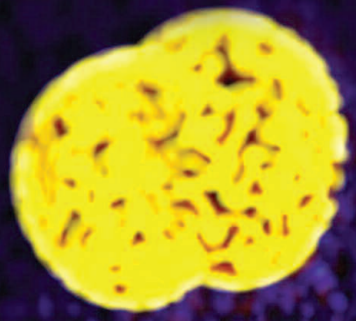
SPRING 2017

biosupply trends

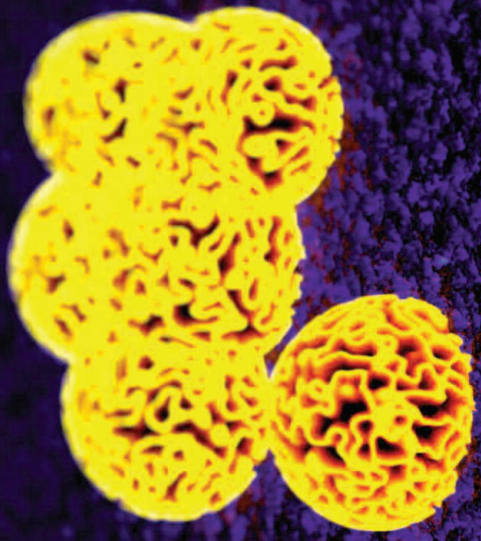
QUARTERLY

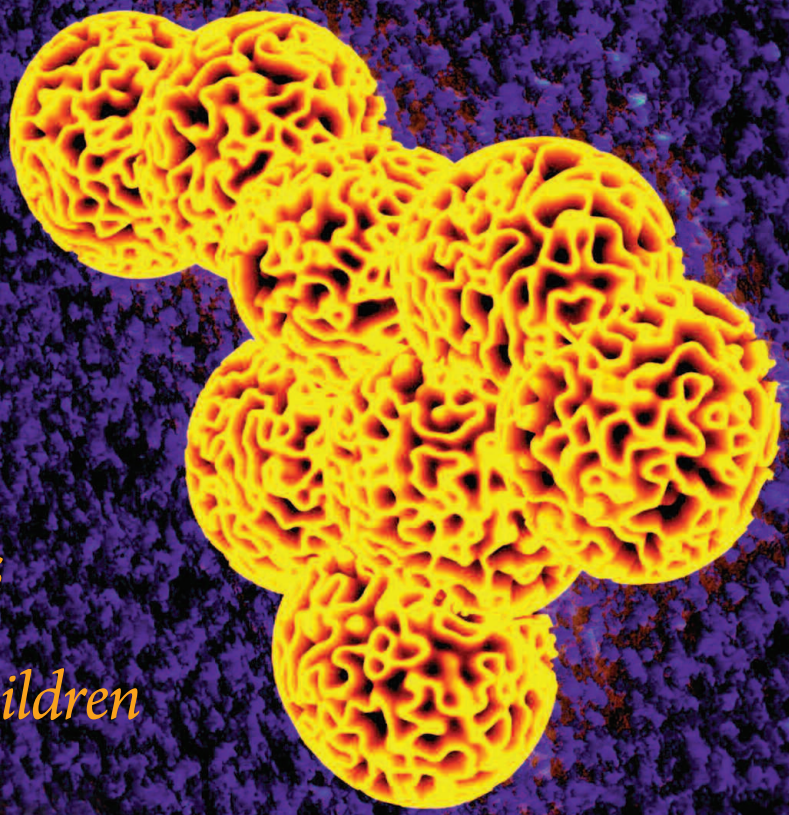
SPECIAL FOCUS:
SAFETY



SUPERBUGS

The Demise of Antibiotics?





OUTLOOK ON *Zika Virus*

Preparing Autistic Children
FOR ADULTHOOD

QUALITY IMPROVEMENT:
Hurdles to Optimizing Care

Fibrin Sealants:
Stop the Bleeding p.44

8 Critical Steps

Purchasing

At FFF, we only purchase products from the manufacturer–never from another distributor or source. This means the integrity of our products is never in question from tampering or mishandling.

Storage

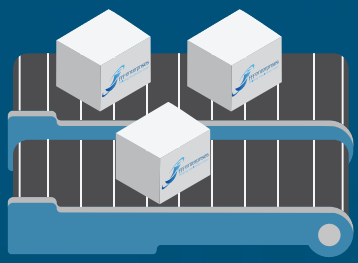
We store and transport viable protein compounds that are sensitive to temperature variations. Temperature controlled, monitored 24/7, and supported with backup generators in the event of power loss.

Specialty Packaging

We use only certified, qualified, environmentally-friendly packaging, taking extra precautions for frozen and refrigerated products.

Interactive Allocation

Assures responsible, demand-based distribution of critical-care products in challenging market conditions. Reduces potential for gray-market purchasing to accommodate critical demand issues.



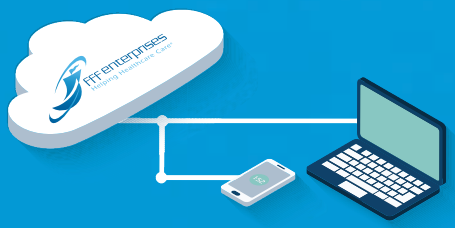
To Guaranteed Channel Integrity™

Delivery

We deliver only to facilities with a state-issued license, and only to the address on the license. We make no exceptions. It is our commitment to do everything in our power to prevent products from entering a secondary distribution channel.

Methods of Delivery

Monitoring and adjusting for extreme weather conditions allows time-sensitive delivery to ensure product integrity.



Verification

In compliance with DSCSA requirements, every product shipped from FFF is accompanied by a packing slip that includes information regarding the manufacturer and presentation, as well as the three T's: Transaction Information, Transaction History and Transaction Statement.

Tracking

To meet DSCSA requirements, FFF provides product traceability information on all packing slips. In addition, Lot-Track® electronically captures and permanently stores each product lot number, matched to customer information, for every vial of drug we supply.

Our commitment to a secure pharmaceutical supply chain is demonstrated by our flawless safety record.

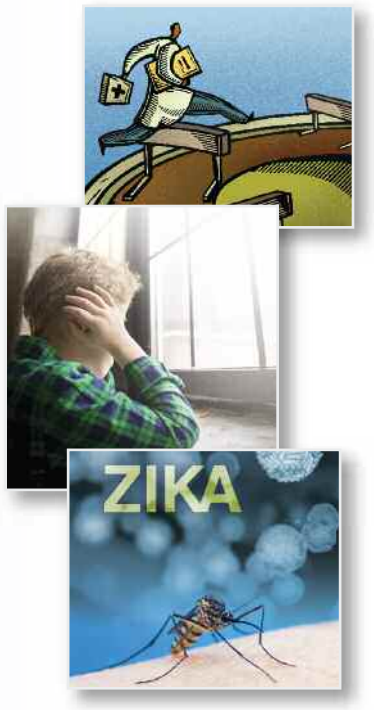
FFF enterprises
Helping Healthcare Care®

More than 28 counterfeit-free years

Since 1988

biosupply trends QUARTERLY

Features



Up Front

BioTrends Watch

BioFocus

BioSources

About BioSupply Trends Quarterly

BioSupply Trends Quarterly is the definitive source for industry trends, news and information for healthcare professionals in the biopharmaceuticals marketplace.

BioSupply Trends Quarterly (ISSN 1948-2620) is a national publication, with quarterly themed issues.

Publisher: FFF Enterprises, Inc., 41093 County Center Drive, Temecula, CA 92591

Subscriptions to *BioSupply Trends Quarterly* are complimentary. Readers may subscribe by calling (800) 843-7477 x1351.

Making Strides in Patient Safety

According to the World Health Organization (WHO), "patient safety is a serious global public health issue," with as many as one in 10 patients harmed while receiving hospital care in developed countries. But, it's not just hospital settings where patient safety is at risk. Emerging diseases, a need for patient engagement and access to medical technologies are but a few of the issues that make patient safety a shared responsibility among all entities.

One of the most pressing problems occurring in hospitals is antimicrobial resistance (AMR) to antibiotics. Once deemed "wonder drugs," antibiotics are poised for demise because superbugs are circumventing them. In our article "Superbug Apocalypse: A Post-Antibiotic Era?" we look at the evolution of antibiotics and how their misuse has allowed a host of deadly infections resistant to treatment to become an ominous threat. Indeed, just this past year, a superbug strain was discovered that is resistant to virtually every known antibiotic. With AMR-related deaths poised to reach 10 million annually by 2050, the superbug threat has caught the world's attention. Healthcare professionals are urged to curb overprescription of antibiotics, laws have been enacted to constrain the use of them in livestock, and scientists are scrambling to develop more sophisticated ones.

Superbugs are but one of the concerns in healthcare settings. Today, there is a drive to measurably improve healthcare services through the implementation of quality improvement programs. As we outline in our article "Quality Improvement Programs: Hurdles to Optimizing Care," several models are being employed to achieve better care. However, change can be challenging, so we underscore what missteps can occur along the way and what essential elements are necessary for improvement by staff at all levels in the healthcare system.

The spread of emerging diseases continues to plague the world. The most recent in the headlines is Zika virus, which WHO has declared a public health emergency. Stemming from a few outbreaks in Brazil and French Polynesia, Zika now threatens the world with outbreaks in more than 75 nations. Our "Update on Zika Virus" article discusses some of the latest research that sheds light on the cause and spread of the virus, as well as what is needed to fight it — from better diagnostic tools, to antiviral drugs and vaccines.

On the home front, autism spectrum disorder (ASD) is becoming more prevalent each year. While dealing with this neurodevelopmental disorder is challenging enough for these children and their families during youth, how to prepare them for adulthood can be even more troublesome. As we explain in our article "Autism: Preparing for Aging Out of the System," children who have received assistance during their youth are more likely to make the transition more smoothly. Even so, many programs available to youth are no longer available to those who have "aged out" of the system. Fortunately, two organizations, Autism Speaks and the Autism Society, provide extensive resources, and help at the federal level in terms of supplemental income and insurance is available for these adults.

In the operating room, patient safety is of the utmost import. The critical need to control bleeding during and after surgery has been a concern for decades. For certain surgeries, scientists have discovered the product best suited for achieving hemostasis — fibrin-based biological adhesives — comes from the human body. Now, as the demand for fibrin sealants continues to increase, there are four U.S. Food and Drug Administration-approved products available.

As always, we hope you enjoy this issue of *BioSupply Trends Quarterly*, and find it both relevant and helpful to your practice.

Helping Healthcare Care,

Patrick M. Schmidt
Publisher

biosupplytrends QUARTERLY

Our mission is to serve as the industry's leading resource for timely, newsworthy and critical information impacting the biopharmaceuticals marketplace, while providing readers with useful tips, trends, perspectives and leading indicators on the topics pertinent to their business.

