MM&M THERAPEUTIC FOCUS

Infectious Diseases

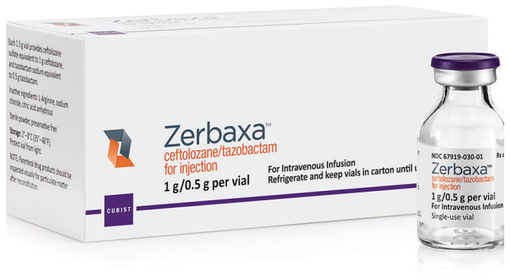
While advances in the treatment of hep.-C have been well noted, the infectious-diseases space has seen considerably less innovation than many other therapeutic areas. Given the stubbornness of superbugs like MRSA and growing antibiotic resistance, the healthcare industry has finally turned its attention to the category. **Rebecca Mayer Knutsen** outlines the potential threats and solutions

Pathogens have barged onto the healthcare scene and do not intend to retreat without a fight. To combat rising rates of bacterial, viral and fungal infections, small biotech firms are poised to swoop in with biological elixirs while legislation is spurring development and luring companies back into the fold.

Infections have entered stage left and taken over the microphone at the global anti-infective drug podium. Concern is at an all-time high over the proliferation of infections, whether those acquired from a misplaced catheter during a hospital stay to the far more serious gram-positive bacteria MRSA, a rapid-spreading superbug.

Hospital-acquired infections ignite a cascade of issues, ranging from high morbidity and mortality rates to increased healthcare costs. And the antibiotics market hasn't welcomed a new class of drugs in more than 25 years, which has left many fearing a future with little control over common bacterial diseases.

"The new generation of antibiotic classes hasn't kept pace with resistance. We are running out of options," says Steve Projan, PhD, head of MedImmune's Innovative Infectious Diseases & Vaccines Unit. This dire situation, he adds, has stimulated interest in alternative pathogen-specific strategies, including the use of monoclonal antibody (mAb) technology.



Zerbaxa has set itself apart from previous entrants in the war on gram-negative bacteria

A call for new solutions has left the front door ajar for small biotech firms focused on combating infections with targeted biologics, with and without the use of antibiotics. Precision medicine will play a key role in future bacterial infection treatment plans but will likely hinge on progress in the biomarker department.

"It's easier to prevent an infectious disease than to treat one," says Eszter Nagy, MD, PhD, president and CSO of Arsanis Biosciences.

Boasting an excellent safety profile, biologics set themselves apart from the antibiotic camp because they don't bind to human molecules; they remain in the bloodstream until they find their target and change the immune response. "Biologics help preserve the body's microbiome. Antibiotics kill the microbes—and some of the body's natural defense system along the way," Nagy notes.

Hospital-acquired infections pose the ultimate battle in infectious-disease management. According to Gil Bashe, EVP of Makovsky's health practice, the industry must address the obvious question: Are our hospitals reducing risk? "The combination of antibiotic overuse and sterile conditions is both problem and opportunity," he says. Indeed, pharma companies with marketed anti-infectives are jumping in to discuss how to avoid hospital infections. "It's an opportunity to talk about the correct use of products and also use the problem as a teaching moment," he suggests.

A new class of antibiotics, RNA-guided nuclease, function with a mechanism of action similar to a vaccine. As such, they hold promise, according to Ric Cavieres, principal and advisory life sciences commercial practice leader at EY. The nuclease targets and kills bacteria with antibiotic resistance and virulence genes but spares the body's good bacteria.

