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Antimicrobial stewardship during a time of rapid antimicrobial development: Potential impact on industry for future investment

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ABSTRACT

In response to the antimicrobial resistance crisis, pharmaceutical industry reinvested in and produced new antibiotics. Antimicrobial stewardship programs influence optimal antimicrobial use, which often places them at the cross-roads of resistance and treatments. We surveyed a clinical administration database of US medical centers between 2014 and 2018 for index antimicrobial utilization date of six Qualified Infectious Diseases Products (QIDP). Among 132 hospitals identified, the median time to use any agent was 398 days (range 13 to >1478 days). QIDP antibiotic use was more likely among academic medical centers (range 34%–88%) and hospitals >400 beds (range 39%–86%) compared to non-academic medical center (3–51%) and smaller and hospitals (range 0–61%). The South was quickest to use all QIDP (median 733 days), while the Northeast was longest at 1370 days. New antimicrobials have limited clinical use, which impacts manufacturers' ability to stay in the antimicrobial market and further risking a depleted antimicrobial pipeline.

1. Introduction

Increasing antimicrobial resistance compounded with significant down-trend in new antimicrobial development has raised serious concerns (Spellberg et al. 2015). Multiple factors influence market availability of novel antimicrobials. Use is modest owing to limited treatment durations and small patient population size compared to chronic conditions with product pricing unequal to the morbidity and mortality benefit gained (Spellberg 2014). Research and development (R&D) of novel antimicrobials is scientifically challenging after decades of discovery and optimization (Spellberg 2014; Spellberg et al. 2015). Limited study subjects, unfavorable drug approval mandates and complicated regulatory processes lead to excessive R&D costs (Spellberg 2014). Lastly, antimicrobials are a unique commodity in that there is a transmissible loss of efficacy over time. This results in low return on investment (ROI), reduction in market share, and antibiotic market failure (Hits New Low n.d.).

Antimicrobial discovery initiatives developed in response to this need. In 2010, the IDSA "10 × '20 Initiative" recommended a goal that 10 new antibiotics be developed by 2020 (Boucher et al. 2013; Infectious Diseases Society of A 2010). Combating Antibiotic Resistant Bacteria (CARB-X), a non-profit partnership provides industry funding in the early antimicrobial development phase (Outterson et al. 2016). NIAID-funded Antibacterial Resistance Leadership Group, supports investigator-initiated studies on antimicrobials for multi-drug resistant (MDR) pathogens (Chambers et al. 2014). The FDA has also streamlined the drug approval process with the Qualified Infectious Disease Product (QIDP) and Limited Population Antibacterial Drug (LPAD) pathway for antimicrobials. A recent update on the 10 × '20 initiative indicates significant development achievements and potential to surpass this goal. However, the limited novelty of approved and in-pipeline agents is not sufficient to address the antibiotic resistance issue, and a diverse pipeline of new agents is still urgent (Talbot et al. 2019).

The 10 QIDP- and one LPAD-designated antimicrobials since 2012 suggest the pharmaceutical industry is responsive to expanded financial opportunities and regulatory incentives (Talbot et al. 2019). Additional compounds are likely to gain FDA approval between 2019 and 2021, including cefiderocol, imipenem-relebactam, and lefamulin. QIDP agents typically offer broad-spectrum activity, a factor often placing QIDP at odds with the principles of Antimicrobial Stewardship Programs

Abbreviations: QIDP, Qualified Infectious Diseases Product; R&D, Research and Development; ROI, Return On Investment; CARB-X, Combating Antibiotic Resistant Bacteria;; MDR, Multi-Drug Resistant; LPAD, Limited Population Antibacterial Drug Pathway; ASP, Antimicrobial Stewardship Program; CDB/RM, Clinical Data Base/Resource Manager™; EMR, Electronic Medical Record; AMC, Academic Medical Centers; DISARM, Developing an Innovative Strategy for Antimicrobial Resistant Microorganisms; CDS, Clinical Decision Support.

