MEDICAL DEVICE DAILY™

THE DAILY MEDICAL TECHNOLOGY NEWS SOURCE

MONDAY, JUNE 27, 2016 VOLUME 20, NO. 123

SEARCHING FOR SUPERBUG'S KRYPTONITE

Resistant superbug's arrival highlights the need for more effective diagnostic products

By Liz Hollis, Staff Writer

Politicians and medical experts worldwide alike have decried the lack of innovation in antibiotics – an area that has been neglected for three decades – but another area is turning out to be just as important: diagnostics.

"Without rapid, precision Dx to target therapy, physicians generally treat empirically, prescribing widely available and inexpensive broad-spectrum antibiotics," according to an executive briefing paper authored by Jonathan Kfoury and Alex Vadas, managing directors, and T.J. Bilodeau, U.S. practice manager in L.E.K. Consulting's Biopharma and Life Sciences practice.

This situation, however, is leading to poor patient outcomes and growing antibiotic

See Diagnostics, page 4

Cut the blame game, infection control is a shared problem

By Amanda Pedersen, Senior Staff Writer

Superbugs tend to evoke a lot of finger pointing and the blame often spreads as wide and fast as the outbreaks themselves. But if the medical device industry learned anything from last year's high-profile duodenoscope debacle it's that infection control is a shared responsibility. Manufacturers, third-party

See Infection, page 5

THREAT OF U.K. RECESSION LOOMS

Med-tech industry tries to find footing in wake of affirmative Brexit vote

By Varun Saxena, Staff Writer

Med-tech stocks are tumbling along with the broader market amid fear and uncertainty over the United Kingdom's looming Brexit from the European Union. Industry bellwethers Medtronic, Abbott and Zimmer are all down more than 2.5 percent following the June 23 U.K.'s vote to leave the E.U. U.K. Prime Minister

See Brexit, page 6

REGULATORY

FDA informs Franken MDRs offer no news on Medtronic's Infuse

By Mark McCarty, Regulatory Editor

The FDA has responded to a query by Sen. Al Franken (D-Minn.) on the point of medical device reports for the Medtronic Infuse bone morphogenic protein device, advising him that the agency not only saw no need for enforcement action for failure to report adverse events, but also that the company's updated MDR report

See Regulatory, page 7

3-D TO GET THE GREEN LIGHT?

South Korea cautiously considering 3-D printed medical instruments

By Haky Moon, Staff Writer

HONG KONG – South Korea is considering allowing 3-D printing to be used to produce medical devices, but it will have to develop stronger regulations before moving forward.

The South Korean Ministry of Food and Drug Safety (MFDS) reported it is it now considering greenlighting the use of

See 3-D, page 8

IN THIS ISSUE

NEUROLOGY EXTRA

Staff Writers Amanda Pedersen on one of med-tech's key sectors

Read this week's Monday Special

Anti-Microbial Resistance

Rapid point-of-care tests for anti-microbial resistance

Shyama Gosh's in-depth analysis on AMR

Read this Special Supplement

OTHER NEWS TO NOTE

Salt Lake City-based **Great Basin Scientific Inc.**, a molecular diagnostic company, reported that the Nasdaq Listing Qualifications Panel granted the company's request for the continued listing of its common stock on the Nasdaq Capital Market.

Dublin-based **Medtronic plc** reported a global partnership with the World Stroke Organization, of Geneva, to increase stroke awareness through several initiatives. The organizations plan to educate, raise awareness, and support effective management of patients who have strokes.

PRODUCT BRIEFS

Bioventrix Inc,, of San Ramon, Calif., received certification for CE marking its Revivent TC Transcatheter Ventricular Enhancement System. Following a myocardial infarction or heart attack, the Revivent TC System implants proprietary micro-anchor pairs to exclude scarred myocardium from the healthy tissue of the left ventricle.

Centric Medical, a division of **Life Spine, Inc.**, based in Huntley, Ill., reported FDA 510(k) marketing clearance for the Subtalar Arthroereisis Implant System for treating hyperpronation of the foot and stabilization of the subtalar joint. The Subtalar Arthroereisis Implant System is a one-piece titanium implant designed to facilitate correction of pathologic flatfoot deformities by blocking forward, downward and medial displacement of the talus, thus allowing normal articulation of the subtalar joint while deterring excessive pronation. The innovation of the system rests in its gradually softened threads which aid in minimizing edge effects that may lead to pain while resisting migration, in addition to being fully cannulated to guide accurate insertion. The Subtalar Arthroereisis Implant System is scheduled for limited release at the end of 2016 with full product release expected in the first quarter of 2017.

San Diego,Calif-based **Epic Sciences Inc.** unveiled a liquid biopsy test that it said more sensitively detects cancers susceptible to PARP inhibitors by targeting homologous recombination deficiency (HRD) in individual circulating tumor cells (CTCs). The new test has already been incorporated into numerous clinical studies of HRD-targeted therapeutics in multiple cancer types. Over 230 clinical trials are investigating novel therapies targeting DNA damage response pathways, including PARP, ATM, ATR, DNA-PK and WEE-1. Drugs targeting these pathways may be effective for a broad spectrum of cancers. However, detecting patients with HRD-positive metastatic disease has proven difficult due to tumor heterogeneity, the invasive nature of tissue biopsies in late stage patients, and the expense and delays involved with genomic testing that often impairs patient enrollment. Epic Sciences and Memorial Sloan Kettering Cancer Center presented data at the annual American Society of Clinical Oncology meeting earlier this month that suggests that Epic's new test can detect a tumor cell's HRD status based solely on analysis of protein expression and cellular morphology, independent of genomic sequencing. An imaging-based screening test would significantly reduce costs and identify patients within one week of a blood draw. The Epic Sciences HRD liquid biopsy test is being offered as part of its expanded menu of Biopharma Solutions.

MEDICAL DEVICE DAILY

Medical Device Daily™ (ISSN# 1541-0617) is published every business day by Thomson Reuters, 115 Perimeter Center Place, Suite 1100, Atlanta, GA 30346 U.S.A. Opinions expressed are not necessarily those of this publication. Mention of products or services does not constitute endorsement. All Rights Reserved. No part of this publication may be reproduced without the written consent of Thomson Reuters (GST Registration Number R128870672).

CONTACT US

medicaldevicedaily.newsdesk@medicaldevicedaily.com

Donald R. Johnston, (770) 810 3118 // Holland Johnson, (770) 810-3122 // Amanda Pedersen, (912) 660-2282 // Omar Ford, (770) 810-3125 // Mark McCarty, (703) 361-2519 // Penney Holland (770) 810-3047 // Lynn Yoffee, (770) 810-3123

OUR NEWSROOM

Lynn Yoffee (News Director), Holland Johnson (Executive Editor), Mark McCarty (Regulatory Editor), Omar Ford, Liz Hollis, Amanda Pedersen & Varun Saxena (Staff Writers) Europe // John Brosky (Staff Writer), Asia//Pearl Liu, Haky Moon, Alfred Romann, Cornelia Zou (Staff Writers), Latin America// Sergio Held// Israel //Joseph Straus

PRACTICAL INFORMATION

For Sales Inquiries: http://ip-science.interest.thomsonreuters.com/Bioworld_Sales_Inquiry. NORTH AMERICA, Tel: (855) 260-5607. Outside of the U.S. and Canada, Tel. +44.203.684.1797. For Customer Service Inquiries, NORTH AMERICA, Tel: (800) 336-4474. Outside of the U.S. and Canada, Tel. +44-203-684-1796. Or email bioworld.support@thomsonreuters.com. Copyright ©Thomson Reuters. Reproduction is strictly prohibited. Visit our website at www.medicaldevicedaily.com.

For ad rates and information, please contact Chris Venezia toll free at (855) 260-5607; outside the U.S. and Canada, call (646) 522-6243 or by email at christopher.venzia@thomsonreuters.com.

For photocopy rights or reprints, please contact Chris Venezia toll free at (855) 260-5607; outside the U.S. and Canada, call (646) 522-6243 or by email at christopher.venzia@thomsonreuters.com.

Send all press releases and related information to medicaldevicedaily.newsdesk@medicaldevicedaily.com.

BUSINESS OFFICE

Donald R. Johnston (Senior Director, Current Awareness), Penney Holland (Web Production Manager)

10 BIGGEST U.S. WINNERS FOR THE WEEK

By Percent		By Dollars	
Mazor Robotics	11.23	The Cooper Cos	4.91
Quest Diagnostics	4.19	Labcorp	3.92
Sunshine Heart	4.06	ICU Medical	3.69
Dehaier Medical	3.76	Quest Diagnostics	3.17
ICU Medical	3.59	Athenahealth	3.12
Delcath Systems	3.12	Intuitive Surgical	3.08
Labcorp	3.12	Stryker	2.21
Accuray	3.08	Mazor Robotics	1.80
The Cooper Cos	3.03	Conmed	1.16
Conmed	2.70	Abiomed	1.14

10 BIGGEST U.S. LOSERS FOR THE WEEK

By Percent		By Dollars	
Checkcap	-23.08	Edwards Lifesci	-2.50
Echo Therapeutics	-17.00	Henry Schein	-2.03
Stereotaxis	-7.77	Steris	-1.95
Intersect ENT	-6.49	Dentsply Internat	-1.91
Titan Medical	-6.13	Cynosure	-1.88
Transenterix	-5.80	Heartware Internat	-1.66
Tearlab	-5.50	Orthofix Internat	-1.33
Heartware Internat	-5.25	Cantel Medical	-1.26
Wright Medical	-5.23	Agilent Technologies	-1.24
RTI Surgical	-4.69	Great Batch	-1.19