Publisher
Patrick M. Schmidt

Editor
Ronale Tucker Rhodes, MS

Assistant Editor
Cheryl Brooks

Art Director
Allan Bean

Advertising Director
Cheryl Brooks

Contributing Writers
Keith Berman, MPH, MBA
Diane L.M. Cook
Dana Henry
Bonnie Kirschenbaum, MS, FASHP, FCSHP
Trudie Mitschang
Jim Trageser

Proofreader
Jackie Logue

Please direct editorial, advertising and marketing communications to
41093 County Center Drive
Temecula, CA 92591
Ph: (800) 843-7477
Email: editor@BSTQuarterly.com

CMS Rule Phases Out Pass-Through Payments

The Centers for Medicare and Medicaid Services (CMS) has released the Use of New or Increased Pass-Through Payments in Medicaid Managed Care final rule, which prevents increases in and the addition of new pass-through payments beyond those in place when the pass-through payment transition periods were established in May 2016 as part of the Medicaid Managed Care final rule. Pass-through payments are amounts paid to Medicaid managed care plans as supplemental payments or "add-ons" to the base capitation rate. Plans are required to pass through the add-on payments to designated contracted providers.

While pass-through payments can continue under the Medicaid Managed Care Organization contract, they must be phased out within 10 years for hospitals and five years for physicians, and for each year of the transition period, there is a new maximum of permitted pass-through payments. In addition, CMS prohibits retroactive adjustments to managed care contracts and rate certifications to add new or increase existing pass-through payments.

The rule applies to all states with Medicaid managed care plans. According to CMS, it is estimated that at least 16 states have paid $3.3 billion in pass-through payments on average every year. Another three have distributed about $50 million a year for nursing facilities. ❖

Cox A. CMS Releases Final Rule on Medicaid Managed Care Pass-Through Payments. Association of American Medical Colleges, Jan. 19, 2017. Accessed at www.aamc.org/advocacy/washhigh/highlights2017/475658/011917cmsreleasesfinalruleonmedicaidmanagedcarepass-throughpayme.html.

Dickson V. Final Pass-Through Pay Rule Would Cost Hospitals More Than $3 Billion a Year. *Modern Healthcare,* Jan. 17, 2017. Accessed at www.modernhealthcare.com/article/20170117/NEWS/170119909.

HHS Final Rule Protects Research Participants and Modernizes Oversight

In January, the U.S. Department of Health and Human Services (HHS), along with 15 other agencies, finalized a rule whose provisions safeguard individuals who participate in research, most of which will go into effect in 2018. The finalized rule updates regulations that have been in place since 1991, often referred to as the "common rule," that were developed when research was conducted predominantly at universities and medical institutions. Elements of the finalized rule include:

- The requirement for consent forms to provide potential research subjects with a better understanding of a project's scope, including its risks and benefits, so participants can make a more fully informed decision about whether to take part;
- The requirement to use a single institutional review board (IRB) for multi-institutional research studies, but allowing for broad groups of studies, rather than just specific studies, to be removed from the requirement;
- For studies on stored identifiable data or identifiable biospecimens, researchers have the option of relying on broad consent obtained for future research rather than seeking IRB approval to waive the consent requirement (consistent with the current rule, researchers will not have to obtain consent for studies on nonidentified stored data or biospecimens);
- The establishment of new exempt categories of research based on the level of risk they pose to participants;
- Removal of the requirement to conduct continuing review of ongoing research studies in certain instances where such review does little to protect subjects; and
- The requirement that consent forms for certain federally funded clinical trials be posted on a public website. ❖

Final Rule Enhances Protections for Research Participants, Modernizes Oversight System. U.S. Department of Health and Human Services press release, Jan. 18, 2017. Accessed at www.hhs.gov/about/news/2017/01/18/final-rule-enhances-protections-research-participants-modernizes-oversight-system.html.

21st Century Cures Act Modifies Medicare Payments for Services

In December, Congress passed the 21st Century Cures Act. The act's major provisions will reform the current standards and appropriations for biomedical research, provide $1.75 billion annually for the National Institutes of Health (NIH) and $110 million for the U.S. Food and Drug Administration (FDA) — funding that will end after five years. Along with an increase in NIH and FDA funding, the bill will reduce regulations on access to medical research and expedite the testing processes of new drugs.

There are several minor provisions in the act, however, that will change how Medicare reimburses providers for services. A *National Law Review* article outlines several key highlights of the provisions:

• *Site-neutral payment methodologies*. This requires Medicare to reimburse providers or suppliers for services, supplies or drugs without regard to whether services were provided in an inpatient or outpatient facility or in a physician's office. However, hospital outpatient departments may be exempt in some instances.

• *Long-term care hospitals (LTCHs)*. The act amends Medicare policies related to certified LTCHs. Specifically, it modifies the standard federal payment rate for LTCH high-cost outlier payments beginning Oct. 1, 2017; extends the prohibition on the Centers for Medicare and Medicaid's (CMS) enforcement of the LTCH 25-percent rule through Sept. 30, 2017; extends the carve-out for Medicare Advantage and site-neutral discharges from the calculation of the 25-day average length-of-stay requirement to LTCHs taking advantage of the moratorium exception; temporarily excepts LTCH site neutral criteria for certain hospitals that treat patients with brain and spinal cord injuries in 2018 and 2019; and grandfathers LTCHs by temporarily excepting LTCH site-neutral criteria for hospitalizations for severe wounds in 2018.

• *Durable medical equipment (DME).* The act requires CMS to consider average travel time, the cost associated with furnishing items, the average volume of items and services furnished in the area, and the number of suppliers in the area when determining adjustments in the use of competitively bid prices for DME items and services furnished on or after Jan. 1, 2019. It also moves up the implementation date of the provision limiting federal Medicaid reimbursement to states for DME, prosthetics, orthotics and supplies to Medicare reimbursement rates by one year from Jan. 1, 2019, to Jan. 1, 2018.

• *Home infusion therapy.* Effective Jan. 1, payments for infusion drugs furnished by DME suppliers are modified from 95 percent of the average wholesale price to the average sales price plus a 6 percent add-on. It is estimated that this change will reduce payments to suppliers by $660 million over a 10-year period. It will not be until Jan. 1, 2021, that the act will reimburse "qualified home infusion therapy suppliers" for providing infusion therapy services in a beneficiary's home. This provision, however, will come with a broad list of new requirements and standards for suppliers of home infusion, and it will require Medicare to reimburse home infusion therapy suppliers based on a single, all-inclusive payment.

• *Medicare Advantage (MA).* Starting in 2019, during the first three months of any year, individuals eligible for MA may change a previous election to receive benefits through original Medicare or an MA plan and elect coverage under Part D. Starting in 2021, individuals with end-stage renal disease (ESRD) may enroll in any MA plan. And it adjusts the ESRD risk adjustment model by directing CMS to take into account the total number of diseases, multiple years of data and dual eligibility status. It also partially limits CMS's ability to terminate MA plans based solely on minimum quality ratings.

In addition to changes in reimbursement, the act reauthorized the Creating Hope Act pediatric priority review voucher program, which will provide researchers and biotechs with financial incentives to develop better treatments for kids with cancer and other serious illnesses until Sept. 20, 2020. In addition, drugs that receive rare pediatric designations by that date will qualify for vouchers as long as they are approved by Sept. 20, 2023. Since 2012, this act has created almost $1 billion in research and development initiatives for pediatric drug development. ❖

Cooper SH. Implications of the Medicare and Medicaid Provisions in the 21st Century Cures Act. *National Law Review*, Dec. 13, 2016. Accessed at www.natlawreview.com/article/implications-medicare-and-medicaid-provisions-21st-century-cures-act.

340B Drug Discount Program in 2017

The 340B Drug Discount Program is a price control program for drugs purchased by nonmilitary and VA healthcare entities overseen by the Health Resources and Services Administration (HRSA) within the Department of Health and Human Services. Briefly, it requires participating drug manufacturers to give certain entities within the healthcare safety net, known as covered entities (see Eligible Entities), access to discounted prices on outpatient drugs. The program's intent is to allow these entities to increase patient services with savings they accrue by purchasing product at a lower cost.

The program started in 1990 when Congress created the Medicaid rebate program to lower the cost of covered outpatient drugs reimbursed by state agencies. Relief from high drug costs for safety-net providers (those that care for people without health insurance, who are poor or who may be on Medicaid) was extended in 1992 when Congress enacted Section 340B of the Public Health Services Act, created under the Veterans Health Care Act of 1992.

The three components of the program include the Office of Pharmacy Affairs (OPA), Pharmacy Services Support Center and 340B Prime Vendor Program. To participate, covered entities must register with HRSA, and if approved, they are added to the approved entities database. Eligibility is redetermined annually. Once approved, they may purchase covered outpatient drugs under the 340B program at or below the 340B ceiling price.

Manufacturers are obligated to calculate 340B prices accurately using a statutorily defined formula and to communicate prices to distributors. At a minimum, the discount is 23.1 percent for brand-name drugs (except clotting factor and drugs approved exclusively for pediatric use, for which the basic rebate is 17.1 percent of average manufacturer price) and 13 percent for generic and over-the-counter drugs. Additional discounts can be negotiated, some up to 60 percent below retail prices and 51 percent less than average wholesale price. With adequate inventory, manufacturers must sell product to enrolled covered entities and cannot condition sales on a promise of compliance. Manufacturers retain the right to audit a covered entity if reasonable evidence suggests noncompliance with prohibition against duplicate discounts or diversion.

Program prohibitions include diversion of drugs to ineligible patients (see Determining Patient Eligibility) and duplicate discounts that occur when a facility is obtaining the 340B discount plus the Medicaid rebate on the same drug. Subjecting drug manufacturers to duplicate discounts on 340B-purchased drugs is prohibited by law, so covered entities are required to report their Medicaid billing status. They can choose to dispense 340B-purchased drugs to Medicaid beneficiaries, and they can indicate their choice in HRSA's covered entity database, which state Medicaid agencies use to identify Medicaid payments for 340B-purchased drugs that are excluded from rebate requests to drug manufacturers.

Eligible Entities

- Federal grantees
- Hemophilia treatment centers
- Federally qualified health centers/look-alikes
- Ryan White programs
- Sexually transmitted diseases/tuberculosis
- Title X family planning centers
- Urban/638 health centers
- Native Hawaiian health centers
- Nongrantees (tax status must be not-for-profit)
- Disproportionate share hospitals (adjustment % > 11.75%)
- Critical access hospitals
- Rural referral centers
- Sole community hospitals
- Children's hospitals
- Free-standing cancer hospitals

340B Oversight: Not What It Used to Be

Due to the increase in number of users of the 340B program by the Affordable Care Act's expansion of it and HRSA's allowance to contract with multiple pharmacies, significant changes in oversight were required, including annual enrollment recertification, audits of 340B covered entities and manufacturer audits.

On Aug. 25, 2015, HRSA released the proposed 340B "mega-guidance" that addressed program eligibility and registration, eligibility of drugs for purchase under 340B, patient eligibility to receive 340B drugs, requirements for covered entities, arrangements for contract pharmacies, manufacturer responsibilities, rebate options for AIDS drug assistance programs and program integrity. But, after multiple comments were received and addressed, on Jan. 30, the White House Office of Management and Budget (OMB) withdrew the final guidance document. It is unknown as of this writing whether HRSA's guidance will move forward with resubmission to the OMB.

What is known is that 340B participants must be confident about the integrity of their 340B program. Myriad details need to be reviewed, including business processes, policies and procedures; enrollment and vendor contracts;

diversion of 340B drugs to ineligible patients; duplicate discounting; the group purchasing organization exclusion requirement; identification and definition of all eligible patients and drugs; issues with accumulator/splitter software; oversight of contract pharmacy activity, inventory balances and contract compliance; duplicate dispenses; replenishment of 340B drugs; orphan drugs; monitoring and reporting of 340B transactions; and identification of missed opportunities to receive 340B discounts.