TOP 25 INFECTIOUS-DISEASE PRODUCTS

Category leaders, ranked by 2014 US sales, and their media spend

Rank	Product	Manufacturer	US sales $ (millions)	Vs. prior 12 mos.	TRx (000s)	Vs. prior 12 mos.	US journal media $ (000s)	Vs. prior 12 mos.
1	**Sovaldi**	Gilead	$7,846.0	10,904.2%	261.9	14,450.0%	$4,413.0	N/A
2	**Atripla**	Gilead/Bristol-Myers Squibb	$2,973.2	2.2%	1,158.0	3.3%	$0.0	N/A
3	**Truvada**	Gilead	$2,515.0	10.8%	1,606.2	5.8%	$238.0	4.8%
4	**Olysio**	Janssen	$1,969.5	17,804.5%	79.1	27,175.9%	$707.0	1,798.2%
5	**Harvoni**	Gilead	$1,550.0	N/A	N/A	N/A	$630.0	N/A
6	**Stribild**	Gilead	$1,351.7	120.6%	424.1	122.0%	$1,438.0	-1.6%
7	**Prezista**	Janssen	$1,153.4	14.9%	818.2	12.7%	$1,798.0	38.8%
8	**Prevnar 13**	Pfizer	$1,104.5	33.4%	266.9	3,729.3%	$0.0	-100.0%
9	**Isentress**	Merck	$1,036.8	1.2%	768.2	0.8%	$771.0	45.3%
10	**Complera**	Gilead	$898.7	41.3%	368.0	36.8%	$1,567.0	8.2%
11	**Reyataz**	Bristol-Myers Squibb	$894.0	-5.2%	622.5	-9.8%	$1,146.0	75.2%
12	**Tamiflu**	Genentech	$850.4	30.6%	6,076.8	14.2%	$0.0	N/A
13	**Gardasil**	Merck	$782.4	15.4%	40.1	-9.3%	$0.0	N/A
14	**Zyvox**	Pfizer	$740.0	1.5%	175.8	-9.2%	$389.0	-46.9%
15	**Xifaxan**	Salix	$716.1	24.1%	632.3	16.7%	$1,320.0	42.9%
16	**Zostavax**	Merck	$678.2	-4.1%	2,243.0	-2.8%	$158.0	N/A
17	**Cubicin**	Cubist	$666.3	6.0%	48.7	-4.5%	$230.0	-68.9%
18	**Synagis**	MedImmune	$655.3	-15.0%	208.3	6.5%	$0.0	-100.0%
19	**Viread**	Gilead	$655.0	7.7%	633.6	5.2%	$0.0	N/A
20	**Epzicom**	ViiV Healthcare	$616.2	13.8%	462.7	8.4%	$2,388.0	251.8%
21	**Varivax**	Merck	$599.9	20.4%	33.4	39.7%	$0.0	N/A
22	**Pneumovax 23**	Merck	$516.6	9.0%	884.6	17.5%	$580.0	222.8%
23	**Norvir**	AbbVie	$479.3	-2.3%	1,386.9	0.3%	$0.0	N/A
24	**Amoxicillin TR/Potassium Clavulanate**	Generic	$451.6	40.7%	24,179.3	2.4%	$15.0	N/A
25	**Valcyte**	Genentech	$446.6	5.9%	125.1	-9.3%	$0.0	N/A

Sources: Sales/TRx, IMS Health; journals, Kantar Media
Note: List includes products FDA indicates as approved for treating AIDS, hepatitis B/C and bacterial infections, as well as vaccines and other antivirals

Notable GAINs

With its recent acquisition of Cubist Pharmaceuticals, Merck has doubled down on the growing issue of drug resistance. Four novel antibiotics approved in 2014, including Cubist's Zerbaxa and Sivextro, were fast-tracked under the Generating Antibiotics Incentives Now (GAIN) Act. The antibacterials joined Durata Therapeutics' Dalvance and the Medicines Company's Orbactiv (see Clinical Corner, p. 40).

The 2012 enactment of the GAIN Act is the biggest thing that has happened in this space in some time, reports Daniel Kracov, partner and FDA and healthcare practice head at Arnold & Porter. "It's fair to say it's been a success," he says. "But the general consensus is that it's not enough."

The GAIN Act is chock-full of incentives for developers, including access to expedited FDA review for approval, fast-track designation and five years of potential market exclusivity for the development of qualified infectious-disease products (QIDP). And yet nearly 80% of antibiotic pipeline products are being studied by small companies, not the pharma giants, Cavieres notes. Once success is imminent, however, the biotech assets will become quite attractive to pharma sharks ready to swoop in for a feeding frenzy.