MDD STOCK REPORT FOR PUBLIC MED-TECH COMPANIES

COMPANY	SYMBOL	CLOSE 6/17	CLOSE 6/24	%CHANGE WK	%CHANGE YTD	VOL (000)
Abbott Laboratories	ABT	37.39	37.91	1.39	-16.74	54612
Abiomed	ABMD	99.23	100.37	1.15	9.91	6698
Accuray	ARAY	4.87	5.02	3.08	-27.85	3319
Agilent Technologies	A	45.36	44.12	-2.73	8.49	14423
Alere	ALR	42.3	41.6	-1.65	8.21	4129
Align Technology	ALGN	79.17	79	-0.21	20.23	3362
Allscripts Healthcare	MDRX	12.43	12.29	-1.13	-19.18	13612
Athenahealth	ATHN	128.64	131.76	2.43	-20.08	1291
Baxter International	BAX	44.44	43.85	-1.33	16.49	29922
BD	BDX	165.79	166.71	0.55	7.59	5091
Biolase	BIOL	1.16	1.16	0.00	37.91	229
Boston Scientific	BSX	22.49	22.37	-0.53	21.96	79138
Bovie Medical	BVX	1.73	1.75	1.16	-17.62	109
C.R. Bard	BCR	225.04	226.16	0.50	18.79	1892
Cantel Medical	CMN	70.31	69.05	-1.79	13.15	994
Cardiovascular Syst	CSII	17.15	17.6	2.62	13.43	1696
Checkcap	CHEK	1.3	0.9999	-23.08	-31.22	311
Conmed	CNMD	43.04	44.2	2.70	-2.29	1171
Cynosure	CYNO	48.4	46.52	-3.88	8.35	1245
Dehaier Medical	DHRM	1.5999	1.66	3.76	-29.27	104
Delcath Systems	DCTH	0.2501	0.2579	3.12	-49.98	4149
Dentsply Internat	XRAY	63.21	61.3	-3.02	3.88	13254
Echo Therapeutics	ECTE	2	1.66	-17.00	40.85	693
Edwards Lifesci	EW	98.54	96.04	-2.54	24.77	7936
Endologix	ELGX	12.45	12.38	-0.56	25.76	5634
Fluidigm	FLDM	9.48	9.4	-0.84	-12.30	646
Great Batch	GB	31.45	30.26	-3.78	-40.10	1536
Haemonetics	HAE	29.66	28.76	-3.03	-8.00	2452
Halyard	HYH	32.2	32.32	0.37	-3.62	3251
Hansen Medical	HNSN	3.97	3.98	0.25	70.39	155
Heartware Internat	HTWR	31.64	29.98	-5.25	-37.22	824
Henry Schein	HSIC	172.9	170.87	-1.17	9.30	2377
Hill-Rom Holdings	HRC	50.9	50.27	-1.24	5.91	2979
Hologic	HOLX	33.81	34.11	0.89	-12.61	21287
iCAD	ICAD	5.16	5.09	-1.36	-0.19	129
ICU Medical	ICUI	102.8	106.49	3.59	-8.85	514
Idexx Laboratories	IDXX	87.66	87.76	0.11	20.21	3151
Inogen	INGN	46.84	46.22	-1.32	16.84	1286
Intersect ENT	XENT	13.72	12.83	-6.49	-39.02	2816
Intuitive Surgical	ISRG	641.74	644.82	0.48	17.45	1551
Iridex	IRIX	14.16	14.5	2.40	52.42	956
Labcorp	LH	125.7	129.62	3.12	1.67	6399
Livanova	LIVN	49	48.14	-1.76	-17.47	8419
Luminex	LMNX	19.47	19.51	0.21	-8.98	1281
Masimo	MASI	50.5	50.96	0.91	21.66	1718
Mazor Robotics	MZOR	16.03	17.83	11.23	57.78	1232
Medtronic	MDT	84.14	83.26	-1.05	9.43	28508
Meridian Bioscience	VIVO	19.02	18.56	-2.42	-7.31	1550
Novocure	NVCR	10.89	10.61	-2.57	-51.30	7401
Nuvasive	NUVA	57.5	57.93	0.75	6.27	2602
Nxstage Medical	NXTM	19.7	19.03	-3.40	-10.09	2828
Orthofix Internat	OFIX	44.08	42.75	-3.02	12.42	1107
Penumbra	PEN	58.73	58.15	-0.99	9.14	4183
Quest Diagnostics	DGX	75.73	78.9	4.19	6.45	7762
Quidel	QDEL	17.58	17.09	-2.79	-17.08	925
RTI Surgical	RTIX	3.84	3.66	-4.69	-3.27	1581
Smith & Nephew	SNN	32.48	32.62	0.43	-8.76	3036
Spectranetics	SPNC	18.16	17.92	-1.32	20.58	2394
St. Jude Medical	STJ	76.44	76.88	0.58	23.75	14327
Stereotaxis	STXS	1.03	0.95	-7.77	38.55	189
Steris	STE	67.39	65.44	-2.89	-10.55	13342
Strata Skin Sciences	SSKN	0.66	0.65	-1.52	-40.54	33138
Stryker	SYK	114.38	116.59	1.93	23.07	10130
Sunshine Heart	SSH	0.4901	0.51	4.06	-63.70	199
Syneron Medical	ELOS	7.3	7.39	1.23	-5.32	449
Tearlab	TEAR	0.6984	0.66	-5.50	-49.76	571
Teleflex	TFX	171.05	171.25	0.12	30.10	1378
The Cooper Cos	COO	161.89	166.8	3.03	20.65	2368
Thermo Fisher Sci	TMO	146.24	145.35	-0.61	3.09	7674
Titan Medical	TITXF	0.6392	0.6	-6.13	-14.77	921
Transenterix	TRXC	1.38	1.3	-5.80	-44.35	4719
Varian Medical	VAR	81.02	80.11	-1.12	0.27	5083
Vascular Solutions	VASC	39.13	38.13	-2.56	13.78	698
Wright Medical	WMGI	17.58	16.66	-5.23	-27.30	13998
Zeltiq Aesthetics	ZLTQ	27.66	26.6	-3.83	-3.05	3967
Zimmer Biomet	ZBH	116.48	116.69	0.18	13.55	15059

NOTES

Trading volumes for Nasdaq, Amex and NYSE are recorded as the total number of shares traded (in thousands) on a weekly basis (cumulative Monday through Friday); the weekly and YTD % changes are from IPO completion, where applicable.

Average Percent Change Week: -0.87%
Range: -23.08% to +11.23%; Number Of Companies: 76
(not market weighted)

Average Percent Change YTD: +1.18%
Range: -63.70% to +70.39%; Number Of Companies: 76
(not market weighted)

Diagnostics

Continued from page 1

resistance. Once these broad-spectrum antibiotics fail to help a patient or susceptibility data returns from the lab – a process that can take two to four days – the doctor then considers a novel or more targeted antibiotic.

With the decline in antibiotic development since the 1980s, there are grave concerns that the number of deaths related to infections could rise sharply. According to the May report released by the U.K.'s Lord Jim O'Neill, who formerly served as chief economist at Goldman Sachs and now is commercial secretary to the Treasury, without some sort of policy intervention, deaths related to antimicrobial agents could climb from the current 700,000 a year to 10 million a year by 2050.

The report encourages the development of new, rapid diagnostics to reduce the unnecessary use of antimicrobials, as there is currently mostly guesswork involved. "The process has remained basically unchanged in decades: most of these tests are lab-based, and would look familiar to a doctor trained in the 1950s, using processes that originated in the 1860s." The problem: the lack of a market for new tests, the report asserts.

CHALLENGES TO EARLY DIAGNOSTIC TESTING

In their executive insights paper, the L.E.K. team identified challenges that constrain the use of diagnostic testing in early treatment decisions for serious bacterial infections, most notably, including slow turnaround time, the lack of capacity to identify the causal pathogen and its susceptibility profile, laboratory workflow challenges, and cost and reimbursement issues.

"While culture-based methods are the gold standard in effectively identifying the causal pathogen and testing its susceptibility to antimicrobial agents, these methods take two to four days, forcing physicians to treat patients empirically until definitive test results arrive," the team writes.

Why does the process take so long? After obtaining a positive blood culture, resistance testing may be done either by using antibiotic sensitivity testing or a molecular approach using polymerase chain reaction (PCR) and a test for a set of known mutations, Vadas told *Medical Device Daily*. "Regardless of the approach, you still need to culture the blood up front, which adds twenty-four plus hours to the testing timeline," he added.

"In terms of solutions, low-cost, broadly available PCR solutions are in development and may have applicability for certain types of infections," he added. He touched on the promise of direct detection, which allows for the discovery of a pathogen from the blood without culture. An example of a company studying this method is Geneweave, which was acquired by Basel, Switzeland-based Roche last year.

See Diagnostics, page 9

ADVANTAGES/DISADVANTAGES OF ESTABLISHED TECHNOLOGIES TO DETERMINE ANTIMICROBIAL RESISTANCE

Culture:

Advantages:

- Works well in determining phenotypic resistance (culture the organism with antimicrobials)
- Is inexpensive
- Is broadly available (legacy technology, most hospitals offer it)

Disadvantages:

- Slow (serious infections may often require empiric treatment before they have resistance data)
- Not amenable to point of care (slow, cumbersome)

PCR:

Advantages:

- Can be a lot faster (emerging point of care can get below 60 minutes)
- Is sensitive
- Can be amenable to point of care, in some instances (not blood stream infections)

Disadvantages:

- Is expensive relative to culture
- Presents reimbursement challenges
- Not broadly available, but that is improving with lower cost, point of care solutions

Source: Alex Vadas, managing director within L.E.K.'s BioPharma and Life Sciences Group in Los Angeles

Infection

Continued from page 1

reprocessing firms, hospitals, regulatory bodies and lawmakers all have a role to play in protecting patients from these deadly diseases.

