Acinetobacter baumannii Resistance Trends in Children in the United States, 1999–2012

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Background. *Acinetobacter baumannii* is a common cause of healthcare-associated infections. Carbapenem-resistant (CR) *A baumannii* is a significant threat globally. We used a large reference laboratory database to study the epidemiology of *A baumannii* in children in the United States.

Methods. Antimicrobial susceptibility data from The Surveillance Network were used to phenotypically identify antibiotic resistance in *A baumannii* isolates in children 1–17 years of age between January 1999 and July 2012. Logistic regression analysis was used to calculate trends in the prevalence of antibiotic resistance in *A baumannii*. Isolates from infants (<1 year old) were excluded.

Results. The crude proportion of cephalosporin-resistant (CephR) *A baumannii* increased from 13.2% in 1999 to 23.4% in 2012 with a peak of 32.5% in 2008, and the proportion of CR *A baumannii* increased from 0.6% in 1999 to 6.1% in 2012 with a peak of 12.7% in 2008. From 1999 to 2012, the proportion of CephR and CR *A baumannii* increased each year by 3% and 8%, respectively (CephR odds ratio [OR] = 1.03, 95% confidence interval [CI], 1.01–1.04; CR OR = 1.08, 95% CI, 1.05–1.12); however, after 2008, a significant decrease in trend was observed (CephR OR = 0.78, 95% CI, 0.71–0.87; CR OR = 0.73, 95% CI, 0.62–0.86), but resistance remained higher than baseline (1999).

Conclusions. Overall, between 1999 and 2012, CephR and CR *A baumannii* isolates increased in children; however, a decreasing trend was observed after 2008. There is a need for ongoing surveillance of *A baumannii* infections and continued assessment of effective prevention strategies in vulnerable populations.

Key Words. *Acinetobacter baumannii*; carbapenems; child; drug resistance; epidemiology.

Acinetobacter is a complex genus of Gram-negative bacteria that cause infections associated with significant morbidity and mortality. *Acinetobacter baumannii* is the most common human pathogen of the genus, and it is well known for its ability to resist desiccation and persist in the environment, which facilitates transmission in healthcare settings [1]. The National Healthcare Safety Network reported in 2009–2010 that *A baumannii* was responsible for 1.8% of all healthcare-associated infections (HAIs), and it is estimated that there are 45 000 cases of *Acinetobacter* infections per year in the United States and 1 million annual cases globally [1–3]. The Centers for Disease Control and Prevention (CDC) noted in a 2013 Antibiotic Resistance Threat report that infection with multidrug resistant (MDR) *Acinetobacter* is a serious and significant antibiotic resistant threat, and that there

are 7300 MDR *Acinetobacter* infections in the United States each year, resulting in 500 deaths [4]. The most common clinical manifestations of *A baumannii* infection are healthcare-associated pneumonia and bacteremia; however, other well described infection types in adults and children include urinary tract infections, wound infections, meningitis, endocarditis, osteomyelitis, and endophthalmitis [2, 5, 6].

The virulence properties of *Acinetobacter* spp are numerous and include capsular polysaccharide enabling immune evasion, allowing for a high density of bacteria that enact lipopolysaccharide Toll-like receptor 4-mediated sepsis. However, the major driver of poor outcomes due to *Acinetobacter* infection is antibiotic resistance, which complicates the selection of effective empiric therapy because genus identification often precedes susceptibility results [1, 6]. *Acinetobacter* has intrinsic low permeability to antibiotics due to reduced outer membrane porins, and it contains a major resistance genomic island comprising 45 resistance genes, enabling resistance to multiple antibiotic classes [1]. β -lactam antibiotics are common empiric therapy options for *A baumannii*, and β -lactam resistance (including penicillins, cephalosporins and carbapenems) is due to multiple mechanisms such as chromosomal, plasmid- or transposon-encoded β -lactamases including class B metallo- β -lactamases,

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class C AmpC cephalosporinases, and class D OXA carbapenemases. Broad-spectrum β -lactamases in combination with active efflux systems, low outer membrane permeability, the absence of PBP-2, and transposon-mediated aminoglycoside, sulfonamide, tetracycline resistance mechanisms have resulted in a perfect storm of highly resistant bacterial populations increasingly being reported worldwide [1, 7–10].

