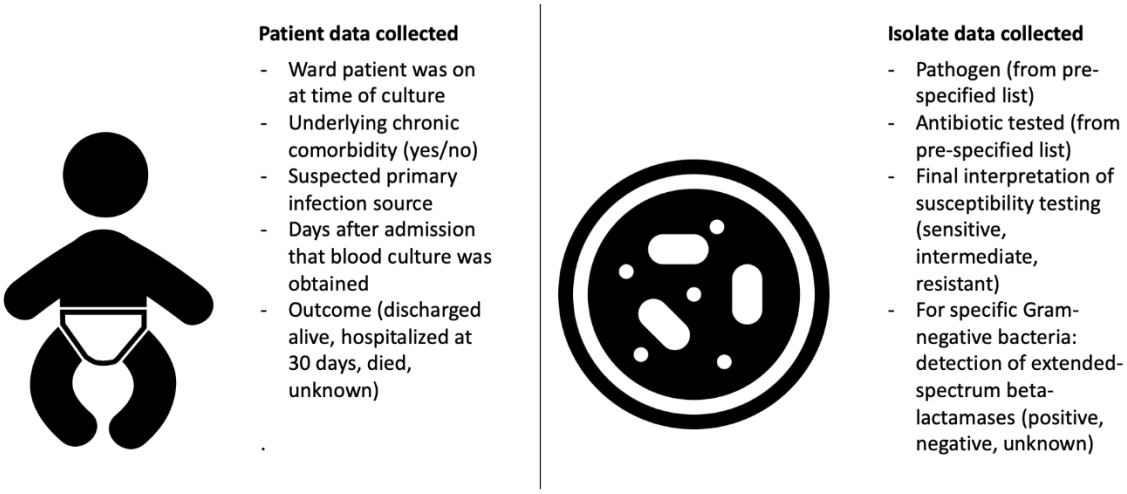

Figure b: Data available in the ARPEC antimicrobial resistance database.

Limited additional data were collected on the patient from whom the blood culture had been taken (Figure b).

All first positive blood cultures from patients under 18 years of age at the time of routine blood culture during the study period with growth of *Staphylococcus aureus*, *Streptococcus pneumoniae*, non-typable *Haemophilus* and *Haemophilus influenzae*, *Enterococcus faecalis* and *E. faecium*, *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*,

Enterobacter spp., *Acinetobacter baumannii*, *Stenotrophomonas maltophilia* and *Salmonella enterica* serovar were included. Any blood cultures originating from the same patient and positive for the same organism within 4 weeks of the original reported blood culture were excluded. For each isolate, antimicrobial susceptibility testing information for any antibiotic from a pre-specified list was recorded as sensitive, intermediate or resistant (Table a). Minimal inhibitory concentrations were not collected.

CODE	ANTIBIOTIC	CODE	ANTIBIOTIC
AMK	Amikacin	LNZ	Linezolid
AMX	Amoxicillin	MEM	Meropenem
AMC	Amoxicillin/Clavulanic acid	MET	Methicillin
AMP	Ampicillin	MFX	Moxifloxacin
AZM	Azithromycin	MUP	Mupirocin
ATM	Aztreonam	NAL	Nalidixic acid
CZO	Cefazolin	NET	Netilmicin
FEP	Cefepime	NIT	Nitrofurantoin
CTX	Cefotaxime	NOR	Norfloxacin
FOX	Cefoxitin	OFX	Ofloxacin
CAZ	Ceftazidime	OXA	Oxacillin
CRO	Ceftriaxone	PEN	Penicillin G
CHL	Chloramphenicol	PNV	Penicillin V
CIP	Ciprofloxacin	PIP	Piperacillin
CLR	Clarithromycin	TZP	Piperacillin/Tazobactam
CLI	Clindamycin	RIF	Rifampin
CLO	Cloxacillin	TEC	Teicoplanin
DIC	Dicloxacillin	TET	Tetracycline
ERY	Erythromycin	TIC	Ticarcillin
FLC	Flucloxacillin	TCC	Ticarcillin/Clavulanic acid
FUS	Fusidic acid	TOB	Tobramycin
GEN	Gentamicin	TMP	Trimethoprim
IPM	Imipenem	SXT	Trimethoprim/Sulfamethoxazole
LVX	Levofloxacin	VAN	Vancomycin

Table a: Antimicrobial susceptibility testing data collected as part of the ARPEC antimicrobial resistance project

To support data interpretation, background information on paediatric specialist services in participating hospitals, annual admissions data and annual data for all positive blood cultures were also collected. Furthermore, information on laboratory/hospital-specific microbiology approaches, including the type of interpretive criteria used for determining susceptibility to tested antibiotics, was of interest.

Data collection used a custom-built database and was completely anonymous. Data were extracted from the laboratory information systems of participating hospitals based on the eligibility criteria outlined above for 2011 and 2012.

The final ARPEC-AMR database included data on >1500 bloodstream infections from 19 centres in 10 European countries. The full ARPEC-AMR data were used for the analyses in chapters 4, 5 and 6 of this thesis.

3.5.2 ARPEC antibiotic use point prevalence survey

Building on the success of point prevalence surveys to evaluate antimicrobial use patterns in the hospital setting for adult patients, this standardized methodology was adapted and validated for collecting data from children as part for the ARPEC project (63, 64).

In brief, participating hospitals conducted a one-day survey on all neonatal and paediatric wards as a means of auditing antimicrobial prescribing rates in hospitalised children. For this, all patients less than 18 years of age admitted overnight were counted and contributed to the denominator, calculated by ward and overall for each hospital. All patients with an antimicrobial prescription at 8 am on the day of the survey contributed to the data on antimicrobial prescribing. Day cases, outpatients, emergency admissions after midnight on the day of survey, psychiatric patients, children admitted to an adult ward and over 18 year-olds admitted to paediatric wards were excluded and did not contribute to either numerator or denominator data.

Data on all systemic antimicrobials defined by WHO Anatomical Therapeutic Chemical (ATC) classification system were of interest (65): Antibacterials, antimycotics and antifungals and antivirals for systemic use, antibiotics used as drugs for the treatment of tuberculosis, intestinal anti-infectives and anti-malarias. For each prescription and treated patient additional information was collected (Figure c).

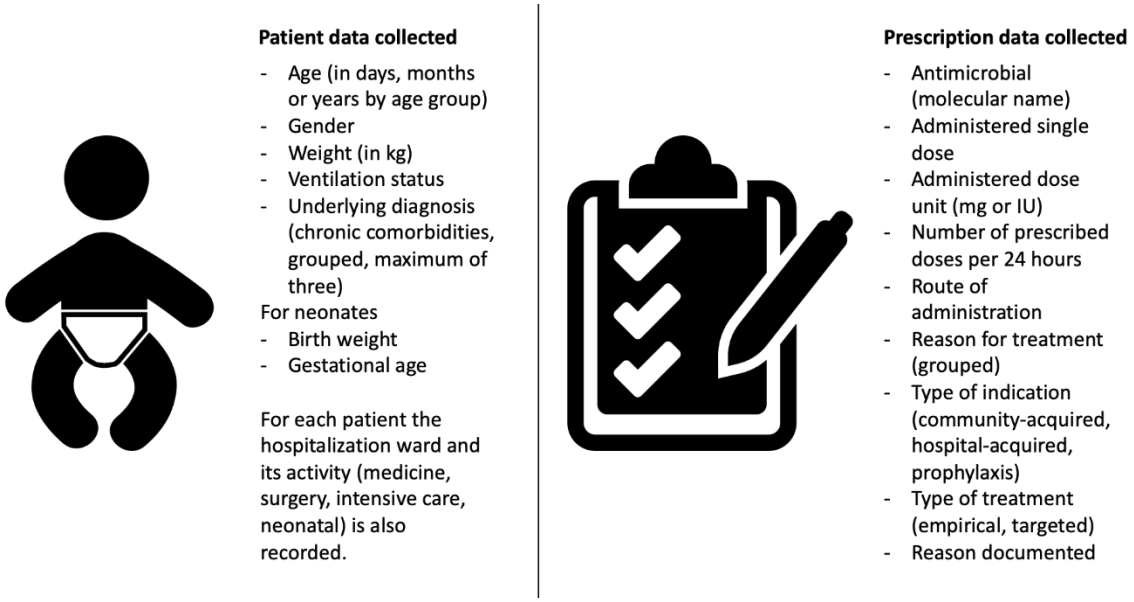

Figure c: Data available in the ARPEC point prevalence study of inpatient neonatal and paediatric antimicrobial prescribing

Data collection used custom-built software and was completely anonymous. Three point prevalence surveys were conducted: A feasibility study in 11 European hospitals, the first ARPEC-PPS in September 2011 in 73 hospitals located in 23 different countries globally and the second ARPEC-PPS in October/November 2012 in 226 hospitals in 41 countries.

The ARPEC-PPS database includes 26,618 surveyed neonates and children of which 9944 were prescribed at least one antimicrobial on the day of survey. In total, the database contained 17,126 prescriptions, of which most were antibacterials for systemic use.

The ARPEC-PPS data were used for the analysis in chapter 8 of this thesis. For this, a data extract containing all antibacterial prescriptions issued to neonates and children with at least on antimicrobial prescription for sepsis was prepared and analysed.

3.5.3 NeoAMR Feasibility survey

Data were collected as part of a feasibility assessment for international sites wishing to take part in a prospective cohort study on neonatal sepsis (NeoOBS). NeoOBS is designed to evaluate healthcare utilization and current clinical practice of antibiotic management of neonatal sepsis, and to assess risk factors for and outcomes of babies with culture-negative and culture-positive sepsis (ClinicalTrials.gov Identifier: NCT03721302).

During the feasibility phase, anonymous aggregate data from an international network of sites were collected using a REDCap™ database, and stored in a secure server at St. George's University of London. The feasibility survey was designated a clinical audit not requiring formal Ethics Committee review in the country of the data host (UK). Contributing centres were individually responsible for obtaining ethical approval according to local regulatory and legal requirements. The feasibility survey covered a number of low and middle-income countries worldwide, however, for this PhD only data from Asian centres were included.

As part of the survey, the prevalence of antimicrobial resistance among blood culture isolates from newborns up to 28 days of age or infants cared for on neonatal units was estimated. Information was collected on bacterial isolates and their susceptibilities cultured between 1 January 2016 and 31 December 2016.

Sites were requested to provide information on nine specific bacteria frequently associated with neonatal sepsis, likely to cause severe disease and requiring optimal early antibiotic therapy, namely *Escherichia coli*, *Klebsiella* spp., *Enterobacter* spp., *Acinetobacter* spp., *Pseudomonas* spp., *Staphylococcus aureus*, *Enterococcus* spp., *Streptococcus agalactiae* (GBS) and *Streptococcus pyogenes* (GAS). For each of the pathogens, participating sites submitted the number of total isolates, the number tested for susceptibility to relevant antibiotics, including aminopenicillins, aminoglycosides, third-generation cephalosporins, carbapenems, and the number of isolates found to be resistant to these (Table b).

The feasibility survey data was analysed alongside data from the literature in chapter 7 of this thesis.

Step			
1	Total number of positive cultures	Total number of bacterial blood culture isolates from neonates during the target period (= Sum of total n for Step 2 plus other bacterial isolates without correction for contaminants or duplicate isolates)	
2	Pathogens of interest	Total n	Antibiotic classes* of interest for susceptibility testing and antibiotic resistance

			Aminopenicillins	Aminoglycosides	Third-generation cephalosporins	Carbapenems	Methicillin resistance	Glycopeptides
	Escherichia coli	X	X	X	X	X		
	Klebsiella spp.	X		X	X	X		
	Enterobacter spp.	X		X	X	X		
	Acinetobacter spp.	X		X	X	X		
	Pseudomonas spp.	X		X	X	X		
	Staphylococcus aureus	X					X	X
	Enterococcus spp.	X	X					X
	Streptococcus agalactiae	X						
	Streptococcus pyogenes	X						

*Susceptibility testing and resistance data were not collected for individual antibiotics within a given class. For example, questions on resistance were phrased “How many of [the tested] isolates [for this pathogen] were resistant to at least one [member of antibiotic class]?”

Table b: Description of feasibility survey data collection for period prevalence of bacterial isolates and their resistance patterns

3.6 Ethics

The research for this thesis was based on data that were exempt from UK National Research Ethics Service (NRES) approval, because data collection was considered to constitute surveillance, service evaluation or audit (see LSHTM review, appendix A). The analysis involved the secondary use of these anonymised pre-exisiting datasets or, in one case, data from the published literature. I did not have access to coded or patient-level data.

4. Estimating clinically relevant resistance in childhood bloodstream isolates from surveillance data

The potential impacts of laboratory practice on assessing resistance prevalence were discussed in subchapter 2.2. Despite the outlined limitations, routine data generated by laboratories applying variable algorithms and interpretive criteria are frequently reported as part of antimicrobial resistance surveillance. For such surveillance, it is usual to request or report on the results for specific pathogen-antibiotic susceptibility tests (for example, third-generation cephalosporins for many Gram-negative bacteria of interest) rather than evaluating the full antibiograms for reported isolates. While not explicit, there is an underlying assumption that resistance in these individual bug-drug combinations is associated with clinically relevant antibiotic resistance and could at least be indicative of the utility of certain empiric regimens.

This chapter comprises of a published paper that investigates the potential impact of routine blood culture microbiology data collection for surveillance on estimating bacterial multidrug resistance. Multidrug resistance is of clinical importance because it is likely to adversely affect coverage of potentially suitable empiric antibiotic regimens (66, 67). In addition, the relationship between resistance percentages for individual bug-drug combinations and multidrug resistance may affect what clinical inferences for selection of empiric antibiotic regimens can be drawn from standard surveillance and hospital antibiogram reporting.

The analysis focuses on bloodstream isolates of Gram-negative bacteria included in European surveillance of antimicrobial resistance for which reporting centres on individual pathogen-antibiotic class combinations. Multidrug resistance was defined based on an algorithm developed for surveillance purposes by the European Centre for Disease Prevention and Control (ECDC) (68).

Data on antimicrobial resistance from the ARPEC project were used for this analysis.

RESEARCH PAPER COVER SHEET

SECTION A – Student Details

Student ID Number	237152	**Title**	Dr
First Name(s)	Julia Anna		
Surname/Family Name	Bielicki		
Thesis Title	Estimating coverage of empiric treatment regimens for childhood bloodstream infection based on routine microbiological data		
Primary Supervisor	Prof. David Cromwell		

If the Research Paper has previously been published please complete Section B, if not please move to Section C.

SECTION B – Paper already published

Where was the work published?	Eur J Clin Microbiol Infect Dis		
When was the work published?	26 Dec 2017		
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion	n/a		
Have you retained the copyright for the work?*	**No**	Was the work subject to academic peer review?	**Yes**

*If yes, please attach evidence of retention. If no, or if the work is being included in its published format, please attach evidence of permission from the copyright holder (publisher or other author) to include this work : **See included copy, open access.**

SECTION C – Prepared for publication, but not yet published

Where is the work intended to be published?	
Please list the paper's authors in the intended authorship order:	
Stage of publication	Choose an item.

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	I together with DA Cromwell and M Sharland conceived the study. I then undertook data preparation and statistical analysis. I wrote the first draft of the manuscript which I modified based on co-author comments.

SECTION E

Student Signature	[redacted]	**Supervisor Signature**	[redacted]
Date	17.08.2020	**Date**	31.08.2020

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ORIGINAL ARTICLE

Surveillance of Gram-negative bacteria: impact of variation in current European laboratory reporting practice on apparent multidrug resistance prevalence in paediatric bloodstream isolates

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Abstract This study evaluates whether estimated multidrug resistance (MDR) levels are dependent on the design of the surveillance system when using routine microbiological data. We used antimicrobial resistance data from the Antibiotic Resistance and Prescribing in European Children (ARPEC) project. The MDR status of bloodstream isolates of *Escherichia coli*, *Klebsiella pneumoniae* and *Pseudomonas aeruginosa* was defined using European Centre for Disease Prevention and Control (ECDC)-endorsed standardised algorithms (non-susceptible to at least one agent in three or more antibiotic classes). Assessment of MDR status was based on specified combinations of antibiotic classes reportable as part of routine surveillance activities. The agreement between MDR status and resistance to specific pathogen–antibiotic class combinations (PACCs) was assessed. Based on all available antibiotic susceptibility testing, the proportion of MDR isolates was 31% for *E. coli*, 30% for *K. pneumoniae* and 28% for *P. aeruginosa* isolates. These proportions fell to 9, 14 and 25%, respectively, when based only on classes collected by current ECDC surveillance methods. Resistance percentages for specific PACCs were lower compared with MDR percentages, except for *P. aeruginosa*. Accordingly, MDR detection based on these had low sensitivity for *E. coli* (2–41%) and *K. pneumoniae* (21–85%). Estimates of MDR percentages for Gram-negative bacteria are strongly influenced by the antibiotic classes reported. When a complete set of results requested by the algorithm is not available, inclusion of classes frequently tested as part of routine clinical care greatly improves the detection of MDR. Resistance to individual PACCs should not be considered reflective of MDR percentages in Enterobacteriaceae.

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Introduction

Bacteria resistant to multiple antibiotics have been identified as a major challenge for patient management and public health [1, 2]. Multidrug-resistant Gram-negative bacteria (MDR-GNB) are considered to be particularly worrying because the therapeutic options are limited [3, 4]. Furthermore, certain MDR-GNB, such as those producing extended-spectrum beta-lactamases or carbapenemases encoded on plasmids, are of concern due to their potential for interspecies plasmid transfer [5, 6].

Large-scale national and international surveillance is an important tool in monitoring MDR-GNB resistance trends [7]. At present, most surveillance relies on collecting results from traditional antibiotic susceptibility testing (AST) to track resistance epidemiology, including multidrug resistance (MDR) [8–10]. It is, therefore, important that the comparability of isolates identified as MDR by surveillance databases is established. Standardised algorithms for reporting isolates as MDR were proposed in 2012 by a group of international experts, but these rely on a large number of antibiotics being

included in AST (Table 1) [11]. The selection of antibiotic classes for routine testing continues to be highly variable [16–19]. This potentially presents a major challenge for estimating and comparing MDR-GNB prevalence from routine data, given that individual laboratories may not test all antibiotic classes required.

The monitoring of specific pathogen–antibiotic class combinations (PACCs) can be an alternative surveillance strategy to make best use of the available routine data [7, 12–14]. Some PACCs have been suggested as being useful for MDR-GNB assessment based on the recognition of an association in resistance between different antibiotic classes [15].

Using data on neonatal and paediatric GNB isolates obtained from the Antibiotic Resistance and Prescribing in European Children (ARPEC) project, this study evaluates the degree to which estimated levels of MDR are dependent on surveillance system design when routine microbiological data are used.

Materials and methods

Data source

The study used data from the ARPEC project, which was co-funded by the European Commission DG Sanco through the Executive Agency for Health and Consumers [20, 21].

ARPEC collected anonymised data on antimicrobial resistance between January 2011 and December 2012 from 19 European laboratories located in 12 different countries, each processing samples for one paediatric department or hospital. ARPEC requested that participating laboratories reported AST results for isolates of a specified set of bacterial species, and that, where possible, laboratories report on specific antibiotics. These included antibiotics required for the European Antimicrobial Resistance Surveillance Network (EARS-Net) 2010 reporting protocol plus some additional antibiotic categories (Table 1) [12, 22]. The AST results for each antibiotic tested were reportable as susceptible/intermediate/resistant (S/I/R) using breakpoints defined by either:

(1) European Committee on Antimicrobial Susceptibility Testing (EUCAST),
(2) Clinical and Laboratory Standards Institute (CLSI),
(3) British Society for Antimicrobial Chemotherapy (BSAC) or
(4) Société Française de Microbiologie standards,

depending on which standards were used in each country [23–27]. Minimal inhibitory concentrations of antibiotics were not collected. Duplicate isolates (same species with same antibiogram from the same patient) identified within 4 weeks of the original isolate were excluded as part of the data collection protocol.

Target bacteria

This study examined MDR patterns for three GNB, namely *Escherichia coli*, *Klebsiella pneumoniae* and *Pseudomonas aeruginosa*.

Interpretation of reported antibiotic susceptibility

Individual antibiotics were grouped into antibiotic classes as defined by the MDR classification algorithms (Table 1) [11]. Isolates reported as I or R to an antibiotic representative of an antibiotic class were classified as non-susceptible to that class. In the case of AST results for multiple antibiotics representative of one class, the isolate was classified as non-susceptible if they were reported as I or R to any of the antibiotics tested from that class. Isolates were defined as MDR-GNB if they were non-susceptible to ≥3 relevant antibiotic classes [11].

Identification of MDR-GNB bacterial isolates

The proportion of isolates of each of the three species considered to show MDR was then calculated using three sets of antibiotic classes (Table 1):

(1) ARPEC set: MDR status was defined by applying the MDR algorithm and based on information from all classes reported to ARPEC;
(2) EARS-Net set: MDR status was defined by applying the MDR algorithm, but based solely on information for classes included in the EARS-Net protocol;
(3) Routine set: MDR status was defined by applying the MDR algorithm, and based on antibiotic classes with a high level of reported results across all ARPEC laboratories. Classes were included in this set if AST information was available for at least 85% of isolates. The level of required reporting was chosen to reflect classes routinely tested for the bacteria of interest in the majority of laboratories.

As both the EARS-Net and routinely tested classes are subsets of the ARPEC classes, an isolate classified as MDR on the basis of either set was also considered to be MDR based on the ARPEC set.

Evaluation of single PACCs

It was also assessed whether specific PACCs, suggested to be critical indicators of MDR by European, US and global professional and/or public health bodies (Table 1), could identify MDR-GNB as detected on the basis of all available data; that is, the ARPEC set [7, 13–15].

The specific PACCs of interest were *E. coli* and higher-generation cephalosporins, fluoroquinolones, aminoglycosides

Table 1 Summary of the sets of antibiotic classes recommended for the detection of MDR-GNB (algorithm) and available from ARPEC and EARS-Net [11, 12]. In addition, pathogen–antibiotic class combinations (PACCs) used by different surveillance networks are shown [7, 13–15]

Pathogens	*E. coli*								*K. pneumoniae*								*P. aeruginosa*[a]							
	Sets				PACCs				Sets				PACCs				Sets				PACCs			
Antibiotic classes	MDR algorithm	ARPEC	EARS-Net	Routine	ECDC	WHO	US	UK	MDR algorithm	ARPEC	EARS-Net	Routine	ECDC	WHO	US	UK	MDR algorithm	ARPEC	EARS-Net	Routine	ECDC	WHO	US[b]	UK
Aminoglycosides	X	X	X	X				X	X	X	X	X					X	X	X	X				
Anti-MRSA cephalosporins	X								X															
Anti-pseudomonal penicillins plus beta-lactamase inhibitor	X	X		X					X	X		X					X	X	X	X				
Carbapenems	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Non-extended spectrum cephalosporins (first- and second--generations)	X	X							X	X														
Extended-spectrum cephalosporins (third- and higher generations)	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X				X
Cephamycins	X	X							X	X														
Fluoroquinolones	X	X	X	X		X		X	X	X	X	X					X	X	X	X				
Folate pathway inhibitors	X	X		X					X	X		X												
Glycylcyclines	X								X															
Monobactams	X	X							X	X							X	X						
Penicillins (ampicillin)	X	X	X	X																				
Penicillins plus beta-lactamase inhibitor	X	X		X					X	X		X												
Phenicols	X	X							X	X														
Phosphonic acids	X								X								X							
Polymyxins	X								X								X							
Tetracyclines	X	X							X	X														
Number of antibiotic classes included in sets used to calculate the % of MDR-GNB isolates	17	13	5	8	–	–	–	–	16	12	4	7	–	–	–	–	8	6	5	5	–	–	–	–

[a] For *P. aeruginosa*, all antibiotic classes only include antibiotics with antipseudomonal activity

[b] Note that *P. aeruginosa* is not included in the US National Healthcare Safety Network (NHSN) surveillance

and carbapenems, *K. pneumoniae* and higher-generation cephalosporins and carbapenems, and *P. aeruginosa* and carbapenems.

We defined its sensitivity as the proportion of isolates classified as susceptible for each PACC among those flagged as MDR from the ARPEC set, and its specificity as the proportion of isolates classified as non-susceptible for each PACC that was identified as not MDR from the ARPEC set.

Statistical analysis

All statistical analyses were carried out using Stata® v12.1, StataCorp, College Station, TX, USA. Whenever 95% confidence intervals (CIs) are given for proportions, these were calculated by applying an exact method for binomial data.

Results

In total, 685 isolates were included in the analysis (375 *E. coli*, 176 *K. pneumoniae*, 134 *P. aeruginosa*).

Antibiotic classes included in the Routine set

The classes with reported AST results for the participating centres were very diverse, and there was no consistent pattern of classes among hospitals located in the same geographical region (data not shown). No laboratory consistently reported on all classes that were included in the ARPEC protocol. There was more consistency for the subset of EARS-Net antibiotic classes, with AST results available for at least 85% of isolates of all three species.

There were several classes for which AST data were also available for at least 85% of isolates. The additional frequently tested PACCs included *E. coli* and *K. pneumoniae* AST results for penicillins/beta-lactamase inhibitor (91 and 96% of isolates), folate pathway inhibitors (86 and 86%) and antipseudomonal penicillins/beta-lactamase inhibitor (85 and 85%). These were then included in the Routine set (Table 1). The only additional ARPEC antibiotic class relevant for *P. aeruginosa* MDR classification was monobactams, for which AST results were reported for only 47% of isolates.

Identification of MDR status according to the EARS-Net, Routine and ARPEC sets

The proportion of MDR isolates based on the most complete ARPEC set was 30% (95% CI 27–34%) for all three GNB. Figure 1 shows the number of isolates classified as MDR using the EARS-Net set, the Routine set and the ARPEC set, and the overall proportion estimated as MDR for each pathogen.

Table 2 shows the proportion estimated as MDR for each set. Extending the set from the limited EARS-Net set to the Routine set identified an additional 96 MDR isolates, more than doubling the estimate of MDR-GNB from 13% (95% CI 11–16%) to 27% (95% CI 24–31%). This was most marked for *E. coli* and *K. pneumoniae* isolates (Fig. 1 and Table 2). A similar underestimation on the basis of the EARS-Net set was not observed for *P. aeruginosa*.

For *E. coli* and *K. pneumoniae*, extending assessment to the Routine set meant that their MDR classification was based on three additional antibiotic classes (Table 1). The Routine set-based MDR status performed much better than categorisation based on the EARS-Net set alone. In contrast, comparing the Routine and ARPEC sets' MDR status, only very few additional isolates were identified as MDR when the more complete ARPEC set was used.

Identification of MDR status based on specific pathogen–drug combinations

The specific PACCs of interest were *E. coli* and higher-generation cephalosporins, fluoroquinolones, aminoglycosides and carbapenems (reported for 98, 99, 98 and 97% of isolates, respectively), *K. pneumoniae* and higher-generation cephalosporins and carbapenems (reported for 99 and 99% of isolates, respectively), and *P. aeruginosa* and carbapenems (reported for 98% of isolates).

Escherichia coli had the following PACC non-susceptibility profiles based on reported AST results: 13% (95% CI 9–16%) for third- and fourth-generation cephalosporins, 13% (95% CI 10–18%) for fluoroquinolones, 13% (95% CI 10–17%) for aminoglycosides and <1% (95% CI 0.1–2%) for carbapenems. For *K. pneumoniae*, resistance percentages for third- and fourth-generation cephalosporins were 32% (95% CI 25–40%) and for carbapenems 6% (95% CI 3–11%). *Pseudomonas aeruginosa* isolates showed 30% antipseudomonal cephalosporin resistance (95% CI 22–38%) and 31% carbapenem resistance (95% CI 24–40%). Resistance to higher-generation cephalosporins was 21% (95% CI 18–24%) for all three species. The corresponding resistance percentage for carbapenems was 8% (95% CI 6–11%).

Figure 2 displays the number and percentage of isolates that would be appropriately classified as MDR for each PACC. Isolates are classified as MDR on the basis of the ARPEC set.

For *E. coli*, resistance to the specified PACCs failed to correctly identify MDR status for more than half of the isolates. Aminoglycosides had the best sensitivity (i.e. ability to identify MDR when it was present) of 41% (Table 3). *Escherichia coli* carbapenem resistance was very rare in the ARPEC dataset, in contrast to MDR *E. coli*, and was of very little value in identifying MDR *E. coli*.

For *K. pneumoniae*, both cephalosporin and carbapenem resistance were more strongly associated with MDR status

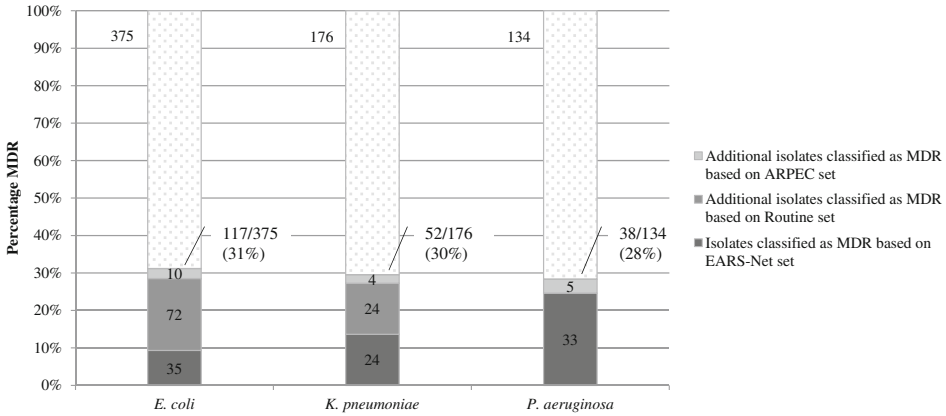

Fig. 1 Number and percentage of isolates classified as MDR based on different sets of antibiotic classes (see Table 1 for definitions of the sets). The total number of isolates for each bacterial species is shown at the top of each bar

than for *E. coli* isolates. Third- or fourth-generation cephalosporin resistance had a sensitivity of 85%. However, again, carbapenem resistance was not predictive of MDR *K. pneumoniae* (sensitivity 21%).

For *P. aeruginosa*, both cephalosporin and carbapenem resistance showed a sensitivity of more than 85% for detecting MDR isolates. For all three GNB, the specificity (the ability to exclude MDR when it was absent) of the selected pathogen–drug combinations was above 90%. Thus, the rate of false classification of isolates as not MDR based on the absence of resistance to the PACCs reviewed was low.

Discussion

The surveillance definition of MDR requires the availability of a large number of susceptibility testing results for the correct classification of isolates [11]. If monitoring and comparison of the prevalence of MDR-GNB is to be an aim for ongoing surveillance activities collecting routine microbiology AST data, the optimal strategy for detecting MDR organisms from such data needs to be established. Current surveillance activities tend to request the AST results for a limited subset of antibiotic classes listed by the expert MDR classification algorithm [12].

In our dataset, the percentage of MDR-GNB isolates was significantly lower (13%) when based on a more limited set of antibiotic classes, such as that used by EARS-Net, compared with the full set available (30%). Utilising the full set of antibiotic classes reportable as part of the ARPEC project, the proportion of paediatric MDR *E. coli*, *K. pneumoniae* and *P. aeruginosa* isolates was around 30% and similar for all three pathogens. Such high levels of isolates with resistance to multiple drugs are concerning and of interest for tracking the epidemiology of resistant GNB over time.