For one of the largest endoscopic device makers, owning up to its share of that responsibility has proven to be a remarkably lengthy and costly lesson. Olympus Corp. of the Americas is in the middle of a major recall of its TJF-Q180V duodenoscopes because the scopes have been linked to widespread carbapenem-resistant *Enterobacteriaceae* (CRE) infections. Some CRE bacteria have become resistant to most available antibiotics, and are able to kill up to half the patients they infect, according to the U.S. Centers for Disease Control and Prevention (CDC). The Center Valley, Pa.-based company allegedly warned European regulators in 2013 and 2014 about the device's potential to spread infection, but did not alert U.S. hospitals until a U.S. Senate investigation brought the issue to light earlier this year. The report, which came from the office of U.S. Sen. Patty Murray (D-Wash.), cited 25 outbreaks of infections across the country and in Europe involving nearly 200 U.S. patients. (See *Medical Device Daily*, Jan. 19, 2016.)

The Senate report came out soon after the FDA cleared a new, easier-to-clean version of Olympus' duodenoscope that features a redesigned component intended to provide a tighter seal in an effort to reduce the risk of infection. Olympus said it will replace the sealing mechanism on about 4,400 devices currently in use by August.

While Olympus has taken the most heat for the problem, all duodenoscopes – including those sold by Fujifilm and Pentax – are inherently difficult to clean because of the moving elevator mechanism at the tip where patient fluids and tissue can potentially get inside the device. Duodenoscopes provide a minimally invasive way of draining fluids from pancreatic and biliary ducts that are blocked by problems like tumors or gallstones. Similar reusable endoscopes, such as bronchoscopes and colonoscopes, also carry a risk of transferring pathogens.

Hospitals like the University of California Los Angeles' Ronald Reagan Medical Center have started to sterilize duodenoscopes with ethylene oxide, but that method requires more wait time between use because the gas is so toxic. The longer sterilization process has driven up the demand for the devices, which are used in up to 600,000 U.S. procedures every year.

MAKING LEMONADE FROM DEADLY LEMONS

Just as combat needs often drive medical innovation, disease outbreaks have opened up a big market opportunity for new infection control products. From tiny cameras that can see inside endoscopes, to mobile apps and analytics software that tracks infectious patients during their hospital stay, med-tech companies can't be accused of sitting out of the superbug fight.

Patient Safe Inc. has developed a new class of small diameter, near field inspection scopes designed to provide access to and imaging of the interior chambers, lumens, and working channels of surgical devices, including endoscopes.

The Sausalito, Calif.-based company was already in the process of bringing its Steriview infection control system to the U.S. market even before Olympus' duodenoscope CRE problem surfaced, CEO Larry Gerrans told *Medical Device Daily*. The

See Infection, page 10

What's inside your IV catheter?

By Amanda Pedersen, Staff Writer

Having spent the bulk of his medical career researching infections in cancer patients undergoing chemotherapy, Stephen Schimpff, a retired CEO from the Baltimore-based University of Maryland Medical Center, knows a lot about how hospitals can make patients sick.

"We know, in many cases, how to reduce and how to prevent infections, but in many cases we just don't do it," Schimpff told *Medical Device Daily*. "An IV catheter should be put in sterilely but it's often not, or it's left in too long."

IV catheters are a lot like the stones found in little streams that run through the woods. The slimy covering on one of those stones in the stream is a biofilm that has formed over a layer of bacteria that has formed on the surface of the rock, Schimpff said.

"It's not just a layer of bacteria. It's a layer of bacteria layed down in a matrix of protein and other chemicals and that biofilm protects them," he said. "The bacteria is quite alive and quite protected, so you can pour chlorine on them and it won't kill them because they're inside this protective coating."

The same thing happens inside the tiny plastic tubes used to deliver drugs and fluids directly into patients' bloodstreams.

Cancer patients undergoing chemotherapy often receive a central venous catheter, which is threaded through a needle to end in a large vein in their chest, near the heart, where there is a lot of blood flow and the drug is diluted quickly. Early in Schimpff's career he occasionally had cancer patients get sick after having one of these catheters in. That's because the catheters furnish bacteria with a superhighway that leads straight into the bloodstream. And biofilms – just like the ones that protect bacteria on rocks in a stream – will eventually form both on the inside and the outside of the catheters.

"I met a guy from Canada who said 'take one of those catheters out sometime and send it to me' ... I'm going to send you the picture back, so he did," Schimpff said. "Inside of these little thin catheters that had been inside veins was this film the entire length of the catheter, and we never knew it. It's actually amazing that patients didn't get sick more often." //

Brexit

Continued from page 1

David Cameron promised to resign by October after his Remain side lost 52 percent to 48 percent.

Global med-tech companies have a fair amount of exposure to the world's fifth largest economy, where a recession is possible due to the uncertainty about the terms of its eventual exit from the E.U. Alpharetta, Ga.-based Halyard Health and Deerfield, Ill-based Baxter International derive 6 percent of their revenue from the U.K., while a plethora of others, including Marlborough, Mass.-based Boston Scientific Corp. and Franklin, N.J.-based Becton Dickinson and Co. count on the market for about 5 percent of their revenues. Less affected companies include Stryker and Intuitive Surgical, according to Stifel equity analyst Rick Wise.

Meanwhile London-based orthopedics company Smith & Nephew plc is experiencing a decline of close to 6 percent on the New York Stock Exchange.

"Possible post Brexit headwinds could include increased currency volatility, potentially more complicated regulatory approval and reimbursement pathways as EU regulations broadly have to be re-calibrated. To the degree that the decision results in a more challenged European/U.K. economy, this could potentially impact procedure volumes and device pricing. Less clear for now are the tax implications for non-U.S. domiciled companies (MDT) and companies with a large E.U. manufacturing presence (BSX)," Wise wrote in analyst note.

But he wasn't overly concerned, writing "we are inclined to believe that over the next twelve months those headwinds will be relatively minor and should prove manageable for industry."

Jefferies equity analyst Raj Denhoy focused on the Brexit's impact on foreign exchange rates due to the British Pound's large decline against the dollar.

"The most obvious impact to U.S. medical device companies following the Brexit vote are the weaker GBP and EUR relative to the USD. Exiting 2Q, the average combined exposure to these currencies was approximately 20 percent across our coverage universe. This, combined with the current 6 percent slippage in GBP and 2 percent slippage in EUR, points to an estimated 1 percent FX annualized translational headwind for 2016 if rates hold at current levels," he wrote.

The rising dollar has already hurt the earnings of U.S. multinationals, including device industry players. During its most recent earnings call in March, Medtronic said currency headwinds caused the company to miss its adjusted operating margin projection by .2 percentage points, but that didn't stop the company's stock from falling almost 4 percent on the news.

Japanese companies will be particularly affected by the latest Brexit-driven currency headwind, for the Japanese Yen rose more than 7 percent against the dollar, making life difficult for companies like Olympus.

OUTCOME OF BREXIT NEGOTIATIONS KEY IN LONG RUN

While investor sentiment is focused on volatile metrics like exchange rates at the moment, the terms of the U.K.'s exit from the EU are ultimately going to determine the economic impact of Brexit. The expectation is that Germany, France and other core EU countries will not make too many concessions in order to ensure that other countries do not try and go down the same the path as the U.K.. Negotiations over an exit could take two years, and the U.K. will have little influence within the EU during its remaining time in the institution.

"Over the coming months the U.K. will begin the process of agreeing the basis of a new relationship with EU partners. Complex negotiations and decisions lie ahead. It will mean a period of considerable uncertainty and we will work with our members and partners to support the med-tech industry through the transition," said Association for British Healthcare Industries CEO Peter Ellingworth.

Brexit comes on the heels of the passage of significant regulations of the European device industry by the European Commission, which sought to increase patient safety after a scandal involving fraudulent breast implants and problematic metal-on-metal hip implants.

Even if the U.K. were to make its regulations following its official Brexit, they would very likely have to be consistent with the existing EU regulations in order for the country's devices to gain access to the common market, consisting of 27 member states (no longer including the U.K.).

"At the moment a U.K. medical device manufacturer goes though the conformity assessment process and gets a certificate. They may then affix a CE mark to the product and market it to the EU Member States, as well as members of the European Free Trade Association (EFTA) with European Economic Area (EEA) agreements, which are Iceland, Liechtenstein, Norway and Switzerland," Hogan Lovells attorney Elizabethann Wright wrote in an April paper on the possibility of Brexit.

The process is set to become more complicated due to the referendum. "Come Brexit, these companies will no longer have this automatic right to the free movement of goods. They would be placed in the same situation as any non-member of the EU applying for device approval. Now all U.K. medical device companies are going to be looking for a representative," Wright wrote.

"There is no doubt a Brexit is going to demand organization, and investment," she told *Medical Device Daily* in April. "For large companies this becomes just more things they have to do. For smaller companies and specialized device manufacturers, this is going to be a challenge, asking them to do all of this additional and costly work. And to have a person on staff assuring the company is in conformity with a new set of rules."

Other sources said that in the event of a Brexit, they expect

See Brexit, page 8

Regulatory

Continued from page 1

offers no new insights into the product's safety profile.

Franken had penned a letter to the FDA earlier this year inquiring into the company's adverse event reporting in connection with the Infuse device, an inquiry prodded at least in part by coverage by the *Minneapolis Star/Tribune*. Among the allegations was that Medtronic had deliberately concealed roughly 1,000 adverse events reports from the FDA in a study of the device conducted between 2002 and 2006, an allegation the company refuted. Medtronic responded to the media coverage by claiming that the records in question had been inadvertently archived in 2008 during a retrospective chart review, which in turn led to a failure to assess those adverse events for reportability. (See *Medical Device Daily*, April 14, 2016.)