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(ASPs). A balance exists between optimized care, fiscal responsibility, and incentive to accelerate antimicrobial R&D. In this study, we investigate trends of six QIDP agents approved from 2014 to 2017 and time to first use in major United States medical centers.

2. Material and methods

2.1. Study design

The Vizient Clinical Data Base-Resource Manager™ (CDB-RM) is a comparative database with discharge and line item data for performance improvement populated by hundreds of health systems and community hospitals nationwide, including nearly all academic medical centers. The CDB-RM is automatically populated by electronic medical record (EMR) medication administration data on a quarterly basis. Data use from CDB-RM was previously described (Arnold et al. 2006; Bonk et al. 2006; Pakyz et al. 2008; Polk et al. 2011). Hospitals were included with an antimicrobial stewardship program and at least one reported administration of a targeted antimicrobial (QIDP) with submitted pharmacy administration data to the CDB-RM. This method for hospital inclusion in the study ensured that order sets were used for drug administration, which correctly identifies hospitals with and without use. Hospital identity was blinded; however, characteristics such as academic/community hospital, bed-size, case-mix index, and geographic region were collected. Hospitals with no QIDP administration or not reporting data to the CDB-RM were excluded. First date of antimicrobial administration was extracted from the CDB-RM. This study used FDA approval dates from the drug label, and time between FDA approval and first use was calculated. For the antibiotics with no use, the study query date was used as the time to first use.

2.2. Statistical analysis

The time to first use was analyzed by Mantel-Cox log-rank test using time to event Kaplan Meier analysis of each antibiotic. For the antibiotics with no use, the time to first use data were right censored at the time of data query to reduce skewing the median. Kruskal-Wallis non-parametric statistics with Dunn's multiple comparisons were used to evaluated median time to first use by case mix index. Categorical data were compared by Fisher's exact test. Statistical analyses were performed in GraphPad Prism 7 with a *P*-value of 0.05 or less for significance.

Table 1
Characteristics of hospital members in the Vizient database.

Hospital Type	Average Bed Size	Case Mix Index	Hospitals Represented, (n)	Average Daily Census
Academic Medical Center Hospitals (n = 365)	**<200**	**All**	**6**	**99**
		2.00–2.14	5	105
		>2.25	1	67
	200–399	**All**	**33**	**276**
		1.30–1.75	1	108
		1.75–1.99	11	280
		2.00–2.14	6	273
		2.15–2.25	5	298
		>2.25	10	280
	400–549	**All**	**104**	**428**
		1.30–1.75	9	288
		1.75–1.99	15	392
		2.00–2.14	27	437
		2.15–2.25	28	433
		>2.25	25	487
	550–749	**All**	**94**	**550**
		1.30–1.75	9	472
		1.75–1.99	18	461
		2.00–2.14	15	558
		2.15–2.25	26	568
		>2.25	26	636
	≥750	**All**	**128**	**811**
		1.30–1.75	2	792
		1.75–1.99	16	836
		2.00–2.14	19	1007
		2.15–2.25	38	724
		>2.25	53	796
Non-Academic Medical Center Hospitals (n = 76)	**<200**	**All**	**33**	**93**
		1.30–1.75	22	92
		1.75–1.99	5	72
		2.00–2.14	1	85
		2.15–2.25	1	142
		>2.25	4	113
	200–399	**All**	**27**	**159**
		1.30–1.75	19	165
		1.75–1.99	4	143
		2.00–2.14	2	132
		>2.25	2	163
	550–749	**All**	**4**	**430**
		1.75–1.99	3	452
		2.00–2.14	1	365
	550–749	**All**	**4**	**430**
		1.75–1.99	3	452
		2.00–2.14	1	365