Despite rising rates of antibiotic resistance and concerning numbers of drug-resistant *A baumannii* infections, the current pediatric literature is limited to single-center experiences, and there have been no pediatric studies assessing national or regional trends in antibiotic resistance in *A baumannii* in children. In this study, we investigated the epidemiology of *A baumannii* isolates from children, excluding those under 1 year of age, and explored trends in antibiotic resistance over a time period of 13.5 years.

METHODS

Antibiotic susceptibility data were obtained from The Surveillance Network Database-USA ([TSN] Eurofin-Medinet, Herndon, VA). The database has been used previously to characterize national antibiotic susceptibility trends [11–13]. In brief, the network consisted of clinical microbiology laboratories that served approximately 300 hospitals. These hospitals were selected to be geographically representative of the 9 US Census Bureau regional divisions, hospital size, and patient population. Laboratories that were included in TSN submitted results from all routine antimicrobial susceptibility testing performed. Clinical Laboratory Standards Institute (CLSI) guidelines were adopted by the reporting facilities at the time of testing and reflect the susceptibilities that were reported to clinicians [14]. Individual laboratory data were validated electronically and merged into a central database.

The database included records with the following information: the organism identified, tested drug and susceptibility result (susceptible, intermediate-resistant, or resistant), the specimen source of the isolate (blood, urine, wound, respiratory, skin), patient characteristics (age, sex), the patient location setting in which the patient sample was collected (outpatient (ambulatory), inpatient intensive care unit (ICU), inpatient (non-ICU) and long-term care settings), the geographical location of the facility where the specimen was collected (state, region), and the date of the drug susceptibility test.

Our analysis considered *A baumannii* isolates obtained from all pediatric patients (ages 1 to 17) who were in ambulatory, ICU, non-ICU, and long-term care settings between January 1, 1999 and June 30, 2012. We excluded isolates obtained from patients <1 year old in this study because the epidemiology of *A baumannii* in neonates, cared for in the neonatal ICU, likely differs from older children. Resistance rates of *A baumannii* to the following 6 classes of antibiotics were examined: cephalosporins

(cefepime, ceftazidime), β -lactam/ β -lactamase inhibitor combination (piperacillin, piperacillin/tazobactam), carbapenems (imipenem, meropenem, and doripenem), fluoroquinolones (ciprofloxacin or levofloxacin), aminoglycosides (gentamicin, tobramycin, or amikacin), or sulbactam (ampicillin-sulbactam). Individual class resistance rates of *A baumannii* were defined as nonsusceptible to at least 1 of the antibiotic agents in the respective class. For example, cephalosporin-resistant (CephR) *A baumannii* was defined as isolates that were nonsusceptible to at least 1 of the 2 agents (ceftazidime, cefepime) in the cephalosporin class, and carbapenem-resistant (CR) *A baumannii* was defined as isolates that were nonsusceptible to at least 1 of the 3 agents (imipenem, meropenem, doripenem) in the carbapenem class. In addition, MDR *A baumannii* was defined using CDC criteria, which includes nonsusceptibility to agent(s) in at least 3 of the following 6 antimicrobial classes: cephalosporins (cefepime, ceftazidime), β -lactam/ β -lactamase inhibitor combination (piperacillin, piperacillin/tazobactam), carbapenems (imipenem, meropenem, and doripenem), fluoroquinolones (ciprofloxacin or levofloxacin), aminoglycosides (gentamicin, tobramycin, or amikacin) or sulbactams (ampicillin-sulbactam) [15].

Only the first isolate from a patient was included in the analysis. The frequency of individual class resistance (for example, resistance to cephalosporin class means nonsusceptibility to at least 1 of the 2 antibiotics ceftazidime or cefepime) and MDR *A baumannii* are reported as the proportion of resistant isolates out of total tested isolates in respective classes. In addition, we examined the susceptibility of *A baumannii* isolates to all individual antibiotics in each of the 6 classes. During the study period, CLSI breakpoints were changed for amikacin, gentamicin, and tobramycin in 2008. An intermediate category was introduced in 2008 for these drugs, and the previous resistant minimum inhibitory concentration (MIC) values were categorized to intermediate. However, although we considered intermediate isolates as resistant, the break point changes would not affect the resistance trends.