In its June 6 letter to Franken, the FDA said Medtronic had penned an August 2013 letter to the agency requesting an exemption from standard MDR requirements for the adverse events reported in a post-approval study that took place between 2006 and 2008. The agency said it gave Medtronic the go-ahead in January 2014, and the Medtronic report is said to have used a summary format for roughly 1,040 adverse events reports for serious injuries, along with 55 reports for device malfunction, four reports associated with patient death, and two serious injury reports that were filed separately.

The FDA advised Franken that the regulation allows for summary reporting of adverse events under chapter 21 of the Code of Federal Regulations under subsection 803.19, and explained further that because the information contained in the previously unreported adverse events offered no indication of a novel safety problem, the filing of individual reports for the entirety of that body of data would have offered little in the way of useful information regarding the device's safety profile.

In response to Franken's question about whether the FDA had considered enforcement action against Medtronic, the agency said it had considered the possibility, but noted that an inspection of Medtronic facilities, which included a review of MDR reporting practices, led the agency to conclude that no enforcement actions were warranted. The FDA reiterated that the late-arriving MDRs offered no new information.

The FDA stated that the adverse events seen in the previously unreported instances included neurological deficit, infection and stenosis, all of which have appeared in other adverse events reports. The agency added that most of the problems are already described in product labeling. However, the agency said that it could not determine what proportion of adverse events were associated with off-label use because those reports did not include sufficient information to determine whether the product was used per the labeled indications.

CADTH EYES COMPANION DIAGNOSTICS

The Canadian Agency for Drugs and Technologies in Health (CADTH) has commenced with a horizon scan for the use of companion diagnostics, and the agency pointed to some impressive numbers regarding the anticipated growth of the market for CDx tests. However, the CADTH also made the case that the base of evidence regarding the use of CDx tests is not particularly well built out, and that as a consequence "it remains uncertain whether the expanded use of these codependent technologies" will reduce costs and improve care.

The report noted that its findings are based largely on feedback offered for the draft version, which the CADTH published two years ago, and a partial update for regulatory information and other data acquired last year. The report pegs the value of the CDx market (for both sales and services) in 2014 at $2.4 billion, and said some projections of compounded annual growth rate are as high as 24 percent per annum. When measuring these tests and services alongside the related therapeutic treatments, the global market may be north of $60 billion by 2019, according to some sources.

Among the impediments to market are reimbursement issues, the report stated, along with regulatory restrictions/review times and the availability of non-validated, lab-developed tests. The authors made note of the domination of the CDx market by a handful of firms, stating that five companies held 86 percent of the market in 2013. The authors cited a study claiming that per-capita utilization of CDx tests was higher in five European Union nations than in the U.S. by 2007, while the same metric in Japan surpassed the U.S. two years later.

The CADTH pointed out that the U.K.'s National Institute for Health and Care Excellence had stipulated in 2013 that the technology appraisal program (TAP) would henceforth require the cost of a CDx in the economic analyses for any applications for pharmaceutical or biotech therapeutic products entering the TAP process.

The authors acknowledged that the FDA "had the most developed and detailed process available" for review of therapeutics and the associated CDx, although the agency has yet to publish a specific co-development guidance for matched therapies and CDx tests. The European Medicines Agency is said to be revising its own set of guidelines for CDx tests, and the authors pointed out that Health Canada has not yet published any formal guidelines for joint applications for drugs and diagnostics.

The coverage/reimbursement picture is, as expected, more fragmented than the regulatory review picture, with the U.K. and Australia credited with more well-defined guidelines for payment than currently exist in the U.S., Canada and New Zealand. The CADTH said the situation in Canada has raised concerns, "particularly in the oncology setting," regarding conflicts between jurisdictions regarding premarket review, reimbursement, and access to tests. The authors stated that another confounder for Canadian patients is an absence of standardized quality assurance approaches for lab-developed tests. //

3-D

Continued from page 1

additive manufacturing (AM), also known as 3-D printing, to make medical instruments for patients that have exhausted all other options for treatment and face emergency situations.

"3-D printers guarantee precision, convenience and speed, making them perfect for broad use in the medical field," said MFDS officials at a public symposium last month. The ministry now plans to develop and revise regulations by November and then expedite the commercialization of 3-D printed medical instruments.

But any moves are likely to be cautious.

"First of all, when it comes to 3-D printing technology, there are no thorough guidelines. Since it's an unprecedented industry there isn't any guidance on 3-D printing, not even in the free trade agreements (FTA)," Lee Sung-hui, an MFDS official that handles oral and digestive tissues told *Medical Device Daily*. "The announcement is nowhere near indicating easing of regulations."

"Keep in mind there were no regulations to begin with," said Lee. "Rather, it's announcing that all the ministries are working towards the construction of a guideline on 3-D printed products, be it medical implants or devices in a timely manner while consulting the industry players."

For the time being, it is difficult to take medical instruments made using 3-D printing to market, in large part because the technology is new and regulations are not particularly thorough, so the approval process could be lengthy.

This approval process is broadly divided into two stages.

Products such as 3-D printed medical implants or instruments are subject to regulatory approval followed by an assessment of their safety and effectiveness.

Once approved, the Health Insurance Review & Assessment Service (HIRA) goes on to assess the medical instrument again. Even if the MFDS has approved a particular instrument, there is no guarantee the HIRA will provide an additional insurance code for the product –a form of approval – which means hospitals cannot charge patients for it.

But South Korea wants to get some of these products to market sooner rather than later. Although the proposed timeline for finalizing the approval regulations for 3-D printed medical instruments is November, regulators have said that they want to get 3-D printed medical instruments in the hands of users as quick as they can.

But the use of any fast-track approval would be attached to a number of conditions. The ministry pointed out that such approval would most likely be limited to one-time use of 3-D printed instruments on patients who are in need of artificial joints and dental prosthesis.

At present, the only 3-D printed medical application to move forward without specific approvals is a 3-D printed cranium. Other bone structures have not been given HIRA numbers, which means hospitals cannot charge for them or risk fines.

Part of the problem is a lack of clear regulation, particularly in regards to insurance. Using the full potential of 3-D printing will also mean complicating the insurance processes; so 3-D printing has not been widely adopted despite a national push.

In 2014, South Korea drew up a state-supported policy to develop the 3-D printing industry. The government created a 3-D Printing Industry Development Council, made up of officials from more than a dozen ministries. Some of the goals proposed were to make South Korea a leader in 3-D printing and to train 10 million creative makers by 2020 while expanding the 3-D printing infrastructure on a national scale.

Change is underway. Some of the leading countries in 3-D printing such as the U.S. have seen 3-D printing proliferating in areas such as orthopedics, cranial implants, surgical instruments, distal restorations, prosthetics and physical anatomical models for surgical planning. The U.S. is driving the growth in the use of 3-D printing, according to MarketsandMarkets, a U.S.-based market research company.

Just last month, the USFDA released a draft guidance titled "Technical Considerations for Additive Manufacture Devices". The guideline was published in response to the advancements and investments in 3-D printing technology.

South Korea may now be following suit. Lee pointed out that the country will be "rolling out more detailed regulations as soon as possible and construct clearer guidelines for those in R&D." //

Brexit

Continued from page 6

the U.K. to negotiate a friendly trade agreement, like Norway, Switzerland and Canada, where medical devices approved in one country are accepted for marketing in the other.

In addition to uncertainty about regulation and the terms of trade, Brexit also introduces the prospect that the U.K. will lose access to EU research funding.

According to the Royal Society at Cambridge University the EU provided research funds of €8.8 billion between 2007 and 2013, while the U.K. contributed €5.4 billion in research funds.

Overall, the U.K. was a net contributor the EU over the period, a fact that contributed to the voter's decision to leave the union.

Finally, EU drug industry regulator, the European Medicines Authority, will likely soon relocate from its London headquarters.

Despite polls indicating the referendum was a toss-up, the Brexit caught the markets by surprise, judging by the swift decline in the British Pound and global stock markets. Like virtually every other global industry, the med-tech sector will have to adjust to the new reality. //

Diagnostics

Continued from page 4

Geneweave's Smarticles technology is designed to identify multidrug-resistant organisms quickly and assesses antibiotic susceptibility directly from clinical samples. It consists of DNA-delivery bioparticles and custom-designed DNA molecules that cause live bacteria to produce light. They are engineered to target a family, genus or species of bacteria. (See table on p. 4.)

EMERGING TECHNOLOGIES FACING HURDLES

Still, some companies are looking beyond culture and PCR. However, even with new tests, the reimbursement hurdle is a tough one to surmount, as obtaining a new code can prove to be a time-consuming and challenging process. In addition, many of these emerging technologies only can identify a limited set of pathogens. And while the identification process takes less than an hour, susceptibility tests may have to run separately.

Emerging technologies include matrix-assisted laser desorption ionization-time of flight (MADLI-TOF), through which results are available in less than an hour. While the cost-per-test is negligible, instruments run more than $200,000.

One company using MALDI-TOF is Billerica, Mass.-based Bruker Corp. with its FLEX series. At the American Society for Microbiology (ASM) Microbe 2016 conference in early June 2016, Bruker reported on a collaboration with the Special Bacteriology Reference Laboratory at the U.S. Centers for Disease Control and Prevention to create an expanded microorganism reference library for the Bruker MALDI Biotyper. The MALDI Biotyper library contains spectra for more than 2,300 species of bacteria and fungi, according to the company.

Another emerging technology is next-generation sequencing, which yields results within one to two days at a cost of more than $100 per test.

