Inpatient Antimicrobial Stewardship in Pediatrics: A Systematic Review

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Background. The clinical and economic outcomes associated with pediatric antimicrobial stewardship programs (ASPs) and other supplemental antimicrobial stewardship (AS) interventions have not been well described or reviewed.

Methods. We performed a systematic review using PubMed to identify studies with any of the following terms in the title or abstract: “antimicrobial stewardship,” “antimicrobial control,” “antibiotic control,” or “antibiotic stewardship.” Studies were further limited to inpatient studies in the United States that contained the terms: “child,” “children,” “pediatric*” (“*” includes all terms with the same stem), “paediatric,” “newborn,” “infant,” or “neonat,” in the title or abstract. Clinical and economic outcomes from each relevant study were summarized.

Results. Nine original studies reported outcomes related to formal pediatric ASPs. An additional 8 studies focused on specific AS interventions; 3 on management of community-acquired pneumonia, 2 on vancomycin-specific initiatives, and 1 each on clinical support, antibiotic restriction, and antibiotic rotation. Reported outcomes include decreases in antimicrobial utilization (11 studies), prescribing errors (3 studies), and drug costs (3 studies). Five studies assessed the potential adverse effects of AS interventions on patient safety and found none. Data to support an association between pediatric AS interventions and antimicrobial resistance are limited.

Conclusions. A small number of pediatric studies evaluating ASPs or other AS strategies have been published. These studies demonstrate reductions in antimicrobial utilization, cost, and prescribing errors with no apparent negative impact on patient safety. Although the studies are promising, the current evidence base is limited. Additional studies focusing on the appropriateness and outcomes of antimicrobial prescribing practices as well as more formalized economic evaluations are needed.

Key words. antimicrobial stewardship; systematic review.

The majority of pediatric patients are treated with an antimicrobial during the course of hospitalization [1]. Unfortunately, a substantial proportion of antimicrobial prescribing is inappropriate, including errors in antimicrobial selection, dose, and duration [2, 3]. Overuse and misuse of antibiotics are primary drivers of antibiotic resistance, which is a rapidly growing global health threat that was recently recognized as a priority by the President of the United States [4]. Antimicrobial stewardship programs (ASPs) are one of the core strategies that can be used to address the problems of antibiotic overuse and resistance. Antimicrobial stewardship programs are designed to ensure that hospitalized patients receive optimal therapy. Through a variety of interventions including prior authorization and prospective-audit-with-feedback, ASPs aid prescribing physicians with proper selection, dosing, de-escalation, and stopping of unnecessary treatment. A growing body of evidence, primarily from adult settings, demonstrates that ASPs improve patient care, including mitigating resistance as well as other important outcomes such as minimizing prescribing errors, enhancing adherence to treatment guidelines, reducing Clostridium difficile infections (CDIs), and reducing antimicrobial costs [2]. As a result, multiple professional organizations, including
METHODS

Study Design
We conducted a systematic review of published studies evaluating the effectiveness of pediatric ASPs and other supplemental AS interventions.

Strategy for Literature Search
The primary literature search used PubMed to identify English language articles about pediatric ASPs and supplemental AS strategies through March 2014. Articles were selected for initial review if any of the following terms were included in the title or abstract: “antimicrobial stewardship,” “antimicrobial control,” “antibiotic control,” or “antibiotic stewardship.” Selection was further limited to those studies that contained the terms: “child,” “children,” “pediatric*” (“*” includes all terms with the same stem), “paediatric,” “newborn,” “infant,” or “neonat*” in the title or abstract. We performed a secondary literature search using the same search terms in Web of Science. We also reviewed the bibliographies of all retrieved studies and used the citation function within Web of Science to identify all papers that cited the studies included in our final analysis.

Study Review and Selection
All 3 authors reviewed the titles and abstracts of studies meeting initial selection criteria from the literature search to identify studies for complete manual review. One author (M. J. S.) reviewed all selected studies for consideration of data abstraction and analysis. Study inclusion was limited to those reporting evaluations and outcomes of pediatric ASPs or supplemental AS strategies in inpatient settings. Examples of supplemental AS strategies include use of guidelines and clinical pathways, antimicrobial order forms, antimicrobial cycling, and use of clinical decision-support tools [2].