3. Results

The data were queried from the CDB-RM on June 8, 2018. From this query, 132 of 146 hospitals (90.4%) reported administration of at least one QIDP antimicrobial and reported pharmacy transaction data to the CDB-RM. These hospitals represent diverse hospital characteristics and geographical spread (Table 1 **and** Fig. 1). The median number of days to use any of the respective QIDP agents (censored for used antibiotics) was 398 days (range 13 to >1478 days) (Table 2). Among all hospitals, those with the highest case index classification (>2.25) had faster time to first use than the 2 lowest case index classes (1.75–1.99 and 1.3–1.7; $P < 0.001$). Academic medical centers (AMCs) and hospitals >400 beds were more likely to use QIDP antimicrobials than smaller and non-academic medical center hospitals, which is consistent with these hospitals having a higher case mix index (Table 1).

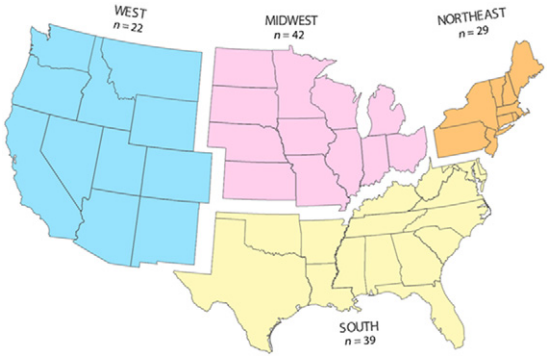
Significant use variability exists by geographic region (Fig. 1). The South was quickest to use all QIDP products, with median time to first use of 733 days, while the Northeast was the longest at 1370 days. For individual antibiotics, ceftazidime/avibactam was initiated significantly sooner in the South compared to the Midwest and West [median 340 vs 898 ($P < 0.001$) and 514 days ($P = 0.012$), respectively, $P = 0.02$]. Isavuconazole was initiated sooner in the West (309 days) compared to both the Northeast (893 days, $P = 0.027$) and Midwest (776 days, $P = 0.028$). No other significant differences occurred in time to first antibiotic use by region.

Large hospitals >400 beds and Academic Medical Centers (AMCs) were more likely to use QIDP products than small hospitals and non-academic hospitals, respectively (Table 3). In hospitals by bed size (≥400 vs <400 beds), there was a significant difference in use of ceftazidime/avibactam (80% with at least one use vs 57%; $P = 0.008$), ceftolozane/tazobactam (86% vs 60%, $P = 0.002$), isavuconazole (85% vs 49%; $P < 0.001$), oritavancin (43% vs 16%, $P = 0.002$), and tedizolid (39% vs 0%, $P < 0.001$). Similar results were found by hospital type (AMC vs non-AMC; Table 3).

The time to use QIDPs was significantly shorter for almost all antibiotics in AMC versus non-AMC hospitals (Fig. 2). Similar results occurrence when analyzing time to event (first use) by bed size of ≥400 vs <400 beds (data not shown), The level of patient acuity and complexity at larger institutions and AMCs is the most likely driver of early adoption.

4. Discussion

Our study demonstrates a significant delay in QIDP utilization. As mentioned previously, 90.4% of Vizient hospitals reporting to the CDB-RM have at least one use of a QIDP. However, looking among individual



Antibiotic	Northeast n = 29	Midwest n = 42	South n = 39	West n = 22
Ceftazidime/avibactam	75.9%	59.5%	89.7%	59.1%
Ceftolozane/tazobactam	71.4%*	73.8%	84.6%	81.8%
Dalbavancin	32.1%*	57.1%	53.8%	54.5%
Isavuconazole	60.7%*	69.0%	79.5%	86.4%
Oritavancin	25.0%*	33.3%	41.0%	31.8%
Tedizolid	17.2%	26.2%	25.6%	36.4%

*reflects percent out of 28 systems

Fig. 1. Regions representing the data analysis and the percentage of institutions which have used the antibiotics at the time of data capture.