Still, as Norman Moore, director of Scientific Affairs, Infectious Disease at Waltham, Mass.-based Alere Inc., told *Medical Device Daily*, diagnostic companies can't do it alone; it is essential to make all stakeholders, including doctors and patients, aware of the potential harms of overprescribing.

With that, tests need to be sensitive and "fast enough to change prescribing habits," Moore added.

HOST OF COMPANIES ENTER ANTIBIOTIC RESISTANCE FRAY

Other companies have recognized this point. In January, a number of drug makers and other stakeholders pledged to help in the fight against antibiotic resistance. Joining the ranks were a number of diagnostics companies that also vowed to help in the fight.

The signatories were a multinational group – Alere Inc., Biomérieux SA, Cepheid, Curetis AG, F. Hoffman-La Roche Ltd., Hemocue AB, Hyrax Biosciences (Pty) Ltd., Mobidiag Oy Ltd., Momentum Bioscience Ltd., Quantumdx Ltd. and Spectromics.

Many of those that signed the pledge touched on what is viewed as the biggest problem facing patients: the time it takes to determine treatment regimen.

Oliver Schacht, CEO of Curetis, told *Medical Device Daily* that his company is looking to make faster tests a reality. His company has made "tremendous progress in the first half of 2016" and is eyeing the launch of its intraabdominal infection cartridge in Europe, following the expected fourth quarter completion of clinical validation. "That panel will most likely also include the antibiotic resistance marker associated with the Colistin resistance in *E. coli* that was at the core of the recent patient case in the U.S.," he said.

Curetis GmbH is the operational subsidiary of Curetis N.V., with its headquarters in Holzgerlingen, Germany. The company expects to establish a U.S. operation in the second half of the year and hopes to announce where it will set up shop shortly, Schacht said.

Simon Travers, managing director at South African-based Hyrax Biosciences, confirmed that his company is working on a number of AMR-related products. "Our next product will be a tool that enables the analysis of sequence data from TB – analyzing either full genome sequences or sequence data generated by targeting specific regions of the genome – that is capable of accurately detecting resistance to all of the currently available TB drugs," he told *Medical Device Daily*.

In addition, Hyrax has developed a similar tool for *Staph aureus* and is expanding its product line to focus on other bacteria.

Travers said his company also is developing databases and analytics tools with a goal of real-time surveillance of infections and resistance at a local, national and international level. "While this will be applicable on an global scale, it will be particularly pertinent for resource-limited settings where our knowledge of the prevalence of antimicrobial resistance is limited," he added.

Formed in 2014, Manchester, U.K.-based Spectromics is working on a rapid test for guiding the use of antibiotics for routine urinary tract infections (UTIs) in the community.

CEO Neil Butler told *Medical Device Daily* that UTIs may not be viewed as severe as sepsis or kidney infections. However, roughly 25 percent of sepsis cases originate from UTIs, resulting in kidney infections that can pass into the blood stream. "Once a patient has sepsis, survival rates are poor, 50 percent or less, and hence better to treat before it becomes a kidney infection," he added.

Butler added that he also sits on the board of U.K.-based Atlas Genetics Ltd., which is developing rapid molecular diagnostic tests for sexually transmitted diseases. The company is developing a test for drug-resistant-gonorrhea.

EXPLORING MORE INTELLIGENT ANTIBIOTIC USE

Located in Newcastle, U.K., Quantummdx is preparing for the launch of its Q-POC technology in 2018. According to company spokeswoman Lucy Harvey, Q-POC will provide

See Diagnostics, page 10

Diagnostics

Continued from page 9

sample-to-result testing in roughly 10 to 20 minutes. "Q-POC will identify the presence and strain of infection, ensuring the right drug is prescribed the first time," said Harvey, who added that the ultimate goal is to facilitate "a more intelligent use of antibiotics."

To that end, globally distributed Q-POC devices will allow for geotagging and the anonymization of pathogen data, which would then be sent to the cloud for real-time disease and drug-resistance monitoring, rapid detection, and pathogen containment. "[T]he data could also be used by public health bodies to allocate resources effectively. We call this system The Internet of Life," Harvey told *Medical Device Daily*.

Indeed, to Kevin Krenitsky, president of Opgen Inc., the field of infectious disease has been "languishing in antiquity," particularly with traditional methods taking days to identify antibiotic resistance.

Although it did not sign the January letter, Gaithersburg, Md.-based Opgen is looking to unveil what Krenitsky has dubbed "very disruptive platform technology," incorporating bioinformatics and "attack[ing] the problem from multiple angles."

The company wants to decrease the time it takes to treat patients with a one-hour test. "What's important here is not the pathogen; it's the resistance within the pathogen," he said in early June 2016 during the LD Micro Invitation in Los Angeles.

With that in mind, the company is looking to leverage its bioinformatics database and rapid array test to inform patient treatment.

The company's goal is to have information about a patient sample back within an hour, including pathogens and resistance genes. The results could be evaluated using the company's Acuitas Lighthouse database, which would reveal the organism causing the disease, as well as the antibiotic resistant genes and the type of treatment regimen that would be most appropriate.

Not only could this technology help a single patient with the appropriate treatment, according to Krenitsky, but it could also prevent the spread of an infection throughout a hospital with timely identification of a pathogen.

Last week, the company unveiled data at AMS Microbe 2016 in Boston demonstrating how its Acuitas Resistome Test can be used in epidemiological studies to aid in routine evaluations for mechanisms of resistance in carbapenem resistant *Enterobacteriaceae*.

The test is intended to detect antibiotic resistance genes associated with *Klebsiella pneumoniae*, *Escherichia coli*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, *Enterobacter cloacae*, and *Citrobacter freundii*. //

Infection

Continued from page 5

system includes the company's Stericam line of software-powered cameras for visual confirmation that endoscopes and other surgical tools are free of bacteria and fluid.

Cleaning these devices after they have been inside of a patient is no easy task. Gerrans likened it trying to get burnt cheese off a frying pan. Fluid tends to cook, or burn, inside the operating channel of endoscopes during a procedure and if those sticky spots are not completely cleaned off before it will inevitably slough off into the next patient, he said.

The idea behind Patient Safe's technology is that the visual inspection it provides will prompt hospital staff to do a better job cleaning the scopes before an infection spreads.

The Steriview was born from another company Gerrans leads, Sanovas Inc., which initially developed the small diameter scopes as a means of going deep into a patient's lungs to diagnose and treat disease.

The technology has been on the market as an infection control system for about a year and the uptake has been quite positive, Gerrans said. In a recently published study, the device found 613 out of 860 inspected instruments to be dirty. That study included endoscopes as well as other laparoscopic devices and tubes.

In addition to infection control, Gerrans said Patient Safe's technology also helps hospitals inspect the integrity of these devices, which are also prone to nicks and scratches that can rust out over time or provide a breeding ground for bacteria.

It's really a multi-faceted problem, Stephen Schimpff, Patient Safe's board chairman, told *MDD*. Schimpff, the retired CEO of the University of Maryland Medical Center, spent the bulk of his medical career researching the causes, prevention, and treatment of infections in cancer patients undergoing chemotherapy. The first challenge with device-related infection control is being able to see the contaminated parts of an endoscope or other device. The next problem is figuring out how to get the bacteria or residual biomaterial out without damaging the device.

"It turns out, in some cases, you can't just put a scope brush down there or a piece of steel wool because you're going to damage the inside of the scope," Schimpff said. "It's a pickle."

ENDOSCOPE CLEANING: THERE'S AN APP FOR THAT

In an age where mobile apps are a regular part of daily living, it's not too surprising that there is an app designed to track an endoscope through each step of the cleaning and sterilization process. What is surprising, perhaps, is the fact that such an app wasn't on the market sooner.

Philadelphia-based Prairie Dog Tech LLC launched the Pd-vision in June as an optional enhancement to its previously-released infection control app called The Observer. Together, the apps are designed to help hospital staff document the

See Infection, page 11

Infection

Continued from page 10

process of disinfecting reusable scopes by creating a database of images that can be searched by time and date, or scope ID.

Prairie Dog Tech's founding member, David Bassion Jr., told *Medical Device Daily* that the idea for a Bluetooth-based endoscope tracking system came from walking around at an endoscopy convention last year and noticing that there were a lot of tracking systems on the market, but most – if not all – of the existing systems relied on information manually recorded by a clinician.

Bassion's team decided to create a tracking system that truthfully tracks the scope through each step of the sterilization process and alerts the staff of potential problems.

"We want everyone to know everything," Bassion said.

OPGEN LIGHTS THE WAY

Opgen Inc. offers a multidrug-resistant organism (MDRO) management system, the Acuitas Lighthouse, that helps hospitals navigate infection control issues.

Kevin Krenitsky, president of Opgen, told *Medical Device Daily* the cloud-based Lighthouse system leverages the company's bioinformatics analytics software to track and prevent the spread of infection from the time an infectious patient enters the hospital. Hospitals can use the system in conjunction with Opgen's rapid MDRO gene test to screen patients for superbugs and other infections, like *Clostridium difficile* (*C. diff*) as soon as they walk through the door.

The Lighthouse system not only helps hospitals track the location of threats but guides preventative actions to nip infections in the bud before they spread.

SEND IN THE ROBOTS

Germ-zapping robots that use ultraviolet (UV) light to disinfect hospital rooms grabbed *Medical Device Daily*'s attention a couple of years ago in the wake of the Ebola epidemic. In 2014, San Antonio, Texas-based Xenex Disinfection Services LLC offered its UV robots to Emory University and the CDC to disinfect the rooms where U.S. Ebola patients were treated and the airplanes that transported those patients. (See *Medical Device Daily*, Aug. 7, 2014.) The Xenex robot is a portable system designed to penetrate the cell walls of microorganisms including bacteria, viruses, mold, fungus, and spores, destroying all the superbugs and pathogens that could be lurking in a hospital room – including the operating room or the emergency room – in five to 10 minutes. The robot is operated by hospital housekeeping staff. After cleaning the room first through traditional methods, the robot is rolled in as an added layer of patient safety, disinfecting high-touch surfaces and difficult-to-clean nooks and crannies. The company launched the first version of its robot in 2010 and a new version of the robot in late 2013.