Unadjusted trends in the prevalence of individual class-resistant and MDR *A baumannii* were examined using logistic regression. For those classes with a significant increase in unadjusted analysis, multivariable logistic regression analysis was used to estimate the prevalence adjusting for time (year), patient characteristics (including age group [1–5, 6–12, and 13–17 years old]), sex, isolate specimen source (blood, urine, wound, respiratory, and skin), patient location (ICU, inpatient non-ICU, outpatient and long-term care facilities), and geographic region of the healthcare facilities (East North Central, East South Central, Mid-Atlantic, Mountain, New England, Pacific, South Atlantic, West North Central, and West South Central). A *P* value of <.05 was considered to be statistically significant. Confidence intervals (CIs) were generated using Wilson score CI method. Data were analyzed using Stata 14.1 (StataCorp, College Station, TX) programming language.

RESULTS

Overall, 6246 pediatric *A baumannii* isolates were identified in the database between 1999 and 2012. The isolates were more often from outpatients (2779 isolates, 44.48%), respiratory source (2761 isolates, 44.18%), 1- to 5-year-old patients (2374 isolates, 37.99%), or males (3337 isolates, 53.39%) (Table 1). Of the 9 regions in the dataset, the largest number of isolates came from the South Atlantic region (1238 isolates, 19.83%).

When we compared *A baumannii* resistance proportions in 1999 and 2012 for various classes, we noted that resistance to carbapenems (0.6% in 1999 vs 6.1% in 2012) and cephalosporins (13.2% vs 23.4%) increased with a peak percentage of resistance in 2008 (CR, 12.7%; CephR, 32.5%) (Figure 1), whereas the resistance proportion decreased for β -lactam/ β -lactamase

inhibitor combination (23.4% vs 18.9%), fluoroquinolones (14.5% vs 9.5%), sulbactams (14.3% vs 8.8%), and MDR isolates (16.1% vs 14.3%) (Supplementary Table 1). *Acinetobacter baumannii* resistance proportions for aminoglycosides were identical in 1999 (17.6%) and 2012 (17.6%).

Analysis of trends using logistic regression showed a significant increase in the proportion of both CR (0.6%–6.1%; $P = .001$) and CephR (13.2%–23.4%; $P = .036$) *A baumannii* isolates between 1999 and 2012. With every year, the proportion of CR *A baumannii* isolates increased by 8% (odds ratio [OR] = 1.08 [95% CI, 1.05–1.12]), whereas the proportion of CephR *A baumannii* isolates increased by 3% (OR = 1.03 [95% CI, 1.01–1.04]). However, there was a significant decrease in the proportion of CR (12.7%–6.1%; OR = 0.73 [95% CI, 0.62–0.86])

Table 1. Distribution of Carbapenem- and Cephalosporin-Resistant *Acinetobacter baumannii* Isolates in Children 1–17 Years of Age, 1999–2012^a

Characteristic	Total Isolates N = 6246	No. of Isolates Tested Against Carbapenems N = 5605	No. of CR ^b Isolates (% of Isolates Tested Against Carbapenems) N = 343	No. of Isolates Tested Against Cephalosporins N = 5876	No. of CephR ^c Isolates (% of Total Tested Against Cephalosporins) N = 1339
Patient Setting					
Inpatient	2269	2042	179 (8.8%)	2170	592 (27.3%)
Inpatient - ICU	1105	1043	88 (8.4%)	1045	325 (31.1%)
Outpatient	2779	2429	62 (2.6%)	2572	393 (15.3%)
Unknown	46	44	6 (13.6%)	42	10 (23.8%)
Long-term care	47	47	8 (17%)	47	19 (40.4%)
Patient Sex					
Male	3337	3014	230 (7.6%)	3138	783 (25%)
Females	2824	2512	109 (4.3%)	2658	541 (20.4%)
Unknown	85	79	4 (5.1%)	80	15 (18.8%)
Specimen Source					
Respiratory	2761	2557	203 (7.9%)	2620	738 (28.2%)
Wound	1567	1435	82 (5.7%)	1506	300 (19.9%)
Urine	901	694	33 (4.8%)	769	137 (17.8%)
Blood	873	795	23 (2.9%)	846	147 (17.4%)
Skin	144	124	2 (1.6%)	136	18 (13.2%)
Age Group					
1–5	2374	2132	95 (5.5%)	2266	456 (20.1%)
6–12	1659	1475	52 (3.5%)	1544	300 (19.4%)
13–17	2213	1998	196 (9.8%)	2066	583 (28.2%)
Region^d					
South Atlantic	1238	1100	56 (5.1%)	1195	253 (21.1%)
Mid-Atlantic	1071	983	90 (9.2%)	1026	273 (26.6%)
East North Central	955	869	27 (3.1%)	817	163 (20%)
West South Central	932	860	50 (5.8%)	854	177 (20.7%)
Pacific	803	722	54 (7.5%)	774	200 (25.8%)
West North Central	612	489	45 (9.2%)	604	156 (25.8%)
East South Central	270	247	7 (2.8%)	247	43 (17.4%)
Mountain	206	181	11 (6.1%)	201	54 (26.9%)
New England	159	154	3 (1.9%)	158	20 (12.7%)