Data Analysis
For studies selected for data abstraction, we determined whether the evaluation measured the impact of the ASP or AS strategy on the following outcome measures: antimicrobial utilization; antimicrobial or healthcare costs; antimicrobial prescribing errors; antimicrobial resistance; patient harm (eg, readmission rates, mortality, potential adverse outcomes of ASP recommendations); or physician satisfaction. We divided our analysis into those studies examining comprehensive ASPs and those evaluating specific AS strategies.

RESULTS

Literature Search and Study Selection
The initial PubMed search identified 71 studies (Figure 1). Based on title, 39 were excluded with consensus by all 3 authors. Thirty-four studies did not report outcomes associated with ASPs or AS interventions, an additional 4 were conducted outside of the United States, and 1 study focused on outpatients. The 32 remaining abstracts were reviewed by all 3 authors, and 23 were selected for full manual review. This review included 14 original studies and 9 review articles. The Web of Science search did not yield additional references. Bibliography review yielded an additional 5 original studies. One author (M. J. S.) critically appraised all 19 original studies. Four original studies were excluded after full review. An additional 2 studies cited at least 1 of the remaining 15 studies and reported an outcome of interest. A total of 17 studies were included for detailed analysis. These included 9 studies of formal ASPs and 8 studies focusing on evaluations of supplemental AS strategies.

Studies Focusing on Formal Antimicrobial Stewardship Programs
The 9 studies that describe formal ASPs originated from 4 centers: John’s Hopkins Children’s Center, Children’s Hospital of Philadelphia (CHOP), duPont Hospital for Children, and Children’s Mercy Hospital (CMH) (Table 1). Two ASPs implemented a prior authorization strategy and 2 used prospective-audit-with-feedback. Most studies reported outcomes from only 1 or 2 categories; specific outcomes for each study are presented in Table 2.

Antimicrobial Utilization. Five studies reported changes in antimicrobial utilization. All 5 of these studies showed...
decreases in utilization, although the specific metrics used differed across studies. Agwu et al [6] from Johns Hopkins reported on the impact of the first year of a web-based ASP on antimicrobial use. They highlight an 11% decrease in daily doses and a 14% decrease in antibiotic-days of restricted antimicrobials. At the same time, there was a 12% decrease in daily doses of unrestricted antimicrobials.

Two studies from DuPont Hospital for Children measured doses/1000 patient days. The first study focused solely on vancomycin use [7]. In the first 3 years of the ASP, there was a 33% decrease from the preintervention baseline of 378 doses of vancomycin per 1000 patient-days per year. A follow-up study from the same institution included additional antimicrobials [8]. Use of antimicrobials targeted by the ASP decreased 21%, whereas total antimicrobial usage decreased 38% during the first 3 years of the program.