Our study raises several important points regarding the potential of capturing MDR-GNB based on currently available routine microbiology data purely for surveillance:

(1) Routine reporting of AST data by the 19 European laboratories participating in ARPEC only variably included results for requested antibiotic classes that are part of the classification algorithms for *E. coli*, *K. pneumoniae* and *P. aeruginosa*. A direct application of the MDR algorithms is, therefore, not possible.
(2) Limited AST result data also cannot be used to reliably estimate the proportion of MDR-GNB. As the ARPEC dataset includes only European isolates, the performance of the current European surveillance system was evaluated. The EARS-Net set of antibiotic classes appeared to lack sensitivity for detecting MDR-GNB. Inclusion of

Table 2 MDR-GNB percentages based on the EARS-Net, Routine and ARPEC sets (see Table 1 for definitions of the sets)

	Total no. of isolates	MDR isolates		
		% MDR based on EARS-Net set (95% CI)	% MDR based on Routine set (95% CI)	% MDR based on full ARPEC set (95% CI)
E. coli	375	9.3 (6.6–12.7)	28.5 (24.0–33.4)	31.2 (26.5–36.2)
K. pneumoniae	176	13.6 (8.9–19.6)	27.3 (20.8–34.5)	29.6 (22.9–36.9)
P. aeruginosa	134	24.6 (17.6–32.8)	n/a	28.4 (20.9–36.8)
All GNB	685	13.4 (11.0–16.2)	27.4 (24.1–31.0)	30.2 (26.8–33.8)

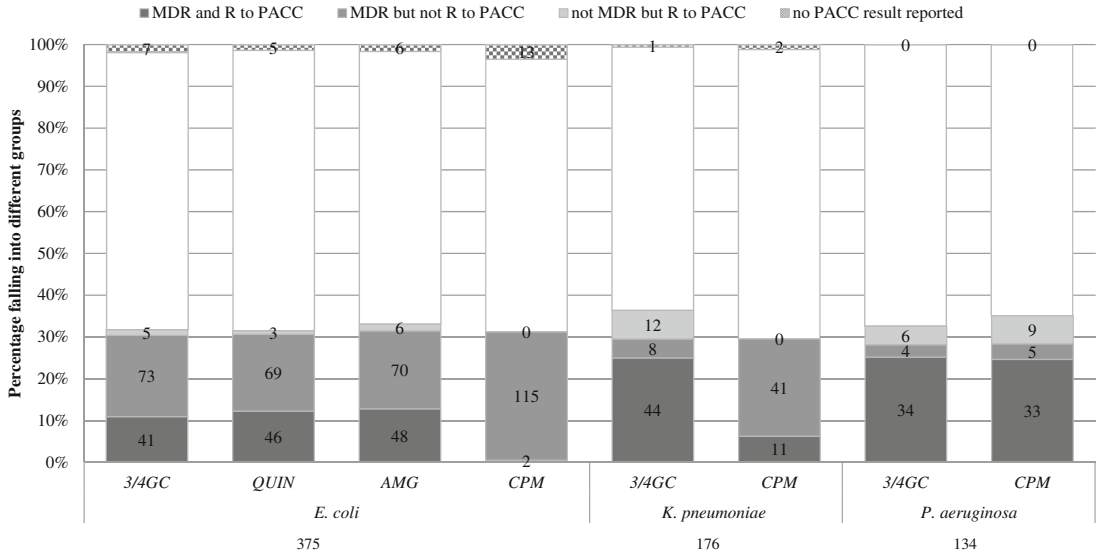

Fig. 2 Number and percentage of isolates identified correctly or incorrectly as MDR based on individual pathogen–antibiotic class combinations (PACCs). The *white stacks* correspond to isolates neither resistant to the PACC nor identified as MDR on the basis of the ARPEC set (see Table 1 for definitions). The total number of isolates for each bacterial species are shown underneath. *3/4GC* third- or fourth-generation cephalosporin, *QUIN* fluoroquinolone, *AMG* aminoglycoside, *CPM* carbapenem. For *P. aeruginosa*, only cephalosporins with antipseudomonal activity were considered

additional frequently tested and reported antibiotic classes increased the detection of MDR *E. coli* and *K. pneumoniae* (from 30% detected by the EARS-Net set to 90% based on the Routine set for *E. coli* and from 46 to 92% for *K. pneumoniae*). This was in contrast to *P. aeruginosa*, for which the ARPEC set included only one additional antibiotic class compared with EARS-Net reporting.

(3) A small number of individual PACCs currently represent the typical method for reporting antimicrobial resistance surveillance internationally. Disappointingly, resistance detected in individual PACCs was not reliable in detecting MDR isolates. This was especially marked for *E. coli* isolates, for which resistance to higher-generation cephalosporins, for example, had a sensitivity of only 36% for detecting MDR. *Escherichia coli* is the GNB with the largest number of antibiotic classes in the MDR classification algorithm and in ARPEC reporting. This may increase the detection of many different resistance combinations, especially if multiple different resistance phenotypes occur.

Table 3 Detection of MDR-GNB when specific PACC antimicrobial susceptibility testing results are assumed to represent MDR status. The percentage of isolates misclassified as MDR or not MDR based on PACC results is compared with MDR based on all ARPEC antibiotic categories (see Table 1)

		MDR classification			
		No. of MDR correctly identified	Sensitivity of PACC in % (95% CI)	No. of not MDR correctly identified	Specificity of PACC in % (95% CI)
E. coli	Third- or fourth-generation cephalosporins	41/114	36.0 (27.2–45.5)	254/259	98.1 (95.6–99.4)
	Fluoroquinolones	46/115	40.0 (31.0–49.6)	255/258	98.8 (96.6–99.8)
	Aminoglycosides	48/116	41.4 (32.3–50.9)	253/259	97.7 (95.0–99.1)
	Carbapenems	2/117	1.7 (0.2–6.0)	245/245	100.0 (98.5–100.0)
K. pneumoniae	Third- or fourth-generation cephalosporins	44/52	84.6 (71.9–93.1)	123/135	91.1 (85.0–95.3)
	Carbapenems	11/52	21.2 (11.1–34.7)	122/122	100.0 (97.0–100.0)
P. aeruginosa	Antipseudomonal cephalosporins	34/38	89.5 (75.2–97.1)	96/102	94.1 (87.6–97.8)
	Carbapenems	33/38	86.8 (71.9–95.6)	96/105	91.4 (84.4–96.0)

Some of the challenges may be explained by the fact that surveillance collects data primarily generated to inform clinical decision-making: approaches to AST are likely to be guided by the need to optimally inform patient therapy rather than by the need to generate a complete AST dataset for MDR classification. This type of selective AST based on clinical needs could introduce bias when these data are interpreted for public health purposes [28]. Bias could be magnified when laboratories engage in so-called first- and second-line testing: some antibiotic classes are evaluated only when resistance to antibiotics included in a first-line panel is detected [16].

Several limitations need to be considered when interpreting the ARPEC data. ARPEC does not cover all antibiotic classes recommended in the recent expert proposal [11]. It is, therefore, possible that some isolates identified as not MDR in ARPEC would, in fact, be MDR if AST data for all relevant classes were available. It is also possible that antibiotic classes tested for some of the reported isolates were suppressed during ARPEC data entry. This seems unlikely, given the relative uniformity of reporting for each species by each laboratory.

The actual percentages of MDR-GNB reported in this study should be interpreted with caution, as hospitals reporting to ARPEC were tertiary institutions with a patient population not representative of patients in other inpatient settings and potentially at higher risk of MDR-GNB [20, 21]. Pooling of data prohibits the identification of any differences between individual participating centres, some of which may have had higher or lower than average MDR-GNB percentages. Finally, the burden of MDR-GNB cannot be estimated because data are presented as resistance percentages rather than infection prevalence or incidence [29].

All isolates represent neonatal or paediatric blood cultures. The antibiotics used to treat bloodstream infections in neonates and children may differ from treatment choices for adults. This could be reflected in the antibiotic classes selected for AST, potentially limiting the transferability of the results to isolates from adults. However, most laboratories process microbiological samples from both adult and childhood patients. It is unlikely that AST strategies will be relevantly different for neonatal and paediatric isolates in these settings.

Surveillance of antimicrobial resistance patterns and trends is necessary to target interventions to reduce the selection and spread of resistant bacteria, and often relies on routine samples collected as part of on-going clinical care. The limitations and biases associated with the use of routine microbiology data in surveillance have been widely discussed [8, 28, 29]. Resistance percentages of individual PACCs and the EARS-Net set currently in use in Europe do not, on the whole, provide reliable MDR estimates. This study shows that, if MDR surveillance is to be added to the task list of on-going international surveillance, interpretation of the new algorithm will be limited by the variability in AST strategies in microbiological laboratories. MDR-GNB detection could be immediately improved by added surveillance of antibiotic classes already widely tested as part of clinical care. As demonstrated, a larger percentage of MDR-GNB isolates is likely to be identified with such an approach.

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Compliance with ethical standards

Funding The ARPEC project was co-funded by DG Sanco through the Executive Agency for Health and Consumers (grant number ARPEC Project A 2009-11-01). The funder had no role in the study design, data collection or data analysis.

Conflict of interest JAB's husband is the senior corporate counsel at Novartis International AG, Basel, Switzerland, and holds Novartis stock and stock options. MS chairs and APJ is a member of the Department of Health Expert Advisory Committee on Antimicrobial Resistance and Healthcare Associated Infection (ARHAI). All other authors have no conflicts of interest to declare.

Ethical approval and informed consent The study was assessed against the National Research Ethics Service "Defining Research" leaflet by the Joint Research Office at the lead centre (St George's, University of London, UK) and was found not to constitute research. The local research ethics committee confirmed that formal evaluation was not required. Participating centres were instructed to seek local ethical approval if legally required in their setting and were asked to confirm this at the time they submitted data. Informed consent was not required as all collected data were fully anonymised, and there was no contact with patients and/or their families and no interventions or changes to treatment and management were made.

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5. Basing empiric antibiotic regimens for childhood bloodstream infection on adult data

This chapter consists of a published paper that addresses whether empiric antibiotic regimens for bloodstream infections in children can be usefully informed by data on adult bloodstream isolates. The key advantage of using such data, for example in the estimation of coverage from a WISCA, would be a greatly increased sample size with more precise estimates.

Concerning children, it must be noted that despite a very large remit of some existing surveillance activities, data on neonatal and paediatric isolates is likely to be very limited accounting for less than 10% of reported isolates (18, 69). If both relative incidence of bacteria and their resistance patterns are comparable between children and adults, then the selection of empiric regimens could be usefully informed by adult-dominated data. If, however, they are not comparable then disaggregation of data is necessary at least by age group (70, 71). Further stratification may be necessary within the neonatal and paediatric population to define empiric regimens for defined subgroups (72).

ARPEC data and publicly available data from the European Antimicrobial Resistance Surveillance Network (EARS-Net) were used to compare resistance percentages for bacteria and antibiotics included in both databases for the same period and countries. EARS-Net includes only all-age data, of which around 10% are estimated to come from children (73). In addition to the comparative analysis of children and adults, the paper also compares resistance percentages between children up to 1 year of age and those 1 year or older within the ARPEC database to evaluate potential differences within the paediatric population. If demonstrated, this could indicate the need for further age-stratification for estimating coverage within the paediatric population.

RESEARCH PAPER COVER SHEET

SECTION A – Student Details

Student ID Number	237152	**Title**	Dr
First Name(s)	Julia Anna		
Surname/Family Name	Bielicki		
Thesis Title	Estimating coverage of empiric treatment regimens for childhood bloodstream infection based on routine microbiological data		
Primary Supervisor	Prof. David Cromwell		

If the Research Paper has previously been published please complete Section B, if not please move to Section C.

SECTION B – Paper already published

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Antibiotic Resistance Prevalence in Routine Bloodstream Isolates from Children's Hospitals Varies Substantially from Adult Surveillance Data in Europe

Julia Anna Bielicki, MD, MPH, Rebecca Lundin, ScD, MPH,† and Mike Sharland, FRCPH*, for the ARPEC Project*

Background: Surveillance of antimicrobial resistance (AMR) is central for defining appropriate strategies to deal with changing AMR levels. It is unclear whether childhood AMR patterns differ from those detected in isolates from adult patients.

Methods: Resistance percentages of nonduplicate *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Enterococcus faecalis*, *Enterococcus faecium*, Escherichia *coli*, *Klebsiella pneumoniae* and *Pseudomonas aeruginosa* bloodstream isolates from children less than 18 years of age reported to the Antibiotic Resistance and Prescribing in European Children (ARPEC) project were compared with all-age resistance percentages reported by the European Antimicrobial Resistance Surveillance Network (EARS-Net) for the same pathogen–antibiotic class combinations, period and countries. In addition, resistance percentages were compared between ARPEC isolates from children less than 1 year of age and children greater than or equal to1 year of age.

Results: Resistance percentages for many important pathogen–antibiotic class combinations were different for ARPEC isolates compared with EARS-Net. *E. coli* and *K. pneumoniae* fluoroquinolone resistance percentages were substantially lower in ARPEC (13.4% and 17.9%) than in EARS-Net (23.0% and 30.7%), whereas the reverse was true for all pathogen–antibiotic class combinations in *P. aeruginosa* (for example, 27.3% aminoglycoside resistance in ARPEC, 19.3% in EARS-Net, 32.8% carbapenem resistance in ARPEC and 20.5% in EARS-Net), and for *S. pneumoniae* and macrolide resistance. For many Gram-negative pathogen–antibiotic class combinations, isolates from children greater than or equal to 1 year of age showed higher resistance percentages than isolates from children less than 1 year of age.

Conclusions: Age-stratified presentation of resistance percentage estimates by surveillance programs will allow identification of important variations in resistance patterns between different patient groups for targeted intervention.

Key Words: antimicrobial resistance, surveillance, routine data, age differences

(*Pediatr Infect Dis J* 2015;34:734–741)

The recent World Health Organization global report on surveillance has confirmed increasing levels of antimicrobial resistance (AMR) as a serious threat to public and individual patient health.[1] The report noted that international surveillance is a key element in developing strategies to deal with changing AMR levels.[1–4] Robust surveillance data are crucial for public health interventions and for empiric treatment choices in clinical practice.[1,5] Age-specific data are not routinely available from the great majority of existing surveillance programs, making focused interventions in this key age group difficult.

In Europe, the European Antimicrobial Resistance Surveillance Network (EARS-Net) collects antimicrobial susceptibility data for isolates from routine blood and cerebrospinal fluid cultures.[6] Data are summarized and published in annual reports and can be accessed online. Patient age to the nearest year is requested as part of the EARS-Net reporting protocol,[7,8] but is not mandatory and therefore may not be available for all isolates. EARS-Net data are not routinely presented stratified by age.

Overall, only very limited information on childhood AMR in Europe is available.[9–12] Over 95% of EARS-Net data are from adult isolates.[9] If there are true differences between childhood and adult AMR patterns, it is unlikely that currently reported pooled surveillance data can be used to adequately describe antibiotic susceptibility of neonatal and pediatric bloodstream isolates.

Here, we present AMR data for bloodstream isolates collected from neonates and children as part of the Antibiotic Resistance and Prescribing in European Children (ARPEC) project and compare them with EARS-Net resistance percentages from adults and children combined for the same period and countries. We also compare resistance percentages between infants (less than 1 year of age) and children (greater than 1 year of age) within ARPEC to determine whether further subdivision by age is appropriate.

MATERIALS AND METHODS

The ARPEC Project

The ARPEC project launched in 2010 as a 3-year initiative co-funded by the European Commission Directorate General for Health & Consumers through the Executive Agency for Health and Consumers with the main aim of evaluating and developing surveillance methodologies to monitor antimicrobial use and AMR in neonates and children.[13] Core activities included (1) assessment of primary care antimicrobial prescribing to children from routine databases, (2) evaluation of a point prevalence survey approach toward inpatient childhood antimicrobial use surveillance,[14] (3) evaluation of bacteremia AMR surveillance for key pathogens based on EARS-Net methodology and (4) the collection and comparison of antibiotic prescribing guidelines for common childhood infections across Europe. Here, we present data collected during ARPEC AMR surveillance.

ARPEC AMR Surveillance

Named partners and collaborators of the project were invited to participate in ARPEC AMR surveillance. Nineteen hospitals from 12 countries (Estonia/one center, France/one center, Germany/7 centers, Greece/one center, Italy/2 centers, Lithuania/1 center, The Netherlands/

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one center, Portugal/one center, Slovenia/one center, Spain/one center, Switzerland/one center, United Kingdom/one center) submitted data for specified blood culture isolates from children less than 18 years of age identified between January 01, 2011 and December 31, 2012. Most of the participating centers were standalone pediatric hospitals or neonatal and pediatric departments integrated into large tertiary centers; most did not participate in EARS-Net surveillance.

ARPEC AMR Data Collection

AMR data from routine susceptibility testing of blood culture isolates were collected annually using a custom-made anonymized password-protected Microsoft Excel® tool. The ARPEC AMR surveillance protocol was based on the EARS-Net 2010 reporting protocol (Table 1).[8] Basic information including the availability of specialist services and the number of neonatal and pediatric beds was also collected from all centers taking part.

EARS-Net Surveillance

EARS-Net data collection has been described in detail elsewhere and is summarized in Table 1.[8] Only publicly available 2012 EARS-Net data, including laboratory and denominator data, were used for the analysis.[15]

Definitions

Level of Aggregation

EARS-Net data always refer to isolates from children and adults. Adult isolates are expected to contribute more than 95% of the total.[9,16]

ARPEC AMR data refer to isolates from children less than 18 years of age including neonates. ARPEC AMR data were further analyzed divided into two age groups: those less than 1 year of age and those greater than or equal to 1 year of age. This grouping was chosen to allow for an approximation of neonatal and childhood AMR patterns, while reflecting the current approach to age coding in EARS-Net (1-year bands starting with a 0-year age band). Isolates from neonates and infants on neonatal intensive care units (NICU) would be expected to contribute substantially to the 0-year group.

Data from Switzerland were excluded, as this country is not represented in EARS-Net.

Selected Pathogens

All first bloodstream isolates of *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Enterococcus faecalis* and *Enterococcus faecium* were of interest. Any blood cultures from a previously included patient positive for the same organism within 4 weeks of the original reported isolate were defined as duplicates and excluded.

Susceptibility Testing Results

Susceptibility test results were reportable for a predefined list of antibiotic classes.[8] Test results were reportable as the final interpretation of susceptibility testing (sensitive—S, intermediate—I or resistant—R); minimum inhibitory concentrations were not collected. Centers used EUCAST, CLSI or BSAC breakpoints to identify isolates as S, I or R. In addition to AMR data, the number of blood culture sets processed during the reporting period was requested.

Resistance Percentages

Isolates reported as I or R to at least one antibiotic of an antibiotic class of interest were classified as resistant to that class. From this information, resistance percentages for specific pathogen–antibiotic class combinations were calculated. For EARS-Net, crude resistance percentages for specific pathogen-antibiotic class combinations were derived from publicly accessible EARS-Net 2012 data.

TABLE 1. Variables Requested for EARS-Net (Based on Reference 8) and ARPEC AMR Surveillance at Isolate Level

	EARS-Net	ARPEC
Isolate information		
Specimen type	Blood; cerebrospinal fluid (M)	Only blood collected, therefore NR
Pathogen	*Streptococcus pneumoniae*, *Staphylococcus aureus*, *Enterococcus faecalis*, *Enterococcus faecium*, *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa* (M)	
Antibiotic	Defined list of antibiotics requested for each pathogen (M)	Same list of antibiotics as for EARS-Net, additional options based on[2] (M)
SIR	Final interpretation of susceptibility testing requested (M)	
ESBL status	Requested (O)	
PCR mecA, PBP2a-agglutination, *S. pneumoniae* serotype, carbapenemase detection	(O)	NR
Source patient information		
Gender	Male, female, other, unknown (W)	NR
Age	In years in integers from 0 (W)	Calculated locally before submission by data collection tool macro, coded in days up to 30 days of age, in months up to 23 months of age, in years thereafter (M)
Patient type	Inpatient, outpatient, other (including emergency department), unknown (W)	Community-acquired: blood culture taken <2 hours after hospitalization, hospital-acquired: blood culture taken ≥2 days after hospitalization; calculated locally from date of birth and date of hospitalization before data transfer (see age and date of hospitalization)
Hospital unit	For pediatrics: pediatric ward, pediatric intensive care (including neonatal intensive care), unknown (W)	Pediatric ward, pediatric intensive care, neonatal intensive care, other (including emergency department), unknown (W)
Date of hospitalization	YYYY-MM-DD (O)	Calculated locally before submission by data collection tool macro as number of days from date of hospitalization to blood culture (W)
Presence of chronic underlying disease	NR	Yes, no, unknown (O)
Outcome at 30 days after isolate identified	NR	Died, inpatient, discharged alive, unknown (O)

M indicates mandatory; SIR, susceptible, intermediate, resistant; ESBL, extended-spectrum beta-lactamases; W, warning—data can be submitted, but warning generated; O, optional; NR, not requested.

The numbers of reported isolates were low for some of the pathogens in ARPEC. To increase power, data were pooled for 2011 and 2012. As the EARS-Net dataset includes a large number of isolates and resistance estimates are expected to be very precise, 95% confidence intervals are not presented for EARS-Net and only data from a single year (2012) were used.

Rates of Positive Blood Cultures

The rates of blood cultures obtained per 1000 occupied bed days (OBD) and the rate of blood cultures positive for the pathogens of interest per 1000 OBD were assessed. The number of OBD was estimated from the number of beds surveyed and from the average bed occupancy reported by EARS-Net for 2012 as number of beds*365*$P_{\text{average bed occupancy}}$.[15] Where bed occupancy was not available from EARS-Net, this was assumed to be 78%, reflecting the average occupancy for OECD countries in 2011.[17]

Statistical Analysis

ARPEC and EARS-Net resistance percentages were compared using χ^2 test or Fisher's exact test, as appropriate. A P value of less than 0.05 was taken to indicate statistically significant differences. Ninety-five percent confidence intervals were calculated by applying an exact method for binomial data. All statistical analyses were undertaken using STATA® 13.1.

Ethical Approval

The ARPEC protocol was submitted to the responsible research ethics committee of the coordinating center. Formal evaluation by a research committee was not required, as the study was classified as surveillance aiming to develop a standardized methodology. Participating centers were responsible for identifying the need for local ethical review and obtaining this, if required.

RESULTS

ARPEC AMR Surveillance Dataset

In total, 1441 relevant isolates from neonatal or pediatric blood cultures processed between January 01, 2011 and December 31, 2012 were reported from 18 centers in 11 countries. The distribution of isolates is shown in Table 2 and Figure 1.

TABLE 2. Distribution of Isolates in ARPEC Dataset (2011/2012) by Age Group and Overall.

Pathogen	<1 Year of age		≥1 Year of age		Total	
	n	%	n	%	n	%
Escherichia coli	226	27.9	122	19.3	348	24.2
Klebsiella pneumoniae	107	13.2	63	10.0	170	11.8
Pseudomonas aeruginosa	49	6.1	79	12.5	128	8.9
Staphylococcus aureus	198	24.5	191	30.2	389	27.0
Streptococcus pneumoniae	44	5.4	103	16.3	147	10.2
Enterococcus faecalis	141	17.4	28	4.4	169	11.7
Enterococcus faecium	44	5.4	46	7.3	90	6.3
All isolates	809	100	632	100	1441	100

The total column percentages may not add up to exactly 100% due to rounding.

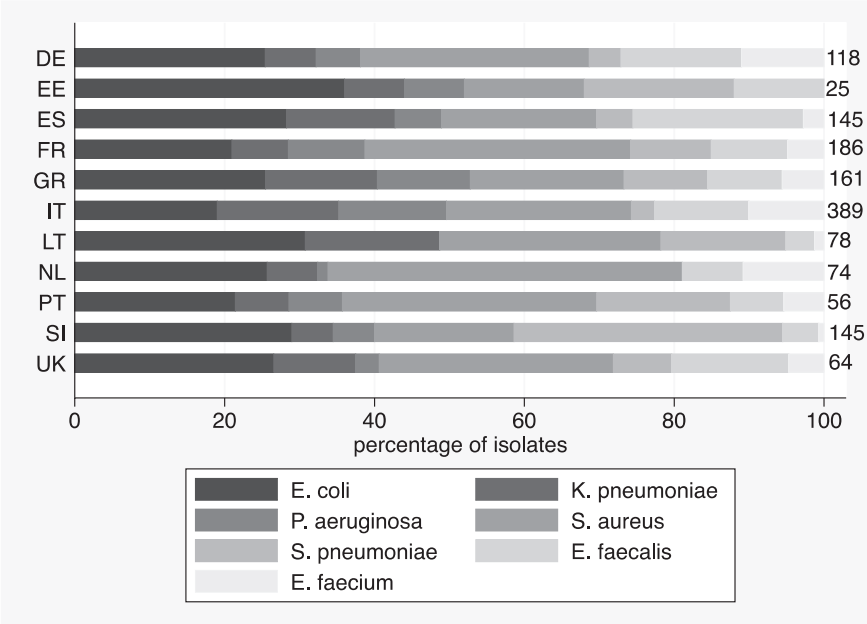

FIGURE 1. Distribution of relevant isolates for each country represented in the ARPEC dataset. The number of isolates from each country is indicated to the right of the bar chart. DE, Germany; EE, Estonia; ES, Spain; FR, France; GR, Greece; IT, Italy; LT, Lithuania; NL, The Netherlands; PT, Portugal; SI, Slovenia; UK, United Kingdom.

S. aureus and *E. coli* were the commonest pathogens in all ages, accounting for 51.2% of the available isolates (n = 389, 27.0% and n = 348, 24.2%, respectively). Overall, *K. pneumoniae* (n = 170, 11.8%) and *Enterococcus faecalis* (n = 169, 11.7%) were the third and fourth most commonly reported pathogens out of the 7 target bacterial species. The patterns differed for isolates for children less than 1 year of age and children greater than or equal to 1 year of age (Table 2).

Information on hospital unit and community- or hospital-acquisition of isolates was available for 88% and 82% of Gram-negative isolates in ARPEC. 23.9% of *E. coli*, 38.8% of *K. pneumoniae* and 29.0% of *P. aeruginosa* isolates were from intensive care units (ICUs). However, 48% of *E. coli*, 17% of *K. pneumoniae* and 30.0% of *P. aeruginosa* isolates were community-acquired.

There was variation in the total number of isolates contributed from different countries in the ARPEC dataset and in the distribution of bacterial species of interest across countries (Fig. 1). Overall, Gram-positive isolates made up 50–65% of isolates.

Comparing EARS-Net and ARPEC Characteristics of Participating Hospitals/ Laboratories and Blood Culturing Practices

Characteristics of participating hospitals/laboratories are shown in Tables 3 and 4. In the ARPEC dataset, 95% of participating centers were tertiary level and a substantial proportion of neonatal and pediatric inpatient beds were ICU beds. In contrast, only 36% EARS-Net hospitals in 2012 were tertiary level. Although blood culture rates in ARPEC were higher than in EARS-Net, the rate of blood cultures growing at least one of the pathogens of interest was lower.

Resistance Percentages in Surveyed Bacterial Species

The crude resistance percentages for EARS-Net and ARPEC are shown in Table 5 and Figure 2A and B for Gram-negative and Gram-positive pathogens, respectively.

Fluoroquinolone resistance in *E. coli* and *K. pneumoniae* was much lower in ARPEC than in EARS-Net isolates (13.4% vs. 23.0% for *E. coli*, 17.9% vs. 30.7% for *K. pneumoniae*). Conversely, aminopenicillin and aminoglycoside resistance percentages for *E. coli* isolates were higher in ARPEC than in EARS-Net isolates (67.9% and 14.6% vs. 57.2% and 11.3%). The resistance percentages for 4 of the 5 pathogen–antibiotic class combinations for *P. aerguinosa* isolates (piperacillin/tazobactam, ceftazidime, aminoglycosides and carbapenems) were also higher for ARPEC compared with EARS-Net isolates. For Gram-positive bacteria, macrolide resistance percentages in *S. pneumoniae* were higher in ARPEC isolates compared with EARS-Net. No relevant differences were detected for the other

TABLE 3. Characteristics of Hospitals Reporting to EARS-Net and ARPEC, Including Number of Beds Surveyed, Proportion of ICU Beds in Participating Hospitals (in %) and Annual Occupancy Rate

Country	Total n Beds Surveyed		% ICU Beds		Annual Occupancy Rate (%)*
	EARS-Net	ARPEC	EARS-Net	ARPEC	
Estonia	No data	111	No data	8	-(78†)
France	127,423	231	6	33	81
Germany	18,700	633	7	21	79
Greece	No data	336	No data	11	-(78†)
Italy	14,892	687	No data	11	80
Lithuania	12,423	450	4	5	74
The Netherlands	No data	101	No data	25	-(78†)
Portugal	8228	94	6	13	74
Slovenia	7377	271	5	21	70
Spain	26,646	191	4	39	79
United Kingdom	18,849	118	No data	36	79

*From reference 15.
†Assumed 78% occupancy from reference 17.

TABLE 4. Estimated Blood Culturing Rates and Estimated Rates of Bacteraemia Caused by the Pathogens of Interest

Country	Estimated Blood Culturing Rate/1000 OBD		Estimated Rate of Bacteraemia/1000 OBD	
	EARS-Net	ARPEC	EARS-Net	ARPEC
Estonia	No data	No data	No data	0.4
France	No data	109	0.4	1.8
Germany	17	130	1.8	1.2
Greece	No data	58	No data	0.8
Italy	No data	85	1.6	1
Lithuania	6	16	0.6	0.3
The Netherlands	No data	54	No data	1.3
Portugal	51	100	2.6	1.1
Slovenia	31	54	1.5	1.0
Spain	40	No data	1.6	1.3
United Kingdom	34	No data	2.5	0.9

TABLE 5. Comparison of EARS-Net and ARPEC Resistance Percentages for Key Pathogen–Antibiotic Class Combinations for Gram-negative and Gram-positive pathogens

Pathogen and Antibiotic Class	EARS-Net	ARPEC
Gram-negative pathogens		
Escherichia coli		
Aminopenicillins*	57.2%	67.9% (62.6–73.1)
Third generation cephalosporins	11.9%	12.9% (9.3–16.5)
Aminoglycosides*	11.3%	14.6% (10.9–18.4)
Fluoroquinolones*	23.0%	13.4% (9.8–17.0)
Carbapenems*	0.1%	0.6% (0.07–2.1)
Klebsiella pneumoniae		
Third generation cephalosporins	31.6%	32.5% (25.5–40.2)
Aminoglycosides	27.6%	31.8% (24.8–39.3)
Fluoroquinolones*	30.7%	17.9% (12.4–24.5)
Carbapenems*	13.5%	6.5% (3.3–11.4)
Pseudomonas aeruginosa		
Piperacillin (± tazobactam)*	17.6%	36.0% (27.1–45.7)
Ceftazidime*	14.8%	25.8% (18.5–34.3)
Aminoglycosides*	19.3%	27.3% (19.8–35.9)
Fluoroquinolones	23.1%	23.4% (16.4–31.7)
Carbapenems*	20.5%	32.8% (24.7–41.8)
Gram-positive pathogens		
Staphylococcus aureus		
Methicillin resistance	21.2%	16.4% (12.7–20.8)
Streptococcus pneumoniae		
Penicillin nonsusceptibility	10.8%	13.4% (7.9–20.9)
Macrolide nonsusceptibility*	15.3%	33.1% (24.8–42.2)
Enterococcus faecalis		
High level gentamicin	30.5%	29.5% (21.0–39.2)
Enterococcus faecium		
Vancomycin	8.3%	9.0% (3.7–17.6)

For ARPEC, the proportion of resistant isolates is shown with the 95% confidence interval.

*Difference between EARS-Net and ARPEC resistance percentages is statistically significant ($P < 0.05$).

pathogen–antibiotic class combinations assessed for Gram-positive bacteria.

Comparing Infants and Children

Of 1441 isolates in the ARPEC dataset, 809 (56%) were from children less than 1 year of age and 489 (34%) were from neonates or infants hospitalized on NICU. The resistance percentages for ARPEC isolates from children less than 1 year of age and children greater than or equal to 1 year of age are shown in Table 6 for Gram-negative and Gram-positive bacteria, respectively.

Overall, resistance percentages were lower in isolates from children less than 1 year of age than in isolates from children greater than or equal to 1 year of age. A notable exception to this was macrolide nonsusceptibility in *S. pneumoniae* isolates, with the highest resistance percentages observed among isolates from children less than 1 year of age (45.5%) compared with isolates from children greater than or equal to 1 year of age (28.4%). A similar trend was observed for penicillin nonsusceptibility in *S. pneumoniae*. There was no difference in the proportion of *S. aureus* isolates identified as MRSA (17.0% in those less than 1 year of age, 15.9% in those greater than or equal to 1 year of age).