Abbreviations: CephR, cephalosporin resistant; CR, carbapenem resistant; ICU, intensive care unit.

^aSource: The Surveillance Network-USA Database.

^bCR means nonsusceptible to at least 1 of the 3 agents (imipenem, meropenem, doripenem).

^cCephR means nonsusceptible to at least 1 of the 2 agents (cefepime, ceftazidime).

^dEast North Central region includes the following states: Illinois, Indiana, Michigan, Ohio, and Wisconsin. East South Central region includes the following states: Alabama, Kentucky, Mississippi, and Tennessee. Mid-Atlantic region includes the following states: New Jersey, New York, and Pennsylvania. Mountain region includes the following states: Arizona, Colorado, Idaho, Montana, New Mexico, Utah, and Wyoming. New England region includes the following states: Connecticut, Maine, Massachusetts, New Hampshire, Rhode Island, and Vermont. Pacific region includes the following states: Alaska, California, Hawaii, Islands, Oregon, and Washington. South Atlantic includes the following states: Delaware, Florida, Georgia, Maryland, North Carolina, South Carolina, Virginia, and West Virginia. West North Central region includes the following states: Iowa, Kansas, Minnesota, Missouri, North Dakota, Nebraska, and South Dakota. West South Central region includes the following states: Arkansas, Louisiana, Oklahoma, and Texas.

Figure 1. Carbapenem- and cephalosporin-resistant *Acinetobacter baumannii* in the United States: 1999–2012.

and CephR (32.5%–23.4%; OR = 0.78 [95% CI, 0.71–0.87]) *A. baumannii* isolates between 2008 and 2012. *Acinetobacter baumannii* resistance rates to 3 other classes (β -lactam/ β -lactamase inhibitor combination, aminoglycosides, and sulbactams) and MDR *A. baumannii* rates showed no significant change (increase or decrease) over the study period, except for fluoroquinolones, which showed significant decrease. With every year, the proportion of fluoroquinolone-resistant *A. baumannii* isolates decreased by 2% (OR = 0.98 [95% CI, 0.96–0.99]; $P = .04$). However, the odds of resistance significantly decreased between 2008 and 2012 for all 4 classes of antibiotics.

Of the total isolates tested for CR and CephR isolates, the highest percentage of CR and CephR isolates were from respiratory sources (203, 7.9% CR; 738, 28.2% CephR), from age category 13–17 (196, 9.8% CR; 583, 28.2% CephR), from males (230, 7.6% CR; 783, 25% CephR), from the long-term care setting (8, 17% CR; 19, 40.4% CephR), and from the Mid-Atlantic region (90, 9.2% CR; 273; 26.6% CephR) (Table 1).

