Appropriate surveillance methodology for assessing childhood antibiotic resistance: where do we stand?

Antibiotic resistance (ABR) is a potentially dramatic threat to individual and public health as we progress through the 21st century (1). Rising antibiotic resistance levels are creating a vicious cycle for clinicians. On the one hand, bacterial infections must be adequately treated in the face of higher prevalence of resistance to first-line conservative agents, and access to effective antibiotics must be secured globally (1). On the other hand, efforts must be made to use broad-spectrum agents judiciously to maintain their effectiveness for patients requiring antibiotics of last resort.

One requirement to successfully tackle ABR is an in depth understanding of the rates of pathogen resistance (1, 2). While population-based surveillance can be used to alert public health practitioners to the appearance of worrying ABR phenotypes or genotypes, such data may be insufficient to target interventions in specific patient groups. Specific groups are of interest, as the patient population is not homogeneous with regard to carriage of pathogens and the bacterial etiology of infection (3, 4). Group B streptococci as a cause of sepsis or meningitis, for example, are almost exclusively seen in newborns and young infants (3, 5).

A number of regional, national and international surveillance programs throughout the world are gathering information on the levels and patterns of ABR, usually derived from routine antimicrobial susceptibility testing of clinical samples rather than from active surveillance (6). The use of these data has the advantages of readily accessible information at relatively low cost, but limits additional microbiological work-up which may be needed for a more detailed understanding of ABR epidemiology. The laboratory work-up of these samples primarily aims to support clinical care.

A number of limitations and biases have been identified for this type of surveillance, including issues around defining cases and denominators, sampling biases and the lack of standardization of laboratory practice (7). Surveillance can therefore broadly indicate geographical ABR hotspots and provide some information on spatial and temporal resistance emergence. However, in its current format it may fail to engage clinical stakeholders who are key to improving antibiotic use and implementing infection control measures. Still, due to the ready availability of such data, it is likely that ABR surveillance globally will continue to rely heavily on this approach.

Although the remit for some of the existing surveillance programs is very large, information on childhood ABR is mostly absent, and the potential implications of this are rarely considered. As neonatal and pediatric isolates make up a small proportion of isolates recorded in population-based ABR surveillance, specific childhood ABR patterns are likely to be dominated by adult trends. The proportion of reported isolates from children under 15 years of age in population-based surveillance of bacteremia is generally only around 10% (3, 8). This only matters if childhood ABR patterns are different to those observed in adults, and children have an important role in the emergence or propagation of resistance.

Neonatal and pediatric medical care is mostly separate to adult care, both in terms of where (in neonatal and pediatric wards) and by whom (neonatologists and pediatricians) it is provided. Consequently, infection control measures and antibiotic stewardship interventions must also be specifically targeted, even when they are primarily delivered by teams working across all specialties (9). In order to achieve this, pediatric practitioners should advocate and provide support for on-going ABR surveillance activities in children

As young children require close physical contact for all aspects of care, they could be particularly efficient at transferring resistant bacteria to their carers and siblings. Infants discharged from a neonatal intensive care unit after an outbreak of extended-spectrum beta-lactamase producing *K. pneumoniae,* for example, were found on average to be carriers for more than 12 months with evidence of transmission to other family members in a third of all studied households (10).

Is it possible then to use adult (or pooled) data to assess the epidemiology of ABR among neonates and children? We suggest that extrapolations from adult data are not suitable, because ABR patterns do differ substantially between adult and pediatric isolates. For the same countries, fluoroquinolone resistance in *E. coli* and *K. pneumoniae* blood culture isolates from neonates and children surveyed as part of the Antibiotic Resistance and Prescribing in European Children (ARPEC) project was much lower (13% and 18%) compared with (mainly adult) European Antimicrobial Resistance Surveillance Network (EARS-Net ) data (23% and 31%) (2). Conversely, ARPEC *P. aeruginosa* isolateshad higher aminoglycoside, ceftazidime and carbapenem resistance levels compared to EARS-Net isolates (27%, 26% and 33% versus 19%, 15% and 21%) (2).