When resistance percentages for ARPEC stratified by age and EARS-Net were considered together, Gram-negative isolates from children greater than or equal to 1 year of age were often those with the highest levels of resistance. For example, the difference

TABLE 6. Comparison of ARPEC Resistance Percentages for Isolates from Children Less than 1 Year of Age and Children Greater than or Equal to 1 Year of Age

Pathogen and Antibiotic Class	Age <1 Year	Age ≥1 Year
Gram-negative pathogens		
Escherichia coli		
Aminopenicillins	64.5% (57.8–71.2)	74.1% (65.7–82.5)
Third generation cephalosporins	10.7% (6.6–14.8)	17.0% (10.2–24.0)
Aminoglycosides	13.5% (9.0–18.0)	16.7% (9.9–23.4)
Fluoroquinolones*	8.5% (4.8–12.2)	22.5% (14.9–30.1)
Carbapenems	0% (0–1.7)	1.7% (0.2–5.9)
Klebsiella pneumoniae		
Third generation cephalosporins	29.9% (21.4–39.5)	37.1% (25.2–50.3)
Aminoglycosides*	26.2% (18.1–35.6)	41.2% (29.0–54.4)
Fluoroquinolones*	7.5% (3.3–14.3)	35.5% (23.7–48.7)
Carbapenems*	1.9% (0.2–6.7)	14.3% (6.7–25.4)
Pseudomonas aeruginosa		
Piperacillin (± tazobactam)*	14.3% (5.4–28.5)	49.3% (37.0–61.6)
Ceftazidime*	12.2% (4.6–24.8)	34.2% (23.8–45.7)
Aminoglycosides	14.3% (5.9–27.2)	35.4% (25.0–47.0)
Fluoroquinolones*	16.2% (7.3–29.7)	27.8% (18.3–39.1)
Carbapenems	26.1% (14.3–41.1)	36.7% (26.1–48.3)
Gram-positive pathogens		
Staphylococcus aureus		
Methicillin resistance	17.0% (11.7–23.4)	15.9% (10.8–22.2)
Streptococcus pneumoniae		
Penicillin nonsusceptibility	20.6% (8.7–37.9)	10.6% (5.0–19.2)
Macrolide nonsusceptibility*	45.5% (28.1–63.6)	28.4% (19.3–39.0)
Enterococcus faecalis		
High level gentamicin*	25.3% (16.7–35.5)	57.1% (28.9–82.3)
Enterococcus faecium		
Vancomycin	7.9% (1.7–21.4)	10.0% (2.8–23.7)

The 95% confidence intervals for point estimates are shown.

*Difference between age group resistance percentages is statistically significant ($P < 0.05$).

in *P. aeruginosa* piperacillin/tazobactam resistance percentages between EARS-Net isolates (17.6%) and ARPEC isolates (36.0%) was strongly influenced by very high resistance percentages in isolates from children greater than or equal to 1 year of age (49.3%). Conversely, the lower ARPEC carbapenem resistance percentages in *K. pneumoniae* (6.5% compared with 13.5% in EARS-Net) were due to a very low carbapenem resistance percentage in isolates from the youngest age group (1.9%). Isolates from children greater than or equal to 1 year of age had a similar carbapenem resistance percentage to that observed in EARS-Net (14.3%).

DISCUSSION

ARPEC adapted the EARS-Net approach to survey AMR in neonatal and pediatric centers across 12 European countries. Resistance percentages for many important pathogen–antibiotic class combinations, especially for Gram-negative bacteria but also for macrolide resistance in *S. pneumoniae*, were higher in ARPEC data compared with EARS-Net data. Higher resistance percentages in ARPEC isolates were largely due to very high resistance levels in isolates from children greater than or equal to 1 years of age, with the exception of *S. pneumoniae*, for which the highest levels of resistance were observed in isolates from children less than 1 year of age. Alarmingly high resistance percentages were observed in Gram-negative isolates from children greater than or equal to 1 year of age (for example, aminoglycoside resistance of 16.7% for *E. coli*, 41.2% for *K. pneumoniae* and 35.4% for *P. aeruginosa*), including carbapenem resistance in *K. pneumoniae* (14.3%) and *P. aerguinosa* (36.7%).

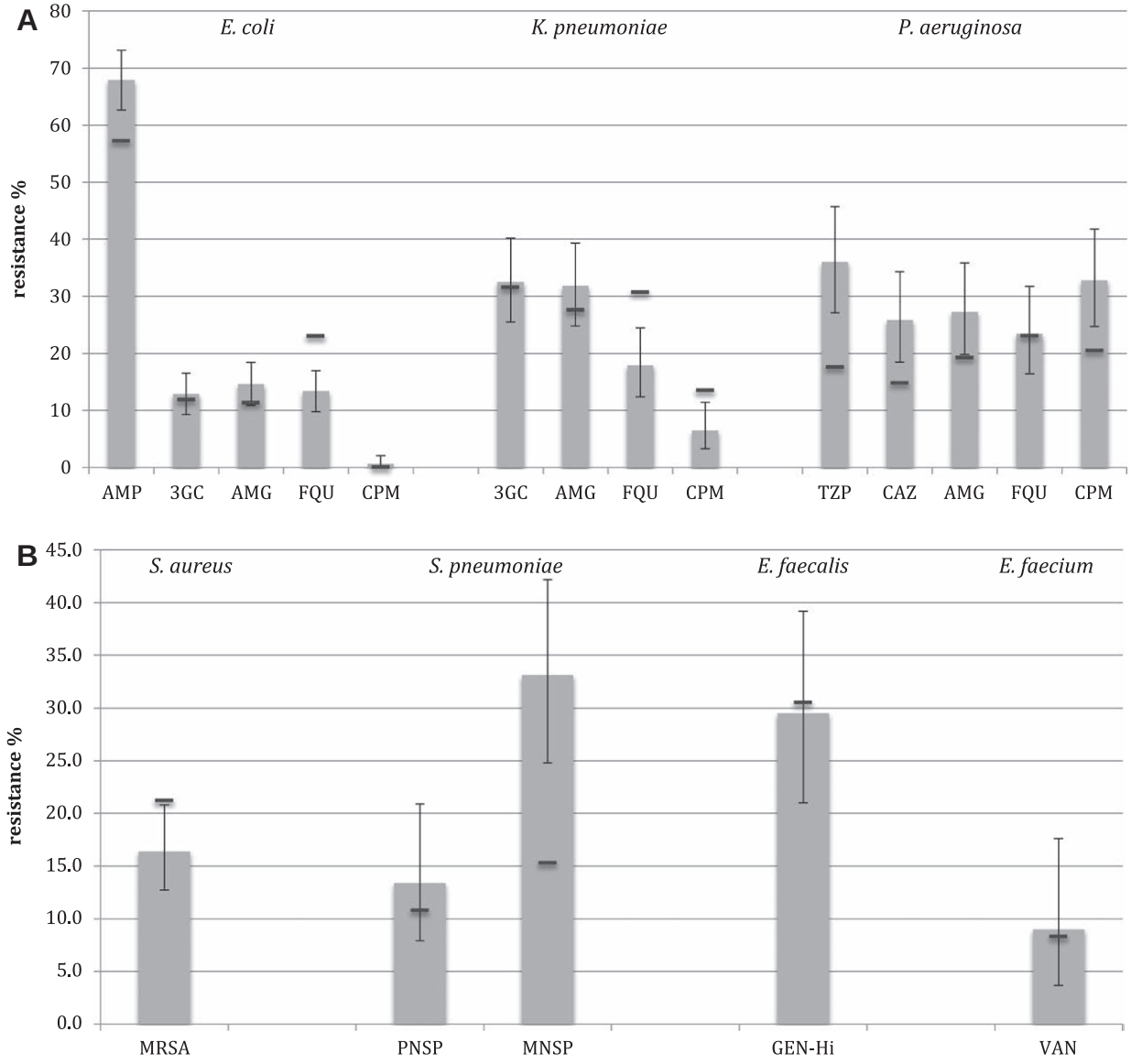

FIGURE 2. Comparison of resistance percentages in EARS-Net and ARPEC for Gram-negative and Gram-positive bacteria. EARS-Net estimates are indicated by the symbol (-). Ninety-five percent confidence intervals are shown for ARPEC estimates. AMP, aminopenicillin; 3GC, third generation cephalosporin; AMG, aminoglycosides; FQU, fluoroquinolone; CPM, carbapenem; TZP, piperacillin ± tazobactam; MRSA, methicillin-resistant *Staphylococcus aureus*; PNSP, penicillin nonsusceptible *Streptococcus pneumoniae*; MNSP, macrolide nonsusceptible *Streptococcus pneumoniae*; GEN-Hi, high level gentamicin resistance; VAN, vancomycin.

The observed differences between ARPEC and EARS-Net could partially be explained by different patterns of antibiotic use between adults and children. For example, ARPEC fluoroquinolone resistance percentages in *E. coli* and *K. pneumonia* were remarkably low compared with EARS-Net. Fluoroquinolone use in children is still rare. Only 2% of antibiotic prescriptions to ambulatory children in the United States involve quinolones, compared with 25% for adults.[18,19] Similarly, inpatient point prevalence surveys in Europe have shown that that only 1.7% of all prescriptions in children involved fluoroquinolones, in contrast to 9.1% in adults for whom this was the second most commonly prescribed antibiotic class.[20,21]

For other pathogens, such as *S. pneumoniae*, a complex interplay of antibiotic utilization, levels of colonization, pneumococcal immunization and other factors likely leads to differences in resistance observed between ARPEC and EARS-Net. Nasopharyngeal carriage of *S. pneumoniae* is much more common in children than in adults and colonizing isolates have been shown to have fourfold higher rates of macrolide resistance.[22]

Within ARPEC, isolates from children less than 1 year of age were overrepresented compared with isolates from children greater than or equal to 1 year of age, presumably reflecting much higher rates of bloodstream infections in the youngest children, especially neonates.[23] The highest resistance percentages, however, were generally observed for isolates from children greater than or equal to 1 year of age. Our data support the observation that isolates from infants on NICUs are less likely to be identified as resistant compared with isolates from adults on intensive care made by Ariffin et al.[24] Because of the higher incidence of bloodstream infections in children less than 1 year of age, the overall burden of resistant bloodstream infections could still be

highest in this group including NICU infants despite lower resistance percentages.

Why were such high resistance percentages observed in ARPEC isolates from children greater than or equal to 1 year of age compared with EARS-Net isolates, especially in Gram-negative pathogens? First, the source patient populations showed important differences between ARPEC and EARS-Net. ARPEC surveillance almost exclusively involved tertiary hospitals with a high proportion of ICU beds. In line with this, the overall proportion of Gram-negative pathogens from ICU patients was 43%. In contrast, an epidemiological review of Gram-negative pathogens in EARS-Net published in 2012 reported that only 7% of *E. coli*, 20% of *K. pneumoniae* and 25% of *P. aeruginosa* isolates were from ICU patients.[16] Isolates from ICU patients may be expected to have higher levels of resistance than isolates from non-ICU patients.[25]

Given such a high proportion of ICU isolates, it may be expected that a very low proportion of Gram-negatives were community-acquired. Surprisingly, however, 32% of ARPEC Gram-negative isolates including a third of *P. aeruginosa* isolates were community-acquired, contrasting with only 13% of *E. coli* and 8% each of *K. pneumoniae* and *P. aeruginosa* isolates reported as community-acquired in EARS-Net.[16] *P. aeruginosa* has previously been reported to be predominantly a nosocomial pathogen.[26–28] Most likely the relatively high proportion of community-acquired Gram-negative isolates reflects that children with serious underlying chronic diseases are overrepresented in ARPEC. These patients are at increased risk of both community-acquired and hospital-acquired invasive bacterial infections, including infections with a fatal outcome.[29–31] Many community-acquired episodes in children with comorbidities have been demonstrated to be healthcare-associated,[23] and are known to resemble hospital-acquired infections in terms of resistance patterns.[32] High carbapenem resistance percentages observed in Gram-negative bacteria in ARPEC could be due to this phenomenon. Our observation of the likely contribution of children with underlying diseases to episodes of community-acquired bloodstream infections also highlights the fact that selection of empiric antibiotic choices for this vulnerable group of patients is likely to be challenging.

Several limitations need to be considered when interpreting ARPEC and EARS-Net data. EARS-Net reports emphasize that (1) variable population coverage; (2) the focus on invasive isolates; (3) differences in blood culturing practices and (4) variability in laboratory methods can all be important sources of bias.[15] Several differences of hospitals contributing to ARPEC and those reporting to EARS-Net, and the likely impact on observed AMR levels have been discussed. In addition, ARPEC centers had a higher rate of blood culture than EARS-Net hospitals, potentially increasing the detection rate of bloodstream infections. At the same time, relevant isolates were observed at a lower rate in ARPEC hospitals. The high blood-culturing rate with lower positivity rate could lead to lower resistance percentage estimates, because it is less likely to be biased (for example, to patients not responding to empiric therapy).[15]

We were unable to compare ARPEC resistance percentages with EARS-Net estimates based on adult isolates only. Because ARPEC data were collected from tertiary hospitals with specialist pediatric services, resistance percentages are likely to largely reflect the microbiological epidemiology in children with multiple comorbidities cared for at highly specialized centers. Overall, ARPEC data should therefore not be used as a basis for empiric treatment selection for otherwise healthy children with community-acquired infection.

Our analysis demonstrates the importance of presenting resistance percentage estimates stratified by age and potentially by other variables, for example separately for intensive care and nonintensive care settings, and of clearly defining the source population for resistance data. In Europe, there is an existing surveillance network that could present such up-to-date childhood data. Many countries taking part in EARS-Net may not at present have the infrastructure or financial means for local evaluations of age-stratified resistance patterns. EARS-Net could provide an important service and should consider publication of age-stratified data to help neonatal and pediatric healthcare providers understand the epidemiology of AMR in their population. Future World Health Organization led global AMR surveillance programs should also include, where possible, age-stratified data. Failure to consider AMR patterns in this manner means that differences in resistance between different patient groups may go undetected and important opportunities for intervention are missed.

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6. Selecting empiric antibiotic regimens for childhood bloodstream infection based on a WISCA

This chapter presents a paper on the development of a Bayesian WISCA. It re-formulates the WISCA as a decision tree model (see figure in published paper). The decision to start empiric antibiotic treatment is represented by the first node (square) with the regimen choices represented by the next nodes (circle). Subsequent branches describe chance events, including the range of possible bacteria causing the target infection syndrome and the susceptibility percentages for each pathogen to the regimen. The combination of probabilities along the decision tree branches corresponds to the expected coverage for each regimen.

Combining this intuitive approach towards estimating coverage with a Bayesian approach has two key advantages. Firstly, it naturally allows for the calculation of credible intervals for the regimen coverage estimates. In the standard weighted average interpretation of coverage, a confidence interval is derived by pooling the variances of the expected values of susceptibility parameters to estimate the variance of the expected coverage. The key limitation of this approach is that it treats the relative frequencies of bacteria as fixed weights, and therefore fails to incorporate uncertainty about their estimated values. When the isolate sample size for estimating coverage is small, this will lead to the precision of expected coverage being overestimated.

The Bayesian perspective allows for the incorporation of uncertainty about estimates of both bacterial incidence and susceptibility to regimens. Adopting such a perspective, the values of incidence and regimen susceptibility parameters for each regimen are defined using an appropriate probability distribution. For the relative incidence of bacteria, the observed data were assumed to be drawn from a multinomial distribution with y possible outcomes (y corresponding to the number of bacterial species or types of bacteria contributing to the WISCA). A non-informative uniform conjugate prior, specified as a Dirichlet (1,1,1,…1) distribution was selected to result in a Dirichlet posterior distribution (1+n1, 1+n2,. . ., 1+n9).

This is the continuous equivalent to the discrete multinomial distribution, and is the generalisation of the Beta distribution to situations described by more than two categories. For regimen susceptibility, the data were assumed to be drawn from a Binomial distribution. A Beta(1,1) distribution was used as a non-informative prior, except for WISCA calculations at hospital level with expected small sample size when a Beta(0.5,0.5) distribution was used to reduce the dominance of the prior.

A consequence of describing uncertainty about parameters with the Dirichlet and conjugate Beta probability distributions is that there is no closed form equation for deriving the interval within which the true value of the coverage is likely to be. The calculation of this interval requires Monte Carlo simulation, which involves running a large number of experiments (1000 runs were used) and combining their results. In each experiment, parameter values for the parameters of interest (relative incidence and pathogen-regimen susceptibility) are randomly drawn from their specified distributions. The values of each parameter are then combined to derive a coverage estimate. Together, the individual coverage estimates from all the experiments give the posterior distribution for the coverage parameter. The 95% "uncertainty" interval, or 95% credible interval, is then calculated as the interval between 2.5% and 97% percentile of this distribution.

In addition to the incorporation of uncertainty for both bacterial incidence and regimen susceptibility parameters, the Bayesian perspective improves handling of missing data, supports correct interpretation of antimicrobial susceptibility testing data for coverage estimating, and allows the integration of evidence from multiple sources. The latter feature is particularly useful when the sample size is small, for example when considering an individual hospital, and there is other information available to augment it.

The second advantage of the Bayesian perspective is an appropriate reflection of intrinsic resistance as informative priors. For bacteria-antibiotic combinations where this was the case, the prior for regimen susceptibility was specified as a Beta(1,9999). This has a standard deviation of 0.01%, regardless of the availability of susceptibility testing information.

Similarly, for bacteria expected to be always susceptible to a specific regimen, the prior for regimen susceptibility was specified as a Beta(9999, 1).

ARPEC data on antimicrobial resistance for nearly 2000 isolates were used for parameter estimation in WISCA calculations. However, this paper demonstrates the limitations of using hospital-level data on bloodstream isolates and antimicrobial resistance for selection of empiric antibiotic regimens: Despite nearly 2000 isolates overall and despite coverage being based on data for multiple species, the total number of isolates for this calculation per hospital is low (range by country: 25-389 with multiple hospitals contributing to countries with higher isolate numbers). Data used for this paper were therefore pooled over two years. Even so, the regimen coverage estimates at hospital level were often imprecise, with the estimated coverage rates having overlapping 95% credible intervals for almost all considered regimens in the two exemplar hospitals.

To improve precision and therefore discrimination of estimated coverage between regimens, WISCAs were also calculated based on the pooled ARPEC dataset. The reliability of these pooled coverage estimates for the two exemplar hospitals was evaluated using a funnel plot technique. Optimal discrimination between regimens to establish which regimen offers the best coverage in this analysis was only possible when coverage estimates were based on pooled data.

RESEARCH PAPER COVER SHEET

SECTION A – Student Details

Student ID Number	237152	**Title**	Dr
First Name(s)	Julia Anna		
Surname/Family Name	Bielicki		
Thesis Title	Estimating coverage of empiric treatment regimens for childhood bloodstream infection based on routine microbiological data		
Primary Supervisor	Prof. David Cromwell		

If the Research Paper has previously been published please complete Section B, if not please move to Section C.

SECTION B – Paper already published

Where was the work published?	J Antimicrob Chemother		
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For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	I together with DA Cromwell conceived the study. I then undertook data preparation, designed the statistical analysis with support from DA cromwell and implemented the statistical analysis. I wrote the first draft of the manuscript which I modified based on co-author and reviewer comments.

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Journal of Antimicrobial Chemotherapy

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.

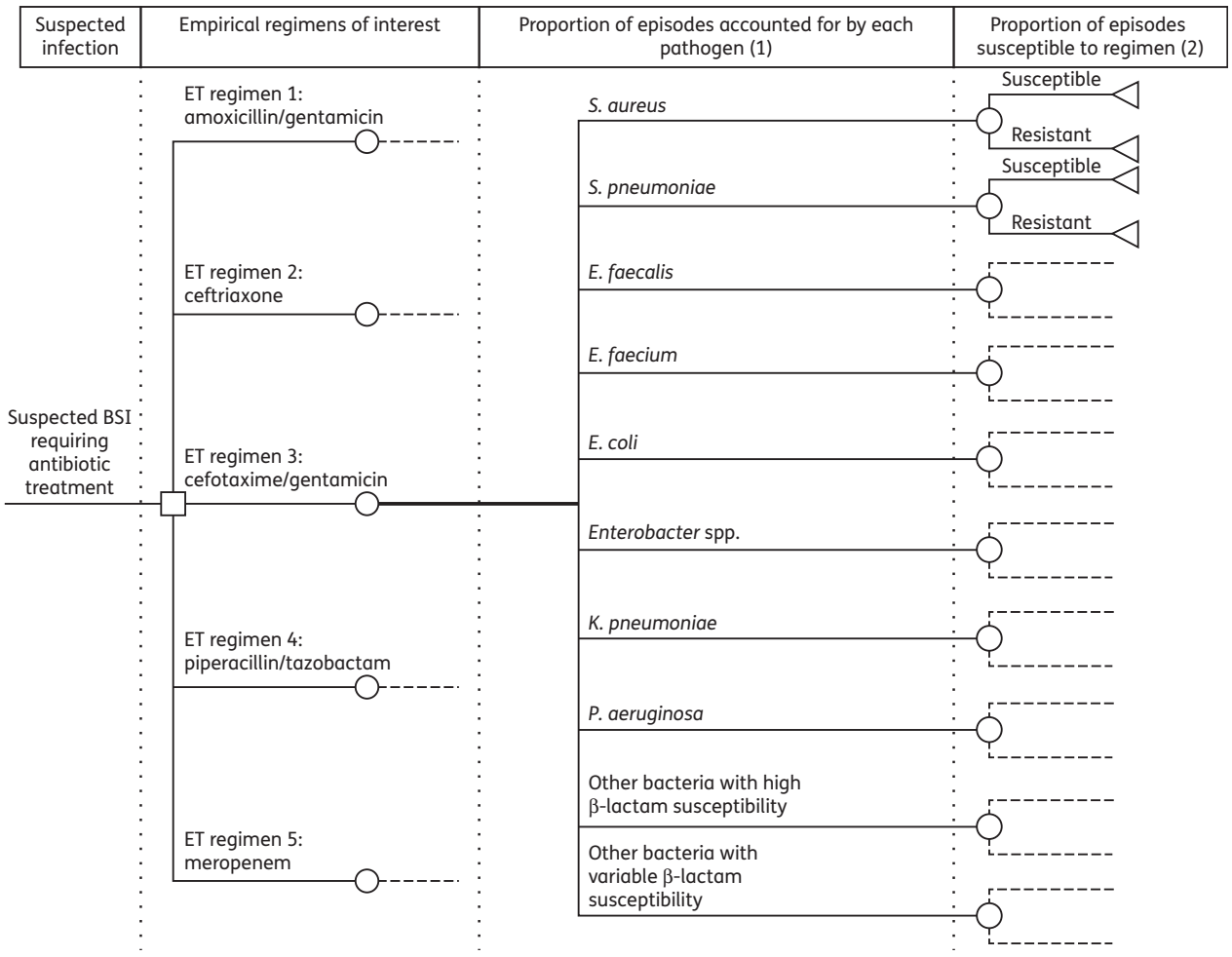

Figure 1. Decision tree for estimating ET regimen coverage.

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,…, 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($1+n_1$, $1+n_2$,…, $1+n_{10}$) where n_j 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

	Hospital 1			Hospital 2			Full ARPEC dataset		
Incidence	*n*	%	95% CrI[a]	*n*	%	95% CrI[a]	*n*	%	95% CrI[a]
S. aureus	20	22%	14%–31%	23	18%	12%–25%	449	23%	21%–25%
S. pneumoniae	5	6%	2%–12%	13	11%	6%–17%	163	9%	7%–10%
E. faecalis	10	11%	6%–18%	3	3%	1%–6%	175	9%	8%–10%
E. faecium	3	4%	1%–9%	1	2%	<1%–4%	95	5%	5%–6%
E. coli	18	20%	12%–28%	24	19%	13%–26%	380	20%	18%–21%
Enterobacter spp.	3	4%	1%–9%	3	3%	1%–7%	122	6%	5%–8%
K. pneumoniae	7	8%	4%–14%	14	11%	7%–17%	183	10%	8%–11%
P. aeruginosa	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%	
	Hospital 1			Hospital 2			Full ARPEC dataset		
Amoxicillin/gentamicin resistance	*n*	% susceptible	95% CrI[b]	*n*	% susceptible	95% CrI[b]	*n*	% susceptible	95% CrI[b]
S. aureus	14	90%	71%–99%	22	98%	89%–100%	421	97%	94%–98%
S. pneumoniae	5	92%	62%–100%	8	94%	73%–100%	152	97%	93%–99%
E. faecalis	10	95%	78%–100%	3	63%	17%–97%	160	93%	89%–97%
E. faecium	3	37%	4%–82%	1	24%	0%–85%	86	15%	8%–23%
E. coli	18	82%	63%–95%	24	82%	66%–94%	378	88%	85%–91%
Enterobacter spp.	3	88%	47%–100%	3	63%	18%–97%	121	90%	85%–95%
K. pneumoniae	7	81%	50%–98%	14	23%	7%–46%	183	75%	68%–80%
P. aeruginosa	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.
[a]Based on a Dirichlet posterior distribution that combines the observed data with a non-informative prior, Dirichlet(1, 1, 1,. . ., 1).
[b]Based on a beta posterior distribution that combines the observed data with a non-informative prior, beta(0.5, 0.5).

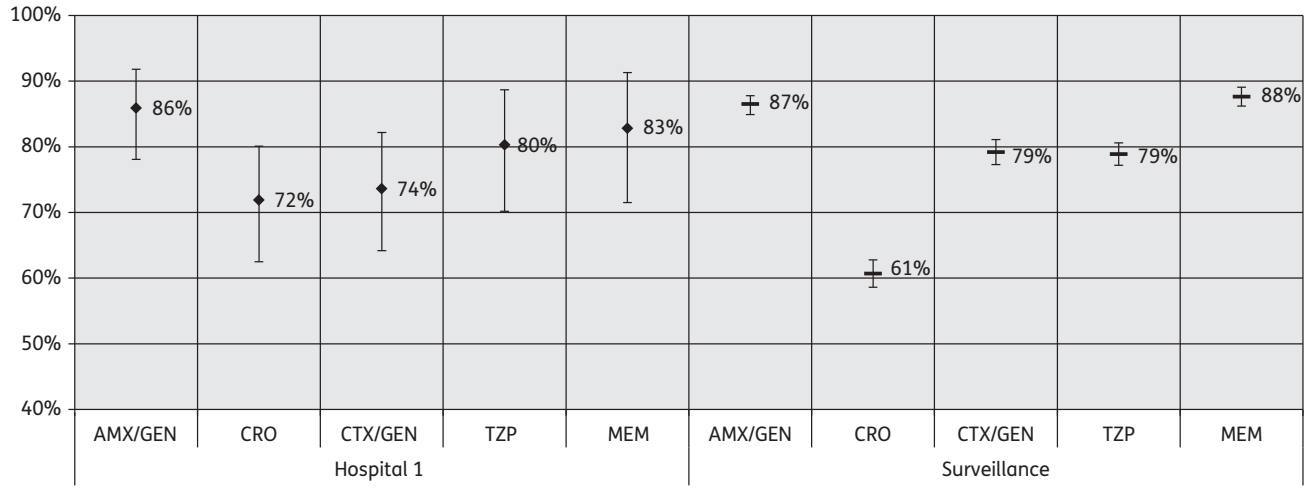

Figure 2. BSI coverage estimates for different ET regimens based on single centre data for Hospital 1 or on the pooled surveillance data. The 95% credible intervals are shown as bars. AMX/GEN, amoxicillin/gentamicin; CRO, ceftriaxone; CTX/GEN, cefotaxime/gentamicin; TZP, piperacillin/tazobactam; MEM,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

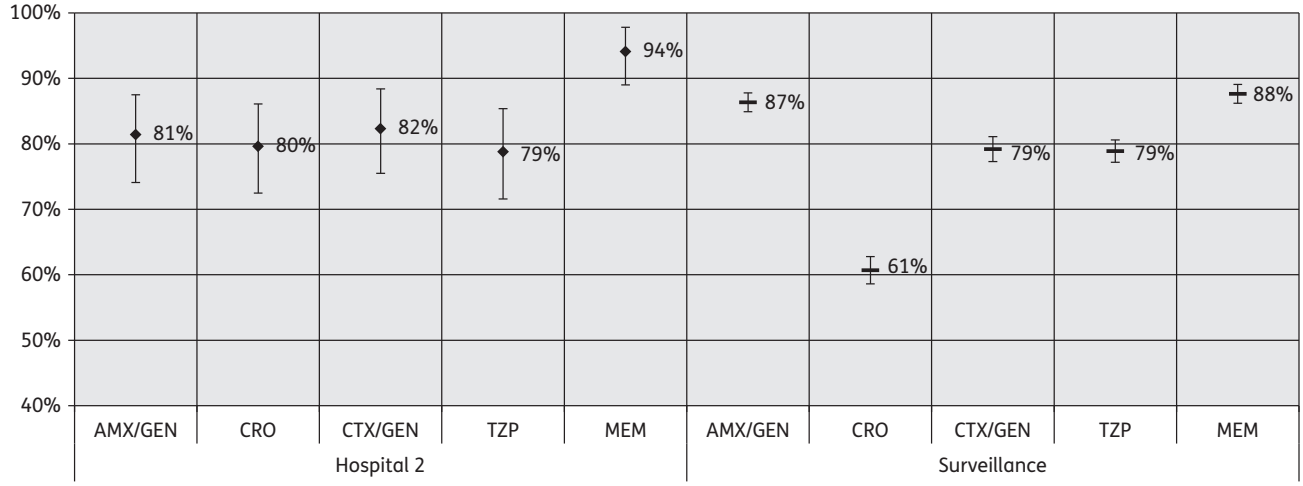

Figure 3. BSI coverage estimates for different ET regimens based on single centre data for Hospital 2 or on the pooled surveillance data. The 95% credible intervals are shown as bars. AMX/GEN, amoxicillin/gentamicin; CRO, ceftriaxone; CTX/GEN, cefotaxime/gentamicin; TZP, piperacillin/tazobactam; MEM,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

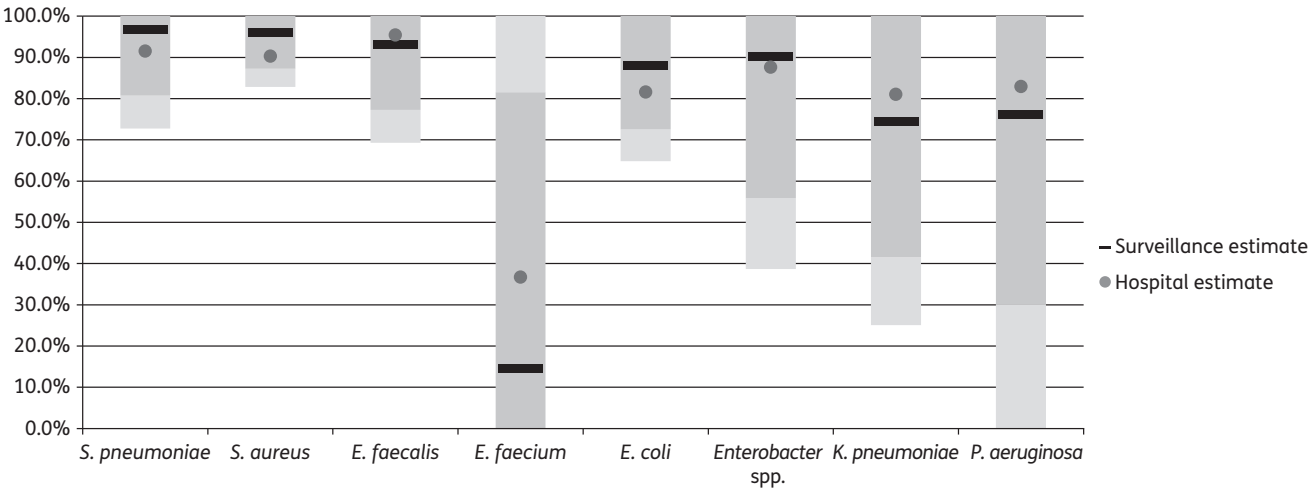

Figure 4. Susceptibility parameters (%) for the amoxicillin/gentamicin regimen for individual pathogens from Hospital 1 and the overall ARPEC cohort of 19 hospitals. The graph shows bullet plots derived from the individual funnel plots. The grey bars indicate the standard inner and outer control limits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

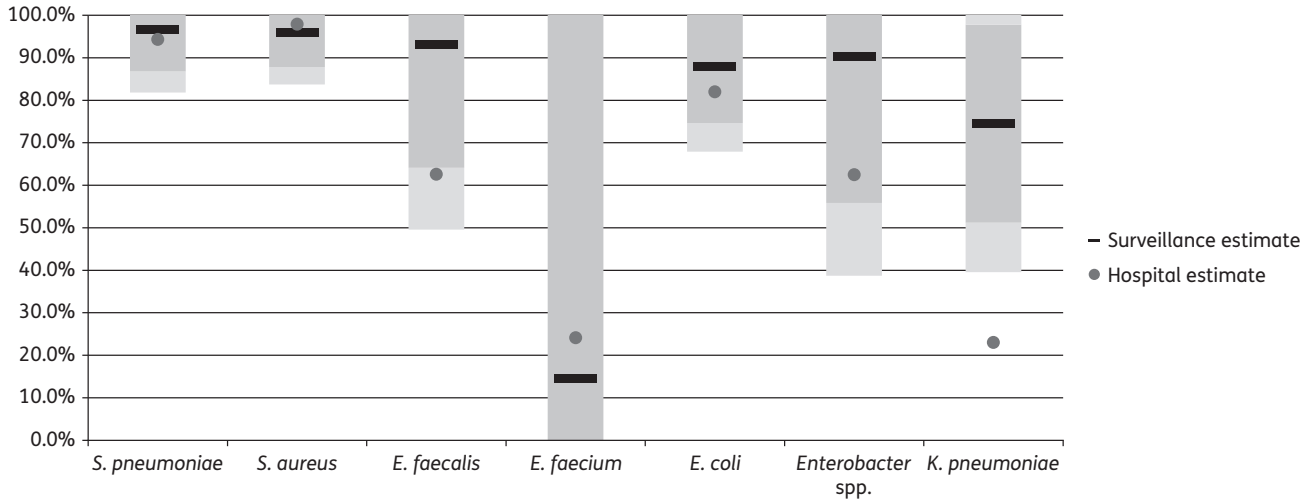

Figure 5. Susceptibility parameters (%) for the amoxicillin/gentamicin regimen for individual pathogens from Hospital 2 and the overall ARPEC cohort of 19 hospitals. The graph shows bullet plots derived from the individual funnel plots. The grey bars indicate the standard inner and outer control limits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

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

[a]Proportion calculated on total of 5037 isolates including unusual pathogens.
[b]Proportion calculated on total of 3678, excluding non-speciated pathogens and unusual pathogens.