After the data were adjusted for year (including years after 2008), patient, and isolate characteristics, patients in the age group 13–17 years had greater odds of the CR and CephR phenotype among *A. baumannii* isolates (OR = 2.32 [95% CI, 1.77–3.04]; OR = 1.54 [95% CI, 1.32–1.78]), compared with 1- to 5-year-old children (Table 2). Among patient locations, patients from long-term care facilities had the greater odds of the CR and CephR phenotype (OR = 5.82 [95% CI, 2.49–14.60]; OR = 3.33 [95% CI, 1.80–6.13]), compared with outpatients. Among specimen sources, respiratory specimens had the greater odds of CR and CephR phenotype (OR = 1.33 [95% CI, 0.89–2.00]; OR = 1.56 [95% CI, 1.26–1.94]), compared with specimens obtained from urine. Among the geographic regions, the Mid-Atlantic Region had greater odds of CR phenotype (OR = 2.80 [95% CI,

1.75–4.46]), whereas the Mountain region had greater odds of CephR phenotype (OR = 1.47 [95% CI, 0.96–2.03]), compared with the East North Central region of United States. *Acinetobacter baumannii* resistance to amikacin showed the highest absolute increase in resistance rates (9.6% in 1999–2003 to 16.6% in 2008–2012), whereas imipenem had the lowest resistance rates among all antibiotics tested (Supplementary Table 2).

DISCUSSION

Overall, we observed significant increases in the prevalence of CR and CephR phenotypes among *A. baumannii* isolates from US children between 1999 and 2012, which was similar to increasing trends we found in other notoriously drug-resistant Gram-negative bacilli isolates in children during the same time period [11, 13, 16]. However, there was a biphasic trend. The prevalence of CR *A. baumannii* and CephR *A. baumannii* isolates increased until 2008, and then a decreasing trend was observed, but resistance remained proportionally higher than the early study period. Children admitted to inpatient settings (both wards and ICU) and long-term care settings, between the ages of 13 and 17 years, and respiratory tract isolates had greater odds of CR and CephR *A. baumannii*. Resistance varied by region. The Mid-Atlantic region of the United States had greater odds of CR *A. baumannii*, whereas the Mountain region had greater odds of CephR *A. baumannii*. Although fluoroquinolone resistance in *A. baumannii* isolates decreased during the time period, the only relevant current indication for quinolone use in the pediatric population is for complex urinary tract infections, which did not represent the majority of the increasing drug-resistant infections, which were respiratory in nature. Of additional concern was the absolute increase in drug resistance in other traditionally reserved second-line antibiotics such as amikacin.

Table 2. Logistic Model of Carbapenem-Resistant and Cephalosporin-Resistant *Acinetobacter baumannii* Adjusted for Patient and Isolate Characteristics in Children 1–17 Years of Age, 1999–2012

Isolate Characteristic	Carbapenem-Resistant <i>A baumannii</i> (n = 5605)		Cephalosporin-Resistant <i>A baumannii</i> (n = 5876)	
	aOR (95% CI)	P Value	aOR (95% CI)	P Value
Time (all 13 years)	1.12 (1.15–1.29)	<.001	1.104 (1.072–1.136)	<.001
Time (2008–2012)	0.75 (0.65–0.86)	<.001	0.79 (0.73–0.86)	<.001
Patient Gender (reference, female)				
Male	1.78 (1.39–2.26)	<.001	1.28 (1.13–1.46)	<.001
Unknown	3.16 (1.03–9.68)	.044	1.42 (0.78–2.58)	.250
Age, Years (reference, 1–5)				
6–12	0.85 (0.60–1.21)	.371	1.05 (0.89–1.24)	.587
13–17	2.32 (1.77–3.04)	<.001	1.54 (1.32–1.78)	<.001
Patient Location (reference, outpatient)				
Inpatient	3.60 (2.64–5.92)	<.001	2.05 (1.77–2.39)	<.001
Inpatient-ICU	3.17 (2.19–4.59)	<.001	2.13 (1.77–2.57)	<.001
Long-term care	5.82 (2.49–14.60)	<.001	3.33 (1.80–6.13)	<.001
Unknown	8.79 (3.35–22.33)	<.001	1.92 (0.92–3.99)	.077
Specimen Source (reference, urine)				
Blood	0.47 (0.27–0.83)	.009	0.85 (0.65–1.11)	.223
Respiratory	1.33 (0.89–2.00)	.168	1.56 (1.26–1.94)	<.001
Skin	0.41 (0.09–1.77)	.231	0.79 (0.4–1.36)	.389
Wound	1.14 (0.74–1.75)	.550	1.10 (0.88–1.38)	.434
Region (reference, East North Central)				
East South Central	0.73 (0.31–1.73)	.472	0.70 (0.48–1.03)	.067
Mid-Atlantic	2.80 (1.75–4.46)	<.001	1.30 (1.03–1.65)	.026
Mountain	1.94 (0.91–4.13)	.087	1.47 (0.96–2.03)	.077
New England	0.35 (0.10–1.19)	.094	0.47 (0.24–0.67)	.004
Pacific	1.71 (1.04–2.82)	.034	1.19 (0.92–1.51)	.176
South Atlantic	1.32 (0.81–2.15)	.272	1.01 (0.75–1.20)	.938
West North Central	2.23 (1.33–3.75)	.003	1.21 (0.87–1.49)	.170
West South Central	1.37 (0.82–2.27)	.228	0.84 (0.63–1.05)	.167