Why the Sudden and Expanded Interest in 340B?

Currently, there is uncertainty about the program, with conflicting viewpoints by opponents (stakeholders and regulatory bodies) and participating supporters, as well as non-340B facilities clamoring to be a part of it due to the astronomical rise in drug prices, especially in the oncology and immunotherapy areas.

However, HRSA is faced with many challenges. To be poised for growth, it must address insufficient capacity, technology restructure and bolstered resources. Certainly, the furor over drug pricing highlighted by congressional hearings is keeping the program in the limelight. Additionally, the January 2016 MedPAC recommendation to Congress to cut Medicare payments to safety net hospitals by 10 percent for drugs purchased under the 340B drug program may still be viable. The Centers for Medicare and Medicaid covered outpatient drug rule and the Medicaid rebate rule may be addressed as well.

Limited distribution drugs, specialty drugs and orphan drugs (some of the most expensive products) are hot-button issues in the 340B program. Orphan drugs, which are excluded from 340B pricing for some participants, are worthy of particular attention since the U.S. Food and Drug Administration continues to receive a record number of requests for orphan drug designation. While drugs can have multiple indications, they qualify for orphan drug designation only when used to treat certain rare diseases or conditions. The rationale for the orphan drug program is to incentivize manufacturers to develop drugs for rare conditions. Designated drugs maintain that status for an indefinite period.

The HRSA website lists more than 3,400 drugs with orphan drug status. Rural referral centers, sole community hospitals, critical access hospitals and free-standing cancer hospitals participating in the 340B program are vulnerable since manufacturers are not required to provide them with orphan drugs under the 340B program. However, manufacturers may, at their sole discretion, offer discounts on orphan drugs to them (see docs.340bpvp.com/documents/public/resourcecenter/Summary_Orphan_Drugs.pdf).

A Time to Prepare

Although the mega-guidance has been stalled, facilities can still prepare by performing audits to manage and confirm compliance with current 340B program requirements, and evaluating the financial and operational effects of any proposed changes. And, because there is no presumptive eligibility in the 340B program, facilities can ensure best practices are in place by:

- Developing and documenting comprehensive 340B policies and procedures;
- Developing concrete methodologies for routine self-monitoring;
- Implementing routine processes for internal corrective action;
- Verifying contract pharmacy arrangements comply with 340B requirements and are properly listed in the OPA database; and
- Creating strong partnerships with state Medicaid agencies to meet state-specific requirements and to ensure prevention of duplicate discounts. ❖

Determining Patient Eligibility

- Covered entity must have an established relationship with the individual and must maintain records of the individual's healthcare.
- Individual must receive healthcare services from providers either employed by the covered entity or maintain contractual/other arrangements (e.g., consult referral) such that the covered entity is responsible for care provided.
- Healthcare services the individual receives from the covered entity are consistent with services for which the entity received grant funding or federally qualified health center look-alike status. Disproportionate share hospitals are exempt from this requirement.

Note: An individual is not considered a patient of a covered entity if the only healthcare service the individual receives from the covered entity is dispensing of a drug or drugs for self-administration or administration at home.

BONNIE KIRSCHENBAUM, MS, FASHP, FCSHP, is a freelance healthcare consultant with senior management experience in both the pharmaceutical industry and the pharmacy section of large corporate healthcare organizations and teaching hospitals. She has an interest in reimbursement issues and in using technology to solve them. Kirschenbaum is a recognized industry leader in forging effective alliances among hospitals, physicians, pharmaceutical companies and distributors and has written and spoken extensively in these areas.

Medicines

FDA Approves Gammaplex 10% to Treat Adult PI and ITP Patients

The U.S. Food and Drug Administration (FDA) has approved Bio Products Laboratory's (BPL) Gammaplex 10% (immune globulin intravenous [human] 10% liquid) for the treatment of primary immunodeficiency (PI) and chronic immune thrombocytopenic purpura (ITP) in adults. Gammaplex 10% is made with the same process as BPL's previously approved intravenous immune globulin, Gammaplex 5%, but has an IgG concentration of 100 g/L and is stabilized with glycine.

Approval was based on a Phase II crossover bioequivalence study comparing Gammaplex 10% and Gammaplex 5% in 33 adult patients with PI. In the study, both Gammaplex 10% and Gammaplex 5% infusion rates were increased incrementally at 15-minute intervals if tolerated. No notable differences were observed in the safety and tolerability between the products, and the Gammaplex 10% infusion rate was increased per the prescribed infusion schedule to maximum infusion rate in 96 percent of infusions. The mean infusion time for Gammaplex 10% was one hour and 51 minutes, which was 57 minutes faster than Gammaplex 5%. The most common adverse reactions were headache (12.5 percent), migraine (6.3 percent) and pyrexia (6.3 percent). No serious product-related adverse effects occurred.

While the safety of Gammaplex 10% has not yet been established in ITP patients, Gammaplex 5% has been studied, and it is anticipated that the safety profile for both formulations are comparable. ❖

FDA Approves Bio Products Laboratory's Gammaplex 10% for Treatment of Primary Immunodeficiency and Chronic Immune Thrombocytopenic Purpura. Bio Products Laboratory press release, Feb. 7, 2017. Accessed at www.prnewswire.com/news-releases/fda-approves-bio-products-laboratorys-gammaplex-10-for-treatment-of-primary-immunodeficiency-and-chronic-immune-thrombocytopenic-purpura-300403379.html.

Research

Infusion of BPX-501 T Cells Renders Haplo-HSCT a First-Line Option for Children with PI

Results from a Phase I/II study indicate that haploidentical hematopoietic stem cell transplantation (haplo-HSCT), after depletion of α/β T cells and B cells followed by adoptive infusion of donor BPX-501 cells, is an effective alternative for children with primary immunodeficiency disease (PI) in need of an urgent allograft or lacking a suitable human leukocyte antigen (HLA)-matched donor. While haplo-HSCT after depletion of α/β T cells/CD19 B cells previously had high success rates, many patients had a delay in recovery of adaptive immunity, sometimes resulting in life-threatening or even fatal events. BPX-501 cells expand in vivo and persist over time, contributing to hasten the recovery of adaptive T-cell immunity and to clear infections.

In the multicenter, prospective trial, 20 children with PIs were enrolled. All patients were transplanted after depletion of α/β T cells and CD19 B cells, employed to prevent graft-versus-host disease (GvHD) and post-transplant lymphoproliferative disorders. No patient was given any post-transplantation GvHD prophylaxis. Four patients were enrolled in the Phase I portion of the trial, which consisted of a classical 3+3 design with three cohorts, with escalating doses of BPX-501 cells of $2.5x10_5$ (one patient), $5x10_5$ (no patients) and $1x10_6$ cells/kg (three patients), respectively. The remaining 16 patients were treated in the Phase II portion, all of whom received the highest dose identified during the Phase I portion ($1x10_6$ cells/kg). All patients engrafted, and no secondary graft failure was recorded. The median time to neutrophil and platelet recovery was 16 days (range 11-35) and 10 days (range 7-14), respectively. BPX-501 cells were infused at a median time of 15 days (range 13-56) after the allograft. Five children experienced grade I (three patients) or grade II (two patients) acute GvHD, which resolved with either topical or systemic steroids in three patients. The other two cases resolved after the infusion of Rimiducid,

which activated the iC9 suicide gene. Two of the patients at risk developed mild (skin-only) chronic GvHD. The median time to discharge was 36 days, with eight patients experiencing one episode of rehospitalization after initial discharge. After a median follow-up of 10 months, all patients are alive and disease-free. ❖

Kapoo N, Bertaina A, Merli P, et al. Outcome of Children with Primary Immune-Deficiencies (PIDs) Enrolled in a Phase I-II Trial Based on the Infusion of BPX-501 Donor T Cells Genetically Modified with a Novel Suicide Gene (inducible Caspase 9, iC9) after T-Cell Depleted HLA-Haploidentical Allogeneic Stem Cell Transplantation (haplo-HSCT). *Blood,* 2016, 182:72. Accessed at www.bloodjournal.org/content/128/22/72?sso-checked=true.

Vaccines

CDC Changes Recommendation for HPV Vaccine for Children

Since 2006 and 2011, respectively, the Centers for Disease Control and Prevention's (CDC) Advisory Committee on Immunization Practices (ACIP) has recommended girls and boys receive three doses of the human papilloma virus (HPV) vaccine before they turn 15. However, in October, ACIP changed its recommendation to only two doses of the vaccine prior to age 15. ACIP's decision was based on results of numerous studies showing that prior to age 15, the two-dose vaccine was just as protective, and even slightly more so, than the three-dose series. But that effectiveness relied heavily on when the second dose was given; when the booster was given only a couple of months after the first shot, the two doses were not as effective, according to Lauri Markowitz, MD, an epidemiologist with the CDC. According to ACIP, while the two-dose schedule is slightly less effective, the difference is not enough to overcome the financial advantage of getting one less shot.

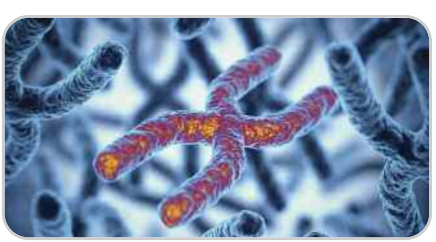
The HPV vaccine is designed to ward off infection by certain strains of the HPV virus that cause cervical, vaginal and vulvar cancers in women; penile cancers in men; and oropharyngeal and anal cancers, as well as genital warts, in both men and women. However, it needs to be administered before a person becomes sexually active for it to be most effective. ACIP recommends children receive their first dose at age 11 or 12, but it can be given as young as 9 years old and is recommended at that age for children who are in a potentially abusive situation. ❖

CDC Advisory Panel Changes Recommendation for HPV Vaccine from 3 Doses to 2 for Young Adolescents. The Immunization Partnership, Oct. 19, 2016. Accessed at www.immunizeusa.org/blog/2016/october/19/cdc-advisory-panel-changes-recommendation-for-hpv-vaccine-from-3-doses-to-2-for-young-adolescents.

Research

Hemophilia B Gene Therapy Is Effective Despite Immune Reactions

In a Phase I/II study of nine patients with hemophilia B who underwent Spark Therapeutics' SPK-9001 gene therapy, two patients experienced adverse autoimmune reactions, necessitating treatment with steroids and resulting in the production of lower levels of the blood-clotting protein factor IX (FIX). However, neither patient has suffered from bleeds or required rescue treatment with FIX infusions, and the company says temporary steroid treatment can arrest the immune response before it causes FIX levels to fall to a point where bleeding risk becomes a problem.



The ongoing study has yielded an average FIX level of 28 percent of normal, measured 12 weeks after the one-time infusion. The company's first treated patient has now been followed for one year and has a FIX level of 33 percent of normal. Another three patients followed for more than seven months have FIX levels ranging from 36 percent to 46 percent. All patients enrolled in the study had FIX levels of approximately 1 percent of normal. According to the company, a minimum FIX level of 12 percent of normal is considered necessary to prevent chronic bleeding in joints; higher FIX levels are better. ❖

Feuerstein A. Spark's Hemophilia Gene Therapy Remains Effective Despite Immune Reactions. TheStreet, Dec. 3, 2016. Accessed at www.thestreet.com/story/13913098/1/spark-s-hemophilia-gene-therapy-remains-effective-despite-immune-reactions.html.

