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

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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

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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.

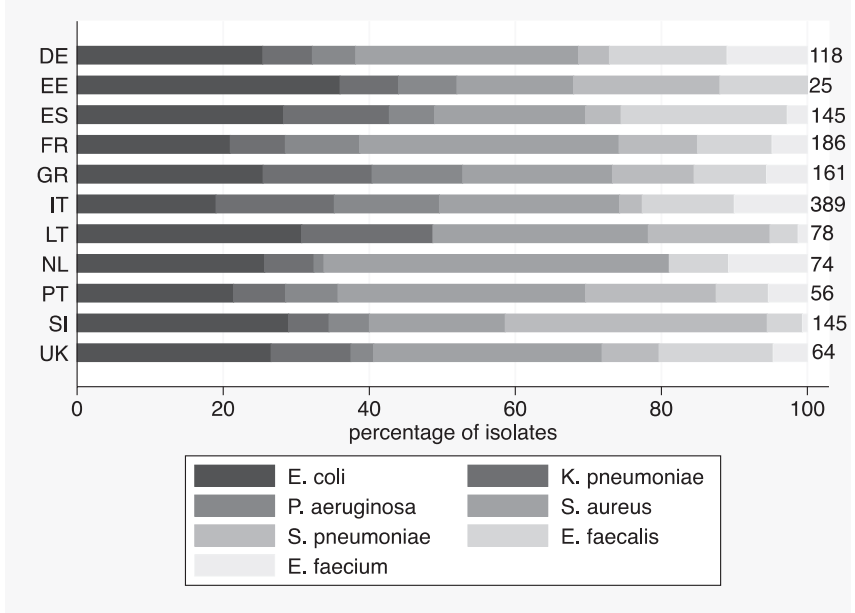

FIGURE 1. Distribution of relevant isolates for each country represented in the ARPEC dataset. The number of isolates from each country is indicated to the right of the bar chart. DE, Germany; EE, Estonia; ES, Spain; FR, France; GR, Greece; IT, Italy; LT, Lithuania; NL, The Netherlands; PT, Portugal;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

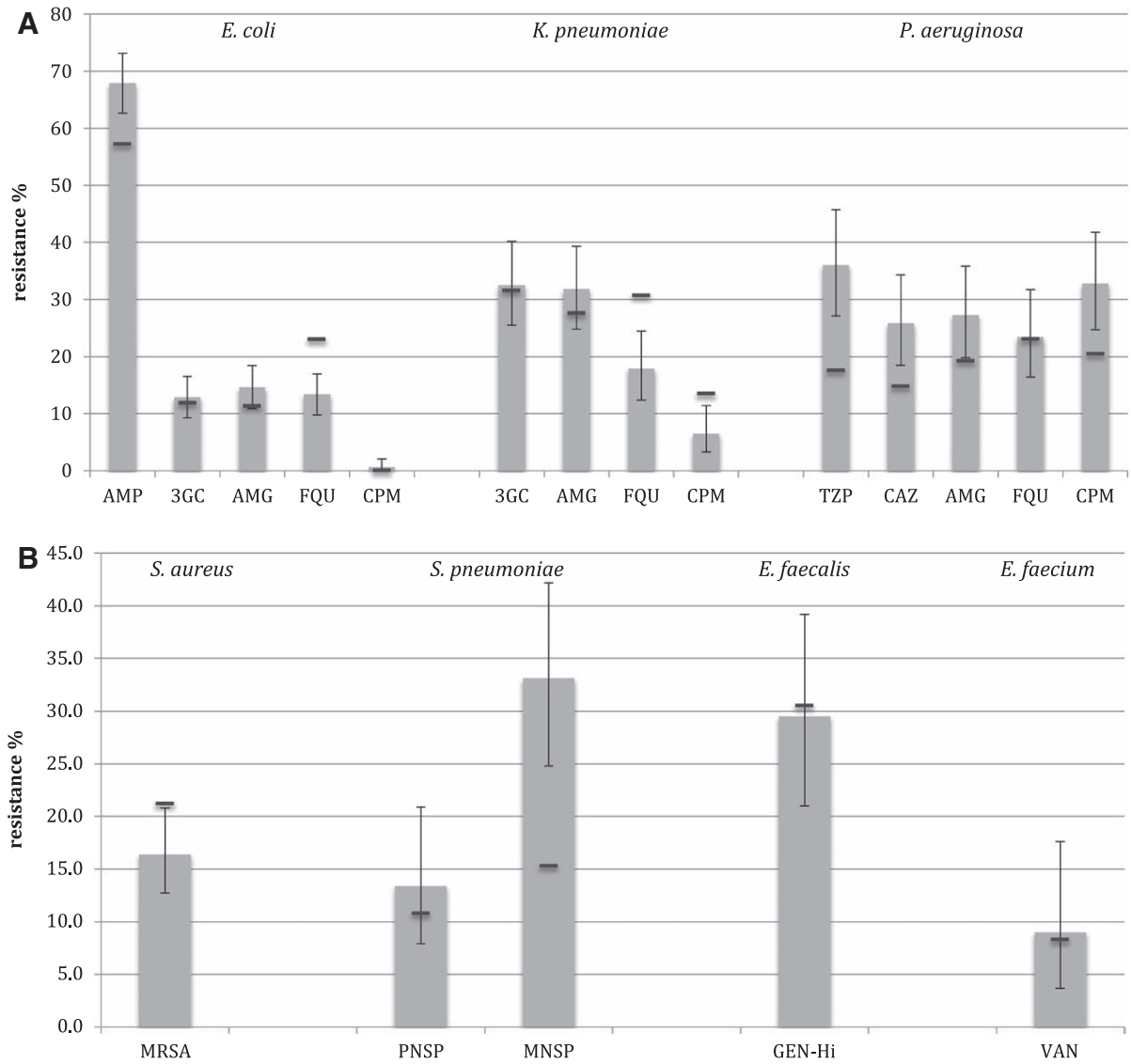

FIGURE 2. Comparison of resistance percentages in EARS-Net and ARPEC for Gram-negative and Gram-positive bacteria. EARS-Net estimates are indicated by the symbol (-). Ninety-five percent confidence intervals are shown for ARPEC estimates. AMP, aminopenicillin; 3GC, third generation cephalosporin; AMG, 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 non-intensive 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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