antimicrobials, the percentage of hospitals that report zero use of a particular QIDP ranges from 21–74%, with up to 4 years after FDA approval to first use. Regional variability also existed in this study, with the South region overall adopting new antimicrobials the fastest. This earlier adoption parallels higher antibiotic use in southern states compared to other regions in the United States (Hicks et al. 2015). Also, AMCs and large hospitals are new therapy early adopters, likely due to patient complexity and specialized services, such as transplantation and tertiary critical care. However, even in AMC institutions, the most rapidly adopted antimicrobials, isavuconazole and ceftolozane/tazobactam, still had 282–289 median days until first use. While delay may occur from FDA approval to product availability, this limitation does not account for the entirety of the adoption lag.

ASPs influence optimal antimicrobial use by ensuring that safety and effectiveness are balanced with social and fiscal responsibility. Both physician and pharmacist leadership are crucial for implementation and operation of necessary components to optimize guideline-driven outcome metrics (Dodds Ashley et al. 2018; Ostrowsky et al. 2018). This is challenging for empiric therapy given the complexities of providing safe, effective therapy with diagnostic uncertainty, epidemiologic resistance patterns, and patient acuity, while maintaining a fiscal margin (Barlam et al. 2016; Dellit et al. 2007). This is often misinterpreted that the least expensive antimicrobial is preferred. This interpretation fails to recognize value. As described by Miller, this approach toward new antibiotics from infectious diseases specialists may appear hypocritical to clamor for new antibiotics but avoid their use at all costs (Miller 2019). This dilemma, however, is one that ID clinicians understand is necessary to sustain antibiotics for future generations.

Value is defined as quality over cost and requires a system boundary to the calculation. Quality is typically the product of safety, effectiveness, and antimicrobial resistance emergence mitigation; cost is limited to the pharmacy department budget. Expanding the system horizon to include the entire hospital, health-system, or US healthcare system provides different value calculation outcomes. Post-marketing analysis encompassing the traditional factors as well as health-system factors helps to identify the healthcare value of antimicrobials. Novel clinical trial designs may help identify the value of new antibiotics. In the examples of ceftazidime/avibactam and meropenem/vaborbactam, these were compared to “best available therapy”, and composite endpoints of safety and efficacy identified high value of these antibiotics for infrequent but serious carbapenem-resistant Enterobacteriaceae infections (van Duin et al. 2018; Wunderink et al. 2018). At a minimum, we believe that value should be calculated at a health-system perspective and optimally at a societal perspective, since antimicrobial misuse impacts patients outside the index system. However, societal value remains difficult to quantify financially. The *Developing an Innovative Strategy for Antimicrobial Resistant Microorganisms* (DISARM) Act proposed in late 2018 may help alleviate some of the cost concerns by allowing Medicare to offer an add-on payment to inpatient hospitals that use a qualifying antibiotic as well as further incentivizing antibiotic research and development (Hatch 2019).

Table 2
QIDP agents, FDA approval date, and time to first use.

QIDP agent	FDA approval	Time to first use, days (median[a], range)
Ceftazidime/avibactam	2/25/2015	463 (48 to >1200)
Ceftolozane/tazobactam	12/19/2014	405 (13 to >1268)
Dalbavancin	5/23/2014	1477 (83 to >1478)
Isavuconazole	3/6/2015	501 (57 to >1191)
Oritavancin	8/6/2014	>1403 (105 to >1403)
Tedizolid	6/20/2014	>1450 (20 to >1450)

[a] Antibiotics with no use were right censored for time to first use.