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Transparency declarations

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7. Application of the WISCA-based evaluation of regimen coverage to neonatal sepsis across Asian countries

Neonatal sepsis is an important driver of sustained high global neonatal mortality and is therefore also a key focus for the optimised selection of empiric antibiotic regimens (74). Current international guidelines include two regimens recommended for empiric treatment of neonatal sepsis: a first-line combination of a penicillin (usually benzylpenicillin or ampicillin) and gentamicin, and a second-line third-generation cephalosporin regimen (usually ceftriaxone or cefotaxime) (9). However, high levels of antimicrobial resistance in blood culture isolates in neonatal blood culture isolates have been noted in several regions, including in Asia (75-77).

This chapter consists of a paper demonstrating the application of the method described in chapter 6 to the specific scenario of empiric antibiotic regimens used for neonatal sepsis in Asian countries. Publications presenting data on the relative bacterial incidence and resistance patterns of blood culture isolates from babies on neonatal units were systematically identified and used to estimate parameters for calculating WISCAs. The coverage of three commonly used empiric regimens was estimated by country. Additional data from a feasibility survey conducted in preparation for a large international cohort study of neonatal sepsis were not included in the accepted manuscript but are provided at the end of the chapter for reference and comparison.

In addition to the assumptions and algorithms described previously relevant to estimating parameters for regimen susceptibility, the selection of bacteria for inclusion is of key importance. In general, relative incidence of bacteria can be directly derived from any observed data. However, inclusion of likely contaminants or low-grade pathogens, such as coagulative-negative staphylococci, could unduly influence coverage estimates. Some of these bacteria have high levels of resistance to many antibiotics commonly included in empiric antibiotic regimens for childhood sepsis, and it is unclear that covering them with empiric antibiotics improves outcomes. Similarly, inclusion of very rarely isolated bacteria is

unlikely to lead to relevant changes in coverage estimates. Therefore a specific approach towards selecting species contributing to coverage estimation based on observed reporting patterns, but excluding coagulase-negative staphylococci, was taken.

WISCA-based estimation of country-level coverage for neonatal sepsis included several further assumptions. For example, although the systematic review for identifying relevant publications was limited to those published after 2014, some eligible publications contained microbiological data from isolates collected before 2010. Limiting the search to more recent publications would have dramatically reduced the number of isolates to inform WISCA calculation for some countries. However, extending the time frame meant that isolates may not reflect the current profile of antimicrobial resistance in included countries. The impact of temporal changes was therefore explored for India, the country with the largest number of isolates, by splitting the relevant data into three periods: studies reporting on data with a start period for collection before 01 January 2011 (time period 1), those reporting on data collected 01 January 2011 to 31 December 2012 (time period 2) and those reporting on data collected after 31 December 2012 (time period 3).

Some variation in coverage estimates was indeed observed (table c). This was mainly influenced by differences in relative incidence of bacteria rather than by differences in susceptibility of the bacteria to the regimens.

Table c: Estimated coverage of three regimens (AMPGEN: ampicillin plus gentamicin, TGC: ceftriaxone or cefotaxime, MEM: meropenem) with 95% credible intervals for India by study period.

Study period	N	AMPGEN		TGC		MEM	
		%	95%CrI	%	95%CrI	%	95%CrI
<01Jan2011	789	44.3	40.8-47.9	16.9	14.5-19.6	74.9	71.8-77.7
01Jan2011-31Dec2012	3056	43.9	42.0-45.9	32.9	31.3-34.5	58.7	56.9-60.5
>31Dec2012	990	50.7	47.6-53.8	33.2	30.5-36.0	70.0	67.2-72.8

For example, the contribution of Acinetobacter spp. varied from 13% in time period 1 to 26% in time period 2 and 9% in time period 3. Variation in estimated coverage over time therefore appeared to be strongly related to shifts in the predominantly observed bacteria and, potentially, bias in reporting and publication.

In addition to the potential impact of temporal changes, I explored challenges related to data pooling for countries with small sample sizes. Specifically, I investigated the merits of informative empirical Bayesian priors for antimicrobial resistance data derived from metaanalysis. In fact, applying this approach to the data presented in the manuscript, there was no improvement in coverage estimates due to considerable between-country heterogeneity and residual high levels of uncertainty due to small country-level sample size for the relative incidence of bacteria.

A similar problem would be encountered at hospital level: The use of even more granular hospital-level data to determine differences in coverage between hospitals within a country will be challenging due to even smaller expected sample sizes. This will be exacerbated when it is desirable to base coverage specifically on recent data to reflect the current (and potentially shifting) microbiological epidemiology of neonatal sepsis. Further development of the meta-analytical approaches for deriving informative empirical Bayesian priors may include combining data pooling with a classification approach as described in chapter 6 for antimicrobial resistance data. Meta-analysis for antimicrobial resistance would then be carried out for isolates collected from relatively homogenous patient groups, for example within a country, effectively controlling coverage estimates for case-mix. This could reduce heterogeneity, result in meaningful empirical Bayesian priors and improve hospital-level coverage estimates.

RESEARCH PAPER COVER SHEET

SECTION A – Student Details

Student ID Number	237152	**Title**	Dr
First Name(s)	Julia Anna		
Surname/Family Name	Bielicki		
Thesis Title	Estimating coverage of empiric treatment regimens for childhood bloodstream infection based on routine microbiological data		
Primary Supervisor	Prof. David Cromwell		

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Original Investigation | Global Health

Evaluation of the Coverage of 3 Antibiotic Regimens for Neonatal Sepsis in the Hospital Setting Across Asian Countries

Julia A. Bielicki, MD; Mike Sharland, MD; Paul T. Heath, FRCPCH; A. Sarah Walker, PhD; Ramesh Agarwal, MD; Paul Turner, PhD; David A. Cromwell, PhD

Abstract

IMPORTANCE High levels of antimicrobial resistance in neonatal bloodstream isolates are being reported globally, including in Asia. Local hospital antibiogram data may include too few isolates to meaningfully examine the expected coverage of antibiotic regimens.

OBJECTIVE To assess the coverage offered by 3 antibiotic regimens for empirical treatment of neonatal sepsis in Asian countries.

DESIGN, SETTING, AND PARTICIPANTS A decision analytical model was used to estimate coverage of 3 prespecified antibiotic regimens according to a weighted-incidence syndromic combination antibiogram. Relevant data to parameterize the models were identified from a systematic search of Ovid MEDLINE and Embase. Data from Asian countries published from 2014 onward were of interest. Only data on blood culture isolates from neonates with sepsis, bloodstream infection, or bacteremia reported from the relevant setting were included. Data analysis was performed from April 2019 to July 2019.

EXPOSURES The prespecified regimens of interest were aminopenicillin-gentamicin, third-generation cephalosporins (cefotaxime or ceftriaxone), and meropenem. The relative incidence of different bacteria and their antimicrobial susceptibility to antibiotics relevant for determining expected concordance with these regimens were extracted.

MAIN OUTCOMES AND MEASURES Coverage was calculated on the basis of a decision-tree model incorporating relative bacterial incidence and antimicrobial susceptibility of relevant isolates. Data on 7 bacteria most commonly reported in the included studies were used for estimating coverage, which was reported at the country level.

RESULTS Data from 48 studies reporting on 10 countries and 8376 isolates were used. Individual countries reported 51 (Vietnam) to 6284 (India) isolates. Coverage varied considerably between countries. Meropenem was generally estimated to provide the highest coverage, ranging from 64.0% (95% credible interval [CrI], 62.6%-65.4%) in India to 90.6% (95% CrI, 86.2%-94.4%) in Cambodia, followed by aminopenicillin-gentamicin (from 35.9% [95% CrI, 27.7%-44.0%] in Indonesia to 81.0% [95% CrI, 71.1%-89.7%] in Laos) and cefotaxime or ceftriaxone (from 17.9% [95% CrI, 11.7%-24.7%] in Indonesia to 75.0% [95% CrI, 64.8%-84.1%] in Laos). Aminopenicillin-gentamicin coverage was lower than that of meropenem in all countries except Laos (81.0%; 95% CrI, 71.1%-89.7%) and Nepal (74.3%; 95% CrI, 70.3%-78.2%), where 95% CrIs for aminopenicillin-gentamicin and meropenem were overlapping. Third-generation cephalosporin coverage was lowest of the 3 regimens in all countries. The coverage difference between aminopenicillin-gentamicin and meropenem for countries with nonoverlapping 95% CrIs ranged from −15.9% in China to −52.9% in Indonesia.

(continued)

Key Points

Question What is the antibiotic coverage offered by empirical neonatal sepsis treatment with aminopenicillin-gentamicin, third-generation cephalosporins (cefotaxime or ceftriaxone), and meropenem in Asian countries?

Findings In this decision analytical model based on a decision tree, 8376 isolates from 10 countries were used to estimate coverage. Meropenem generally had the highest coverage (from 64.0% in India to 90.6% in Cambodia) followed by aminopenicillin-gentamicin (from 35.9% in Indonesia to 81.0% in Laos) and cefotaxime or ceftriaxone (from 17.9% in Indonesia to 75.0% in Laos); in all countries except Laos and Nepal, meropenem coverage was higher than that of the other 2 regimens.

Meaning The findings suggest that noncarbapenems may provide limited empirical neonatal sepsis coverage in many Asian countries.

+ Invited Commentary

+ Supplemental content

Author affiliations and article information are listed at the end of this article.

Abstract (continued)

CONCLUSIONS AND RELEVANCE This study's findings suggest that noncarbapenem antibiotic regimens may provide limited coverage for empirical treatment of neonatal sepsis in many Asian countries. Alternative regimens must be studied to limit carbapenem consumption.

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Introduction

Although overall maternal and child mortality have substantially declined worldwide since the early 2000s, neonatal mortality associated with bacterial infection has remained high, with nearly half a million estimated annual deaths due to neonatal sepsis.[1] Most of these deaths occur in low- and middle-income countries (LMICs), including many thousands in Asia.[2]

In a recent prospective cohort study[3] of more than 13 500 live births in India, the case-fatality rate of culture-positive neonatal sepsis episodes was nearly 50%. Recent systematic reviews[4-7] indicate a high level of bacterial resistance to World Health Organization (WHO)–recommended empirical treatment regimens for serious neonatal and pediatric infections in LMICs, especially in bloodstream isolates. Globally, antimicrobial resistance is estimated to be implicated in up to one-third of neonatal sepsis deaths annually.[8]

Clinicians and guideline-setting bodies can be assisted in selecting optimal empirical antibiotic regimens by knowing the coverage of alternative regimens.[9] Regimen coverage refers to the proportion of infection episodes that would be treated by the regimen at a stage when the causative pathogen is not yet known, therefore incorporating the frequencies of different causative bacteria and their resistance patterns. Several techniques are available to estimate coverage. One example is the weighted-incidence syndromic combination antibiogram (WISCA),[9-11] which estimates coverage by accounting for the relative incidence of different bacteria and their resistance patterns for a specific infection syndrome, in this case neonatal sepsis. Coverage can be estimated for both single-drug and combination treatment regimens.

International guidelines provide recommendations for the empirical antibiotic treatment of neonatal bacterial infections and should aim to provide adequate coverage in target settings, especially LMICs.[12] The objective of this decision analytical model study was, therefore, to evaluate the coverage offered by 3 prespecified antibiotic regimens according to WISCAs and focusing on Asia, a region with a high prevalence of bacterial resistance.

Methods

We estimated coverage using data on antimicrobial resistance that were used to create WISCAs for each country with reported data,[9] as identified by a systematic review of the literature. Because only published data were used in the analysis, no formal ethical review was required according to guidance by the NHS Health Research Authority. This study follows the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) reporting guideline, because it is broadly applicable to any decision-model based analyses (eAppendix in the Supplement).[13]

Regimens Selected for Coverage Estimation

The 3 regimens evaluated in this study were aminopenicillin-gentamicin (WHO-recommended first-line treatment; alternatives, benzylpenicillin or cloxacillin plus gentamicin), third-generation cephalosporins (WHO-recommended second-line treatment, assumed to be cefotaxime or ceftriaxone, not ceftazidime), and meropenem.[12] The last regimen was evaluated because it has now been reported to be the most commonly used empirical treatment in LMICs for neonatal sepsis.[14]

Identification of Relevant Data for Parameter Estimation

A systematic search of the literature was conducted in Ovid MEDLINE and in Embase on January 23, 2019. Using both free-text and MeSH terms, publications on "sepsis" and "antibiotic resistance" and ("neonates" or infants") and "Asia" were identified (eAppendix in the Supplement). Given increasing antimicrobial resistance, and to obtain contemporaneous estimates, we arbitrarily limited the search to articles published from 2014 onward. No additional limits were applied. Studies were reviewed against prespecified eligibility criteria, and data were extracted using a standardized prepiloted form implemented in REDCap[15] (eAppendix in the Supplement).

Extracted data for WISCA calculation included information on the total number of bacterial isolates from relevant blood cultures, the number of isolates of specific bacterial species or genera, the number of isolates tested for susceptibility to the antibiotics relevant for establishing coverage offered by the prespecified regimens of interest, and the number of isolates found to be susceptible to these antibiotics. We excluded bacteria known to frequently represent contamination rather than true infection, most importantly coagulase-negative staphylococci.[16] The exclusion of coagulase-negative staphylococci is likely to result in the overestimation of coverage for β-lactam–based regimens because of very high expected rates of methicillin resistance of 66% to more than 90%.[17,18]

Estimation of WISCA Parameters

Tables containing the parameter values required for coverage estimation were created by country and regimen. The relative incidence parameters were based only on bacteria reported as contributing to neonatal sepsis in more than 50% of the eligible studies. This meant that estimated coverage was based on the most important and frequent pathogens identified in blood cultures from neonates in the target region. Including rare pathogens within the WISCA would have a minimal impact on the estimated coverage, and including those likely to be contaminants or unusual pathogens (potentially observed as part of unidentified outbreaks) could introduce substantial bias. For the bacteria identified in this way, their relative incidence was based on the frequency reported in the studies. Similarly, regimen susceptibility was derived directly from reported data with the number of tested isolates representing the denominator. Details of the assumptions for determining susceptibility of pathogens to each regimen are provided in the eAppendix in the Supplement.

Statistical Analysis

Regimen coverage was estimated using a previously described Bayesian WISCA.[9] This approach has various advantages. It addresses the typical clinical approach of treating an infection syndrome, often with incomplete knowledge about the frequency of causative bacteria and their susceptibilities. The Bayesian WISCA also explicitly deals with intrinsic resistance and handles imprecision attributed to a small sample size or incomplete susceptibility testing data.

In brief, the WISCA gives the expected levels of therapeutic coverage for an antibiotic regimen—in our case, regimens used to treat neonates with sepsis. The WISCA can be represented as a decision tree (eFigure 1 in the Supplement). Combining the probabilities along the regimen tree branches generates coverage estimates from relative bacterial incidence and proportions of each included pathogen susceptible to the antibiotic regimen. In essence, the WISCA is a weighted mean of the susceptibilities of the bacteria, with the weights defined by their relative incidence.

The observed data on pathogen incidence and their susceptibility to the 3 regimens were combined with an appropriate Bayesian prior distribution that corresponded to our prestudy beliefs about these parameters. We had no strong prior belief about the relative incidence of the pathogens or for the majority of what level of susceptibility there might be within a country, and a noninformative prior was used in these cases. However, in some circumstances, specific pathogens were expected to have intrinsic resistance to the regimen and, consequently, not to have susceptibility regardless of reported susceptibility testing results.[19,20] In these situations, an informative prior was used to dominate the observed data. On the basis of European Committee for Antimicrobial Susceptibility Testing (EUCAST) recommendations,[19,20] enterococci, as well as

Acinetobacter species and *Pseudomonas* species, were assumed to be intrinsically resistant to recommended third-generation cephalosporins and therefore not susceptible to third-generation cephalosporins.

The value of the pathogen incidence and pathogen regimen-susceptibility parameters were defined as probability distributions to reflect the uncertainty in their respective values. The relative incidence of pathogens was modeled using a Dirichlet distribution, and the susceptibility parameters were defined as beta distributions; 95% credible intervals (95% CrIs) for the coverage estimates were calculated using Monte Carlo simulations, based on 1000 runs (eAppendix in the Supplement). All modeling was undertaken using Stata statistical software version 13.1 (StataCorp) and Excel spreadsheet software version 2010 (Microsoft Corp). Data analysis was performed from April 2019 to July 2019.

Results

Description of Data Set

The literature review included data from 48 publications (eFigure 2 in the Supplement) representing 52 centers in 10 Asian countries (1 center in Cambodia, 5 in China, 33 in India, 1 in Indonesia, 1 in Laos, 1 in Malaysia, 6 in Nepal, 2 in Pakistan, 1 in Taiwan, and 1 in Vietnam). Of the 52 centers, 34 were university or tertiary hospitals, 10 were nonteaching or district hospitals (9 in India and 1 in China), and 8 were maternity or pediatric hospitals (1 in Cambodia, 2 in China, 4 in Nepal, and 1 in Vietnam).

Ten articles were published in 2014, 13 in 2015, 10 in 2016, 8 in 2017, 6 in 2018, and 1 in 2019. For 32 of 48 publications, the observation period started in 2010 or later, with the earliest start date being January 1, 1990 (eTable 1 in the Supplement). Five publications did not report calendar dates for their observation period, but 4 of 5 indicated its duration. The median observation period was 2 years, with the shortest and longest periods being 2 months and 12 years, respectively.

Most publications (33 of 48) reported on bloodstream isolates from neonates with clinical community-acquired or nosocomial sepsis. Another 12 publications based reporting on microbiologically defined bacteremia. Only 4 publications focused on either nosocomial or community-acquired infections (2 each). Reporting of information on sample processing, including species identification, antibiotic susceptibility testing methods, and interpretive guidelines, was variable (eTable 2 in the Supplement).

Reported Bloodstream Isolates

Individual publications included between 15 and 2112 isolates, with a median of 98 isolates (eTable 3 in the Supplement). The following bacteria were most frequently reported as contributing to neonatal sepsis or bacteremia: *Escherichia coli* (46 of 48 publications), *Klebsiella* species and *Staphylococcus aureus* (45 of 48 publications each), *Pseudomonas* species (35 of 48 publications), *Acinetobacter* species (32 of 48 publications), *Enterobacter* species (26 of 48 publications), and *Enterococcus* species (25 of 48 publications). In addition, coagulase-negative staphylococci were reported in 40 of 48 publications. All other bacteria, including *Citrobacter* species and *Streptococcus agalactiae*, were reported in less than one-half of the publications. On the basis of the prespecified criteria, *E coli*, *Klebsiella* species, *S aureus*, *Pseudomonas* species, *Acinetobacter* species, *Enterobacter* species, and *Enterococcus* species were selected for antibiotic regimen coverage estimation.

Parameter Values: Isolates Reported and Susceptibility

In total, 11 467 isolates were reported, with the greatest number coming from India (6284), China (2043), Pakistan (1875), and Nepal (640) (**Table 1**). Given the small number of reported isolates from Taiwan (36) and Malaysia (29), antibiotic regimen coverage was not estimated for these 2 countries. Most reported isolates (8584 of 11 467 [74.9%]) were from university or tertiary hospitals, with nonteaching or district hospitals contributing 11.5% (1319 of 11 467) and maternity or pediatric hospitals contributing another 13.6% (1564 of 11 467).

In total, 8376 isolates from 10 countries were used to estimate coverage. The proportion of reported isolates contributing to antibiotic regimen coverage estimation ranged from 91.9% (1723 of 1875) in Pakistan to 44.2% (905 of 2043) in China. Disregarding coagulase-negative staphylococci, the proportion of reported bacterial isolates contributing to coverage estimation ranged from 98.0% (51 of 52) in Vietnam to 69.5% (905 of 1302) in China.

Availability of susceptibility testing information for aminopenicillin-gentamicin coverage ranged from 68.8% (623 of 905) in China to 100% in Indonesia (**Table 2**). For third-generation cephalosporins, this was available for 100% in Cambodia and Indonesia and 76.5% (39 of 51) in Vietnam (**Table 3**). For meropenem, available susceptibility testing information ranged from 100% in Indonesia to 60.3% (295 of 489) in Nepal (**Table 4**).

Coverage Estimates at Country Level

Coverage was consistently lowest for third-generation cephalosporin monotherapy, with some variation across the individual countries, ranging from 56.6% (95% CrI, 52.2%-60.7%) in Nepal to 17.9% (95% CrI, 11.7%-24.7%) in Indonesia (**Figure**). Similarly, although meropenem had the highest estimated coverage in each country, the proportion of neonates for whom it would be effective empirical treatment varied considerably, from 90.6% (95% CrI, 86.2%-94.4%) in Cambodia to 64.0% (95% CrI, 62.6%-65.4%) in India (Figure). Aminopenicillin-gentamicin offered the second highest level of coverage within each country behind meropenem. Nonetheless, there was again considerable variability in country-level estimates, from 74.3% (95% CrI, 70.3%-78.2%) in Nepal to 35.9% (95% CrI, 27.7%-44.0%) in Indonesia (Figure).

Aminopenicillin-gentamicin coverage was higher than that offered by third-generation cephalosporins in China (60.6% [95% CrI, 54.2%-67.5%] vs 44.2% [95% CrI, 40.9%-47.9%]), India (45.1% [95% CrI, 43.7%-46.6%] vs 30.4% [95% CrI, 29.2%-31.6%]), Indonesia (35.9% [95% CrI, 27.7%-44.0%] vs 17.9% [95% CrI, 11.7%-24.7%]), and Nepal (74.3% [95% CrI, 70.3%-78.2%] vs 56.6% [95% CrI, 52.2%-60.7%]). There was greater uncertainty about whether the differences observed for Cambodia (47.4% [95% CrI, 38.1%-56.6%] vs 32.6% [95% CrI, 25.8%-39.9%]), Laos (81.0% [95% CrI, 71.1%-89.7%] vs 75.0% [95% CrI, 64.8%-84.1%]), Pakistan (42.2% [95% CrI, 39.1%-45.0%] vs 37.4% [95% CrI, 34.4%-40.3%]), and Vietnam (36.2% [95% CrI, 24.5%-49.0%] vs 21.5% [95% CrI, 12.0%-32.9%]) were due to chance variation.

Table 1. Relative Incidence Data

Pathogen	Isolates, No. (%)[a]										
	Cambodia (n = 185)	China (n = 2043)	India (n = 6284)	Indonesia (n = 225)	Laos (n = 75)	Malaysia (n = 29)	Nepal (n = 640)	Pakistan (n = 1875)	Taiwan (n = 36)	Vietnam (n = 75)	Total (N = 11 467)
Contributing to WISCA											
Escherichia coli	25 (16)	300 (33)	671 (14)	0	8 (13)	6 (33)	50 (10)	976 (57)	11 (92)	2 (4)	2049 (24)
Klebsiella species	60 (39)	264 (29)	1065 (22)	49 (40)	9 (14)	1 (6)	45 (9)	159 (9)	1 (8)	18 (35)	1671 (20)
Enterobacter species	18 (11)	58 (6)	167 (3)	20 (17)	4 (6)	0	30 (6)	0	0	6 (12)	303 (4)
Acinetobacter species	16 (10)	27 (3)	992 (21)	21 (17)	2 (3)	0	63 (13)	0	0	17 (33)	1138 (14)
Pseudomonas species	6 (4)	53 (6)	430 (9)	31 (26)	1 (2)	1 (6)	25 (5)	199 (12)	0	4 (8)	750 (9)
Staphylococcus aureus	33 (21)	112 (12)	1235 (26)	0	37 (58)	10 (55)	261 (53)	388 (23)	0	4 (8)	2080 (25)
Enterococcus species	0	91 (10)	275 (6)	0	3 (5)	0	15 (3)	1 (<1)	0	0	385 (5)
Total reported during observation period											
Total contributing to WISCA	158 (85)	905 (44)	4835 (77)	121 (54)	64 (85)	18 (62)	489 (76)	1723 (92)	12 (33)	51 (68)	8376 (73)
Other (not contributing to WISCA)	27 (15)	1138 (56)	1449 (23)	104 (46)	11 (15)	11 (38)	151 (24)	152 (8)	24 (67)	24 (32)	3091 (27)
Coagulase-negative staphylococci (not contributing to WISCA)	0	741 (36)	980 (16)	63 (28)	0	0	137 (21)	28 (1)	0	23 (31)	1972 (17)

Abbreviation: WISCA, weighted-incidence syndromic combination antibiogram.

[a] Percentages may not add to 100% because of rounding.

Table 2. Susceptibility Testing and Susceptibility Data for Aminopenicillin Plus Gentamicin

Pathogen	No. of Isolates																					
	Cambodia			China			India			Indonesia			Laos			Nepal			Pakistan			Vietnam			Total		
	N	T	S	N	T	S	N	T	S	N	T	S	N	T	S	N	T	S	N	T	S	N	T	S	N	T	S
Escherichia coli	25	25	13	300	290	182	671	655	426	0	NA	NA	8	8	6	50	50	31	976	976	340	2	0	NA	2033	2004	998
Klebsiella species	60	60	10	264	256	193	1065	1026	402	49	49	3	9	9	7	45	42	23	159	159	36	18	11	2	1669	1612	676
Enterobacter species	18	18	8	58	20	11	167	154	42	20	20	18	4	0	NA	30	30	21	0	NA	NA	6	5	3	303	247	103
Acinetobacter species	16	0	NA	27	0	NA	992	930	226	21	21	11	2	0	NA	63	62	34	0	NA	NA	17	17	3	1138	1030	274
Pseudomonas species	6	0	NA	53	0	NA	430	422	238	31	31	9	1	0	NA	25	23	18	199	199	74	4	4	1	749	679	340
Staphylococcus aureus	33	33	32	112	56	31	1235	1142	655	0	NA	NA	37	37	37	261	227	195	388	88	63	4	3	3	2070	1586	1016
Enterococcus species	0	NA	NA	91	1	0	275	132	44	0	NA	NA	3	0	NA	15	15	12	1	0	NA	0	NA	NA	385	148	56

Abbreviations: N, total isolates; NA, not applicable; S, isolates identified as susceptible on testing; T, susceptibility testing available for regimen of interest.

Table 3. Susceptibility Testing and Susceptibility Data for Third-Generation Cephalosporins

Pathogen	No. of Isolates																							
	Cambodia			China			India			Indonesia			Laos			Nepal			Pakistan			Vietnam			Total		
	N	T	S	N	T	S	N	T	S	N	T	S	N	T	S	N	T	S	N	T	S	N	T	S	N	T	S
Escherichia coli	25	25	13	300	289	165	671	657	339	0	NA	NA	8	8	7	50	43	25	976	976	317	2	0	NA	2033	1998	866
Klebsiella species	60	60	4	264	251	122	1065	1031	346	49	49	2	9	9	6	45	42	12	159	159	52	18	11	1	1669	1612	545
Enterobacter species	18	18	1	58	20	14	167	167	59	20	20	17	4	0	NA	30	28	12	0	NA	NA	6	4	1	303	257	104
Acinetobacter species[a]	16	16	0	27	27	0	992	992	0	21	21	0	2	2	0	63	63	0	0	NA	NA	17	17	0	1138	1138	0
Pseudomonas species[a]	6	6	0	53	53	0	430	430	0	31	31	0	1	1	0	25	25	0	199	199	0	4	4	0	749	749	0
Staphylococcus aureus	33	33	32	112	56	31	1235	1142	655	0	NA	NA	37	37	37	261	227	195	388	88	63	4	3	3	2070	1586	1016
Enterococcus species[a]	0	NA	NA	91	91	0	275	275	0	0	NA	NA	3	3	0	15	15	0	1	1	0	0	NA	NA	385	385	0

Abbreviations: N, total isolates; NA, not applicable; S, isolates identified as susceptible on testing; T, susceptibility testing available for regimen of interest.

[a] Not based on susceptibility testing because pathogen was assumed to be intrinsically resistant.

Table 4. Susceptibility Testing and Susceptibility Data for Meropenem

Pathogen	No. of Isolates																							
	Cambodia			China			India			Indonesia			Laos			Nepal			Pakistan			Vietnam			Total		
	N	T	S	N	T	S	N	T	S	N	T	S	N	T	S	N	T	S	N	T	S	N	T	S	N	T	S
Escherichia coli	25	24	24	300	289	289	671	439	379	0	NA	NA	8	0	NA	50	3	1	976	811	768	2	0	NA	2033	1566	1461
Klebsiella species	60	60	60	264	253	228	1065	882	667	49	49	49	9	0	NA	45	27	27	159	102	87	18	9	9	1669	1382	1127
Enterobacter species	18	18	17	58	20	20	167	157	122	20	20	19	4	0	NA	30	16	14	0	NA	NA	6	3	3	303	234	195
Acinetobacter species	16	16	14	27	0	NA	992	926	475	21	21	21	2	0	NA	63	7	3	0	NA	NA	17	16	15	1138	986	528
Pseudomonas species	6	5	5	53	0	NA	430	415	354	31	31	23	1	0	NA	25	0	NA	199	199	188	4	3	3	749	653	573
Staphylococcus aureus	33	33	32	112	56	31	1235	1142	655	0	NA	NA	37	37	37	261	227	195	388	88	63	4	3	3	2070	1586	1016
Enterococcus species[a]	0	NA	NA	91	91	0	275	275	0	0	NA	NA	3	3	0	15	15	0	1	1	0	0	NA	NA	385	385	0

Abbreviations: N, total isolates; NA, not applicable; S, isolates identified as susceptible on testing; T, susceptibility testing available for regimen of interest.