According to the company, the Xenex robot is powered by xenon, an environmentally-friendly gas, instead of mercury, which is what most of the competing systems on the market use. In addition to being toxic, mercury-based UV robots only operate in one spectrum and can take hours to disinfect a single room, Xenex said. Yet, according to one of such competitor, Tru-d SmartUVC LLC, of Gaithersburg, Md., the fear around mercury is a misconception.

Tru-d bulbs use ultra-low levels of mercury vapor that are consistent with modern fluorescent and compact fluorescent bulbs found throughout virtually every U.S. hospital that are endorsed by the Environmental Protection Agency and the Department of Energy. No mercury byproduct is emitted by the bulbs either, CEO Chuck Dunn said.

Until recently, Tru-d's biggest adoption barrier was a lack of evidence showing a direct correlation between the elimination of MDROs and the reduction of infections throughout a facility using no-touch disinfection technology. The randomized BETR-D study (Benefits of Enhanced Terminal Room Disinfection), funded by the CDC, eased those concerns, Dunn said.

BETR-D compared four methods of terminal room-cleaning strategies at nine hospitals over 22,000 patient days. The researchers found that Tru-d reduced the cumulative number of hospital-acquired infections by about 30 percent for patients who stay in rooms previously occupied by an infected patient.

Dunn told *MDD* that the company's Sensor360 technology sets Tru-D apart from its peers in the UV disinfection space. The technology measures the amount of UV energy that is reflected back to the robot, he said, enabling it to overcome room variables such as size, shape, and contents to deliver the precise, lethal dose of UVC light needed. Tru-d touts that its device kills up to 99.9 percent of pathogens in a room from a single position with a single cycle of UV energy. //

PRODUCT BRIEFS

Freehold, N.J.-based **Medfirst Solutions Inc.** provided an update shareholders regarding its 510(k) submission for its Time Machine TTML-8102000 laser thermal therapeutic device. Medifirst has completed its response to the FDA's request for more information and The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has received and accepted the submission and it is currently under review. The company said it anticipates a response from the FDA in the upcoming weeks, and is currently developing its national sales, marketing and social media strategy for both domestic and international sales and distribution of the system.

APPOINTMENTS AND ADVANCEMENTS

Tokyo-based **Pentax Medical**, a division of Hoya Corp., appointed Hudson Garrett to the position of global chief clinical officer. Garrett will lead all Pentax clinical-related activities globally. Pentax sells endoscopic imaging devices and solutions. The company noted that Garrett has experience in infection control at various medical institutions.

NEUROLOGY EXTRA

Keeping you up to date on recent developments in neurology

By Amanda Pedersen, Senior Staff Writer

NGS may improve diagnosis rate for brain infections

Baltimore-based Johns Hopkins experts reported that they were able to diagnose or rule out suspected brain infections using next-generation genetic sequencing (NGS) technology on samples of brain tissue. The team of doctors and bioinformatics experts said the proof-of-concept study, published online in *Neurology: Neuroimmunology & Neuroinflammation*, demonstrated that using computers to rapidly analyze huge amounts of genetic and biological information could be a cost-effective lab tool. More than 50 percent of inflammatory disorders and infections of the brain go undiagnosed, which can lead to treatments for individual symptoms that can do more harm than good, the authors noted. By incorporating modern NGS techniques into pathology diagnostics, the researchers were able to investigate the potential presence of infection in 10 subjects and found appropriate explanations of clinical problems in eight out of 10 patient cases they examined in the study. Carlos Pardo-Villamizar, an associate professor of neurology at the Johns Hopkins University School of Medicine, said the team will try to develop the technique further as a way to bring the diagnosis rate of inflammatory brain disorders and infections closer to 100 percent in order to treat patients more effectively. In the study, the researchers first identified 10 people at The Johns Hopkins Hospital – six males and four females between the ages of 16 and 68 – with clinical signs of a brain infection, such as fever and rapid onset of neurological symptoms, like weakness in limbs, partial paralysis numbness, headache or seizures. Each patient had a biopsy of a brain lesion that had been identified by MRI. Using commercially available genetic sequencing technologies that read millions of pieces of DNA at once, the researchers sequenced the DNA of the brain tissue for each person and compared the results to a database containing human and nonhuman DNA sequences, 2,817 bacterial genomes, 4,383 viral genomes, and 26 single-cell pathogen genomes. After subtracting out the human DNA results, they ranked the top three other species found in each sample that were thought to be potential infectious organisms. In three patients, they said genetic sequencing definitively identified the cause of the infection as Mycobacterium tuberculosis, the bacterium that causes tuberculosis and sometimes infects the brain; JC virus, which is found in most people but is only typically infectious in people with weakened immune systems; or Epstein-Barr virus, a herpes virus most commonly known to cause mononucleosis in humans.

Drugs that lead to dementia-like changes

Researchers at Pomona, Calif.-based Western University may have found an explanation for why the long-term use of common anticholinergic drugs used to treat conditions like allergies and overactive bladder lead to an increased risk of dementia later in life. The findings, published in the journal *Cerebral Cortex*, show that long-term suppression of the neurotransmitter acetylcholine – a target for anticholinergic drugs – results in dementia-like changes in the brain. Previous studies have showed that people who use these drugs for a long time increase their risk of dementia, so the team from Western sought to find out why. It turns out, there is a causal relationship between blocking acetylcholine and Alzheimer's-like pathology in mice. The researchers said that by understanding what is happening in the brain due to the loss of acetylcholine, they might be able to find new ways to decrease Alzheimer's pathology. The study showed that blocking acetylcholine-mediated signals in neurons causes a change in roughly 10 percent of the messenger RNAs in a region of the brain responsible for declarative memory. Messenger RNA encodes for specific amino acids, which are the building blocks for proteins, and several of the changes the team uncovered in the brains of mutant mice are similar to those observed in Alzheimer's disease. The study, conducted at Western's Robarts Research Institute, used human tissue samples to validate the mouse data and mouse models to show not only the physical changes in the brain, but also behavioral and memory changes. The researchers were able to show that long-term suppression of acetylcholine caused brain cell to die and, as a consequence, decrease memory in the aging mice.

Surprising diversity in brain's landscape

A team of scientists at The Scripps Research Institute (TSRI), University of California, San Diego, and Illumina Inc., has completed what is believed to be the first large-scale assessment of single neuronal "transcriptomes." Their research reveals a surprising diversity in the molecules that human brain cells use in transcribing genetic information from DNA to RNA and producing proteins. The researchers isolated and analyzed single-neuronal nuclei from the human brain, allowing classification of 16 neuronal subtypes in the brain's cerebral cortex, the "gray matter" involved in thought, cognition, and other functions. TSRI professor and neuroscientist Jerold Chun, who co-led the study, said the team found "an enormous amount of transcriptomic diversity from cell to cell that will be

Continues on next page

Continued from previous page

relevant to understanding the normal brain and its diseases such as Alzheimer's, Parkinson's, ALS, and depression." The study was published in the journal *Science*.

Cracking the genetic code of fear learning

Researchers at The Saban Research Institute of Children's Hospital Los Angeles (CHLA) have identified a new genetic candidate for testing therapies that might affect fear learning in people with Post-traumatic stress disorder (PTSD) or other conditions. The study results were published in the Journal of *Neuroscience*. According to the researchers, people with trauma- and stress-related disorders can manifest symptoms of these conditions in a variety of ways. Genetic risk factors for these and other psychiatric disorders have been established, the researchers noted, but do not explain the diversity of symptoms seen in the clinic. In other words, they wanted to know, why are some people affected more severely than others, and why do some respond better than others to the same treatment? Instead of focusing on a single gene identified for a given condition, the team at CHLA tried a different approach to discover genes that may impact symptom severity. Using a population-based mouse model, they studied normal variation in how well the mice detected threats and fears. They used mice that are well-characterized for learning behavior, and also exhibit a wide range of "high" and "low" anxiety, modeling the range found in humans. The investigators tested to see how well the mice learned to detect threats, a form of fear learning that all humans and animals do. When this learning is exaggerated in children or adults, symptoms of PTSD and anxiety are expressed. The researchers said that by understanding the biological origins of individual behavioral differences – in this case a measure of anxiety – they can move beyond a single disorder diagnosis and treat the dimensions that produce a behavior spanning a multitude of diagnoses. Using genetic tools, the researchers found a number of candidate genes that might influence learning of fear, and ultimately narrowed down to a single gene, Hcn1. The researchers were able to further demonstrate the impact of the Hcn1 gene on fear learning by interfering with the function of this gene before the learning challenge. They found that the mice did not learn fear. Even when the researchers disrupted gene function after the mice learned the fear, the mice were unable to express it. Pat Levitt, principal investigator of the study and the Simms/Mann chair in developmental neuorgenetics at CHLA, said the findings suggest that instead of focusing only on the genes that are thought to cause a disorder, such as PTSD or anxiety, it is important to discover those genes that can have a profound effect on how severely an individual is impacted by their disorder.