Newland et al [9] used 2 different metrics to assess antimicrobial use: length of therapy (LOT) and days of therapy (DOT). Regardless of which metric was used, ASP formation was associated with decreases in both ASP-targeted and overall antimicrobial use. This is the only pediatric antimicrobial stewardship study to compare results to other hospitals. Compared with 25 other CHA hospitals, the authors found an 8% decrease in LOT and 7% monthly decrease in DOT for all antimicrobials after ASP
<table>
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C: Cost of restricted AMs decreased by $370 K (21.6%) in first year  
S: Prescriber satisfaction with ASP 22% before internet period and 68% during the post-internet period |
| Sick et al [10] | PA | Same | Same | Retrospective cohort | 2005–2011 | C | C: $103,787 saved per year. After initiation and maintenance costs, estimated $46,397 saved in first year and $86,497 in subsequent years |
| Metjian et al [11] | PA | 2 clinical pharmacists with oversight by ID physician. Night and weekend coverage by fellows | 1990s | Descriptive study covering 4-month period | 2005 | C, H | C: $50,090 saved over a 4-month period  
H: 3 of 62 children developed infection after ASP-recommended change in therapy. 0 of 22 children developed infection after ASP recommended no therapy |
| Newland et al [9] | F | 1 FTE clinical pharmacist; 0.3 FTE ID clinician; 0.5 FTE data analyst | 2008 | Quasi-experimental with control group | 2004–2010 | U, H | U: All AM use decreased from 883 DOT/1000 days to 787 DOT/1000 days. Select AM: 353 to 311. All AM use decreased from 567 LOT/1000 days to 523 LOT/1000 days. Select AM: 294 to 256 decrease in monthly usage: Overall: 6% (LOT and DOT) Select: 12% DOT, 13% LOT after controlling for CMI: 19% both  
H: No significant change in rates of mortality or readmission  
S: Most respondents agreed ASP had improved use for antibiotics (83%), decreased inappropriate use (84%), and improved quality of patient care (82%). 90% reported the ASP provided education. Only 11% reported loss of autonomy, and 6% felt the ASP interfered with patient care |
| Stach et al [13] | F | Same | Same | Electronic survey | 2010 | S | S |
| DiPentima and Chan [12] | F | Daily report review by ID pharmacist with PID physician | 2004 | Descriptive | 2004–2005 | E | E: 332 of 493 interventions were for prescription errors (48% significant, 25% severe, 27% minimal). Early detection of errors led to enhanced therapy (47%), cost reduction (28%), and prevention of ADEs (25%) |
| DiPentima et al [7] | F | Full-time clinical pharmacist with postdoctoral training in ID. Physician director board-certified in PID | Same | Descriptive | 2004–2007 | U, E, R | U: Vancomycin use decreased from 378 to 255 doses/1000 patient days from preimplementation to last year of study  
E: Vancomycin prescription errors noted in 190 interventions in 139 patients  
R: VRE decreased from 10 patients/year to 2 patients/year |
| DiPentima et al [8] | F | Same | Same | Pre-post | 2001–2007 | U, R | R: No significant change in rates of AM resistance among gram-negative organisms  
U: Targeted AMs decreased from 1250 to 98 doses/1000 patient days. Nontargeted AMs decreased from 1839 to 916 doses/1000 patient days |
| Flannery et al [14] | F | Same | Same | Electronic survey | Not specified | S | S: Recommendations from ID pharmacist rated more than somewhat helpful by 92% of respondents. All elements of ASP rated more than somewhat helpful by greater than 60%. 94% never experienced an adverse event associated with an ASP intervention |

**Abbreviations:** ADE, adverse drug event; AM, antimicrobial; ASP, antimicrobial stewardship program; C, cost; CMI, case-mix index; DOT, days of therapy; E, prescription errors; F, prospective-audit-with-feedback; FTE, full-time equivalent; H, patient harms; ID, infectious disease; LOT, length of therapy; PA, prior authorization; PID, pediatric ID; R, antimicrobial resistance; S, physician satisfaction; U, utilization; VRE, vancomycin-resistant Enterococcus.
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<td>Newman et al [15]</td>
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<td>3-stage least squares</td>
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<td>U: Ampicillin use for CAP 13% preintervention; 63% postintervention H: Treatment failures 1.5% preintervention; 1% postintervention</td>
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<td>Ambroggio et al [17]</td>
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<td>Toltzis et al [22]</td>
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<td>Mullet et al [20]</td>
<td>Clinical decision support system</td>
<td>Pre-post</td>
<td>1999</td>
<td>U, C, E, S</td>
<td>U: No changes in anti-infective utilization after introduction of decision support tool E: Number of orders per anti-infective course decreased 11.5%. 59% decrease in pharmacist interventions for erroneous dosing S: 28 of 31 users returned questionnaires based on Likert scale. Users reported improved overall antibiotic choices (81%), increased awareness of renal function (79%), beneficial dosage calculation assistance (96%), fewer adverse drug events (89%), and improved quality of care (81%). 93% would recommend such a system to others</td>
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Abbreviations: ASP, antimicrobial stewardship program; CAP, community-acquired pneumonia; CPG, clinical practice guideline; E, prescription errors; H, patient harms; R, antimicrobial resistance; S, physician satisfaction; U, utilization.
formation. This was more pronounced for targeted antimicrobials for which monthly decreases of 17% (LOT) and 18% (DOT) were observed.

Cost. Three studies reported changes in antimicrobial costs after introduction of an ASP; all 3 studies showed declines. Agwu et al [6] reported a decrease of $370,069 in the costs of restricted antimicrobials after the first year of their ASP. A follow-up study assessed the same program through year 6 and estimated an average annual savings of $104,000 [10]. After accounting for estimated start-up costs of $39,900 and yearly maintenance of $17,290, the authors report an overall net savings of $46,597 for the first year of the program and $86,497 each subsequent year.