[a] Not based on susceptibility testing because pathogen was assumed to be intrinsically resistant.

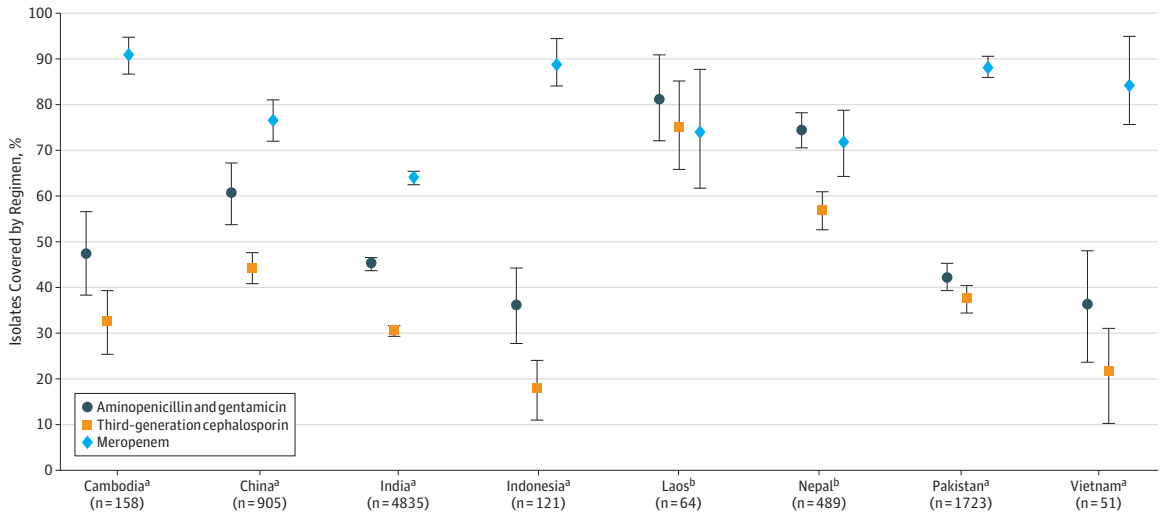
Meropenem coverage was higher than aminopenicillin-gentamicin coverage in Cambodia (90.6% [95% CrI, 86.2%-94.4%] vs 47.4% [95% CrI, 38.1%-56.6%]), China (76.5% [95% CrI, 71.8%-80.9%] vs 60.6% [95% CrI, 54.2%-67.5%]), India (64.0% [95% CrI, 62.6%-65.4%] vs 45.1% [95% CrI, 43.7%-46.6%]), Indonesia (88.8% [95% CrI, 83.2%-93.6%] vs 35.9% [95% CrI, 27.7%-44.0%]), Pakistan (88.1% [95% CrI, 85.6%-90.3%] vs 42.2% [95% CrI, 39.1%-45.0%]), and Vietnam (84.1% [95% CrI, 73.2%-92.6%] vs 36.2% [95% CrI, 24.5%-49.0%]) on the basis of nonoverlapping 95% CrIs. The largest percentage differences in coverage were observed in Indonesia (52.9%), Pakistan (45.9%), and Cambodia (43.2%); the smallest was in China (15.9%). For meropenem and third-generation cephalosporins, the percentage difference was largest for Indonesia (70.9%), Vietnam (62.6%), and Cambodia (58.0%). Of note, for Laos and Nepal, imprecision around estimated meropenem coverage, which was comparable with that of aminopenicillin-gentamicin with overlapping 95% CrIs, was largely because of low proportions of isolates (62.5% [40 of 64] for Laos and 60.3% [295 of 489] for Nepal) contributing to the meropenem susceptibility parameter.

Discussion

We estimated the coverage offered by 3 antibiotic regimens—aminopenicillin-gentamicin (WHO-recommended first-line regimen), third-generation cephalosporins (WHO-recommended second-line regimen), and meropenem—in Asian countries for the empirical treatment of neonatal sepsis caused by 7 specified bacteria. The coverage estimates were based on a systematic review of recent studies reporting on the relative incidence of common bacteria and their resistance.

In general, coverage estimates supported the identification of better-performing or worse-performing regimens for most countries. Coverage offered by aminopenicillin-gentamicin (WHO-recommended first-line regimen) was less than 50% for Cambodia, India, Indonesia, Pakistan, and Vietnam and less than 75% for China and Nepal. Even lower coverage was offered by the WHO-recommended second-line third-generation cephalosporin monotherapy regimen: below 50%

Figure. Coverage Estimates for 8 Asian Countries



Point estimates are shown with 95% credible intervals, as denoted by error bars. Nonoverlapping 95% credible intervals indicate likely within-country differences in regimen coverage. Countries are shown together with the overall number of isolates used for estimating coverage.

[a] The highest coverage offered by meropenem was in Cambodia (90.6%), China (76.5%), India (64.0%), Indonesia (88.8%), Pakistan (88.1%), and Vietnam (84.1%).

[b] The highest coverage offered by aminopenicillin-gentamicin combination was in Laos (81.0%) and Nepal (74.3%).

in all represented countries except Laos (75.0%) and Nepal (56.6%). Meropenem coverage was generally highest and was greater than 80% in Cambodia, Indonesia, Pakistan, and Vietnam, but lower than 80% in China, Laos, and Nepal and as low as 64.0% in India. Considerable between-country differences were observed for all 3 regimens, even for countries bordering each other, such as Cambodia, Laos, Thailand, and Vietnam.

Coverage estimates are clinically highly relevant for the development of local and national empirical treatment guidelines, incorporating both the relative incidence of bacteria and their susceptibility.[9] This concept has not, to our knowledge, been previously applied to neonatal sepsis in LMICs. Instead, reports have focused on susceptibility for individual pathogen-drug combinations, an approach that does not directly incorporate the spectrum of causative bacteria.[4,6,7]

One important question is whether global setting-independent recommendations for empirical neonatal sepsis treatment can be supported in an era of changing and highly variable epidemiology. In some settings, difficult-to-treat pathogens and multidrug-resistant isolates now contribute considerably to neonatal sepsis.[3] Stratified guidance moving between recommended regimens according to microbiology and coverage by patient-level factors (eg, presence of certain underlying conditions or timing of sepsis onset) or setting, may be a solution. One challenge will be the lack of defined coverage thresholds to move between regimens.[21] Given sufficiently large data sets, coverage estimates could help inform such shifting by supporting inferences about true differences between regimens.

Limitations

This study has some limitations. Our coverage estimates were based on data from predominantly university or teaching hospitals. Infants with complex medical issues and those at higher risk of nosocomial bloodstream infections may, therefore, be overrepresented. At the same time, microbiology data from infants managed in district hospitals are lacking precluding confirmation that presented coverage estimates are applicable to them as well. Clinicians applying WHO recommendations to infants with nosocomial infection or those managed in tertiary hospitals would, on the basis of our observations, need to consider alternatives for this population.

We chose to estimate coverage according to the pathogens frequently reported across included studies, which are likely to be associated with severe neonatal sepsis and the so-called ESKAPE organisms (ie, *Enterococcus faecium*, *S aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, and *Pseudomonas aeruginosa*), which are known to be problematic in terms of emerging antimicrobial resistance.[22] Inclusion of other pathogens would be expected to have a variable influence on the expected coverage of considered antibiotics, leading to either higher or lower estimates. This may be particularly important in individual hospitals with ongoing outbreaks where a single bacterial strain is dominant. In such situations, regional coverage estimates may not be applicable.

Coverage estimation requires a number of assumptions to be made when calculating the susceptibility parameters, such as the incorporation of intrinsic resistance, extrapolations from susceptibility testing for 1 representative of an antibiotic class to other members of this class, and the interpretation of multiple testing for 1 antibiotic class. We based our calculations of regimen susceptibility on EUCAST algorithms and, whenever possible, used susceptibility testing information for the specific drug of interest.[19] Importantly, however, all included studies used versions of Clinical and Laboratory Standards Institute interpretive criteria,[23] which may diverge from EUCAST in terms of both break points and assumptions about intrinsic resistance. Debate about the merits and challenges of switching from Clinical and Laboratory Standards Institute to EUCAST and about the implications of such a transition for interpretation of routine data in the context of surveillance is ongoing.[23,24]

To support coverage estimation, it is important that the microbiological data used are collected in equivalent ways. However, the data used for this analysis may have been subject to various random or systematic errors that could bias the coverage estimates. Possible sources of error include duplicate isolates, contaminants, nonstandardized susceptibility testing, combining data from

different patient populations (children and adults), and reflex susceptibility testing based on resistance identified in a first-line testing panel.[25] These requirements have important implications for global surveillance initiatives, such as the Global Antimicrobial Resistance Surveillance System,[26] if data collected are to be used at the interface between surveillance and clinical practice.

Conclusions

Recently, machine learning approaches and more elaborate multivariable Bayesian models using clinical and demographic information combined with microbiological data have been proposed as optimizing the selection of empirical antibiotic treatment for sepsis.[27,28] Although these models may help in selecting patient-adapted regimens, the approach used in our study only requires estimates of pathogen incidence and susceptibility and could already substantially improve clinical decision-making based on routine microbiological data alone, provided that the data used to produce these estimates are of sufficient quality. Our analysis indicates that the recommendation for third-generation cephalosporin monotherapy as a second-line regimen may no longer be valid for many infants receiving treatment for neonatal sepsis in several Asian countries. Our findings could explain the high reported empirical meropenem use in this population in Asia.[14,29] Evaluation of potential alternatives will be essential to reducing consumption of last-resort antibiotics for the empirical treatment of neonatal sepsis in settings with a high prevalence of antimicrobial resistance.

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Author Contributions: Dr Bielicki had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Drafting of the manuscript: Bielicki, Heath.

Critical revision of the manuscript for important intellectual content: All authors.

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SUPPLEMENT.

eAppendix. Supplemental Methods
eFigure 1. Illustration of Decision Tree for Estimating Coverage From Weighted Incidence Syndromic Combination Antibiograms for Three Antibiotic Regimens of Interest
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eTable 1. Description of Included Publications
eTable 2. Information on Sample Processing Provided in Included Publications
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Supplementary Online Content

Bielicki JA, Sharland M, Heath PT, et al. Evaluation of the coverage of 3 antibiotic regimens for neonatal sepsis in the hospital setting across Asian countries. *JAMA Netw Open*. 2020:3(2):e1921124. doi:10.1001.jamanetworkopen.2019.21124

This supplementary material has been provided by the authors to give readers additional information about their work.

eAppendix. Supplemental Methods

Search strategy for systematic literature review

Ovid MEDLINE® 1946 to April 25 2019

1 exp SEPSIS/ or exp NEONATAL SEPSIS/
2 exp BACTEREMIA
3 bacter?emia.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
4 (blood?stream adj3 infect*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
5 (blood adj2 culture adj2 (positive* or isolat*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
6 1 or 2 or 3 or 4 or 5
7 ((anti?biotic* or anti?infect* or anti?microb*) adj2 (resist* or suscep* or sensitive*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
8 exp Drug Resistance, Microbial/
9 7 or 8
10 exp infant/ or exp infant, newborn/
11 (infant* or neonat* or new?born).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
12 10 or 11
13 6 and 9 and 12
14 Exp ASIA/
15 13 and 14
16 Limit 15 to yr=”2014-Current”

Embase 1974 to 2019 Week 16

1 exp bacteremia/
2 exp sepsis/ or newborn sepsis/
3 bacter?emia.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
4 (blood?stream adj2 infect*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
5 (blood adj2 culture adj2 (positive* or isolate*)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
6 1 or 2 or 3 or 4 or 5
7 ((anti?biotic* or anti?infect* or anti?microb*) adj2 (resist* or suscep* or sensitiv*)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
8 exp antibiotic resistance/
9 7 or 8
10 infant/
11 newborn/
12 (infant or new?born or neonat*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
13 10 or 11 or 12
14 6 and 9 and 13
15 14
16 14 and 15

17 limit 16 to yr=”2014-Current”

Systematic review of the literature: selection of publications
Studies were eligible for inclusion if they examined blood culture isolates and (i) provided information specific to newborns up to 28 days of age or infants managed on neonatal units, (ii) reported on the relative incidence of different bacteria at species or genus level during the indicated surveillance period and (iii) included data on antimicrobial resistance for at least one bacterial species or genus. Publications reporting on isolates from sources other than blood, and those from which data for neonatal blood cultures (e.g. reporting pooled data across age groups) could not be extracted were excluded. Equally studies focusing on single organisms from which the relative incidence of other bacteria could not be obtained were excluded. Further we excluded studies presenting only aggregate data by region or internationally.

After exclusion of duplicates, titles or abstracts of retrieved studies were reviewed by one author (JB) to identify those meeting inclusion criteria. A random subset of retrieved studies was reviewed by a second author (MS) to ensure consistency in selection based on the pre-specified inclusion and exclusion criteria with no disagreements.

Selected publications were primarily used to inform parameter estimation for calculating coverage. Additional extracted data included contextual information (namely the year of publication, the country from where the data originated, the surveillance/reporting period, and the number and type of hospitals surveyed), and whether studies reported on blood culture isolates from community-acquired infections, hospital-acquired infections or both. Early onset of neonatal sepsis defined as infection occurring in the first 3 days of life was considered a community-acquired infection. We also extracted information on approaches to species identification, susceptibility testing and evaluation of testing results, if provided. Species identification and susceptibility testing results were recorded as reported. As the study was focused on the reporting of routine microbiological or surveillance data, we did not undertake a formal grading of the quality of the studies or an evaluation of the appropriateness of microbiological approaches.

Assumptions for determining susceptibility of pathogens to pre-specified regimens
- Aminopenicillin susceptibility was based on either ampicillin or amoxicillin susceptibility testing results, whichever was available.
- Gentamicin susceptibility was based on results for gentamicin rather than other aminoglycosides whenever possible, because susceptibility to gentamicin cannot be reliably inferred from results for other aminoglycosides. If no gentamicin susceptibility data were provided, data from other aminogylcosides (mostly amikacin) were used.
- Third-generation cephalosporin susceptibility was based on either cefotaxime or ceftriaxone, whichever was available.
- Meropenem susceptibility was based on results for meropenem rather than other carbapenems whenever possible, because susceptibility to meropenem cannot be reliably inferred from results for other carbapenems. If no meropenem susceptibility data were provided, data from other carbapenems (mostly imipenem) were used.
- For *Staphylococcus aureus*, third-generation cephalosporin and meropenem susceptibility was derived from information on methicillin resistance, as these antibiotics are not generally specifically tested for *S. aureus*.
- For the combined regimen (i), the one with the higher susceptibility was taken to reflect overall susceptibility. For example, if *Escherichia coli* in a specific country exhibited 20% ampicillin susceptibility and 70% gentamicin susceptibility, susceptibility to aminopenicillin plus gentamicin for *E. coli* was assumed to be 70%.

Technical appendix on calculation of the weighted-incidence syndromic combination antibiogram (WISCA)
In the WISCA decision tree, the first square node represents the clinical decision to start empiric antibiotic therapy and the regimen choices. Subsequent circular nodes and branches describe chance events, which are the range of relevant bacteria causing neonatal sepsis, their relative incidence and the percentages of each pathogen susceptible to each antibiotic regimen. Combining the probabilities along the regimen tree branches provides an estimate of coverage for each regimen.

A difficulty in adopting a Bayesian perspective is the specification of the prior distributions for the parameters. The value of the relative incidence and pathogen–regimen susceptibility parameters for each regimen were therefore defined as probability distributions that reflected the uncertainty in their value. Given that susceptibility percentages are simple proportions, we selected a binomial distribution to describe our prior belief defined using the conjugate Beta distribution. This approach results in the posterior also being a Beta distribution. The relative incidence data were assumed to be drawn from a multinomial distribution with nine possible outcomes. The prior was accordingly modeled as a Dirichlet (1,1,1,…,1) distribution. This is the continuous equivalent to the discrete multinomial distribution, and is the generalisation of the Beta distribution to situations described by more than two categories.

In the absence of any strong prior beliefs, a common solution is to use a "non-informative" uniform prior. Doing this means that the posterior distribution is largely determined by the observed data. Using the Dirichlet distribution as the prior, for example, results in the posterior taking the form Dirichlet (1+n1, 1+n2,. . ., 1+n9). Equally, in most cases, when there were no strong prior beliefs about pathogen-regimen susceptibility, the non-informative prior beta(1,1) was used.

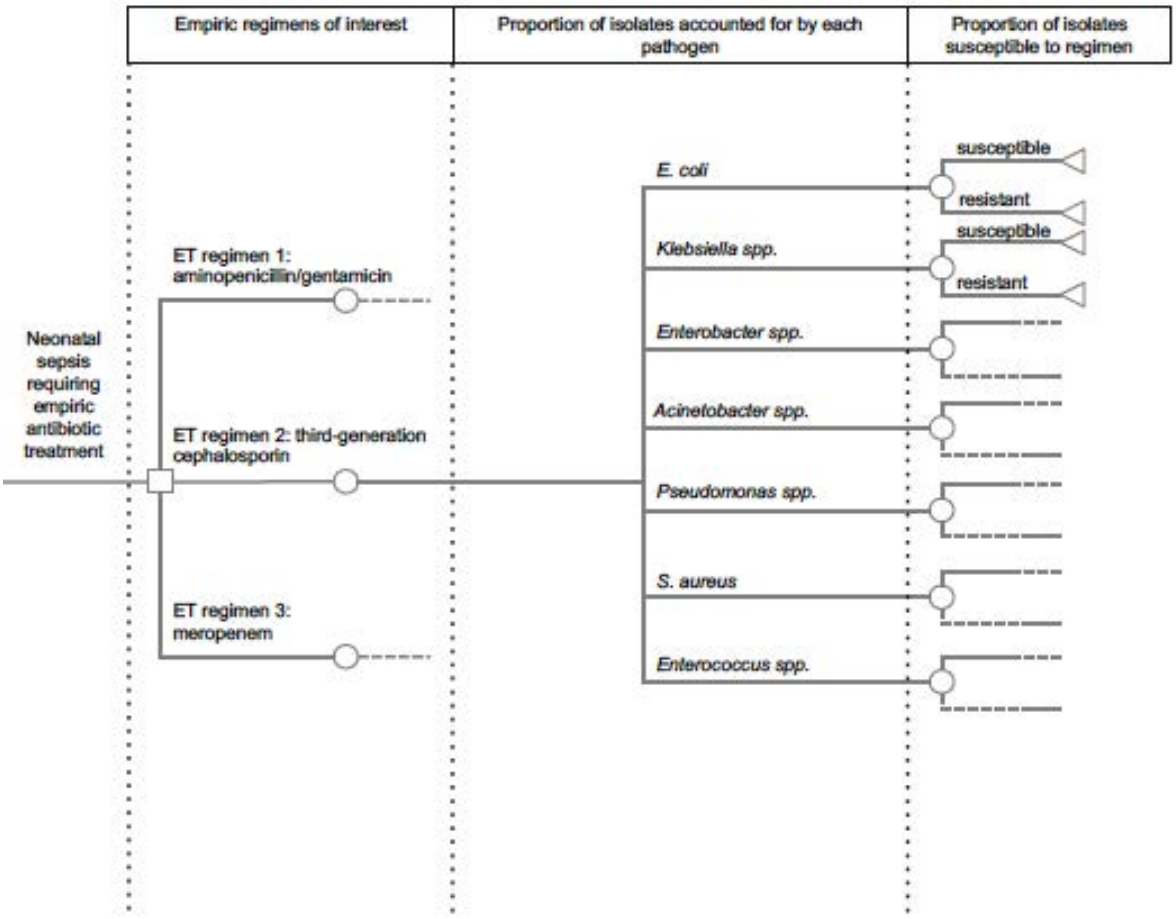
Adopting a Bayesian perspective allows the use of informative priors for the situation in which a pathogen has intrinsic resistance or is assumed to be fully susceptible. For these, we chose a pragmatic posterior Beta distribution, chosen to have an appropriate standard deviation. For example, susceptibility for a pathogen with intrinsic resistance was specified as a Beta(1,9999), which has a standard deviation of 0.01%. Sampling from this distribution only gives pathogen resistance below 99.9% in 1 in 20000 draws.

The calculation of the 95% credible interval describing the precision of coverage estimates requires Monte Carlo simulation, which involves running a large number of experiments (in our case 1000) and combining their results. In each experiment, parameter values for the parameters of interest (relative incidence and pathogen-regimen susceptibility) are randomly drawn from their specified distributions. The values of each parameter are then combined to derive a coverage estimate. Together, the individual coverage estimates from all the experiments give the posterior distribution for the coverage parameter. The 95% "uncertainty" interval, or 95% credible interval, is then calculated as the interval between 2.5% and 97% percentile of this distribution.

Analytical steps for basic WISCA coverage estimation using a Bayesian decision tree model.

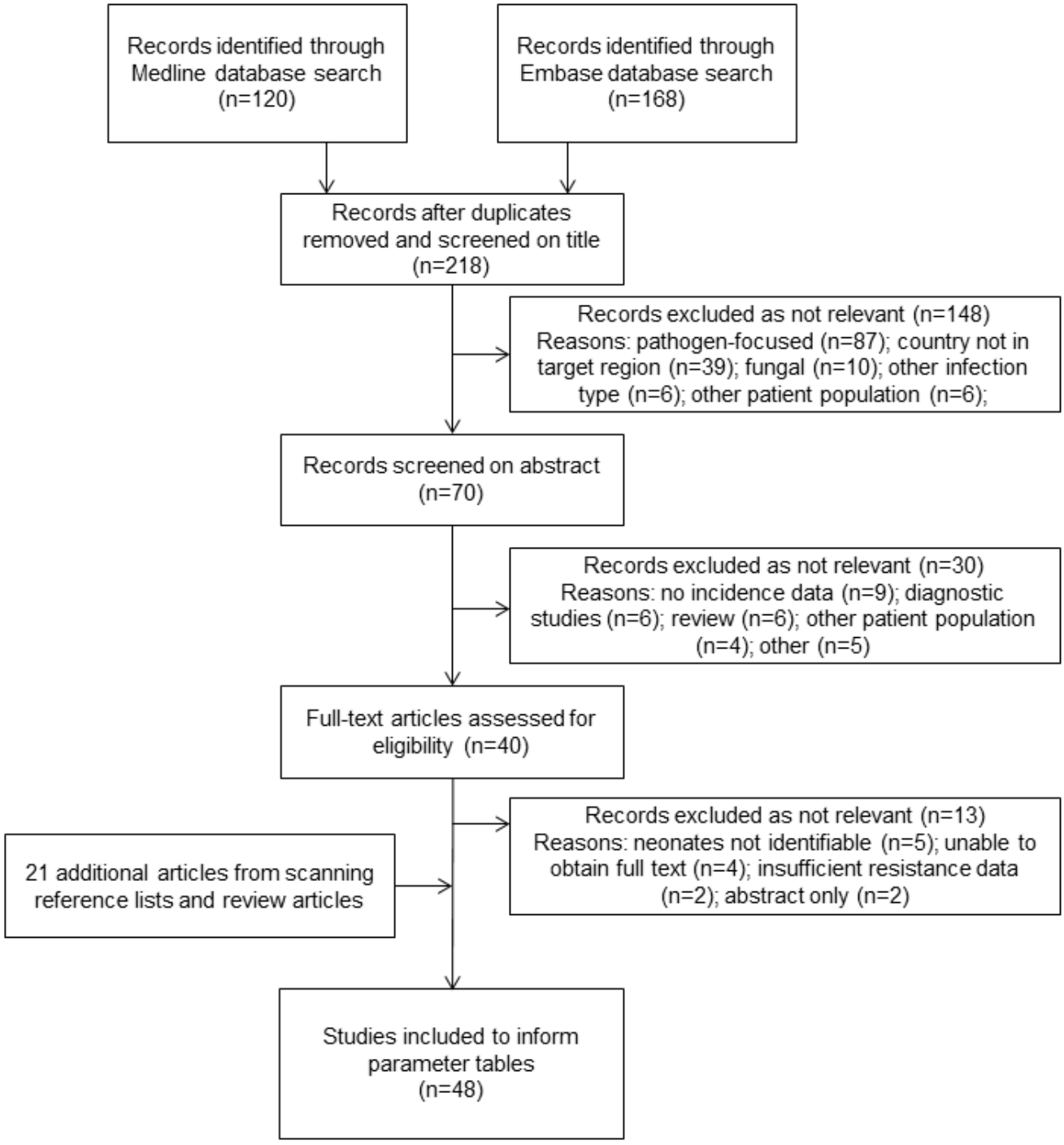
1. Identify the total number of isolates contributing to the infection syndrome of interest for a given setting and period.
2. Select from 1. clinically relevant bacteria contributing to the infection syndrome and with data available to define model parameters.
3. Specify assumptions used for determining susceptibility to the regimen, including extrapolation from standard bug-drug susceptibility testing, definitions of intrinsic resistance and, when relevant, intrinsic susceptibility (corresponding to unusual resistance phenotypes)
4. For the bacteria specified in 2. identify the number of isolates contributed by each (to determine relative frequency = first circular node and branches) and the number of isolates tested for and susceptible to the regimen of interest (second circular node and branches).
5. Select appropriate informative priors for bacteria with intrinsic resistance or expected susceptibility as set out in 3.
6. Select non-informative priors for relative bacterial incidence and susceptibility with the exceptions as outlined in 5.
7. Use appropriate probability distributions to reflect uncertainty in the relative frequency of bacteria (multinomial, Dirichlet distribution) and susceptibility to the regimen (binomial, Beta distribution).
8. Model coverage by running a Monte Carlo simulation with n experiments sampling parameter values for relative bacterial frequency and regimen susceptibility from their specified distributions.
9. Combine estimates from n experiments to calculate coverage estimates with their 2.5% and 97% percentiles, corresponding to the 95% uncertainty or credible interval.
10. Repeat this process for each regimen of interest, noting that for comparisons within a given setting the bacteria included in the WISCA should stay the same (meaning that number of isolates contributed by each will be the same), but that the number tested and susceptible will vary by regimen.

eFigure 1. Illustration of Decision Tree for Estimating Coverage From Weighted Incidence Syndromic Combination Antibiograms for Three Antibiotic Regimens of Interest



ET: empiric therapy. Square node: clinical decision to treat; circular node: chance event (causal bacteria and their regimen susceptibility). The decision tree is shown for illustration only, and dashed lines indicate where the decision tree has been left incomplete. All branches are included in the WISCA calculations to estimate coverage.

eFigure 2. Flow Chart: Systematic Review of the Literature



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eTable 1. Description of Included Publications

Publication year, First author, Journal			Country, City/Town		N hospitals, type		Observation period start and end*		Infections surveyed
2014	Adhikari	Nepal Medical College Journal	Nepal	Thapathali	1	Maternity	01Aug11	31Mar12	Sepsis with positive BC
	Anderson	Journal of Tropical Pediatrics	Laos	Vientiane	1	U/T	01Feb00	01Sep11	Sepsis with positive BC
	Javali	Journal of Evidence Based Medicine & Healthcare	India	Raichur	1	NT/D	01Jun13	30Jul13	LONS with positive BC
	Khanal	Journal of Nepal Paediatric Society	Nepal	Kathmandu	1	Maternity	01Dec10	31Mar11	Sepsis with positive BC
	Mehta	International Journal of Biomedical And Advance Research	India	Bhanpur	1	U/T	01Jul12	31Dec13	Sepsis with positive BC
	Mustafa	Journal of Medical and Allied Sciences	India	Hyderabad	1	U/T	Unknown (1 year)		Sepsis with positive BC
	Nayak	Archives of Medicine and Health Sciences	India	Deralakatte	1	U/T	01Jun11	31May12	Sepsis with positive BC
	Patel	The Indian Journal of Pediatrics	India	Karamsad	1	NT/D	01Nov07	31Oct11	Bacteraemia
	Tudu	Journal of Evoluation of Medical and Dental Science	India	Kenduadihi	1	U/T	01Jun13	31Aug13	Sepsis with positive BC
	Venkatnarayan	Journal of Nepal Paediatric Society	India	Pune	1	U/T	01Jan11	01Jul12	Sepsis with positive BC
2015	Agarwal	Journal of International Medicine and Dentistry	India	Mangalore	1	U/T	01Feb14	31Jul14	Sepsis with positive BC
	Ambade	Journal of Medical Science and Clinical Research	India	Dhule	1	U/T	01Aug12	31Jul14	Sepsis with positive BC
	Chapagain	Journal of the Nepalese Health Research Council	Nepal	Kathmandu	1	Paediatric	01Aug14	01Aug15	Sepsis with positive BC
	Dhanalakshmi	Journal of Clinical and Diagnostic Research	India	Madurai	1	U/T	01Dec13	30Sep2014	Sepsis with positive BC
	Gupta	International Journal of Pharma and Bio Sciences	India	Rohtak	1	NT/D	Unknown (1year)		Bacteraemia
	Kamble	International Journal of Current	India	Ambajogai	1	U/T	01Jun08	21Dec10	Sepsis with positive BC

		Microbiology and Applied Sciences							
	Madavi	International Journal of Current Research and Review	India	Nagpur	1	U/T	01Aug11	01Sep13	Sepsis with positive BC
	Marwah	Indian Pediatrics	India	Chandigarh	1	U/T	01Jan08	31Dec12	Bacteraemia
	Muley	Journal of Global Infectious Diseases	India	Pune	1	NT/D	Unknown		Bacteraemia
	Ponugoti	Journal of Medical Science And Clinical Research	India	Nellore	1	U/T	Unknown (6 months)		Sepsis with positive BC
	Sarangi	International Journal of Advances in Medicine	India	Bhubaneswar	1	U/T	01Nov12	30Apr14	Sepsis with positive BC
	Ting	Journal of Microbiology, Immunology and Infection	Republic of (Taiwan)	Taipei	1	U/T	01Jan02	31Dec11	CA bacteraemia, limited to 0-7 day-olds
	Tran	Journal of Perinatology	Vietnam	Da Nang	1	Maternity/ Paediatric	01Nov10	31Oct11	Sepsis with positive BC
2016	Abu	Medical Journal of Malaysia	Malaysia	Baru Selayang	1	U/T	01Jan01	31Dec11	CA bacteraemia excluding EOS
	Amin	International Journal of Pharmaceutical Sciences and Research	India	Vadodara	1	U/T	01Apr13	30Sep13	Sepsis with positive BC
	DeNIS	Lancet Global Health	India	Delhi	3	U/T	18Jul11	28Feb14	Sepsis with positive BC
	Jiang	Internal Medicine	China	Missing	1	Maternity/ Paediatric	01Jan08	31Dec12	Sepsis with positive BC
	Lu	Journal of Pediatrics and Child Health	China	Chongqing	1	Paediatric	01Jan90	31Dec14	Sepsis with positive BC
	Mahmood	Pakistan Journal of Medical and Health Sciences	Pakistan	Faisalabad	1	U/T	01Jan13	01Jan15	Bacteraemia
	Pandita	International Journal of Contemporary Pediatrics	India	Dehradun	1	U/T	01Jan13	30Jun15	Sepsis with positive BC
	Singh	European Journal of Pharmaceutical and Medical Research	India	Raipur	1	U/T	01Jan13	31Dec13	Sepsis with positive BC
	Thakur	Indian Journal of Medical Microbiology	India	Tanda	1	NT/D	01Apr12	31Mar13	Sepsis with positive BC