Research

No Link Between Flu or Flu Vaccine and Autism, Study Finds

While previous studies looking at possible links between influenza (flu) during pregnancy and autism spectrum disorder (ASD) have produced mixed results, a new study shows that babies of pregnant women who get the flu or who are vaccinated against the flu do not have an increased risk for ASD. In the study, researchers analyzed data on 196,929 children born between 2000 and 2010 in the Kaiser Permanente Northern California healthcare system after at least 24 weeks' gestation. During follow-up periods ranging from two to 15 years, only 1.6 percent of children were diagnosed with ASD. And, of those mothers, fewer than 1 percent had the flu while pregnant, and 23 percent had gotten a flu vaccine.

A second study published in the same issue of *JAMA Pediatrics* also found no link between vaccines against influenza A (H1N1) during pregnancy in 2009-2010 and complications later in life for more than 60,000 Danish children. "There have been a lot of fears about vaccines, but the data suggest they are effective and don't increase the risk of autism and other perinatal complications," said Loralei Thornburg, MD, a high-risk pregnancy expert at the University of Rochester Medical Center in New York. ❖

Seaman AM. Flu or Flu Vaccine in Pregnancy Not Tied to Autism in Kids, Study Suggests. InForum, Dec. 3, 2016. Accessed at www.inforum.com/news/4168807-flu-or-flu-vaccine-pregnancy-not-tied-autism-kids-study-suggests.

Research

IVIG Treatment May Lead to Poorer Outcomes in GBS Patients

A new study shows that individuals treated with intravenous immune globulin (IVIG) for Guillain-Barré syndrome (GBS) are at increased risk of developing hypoalbuminemia (reduced albumin levels), which may result in a more severe disease course and worse outcome. In the study, serum samples from 174 patients with GBS were analyzed before and after IVIG treatment at four time points to determine albumin levels and related muscle weakness, respiratory failure and walking ability. Before IVIG treatment, the median serum albumin level was 4.2 g/dL in 20 out of 156 patients with hypoalbuminemia. After two weeks of 2g/kg of IVIG treatment, the median

serum albumin level fell to 3.7 g/dL, with 60 out of 174 patients experiencing hypoalbuminemia. Hypoalbuminemia was associated with increased levels of respiratory failure in 16 of 44 patients before and 29 of 53 patients after IVIG treatment. And, hypoalbuminemia was associated with decreased ability to walk unaided in 21 out of 60 patients after treatment versus six out of 114 patients before treatment, and increased severe muscle weakness at four weeks and six months after treatment. The researchers concluded that more research is needed to confirm whether serum albumin can be used as a biomarker to monitor disease activity and treatment response to IVIG in patients with GBS. ❖

Fokking WR, Walgaard C, Kuitwaard K, et al. Association of Albumin Levels with Outcome in Intravenous Immunoglobulin-Treated Guillain-Barré Syndrome. *JAMA Neurology*, Dec. 27, 2016. Accessed at jamanetwork.com/journals/jamaneurology/article-abstract/2594534.

Did You Know?

Octapharma made a charitable donation of 4.5 million units of its fourth-generation, human cell-line-derived recombinant factor VIII (FVIII) product, Nuwiq, to the World Federation of Hematology (WFH) Humanitarian Aid Program. The donation will help to provide access to FVIII therapy in developing countries that may otherwise be unable to fully meet the treatment requirements of all patients. "For lasting change to occur in countries most in need, it is imperative that we all come together to support the WFH Humanitarian Aid Program," said Alain Weill, WFH president. "Treatment for all is truly the responsibility of all."

Vaccines

Scientists Develop Vaccine to Block Opioid Drugs' Effects

With the rising epidemic of opioid drug overdoses, a new vaccine that blocks the pain-numbing effects of the drugs oxycodone (oxy) and hydrocodone (hydro) has shown success in animal models. When opioid drugs reach receptors in the brain, they reduce pain and elicit feelings of euphoria. But, the new oxy/hydro vaccine uses the immune system to recognize, seek out and neutralize the drug's molecule.

To develop the vaccine, scientists at The Scripps Research Institute (TSRI) combined a signature opioid structure with a molecule to trigger an immune response. When injected, the vaccine teaches the immune system to bind to the drug molecule and remove it from circulation, thus depriving a person of the effects of the drug. According to the scientists, it's possible that the vaccine could have an advantage over current opioid addiction therapies because it would not alter brain chemistry like many of today's anti-addiction therapies.

In studies, the researchers found that the oxy/hydro vaccine blocked pain perception in most mice, which meant they did not display the usual symptoms of a drug high such as ignoring pain and discomfort. In addition, they appeared less susceptible to fatal overdose, and the vaccine remained effective for the entire 60-day study period. In those that did succumb to the opioid's toxic effects, it took much longer for the drug to impart its toxicity.

While this is not the first vaccine tested to block the effects of opioids, it is the first to use a faithful representation of the opioid in its design. The next steps will be to investigate the vaccine's optimal dose and schedule. ❖

Scientists Develop Vaccine Against Fatal Prescription Opioid Overdose. Phys.org, Nov. 23, 2016. Accessed at phys.org/news/2016-11-scientists-vaccine-fatal-prescription-opioid.html.

Research

Study Shows High Prevalence of Anti-TSH Receptor Antibody in Fibromyalgia

A study has found that patients with fibromyalgia have a high prevalence of anti-thyroid-stimulating hormone (TSH) receptor antibody (TRAb). In the study, researchers from the Juntendo University Graduate School of Medicine in Tokyo tested 207 patients with fibromyalgia for titers of free triiodothyronine, free thyroxine, TSH, antithyroid peroxidase antibody (TPOAb), antithyroglobulin antibody (TgAb) and TRAb, 25 of whom with subclinical hyper- or hypothyroidism were excluded. In the remaining 182 patients, 69 patients were identified as having autoimmune thyroid diseases, for whom the prevalence of positivity for TRAb was 20.3 percent, TgAb was 16.5 percent and TPOAb was 13.2 percent. Compared with previous studies of fibromyalgia patients, the prevalence of TPOAb and TgAb positivity was not significantly higher; however, compared with control populations in previous studies, TRAb titers were low. Identical clinical symptom profiles were seen for fibromyalgia patients with and without autoimmune thyroid disease. ❖

Researchers Find High Prevalence of Anti-TSH Receptor Antibody in Fibromyalgia. Endocrinology Advisory, Dec. 13, 2016. Accessed at www.endocrinologyadvisor.com/thyroid/thyroid-function-and-fibromyalgia/article/578542.

Research

Ebola Symptoms Absent in Some Infected Persons

A recent study shows that people can be infected with the Ebola virus and not show any symptoms. In the study, researchers from Partners in Health, which provided medical aid during the Ebola outbreak, tested 187 people in the 900-person village of Sukudu in Sierra Leone for evidence of being infected with the virus. They found that 14 had Ebola-related antibodies in their blood, which means they had been infected at some point with the virus; however, none of those 14 were included in the original 34 residents who had contracted the virus. "Because minimally symptomatic individuals were not vomiting or having diarrhea, it is highly unlikely they were a source of significant viral transmission," said Dr. Eugene Richardson, a PhD candidate in anthropology at Stanford University. "However, they still represent an instance where the health system failed to prevent human-to-human transmission of the virus."

Ebola is highly contagious because the bodily fluids can be hard to avoid by people close to those infected. As such, the study suggests that many instances of Ebola transmission between people may have gone unidentified during the outbreak,

and that Ebola has a wider variety of symptoms, which could have implications for how outbreaks are dealt with in the future. ❖

Sifferlin A. Some People Who Get Ebola Don't Show Symptoms: Study. *Time*, Dec. 12, 2016. Accessed at time.com/4596928/some-people-who-get-ebola-dont-show-symptoms-study.

Research

C. Diff Vaccine Shows Promise in Phase II Trial

Results of a Phase II clinical trial of Pfizer's preventive vaccine against Clostridium difficile (C. diff) showed the vaccine was safe and stimulated a C. diff-targeted immune response. PF-06425090 is a three-dose recombinant vaccine designed to stimulate an antibody against the two main toxins (A and B) produced by C. diff, which cause the characteristic diarrhea and colitis caused by the bacteria. The results clear the way for the vaccine to enter a Phase III trial in the first half of 2017.

Pfizer also has another C. diff vaccine in development, VLA84, which successfully completed Phase II trials in France last July. The company is now seeking a partner to help fund a Phase III study. In addition, Sanofi has an ongoing Phase III trial of a C. diff toxoid vaccine based on inactivated toxins A and B, which started in 2013 and generated positive Phase II data in 2014. That vaccine is predicted to reach the market in 2019. ❖

Taylor P. Chasing Sanofi, Pfizer Tees Up Phase 3 Trials for C. Diff Vaccine. Fierce Biotech, Jan. 27, 2017. Accessed at www.fiercebiotech.com/biotech/chasing-sanofi-pfizer-tees-up-phase-3-trials-for-c-diff-vaccine.

Research

Scientists Discover Post-Exposure Treatment with Horse Antibodies Is Effective for Ebola

Researchers in Melbourne have developed an effective, rapid and economical treatment for Ebola using antibodies from horses. In the study, the equine antibodies were administered over five days to cynomolgus macaques infected 24 hours previously with a lethal dose of Ebola virus. The researchers found that the antibodies suppressed viral loads by more than five logs and protected animals from mortality. "Animals generated their own Ebola glycoprotein-specific IgG responses 9 [to] 15 days after infection, with circulating virus undetectable by day 15 [through] 17."

Previously and subsequent to the largest recorded Ebola outbreak from 2014 to 2016 that infected 30,000 people and killed more than 11,000 primarily in West Africa, monoclonal antibodies were developed in the United Kingdom to treat infected healthcare workers returning from Africa. But, monoclonal antibodies require considerable investment in manufacture scale-up and are expensive. Equine antibodies, on the other hand, are a cheaper alternative. "This is a cost-effective treatment that can be used in low-income countries in Africa where equine production facilities are already in operation for producing snake-bite antivenin," said Alexander Khromykh, professor at University of Queensland in Australia. The post-exposure treatment made with the equine antibodies could be used in the next Ebola outbreak, the researchers said. ❖

Scientists Find Cure for Ebola: Horse Antibodies. *Mumbai Mirror,* Feb. 7, 2017. Accessed at mumbaimirror.indiatimes.com/others/health-lifestyle/scientists-find-cure-for-ebola-horse-antibodies/articleshow/57020727.cms.

Pyankov OG, Setoh, YX, Bodnev SA, et al. Successful Post-Exposure Prophylaxis of Ebola Infected Non-Human Primates Using Ebola Glycoprotein-Specific Equine IgG. *Scientific Reports* 7, Article number: 41537 (2017). Accessed at www.nature.com/articles/srep41537.