Metjian et al [11] from CHOP also report on cost savings of their ASP. Over a 4-month study period, interventions performed by a clinical pharmacist working 8 hours a day from Monday to Friday were associated with a savings of $30,090 in drug acquisition costs.

Prescribing Errors. One study focused on prescribing errors [12]. The authors report that 67% (332 of 493) of ASP interventions during the first year of the ASP program were associated with prescription errors, most commonly dose-related. In a subsequent report of the first 3 years of the program, the authors report that 377 (23%) of ASP interventions resulted in renal dose adjustment and laboratory monitoring and that 97 (6%) of the interventions resulted in alternative dosing or changing or stopping therapy [8].

Antimicrobial Resistance. Two studies, both from duPont, reported on antimicrobial resistance. In one study that focused on vancomycin use, the authors reported a reduction in the incidence of vancomycin-resistant Enterococcus from 10 patients/year pre-ASP to 2 patients/year in first 2 years after implementation [7]. A follow-up study at the same institution found no significant change in resistance patterns of gram-negative organisms based on review of antibiograms over a 5-year period after introduction of the ASP [8].

Potential Adverse Outcomes of ASP Recommendations. Metjian et al [11] reviewed medical records of all children for whom the ASP recommended an alternative agent or no therapy. Three of 62 children for whom antimicrobial coverage was broadened (n = 17) or narrowed (n = 45) ultimately proved to develop an infection not covered by the ASP recommended therapy. None of the 22 children for whom the ASP determined there was no indication for antimicrobials were found to subsequently develop an infection requiring therapy. Newland et al [9] reported no temporal association between ASP formation and monthly mortality or readmission rates during a period when antimicrobial utilization was significantly reduced.

Physician Satisfaction With ASP. Three studies included information about physician satisfaction with the ASP. Agwu et al [6] reported that the transition to an internet-based ASP was associated with an increase in physician satisfaction with the ASP, from 22% in the preinternet period to 68% after implementation. Two additional studies report the results of surveys specifically designed to assess satisfaction with an ASP. A study of 205 physicians (56% response rate) at CMH found that most clinicians felt favorably about the ASP [13]. Specifically, respondents noted improvements in use of antibiotics (84%) and quality of care (82%) after ASP initiation. Only a few reported negative feelings about the ASP; 11% reported loss of autonomy, and 6% reported the ASP interfered with clinical decision-making. A survey study from duPont Hospital for Children reached similar conclusions [14]. Physicians were asked to rate multiple aspects of the ASP using a 5-point Likert scale. All aspects of the ASP were rated more than somewhat helpful (scores of 4 or 5) by at least 60% of all respondents.

Studies of Supplemental Antimicrobial Stewardship Interventions

In addition to the studies focusing on formal ASPs, we identified 8 studies of specific AS strategies (Table 3). Most of these focused on antimicrobial utilization. Three studies assessed antimicrobial use for community-acquired pneumonia (CAP), 2 studies assessed the effectiveness of interventions designed to reduce vancomycin use, and 1 study described the impact of a clinical decision support system on antimicrobial prescribing. An additional 2 intensive care unit (ICU)-based studies used antimicrobial resistance rates to assess the impact of antibiotic restriction and rotation policies.

Antimicrobial Utilization. Newman et al [15] described the impact of a CAP clinical practice guideline (CPG) that was introduced 4 months after ASP implementation. Among children with uncomplicated CAP, the authors reported an increase in ampicillin use from 13% pre-CPG to 63% post-CPG. The CPG was also associated with a significant increase in prescription of amoxicillin at discharge, whereas amoxicillin-clavulanate and cefdinir were the predominant antibiotics prescribed at discharge before the CPG. Two other studies report increases in ampicillin prescribing in centers without formal ASPs. Smith et al [16] assessed the impact of empiric guidelines for antimicrobial use on ampicillin prescribing for CAP and found increases in ampicillin prescribing from 8% pre-guideline to 44% post-guideline. This improvement

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was attributed to supplementary strategies including didactic lectures and guideline dissemination. Another center used existing quality improvement infrastructure to drive appropriate first-line treatment for CAP to 100% [17]. Key interventions included presentations at a guideline seminar, resident morning report and grand rounds, as well as creation of a reference card that was disseminated to all residents and ultimately included in a resident handbook [17].