Abbreviations: aOR, adjusted odds ratio; CI, confidence interval; ICU, intensive care unit.

The decreasing trend in the prevalence of CR *A baumannii* and CephR *A baumannii* isolates after 2008 may be attributable (1) to calls for improvements in infection control practices to combat MDR *A baumannii* during this time period and (2) the Infectious Diseases Society of America and the Society for Healthcare Epidemiology expert guidance released in 2007 advising implementation of antimicrobial stewardship programs in acute care settings [17, 18]. Improvements in infection control practices and implementation of antimicrobial stewardship programs in acute care settings would also explain the decrease in the proportion of inpatient isolates (both wards and ICU), which are associated with higher odds of resistance compared with outpatient isolates after the year 2008.

Disruption of anatomic barriers due to catheterization, endotracheal intubation, surgery, or trauma is the major driving force for *A baumannii* infection, and the most common infections are healthcare-associated pneumonia and bacteremia [1]. In our study, we did not find an increase in resistant *A baumannii* in blood isolates; however, the findings in this analysis of increasing CR and CephR *A baumannii* in respiratory isolates are consistent with US CDC data describing high HAI rates due to pneumonia [19].

Because ICUs and long-term care facilities harbor critically and chronically ill children and involve high antibiotic and device usage rates, it is not surprising that we found greater odds of CR and CephR *A baumannii* isolates in these settings. The higher odds of CR and CephR *A baumannii* in inpatient non-ICU settings is not as easily explained, because patient populations traditionally hospitalized for prolonged periods such as those with suppression or depletion of leukocytes are not thought to represent a significant proportion of those with *A baumannii* infections.

Acinetobacter can possess an XDR phenotype, which is defined as “resistant to all FDA-approved, systemically active antibacterial agents except for those known to be substantially more toxic than or inferior in efficacy to alternative agents when used to treat susceptible organisms” [20]. In adults, the CR *A baumannii* phenotype is typically XDR, and it has been associated with plasmid- and transposon-based carbapenemases such as the Class D carbapenemases and the Class B metallo- β -lactamases, which typically co-occur with additional resistance genes. We did not find an increase in MDR or XDR *A baumannii* in our study. It is possible that the CR phenotype in our isolates is due to a combination of intrinsic resistance mechanisms

and selection pressure for the CR phenotype due to broad antibiotic exposure; it is also possible that the *A baumannii* was misidentified and represents another species of less virulent *Acinetobacter*, because, until the recent availability of newer diagnostic platforms, it was difficult for some microbiology laboratories to differentiate *A baumannii* from *Acinetobacter calcoaceticus* [1, 21, 22].

Acinetobacter baumannii often has a polyclonal endemicity in healthcare settings. Therefore, antimicrobial stewardship programs and comprehensive infection control measures (including ventilator associated complication bundles) may be equally necessary to control spread and reduce length of stay and lower mortality due to antibiotic-resistant *A baumannii* in both endemic and outbreak settings [18, 23–26]. Revolutionary advances in rapid molecular diagnostics may assist in the differentiation of patients who might more definitively benefit from antibiotic therapy and yield the correct identification of *A baumannii* from other less pathogenic species [27–31].