	Ullah	Archives of Iranian Medicine	Pakistan	Peshawar	1	U/T	01Jan12	31Dec15	Bacteraemia
2017	Dalal	International Journal of Research in Medical Sciences	India	Rohtak	1	U/T	01Jul10	30Sep13	Sepsis with positive BC
	Dong	BMC Pediatrics	China	Bengbu	1	NT/D	01Jan10	31Aug14	Sepsis with positive BC
	Ingale	International Journal of Contemporary Pediatrics	India	Pune	1	U/T	Unknown (1 year)		Sepsis with positive BC
	Kanodia	Journal of College of Medical Sciences – Nepal	Nepal	Dharan	1	U/T	01Jan14	31Dec14	Sepsis with positive BC
	Panigrahi	Journal of Perinatology	India	Multiple in area of Odisha	2	NT/D	01Apr02	31Mar05	Invasive bacterial infections
	Pavan	Journal of Family Medicine and Primary Care	India	Dindigul	1	NT/D	01Oct13	30Sep15	Sepsis with positive BC
	Roy	Journal of Postgraduate Medicine	India	New Delhi	1	U/T	01Jan11	31Dec14	Bacteraemia
	Sari	Asian Journal of Pharmaceutical and Clinical Research	Indonesia	Yogyakarta	1	U/T	01Jan14	31Dec15	Bacteraemia
2018	Dhaneria	Diseases	India	Ujjain	1	U/T	01Jun12	31Jan14	Nosocomial bacteraemia, including EONS and LONS
	Fox-Lewis	Emerging Infectious Diseases	Cambodia	Siem Reap	1	Paediatric	01Jan07	31Dec16	Invasive bacterial infections
	Jajoo	PloS One	India	Delhi	1	NT/D	01Jul11	31Jan15	Sepsis with positive BC
	Pokhrel	BMC Pediatrics	Nepal	Lalitpur	1	U/T	15Apr14	15Apr17	Sepsis with positive BC
	Wang	Journal of Tropical Pediatrics	China	Chongqing, Henan	2	U/T	01Jan03	31Dec13	Nosocomial bacteraemia
	Yadav	BMC Research Notes	Nepal	Kathmandu	1	Paediatric	01Apr15	30Sep15	Sepsis with positive BC
2019	Li	Medicine	China	Shanghai	1	U/T	01Jan13	31Aug17	Sepsis with positive BC

U/T hospital: University/Tertiary hospital; NT/D hospital: Non-teaching/District hospital
*Start year of data collection for all studies with exception of Lu *et al*, 2016 in the 2000s, end year for all studies in the 2000s.

eTable 2. Information on Sample Processing Provided in Included Publications

Publication year, First author					
		Species identification	Antibiotic susceptibility testing method	Interpretive guidelines	Other comments
2014	Adhikari	Yes (Standard bacteriological techniques)	Yes (Disc diffusion)	Yes (CLSI M2-A9, 2006)	
	Anderson	No details provided (standard blood culture)	Yes (Disc diffusion)	Yes (CLSI M100-S20, 2010)	ESBL detection by cefpodoxime screening with confirmation by CLSI-recommended disc diffusion methods
	Javali	No details provided (standard blood culture)	Yes (Disc diffusion)	Yes (CLSI, 2008)	
	Khanal	Yes (Standard bacteriological techniques)	Yes (Disc diffusion)	Yes (CLSI M100-S16, 2007)	
	Methta	Yes (Standard bacteriological techniques)	Yes (Disc diffusion)	Yes (CLSI M100-S18, 2010)	Meropenem SIR based on imipenem susceptibility testing
	Mustafa	Yes (Standard bacteriological techniques)	Yes (Disc diffusion)	Yes (CLSI, not specified)	ESBL confirmation by phenotypic confirmatory test (ceftazidime/cefotaxime +/- clavulanate disc diffusion)
	Nayak	Yes (Standard bacteriological techniques)	Yes (Disc diffusion)	Yes (CLSI, not specified)	Use of control strains Meropenem SIR based on imipenem susceptibility testing
	Patel	Yes (BacT/ALERT, API)	Yes (automated API)	No details provided	
	Tudu	Yes (BacT/ALERT, API)	Yes (Disc diffusion)	Yes (CLSI, no specified)	Gentamicin SIR based on amikacin susceptibility testing, meropenem SIR based on imipenem susceptibility testing
	Venkatnarayan	No details provided	No details provided	No details provided	Gentamicin SIR based on amikacin susceptibility testing
2015	Agarwal	Yes (BacT/ALERT, Vitek II)	Yes (Disc diffusion)	Yes (CLSI M02-A11, 2012)	ESBL confirmed using CLSI-recommended disc diffusion methods,

					MRSA detection using cefoxitin disc
	Ambade	Yes (Standard bacteriological techniques)	Yes (Disc diffusion)	Yes (CLSI, not specified)	
	Chapagain	No details provided	No details provided	No details provided	Gentamicin SIR based on amikacin susceptibility testing
	Dhanalakshmi	Yes (Standard bacteriological techniques)	Yes (Disc diffusion)	No details provided	
	Gupta	Yes (Standard bacteriological techniques)	Yes (Disc diffusion)	Yes (CLSI M100-S24, 2014)	Use of control strains
	Kamble	Yes (Standard bacteriological techniques)	Yes (Disc diffusion)	Yes (CLSI, not specified)	Extensive detail on testing for ESBL and Metallo-beta-lactamases provided Meropenem SIR based on imipenem susceptibility testing
	Madavi	No details provided	No details provided	No details provided	Meropenem SIR based on imipenem susceptibility testing
	Marwah	Yes (Standard bacteriological techniques)	No details provided (standard methods)	Yes (CLSI, incorrect referencing)	Meropenem SIR based on imipenem susceptibility testing
	Muley	Yes (standard bacteriological techniques)	Yes (Disc diffusion)	Yes (CLSI M100-S21, 2011)	
	Ponugoti	Yes (standard bacteriological techniques)	Yes (Disc diffusion)	Yes (CLSI M2A7 Vol.20 No1 & 2, 2000)	Meropenem SIR based on imipenem susceptibility testing
	Sarangi	Yes (BacT/ALERT)	Yes (automated API)	No details provided	
	Ting	No details provided	No details provided	Yes (CLSI, not specified)	
	Tran	Yes (Standard bacteriological techniques)	Yes (Disc diffusion)	No details provided	Meropenem SIR based on imipenem susceptibility testing
2016	Abu	Yes (API/Vitek)	Yes (Disc diffusion)	Yes (CLSI M100-S24)	ESBL confirmation by phenotypic confirmatory test (ceftazidime/cefotaxime +/- clavulanate disc diffusion)
	Amin	Yes (Standard bacteriological techniques)	Yes (Disc diffusion)	Yes (CLSI, not specified)	Microbiology laboratory accredited by National Accreditation Board for

					Testing and Calibration Laboratory in India
	DeNIS	Yes (Standard bacteriological techniques)	No details provided	Yes (CLSI M100-S21 & M100-S22 & M100-S23, 2011-2013)	Flowchart of sample handling provided in web-extra material
	Jiang	Yes (BacT/ALERT, API/Vitek)	Yes (Disc diffusion or Etests)	Yes (CLSI, not specified)	
	Lu	No details provided	No details provided	No details provided	Results recorded based on routine laboratory testing Meropenem SIR based on imipenem susceptibility testing
	Mahmood	No details provided	No details provided	No details provided	Standard procedures for sample processing and interpretation
	Pandita	Yes (Bactec/API)	Yes (Disc diffusion)	Yes (CLSI M100-S21, 2011)	Meropenem SIR based on imipenem susceptibility testing
	Singh	Yes (Standard bacteriological techniques)	Yes (Disc diffusion)	Yes (CLSI M100-S18, 2008)	Gentamicin SIR based on amikacin susceptibility testing
	Thakur	Yes (Standard bacteriological techniques)	Yes (Disc diffusion)	Yes (CLSI M100-S21, 2011)	Use of control strains, MRSA screening using cefoxitin disc, ESBL screening using ceftazidime disc, confirmation of ESBL by double disc synergy test Meropenem SIR based on imipenem susceptibility testing
	Ullah	Yes (Standard bacteriological techniques)	Yes (Disc diffusion)	Yes (CLSI, not specified)	Meropenem SIR based on imipenem susceptibility testing
2017	Dalal	No details provided (standard blood culture)	Yes (Disc diffusion)	No details provided	Meropenem SIR based on “carbapenem” susceptibility testing
	Dong	Yes (BacT/ALERT)	Yes (Disc diffusion)	No details provided	Additional information on species identification

					and susceptibility testing provided in methods
	Ingale	Yes (Bactec/API)	Yes (Disc diffusion)	Yes (CLSI M100-S23, 2013)	Extensive detail on microbiological sample handling provided
	Kanodia	No details provided	Yes (Disc diffusion)	No details provided	
	Panigrahi	Yes (Bactec/API)	No details provided	Yes (CLSI M23-A2, 2001)	Extensive detail on microbiological sample handling provided Meropenem SIR based on imipenem susceptibility testing
	Pavan	Yes (Bactec/API)	Yes (automated API)	No details provided	
	Roy	Yes (Standard bacteriological techniques)	Yes (Disc diffusion)	Yes (CLSI M100-S19, 2009)	Extensive detail on microbiological sample handling provided; ESBL confirmation by phenotypic confirmatory test (ceftazidime/cefotaxime +/- clavulanate disc diffusion); Use of control strains; MRSA screening using oxacillin disc Gentamicin SIR based on amikacin susceptibility testing
	Sari	Yes (Vitek)	Yes (Disc diffusion)	No details provided	
2018	Dhaneria	Yes (Standard bacteriological techniques)	Yes (Disc diffusion, confirmation using Vitek 2)	Yes (CLSI M100-S21, 2011)	Extensive detail on microbiological sample handling provided Meropenem SIR based on imipenem susceptibility testing
	Fox-Lewis	Yes (Standard bacteriological techniques)	Yes (Disc diffusion or Etests)	Yes (CLSI, 2012)	Meropenem SIR based on imipenem susceptibility testing
	Jajoo	Yes (Bactec/Vitek)	No details provided	Yes (CLSI M100-S21 & M100-S22 & M100-S23, 2011-2013)	Aminoglycosides and carbapenems grouped in susceptibility reporting
	Pokhrel	Yes (Bactec)	Yes (Disc diffusion)	Yes (CLSI M100-S24, 2014)	

	Wang	Yes (Vitek/API)	Yes (Disc diffusion)	Yes (CLSI, 2015)	Use of control strains, ESBL screening using ceftazidime disc, confirmation of ESBL by combination discs Meropenem SIR based on imipenem susceptibility testing
	Yadav	Yes (Standard bacteriological techniques)	Yes (Disc diffusion)	Yes (CLSI M100-S23, 2014)	Use of control strains
2019	Li	No details provided	Yes (Disc diffusion)	Yes (CLSI, not specified)	

CLSI: Clinical and Laboratory Standards Institute; ESBL: extended-spectrum beta-lactamases; MRSA: methicillin-resistant *Staphylococcus aureus*

eTable 3. Relative Incidence of Bacteria in Included Studies

Publication year, First author		Total bacterial isolates	Bacteria reported in studies (% incidence within study shown)																						% accounted for by 7 target species	% accounted for by 7 target species excluding CONS
			Acinetobacter spp.[1]	*Burkholderia* spp.	*Citrobacter* spp.	CONS	*E. coli*	*Enterobacter* spp.[2]	*Enterococcus* spp.	*H. influenzae*	*Klebsiella* spp.[3]	*L. monocytogenes*	*Morganella* spp.	*N. meningitidis*	*Proteus* spp.	*Pseudomonas* spp.[4]	*S. agalactiae*	*S. aureus*	*S. pneumoniae*	*S. pyogenes*	*Salmonella* spp.	*Serratia* spp.[5]	Other streptococci	Others		
2014	Adhikari	94				57	27				4					1		11							43	100
	Anderson*	75	3	3			11	5	4		12	1			1	1	3	49	3	3	1				85	85
	Javali	32	9			34	13				19							9					9	6	50	77
	Khanal	61				77	10		4		2							7							23	100
	Mehta	169	5		2	9	4		5		14					5		56							89	98
	Mustafa	62				11	23				35					7		24							89	100
	Nayak	67	20		3	5	4		3		31					4		20							82	96
	Patel*	249	5			12	10	10	2		47					6		1						6	81	93
	Tudu	22				5	9		18		9	5						55							91	95
	Venkatnarayan	15				13	20									13	7	47							80	92
2015	Agarwal*	34	15			9	24	3			27							21							90	100
	Ambade	119	6			10	14				35					13		22							90	100
	Chapagain	30	7			7		3					3					80							90	97
	Dhanalakshmi	41				10	10				68				5	7									85	94
	Gupta	325	12		5	13	8	2	8		13					20		20							83	94
	Kamble	71	14		1	17	7	1	6		23					21		7	1						79	98
	Madavi	103	19		1	16	6	1	7		22					17		5	<1		1			5	77	92
	Marwah	167	15				7				15							47						16	84	84
	Muley	48	10			6	17				35					8		23							93	100
	Ponugoti	188	2		3	15	22	19	1		25					2		12							83	97
	Sarangi	74	3	5		62	11	8										8			3				30	79
	Ting*	36					31				3	8					42							17	34	34
	Tran	75	23			31	3	8			24					5		5					1		68	99
2016	Abu*	29					21			3	3					3	21	35		3			7	3	62	63
	Amin	101	23			4	12		13		28					8		13							97	100
	DeNIS	998	22			15	14	4	6		17					7	1	12						1	82	98
	Jiang*	131	1	1		43	19	6	5		13	3					1	6					1	1	50	88
	Lu*	929	3			26	14	3	7		12	2				4		6					5	18	49	66

	Mahmood	341					48		<1		17				9			26	<1						91	91
	Pandita	124	6		6	26	11	6	2		27					3		8					1	4	63	85
	Singh	141				5	27		4		50					8		7							96	100
	Thakur*	188	1		4	19	5	5			10					15	2	40							76	93
	Ullah	1534				2	53				7				6	13		20			<1				93	94
2017	Dalal	356	15			4	12	1	2		4					47		12							93	100
	Dong*	93				73	6	2	1		11	1				1		2					1	1	23	88
	Ingale	48	13			25	2	6	10		29					13		2							75	100
	Kanodia	327	14		1	2	3	3	4		1					6		62					3		93	96
	Panigrahi*	56					14		2		52							20						12	88	88
	Pavan	28					11				21					4		36					4	24	72	72
	Roy*	2112	21			21	8		5		8							25						12	67	85
	Sari	225	9	9		28		9			22					14						9			54	75
2018	Dhaneria*	46				17	11				24				9	13		21						5	69	83
	Fox-Lewis*	185	9	2			14	10		1	32			1		3		18	1	9	1				86	85
	Jajoo	300	15	4	1	14	11	8	5	<1	18		<1		1	1	1	6	1	1	<1	<1	<1	12	64	75
	Pokhrel*	69	12			20	4	19			33					3		2				4	2	2	73	90
	Wang	571				39	18	3			17							5	2					16	43	70
	Yadav	59	12		2	10	7	10			15					7		36			2				87	96
2019	Li*	339	<1			44	10	1	6		9	<1				5	6	5				1	3	10	36	64

**a priori* exclusion of contaminants with or without definitions for exclusion process provided
[1]includes *A. baumannii, A. lwoffi*
[2]includes *E. cloacae*
[3]includes *K. pneumoniae, K. ornithinolytica, K. oxytoca, K. ozaenae*
[4]includes *P. aeruginosa*
[5]includes *S. marcescens*, *S. rubidaea*

7.1 Feasibility survey data coverage estimates

Additional data not included in the paper were analysed alongside those identified from a systematic review of the literature. Coverage based on the feasibility data was estimated applying the same methods as presented in the accepted manuscript for data from the literature.

In total, 21 centres in five Asian countries (three Bangladesh, one Cambodia, six China, seven India and four Thailand) contributed data from the feasibility survey to this analysis. From these, 1066 isolates relevant for regimen coverage estimation were reported with India and China contributing the greatest number, 640 and 301 isolates, respectively (Table 4).

Table d: Parameter table – feasibility survey relative incidence data

	Bangladesh	Cambodia	China	India	Thailand
	N (% of those contributing to WISCA)*				
E. coli	2 (3%)	4 (36%)	64 (21%)	75 (12%)	10 (18%)
Klebsiella spp.	32 (54%)	2 (18%)	49 (16%)	191 (30%)	4 (7%)
Enterobacter spp.	1 (2%)	1 (9%)	34 (11%)	35 (6%)	12 (22%)
Acinetobacter spp.	18 (31%)	2 (18%)	35 (12%)	86 (13%)	12 (22%)
Pseudomonas spp.	5 (9%)	0	5 (2%)	23 (4%)	3 (6%)
S. aureus	1 (2%)	2 (18%)	33 (11%)	158 (25%)	8 (15%)
Enterococcus spp.	0	0	51 (17%)	53 (8%)	1 (2%)
GAS	0	0	15 (5%)	2 (<1%)	2 (4%)
GBS	0	0	15 (5%)	17 (3%)	3 (6%)
	N (% of total reported during study period)				
Total contributing to WISCA	59 (77%)	11 (26%)	301 (31%)	640 (79%)	55 (31%)
Other (not contributing to WISCA)	18 (23%)	32 (74%)	671 (69%)	172 (21%)	123 (69%)

* Percentages may not add to 100% due to rounding.

Among these, information on susceptibility to incorporate into coverage estimation was often available for a limited proportion and as few as 10 isolates for Cambodia (Tables 5-7).

For tables 5-7 the following apply: N indicates the total number of reported isolates for each bacterial species specifically requested as part of the feasibility survey reporting; T indicates the number of isolates with susceptibility testing available for the regimen of interest. This includes susceptibility testing for the antibiotics in the regimen but also any susceptibility testing results that support infererences about resistance or susceptibility to the regimen based on standard algorithms (see accepted manuscript for detailed description) ; S indicates the number of isolates identified as susceptible on testing; *indicates that susceptibility is assumed and not based on susceptibility testing; †indicates that resistance is assumed due to intrinsic resistance and this is not based on susceptibility testing.

Table e: Parameter table - feasibility survey susceptibility testing and resistance data for aminopenicillin plus gentamicin

AMP/GEN	Bangladesh			Cambodia			China			India			Thailand		
	N	T	S	N	T	S	N	T	S	N	T	S	N	T	S
E. coli	2	2	2	4	4	0	64	50	31	75	74	44	10	9	8
Klebsiella spp.	32	32	2	2	2	2	49	39	31	191	190	102	4	3	3
Enterobacter spp.	1	1	0	1	1	1	34	25	17	35	35	17	12	2	2
Acinetobacter spp.	18	18	0	2	2	2	35	35	33	86	85	52	12	6	0
Pseudomonas spp.	5	5	0	0			5	5	5	23	23	19	3	3	2
S. aureus	1	0		2	1	1	33	26	8	158	133	47	8	7	7
Enterococcus spp.	0			0			51	24	16	53	13	4	1	1	1
GAS	0			0			15	15*	15*	2	2*	2*	2	2*	2*
GBS	0			0			15	15*	15*	17	17*	17*	3	3*	3*

Table f Parameter table - feasibility survey susceptibility testing and resistance data for ceftriaxone or cefotaxime

TGC	Bangladesh			Cambodia			China			India			Thailand		
	N	T	S	N	T	S	N	T	S	N	T	S	N	T	S
E. coli	2	2	1	4	4	0	64	50	29	75	71	14	10	9	9
Klebsiella spp.	32	32	1	2	2	1	49	37	4	191	141	28	4	4	2
Enterobacter spp.	1	1	0	1	1	0	34	25	12	35	35	19	12	12	8
Acinetobacter spp.	18	18†	0†	2	2†	0†	35	35†	0†	86	86†	0†	12	12†	0†
Pseudomonas spp.	5	5†	0†	0			5	5†	0†	23	23†	0†	3	3†	0†
S. aureus	1	0		2	1	1	33	26	8	158	133	47	8	7	7
Enterococcus spp.	0			0			51	51†	0†	53	53†	0†	1	1†	0†
GAS	0			0			15	15*	15*	2	2*	2*	2	2*	2*
GBS	0			0			15	15*	15*	17	17*	17*	3	3*	3*

Table g: Parameter table - feasibility survey susceptibility testing and resistance data for meropenem

MEM	Bangladesh			Cambodia			China			India			Thailand		
	N	T	S	N	T	S	N	T	S	N	T	S	N	T	S
E. coli	2	2	2	4	4	4	64	63	63	75	73	67	10	10	10
Klebsiella spp.	32	32	5	2	2	2	49	39	32	191	190	154	4	4	4
Enterobacter spp.	1	1	1	1	1	1	34	31	30	35	31	23	12	12	12
Acinetobacter spp.	18	18	2	2	2	2	35	33	32	86	85	34	12	11	5
Pseudomonas spp.	5	5	2	0			5	5	4	23	21	20	3	3	3
S. aureus	1	0		2	1	1	33	26	8	158	133	47	8	7	7
Enterococcus spp.	0			0			51	0		53	0		1	0	
GAS	0			0			15	15*	15*	2	2*	2*	2	2*	2*
GBS	0			0			15	15*	15*	17	17*	17*	3	3*	3*

The coverage estimates are shown in Table 8. Similar to data based on the literature review presented in the manuscript above, coverage was consistently lowest for third-generation cephalosporin monotherapy.

Table h: Coverage estimates for three regimens and Asian countries represented in the NeoAMR feasibility survey

	Total n isolates	Aminopenicillin + gentamicin	Third-generation cephalosporin	Meropenem
		% regimen coverage (95% credible interval)		
Bangladesh	59	16·6 (9·2-26·1)	10·9 (5·0-18·8)	26·7 (17·0-37·0)
Cambodia	11	53·9 (34·5-72·7)	35·2 (18·1-54·8)	74·5 (55·5-89·8)
China	301	70·0 (63·9-75·6)	33·4 (27·8-39·0)*	78·5 (68·8-87·7)
India	640	51·2 (46·8-55·4)	23·3 (20·1-26·7)*	63·2 (57·4-69·1)*
Thailand	55	66·7 (53·0-79·2)	55·7 (43·6-67·0)	80·1 (69·9-89·2)

Coverage estimates from the three countries represented in both datasets (Cambodia, China and India) were broadly comparable for both datasets with the largest difference observed for meropenem coverage in Cambodia (literature review 90.6%, feasibility survey 74.5%, difference: 16.1%). Differences might be expected due to a slightly different approach to inclusion of pathogens for coverage estimation in the two datasets, differences between contribution hospitals and case-mix, different timeframes, and the different method of data collection.

Of note, the feasibility data demonstrates the limitations for comparisons of regimen coverage due to small sample size. For Cambodia and Bangladesh, country-level estimates were not sufficiently precise to conclude that aminopenicillin/gentamicin and meropenem gave different levels of coverage. In both datasets, it was only when countries contributed at least 300 isolates that coverage estimates became sufficiently precise to reveal potentially clinically relevant differences between regimens.

8. Identifying drivers of prescribing of last-resort antibiotics in childhood sepsis

This chapter comprises a paper exploring the factors associated with the prescription of carbapenems, glycopeptides and linezolid, three last-resort antibiotics that may be used in childhood. ARPEC point prevalence survey data on 1281 patients with at least one antibiotic prescription for neonatal or paediatric sepsis were used (78, 79).

Considering hospital-level coverage estimates and the potential need to base selection of empiric antibiotic regimens for childhood sepsis on pooled data, it may be important to account for patient and episode characteristics in regimen selection. This implies that antibiotic regimens should not be primarily selected on the basis of location (hospital) but based on patient and episode factors associated with specific bacteria and resistance patterns.

As insufficient data were available within the ARPEC antimicrobial resistance database for such an analysis, the research instead explored the influence of patient and episode factors on prescribing of three defined last-resort antibiotics using data from ARPEC point prevalence surveys. These data describe actual clinician behaviour. Highly variable antibiotic prescribing patterns in hospitalised children across different geographical locations were noted and have since been confirmed in other datasets, including for childhood sepsis (78-80). The comparison of figures on prescribing derived from such global data would be improved if differences in the case-mix of patients could be taken into account.

One approach to account for differences in case-mix is to use standard statistical methods to identify factors associated with exposure. This approach may result in complex models that can be difficult to interpret with limited direct applicability to clinical practice. Another method is to apply a stratification system and examine practice within groups of similar patients. An example of this method from another area of medical practice is the Robson classification, which stratifies pregnant women according to simple and widely available clinical characteristics that influence their a priori risk of having a Caesarean delivery (81-83).

Maternity units can then identify groups of women with unusually high Caesarean section rates, highlighting areas for specific local quality improvement interventions (84, 85).

In this research, a risk-adjustment model was developed and used to investigate the relationship between the exposure to any of the three antibiotics and key patient and infection episode characteristics. The results of this multivariable logistic regression model were then used to propose a simple classification system. The patient and episode characteristics of interest were patient age, type of department where the patient was at the time of blood culture, presence of underlying chronic comorbidities, community or hospital acquisition of infection and prescribing of empiric or targeted treatment. All variables were strongly associated with exposure to last-resort antibiotics. For the classification, the same variables were considered to define the following six mutually exclusive and comprehensive groups based on their likelihood of receipt of last-resort antibiotics:

1) Newborns with early sepsis (infants ≤3 days of age)
2) Community-aquired sepsis in otherwise healthy infants > 3 days of age and children
3) Community-aquired sepsis in the same age group as 2) but in patients with underlying chronic comorbidities
4) Empiric treatment of hospital-aquired sepsis outside of PICU (any age)
5) Targeted treatment of hospital-acquired sepsis outside of PICU (any age)
6) Hospital-acquired sepsis treated in PICU (any age)

Exposure to last-resort antibiotics in the dataset was high. The risk-adjustment model and the classification model demonstrated comparable good discrimination and calibration and reduced regional variation in exposure to last-resort antibiotics among children with sepsis, improving comparability.

RESEARCH PAPER COVER SHEET

SECTION A – Student Details

Student ID Number	237152	**Title**	Dr
First Name(s)	Julia Anna		
Surname/Family Name	Bielicki		
Thesis Title	Estimating coverage of empiric treatment regimens for childhood bloodstream infection based on routine microbiological data		
Primary Supervisor	Prof. David Cromwell		

If the Research Paper has previously been published please complete Section B, if not please move to Section C.

SECTION B – Paper already published

Where was the work published?	Plos One		
When was the work published?	6 July 2018		
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PLOS ONE

RESEARCH ARTICLE

Using risk adjustment to improve the interpretation of global inpatient pediatric antibiotic prescribing

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Abstract

Objectives

Assessment of regional pediatric last-resort antibiotic utilization patterns is hampered by potential confounding from population differences. We developed a risk-adjustment model from readily available, internationally used survey data and a simple patient classification to aid such comparisons.

Design

We investigated the association between pediatric conserve antibiotic (pCA) exposure and patient / treatment characteristics derived from global point prevalence surveys of antibiotic prescribing, and developed a risk-adjustment model using multivariable logistic regression. The performance of a simple patient classification of groups with different expected pCA exposure levels was compared to the risk model.

Setting

226 centers in 41 countries across 5 continents.

Participants

Neonatal and pediatric inpatient antibiotic prescriptions for sepsis/bloodstream infection for 1281 patients.

Results

Overall pCA exposure was high (35%), strongly associated with each variable (patient age, ward, underlying disease, community acquisition or nosocomial infection and empiric or targeted treatment), and all were included in the final risk-adjustment model. The model demonstrated good discrimination (c-statistic = 0.83) and calibration (p = 0.38). The simple

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Competing interests: JAB's husband is senior corporate counsel at Novartis International AG, Basel, Switzerland, and holds Novartis stock and stock options. MS chairs the UK Department of Health Expert Advisory Committee on Antimicrobial Resistance and Healthcare Associated Infection (ARHAI). All other authors declare no competing interest. This does not alter our adherence to PLOS ONE policies on sharing data and materials.

classification model demonstrated similar discrimination and calibration to the risk model. The crude regional pCA exposure rates ranged from 10.3% (Africa) to 67.4% (Latin America). Risk adjustment substantially reduced the regional variation, the adjusted rates ranging from 17.1% (Africa) to 42.8% (Latin America).

Conclusions

Greater comparability of pCA exposure rates can be achieved by using a few easily collected variables to produce risk-adjusted rates.

Introduction

Antibiotics are among the most commonly used medications for hospitalized children [1]. On any day, 30% to 60% of children admitted to hospital around the world will receive at least one antibiotic, with many being prescribed multiple systemic antimicrobials [2,3].

Antimicrobial stewardship interventions can improve antibiotic use in this vulnerable population and are usually implemented at a high level of aggregation, for example at hospital level [4,5]. It is often desirable to compare the use of antibiotics, especially of last-resort agents, between hospitals or regions to identify outliers and therefore areas for intervention. However, merely comparing the overall volume of use or crude proportions for antibiotics of interest is unlikely to be useful because prescription patterns vary markedly, and this is partially due to differences in patient case-mix [6–11].

In many areas of infection control, regression models are used to adjust metrics for differences in patient case-mix [12–14]. However, these risk-adjustment models can easily become complex, may be based on specific data that are not widely available and/or comparable, and can require the adoption of extensive, costly data collection processes.

Another method is to apply a stratification system and examine exposure within groups of similar patients. An example of this method from another area of medical practice is the Robson classification, which stratifies pregnant women according to simple and widely available clinical characteristics that influence their a priori risk of having a Caesarean delivery [15–17].

We examined whether a risk-adjustment model could be developed from readily available variables that would facilitate the fair comparison of statistics from point prevalence surveys (PPS) on the prescribing of antibiotics to children with sepsis/bloodstream infections. We focused on three "pediatric conserve antibiotics" (pCAs) for severe Gram-negative and Gram-positive neonatal and pediatric infections. These antibiotics are part of the newly defined World Health Organization Watch group of antibiotics. This group has been identified to have a higher resistance potential, and should only be used for specific indications or in infections caused by bacteria suspected or proven to be resistant to less broad-spectrum options [18]. We evaluated whether available variables enabled the creation of: (i) a risk-adjustment model to fairly compare the prevalence rates across world regions, and (ii) a simple stratification system that identified patient groups who would be expected to have similar exposures due to their characteristics.

Materials and methods

Data collection

The study used data collected as part of the Antibiotic Resistance and Prescribing in European Children (ARPEC) project global PPS [3]. PPS are simple, standardized tools used widely internationally to collect data on antimicrobial use to facilitate monitoring within centers and

countries [19]. Participating centers were asked to conduct a one-day cross-sectional survey of antimicrobial prescriptions for inpatients on neonatal and pediatric wards during three periods in 2011/2012 [2,3]. During each PPS all neonatal and pediatric wards in participating institutions had to be surveyed once within the defined auditing period. All patients present in the wards at 8:00 am, and at least since midnight on the day of the survey, were recorded. For each patient treated with at least one antimicrobial, detailed data on the prescription as well as about the patient were collected according to a standardized protocol.

The ARPEC PPS were conducted in 226 participating centers located in 41 countries, which were grouped into continental regions (Africa, Asia, Australia, Europe–East, Europe–North, Europe–South, Europe-West, Latin/South America and North America) according to the UN geoscheme classification [2,3].

The PPS methodology and data collection approaches have previously been described in detail [2,3]. During data collection no unique identifiers, such as hospital numbers or dates of birth, were recorded. As the PPS was therefore a completely anonymized audit of antimicrobial prescribing to inpatient neonates and children, formal ethical review was not a requirement. Individual participating centres were asked to ascertain any local requirements for ethical review. By entering data, centres confirmed that they had taken the required steps according to their local and national regulatory and legal requirements.

Study population and definition of patient and treatment characteristics

The study used the records of surveyed patients who were prescribed systemic antibiotics (J01) [20] for the most common indication of suspected or definitive sepsis/bloodstream infection [3], excluding febrile neutropenia and catheter-related bloodstream infection. A single key infection syndrome was selected as different factors may drive prescribing of antibiotics depending on the type of infection being treated. Relevant prescriptions were identified from the PPS information on "reason for prescription".