Two studies report on the effectiveness of interventions designed to reduce vancomycin use. Bolon et al [18] described vancomycin use after introduction of an antibiotic order form that required providers to select a preapproved indication for vancomycin at a tertiary-care pediatric hospital. Introduction of the form was associated with an increase in inappropriate prescribing, in large part due to noncompliance and confusion with the order form. A smaller study performed at 2 academic neonatal ICUs (NICUs) focused on vancomycin use in neonates ≥72 hours of age [19]. The guideline recommended replacing empiric vancomycin with either nafcillin or oxacillin for neonates with presumed hospital-acquired infection. In the first year after implementation, empiric vancomycin use decreased by 35% at one NICU and 62% at the other.

**Prescribing Errors.** Only 1 study of supplemental stewardship strategies reported an impact on prescribing errors [20]. Although the introduction of a clinical decision support system did not lead to any changes in antimicrobial utilization, it was associated with more appropriate dosing as indicated by fewer orders per antimicrobial course, a 59% decrease in pharmacist interventions for erroneous dosing, and a 32% decrease in LOT that fell outside recommended guidelines.

**Antimicrobial Resistance.** Two ICU-based studies used gram-negative resistance patterns to assess the effectiveness of antimicrobial restriction policies. A study in a 16-bed pediatric ICU assessed resistance patterns before and up to 12 months after introduction of a ceftazidime-restriction policy [21]. Although ceftazidime use decreased by 96% during the intervention period, the incidence of ceftazidime-resistant organisms increased. Another study in a 38-bed NICU compared resistance rates among neonates admitted to 2 teams: one with a monthly rotating schedule for empiric gram-negative coverage (gentamicin, piperacillin-tazobactam, ceftazidime) and the other with standard of care dosing [22]. Although the protocol did impact antimicrobial utilization, no differences in incidence of resistance patterns between the 2 teams were noted during the 12-month study period.

**Potential Adverse Outcomes of Stewardship Interventions.** Two of the CAP studies assessed potential negative outcomes of implementing new guidelines. Newman et al [15] reported no significant difference in treatment failures for CAP before and after CPG implementation. Likewise, Smith et al [16] found no differences in readmissions for CAP after guideline introduction, and they also verified that children with discharge diagnoses of empyema or *Pseudomonas* pneumonia were not inappropriately treated with empiric ampicillin—a potentially unintended consequence of the guideline.

**Physician Satisfaction.** Only 1 supplemental AS study included information about user satisfaction. Users of the clinical decision support system reported by Mullett et al [20] reported improved overall antibiotic choices (81%), increased awareness of renal function (79%), beneficial dosage calculation assistance (96%), fewer adverse drug events (89%), and improved quality of care (81%). Ninety-three percent of users would recommend a similar system to other physicians.

**DISCUSSION**

Although ASPs have been recommended by the IDSA since 2007, published evaluations of pediatric ASPs are limited. Our search identified 9 studies that evaluated outcomes associated with formalized pediatric ASPs originating from only 4 centers. In contrast, a recent systematic review of adult ASPs included 37 articles [23]. Although limited in number, the existing pediatric studies demonstrate that ASPs can reduce antimicrobial utilization, antimicrobial drug costs, and prescribing errors. At the same time, the introduction of these ASPs was not associated with any detected adverse outcomes and was viewed favorably by the majority of physician users. We also identified 8 studies that described the impact of focused AS strategies and interventions. It is clear that a variety of strategies, whether associated with formal ASPs or not, can drive appropriate treatment of pediatric CAP. The results of other interventions were mixed. Vancomycin order forms were effective at one center but not another, and antibiotic restriction and antibiotic cycling were not associated with improved resistance patterns.

Across all studies, the most commonly reported outcome was change in antimicrobial utilization. Each study used a different metric, but all showed a significant decrease in use of antimicrobials targeted by the ASP. Some studies also reported decreases in nontargeted antimicrobials after ASP formation. One study compared utilization to other peer hospitals concurrently [9]. The use of this control group makes a more epidemiologically rigorous case for the effectiveness of the ASP. More importantly, it establishes a precedent for benchmarking antimicrobial use across
institutions. The ideal mechanism to promote benchmarking among non-CHA hospitals remains to be elucidated.