Even within the childhood population, further stratification is necessary to gauge the extent of the challenges posed by ABR pathogens for defined groups. For example, the ARPEC study found that *K. pneumoniae* isolates from children over 1 year of age had significantly higher percentages of aminoglycoside and carbapenem resistance (41% and 14%) than isolates from infants less than 1 year of age (26% and 2%) (2). Neonates in particular are at high risk of bacterial infection and are also likely to experience poor outcomes. For them, ABR could be an additional factor adding to the burden of serious bacterial infection: It is estimated that each year more than 200,000 neonatal sepsis deaths globally are attributable to antibiotic resistant pathogens (11). These estimates are currently based on a number of broad assumptions, as suitable data to calculate a population-attributable fraction for neonates are not presently available, so systematic collection of high quality surveillance data in this group should be prioritised (11).

Is it possible to rapidly improve access to childhood-specific data from existing surveillance initiatives? EARS-Net, for example, already collects relevant parameters for the presentation of age-stratified data (12). Unfortunately, age information of sufficient granularity to identify specific subgroups, such as neonates (EARS-Net collects age in full years), is not gathered. However, in the current format these and similar initiatives could investigate differences in ABR between adults and children more broadly. To support optimal use of these data for childhood surveillance, it would be important to encourage the complete reporting of key patient-level variables, including age and ward type.

One particular challenge remains for age-stratified presentation of current surveillance data: Sample size is likely to be limited for childhood isolates, especially when stratification within the pediatric population is desirable. Despite infants <1 year of age consistently being among those patients with the highest rate of bloodstream infections (500-700/100,000 population), the proportion of recorded isolates from this age group in population surveillance is often relatively small (around 3.5-5%) (3, 8).

Small sample sizes mean that assessments of ABR among neonates and children will likely be imprecise. Extending the period of time over which data are pooled can improve precision, but this can be associated with a loss of information on temporal trends. A potential novel solution to this could be the use of new metrics, such as those calculated for weighted incidence syndromic combination antibiograms (WISCAs), summarizing ABR data across several pathogens (13, 14). These would not replace current pathogen-specific resistance percentages for antibiotics of interest, but could be presented in addition to bug-drug ABR data.

Antibiotic resistance is usually primarily considered at the level of individual bacterial species. However, it may be desirable to summarize observed susceptibilities across a number of pathogens, focusing instead on a specific sample type (such as blood cultures) as representing a certain type of infection (bacteremia or bloodstream infection). This can be achieved using a WISCA and has the advantages of simultaneously increasing sample size and improving the clinical relevance of surveillance data (13). While novel metrics, such as the WISCA, could be helpful to improve precision for childhood ABR surveillance data, their use for other distinct patient groups may also be valuable.

As an example ARPEC carbapenem resistance percentages for individual Gram-negative bacteria, for example, were relatively imprecise, despite being calculated across all age groups (*E. coli* 0.1%, 95%CI 0.1-2%; *K. pneumoniae* 14%, 95%CI 3-11%; *P. aeruginosa* 33%, 95%CI 25-42%) (2). When estimated using a WISCA methodology, Gram-negative bacterial carbapenem resistance was 11% with a tighter 95% confidence interval of 9-14% (14). In certain settings, such summary data could be the basis for selecting between alternative empiric treatment recommendations (similarly to those proposed by the British National Formulary for Children, for example) when individual and/or detailed local microbiological information is unlikely to be available (15).

In summary, pooled population data is generally dominated by information derived from adult isolates and will not provide a truthful reflection of ABR patterns in neonates and children. Conversely, when age-stratified data are presented, the lack of precision due to small sample sizes is likely to be a challenge for childhood ABR surveillance. To overcome this limitation and to improve relevance of surveillance information for clinical practice, alternative methods of summarizing childhood ABR surveillance data should be explored. Given the rising burden of ABR and its consequences, such efforts should now be prioritized.

**Financial & competing interests disclosure**

JA Bielicki’s husband is senior corporate counsel at Novartis International AG, Basel, Switzerland, and holds Novartis stock and stock options. M Sharland chairs the Department of Health Expert Advisory Committee on Antimicrobial Resistance and Healthcare Associated Infection (ARHAI) in the United Kingdom. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

**References**

1. Laxminarayan R, Duse A, Wattal C*, et al.* Antibiotic resistance-the need for global solutions. *The Lancet Infectious diseases*. 2013;**13**:1057-98 doi: 10.1016/s1473-3099(13)70318-9 [published Online First: 2013/11/21].