Rapid point-of-care tests for anti-microbial resistance

By Shyama Gosh, Incidence and Prevalence Database Editor

Antibiotic resistance among microbial pathogens has increased significantly, and the WHO recognizes this to be a major threat to human health. The following figure projects the estimated number of patient deaths due to antimicrobial resistance every year by 2050:

THE CASE OF COLISTIN

The antibiotic colistin is reserved for clinical cases where most of all other antibiotics have failed. The mcr-1 gene confers bacterial resistance to colistin in both animals and human beings and there is the fear of possible transmission of mcr-1-harboring Escherichia coli between companion animals and humans.

Now, the recent reporting of a first clinical case of colistin resistance in the U.S., together with evidence from Asia (China, Malaysia, Vietnam), Europe (Italy, Germany, the Netherlands, Denmark, Switzerland, Belgium), and Africa stresses the need for continued surveillance for mcr-1 gene frequency worldwide. Colistin use in animals and particularly in pig production has been singled out as responsible for the emergence of colistin resistance. Screening of rectal swabs collected during 2011–12 in Belgium from post-weaning diarrhea in pigs found a 13.2 percent (7/53) prevalence of colistin resistance. Investigators realize the need to find alternative antibiotics, so as to preserve the effectiveness of colistin for the treatment of multi-drug-resistant gram-negative bacteria infections in human medicine.

Rapid point-of-care test platforms are designed to be fast and effective diagnostics aimed at identifying microbial infections. Investigators are questioning the adequacy of current day diagnostic technology, as well as the expense, speed, availability and novelty of this pipeline. While diagnosing an infection, terms such as biomarkers, point of care and speed need to be well defined. Is the biomarker a microbial marker, a pathological marker for establishing diagnosis, or used to track therapeutic intervention? Does the presence of DNA in a sample reflect infection? Where is the point of care? Is it at the physician's office, at the central lab in a hospital, or in the field? How rapid is rapid? 24 hours? 4 hours? 2 hours? 2 minutes?

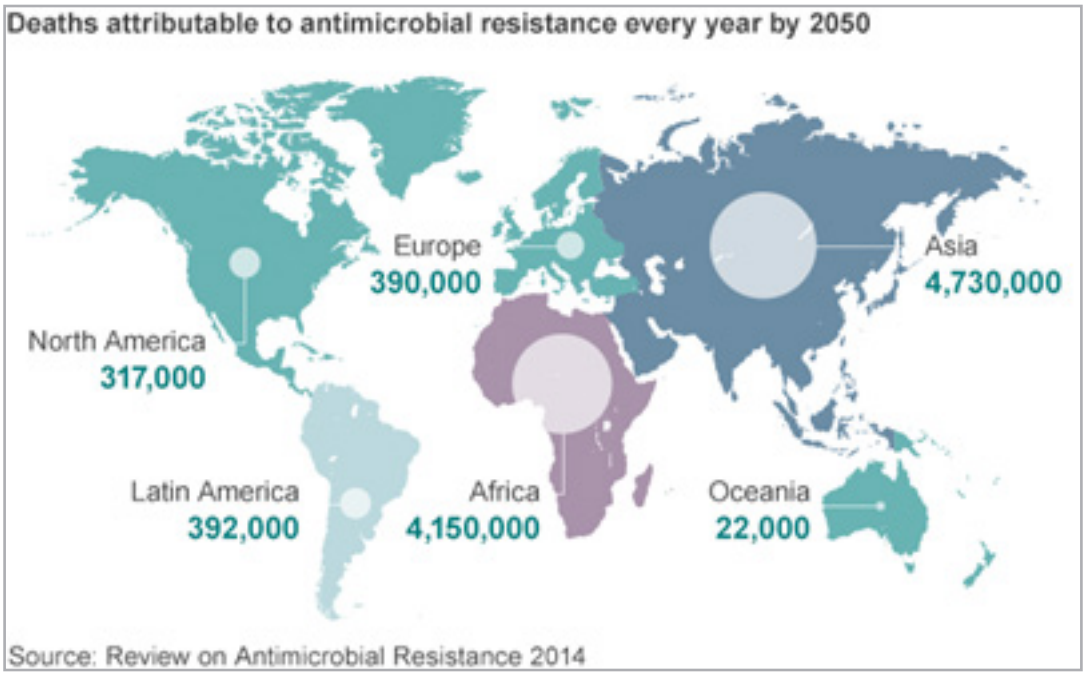
THE BELGIUM SCENARIO

Driven by the inappropriate use of ineffective antibiotics, this section focuses on the status of antimicrobial resistance (AMR) in Belgium. Faced with the challenge of AMR in the country, extensive research is ongoing to develop rapid point-of-care test platforms for blood stream infections, lower respiratory tract infections (LRTI, including community-acquired pneumonia [CAP] and ventilator-associated pneumonia [VAP], and tuberculosis [TB]). Antimicrobial research in Belgium is spread over 5 universities in Flanders. Herman Goossens is Professor of Microbiology at the University of Antwerp and Director of the Dept. of Clinical Pathology at the University Hospital, Antwerp. Holding several expert positions in Belgium, the EU, The U.S., and the WHO, Goossens was elected chair of the Scientific Advisory Board of the Joint Programming Initiative on Antimicrobial Resistance and he is the initiator of the annual European Antibiotic Awareness Day.

RAPP-ID

Goosens is the academic coordinator of the RAPP-ID (Development of RApid Point-of-Care test Platforms for Infectious Diseases) project (www.rapp-id.eu), which was initiated in 2011, and is coordinated by Jorge Villacian (Janssen

Continues on next page



Continued from previous page

Research & Development, Beerse, Belgium), with other member companies including GlaxoSmithKline R&D, U.K., Merck, U.S., Novartis Vaccines and Diagnosis Srl, Italy, and Sanofi-Aventis R&D, France.

Since available technology and diagnostic methods often take at least 2 days to produce results, the RAPP-ID aims to develop Point-of-Care Tests (POCTs) for the rapid detection of bacteria, mycobacteria, fungi, as well as viruses and host biomarkers by combining novel specific probes, novel methods of sample preparation, and demonstrating ultra-high sensitive detection methods in hospital patients in less than 2 hours and for outpatients in less than 30 minutes. The platforms will also determine resistance to antimicrobial drugs and will focus on pathogens and host biomarkers involved in blood stream infections, LRTI, including CAP and VAP, and TB.

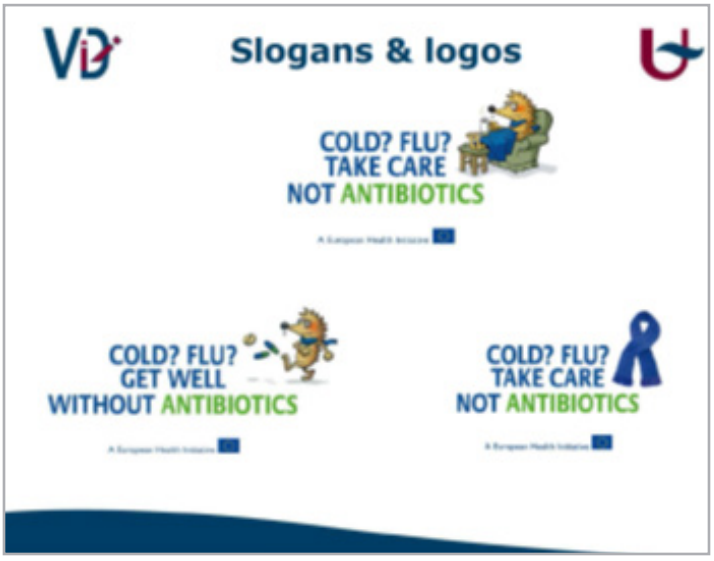
RAPID DIAGNOSTIC TESTS

Rapid diagnostic tests that have been developed include those based on immunochromatographic tests (e.g. HIV, hepatitis C, syphilis) and target amplification techniques (e.g., polymerase chain replication [PCR], transcription-mediated amplification, recombinase polymerase amplification, helicase-dependent amplification, isothermal amplification). The Genexpert system (Cepheid) is a platform developed for testing for multiple diseases (TB and rifampicin resistance, HIV viral load, *Chlamydia trachomatis*, *Neisseria gonorrhea*) based on real-time PCR, giving results in under 2 hours. One disadvantage of molecular-based tests is that the presence of DNA in a sample from a particular pathogen does not necessarily mean that the patient is suffering from an active infection due to the presence of that organism. Some pathogens are also present in the normal flora but do not cause the host any symptoms.

Rapid diagnostic tests are necessary for respiratory tract infections (RTIs) as there is an immediate clinical need to distinguish between bacterial and viral infections and also to rapidly detect drug resistance profiles. Acute cough is the most common reason for antibiotics being prescribed in the community - however, only about 20 percent of acute cough cases are bacterial, thus resulting in antibiotics overuse. Empirical broad-spectrum antibiotic treatment is associated with increased mortality. In patients with VAP, delayed or inappropriate therapy (due to resistance) results in increased mortality.

The Influenza POCT is being developed as a patient-friendly, rapid qualitative test to detect influenza virus in a breath sample within minutes after sampling, together with improved sensitivity compared with commercially available assays.

The CA-LRTI POCT (rapid qualitative test) differentiates bacterial pathogens during a RTI, within minutes after sampling. The test will identify the most important pathogens, enabling appropriate antibiotic treatment. The Theraedge project (funded under the 7th EU Framework Program for Research and technological development), developed a bacterial lysis and DNA purification protocol on a prototypal microfluidic chip to use in an assay for CA-LRTIs. The GRACE



project (funded under the 6th EU Framework Program for Research and technological development), compared the number of *Streptococcus pneumoniae* DNA copies detected by PCR, between patients with CA-LRTIs and healthy controls.