Although the introduction of pediatric ASPs seems to lead to decreases in antimicrobial utilization, an important limitation of utilization metrics such as DOT/1000 patient days is that it does not specifically capture important aspects of care including antimicrobial selection patterns, de-escalation, or adherence to evidence-based guidelines, all of which may be related to appropriateness or quality.

We identified 3 studies that assessed appropriateness of therapy—as defined by adherence to a national guideline—for CAP. Although conducting future studies focusing on appropriateness of therapy for infections with existing national guidelines is straightforward, assessing appropriateness of therapy when no gold standard therapy exists is more challenging. One approach, at the aggregate level, could be to compare broad-spectrum days to narrow-spectrum days. For example, studies have documented wide variability in broad-spectrum antibiotic use for children with similar diagnoses, revealing important stewardship targets [1, 24, 25]. Prescription errors are another important quality outcome. Both formal ASP review and use of clinical decision-support decreased errors in dosing, frequency, and LOT.

Three studies quantified cost savings related to ASPs, with estimates ranging from $46,000 to $370,000 in annual savings. These ranges for cost reduction are on par with those reported in studies from adult centers. However, the true value of ASPs extends beyond drug acquisition. Examples of additional cost savings relevant to ASPs include decreased drug administration rates and savings associated with transition from intravenous to oral antibiotics, as well as the unmeasured costs averted by reduction in the burden of infections due to antimicrobial-resistant pathogens—all of which could substantially expand cost savings [26]. Indeed, it has been proposed that the total cost of hospital care rather than drug acquisition alone may be a more appropriate metric for antimicrobial stewardship [27]. Such comprehensive economic analyses of pediatric ASPs have not been performed and are scant even in the adult literature. Formal economic studies, including input from health economists, are needed and will likely show that the economic impact of ASPs has been underestimated. Nevertheless, the greatest value of ASPs may lie in their ability to create more efficient care through improved clinical outcomes and decreased length of stay. These outcomes have been demonstrated after infectious diseases consultation in adult patients but have not been fully explored relative to ASPs or pediatric infectious diseases consultation [28]. Shifting the emphasis from strictly cost savings to improved quality of care may also be more likely to garner support for antimicrobial stewardship activities from administrators and patient safety advocates [29, 30].

The IDSA stewardship guidelines recommend that ASPs monitor both process (antimicrobial use) and outcome measures [2]. Common outcomes reported in the adult literature include reductions in antimicrobial resistance, adverse drug events, cost, and rates of CDI. Most published pediatric studies have focused on utilization, with less emphasis on cost, safety, and antimicrobial resistance. We did not identify any pediatric studies that assessed the impact of ASPs or other stewardship strategies on rates of CDI. Another important outcome is physician satisfaction with ASPs. Only a few of the included studies focused on clinician satisfaction, but it appears that ASPs are well accepted by pediatricians despite theoretical concerns about loss of provider autonomy [10, 13, 31].

Our study had limitations. Because there is no Medical Subject Heading (MeSH) term for antimicrobial stewardship, we had to rely on the basic text word searches described in the METHODS section. As a result, we may not have identified all pediatric stewardship studies. For example, studies of guidelines and clinical pathways that impact antimicrobial use but did not focus on antimicrobial stewardship per se were not included. In addition, we only included published studies in this review. Although only 4 centers contributed the studies of formal ASPs, the number of pediatric hospitals with ASPs has significantly increased since 2007. The PIDS has sponsored a Pediatric Antimicrobial Stewardship conference since 2010, and the annual IDSA meeting has had a pediatric stewardship session since 2012. Research presented at these and other venues may offer additional data to support pediatric ASPs. We also excluded studies regarding outpatient stewardship interventions. Although some studies have assessed compliance with national guidelines, only a few have described the effectiveness of interventions designed to improve judicious use of antibiotics. Additional studies in this arena are needed as well.

CONCLUSIONS

Despite these limitations, this report highlights the documented impact of pediatric ASPs and other stewardship strategies. Similar to ASPs at adult hospitals, pediatric ASPs reduce antimicrobial utilization, costs, and prescribing errors, with no evidence of adverse effects. However, the true value of pediatric ASPs has likely been underestimated. These findings have important implications for infectious diseases clinicians and pharmacists, researchers, and hospital administrators alike.
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