How can we change the value equation? We can demonstrate improved safety, efficacy, or reduce the cost by lowering R&D expenses. Non-inferiority studies leave us challenged to prove a new agent is more effective than the standard of care. Therefore, the benefit assigned to QIDP is only realized with patent exclusivity extension. Our data demonstrate an overall lack of QIDP use, and most use is confined to a limited number of hospitals and health-systems. Pharmaceutical manufacturers need to realize a rapid ROI to meet investors' expectations. Recent NASDAQ reports of low share prices resulted in cutbacks, bankruptcy, and fear of manufactures leaving the industry completely. The most recent and stark example of this plazomicin from Achaogen, Inc., which filed for bankruptcy within 10 months of FDA approval of the antibiotic. Improved reimbursement models could alleviate this issue such as “pull incentives” from governments to allow companies to endure the time from market entry to sustainability (McKenna 2019).

Stewardship must continue to ensure optimal antimicrobial therapy. ASPs should contribute to the decisions about which patients receive QIDP products and consider the fiscal impact to the healthcare entity rather than just pharmacy budgets. While the hospitals in this study have ASPs, the ASP impact in the hospital and influence on formulary decisions was not available. Rapid diagnostics and clinical decision support (CDS) tools may be bridges to finding the right patient for QIDP products (Kullar et al. 2013). Early identification of bacterial resistance and initiation of preferred treatment improves the probability of appropriate therapy, positive outcome and value. Unfortunately, new resistance mechanisms outpace the development of comprehensive rapid diagnostic panels. In addition while new antimicrobials are approved, persistent difficulty in testing for antibiotic susceptibility of new antibiotics hinders clinical assessment of appropriateness of therapy (Humphries and Hindler 2016). CDS can augment empiric therapy decision-making by identifying patients with a history of resistance or who may benefit from QIDP administration (Forrest et al. 2014). These initiatives are needed to foster antimicrobial development while balancing the goals of ASPs.

Finally, current QIDP products are broad-spectrum yet also target a very specific resistance mechanism. A general stewardship principle promotes the use of broad-spectrum empiric therapy and narrow spectrum definitive therapy (Dellit et al. 2007). The breadth of QIDP products

Table 3
QIDP agents and percentage of institutions with at least one use by bed range and center type.

QIDP agent	Bed range (% used)			Center type (% used)		
	<400	≥400	*P*-value[a]	Non-AMC	AMC	*P*-value[a]
Ceftazidime/avibactam	57% (25/44)	80% (70/88)	0.008	49% (17/35)	80% (78/97)	<0.001
Ceftolozane/tazobactam	60% (26/43)	86% (76/88)	0.001	51% (18/35)	88% (84/96)	<0.001
Dalbavancin	40% (17/43)	56% (49/88)	0.096	46% (16/35)	52% (50/96)	0.558
Isavuconazole	49% (21/43)	85% (75/88)	<0.001	46% (16/35)	83% (80/96)	<0.001
Oritavancin	16% (7/44)	43% (37/87)	0.003	23% (8/35)	38% (36/96)	0.145
Tedizolid	0% (0/44)	39% (34/88)	<0.001	3% (1/35)	34% (33/97)	<0.001

[a] Fisher's exact test.

will limit definitive therapy use except for polymicrobial infections. However, development of narrow-spectrum, highly-specific antimicrobials risks developing a niche market resulting in exorbitant acquisition costs, like the monoclonal antibody market. This is not a criticism of this sphere or a statement of inappropriateness; however, it is a major paradigm shift from historically inexpensive antimicrobials. It is unlikely that the US healthcare system could support this charge structure.

In response to the rising threat of resistance, many clinicians called for renewed investment in novel antimicrobials. Aided by economic support packages, pharmaceutical manufacturers responded by entering the market and delivering needed products. However, manufacturers are still struggling to stay in the antimicrobial market, and our study demonstrates the delay in market uptake of antimicrobials nationwide. Incentives to use new antimicrobials are appropriately met