CHALLENGES

Challenges in developing rapid diagnostics for RTIs include the correct selection of the clinical specimen to be collected and how to collect it; the choice of pathogen(s) to be detected; and distinguishing colonization from infection. *S. pneumoniae*, *Hemophilus influenzae* and *Moraxella catarrhalis* can cause CA-LRTIs but can also be present in the flora of asymptomatic carriers, therefore cut-offs between colonization and infection need to be experimentally delineated.

Another challenge is sample preparation, which represents a major bottleneck in developing POCTs. Macroscale lab tests are laborious and can take a few hours, reagents are often refrigerated or frozen, large sample volumes are required and specialized equipment such as centrifuges and bead beaters are used. Rapid POCTs should use reagents stable at room temperature, microliter volumes and the results should be ready in minutes.

The nucleic acid based VAP POCT (rapid [less than 2 hours] highly multiplexed POCT) detects key pathogens and associated antibiotic resistance markers for VAP. The cartridge-based platform allows the fully automated, hands-off processing of endotracheal aspirates, while the padlock probes make the assay highly flexible with regard to the addition of additional targets.

DNA sequence-based techniques as rapid tests for AMR hold promise, yet some pose limitations. DNA sequencing can predict known resistance, but there is scepticism about it predicting susceptibility. On the other hand, culture-based methods are slower but have the advantage of being able to detect new resistance and to recognize susceptibility.

Targeted antibiotic treatment avoids the use of highly toxic last-line and less efficient drugs, reduces mortality among patients and also benefits the clinicians who can develop algorithms

Continues on next page

Continued from previous page

for better diagnosis and tailor-made antibiotic treatment. Improved infection control will result in health care facilities encountering reduced transmission of multi-drug resistant organisms, whereas the use of such rapid diagnostics by the pharmaceutical industry will reduce the number of patients, time for enrollment and costs of development via the optimal identification of patients that are eligible for the study.

Overall, a need exists for point-of-care technologies in primary care in Belgium. A variety of multi-faceted interventions combining physician, patient and public education may successfully reduce inappropriate antibiotic prescription in this country.

Global Burden of Anti-Microbial Resistance - Epidemiology data from the Incidence and Prevalence Database

In the United States, antibiotic resistance has been blamed for at least 2 million illnesses and 23,000 deaths annually. 30 percent-50 percent of antibiotics prescribed in hospitals are unnecessary or incorrect, contributing to antibiotic resistance. The Incidence and Prevalence Database (IPD) of Thomson Reuters reviews the burden of antimicrobial resistance worldwide. The IPD summarized U.S. data from the Antibiotic Resistance Patient Safety Atlas reported by 4,403 health care facilities to the CDC's National Health care Safety Network (NHSN) during 2011-2014. The summary metrics produced by this Atlas reflected the health care-associated infections (HAIs) and reported on the percent of bacteria causing the HAI that were resistant to a specific antibiotic (percent resistant).

ANTIBIOTIC-RESISTANT BACTERIA CAUSING HAI IN U.S.

Among the U.S. states, the percent of bacteria causing health care-associated infections were reported as follows: *Enterobacteriaceae* resistant to carbapenems (CRE), 0 percent–27.9 percent (3.5 percent nationally); *Staphylococcus aureus* resistant to methicillin (MRSA), 32.5 percent–67.8 percent (46.4 percent nationally); *Pseudomonas aeruginosa* resistant to antibiotics in at least 3 categories (multidrug-resistant P. aeruginosa), 3.1 percent–46.9 percent (14.2 percent nationally); *Acinetobacter* resistant to antibiotics in at least 3 categories (multidrug-resistant Acinetobacter), 5.0 percent–88.1 percent (54.8 percent nationally); *Enterobacteriaceae* resistant to extended-spectrum cephalosporins (indicative of extended-spectrum beta–lactamase presence) (*E. coli*, 0 percent–24.4 percent [13.4 percent nationally], Klebsiella spp., 0percent–73.0 percent [20.0 percent nationally], *Enterobacter spp*., 15.0 percent–43.2 percent [28.5 percent nationally]); *Enterococcus* resistant to vancomycin (vancomycin-resistant *Enterococcus spp*. [VRE]) (*E. faecium*, 38.5 percent–86.5 percent [77.3 percent nationally], *E. faecalis*, 0 percent–17.8 percent [6.9 percent nationally]); *Staphylococcus aureus* resistant to methicillin (MRSA) and additional antibiotics suggesting origin in the community (community-associated MRSA), 10.0 percent–55.5 percent [31.2 percent national resistance]); *Staphylococcus aureus* resistant to methicillin (MRSA) and additional antibiotics commonly used to treat MRSA (linezolid, 0.7 percent; daptomycin, 1.3 percent; or intermediate/ resistance to vancomycin, 0.2percent); *E. coli* resistant to fluoroquinolone (a commonly prescribed class of antibiotics for infections thought to be caused by *E.coli* and related organisms), 12.1 percent–50.5 percent (33.0 percent national resistance); *P. aeruginosa* resistant to piperacillin/tazobactam, 0 percent–41.7 percent (10.0 percent national resistance).

HEALTH CARE-ASSOCIATED INFECTIONS IN EUROPE

The IPD also reported corresponding data from the European Center for Disease Prevention and Control. The Annual Epidemiological Report 2013 gave an overview of the epidemiology of communicable diseases of public health significance in Europe, drawn from surveillance information from countries on the communicable diseases and health issues for which surveillance is required in the European Union (EU) and European Economic Area (EEA) countries. Surveillance systems capture only a proportion of the cases actually occurring: some cases of disease remain undiagnosed (under-ascertainment), and some are diagnosed but not reported to public health authorities (underreporting). The pattern of this under-ascertainment and underreporting varies by disease and country, being a complex mix of health care-seeking behavior, access to health services, availability and use of diagnostic services, reporting practices by doctors and others, and the operation of the surveillance system itself. For these reasons the direct comparison of disease rates between countries should be undertaken with caution.

In 2011-2012, 29 EU/EEA Member States and Croatia participated in the first EU-wide, European Center for Disease Prevention and Control (ECDC)-coordinated point prevalence survey (PPS) of HAIs and antimicrobial use in European acute care hospitals. ECDC received data for a total of 273,753 patients in 1149 hospitals. Of these, 231,459 patients from 947 hospitals were included in the final European sample for analysis.

PREVALENCE OF INFECTIONS IN EUROPE

The prevalence of patients with at least one health care-associated infection in acute care hospitals in the PPS sample was 6.0 percent (country range: 2.3 percent to 10.8 percent). When extrapolated to the average daily number of occupied beds per country, the health care-associated infection prevalence was estimated at 5.7 percent. The number of patients with at least one health care-associated infection on any given day in European acute care hospitals was estimated at 81,089. The annual number of patients with at least one health care-associated infection in European acute care hospitals was estimated at 3.2 million.

Of a total of 15,000 reported health care-associated infections, the most frequently reported types of health care-associated

Continues on next page

Continued from previous page

infections were respiratory tract infections (pneumonia and lower respiratory tract, 19.4 percent and 4.1 percent, respectively), surgical site infections (SSIs; 19.6 percent), urinary tract infections (19.0 percent), bloodstream infections (10.7 percent) and gastrointestinal infections (7.7 percent). Health care-associated infection prevalence was the highest in patients admitted to intensive care units, where 19.5 percent patients had at least one health care-associated infection, compared with 5.2 percent on average for all other specialties combined. 23 percent of health care-associated infections were present on admission. One-third of health care-associated infections on admission were SSIs.

SURGICAL SITE INFECTIONS IN EUROPE

In 2011, 16 countries participated in the surveillance of SSIs according to the ECDC HAI-Net SSI protocol. Three countries submitted data on SSIs for the first time in 2011. A total of 424,871 surgical operations were included and a total of 8,371 SSIs were reported. Approximately half of all SSIs were reported after patient discharge from the hospital. The cumulative incidence of SSIs varied from 0.7 percent after knee prosthesis to 9.2 percent after colon surgery.

ANTIMICROBIAL USE AND RESISTANCE IN EUROPE

The prevalence of antimicrobial use was estimated at 32.7 percent, with 466,226 patients receiving at least one antimicrobial on any given day in European acute care hospitals in 2011-2012.

For selected microorganisms reported in health care-associated infections in 2011-2012, the number tested was reported as follows, with (in parentheses) the percentage that were non-susceptible. Gram-positive cocci: methicillin-resistant *Staphylococcus aureus*, 1,071 (41.2 percent); vancomycin-resistant *Enterococcus spp.*, 755 (10.2 percent); vancomycin-resistant *E. faecalis*, 455 (5.5 percent); vancomycin-resistant *E. faecium*, 205 (19.0 percent). *Enterobacteriaceae* (third-generation cephalosporin non-susceptible), 2,851 (33.4 percent): *Escherichia coli*, 1,292 (23.5 percent); *Klebsiella spp.*, 726 (53.0 percent); *K. pneumoniae*, 594 (56.7 percent); *K. oxytoca*, 87 (24.4 percent); *Enterobacter spp.*, 343 (40.5 percent). *Enterobacteriaceae* (carbapenem non-susceptible), 2,787 (7.6 percent): *E. coli*, 1,267 (3.6 percent); *Klebsiella spp.*, 719 (19.3 percent); *K. pneumoniae*, 589 (22.6 percent); *K. oxytoca*, 84 (0 percent); *Enterobacter spp.*, 340 (3.5 percent). Other Gram-negative bacteria (carbapenem non-susceptible): *Pseudomonas aeruginosa*, 756 (31.8 percent); *Acinetobacter baumannii*, 292 (81.2 percent).

CONCLUSION

For more information on infection with drug-resistant microorganisms, antibiotic resistance, drug resistance (treatment resistance), multidrug resistance, see the IPD database, with IPD map reports reflecting the countries/regions with the most published incidence and prevalence data available in the database. //