In terms of antibiotic use, we focused on carbapenems (J01DH), glycopeptides (J01XA) and linezolid (J01XX08). Prescribing of these antibiotics may reflect actual or feared infection caused by resistant organisms, such as extended-spectrum beta-lactamase producing Gram-negative bacteria or methicillin-resistant *Staphylococcus aureus*. The World Health Organization confirms these antibiotics, among others, as key targets for national antibiotic stewardship [18]. Our study is limited to the indicated groups and follows the same approach as a recent study evaluating the impact of antimicrobial stewardship on antibiotic prescribing in US children's hospital [21]. Exposure to pCAs was defined at the patient level, with a patient classified as exposed if one or more of the antibiotics listed above was prescribed.

At the patient level, the ARPEC dataset included information on a patient's age, whether they had any chronic conditions, and the type of ward the patient was on. Data were also collected on the type of prescription (empiric or targeted). Neither the microbiological results for individual patients nor hospital antibiograms were available. Finally, timing of prescription was available as having been issued >48 hours after hospitalization (hospital-acquired) or ≤48 hours after hospitalization (community-acquired). Any prescription for sepsis/bloodstream infection in the first three days of life was considered neonatal early onset sepsis. Wards were classified as either a neonatal intensive care unit (NICU, all care levels), pediatric intensive care unit (PICU) or other pediatric wards. Patients with any recorded underlying disease from a predefined list including surgical malformations, chronic neurological, gastrointestinal, endocrine, lung and renal disease as well as congenital heart disease, oncologic/hematologic diseases, genetic or metabolic disorders, rheumatological or autoimmune disease and chronic infections were labeled as having underlying disease (S1 File). Patients receiving any targeted

prescriptions for a sepsis/bloodstream infection (according to the ARPEC protocol based on pathogen identification and/or antimicrobial susceptibility testing) were defined as receiving targeted treatment, even when additional prescriptions were empiric. All other patients were labeled as receiving empiric treatment.

Statistical analysis

Logistic regression was used to assess the association between pCA exposure and the individual patient and treatment characteristics. Age was dichotomized into neonates aged 3 days or younger versus infants aged 4 days or older and children (reflecting clinical differences between early-onset and late-onset sepsis among neonates).

We then developed a risk model using multivariable logistic regression.

The model was developed by sequentially adding each available patient variable, starting with the variable that had the strongest univariate association and ending with the weakest. A Wald test was used to assess the contribution of an added variable to the model and a p value of 0.05 was used as the threshold for inclusion. Following this, interactions between included variables were explored. The performance of the model was assessed in terms of its calibration and discrimination. Calibration describes the level of agreement between the predicted and observed risks, and was evaluated using the Hosmer-Lemeshow test. Discrimination indicates the ability of a model to distinguish patients with a lower and higher risk of pCA prescription. We evaluated this by using the c-statistic (equivalent to the Area under the ROC curve).

The regression model was used to calculate risk-adjusted regional pCA exposure rates. These were derived using indirect standardization, which involved multiplying the ratio of observed/expected exposure rates by the mean exposure rate in the whole cohort [9]. Approximate 95% confidence intervals were derived for proportions and indirectly standardized rates using the Wilson Score and Byar's Method, respectively.

As a sensitivity analysis, we repeated the above process using a multilevel logistic model, which incorporated a random-intercept term for the subregions as well as the explanatory variables. This accounted for any lack of independence in the data due to patients being clustered within subregions.

Finally, a small number of mutually exclusive and comprehensive patient subgroups were defined on the basis that they described clinical situations in which we would expect a patient's chance of receiving pCA to be similar given the seriousness of the situation and the effectiveness of current antiobiotics. We used the same variables that were considered in the risk-model development process because they represented information that is easy to collect and can be standardized. Inspection of the variables identified six patient groups that were expected to be associated with different levels of exposure to pCA:

1) Neonatal early onset sepsis (infants $\leq$3 days of age): High reported coverage provided by narrow-spectrum regimens [22].
2) Community-acquired sepsis in otherwise healthy infants >3 days of age and children: Lower levels of colonization and infection by multidrug-resistant pathogens [23].
3) Community-acquired sepsis in infants >3 days of age and children with underlying disease: Colonization by multidrug-resistant pathogens possible with reported epidemiology similar to hospital-acquired bloodstream infection [23].
4) Empiric treatment of hospital-acquired sepsis in infants and children of any age outside of PICU: Colonization by multidrug resistant pathogens possible, but colonization pressure less than in intensive care [24].

5) Targeted treatment of hospital-acquired sepsis in infants and children of any age outside of PICU: May include patients having been discharged from intensive care to complete treatment after stabilization, therefore likely to partially reflect intensive care epidemiology [25].

6) Hospital-acquired sepsis in infants and children of any age in PICU: Colonization by multi-drug-resistant bacteria expected with high colonization pressure in intensive care [25].

We examined the ability of these subgroups to reduce the heterogeneity within the patient population using the measures of discrimination and calibration described above. All statistical analyses were carried out using Stata/IC 13.1®, Statacorp, USA.

Results

Description of cohort

The complete global ARPEC PPS cohort contained data on 11899 prescriptions on 6499 patients. Among these, there were 2668 prescriptions for sepsis, but limiting the cohort to patients with complete records led to the exclusion of a further 415 prescription records (Fig 1). The final dataset contained 2253 systemic antibiotic prescriptions for 1281 infants and children, representing 19% of a total of 11899 recorded prescriptions.

Overall pCA exposure

Of the 1281 included patients, 445 patients (34.7%; 159 children ≤30 days of age of which two were ≤3 days of age, 286 children >30 days of age) were exposed to pCAs. In total, 18.4% (235/1281) were receiving carbapenems, 25.4% (325/1281) glycopeptides and 1.2% (16/1281) linezolid. For each of the patient and treatment characteristics, the proportion of exposed patients varied across the levels of each variable by at least 10%, as shown in Table 1.

Multivariable logistic regression model for exposure to pCA

Each individual patient and treatment characteristic was found to be associated with antibiotic use, and improved the performance of the multivariable logistic model when added (Table 1). There was evidence of an interaction between the variables "ward" and "acquisition of infection" as well as between the variables "underlying disease" and "type of treatment". These separate variables were replaced by variables that captured the combination of categories. Table 2 shows the results of the model that takes into account these interactions. Overall, the following were associated with increased odds of pCA exposure: (1) presence of any underlying disease, (2) treatment in PICU; (3) receiving targeted treatment; (4) treatment for hospital-acquired infection. Being ≤3 days old was associated with lower odds of pCA exposure.

This final model demonstrated strong discrimination, with a c-statistic of 0.83. There was also evidence of good calibration (Hosmer-Lemeshow test, p = 0.38, see Fig 2 for calibration plot).

Multilevel random-intercept logistic model for exposure to pCA

The analysis using the multilevel model gave similar results to the main analysis. We found only modest variation in the random-intercepts of the subregions (variance = 0.21; SE(var) = 0.14) and the coefficients of the explanatory variables were similar to those estimated in the standard model. In addition, the Pearson correlation coefficient between the predicted risks for individuals from the two models was 0.97, with the predictions from the multilevel model producing to almost identical calibration and discrimination figures.

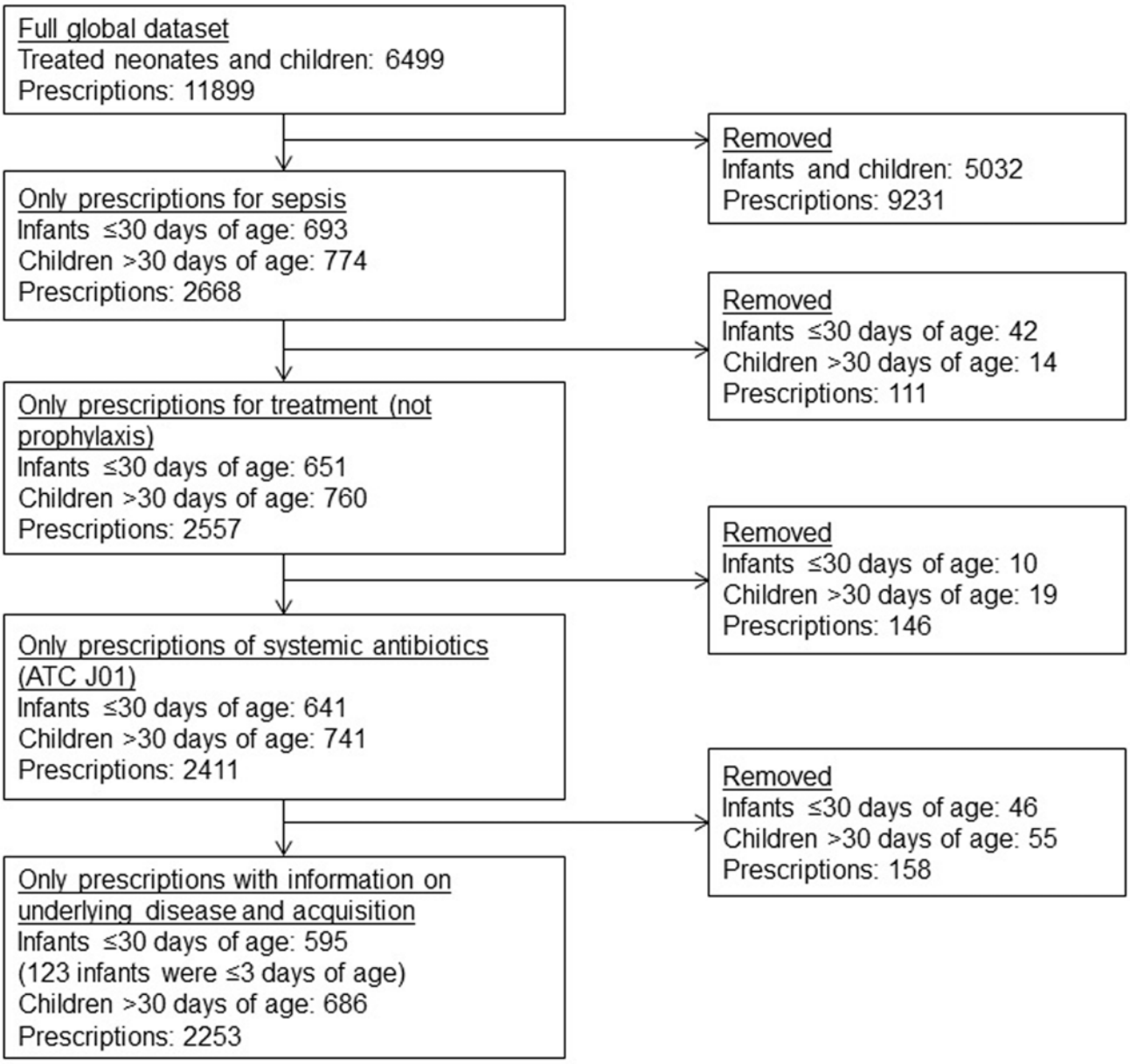

Fig 1. Flow chart of prescription and patient inclusion.

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Adjusted regional patterns of pCA exposure

Fig 3 demonstrates the impact of using the risk model to adjust for differences in patient characteristics on regional pCA exposure levels. Crude regional exposure rates ranged from 10.3% (Africa) to 67.4% (Latin America). After adjustment, there was substantially less variation between the regions, with the adjusted regional exposure rates ranging from 17.1% (Africa) to 42.8% (Latin America). The 95% confidence intervals around adjusted pCA exposure rates

Table 1. Association of key patient characteristics with exposure to pCA antibiotics (group comparisons using X^2 testing).

	Total patients with sepsis/BSI	% in group	pCA-exposed	% exposed	p-value
Age					
Neonate ≤3 days of age	123	9.6	2	1.6	p<0.001
Infant or child >3 days of age	1158	90.4	443	38.3	
Ward					
Pediatric ward	466	36.4	117	25.1	p<0.001
Neonatal intensive care	635	49.6	219	34.5	
Pediatric Intensive care	180	14.1	109	60.6	
Underlying disease					
Absent	311	24.3	32	10.3	p<0.001
Present	970	75.7	413	42.6	
Acquisition of infection					
Community	649	50.7	78	12.0	p<0.001
Hospital	632	49.3	367	58.0	
Type of treatment					
Empiric	980	76.5	285	29.1	p<0.001
Targeted	301	23.5	160	53.2	
Total	1281		445	34.7	

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indicate that, with the exception of Africa, regional estimates may not differ from the overall cohort mean pCA exposure level once key characteristics have been taken into account.

pCA exposure in predefined groups

Table 3 shows the characteristics of the six patient groups that were derived from clinical reasoning.

Table 4 shows the distribution of patient groups by region.

Overall, nearly 50% of children fell into groups 4 to 6, as they were being treated for hospital-acquired sepsis/bloodstream infection. In terms of the pCA exposure rates, levels were

Table 2. Logistic regression results showing adjusted odds ratios for exposure to pediatric reserve antibiotics (pCAs) with 95% confidence intervals.

Group	Adjusted OR	95%CI
Patients according to ward type and acquisition of infection		
Non-ICU / community-acquired	Ref	-
Non-ICU / hospital-acquired	5.0	3.0–8.3
NICU / community-acquired	0.6	0.3–1.1
NICU / hospital-acquired	5.7	3.7–8.8
PICU / community-acquired	4.2	2.2–8.1
PICU / hospital-acquired	12.7	7.3–22.2
Patients according to underlying disease and type of prescription		
No underlying disease / empiric	Ref	-
No underlying disease / targeted	4.3	1.8–10.0
Underlying disease / empiric	3.8	2.2–6.7
Underlying disease / targeted	7.1	3.9–13.0
Patients according to age		
Neonate ≤3 days of age	Ref	-
Neonate >3 days of age, infant or child	16.9	4.0–70.9

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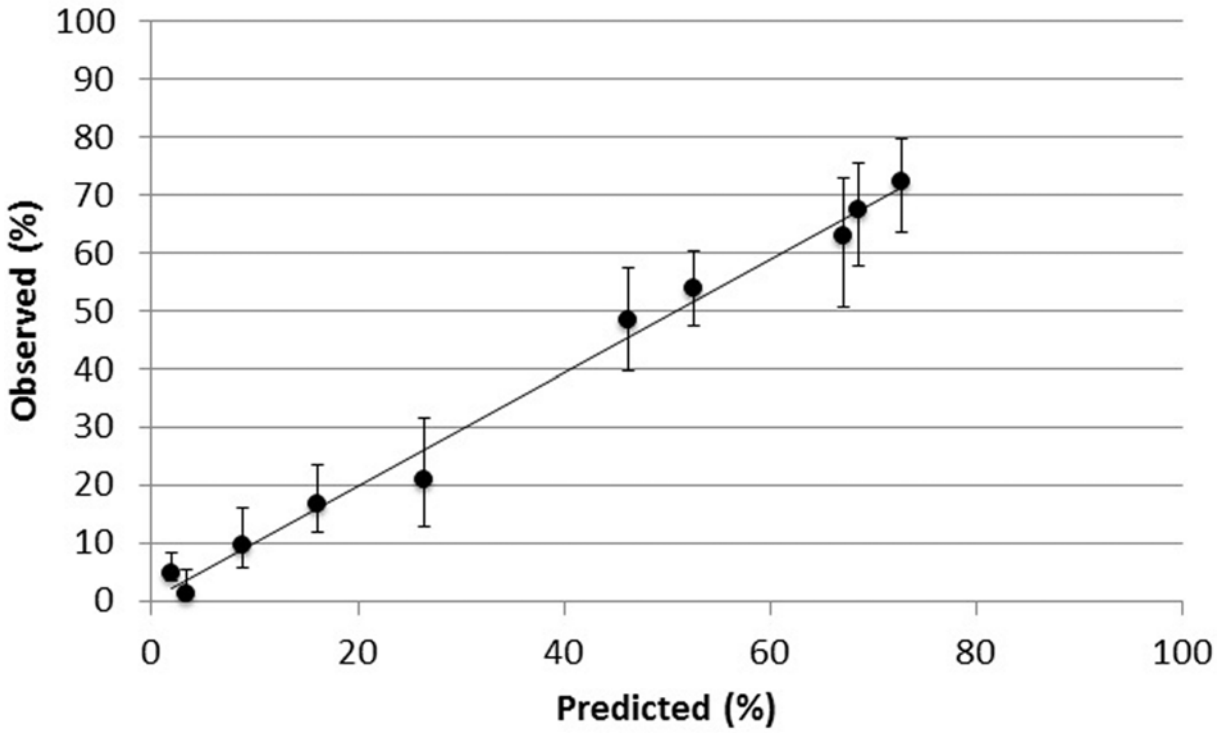

Fig 2. Calibration plot for logistic regression risk model of pCA exposure.

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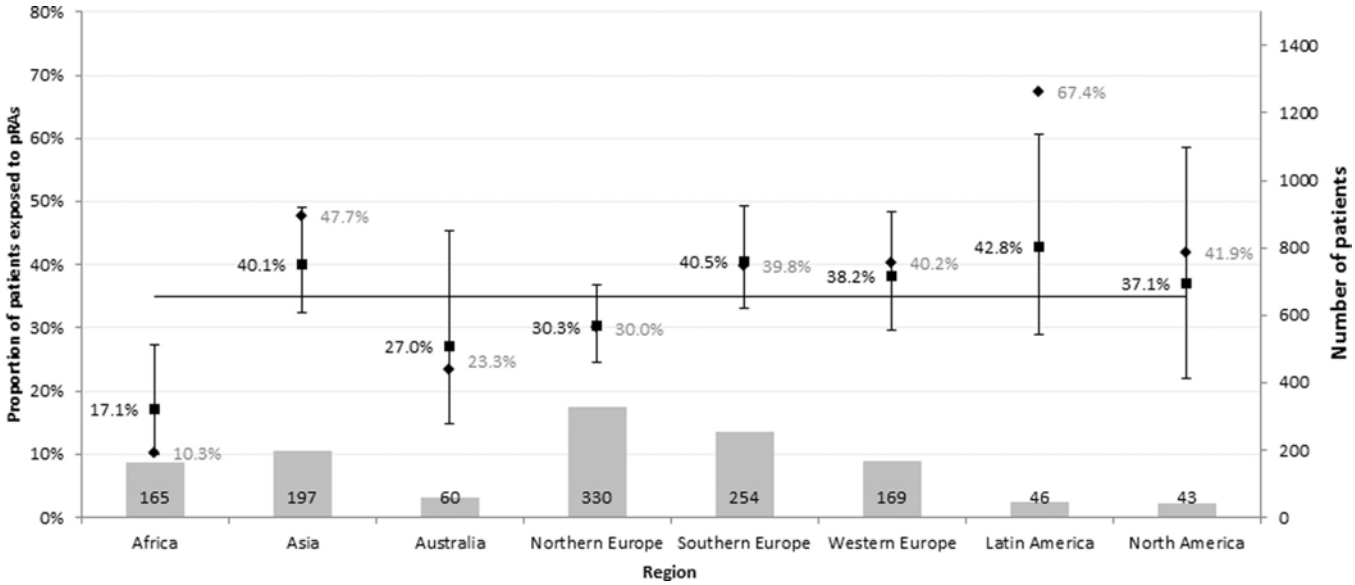

Fig 3. Crude and risk adjusted regional exposure rates for pediatric reserve antibiotics. Bars correspond to crude rates, squares to adjusted rates (shown with 95% confidence intervals). Data for Eastern Europe have been omitted due to low number of patients surveyed (n = 17) The horizontal line indicates the mean pCA exposure rate in the whole cohort. Patient numbers for each region are shown at the bottom of each bar.

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Table 3. Overall proportions of treated patients within predefined group and the expected rate of exposure to pediatric reserve antibiotics (pCAs).

	Patient group	Total patients (n)	% in group	Exposed to pCAs (n)	% Exposed	95% CI
1	Neonatal early onset sepsis	123	10%	2	1.6%	0.2 to 5.8
2	CA sepsis/BSI in otherwise healthy infants and children	251	20%	17	6.8%	4.0 to 10.6
3	CA sepsis/BSI in infants and children with underlying disease	295	23%	60	20.3%	15.9 to 25.3
4	Empiric treatment of HA sepsis/BSI outside of PICU	327	25%	162	49.5%	44.0 to 55.1
5	Targeted treatment of HA sepsis/BSI outside of PICU	173	13%	120	69.4%	61.9 to 76.1
6	HA sepsis/BSI on PICU	112	9%	84	75.0%	65.9 to 82.7
		1281		445	34.7%	

CA: community-acquired, HA: hospital-acquired, BSI: bloodstream infection, PICU: pediatric intensive care unit.

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lowest in neonates treated for early onset sepsis (1.6%) and highest in patients with hospital-acquired sepsis on PICU (75.0%). We assessed the performance of this simple classification by using a logistic regression model that included only these six predefined groups. The model had a similar level of performance as the full risk model, with good levels of discrimination (c-statistic = 0.81) and calibration (Hosmer-Lemeshow test, p = 0.813; Fig 4). The regional distribution of patients may explain very high crude pCA exposure levels in Latin America: Nearly 80% of patients in this region fell into groups 4 to 6 compared with maximally 50–60% in other regions. These patients would be expected to have higher pCA exposure rates than patients in groups 1 to 3.

Discussion

The data from global point prevalence surveys of inpatient neonatal and pediatric systemic antibiotic prescriptions for sepsis/bloodstream infection revealed large differences in the crude pCA prevalence rates across the regions. But, the interpretation of these differences is hampered by the considerable systematic differences between the regions in the patterns of disease, antimicrobial resistance and population structure. In this study, we demonstrated that having data on a few easily collected variables related to patient and treatment characteristics, it is possible to develop a risk adjustment model to produce adjusted pCA exposure rates, thereby

Table 4. Distribution of included patients for 6 predefined groups by region.

	Patient group	Subregion															
		Africa		Asia		Australia		Northern Europe		Southern Europe		Western Europe		Latin America		North America	
		n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
1	Neonatal early onset sepsis	17	10.3	12	6.1	10	16.7	43	13.0	18	7.1	18	10.7	0	0	5	11.6
2	CA sepsis/BSI in otherwise healthy infants and children	38	23.0	24	12.2	14	23.3	64	19.4	70	27.6	28	16.6	1	2.2	4	9.3
3	CA sepsis/BSI in infants and children with underlying disease	74	44.9	54	27.4	12	20.0	55	16.7	40	15.8	44	26.0	9	19.6	10	23.3
4	Empiric treatment of HA sepsis/BSI outside of PICU	24	14.6	54	27.4	15	25.0	102	30.9	65	25.6	30	17.8	14	30.4	16	37.2
5	Targeted treatment of HA sepsis/BSI outside of PICU	11	6.7	27	13.7	4	6.7	47	14.2	35	13.8	30	17.8	12	26.1	5	11.6
6	HA sepsis/BSI on PICU	1	0.6	26	13.2	5	8.3	19	5.8	26	10.2	19	11.2	10	21.7	3	7.0
	Carbapenem exposure	17	10.3	57	28.9	5	8.3	44	13.3	53	20.9	33	19.5	20	43.5	3	7.0
	Glycopeptide exposure	12	7.3	59	30.0	12	20.0	74	22.4	75	29.5	56	33.1	19	41.3	17	39.5
	Total n	165		197		60		330		254		169		46		43	

CA: community-acquired, HA: hospital-acquired, BSI: bloodstream infection, PICU: pediatric intensive care unit. The proportions refer to contributions of each group for the region in question.

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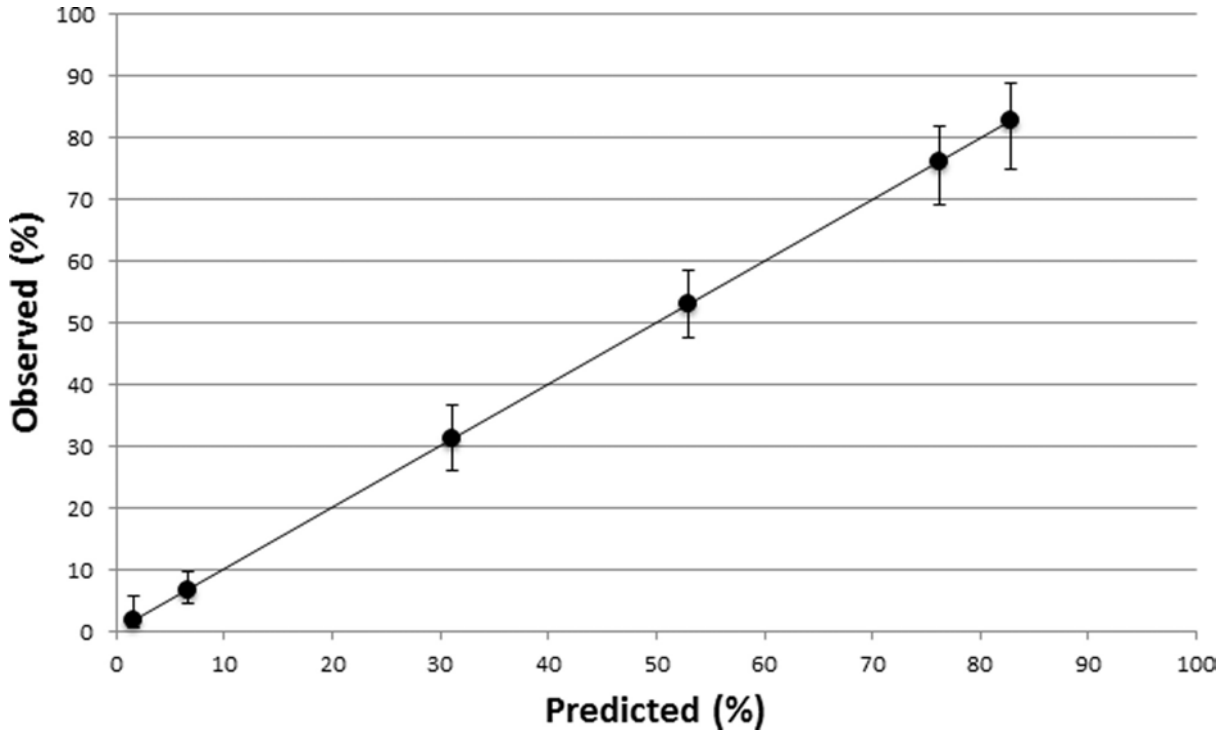

Fig 4. Calibration plot for logistic regression classification model of pCA exposure.

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allowing a fairer comparison of regions. In addition, the variables could be combined into a simple patient classification that differentiated various clinical situations in which the expected pCA exposure rates would be expected to differ. While a risk-adjustment approach based on logistic regression is preferable for making comparisons against a standard population, the classification facilitates benchmarking by creating relatively homogenous groups of patients who would be expected to have similar exposure to pCA due to their clinical circumstances. When evaluated, both approaches performed well at discriminating between children in terms of their likely exposure to pCA.

Overall, the average pCA exposure rate was high at 35%. Exposure rates to pCA were higher among older children, those on PICU, children with underlying disease, and receiving targeted treatment for hospital-acquired sepsis/bloodstream infection. That targeted treatment was strongly associated with higher pCA exposure may reflect a high rate of resistant bacteria identified in those children with culture-confirmed sepsis/bloodstream infection. Given the reported high rates of antimicrobial resistance in key pathogens globally, but especially in low- and middle-income countries [26–28], this is a worrying sign of the prevalence of multidrug-resistant infections, especially among hospital-acquired infections, in this population.

Regional crude prevalence rates varied considerably, the lowest and highest differing by a factor of 6.5. After adjustment, the prevalence rates varied by a factor of 2.5, demonstrating that a large proportion of variation arose from differences in the distribution of the measured patient and prescription characteristics. Previous analyses of case-mix adjustment in benchmarking of inpatient antibiotic prescribing have used variables that require detailed knowledge about each patient [7,9] or detailed hospital-level data [8,10,11]. While models based on these variables may have demonstrated even better discrimination and calibration in this dataset,

the value of our study is to demonstrate that pCA prescribing rates from prevalence surveys can be adequately risk-adjusted using easily collected variables. The effectiveness of this approach needs to be replicated in other datasets, and the benefit of including other factors also needs evaluation. Nonetheless, the results underline the importance of focusing on the complete and accurate measurement of important patient-level variables and treatment characteristics during data collection to enable optimal utilization of PPS data.

The predefined patient groups based on clinical reasoning proved to have a similar level of performance to the full logistic regression model. In practice, the application of a logistic regression model to inform quality improvement at a hospital level could be challenging because it produces a single composite statistic that describes overall performance. In contrast, a classification-based approach makes it possible to monitor the prevalence of pCA in distinct types of patients, for which the action required to tackle above average rates is likely to be different. This has been found to be a key issue in the development and use of classification systems in other circumstances [15,16]. The clinical logic underpinning the classification gives it a face-validity that suggests it could be applicable in other situations. But, we recommend that, before it is adopted for use in other infection syndromes and healthcare settings (e.g. adult care), its performance is evaluated further using data collected in that setting.

Our analysis has a number of limitations. First, despite this being as far as we are aware the largest neonatal and pediatric antibiotic prescribing PPS database globally, some regions contributed only a small number of patients. With a larger sample size, we would have been able to better estimate true differences in regional pCA exposure rates. Sample size limitations will also impact the application of our approach at hospital-level. Assuming that prescribing practices remain relatively stable, the pooling of data from several PPS may be one approach to overcome small sample sizes. Second, we only included prescriptions that were recorded as being for sepsis/bloodstream infection. Patients in our cohort may have received additional antibiotics for another indication (e.g. lower respiratory tract infection), which we did not include in our evaluation. Whether the same risk factors are associated with pCA exposure in patients treated for other infections needs to be tested. Third, data on the causative organism in targeted treatment were not recorded. We therefore rely on local contributors having correctly identified the recorded treatment as the most suitable narrow-spectrum antibiotic option for the target pathogen. In the future, pCA exposure rates should be interpreted together with information on actual resistance at patient or aggregate levels [29,30] to gauge whether pCA exposure levels are high in response to high antibiotic resistance rates or are mainly driven by prescriber behavior. Fourth, PPS data provides no information on duration of pCA exposure, which may have an important impact on the volume of pCAs used in a specific setting. Fifth, our analysis would need to be repeated analyzing data from a variety of hospitals. ARPEC PPS participant centers were predominantly tertiary and/or university hospitals, and the relevance of our findings for benchmarking involving smaller secondary hospitals would have to be confirmed. Finally, the cluster sizes of the participating centers were too small to support a multilevel model with centre as the cluster. Instead, we fitted a random-intercept logistic model with subregions to take account into account the hierarchical structure of the data. This did not change the conclusions about each variable and there was excellent agreement between the predictions from the two models. We therefore chose to present the results from the simpler standard logistic model.

In addition to conventional case-mix adjustment approaches, predefined patient groups, such as those described in our analysis, enable the generation of aspirational targets for aggregate pCA exposure rates, either in local, regional or national settings. These targets could be based on current average levels of exposures or be based on expert consensus about desirable practice. This would allow the comparison of (i) overall standardized exposure rates; (ii)

variations in distribution of patient strata; (iii) variations in exposure rates for specific patient groups. The advantages of this approach is that evaluations of pCA exposure would take into account key characteristics of the patients and infection episodes that are highly likely to influence pCA prescribing decisions and as such reflect justified use of these antibiotics. This may enable identification of specific target areas for intervention, while taking into account that what is appropriate may differ between facilities and/or regions. For such comparisons and target setting treatment and patient characteristics need to be captured, as described in this manuscript and as is standard during point prevalence surveys. Given the good performance of the logistic regression classification model in our analysis, the level of detail for the variables included in the ARPEC PPS may be sufficient for evaluations of childhood antibiotic use. However, additional or different variables are likely to be useful for similar analyses in other patient groups.

Case-mix adjustment, preferably using a few easy-to-collect patient and prescription characteristics, is key to accurately and fairly comparing prescribing patterns between health care providers, regional health care administrations and countries. Furthermore, assessing antibiotic exposure rates in a clinically relevant manner within homogenous and easily identifiable patient groups can be a rich source of information about key areas for intervention to improve antibiotic prescribing. Quality of antibiotic prescribing could then be assessed in such patient groups using validated indicators. In this way, interventions that will achieve a safe and reasonable reduction in the use of critically important antibiotics at aggregate level can be defined and evaluated.

Supporting information

S1 File. Excerpt of data collection instructions for coding of underlying disease for ARPEC PPS.
(PDF)

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</References>

Supporting Information

Excerpt of data collection instructions for coding of underlying disease for ARPEC PPS [2, 3].