Our study has several limitations. First, as with any laboratory-based surveillance, we could not differentiate between true infection and colonization. Second, we did not have MIC values. Although CLSI methods were applied by participating laboratories, some margin of uncertainty could be introduced due to local discrepancies. Third, we excluded isolates from Nevada for the entire study period due to an unusually high number of CR isolates in 2006 (51%) and 2007 (49%) from participating laboratories. We could not find any published reports of CR *A baumannii* outbreak for these 2 years in Nevada. From 2009, the participating laboratories in Nevada did not report data into TSN. Because we could not establish a reason for this unusually high resistance rate, we were concerned about the reliability of those data and excluded the isolates. Fourth, the number of laboratories reporting data in the final years of study was reduced. The decrease in the prevalence of CR *A baumannii* and CephR *A baumannii* after 2008 could be attributed to decrease in the laboratories reporting data. However, we would expect a uniform reduction in all isolates; instead, we observed a selective reduction in inpatient isolates. This reduction in inpatient isolates could be attributed to improved infection control practices and/or antimicrobial stewardship programs, or it could be that hospitals contributing higher number isolates from settings were not represented after 2008. Finally, we do not have more recent data (beyond 2012) because TSN stopped collecting data after 2012; however, these represent the only national level data available.

CONCLUSIONS

Carbapenem-resistant and CephR *A baumannii* infections are a significant threat to all patients, including children. Although there was decreasing prevalence of CR and CephR *A baumannii* isolates between 2008 and 2012, they remain higher than

baseline. Our study highlights the need for continued surveillance of *A baumannii* infections in children and continued assessment of effective prevention strategies in vulnerable populations.

Supplementary Data

Supplementary materials are available at the *Journal of The Pediatric Infectious Diseases Society* online (<http://jpid.oxfordjournals.org>).

Notes

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References

- Wong D, Nielsen TB, Bonomo RA, et al. Clinical and pathophysiological overview of acinetobacter infections: a century of challenges. *Clin Microbiol Rev* 2017; 30:409–47.
- Sievert DM, Ricks P, Edwards JR, et al. Antimicrobial-resistant pathogens associated with healthcare-associated infections: summary of data reported to the National Healthcare Safety Network at the Centers for Disease Control and Prevention, 2009–2010. *Infect Control Hosp Epidemiol* 2013; 34:1–14.
- Spellberg B, Rex JH. The value of single-pathogen antibacterial agents. *Nat Rev Drug Discov* 2013; 12:963.
- Center for Disease Control and Prevention. Antibiotic Resistance Threats in the United States, 2013. Available at: <https://www.cdc.gov/drugresistance/pdf/ar-threats-2013-508.pdf>. Accessed November 9, 2017.
- Hu J, Robinson JL. Systematic review of invasive *Acinetobacter* infections in children. *Can J Infect Dis Med Microbiol* 2010; 21:83–8.
- Munoz-Price LS, Weinstein RA. *Acinetobacter* infection. *N Engl J Med* 2008; 358:1271–81.
- Vila J, Martí S, Sánchez-Céspedes J. Porins, efflux pumps and multidrug resistance in *Acinetobacter baumannii*. *J Antimicrob Chemother* 2007; 59:1210–5.
- Sato K, Nakae T. Outer membrane permeability of *Acinetobacter calcoaceticus* and its implication in antibiotic resistance. *J Antimicrob Chemother* 1991; 28:35–45.
- Adams MD, Goglin K, Molyneux N, et al. Comparative genome sequence analysis of multidrug-resistant *Acinetobacter baumannii*. *J Bacteriol* 2008; 190:8053–64.
- Blackwell GA, Hamidian M, Hall RM. IncM plasmid R1215 is the source of chromosomally located regions containing multiple antibiotic resistance genes in the globally disseminated *Acinetobacter baumannii* GC1 and GC2 clones. *mSphere* 2016; 1.
- Logan LK, Braykov NP, Weinstein RA, Laxminarayan R. Extended-spectrum β -lactamase-producing and third-generation cephalosporin-resistant *Enterobacteriaceae* in children: trends in the United States, 1999–2011. *J Pediatric Infect Dis Soc* 2014; 3:320–8.
- Braykov NP, Eber MR, Klein EY, et al. Trends in resistance to carbapenems and third-generation cephalosporins among clinical isolates of *Klebsiella pneumoniae* in the United States, 1999–2010. *Infect Control Hosp Epidemiol* 2013; 34:259–68.
- Logan LK, Renschler JP, Gandra S, et al. Carbapenem-resistant *Enterobacteriaceae* in children, United States, 1999–2012. *Emerg Infect Dis* 2015; 21:2014–21.
- Clinical and Laboratory Standards Institute. Performance Standards for Antimicrobial Susceptibility Testing. CLSI M100-S20U. Wayne, PA: Clinical and Laboratory Standards Institute, 2010.
- Center for Disease Control and Prevention. Multidrug-Resistant Organism & *Clostridium difficile* Infection (MDRO/CDI) Module. Available at: https://www.cdc.gov/nhsn/PDFs/pscManual/12pscMDRO_CDADcurrent.pdf. Accessed 23 January 2017.
- Logan LK, Gandra S, Mandal S, et al. Multidrug- and carbapenem-resistant *Pseudomonas aeruginosa* in children, United States, 1999–2012. *J Pediatric Infect Dis Soc* 2017; 6:352–9.