Research

Study Identifies Why TB Vaccines Are Ineffective

While the tuberculosis (TB) vaccine, Bacillus Calmette-Guérin (BCG), has been around for nearly a century, it reduces the chance of infection by only 20 percent, whereas a truly effective vaccine such as the one for measles reduces infection by 95 percent or more. Recently, however, researchers at the Washington University School of Medicine in St. Louis have discovered that the reason the BCG vaccine and investigational vaccine candidates are not more effective is because the immune response is too slow; it's not because the vaccines elicit an immune response that is too weak to control the infection. In people who are vaccinated against TB and later infected with the bacteria, activation of immune cells is delayed, allowing the bacteria to multiply. "It's not a question of the magnitude of the immune response, it's the timing," said Shabaana Abdul Khader, PhD, an associate professor of molecular microbiology at the university. "Many people in the field of TB vaccine development have been working on increasing the strength of the immune response, and we could go on doing that, but if the timing is the same as for every other vaccine, it's not going to change the outcome."

Previous researchers found that vaccination with either BCG or investigational vaccine candidates doesn't speed up the immune response against TB. Even in vaccinated mice, an immune response to the infection doesn't start until two weeks after infection, giving the bacteria time to multiply to high levels. In an effort to determine whether speeding up the immune response would make a vaccine more effective, Dr. Khader and colleagues vaccinated mice with BCG, boosted a month later and a month after that, and challenged the mice with Mycobacterium tuberculosis, the bacteria that causes TB, while also giving the mice immune cells specially prepared to activate T cells. With the extra immune cells, the T cells started to fight infection seven to eight days after infection, rather than 12 to 14 days, causing the bacteria to drop by a factor of 10 or 100 and even to nearly undetectable levels.

Unfortunately, the technique can't be replicated in real life since there is no way of knowing when people will be exposed to the bacteria. "In a way, this is really disappointing," Dr. Khader said. "We start thinking that maybe none of the vaccines we have for TB will work. But then we come back to the table and say, 'Let's put our disappointment aside and figure out what we can really do from here.' We might have to design an entirely different kind of vaccine if we want to elicit an immune response that eradicates infection. Or, maybe eradicating infection isn't a realistic goal, but we can still make a vaccine that prevents disease or delays TB reactivation. We're looking at TB from a different point of view now, and that's exciting." ❖

Bhandari T. Study Helps Explain Why Tuberculosis Vaccines Are Ineffective. Washington University School of Medicine in St. Louis, Dec. 22, 2016. Accessed at medicine.wustl.edu/news/study-helps-explain-tuberculosis-vaccines-ineffective.

Research

Alzheimer's Could Be Detected Seven Years Prior to Symptoms

A new study shows that brains of people genetically inclined toward Alzheimer's are likely to show abnormal immune reactions as early as seven years before the expected onset of the disease. The researchers measured the levels of TREM2, a protein found in the cerebrospinal fluid, in 127 individuals with an average age of 40 who had a genetic predisposition to Alzheimer's and who showed no symptoms of dementia or had only minor cognitive impairments. They found that a rise in TREM2 levels is associated with an increase in immune activity of the brain, which can be traced to the progression of Alzheimer's. By monitoring these levels years before the expected occurrence of Alzheimer's symptoms, the timing for the onset of the disease can be precisely predicted. "TREM2 levels could therefore be a biomarker used to track immunity activity while Alzheimer's is progressing, irrespective of whether the disease is genetic or not," explained Michael Ewers, professor at Ludwig Maximilian University in Munich, Germany. "TREM2 may also serve as a therapeutic marker to monitor drug response." ❖

New Study May Help Detect Alzheimer's 7 Years Before Symptoms Show Up. *The Economic Times,* Dec. 17, 2016. Accessed at economictimes.indiatimes.com/magazines/panache/new-study-may-help-detect-alzheimers-7-years-before-symptoms-show-up/articleshow/56031826.cms.

Policy

AMA Joins with Other Organizations to Reform Prior-Authorization Requirements

The American Medical Association (AMA) and a coalition of 16 other organizations representing physicians, medical groups, hospitals, pharmacists and patients have devised a set of 21 principles to guide reform of utilization-management (UM) programs, including prior-authorization and step-therapy requirements. The 21 principles are divided into five broad categories: 1) clinical validity, which includes UM criteria being based on up-to-date clinical criteria rather than cost alone, as well as flexibility to meet patient-specific needs; 2) continuity of care, designed to ensure that patients' care isn't disrupted by prior-authorization requirements; 3) transparency and fairness, addressing the need for detailed explanations for denials and full public disclosure of all coverage restrictions in a searchable, electronic format; 4) timely access and administrative efficiency, which establishes maximum-response time for UM decisions and seeks health plans' acceptance of electronic prior authorizations; and 5) alternatives and exemptions, which calls for health plans to offer at least one alternative to prior authorization.

In 2016, the AMA House of Delegates adopted in-depth policy on standardization and simplification of prior authorization. Several states have already passed legislation to protect patients from overly burdensome UM requirements. "Strict or bureaucratic oversight programs for drug or medical treatments have delayed access to necessary care, wasted limited health-care resources and antagonized patients and physicians alike," said AMA President Andrew W. Gurman, MD. "The AMA joins with other coalition organizations in urging health insurers and others to apply the reform principles and streamline requirements, lengthy assessments and inconsistent rules in current prior-authorization programs." ❖

O'Reilly KB. 21 Principles to Reform Prior-Authorization Requirements. *AMA News,* Jan. 25, 2017. Accessed at wire.ama-assn.org/ama-news/21-principles-reform-prior-authorization-requirements.

Research

Sunlight Produces Faster T Cells to Boost Immunity

Researchers have found that in addition to providing the body with vitamin D, sunlight's rays also speed up helper and killer T cells in the skin, enhancing their ability to travel to infection sites and orchestrate an immune response. The new findings at Georgetown University show that the sun-enhanced immune response is independent of the production of vitamin D. "We found a completely separate role of sunlight on immunity," said Gerard Ahern, PhD, an associate professor in Georgetown University's Department of Pharmacology and Physiology. "Some of the roles attributed to vitamin D on immunity may be due to this new mechanism." And, importantly, while vitamin D production requires UV light, which can promote skin cancer, enhanced T-cell mobility only requires blue light that can be provided by the sun or special lamps, which is safer.

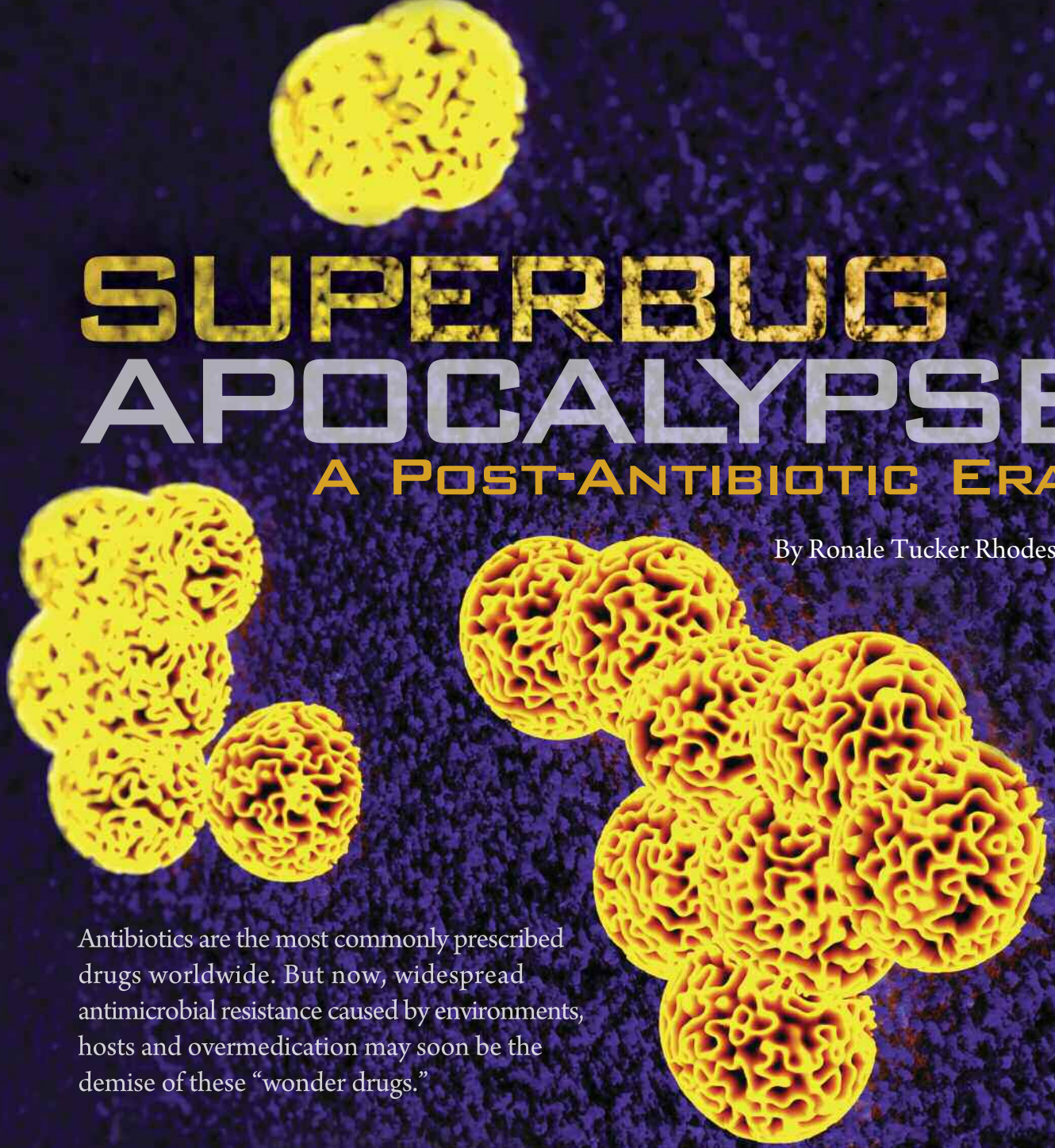
According to Dr. Ahern, sunlight drives the motility response by synthesizing hydrogen peroxide, which activates a signaling pathway that increases T-cell movement. Hydrogen peroxide is a compound that white blood cells release when they sense an infection in order to kill bacteria and activate T cells and other immune cells to mount an immune response. While the impact of these findings is not yet known, the researchers suggest that it's possible that offering patients blue light therapy can boost their immunity. ❖

Phan TX, Jaruga B, Pingle SC, et al. Instrinsic Photosensitivity Enhances Motility of T Lymphocytes. *Scientific Reports,* Dec. 20, 2016. Accessed at www.nature.com/articles/srep39479.

SUPERBUG APOCALYPSE

A Post-Antibiotic Era?

By Ronale Tucker Rhodes, MS



Antibiotics are the most commonly prescribed drugs worldwide. But now, widespread antimicrobial resistance caused by environments, hosts and overmedication may soon be the demise of these "wonder drugs."