Arsanis, Achaogen and MedImmune share a focus on developing antibody-based programs to combat the high-level medical needs in the ICU setting. Arsanis's ASN-100 is a monoclonal antibody cocktail in preclinical development to prevent and treat severe hospital-associated *Staphylococcus aureus* infections. Achaogen is developing plazomicin for the treatment of serious bacterial infections due to multidrug-resistant (MDR) *Enterobacteriaceae*, including carbapenem-resistant *Enterobacteriaceae* (CRE), identified by the CDC as one of three immediate public health threats.

"Carbapenems are the last stand we have against bad infections," says Barry Eisenstein, MD, distinguished physician, antimicrobials, at Merck. "Once those go, we're in deep trouble."

MedImmune is focused on drug-resistant *S. aureus*, *Pseudomonas aeruginosa*, respiratory syncytial virus (RSV) and influenza. According to the CDC, about 13% of healthcare-associated infections caused by *P. aeruginosa* and 63% of those caused by *Acinetobacter baumannii* are multidrug resistant.

Synagis (palivizumab), marketed by MedImmune for RSV, is the first monoclonal antibody developed to help prevent an infectious disease. Synagis binds the RSV envelope fusion protein on the virus's surface, which prevents the virus from fusing with a cell membrane and infecting healthy cells.

MedImmune received fast-track designation for MEDI3902 for the prevention of nosocomial pneumonia caused by *P. aeruginosa;* MEDI4893 for the prevention of nosocomial pneumonia caused by the bacterium *S. aureus;* and MEDI8897, a monoclonal antibody, for the prevention of lower respiratory tract illness (LRTI) caused by RSV in infants and young children.

For more than 25 years, complicated urinary tract infections were treated with category standards, including ciprofloxacin, the second-generation fluoroquinolone, and Merck's Invanz (ertapenem). However, the hefty market share of these drugs could soon be threatened. Tetraphase's lead compound, eravacycline, is positioned to change the treatment paradigm. The drug is in Phase-III trials for two indications: cUTI and intra-abdominal infections.

"Eravacycline is an IV to oral transition therapy," explains Guy Macdonald, president and CEO, Tetraphase Pharmaceuticals. "This

CLINICAL CORNER

Zerbaxa earned the distinction of being the first new antibiotic to capture the FDA's green light under the Generating Antibiotic Incentives Now (GAIN) Act for the treatment of gram-negative bacteria. Ceftolozane/tazobactam gained 2014 approval to treat adults with complicated urinary tract infections (cUTI) and complicated intra-abdominal infections (cIAI), in combination with metronidazole.

The medication, a combination of a cephalosporin and a beta lactamase inhibitor, followed a path from developer Calixa to Cubist Pharmaceuticals and then, most recently, to Merck. On the heels of its January acquisition of Cubist, Merck made a public recommitment to its work in the infectious disease arena in April, aligning with an all-time high alert regarding gram-negative bacteria.

Barry Eisenstein, MD

E. coli and other gram-negative bacteria have caught global attention as serious public health concerns. While *E. coli* is responsible for most UTIs, cases of cUTI caused by *Pseudomonas aeruginosa* are increasing.

In 2013 the CDC released a report deeming nearly half of all prescribed antibiotics as unnecessary. "Overuse of anti-infectives is a serious part of the problem," says Gil Bashe, EVP of Makovsky's health practice. "Data show that patients want a prescription and physicians are overly customer friendly when it comes to prescribing antibiotics."

Zerbaxa, however, has set itself apart from previous entrants in the war on gram-negative bacteria. "The bacteria become resistant not by acquiring enzymes but rather by activating a 'pump system' similar to a basement sump pump, adapted to getting rid of toxins," Bashe explains. Toxins, in this scenario, are the antibiotics. The bacteria hinder the effects of many antibiotics, even the strongest ones.

Barry Eisenstein, MD, distinguished physician, antimicrobials at Merck (who joined via the Cubist camp), notes Zerbaxa's unique ability to withstand *Pseudomonas*, a common form of gram-negative bacteria. Zerbaxa is effective because "ceftolozane is unable to be pumped out by the *Pseudomonas* pump," he says. "We don't fully understand the mechanism, but we're working on it."