17. Eliopoulos GM, Maragakis LL, Perl TM. *Acinetobacter baumannii*: epidemiology, antimicrobial resistance, and treatment options. Clin Infect Dis **2008**; 46:1254–63.
18. Dellit TH, Owens RC, McGowan JE Jr, et al. Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America guidelines for developing an institutional program to enhance antimicrobial stewardship. Clin Infect Dis **2007**; 44:159–77.
19. Magill SS, Edwards JR, Bamberg W, et al. Multistate point-prevalence survey of health care-associated infections. N Engl J Med **2014**; 370:1198–208.
20. Infectious Diseases Society of America. White paper: recommendations on the conduct of superiority and organism-specific clinical trials of antibacterial agents for the treatment of infections caused by drug-resistant bacterial pathogens. Clin Infect Dis **2012**; 55:1031–46.
21. Jeong S, Hong JS, Kim JO, et al. Identification of acinetobacter species using matrix-assisted laser desorption ionization-time of flight mass spectrometry. Ann Lab Med **2016**; 36:325–34.
22. Toh BE, Paterson DL, Kamolvit W, et al. Species identification within *Acinetobacter calcoaceticus-baumannii* complex using MALDI-TOF MS. J Microbiol Methods **2015**; 118:128–32.
23. Sunenshine RH, Wright MO, Maragakis LL, et al. Multidrug-resistant *Acinetobacter* infection mortality rate and length of hospitalization. Emerg Infect Dis **2007**; 13:97–103.
24. Cheon S, Kim MJ, Yun SJ, et al. Controlling endemic multidrug-resistant *Acinetobacter baumannii* in intensive care units using antimicrobial stewardship and infection control. Korean J Intern Med **2016**; 31:367–74.
25. Manchanda V, Sanchaita S, Singh N. Multidrug resistant *Acinetobacter*. J Glob Infect Dis **2010**; 2:291–304.
26. DeTorres O, DeWindt S. Antimicrobial stewardship can lower the mortality from *Acinetobacter* infections. Int J Infect Dis **2014**; 21:211.
27. Klompas M, Branson R, Eichenwald EC, et al. Strategies to prevent ventilator-associated pneumonia in acute care hospitals: 2014 update. Infect Control Hosp Epidemiol **2014**; 35(Suppl 2):S133–54.
28. Cocoros NM, Priebe GP, Logan LK, et al. A pediatric approach to ventilator-associated events surveillance. Infect Control Hosp Epidemiol **2017**; 38:327–33.
29. Dong T, Zhao X. Rapid identification and susceptibility testing of uropathogenic microbes via immunosorbent ATP-bioluminescence assay on a microfluidic simulator for antibiotic therapy. Anal Chem **2015**; 87:2410–8.
30. Bauer KA, Perez KK, Forrest GN, Goff DA. Review of rapid diagnostic tests used by antimicrobial stewardship programs. Clin Infect Dis **2014**; 59(Suppl 3):S134–45.
31. Nolte FS. Molecular diagnostics for detection of bacterial and viral pathogens in community-acquired pneumonia. Clin Infect Dis **2008**; 47(Suppl 3):S123–6.