IT WAS CONSIDERED nothing short of miraculous when, in 1940, Oxford University scientists Howard Florey and Ernst Chain figured out how to isolate the antibacterial element penicillin, discovered in 1928 by Alexander Fleming in a discarded petri dish contaminated by mold. More than a decade after the "wonder drug's" discovery, penicillin was at last able to be used to cure infections caused by deadly bacteria. Since its first use in 1942 during World War II, it is estimated penicillin has saved at least 200 million lives.[1]

But now, scientists are questioning just how miraculous penicillin, as well as the other classes of antibiotics, really are. Since bacteria's discovery, strains have continued to evolve, making them more and more resistant to conventional antibiotics. According to the U.S. Centers for Disease Control and Prevention (CDC), each year, these drug-resistant bacteria infect more than two million people in the U.S. and kill at least 23,000.[2] Indeed, only one antibiotic, colistin, which is used only when all other antibiotics fail because of its harsh side effects, has been known to work against particularly dangerous types of superbugs, including a family of bacteria known as carbapenem-resistant Enterobacteriaceae (CRE), which health officials have dubbed "nightmare bacteria."[3]

Until now. In May 2016, the antibiotic-resistant strain was found in the urine of a 49-year-old Pennsylvania woman who Defense Department researchers determined carried a strain of Escherichia coli (E. coli) resistant to colistin. Most recently, in September, a 70-year-old woman from Nevada died of an infection found to be immune to all 26 antibiotics available in the U.S.[4]

Does this spell the demise of antibiotics? Or, will better ones or even something different replace them?

History of Antibiotics

The first patient to be treated with penicillin was a policeman who contracted a severe staphylococcal infection. It was 1941, and Florey and Chain were conducting the drug's first clinical trial. After showing remarkable improvement, the policeman died, not because the penicillin didn't work, but because supplies of it ran out after just five days. Because of its initial potential in the trial, production of penicillin expanded during World War II, helping to save thousands of soldiers' lives. An advertisement in *Life* magazine in 1944, when the drug became available to the public, read, "Thanks to penicillin … he will come home!"[5]

Penicillin, it was found, was even more effective than previously discovered antimicrobial agents that reduced infection rates of diseases that once caused great pandemics such as the Black Death that killed 30 percent to 60 percent of Europeans in the 14th century and the 1918 Great Influenza pandemic that killed more than 50 million people around the world. Immediately, widespread use of penicillin ensued with the promise of preventing deaths caused by staphylococcus and streptococcus, and others that caused diphtheria, pneumonia and meningitis.[6]

But with its widespread use, resistance to penicillin quickly developed. In response, scientists introduced a new family of penicillin-type drugs, including one called methicillin in 1960. Discouragingly, a strain of staphylococcus resistant to methicillin, known as methicillin-resistant Staphylococcus aureus, or MRSA, developed within one year.[6]

The race to produce antibiotics, thus, began. Today, there are well over 100 antibiotics, the majority of which come from seven types of drugs, with 26 available in the U.S.[7] But their explosive use in both humans and livestock has brought with it great consequence. According to award-winning journalist Maryn McKenna in her book *Superbug: The Fatal Menace of MRSA*: "It became evident that broad use of antibiotics not only caused drug-resistant infections; it also made people who had no symptoms of infection into silent carriers of drug-resistant strains."[6]

Antimicrobial Resistance (AMR): Survival of the Fittest

When Fleming, Florey and Chain received the Nobel Prize in Medicine or Physiology, Fleming warned of antimicrobial resistance: "It is not difficult to make microbes resistant to penicillin in the laboratory by exposing them to concentrations not sufficient to kill them, and the same thing has occasionally happened in the body."[4] Indeed, Fleming's warning proved true. Antibiotics are effective only when they are used as needed and as directed. Too much antibiotic use results in more resistant mutants of the bacteria. When the full course of antibiotics is cut short, the resistant strains multiply and spread.

How does bacterial resistance occur? It's Darwin's idea of survival of the fittest.

Resistance to antibiotics can occur in one of three ways: epigenetic adaptation, genetic adaptation and genetic acquisition, the latter of which is the major culprit of AMR. Epigenetic adaptation occurs when bacteria consistently encounter subinhibitory levels of an antibiotic, causing temporary resistance, but no permanent genetic changes that can be inherited by subsequent generations of bacteria. Genetic mutations, on the other hand, are permanent changes in genetic code that can occur due to a single mutation or multiple mutations. Resistance to some antibiotics can occur because of a single mutation, while other antibiotics require bacteria to develop multiple mutations.

Today, there are well over 100 antibiotics, the majority of which come from seven types of drugs, with 26 available in the U.S.

Genetic acquisition occurs when bacteria acquire large chunks of foreign DNA that contain many genes. They acquire these through one or all of five techniques: 1) plasmids, mobile pieces of DNA that bacteria can easily trade among themselves or acquire from the environment; 2) transposons, sections of DNA that can jump from one place in the genetic code to another, or even to the genetic code of another organism; 3) viruses, which can infect bacteria by copying and pasting genetic code into the genomes of the bacteria they infect; 4) conjugation, which occurs when two bacteria directly adjacent to each other share DNA; and 5) naked DNA, which bacteria find in the environment and internalize.[8]

Table 1. Centers for Disease Control and Prevention's Antibiotic-Resistant Threats in the United States, 2013

	Pathogen	Statistics
Urgent Threat Level Pathogens	C. difficile	250,000 infections per year requiring hospitalization or affecting hospitalized patients; 14,000 deaths per year
	CRE	Out of approximately 140,000 healthcare-associated infections per year, more than 9,000 are caused by CRE
	N. gonorrhoeae	Of the 820,000 cases per year, 30 percent now demonstrate resistance to at least one antibiotic
Serious Threat Level Pathogens	Multidrug-resistant Acinetobacter	12,000 healthcare-associated infections in the U.S. of which 7,000 are multidrug-resistant; approximately 500 deaths per year
	Drug-resistant Campylobacter	1.3 million infections, 13,000 hospitalizations and 120 deaths per year; 310,000 drug-resistant infections each year
	Fluconazole-resistant Candida	Of 46,000 yeast infections per year, 3,400 (30 percent) with bloodstream infections with drug-resistant Candida die during hospitalization
	Extended-spectrum β-lactamase producing Enterobacteriaceae	Of 140,000 infections per year, 26,000 are drug-resistant causing 1,700 deaths
	Vancomycin-resistant Enterococcus	Of 66,000 infections per year, 20,000 are drug-resistant causing 1,300 deaths
	Multidrug-resistant Pseudomonas aeruginosa	Of 51,000 infections per year, 6,700 are multidrug-resistant causing 440 deaths
	Drug-resistant non-typhoidal Salmonella	1.2 million infections per year, of which 100,000 are drug-resistant resulting in 23,000 hospitalizations and 450 deaths per year
	Drug-resistant Salmonella typhi	Of 21.7 million infections worldwide, 5,700 illnesses in the U.S. with 3,800 (67 percent) of infections drug-resistant resulting in 620 hospitalizations each year
	Drug-resistant Shigella	500,000 illnesses, 5,500 hospitalizations and 40 deaths each year in the U.S.
	MRSA	Over 80,000 invasive infections and 11,285 related deaths per year (in 2011)
	Drug-resistant Streptococcus pneumoniae	Of 4 million disease incidents and 22,000 deaths, 1.2 million are drug-resistant resulting in 19,000 excess hospitalizations and 7,900 deaths
	Drug-resistant tuberculosis	Of 10,528 cases in the U.S. in 2011, 1,042 (9.9 percent) were resistant to antibiotics resulting in 50 deaths

Source: www.whitehouse.gov/sites/default/files/docs/national_action_plan_for_combating_antibotic-resistant_bacteria.pdf

The unique ability of genetic material to transfer DNA through plasmids is a great threat. While most genetic material is transmitted only from parent to offspring, plasmids can be transferred horizontally, from neighbor to neighbor. In fact, horizontal gene transfer in clinical settings is by far the most common mechanism through which bacteria become drug-resistant. "Resistance works differently in the bacterium," explains Stuart Levy, director of the Center for Adaptation Genetics and Drug Resistance at Tufts University School of Medicine. "Their resistance can be transferred. It's a little frightening to realize that you're running after something that can transfer its football to somebody else right away."[5]

The Dangerous Superbugs

In the past, some of the most dangerous superbugs have been confined to healthcare settings where people who are sick or in a weakened state are more susceptible to picking up infections. But superbug infections aren't limited to hospitals.

In March 2015, the White House released a comprehensive plan outlining steps to combat drug-resistant bacteria. The plan identified 15 of the most dangerous superbugs, three of which pose an urgent threat, and the remaining 12 posing a serious threat (Table 1). On the urgent list are Clostridium difficile (C. diff), CRE and Neisseria gonorrhoeae (N. gonorrhoeae).[9]

C. diff is a bacteria that lives in the intestines, causing

life-threatening diarrhea, and is mostly contracted by people receiving medical care. Previously, doctors used antibiotics called fluoroquinolones to treat C. diff, but they don't always work. From 2000 to 2007, deaths spiked 400 percent when a new drug-resistant strain of C. diff appeared.[10]

CRE is a family of bacteria normally found in the gut (e.g., E. coli), and mostly occurs in people who are in the hospital or in a medical care facility such as a nursing home. CRE is resistant to all antibiotics, resulting in death in up to 50 percent of patients who contract it,[10] including the 70-year-old Nevada woman who died in September. This woman was infected with a bacteria called Klebsiella pneumoniae, which belongs to the CRE class of drug-resistant bugs. She had been hospitalized in India just two months previously, one of several hospitalizations due to complications from a thighbone fracture. Upon returning to the U.S., she was admitted to a Reno hospital, and after doctors tried switching antibiotics accordingly, she died of septic shock.[11]

CRE is particularly troubling because a recent study found that the superbug may be spreading more widely than previously thought. A Harvard-MIT research team examined genetic sequences from approximately 250 samples of patients who had CRE in four hospitals in Boston and Irvine, Calif., over a 16-month period. They found little evidence of direct transmission between patients who became sick, leaving them to believe transmission may be occurring without causing symptoms. This means people colonized with these germs may spread them without ever becoming sick. According to Alex Kallen, MD, a medical officer in the CDC's Division of Healthcare Quality Promotion, "the most common source of transmission with CRE is asymptomatic."[12]

N. gonorrhoeae is a sexually transmitted disease that commonly spreads during oral, anal or vaginal contact. Pregnant women can pass the infection to their babies during childbirth. And, people can spread the bacteria without knowing it. While it used to be treated with antibiotics, the bacteria are becoming more resistant to current drugs.[10]

Antibacterial threats on the serious list include multidrug-resistant Acinetobacter, drug-resistant Campylobacter, fluconazole-resistant Candida, extended spectrum β-lactamase producing Enterobacteriaceae, vancomycin-resistant Enterococcus, multidrug-resistant Pseudomonas aeruginosa, drug-resistant non-typhoidal Salmonella, drug-resistant Salmonella typhi, drug-resistant Shigella, MRSA, drug-resistant Streptococcus pneumoniae and drug-resistant tuberculosis.[9]

Who's to Blame?