Underlying diagnoses groups (paediatric patients):

Surgical disease/Malformations including all problems requiring surgical intervention/follow up, e.g. gut malformations/atresia, Urinary malformations, Sacral agenesis, Central Nervous System malformations, skin anomalies treated surgically including abscesses, any device insertion including gastrostomies, urinary catheter or Ventricular-peritoneal shunt, etc.

Chronic Neurological and Psychiatric disorders including Cerebral Palsy, Global Developmental Delay (GDD), all seizure disorders (epilepsy, West syndrome, etc.), progressive neurological and neuromuscular syndromes.

Gastroenterological disease including inflammatory bowel disorders, Gastrooesophageal reflux requiring treatment, Celiac disease, chronic non-infectious liver diseases, etc.

Congenital Heart Disease (CHD) including all the cardiac malformations and acquired cardiac disease e.g. Kawasaki syndrome, and cardiac surgery

Oncologic/Hematologic diseases and Bone Marrow Transplantation except immune deficiencies unless after bone marrow transplantation and all Solid Organ Transplantation.

Chronic Endocrinological Diseases including Cushing syndrome, thyroid disorders, pituitary gland disorders, etc.

Chronic Renal Disease, including Vesico-ureteric reflux.

Chromosomal/Single gene/Metabolic disorders (diabetes).

Rheumatological, autoimmune and chronic inflammatory diseases such as LED, sarcoidosis etc.

Chronic lung diseases including cystic fibrosis and chronic lung disease in ex preterm patients.

Chronic infectious diseases such as HIV, tuberculosis with ongoing treatment and chronic hepatitis B or C infection or primary immunodeficiencies.

Underlying diagnoses groups (neonatal patients):

Maternal prolonged rupture of membranes (>18 hours before delivery) or suspected or proven maternal peri-partum infection.

Intra Uterine Growth Retardation/Growth restriction.

Respiratory: Respiratory Distress Syndrome (RDS), Meconium aspiration syndrome, Chronic Lung Disease (Oxygen-dependency beyond 28th day of life). Persistent pulmonary hypertension of the newborn.

Cardiovascular: Congenital Heart Disease (CHD), including treated Patent Ductus Arteriosus (PDA).

Gastrointestinal: Necrotizing Enterocolitis (NEC).

Surgical problems/Malformation including all the malformations and surgical problems with the exception of NEC and CHD, e.g. Gut and central nervous system (CNS) Malformations, Cleft Palate, Hydrocephalus (including post hemorrhagic hydrocephalus), Ambiguous Genitalia, etc.

Confirmed or suspected chromosomal/single gene/metabolic disorders.

Electrolyte/Glycaemia disorders including iatrogenic if requiring active management.

Neonatal immune deficiency, including haematological malignancies.

Neurological conditions including neonatal seizures, severe asphyxia, hypoxic-ischaemic encephalopathy etc.

Haematological disease including indirect hyperbilirubinaemia requiring treatment.

Toxicological problems, such as monitoring for neonatal abstinence syndrome.

9. Discussion

The research presented in this thesis addressed a number of questions, each relating to the overarching challenge of how to use routine bloodstream infection data to inform empirical antibiotic prescribing in neonates and children.

The next section outlines the key findings in relation to the original objectives. Following this, the implications of the research for clinical and surveillance practice are outlined, including a discussion of the potential benefits and limitations for the use of routine bloodstream infection data in decision-making about empiric antibiotic regimens. Finally, implications for future work in this area are discussed.

9.1 Key findings

The research presented in this thesis addresses the persistent challenge of how to determine optimal empiric therapy regimens for the treatment of severe bacterial infections, most importantly bloodstream infections, in neonates and children. Empiric therapy should be based on the observed microbiological epidemiology of bloodstream infection in this group. This can be determined from blood cultures obtained as part of routine patient management.

Blood culture isolates are already being used to describe the microbiology of bacterial infections, for example, as part of hospital antibiograms. This type of cumulative antibiogram is the most common format of communicating about the microbiological epidemiology observed at a given hospital with clinicians, and also underpins surveillance reporting. By focusing on reporting of the susceptibility of particular bacteria to individual antibiotics (so-called bug-drug combinations), cumulative antibiograms are of limited value for informing antibiotic choices when treatment is in the critical empiric phase (when the bug is unknown). Empiric regimens need to provide adequate coverage for the overall spectrum of possible causative bacteria for the targeted infection. Regimen coverage cannot be directly derived from cumulative pathogen-based antibiograms.

Whether a certain isolate is indeed covered by a given regimen cannot be determined based on individual bug-drug combinations alone. Instead, agreed interpretive algorithms can be applied to maximise coverage information derived from individual bug-drug combinations. To date, few data have been presented on the utility of typically collected and reported data for a more comprehensive assessment of coverage. Chapter 4 demonstrates the impact of laboratory methods and the way laboratory data are collected and reported in clinical and surveillance cumulative antibiograms on the assessment of multidrug resistance in Gram-negative bacteria. A robust evaluation of multidrug resistance is not possible if laboratory

testing algorithms omit the evaluation (or reporting) of susceptibility for specific antibiotic classes of interest. Estimating the prevalence of multidrug resistance from surveillance data, typically focused on a few specific bug-drug combinations, is even more problematic because resistance in individual or a few combinations is often poorly reflective of multidrug resistance. This has implications for coverage estimates because these statistics rely heavily on comprehensive microbiological data being available.

Even when detailed microbiological data on identified bacteria and their antibiotic susceptibility are available, sample sizes for paediatric cohorts are expected to be small, especially for local guidance. Chapter 5 therefore investigated whether extrapolation from adult data could be suitable to improve precision and allow a more frequent assessment of coverage at local level. The analysis clearly demonstrated clinically relevant differences in resistance prevalence for some key pathogens between adults and children. Therefore, while there may be a benefit of augmenting paediatric datasets with information from adult datasets, a direct extrapolation approach does not seem suitable.

Analyses preceding the research in this thesis had already identified the need to reflect antibiotic regimen coverage from microbiological data rather than relying on simple cumulative antibiograms (53, 55, 86). Coverage can be established in the form of a weighted- incidence syndromic combination antibiogram or WISCA (55). In essence, this is a clinically relevant multi-pathogen cumulative antibiogram estimating the coverage provided by a given regimen for a given infection syndrome.
Chapter 6 describes an approach towards estimating a regimen WISCA that has several important advantages over standard methods: The Bayesian decision tree analytical model ensures that data on relative incidence of pathogens and their resistance patterns are combined in a robust and reproducible manner. Furthermore, uncertainty resulting from limited sample sizes for both can be fully reflected in the coverage estimate through the calculation of 95% credible intervals from a Monte Carlo simulation. Lastly, the Bayesian approach allows for the incorporation of prior knowledge of susceptibility or resistance (for example, intrinsic resistance) through informative priors.

Chapter 6 focuses on the application of the WISCA derived from a Bayesian decision tree analytical model at the hospital level in a set of European paediatric centres. In particular, the relationship between WISCAs derived from pooled data compared with local data was explored. Even though data from referral centres for neonatology and paediatrics were used, precision was limited for individual sites. Pooling improved the ability to detect differences in coverage between regimens unlikely to have arisen purely by chance. However, this is essentially a meta-analytical approach and as such, it is necessary to identify heterogeneity that would indicate that pooling could be inappropriate. In other words, to support pooling, it

is necessary to evaluate the degree to which relative incidence and resistance prevalence differ between the target hospital for which coverage is to be estimated and the pooled data set. For resistance prevalence, this can be done using funnel-plot derived bullet blots as a general method to identify outlier hospitals. For these, pooled data should not be assumed to reflect local resistance patterns.

In chapter 7, the Bayesian decision tree analytical model for estimating coverage was applied to investigate the likely coverage of commonly used empiric antibiotic regimens for neonatal sepsis. Only published data from countries in Asia, a hotspot of antimicrobial resistance in hospitalised neonates, were used. Coverage for the three investigated regimens was found to vary considerably between contributing countries with pooling therefore likely inappropriate. At a clinical level, regional coverage estimates and in fact national estimates may not be applicable for individual sites, particularly if substantial variations in either relative incidence of pathogens or their resistance patterns are expected. Worryingly, coverage for the regimen primarily involving a last-resort antibiotic (meropenem) was indeed higher than that provided by the investigated narrower-spectrum alternatives.

Finally, chapter 8 reports on the use of last-resort antibiotics in sepsis or bloodstream infection in hospitalised neonates and children. The meropenem regimen evaluated in chapter 7 is such a last-resort antibiotic regimen. There was a clear impact of patient characteristics on use of last-resort antibiotics, most likely reflecting clinical risk assessment for sepsis caused by bacteria not covered by regimens offering a narrower spectrum. Key risk factors for the use of last-resort antibiotics were infections being hospital-acquired and patients being treated in an intensive care unit setting. Interestingly, targeted treatment, that is treatment that is based on microbiology results, was also more likely to involve last-resort antibiotics, potentially indicating that clinicians are observing higher rates of bloodstream infection being caused by resistant bacteria. The implications for coverage estimations of the findings in chapter 8 are that despite consequent further reductions in sample size, it may be important to consider regimen coverage stratified by a priori patient and treatment characteristics that are already guiding clinical decision-making.

9.2 Strengths and limitations

Strengths and limitation of each individual analysis are discussed in the relevant chapters. The following discussion focuses on the strengths and limitations of the described WISCA-approach for evaluating coverage of empiric antibiotic regimens for neonatal and childhood bloodstream infection based on routine microbiological data.

9.2.1 Clinically relevant presentation of microbiological data for decision-making

From on-going discussions about the optimal method to select empiric antibiotic treatment regimens for bacterial infections, including for childhood bloodstream infections, it is clear that currently available data presentation methods are not clinically informative. Furthermore, as demonstrated in chapter 5, extrapolations from adult data are unlikely to be relevant.

The WISCA utilizes information on the relative incidence of bacteria and their resistance patterns to comprehensively reflect the observed microbiological epidemiology of the targeted infection in a specific patient population. As shown in chapters 6 and 7, routine microbiological data can be used to determine likely coverage by generating regimen-specific WISCAs based on a straightforward yet extendable decision tree analysis. Data for estimating model parameters take a relatively simple form that can easily be extracted from electronic laboratory information management systems, potentially supporting an automated or semi-automated process. Many laboratories already provide a programmed extract from the information systems for surveillance purposes, and it may be feasible to use these directly for automated coverage estimates.

While coverage estimated from a WISCA is likely to be clinically more relevant than data presented in a cumulative pathogen-specific hospital antibiogram, it is important to emphasize the impact of the selection of pathogens incorporated in the model. Full datasets of neonatal and childhood bloodstream isolates from a selection of sites were not available for the presented analyses. Rather, these relied on routine data reported to typical surveillance databases, many of which continue to focus on selected bacteria. Therefore, the WISCAs underpinning coverage estimates in chapters 6 and 7 should be considered specific to the selection of bacteria on which they are based. In fact, similar species are incorporated in both analyses reflecting bacteria that are considered particularly important not only for surveillance but also clinically.

For example, certain Gram-negative bacteria, such as *Klebsiella* spp., *Enterobacter* spp., *Pseudomonas* spp. and *Acinetobacter* spp., are both commonly isolated from blood cultures in patients with sepsis and are associated with a particularly severe clinical picture. The need to ensure early concordant therapy for optimised outcomes has been demonstrated in adults. It could therefore be important to ensure a regimen has coverage for these pathogens over rarer bacterial causes of bloodstream infection. The impact and added value of the inclusion or exclusion of certain pathogens is currently unclear, in particular, for bacteria that can cause bloodstream infection but are also skin colonizers and therefore may contaminate blood cultures, such as coagulase-negative staphylococci.

The assumption that concordance is clinically important is at the heart of the discussion around selection of optimal treatment, but needs further investigation beyond the scope of this thesis. In general, data clearly demonstrating a strong association between concordant antibiotic treatment and improved clinical outcomes are lacking for neonates and children.

9.2.2 Maximising use of data and dealing with imprecision

The Bayesian WISCA presented in chapters 6 and 7 incorporates several features that may result in better validity for coverage estimation compared to alternative described methods.

Because of the decision tree structure, parameter estimation is explicitly required (and separate) for all branches, most importantly the relative incidence and resistance patterns of included pathogens. The parameter tables clearly show those based on a small overall sample size of isolates or when antibiotic susceptibility testing done in only a subset of isolates. The Bayesian approach also allows uncertainty in both to be fully taken into account and 95% credible intervals generated. This is important because it will provide better information about differences in coverage between regimens. Considering point estimates alone may result in the automatic preference of “higher coverage” regimens by clinicians. Displaying these with 95% credible intervals may demonstrate that differences may have resulted by chance supporting clinicians in selecting slightly lower coverage regimens especially when their negative impacts, for example on resistance selection, are considerably lower .

Earlier publications on WISCAs did not address the issue on imprecision resulting from small sample sizes. These can occur when coverage is estimated using data from a specific hospital, given that bloodstream infections (either primary or secondary) are a rare event. In addition, selective antimicrobial susceptibility testing, for example the use of second line panel only when there is resistance to antibiotics in a first line panel, can also have an impact when isolates without results to determine concordance or discordance do not contribute to parameter estimation of the resistance branch of the decision tree model.

While the decision tree analysis ensures that imprecision due to sample size limitations is made visible, the Bayesian component of the model allows prior knowledge or beliefs about either relative incidence of bacteria or their resistance patterns to be incorporated. This is particularly important for intrinsic resistance or expected susceptibility (when resistance would reflect a highly unusual phenotype, for example vancomycin-resistance for streptococci), and counterbalances sample size limitations that result from lacking susceptibility testing for such bug-drug combinations. The lack of testing results from the results already being “known” and such information can and should be used to define

concordance or discordance of isolates and regimens as knowledge of intrinsic resistance reflects a strong prior belief.

Similarly, parameter estimation for the decision tree analytical model enables maximal exploitation of all available susceptibility testing data which is not typically reflected in hospital antibiograms. In the latter case, bug-drug combinations are usually reported as tested. For the WISCA, it is possible to apply all available recommended interpretive criteria and algorithms to determine concordance or discordance for included isolates. To do this, it is necessary to explicitly adopt a set of interpretive criteria since internationally used algorithms and criteria can yield different results for concordance and discordance (87). For this thesis, the EUCAST interpretive criteria were used throughout. It is known that for some bug-drug combinations different results may be obtained if, for example, CLSI criteria were applied (88). Since EUCAST are now engaged in formalised on-going review of the clinical breakpoints informing susceptibility testing interpretation, sometimes with substantial shifts, it will be important to state the actual version of EUCAST criteria being used going forward.

Chapter 8 demonstrates that such stratified evaluation of coverage will be necessary to align with the on-going clinical practice of prescribing being reflective of a major patient and episode characteristics. When coverage is to be calculated for a patient subgroup, for example neonates, sample sizes generally become so small that a meta-analytical approach becomes necessary to improve precision. The method of WISCA calculation presented in this thesis would allow for several approaches towards this. Firstly, straightforward data pooling with some evaluation of heterogeneity as presented in chapter 6 could be used. This can support data pooling when the target group or hospital for which coverage estimates are being investigated is similar to the pool in both relative incidence and resistance patterns. However, it does not resolve the problem of coverage estimates when there is a lot of heterogeneity. Other methods, such as the use of true Bayesian priors or empirical Bayesian priors from meta-analysis of contributing relative incidence or resistance data, may address this, but were not fully explored in this thesis.

9.2.3 Potential sources of bias

A major challenge for any coverage assessment based on routine data is that there may be inherent bias in the underlying data. This is true also for the Bayesian decision tree analytical model for calculating WISCAs. In particular, there may be sampling bias (blood cultures are not all patients with the target infection syndrome), multiple counting (poor responders are repeatedly cultured and contribute more than one isolate, often a difficult to treat or drug-resistant pathogen) and bias arising from selective testing.

Sampling bias is known to be problematic for lower-acuity infections, in particular urinary tract infections for which cultures may be obtained only when the patient is not getting better on first-line empiric therapy. Sampling bias should be relatively low for patients presenting with probable severe bacterial infections in high-income settings due to the perceived risks of missing a bloodstream infection. This is particularly true for neonates and children for whom on the whole the blood culture rates in Europe are higher than for adults (see chapter 5). However, children frequently present signs of bloodstream infection or sepsis when they are already on antibiotics. This is likely to introduce a pre-treatment bias with children who are slow responders but are in fact responding to their empiric regimen likely to have negative cultures whereas poor responders may have a higher frequency of positive cultures and may have episodes caused by difficult to treat bacteria. Similar problems are likely to be encountered in LMICs when in some cases blood cultures would only be taken in patients no improving on empiric treatment. Information on blood culture rate and antibiotic pre-treatment is not generally captured by most surveillance systems or reported for hospital antibiograms even though these data would be accessible.

Multiple counting of episodes can be addressed by methods used in chapters 4, 5, and 6 when a definition is provided for “an episode”, and isolates constituting a single episode are only included once for coverage estimation. This is not done consistently by hospitals when producing antibiograms, but is usually requested for surveillance purposes. Queries for electronic laboratory information management systems can be automated to ensure that only one isolate per episode is reported, but this is more work-intensive if a manual process is required.

Most critical, perhaps, is the issue of bias arising from selective testing. For the WISCA approach described, it is desirable to maximise the use of information on susceptibility testing to support coverage estimation for a range of potential empiric regimens. Selective approaches towards laboratory testing and subsequent interpretation of these data are particularly problematic when inferences about susceptibility and resistances are not straightforward, as demonstrated in chapter 4. The unbiased application of interpretive algorithms can be difficult, in particular when inferences are unidirectional: resistance to beta-lactams can be inferred from methicillin-resistance in *S. aureus* but susceptibility to beta-lactams cannot be inferred from lack of methicillin-resistance; susceptibility to piperacillin-tazobactam in certain Gram-negative bacteria can be inferred from susceptibility to piperacillin, but not vice versa. In the approach for coverage estimation presented in this thesis any divergences between number of isolates and number of tested isolates for a given pathogen and regimen are visible, allowing the identification of potential sources of bias,

such as reflex susceptibility testing. If present, however, the only method for addressing them would be to use informative priors based on observed testing patterns.

A further bias in susceptibility testing results from this being done to inform clinical decision-making at the level of the individual patient. Most hospitals have a range of antibiotics and therefore regimens that are included in an antibiotic formulary and can be used for patient treatment. However, it may be desirable to estimate coverage not only for current regimens but for empiric regimens that could potentially be used. Antibiotics not on the current formulary are unlikely to be used in susceptibility testing or, if they are used, unlikely to be requested or reported for hospital antibiograms or as part of surveillance.

9.3 Implications and recommendations for future work

The research presented in this thesis has implications for clinical practice and surveillance, as well as resulting in a number of avenues for further research.

9.3.1 Implications for clinical practice

Hospital antibiograms continue to be the main method of communicating microbiological data to clinicians and others involved in identifying suitable antibiotic regimens for local use. For example, the use of hospital antibiograms as means of tracking local resistance and to inform antibiotic selection is recommended as one key element of antibiotic stewardship in the UK and elsewhere. Based on the work presented in this thesis, the use of alternative methods that better reflect clinical reality and the coverage of considered regimens should be strongly encouraged.

Moving to coverage-based metrics at hospital-level has several implications. Most importantly, a detailed exchange between clinicians and microbiologists needs to take place to address the following aspects:

- What is the expected number of annual isolates for the target infection syndrome, and will this be sufficient to inform coverage estimation?
- Are there any known algorithms, such as recommendations for obtaining cultures that are likely to bias the observed microbiological epidemiology, and can these be addressed without undue burden on patients or staff? What is the definition of a “clinical episode” to be used to ensure that repeat isolates of the same pathogen from the same patient can be eliminated from the source dataset for estimating coverage?
- Are any susceptibility testing algorithms being used that could limit a full application of interpretive algorithms and result in biased coverage estimates?

- Is it possible to include antibiotics in susceptibility testing that are not currently used but could be of interest as alternatives to currently recommended options?

Clinicians may feel strongly that recommendations for empiric regimens should be stratified by patient and other clinical factors. Suitable stratification factors to support tailoring empiric regimens to individual patient groups are likely to be similar across hospitals and include, for example, patient age, level of care (general ward or critical care), presence of underlying comorbidities (with repeated exposure to the healthcare system), type of infection (healthcare-associated or community acquired and so on. Stratification down to unit-level (for example, a particular orthopaedic ward in a specific hospital) may not actually be effective in supporting decision-making about empiric antibiotics for two reasons: The sample size by unit is likely to be extremely small, and important variations in key stratifying variables are likely to be lost, meaning that selected empiric regimens are actually insufficiently "personalised". Grouping patients by stratification factors across the hospital for commonly targeted infection syndromes may instead adequately reflect any impact of the local microbiological epidemiology while still supporting the use of empiric regimens matched to risk level for difficult to treat infections.

9.3.2 Implications for surveillance of antimicrobial resistance

The purpose of surveillance is to establish antimicrobial resistance prevalence in a given setting or location and to track this over time. As outlined, this has traditionally been done by collecting data on indicator bacteria focusing on their resistance to specific antibiotic groups. In general, this currently relies on routine microbiological data which itself is obtained to address clinical problems.
Surveillance could be modified or augmented to ensure that any data provided is also suitable for estimating coverage. To achieve this, the type of required data needs to be clearly defined. This would limit the number of programmed enquiries, where surveillance asks for data submission in a specific format, or could ensure that data ready to use for coverage estimation can be returned to sites, where all microbiology data are unselectively "sucked" into a surveillance database.

Data required for estimating coverage based on the WISCA calculation method presented in this thesis have a very simple format: number of isolates (for each pathogen to be included in WISCA), number of isolates tested for concordance for the regimen of interest, number of isolates concordant for the regimen of interest. These data could easily be extracted from laboratory information systems in an automated query or identified from a comprehensive hospital microbiology dataset. Importantly, it may be necessary to expand the type and

number of surveyed bacteria to ensure that the resulting WISCAs adequately reflect the targeted microbiological epidemiology.

To successfully implement such a strategy, it would be important to collect more comprehensive antibiotic susceptibility testing information than is currently done. Furthermore, oversight bodies charged with surveillance at a national or international level would need to be explicit about any assumptions and underlying algorithms for estimating coverage, including which interpretive criteria are used and how changes in criteria are addressed. This may have important implications for comparisons across time with sudden "jumps" in coverage. Currently, the impact of changes in the interpretation of susceptibility testing results is unknown as many surveillance databases do not collect these data.

Ensuring that regimen coverage can be estimated from the same dataset also used for surveillance would increase the clinical relevance of these data, but also be more informative on the state of resistance in a given setting: changes in pathogen susceptibility to individual antibiotics are much more concerning if they result in reduced coverage compared to the next "broader" alternative. In fact, in addition to reporting on pathogen-specific antimicrobial resistance, it may be of interest to provide stratified WISCAs, for example by age group or by basic patient characteristics, which are generally reportable to surveillance databases as well. While coverage estimates at this level of pooling should not be directly used to inform clinical practice, they would nonetheless be informative to identify specific patient groups in whom antimicrobial resistance is consistently high or low across a range of geographical settings.

9.3.3 Further development of the WISCA tool

Chapters 4 and 5 addressed the potential limitations of using routine laboratory data or using adult data, respectively, to select the optimal empiric treatment regimens for childhood bloodstream infection. Chapters 6 and 7 outline an alternative approach to currently used cumulative antibiograms that can account for the target of empiric treatment being an infection syndrome rather than a specific pathogen, can adequately reflect variations in relative incidence and resistance patterns and can fully reflect the impact of limited sample size on the precision of coverage estimates.

The explicit structure of the Bayesian decision tree reveals that coverage estimates may be strongly influenced by the selection of bacteria contributing to the WISCA. While it can be argued that coverage estimates should primarily be based on clinically important bacteria accounting for the majority of isolates in a given infection syndrome, the approach taken in chapter 7, it will be necessary to explore the impact of including or excluding certain pathogens on coverage estimates. Similarly, the impact of omitting information for infrequent

bacteria should be explored to ensure that rare but difficult to treat organisms do not exert a strong influence on overall coverage estimates. At the same time, the best and most clinically relevant approach towards composing the WISCA for coverage estimation should be discussed with clinicians. This should include the clinical validity of a WISCA90% (i.e. based on 90% of isolates identified in the target infection) or a Gram-negative/Gram-positive WISCA (which could be used to adapt empiric therapy after the causative species has been identified but prior to antimicrobial susceptibility data being available).

The optimal method of meta-analysis for a decision-analytical tree based WISCA needs to be further defined. Most importantly, this needs to determine the role of and best approach towards data pooling. In particular, the role of empirical data-driven Bayesian priors or full Bayesian priors needs to be defined. Hierarchical analytical approaches could be necessary but would render coverage less interpretable to practising clinicians. Similarly, the need for and additional informational value of stratified coverage estimates should be explored. As shown in chapter 8, clinicians are strongly guided by patient characteristics in their decisions about whether antibiotics covering difficult to treat bacteria are required or not. Confirming or refuting this necessity based on microbiological data may strongly influence empiric regimen prescribing patterns.

The best way of combining information across different patient groups needs to be further explored. Direct extrapolation from adults to children is unlikely to be valid, as shown in chapter 5. However, it is likely that regions with higher resistance levels in bacteria isolated from adults would also have higher resistance levels, albeit potentially affecting different bacteria and of a different pattern, in children. Combining data from different patient groups could be important to improve accuracy and precision of coverage estimates, but needs to be done in a valid and robust way.

When stratified recommendations are desirable, it may not be possible to estimate coverage precisely enough to be informative for clinical decision-making. In such instances, it would be important to pool data across settings with low expected heterogeneity: This could be data on antimicrobial resistance in specific organisms within a network of centres with similar case-mix, data on relative incidence and resistance of pathogens in a homogenous patient group or use of data from multiple sources combined with prior knowledge on the epidemiology of the target infectious syndrome for a specific geographical region (89).

Consideration needs to be given to the optimal method of presentation of WISCA-based coverage estimates to be clinically useful. In the first instance, presenting coverage estimates in network, regional, national or supranational antimicrobial resistance reports would ensure that surveillance outputs include clinically relevant data. Several regions and

countries, for example England, Germany, the Netherlands and Switzerland, already offer web-based applications summarizing antimicrobial resistance surveillance. The reports generated by these applications likely already include data needed to estimate coverage given the correct programming. Taking a hospital-based perspective, it may be possible to provide simple tools based on the WISCA principle to support coverage estimation from local data.

9.3.4 Addressing limitations and next steps

Coverage estimates based on a WISCA reflect an aggregate analysis, and are based on the assumption of a strong association between discordant empiric treatment in severe infection and poor clinical outcomes. However, data supportive of this assumption for neonates and children are lacking and treatment outcomes in neonatal and childhood infection according to concordance or discordance of the eventually cultured bacteria with the empiric regimen used need to be evaluated. It is feasible to extend the decision-tree based coverage estimates to include clinical outcomes. This approach could be used to investigate the impact of discordant empiric antibiotic therapy on outcomes, but also to ensure that bacteria for which an important association between discordant treatment and mortality is demonstrated can be appropriately weighted in the WISCA.

The use of clinical decision support systems that use all available data at the patient level to predict whether an episode of severe infection is likely to be covered by a given regimen or not may supersede WISCA-based coverage estimation in certain settings. Such systems have been demonstrated to perform well when detailed information on factors likely to influence the probability of a specific pathogen with known expected resistance patterns is available electronically, for example from electronic hospital records (90). However, such systems rely on available data being complete and accurate to apply complex algorithms and machine learning to provide clinical feedback. Coverage estimates based on a WISCA already diverge considerably from current clinical practice, but may be more reliable in real life, where data completion of routine records can be patchy, and could well be more intuitively interpretable to clinicians than an automated alert based on a complex computer algorithm.

Stratified coverage estimates based on the WISCA approach would allow for a risk factor-based selection of optimal empiric antibiotic therapy. Evaluating coverage accounting for simple risk factors, such as patient age, need for intensive care support or infection being community- or hospital-acquired as was done in chapter 8 for use of last-resort antibiotics, would likely increase the clinical acceptability and relevance of the resulting treatment recommendations.

It is currently unclear how and when empiric regimens should be adapted in response to local outbreaks of difficult to treat bacteria as have been described, for example, for neonatal intensive care units. Such outbreaks may be prolonged with the outbreak pathogen potentially dominating the microbiological epidemiology in the affected unit for the duration of the outbreak. It will be necessary whether there is a threshold at which empiric regimens should be shifted to accommodate the “new” epidemiology (and therefore lower coverage of “old” regimens) and for shifting back once an outbreak has been brought under control. This can result in a unit-level escalation of empiric antibiotic regimens without any method for decision-making about unit-level de-escalation. Stratified analyses based on key patient and episode factors may be highly beneficial to ensuring that outbreaks do not skew coverage estimates at a higher level of aggregation, for example a neonatal intensive care unit outbreak having undue influence on coverage estimates for all neonates and children in a given hospital.

Traditional approaches towards microbiological evaluation may soon be transformed by the advent of newer, more rapid and potentially more in-depth methods. For example, genotypic methods towards establishing antimicrobial resistance are rapidly becoming more available and widespread. For some pathogens, for whom there is a strong known association between genotype and antibiotic susceptibility phenotype, such as *S. aureus*, *mec* gene presence and methicillin-resistance, direct testing for the presence of relevant genes is already part of mainstay laboratory practice. However, the relationship between genotype and susceptibility phenotype can be complex, and this will need to be taken into account when coverage estimates are based on genotypic information.

Even more importantly, the microbiological evaluation of individual critically ill patients is laborious, time-intensive, and currently still associated with a substantial delay between the identified need for treatment and final determination of the causative pathogen(s) and resistance patterns. Despite modern technologies shortening the time to completion of various steps, such as more rapid species identification using MALDI-TOF, direct PCR diagnostics from blood or other sample types so far have not been found to be reliable enough to supersede culture-based diagnostics. However, the fact that many severe bacterial infections are most likely caused by pathogens that previously colonize the affected host provides a unique opportunity to explore whether coverage estimates based on the resistome (i.e. the collection of resistance genes found in important microbiological niches) could provide a shortcut to better coverage estimates. Many key colonization sites, including the gut, throat and skin, are very accessible and can be sampled in a minimally invasive and virtually pain-free way. Some groups are already working to determine the relationship between coverage calculated based on invasive isolates and coverage

estimated from resistome data, the latter being based on testing of colonizing isolates from patients representative of the target population. Initial results are encouraging, but may need to address the need to ensure true representativeness of the patients providing resistome date of those eventually empirically treated for potential resistant infection. For example, basing coverage estimates for neonates on screening of the skin and gut resistome of all infants born at a given facility may not reflect the fact that newborns subsequently in need of antibiotic treatment may differ from health live-borns discharged after a short stay on a postnatal ward.

9.3.5 Conclusion

Clinical decision-making regarding empiric regimens for severe neonatal and paediatric bacterial infections needs to take account of the microbiological epidemiology of the targeted infection syndrome. Relevant data are readily available for some infections in most high-income settings, including for bloodstream infections which can present with critical illness and require timely concordant antibiotic therapy. Current methods of presenting these data are suboptimal in that the relative incidence of bacteria and resistance patterns in the target infection syndrome are not generally taken into account. Furthermore, point estimates are often presented without an indication of precision, preventing fair comparisons between the coverage offered by different empiric regimens.

The weighted incidence syndromic combination antibiogram (WISCA) addresses several of these limitations. When interpreted as a Bayesian decision tree, the WISCA can be used to estimate coverage, reflect imprecision of these estimates and investigate a range of scenarios (inclusion/exclusion of pathogens, non-informative vs. informative priors and others). While more sophisticated approaches, such as clinical decision support tools, may enable more personalised empiric regimen choices, the decision tree-based WISCA could be useful in all settings with established clinical microbiological services. In particular, coverage using the presented approach could also be estimated based on other, more easily accessible microbiological data, for example from colonizing bacteria. Further development of this approach should address best ways of dealing with limited sample size, optimal methods for meta-analysis and the added value of stratification

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