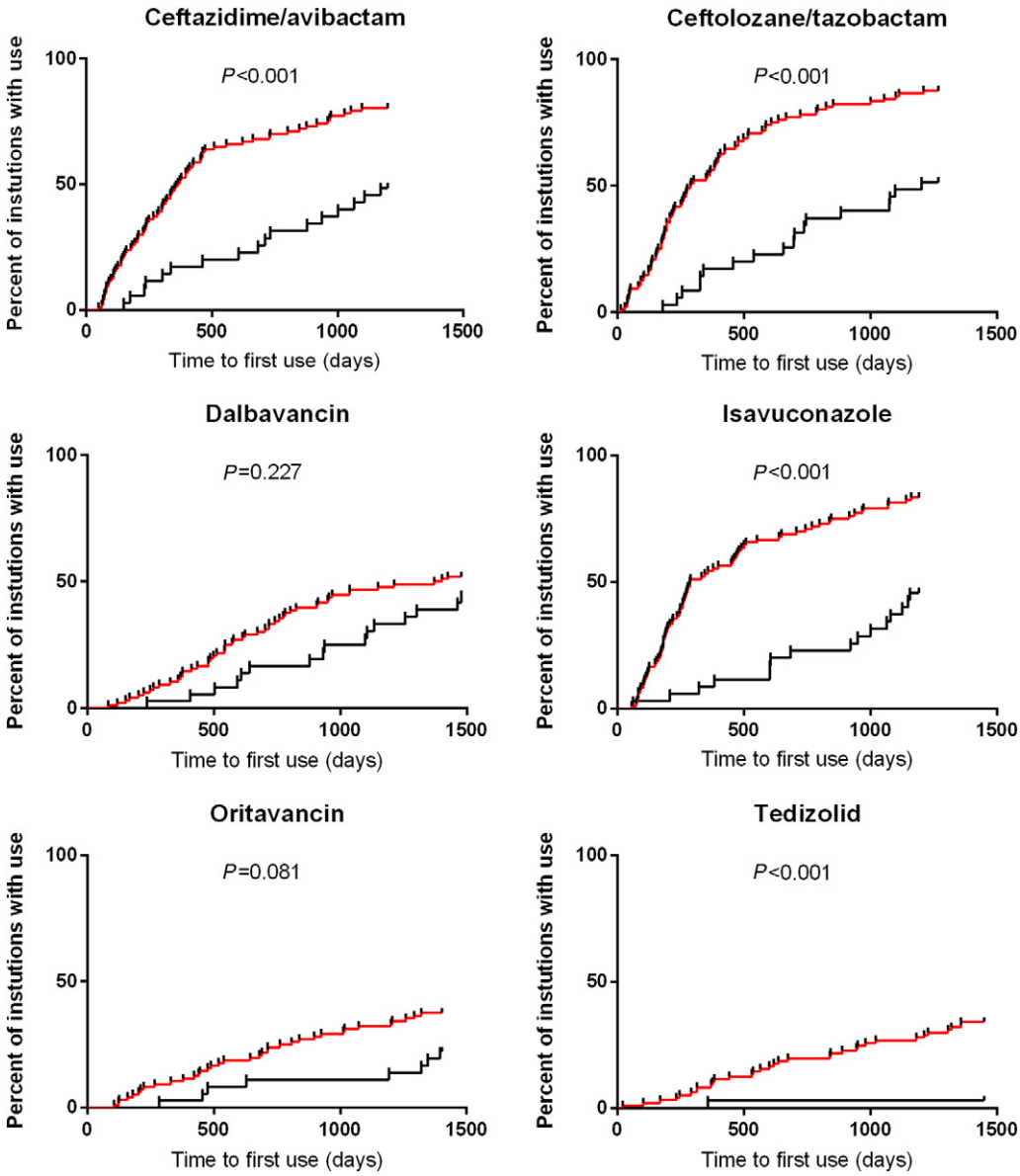


Fig. 2. Time to event (first use) curves for the 6 QIDP products compared by AMC vs non-AMC institutions.

with concern over efficacy, safety, and risk of resistance development. A better reimbursement model for antibiotics may help industry pursue antimicrobial development despite limited use.

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