Regrettably, we've overused these "miracle drugs" to the point that they've lost their potency. A CDC study conducted in 2013 found that U.S. doctors are prescribing enough antibiotics to give them to four out of five Americans every year. Specifically, it found that doctors and other healthcare providers prescribed 258 million courses of antibiotics in 2010 for a population just shy of 309 million, which translates to 833 antibiotic prescriptions for every 1,000 people, on average. The study also found that the most frequently prescribed antibiotic was azithromycin, which is commonly used for bronchitis symptoms. The problem with this is bronchitis is usually caused by a virus, and antibiotics like azithromycin don't work against viruses.[13]

In 2015, the most in-depth study yet to examine the use and misuse of antibiotics found nearly one-third of antibiotics prescribed in doctors' offices, emergency rooms and hospital-based clinics in the U.S. are not needed. This means approximately 47 million unnecessary prescriptions are given for conditions that don't respond to antibiotics. The study analyzed data collected from two major CDC surveys from 2010 to 2011. It found that 13 percent of all outpatient visits in the U.S. (approximately 154 million annually) result in an antibiotic prescription; more than four in 10 (44 percent) are written to treat patients with acute respiratory conditions; and half of these prescriptions are unnecessary because they are for viral illnesses. What's more, an accompanying editorial published in the same journal issue as the study noted the numbers are likely an undercount because they don't include the times antibiotics are given when patients talk to doctors over the telephone or when they seek medical care at urgent care clinics, retail pharmacies and dental offices.[14]

Resistance to antibiotics can occur in one of three ways: epigenetic adaptation, genetic adaptation and genetic acquisition, the latter of which is the major culprit of AMR.

But, it's not just overuse. Antibiotic resistance is facilitated by a combination of two other factors: environments and hosts.

Hospitals are the perfect environment for bacteria to develop, acquire and maintain high-level antibiotic resistance because there are a lot of infected people and contaminated surfaces, a high number of patients who are potential hosts and frequent and sustained use of antibiotics. Not only are bacteria spread among patients, but bacterial infections are associated with procedures

like surgery and devices used in medical procedures. Despite the sterility of hospitals, hospital-acquired infections are one of the leading causes of morbidity among patients in the U.S.[8]

Antibiotic resistance is in large part contributed to by industrial animal farming, which consumes more antibiotics than are used in human medicine. Indeed, 80 percent of antibiotics in the U.S. are used on livestock, with North Carolina farm animals receiving more than all Americans combined.[15] In these operations, antibiotics are used prophylactically to prevent disease outbreaks. But, the facilities mimic unsanitary and overcrowded hospitals often found in developing countries, which drives the evolution of antibiotic resistance in bacteria. What's more, animal waste contains significant levels of unmetabolized antibiotics, which encourages the transfer of antibiotic resistance genes among different species of bacteria. And, it doesn't stop there. These facilities cause the spread of antibiotic resistant bacteria to neighboring wildlife and in rivers, lakes and other waterways.[8]

Regrettably, we've overused these "miracle drugs" to the point that they've lost their potency.

Looking at Solutions

The frightening rise in antibiotic resistance has been growing for decades. So, why isn't more being done to counteract the problem before there are no other alternatives? Pharmaceutical companies say they are at least partially to blame for AMR by neglecting to develop new and more sophisticated antibiotics that could keep up with bacterial resistance. The reason: There's not much money to be made with antibiotics. There's a lot more money to be made in cancer, diabetes and hypertension drugs, for example, that have small margins but generate profits over time because patients use them for life.[16] Global sales of antibiotics are roughly $4.7 billion a year, about as much as a single top-selling cancer drug.[17] Since the correct way to use an antibiotic is only briefly, from an economic standpoint, the developer is not getting the return on its investment. It costs between $600 million and $1 billion to bring a drug to market, so it makes sense for drug developers to turn to other drugs to bring revenue back to their shareholders.[18]

Aaron Kesselheim, director of the Program on Regulation, Therapeutics and Law at Brigham and Women's Hospital, suggests changing the current model for reimbursement. Currently, drugs are reimbursed on a per-prescription basis, which encourages the overprescription of antibiotics. The goal of a new model, he says, should be to get a return on investment, as well as ensuring the conservation of antibiotics that are needed for future generations — not overusing them during the initial period of market exclusivity, when it makes the most financial sense to companies that develop the drugs. That would mean "linking the patent life to actual prudent use of the antibiotics and appropriate use of the antibiotics," says Kesselheim. "Right now what happens is when a new antibiotic hits the market, the pharmaceutical companies are interested in promoting the product as much as possible, and getting as much prescription of it as possible for that limited period of time that they have exclusive rights over it. And that's not consistent with public health goals."[18]

In years past, the U.S. Food and Drug Administration (FDA) and CDC launched antibiotic resistance campaigns aimed at healthcare professionals and the public to discourage overprescribing and overuse. And, a nationwide ad campaign developed by FDA's Center for Drug Evaluation and Research emphasizes to healthcare professionals the prudent use of antibiotics and offers them an educational brochure to distribute to patients.[19] But, clearly, as evidenced by CDC studies, overprescribing and overuse persists.

Heightened consumer awareness of the superbug threat, however, appears to be altering consumer behavior somewhat. In 2014 and 2015, sales of antibiotic-free meats jumped 20 percent.[15] And, government is stepping in to curb the use of antibiotics in livestock, too. In December 2013, FDA put in place a major new policy to phase out the indiscriminate use of antibiotics in cows, pigs and chickens raised for meat. Phased in over three years, the policy made it illegal for farmers and ranchers to use antibiotics to make animals grow bigger. Additionally, FDA required that licensed veterinarians supervise the use of antibiotics, requiring farmers and ranchers to obtain prescriptions to use the drugs for their animals.[20] Most recently, regulations are being enacted to shift to antibiotic-free meats. In October 2015, California passed a strict law limiting the use of antibiotics in agriculture.[15]

A report commissioned by United Kingdom Prime Minister David Cameron and the Wellcome Trust in May 2016, which outlines how to tackle the spread of AMR and how to pay for it, is attracting the attention of world leaders. The report calls for a "two-tiered approach: Lower the use of available antimicrobials, and increase the supply by stimulating the development of new ones." According to the report, reducing use could be achieved by improving hygiene, faster and better diagnostics and new

vaccines. In addition, a worldwide campaign to educate consumers about the dangers of resistance could keep patients from demanding the drugs and doctors from prescribing them. The report also calls for not using antibiotics in agriculture at all. And, it offers concrete suggestions for how to boost the development of drugs effective against resistant infections: "A Global Innovation Fund endowed with up to $2 billion is needed to fund early-stage research; a bonus of $1 billion for a company that develops a new drug that is effective against resistant infections could also help. The money could be raised as a levy from these companies through a 'pay-or-play' strategy, in which companies can either pay up or invest it in research and development to fight AMR."[17]

Still, 80 years after the discovery of penicillin, it is still not really known how to develop a good antibiotic. And, the responsibility is falling increasingly to academic researchers. Harvard's Program on Antibiotic Resistance organized in 2009 has seven independent labs that study antibiotic-resistant S. aureus. Its goal is not necessarily to develop new drugs, but to develop innovative approaches to finding them. "We explore new drug targets that are higher risk than those a company would work on," explains Suzanne Walker, professor of microbiology and immunology. "It's hard to beat a company at developing a compound, and there's no reason to do that. But I think it's up to academics to lay the groundwork."[5]

But not all academic researchers are going down that path. At Stanford University's Chemistry, Engineering and Medicine for Human Health Institute, a group of undergraduate students is working on "novel antibiotics from scratch that might one day stand up to superbugs." They are focusing on two bacteria with high mortality rates that are resistant to nearly all antibiotics: Pseudomonas aeruginosa and Acinetobacter baumannii.[16]

There also are some drug developers that are making headway. France-based Eligo Bioscience is researching a potential CRISPR-based solution to the AMR problem; Iterum Therapeutics is launching an antibiotic licensed by another manufacturer called Dalvance that is used to treat adults with skin infections; and in September 2016, AstraZeneca, GlaxoSmithKline, Johnson & Johnson, Merck & Co., Novartis AG, Pfizer and Sanofi SA were among the signatory companies to an "Industry Roadmap for Progress on Combating Antimicrobial Resistance."[16]

A Five-Year Plan

The threat to the usefulness of antibiotics can't be overstated. By 2050, it is estimated that AMR-related deaths could total 10 million annually (cancer kills about 8.2 million people worldwide annually).[16] And, the global economic tally from antibiotic-resistant bacteria could be as high as $100 trillion.[15] Politicians and the medical community agree that to counteract the threat of superbugs, abuse in both medicine and agriculture must be restrained, and new drug development must be stimulated.

Last year, the Obama administration announced a five-year plan to combat superbugs, asking Congress to double funding to $1.2 billion. In the "National Action Plan for Combating Antibiotic-Resistant Bacteria," the administration set a target of reducing inappropriate antibiotic use in outpatient settings by half by 2020, resulting in approximately 23 million fewer antibiotics prescribed annually. According to the report, the plan's goals are to "slow the emergence of resistant bacteria and prevent the spread of resistant infections; strengthen national One-Health surveillance efforts to combat resistance; advance development and use of rapid and innovative diagnostic tests for identification and characterization of resistant bacteria; accelerate basic and applied research and development for new antibiotics, other therapeutics and vaccines; and improve international collaboration and capacities for antibiotic-resistance prevention, surveillance, control and antibiotic research and development."[9] ❖

RONALE TUCKER RHODES, MS, is the editor of *BioSupply Trends Quarterly*.

References

1. New World Encyclopedia. Alexander Fleming. Accessed at www.newworldencyclopedia.org/entry/Alexander_Fleming.
2. Centers for Disease Control and Prevention. Antibiotic/Antimicrobial Resistance. Accessed at www.cdc.gov/drugresistance/index.html.
3. Gano R. E-Coli Superbug In US — Totally Resistant To Antibiotics — The End of The Road. *Prophezine*, May 26, 2016. Accessed at raygano.com/breaking-news-e-coli-superbug-in-us-totally-resistant-to-antibiotics-the-end-of-the-road.
4. Kirkey S. Superbug Immune to Virtually Every Known Antibiotic Kills U.S. Woman. *National Post*, Jan. 13, 2017. Accessed at news.nationalpost.com/news/0114-na-superbug.
5. Xue K. Superbug: An Epidemic Begins. *Harvard Magazine*, May-June 2014. Accessed at harvardmagazine.com/2014/05/superbug.
6. Meakin J. Superbugs! The End of the Antibiotic Era. *Tomorrow's World*, January-February 2016. Accessed at www.tomorrowsworld.org/magazines/2016/january-february/superbugs-the-end-of-the-antibiotic-era.
7. eMedicineHealth. Types of Antibiotics. Accessed at www.emedicinehealth.com/antibiotics/page2_em.htm.
8. Science of Acne. How Do Bacteria Become Resistant to Antibiotics? Accessed at thescienceofacne.com/how-do-bacteria-become-resistant-to-antibiotics.
9. The White House. National Action Plan for Combating Antibiotic-Resistant Bacteria, March 2015. Accessed at www.whitehouse.gov/sites/default/files/docs/national_action_plan_for_combating_antibotic-resistant_bacteria.pdf.
10. Miller K. Superbugs: What They Are and How You Get Them. WebMD, April 17, 2015. Accessed at www.webmd.com/a-to-z-guides/news/20150417/superbugs-what-they-are#1.
11. Mohny G. What You Need to Know About the Deadly 'Superbug' Infection Resistant to All FDA-Approved Antibiotics. Yahoo News, Jan. 16, 2017. Accessed at gma.yahoo.com/know-deadly-superbug-infection-resistant-fda-approved-antibiotics-233300910--abc-news-wellness.html.
12. Scutti S. Drug-Resistant Superbug May Be More Widespread Than Previously Known. CNN, Jan. 17, 2017. Accessed at www.cnn.com/2017/01/16/health/cre-superbug-disease-study/index.html.
13. Stobbe M. Study Shows Overuse of Antibiotics. *USA Today*, April 10, 2013. Accessed at www.usatoday.com/story/news/nation/2013/04/10/medication-antibiotic-overuse/2071899.
14. Sun LH. 1 in 3 Antibiotics Prescribed in U.S. Are Unnecessary, Major Study Finds. *The Washington Post*, May 3, 2016. Accessed at www.washingtonpost.com/news/to-your-health/wp/2016/05/03/1-in-3-antibiotics-prescribed-in-u-s-are-unnecessary-major-study-finds/?utm_term=.ebcc8225a488.
15. Mansharamani V. Superbugs: The $100 Trillion Risk. *Fortune*, June 1, 2016. Accessed at fortune.com/2016/06/01/antibiotic-superbugs-bacteria-e-coli.
16. Dittman D. Superbugs: How Antibiotic-Resistant Bugs Are Killing Mankind. *Wall Street Daily*, Oct. 19, 2016. Accessed at www.wallstreetdaily.com/2016/10/19/superbugs-antibiotic-resistant-bacteria.
17. Kupferschmidt K. Long-Awaited Report Outlines How to Fight Antimicrobial Resistance — And How to Pay for It. *Science*, May 18, 2016. Accessed at www.sciencemag.org/news/2016/05/long-awaited-report-outlines-how-fight-antimicrobial-resistance-and-how-pay-it.
18. Battling Drug-Resistant Superbugs: Can We Win? The Forum at Harvard School of Public Health, Feb. 5, 2014. Accessed at theforum.sph.harvard.edu/events/battling-drug-resistant-superbugs/.
19. U.S. Food and Drug Administration. Battle of the Bugs: Fighting Antibiotic Resistance. Accessed at www.fda.gov/Drugs/ResourcesForYou/Consumers/ucm143568.htm.
20. Tavernise S. F.D.A. Restricts Antibiotics Use for Livestock. *The New York Times*, Dec. 11, 2013. Accessed at www.nytimes.com/2013/12/12/health/fda-to-phase-out-use-of-some-antibiotics-in-animals-raised-for-meat.html.