2. Bielicki JA, Lundin R, Sharland M, Project A. Antibiotic Resistance Prevalence in Routine Bloodstream Isolates from Children's Hospitals Varies Substantially from Adult Surveillance Data in Europe. *Pediatr Infect Dis J*. 2015;**34**:734-41 doi: 10.1097/INF.0000000000000652 [published Online First: 2015/01/22].

3. Wilson J, Elgohari S, Livermore DM*, et al.* Trends among pathogens reported as causing bacteraemia in England, 2004-2008. *Clinical microbiology and infection : the official publication of the European Society of Clinical Microbiology and Infectious Diseases*. 2011;**17**:451-8 doi: 10.1111/j.1469-0691.2010.03262.x [published Online First: 2010/05/25].

4. Regev-Yochay G, Meir R, Dagan R*, et al.* Nasopharyngeal Carriage of Streptococcus pneumoniae by Adults and Children in Community and Family Settings. *Clinical Infectious Diseases*. 2004;**38**:632-39 Online.

5. Vergnano S, Menson E, Kennea N*, et al.* Neonatal infections in England: the NeonIN surveillance network. *Archives of disease in childhood Fetal and neonatal edition*. 2010; doi: 10.1136/F2 of 6 adc.2009.178798 [published Online.

6. Dar OA, Hasan R, Schlundt J*, et al.* Exploring the evidence base for national and regional policy interventions to combat resistance. *Lancet*. 2016;**387**:285-95 doi: 10.1016/s0140-6736(15)00520-6 [published Online First: 2015/11/26].

7. Rempel OR, Laupland KB. Surveillance for antimicrobial resistant organisms: potential sources and magnitude of bias. *Epidemiol Infect*. 2009;**137**:1665-73 Online.

8. Skogberg K, Lyytikäinen O, Ollgren J, Nuorti JP, Ruutu P. Population-based burden of bloodstream infections in Finland. *Clinical Microbiology and Infection*. 2012;**18**:E170-E6 doi: 10.1111/j.1469-0691.2012.03845.x [published Online.

9. Hyun DY, Hersh AL, Namtu K*, et al.* Antimicrobial stewardship in pediatrics: how every pediatrician can be a steward. *JAMA pediatrics*. 2013;**167**:859-66 doi: 10.1001/jamapediatrics.2013.2241 [published Online First: 2013/07/17].

10. Löhr IH, Rettedal S, Natås OB, Naseer U, Øymar K, Sundsfjord A. Long-term faecal carriage in infants and intra-household transmission of CTX-M-15-producing Klebsiella pneumoniae following a nosocomial outbreak. *J Antimicrob Chemother*. 2013; doi: 10.1093/jac/dks502 [published Online.

11. Laxminarayan R, Matsoso P, Pant S*, et al.* Access to effective antimicrobials: a worldwide challenge. *The Lancet*. 2016;**387**:168-75 doi: <http://dx.doi.org/10.1016/S0140-6736(15)00474-2> [published Online.

12. European Centre for Disease Prevention and Control. Antimicrobial Resistance (AMR) reporting protocol 2015; European Antimicrobial Resistance Surveillance Network (EARS-Net) surveillance data for 2014. Stockholm, Sweden: ECDC 2015.

13. Hebert C, Ridgway J, Vekhter B, Brown EC, Weber SG, Robicsek A. Demonstration of the weighted-incidence syndromic combination antibiogram: an empiric prescribing decision aid. *Infection Control & Hospital Epidemiology*. 2012;**33**:381-8 Online.

14. Bielicki JA, Sharland M, Johnson AP, Henderson KL, Cromwell DA. Selecting appropriate empirical antibiotic regimens for paediatric bloodstream infections: application of a Bayesian decision model to local and pooled antimicrobial resistance surveillance data. *The Journal of antimicrobial chemotherapy*. 2016;**71**:794-802 doi: 10.1093/jac/dkv397 [published Online First: 2015/12/03].

15. Paediatric Formulary Committee. British National Formulary for Children 2015-2016. London, Uk: BMJ Group, Royal Pharmaceutical Press, and RCPCH Publications 2015.