Under the GAIN Act, Zerbaxa received QIDP status, making it eligible for benefits including a five-year extension of Hatch-Waxman exclusivity. Zerbaxa is currently under review in the European Union for both cUTI and cIAI indications (a decision is expected later this year). Merck is studying the drug for hospital-acquired bacterial pneumonia/ventilator-associated bacterial pneumonia at a 3g dose.

The rising number of gram-negative bacterial infections worldwide leads analysts to expect that Zerbaxa will reach blockbuster status—which means that it isn't likely to be alone for long. With the February approval of Actavis's Avycaz and with Tetraphase's eravacycline in development, the category could get crowded quickly.

Developers need to step up their R&D and antibiotic stewardship efforts to fight against gram-negative bacteria. "Pharma companies must be part of the solution of proper use and innovation," Bashe says.

method provides physician flexibility and shortens the hospital stay."

Tetraphase aims to file an NDA by year-end and reach the market by mid-2016. "The antibiotic regulatory environment has improved dramatically," Macdonald adds. "FDA will approve two indications at once, which is more cost effective for developers."

Merck's Sivextro, acquired through Cubist, also aims to improve patient convenience with its once-a-day, six-day course of IV or oral treatment for MRSA. Sivextro is more convenient and less toxic than first-generation treatments, including Pfizer's Zyvox, which is given two times a day for 10 to 14 days.

As for big pharma, it is likely abandoning the anti-infective market because the products aren't profitable enough, Nagy says. "The price acceptance isn't as great as it is for cancer drugs. Cancer drugs extend life for a few months at an astronomical cost, but it's not lifesaving like an antibiotic. We have a skewed perspective."

AstraZeneca has spun its early-stage anti-infectives research arm into a stand-alone subsidiary, with a focus on novel gyrase inhibitor AZD0914, currently in Phase-II development for gonorrhea. Indeed, Eisenstein identifies gonorrhea as an impending problem. "The bacterial infection is a lethal disease that needs to be treated easily and quickly," he says. GlaxoSmithKline, Melinta Therapeutics and Cempra are studying products for uncomplicated gonorrhea.

Dificid (fidaxomicin) tablets, developed by Optimer and later acquired by Cubist, gained approval in May 2011 to treat *Clostridium difficile*–associated diarrhea. Cubist has added a Phase-III compound to Merck's arsenal, including its own combo product in development. Pfizer's *C. difficile* vaccine candidate, PF-06425090, was granted fast-track status and is in Phase-II development.

The post-Ebola landscape

With the world still on edge in the wake of the Ebola threat of 2014, we're now collectively more aware that individuals traveling with a virus can spark widespread health mobilizations. "Infections can spread transgeographically through human contact," Bashe says.

ViiV Healthcare's Triumeq, a new entrant in the integrase inhibitor category for HIV, is expected to overcome market leader Atripla. The Gilead Sciences/BMS blockbuster raked in $3 billion in 2014. "A cancer drug enabled the destruction of hepatitis B–infected liver cells while leaving normal cells unharmed in 100% of cases in pre-clinical testing. When the cancer drug was administered with an antiviral, the infection was cleared twice as fast," Cavieres explains.

To prevent the emergence of drug-resistant strains of HBV, treatments need to force the host cell to kick the virus out, instead of targeting the virus itself. Bashe draws an analogy: "It's similar to mowing your grass to have a nice lawn but knowing weeds are spreading in the ground. What's growing under the surface becomes the genesis of the problem itself."

Hep.-C redux

The onslaught of hepatitis-C medications, including Gilead's Harvoni, Janssen's Olysio and AbbVie's Viekira Pak—has overwhelmed the market and payers alike. The hep.-C environment is more optimistic these days, according to Brian Whalen, PhD, VP at Evoke. He points to increased likelihood of treatment success, multiple treatment options and a recommendation for earlier treatment as vast improvements.

The pricing war will come to ahead again as Merck's grazoprevir and elbasvir combo hep.-C solution awaits approval. ■