Quality Improvement Programs: Hurdles to Optimizing Care

Many QI programs are subject to missteps, but approaches that implement QI essentials can bring healthcare closer to realizing its potential.

By Dana Henry

THE HEALTH RESOURCES and Services Administration defines quality improvement (QI) as the systematic and continuous actions that lead to measurable improvement in healthcare services and the health status of targeted patient groups.[1] At first glance, QI seems like a straightforward concept: Use practices that improve the quality of care provided, and minimize or eliminate those that have the opposite effect. In other words, provide healthcare in keeping with The Institute of Medicine's definition: "The degree to which health services for individuals and populations increase the likelihood of desired health outcomes and are consistent with current professional knowledge."[2]

QI can confer numerous benefits:[3]

• Helping organizations prepare for the transition to value-based payment models

• Allowing organizations to participate in the public reporting of physician-quality data

• Giving organizations the opportunity to participate in federal QI incentive programs

• Equipping organizations with the skills necessary to apply for and complete national recognition programs

Several elements are fundamental to QI, including establishing a culture of quality, determining and prioritizing potential areas for improvement, collecting and analyzing data, communicating results and committing to ongoing evaluation.[3]

Unlike quality assurance programs, which are reactive and retrospective, QI programs are both retrospective and prospective. Their purpose is to help an organization determine its status and evaluate ways to improve.[4]

QI programs are used widely in healthcare. Numerous agencies and organizations, such as the Agency for Healthcare Research and Quality, The Joint Commission and the National Quality Forum, are dedicated to providing better care using numerous process improvement models such as DMAIC, FADE, Lean, PDSA and Six Sigma (see Five QI Models).[5] Yet, with resources in place, and so many QI programs being implemented, it is still difficult for healthcare to realize its full potential.[6]

The Case for Improving QI

Paul Batalden, active emeritus professor at Dartmouth College's Geisel School of Medicine, and Frank Davidoff, adjunct professor of The Dartmouth Institute and executive editor at the Institute for Health Improvement, define QI as "the combined and unceasing efforts of everyone — healthcare professionals, patients and their families, researchers, payers, planners and educators — to make the changes that will lead to better patient outcomes (health), better system performance (care) and better professional development (learning)." They add that change-making must become an intrinsic part of everyone's job "every day, in all parts of the system."[6]

The two warn that not all changes are improvement. To avoid pitfalls of changes that aren't beneficial, they argue that change should be driven by generalizable scientific evidence that is systematically incorporated. In addition, settings in which care is delivered need to be characterized. And, to know that improvement is occurring, accurate and powerful measurements of what is happening are needed.[6] These emphases lead to better knowledge, but it still takes people on all levels to effect change using that knowledge. "It is one thing to expect a specially commissioned 'QI team' to be actively engaged in designing and testing the many changes needed for better patient and population outcomes, better system performance and better professional development; it is quite another to expect everyone involved in healthcare to do so, and do so all the time," they write.

Five QI Models

DMAIC (Lean Six Sigma). DMAIC combines Lean and Six Sigma to create a framework that provides a means for assessing the value of potential QI efforts and an approach to executing QI projects. The five phases of Lean Six Sigma are define, measure, analyze, improve and control.[3]

FADE. The FADE model includes several steps: focus, analyze, develop, execute and evaluate.[14]

Lean. Developed by the Toyota Motor Company, Lean focuses on the customer and determines what the customer considers of value. In the healthcare context, customers include patients, regulatory bodies, payers and providers. Lean emphasizes empowering individual employees to improve quality and expects every individual to identify and address poor quality and waste. Its applications in healthcare include improving patient flow, eliminating central line infections and removing waste from the system.[15]

PDSA. The PDSA cycle involves developing a plan to test the change (plan), carrying out the test (do), observing and learning from the consequences (study), and determining what modifications should be made to the test (act). Walter Shewhart of Bell Telephone Research Laboratories in New York developed the concept.[16,17]

Six Sigma. The Six Sigma model, which began at Motorola, identifies sources of variation in a process and work to reduce that variation, thus reducing potential sources of error. Six Sigma refers to a level of variability that is error-free to six standard deviations of a normal distribution. That translates to a mere 3.4 errors per one million attempts. For reference, hospital injuries operate at the three- to four-sigma level, with about 10,000 errors per one million opportunities. Applications of Six Sigma include efforts to reduce medication errors, improve hand-hygiene compliance and reduce catheter-related bloodstream infections.[15]

QI Missteps

Believing technology has all the answers. "Somewhere near 80 percent of your system's data exists outside your EMR [electronic medical record] or ERP [enterprise resource planning] system.

That means operational and clinical decisions are being made with only a fraction of the available data," according to Conduent, a business process services company. In short, keeping accurate digital records is critical, but it's not the whole story in terms of healthcare delivery. Unstructured data, such as that which resides in free-text or semi-structured documentation, is as important as that found in the electronic record.[7,8]

Despite the hurdles of QI, achieving better care is possible.

Unstructured data capture often arises to avoid hindering the healthcare-delivery process, according to Dan LeSueur, senior vice president of technical operations at Health Catalyst, a data warehousing, analytics and outcomes-improvement company for the healthcare industry. "As a result," he writes, "much of the data captured in this manner is difficult to aggregate and analyze in any consistent manner."[9]

Adopting a "work-harder" approach. The work-harder approach to QI assumes employees must do more with the same time, resources and supports. "Many recent quality improvement initiatives have counted on the healthcare workforce, especially staff at the point of care, to implement the desired changes, effectively layering additional workload on an already busy environment, complex and generally inefficient system," write Batalden, Christopher Hayes, associate scientist at the Li Ka Shing Knowledge Institute in Toronto, and Donald Goldmann, professor at Harvard School of Public Health and senior physician at Boston Children's Hospital.[10]

Nurses may be required to do more work because important (but time-consuming) steps have been added to their routines. Tasks such as patient intake may take front office staff longer after improved procedures have been identified and adopted. In the work-harder model, employees have more to do and less time to do it. Their accuracy and reliability may decrease, or they may pay less attention to other tasks — or to patients.[10]

Hayes, Batalden and Goldmann say there is ample evidence that the work-harder approach leads to change fatigue, resistance, cynicism, burnout and turnover.

Forgetting the patient. Perhaps the most important item on the misstep list is leaving the patient out of the QI program. Meeting the needs and expectations of patients is a central aspect of QI. Patient safety, coordination of care within the larger healthcare system, and cultural competence are just a few of the patient-oriented services that QI can address.[1,7]

Other issues. Several other mistakes can undermine QI initiatives. Two that fall under the banner of "not all change is good change" are reinventing the wheel and throwing out what's working. Additional errors include underestimating change management, not being clear about the desired state, conflating strategy and execution, failing to align the business and clinical sides of the organization, waiting for government to design change, and using a bottom-up approach.[7]

QI Essentials

Having strong leadership. Ronda G. Hughes, senior health scientist administrator at the Agency for Healthcare Research and Quality, says the importance of having strong leadership commitment and support cannot be overstated. "Without the commitment and support of senior-level leadership, even the best intended projects are at great risk of not being successful," she says.[11]

Peter Lachman, deputy medical director for safety at Great Ormond Street Hospital in London, agrees. He says a new approach to leadership is needed for successful QI. "There needs to be a change in the mental model of leadership in which one talks about patients as partners," he explains. "One talks about listen [sic] to the front line and understand what it's like to be on the front line."

This requires a softening of the boundaries between different areas of healthcare, in particular those that typically work in isolation. "You have to break down the boundaries between different groups of professionals and between professionals themselves," Lachman says. And, to be a quality leader, he says, one needs to understand QI methodology, as well as how to measure and how to question. In addition, leaders must know how to involve all kinds of people in the QI program.[12]

Clearly defining the project. Good programs start with a good sense of the problem. The problem statement should be defined at the outset, the vision should be clear, and the project scope should be defined. Covering these bases will allow everyone involved to know what the goal is and what to expect. Objectives should be clear and measurable. Deliverables and responsible parties should be spelled out. Resources should be allocated to ensure the project's success.[13]

Including everyone in the process. Knowledge of what needs to improve is only half of QI. The other half is involving everyone from care providers to support staff in the process. "Drawing everyone actively into the process of testing change, all the time, presumes that everyone will develop a basic under-

standing of the standards of their work, as well as the skills they need to test changes in that work," Batalden and Davidoff write. "Making improvement happen also requires leadership that enables connections between the aims of changes and the design and testing of those changes; that pays serious attention to the policies and practices of reward and accountability; and unshakeable belief in the idea that everyone in healthcare really has two jobs when they come to work every day: to do their work and to improve it."[6]

Other essentials. Additional elements of successful QI include having a culture of safety and improvement, understanding the problem and its root causes, using a methodologically sound approach, standardizing care processes, keeping plans flexible and recognizing that change takes time.[11]

Better Care Is Possible

Despite the hurdles of QI, achieving better care is possible. The best approaches to QI avoid many of the pitfalls by understanding what areas need to be improved before committing to a QI program, including staff at all levels and committing to ongoing evaluation of change initiatives to ensure they are, in fact, beneficial. ❖

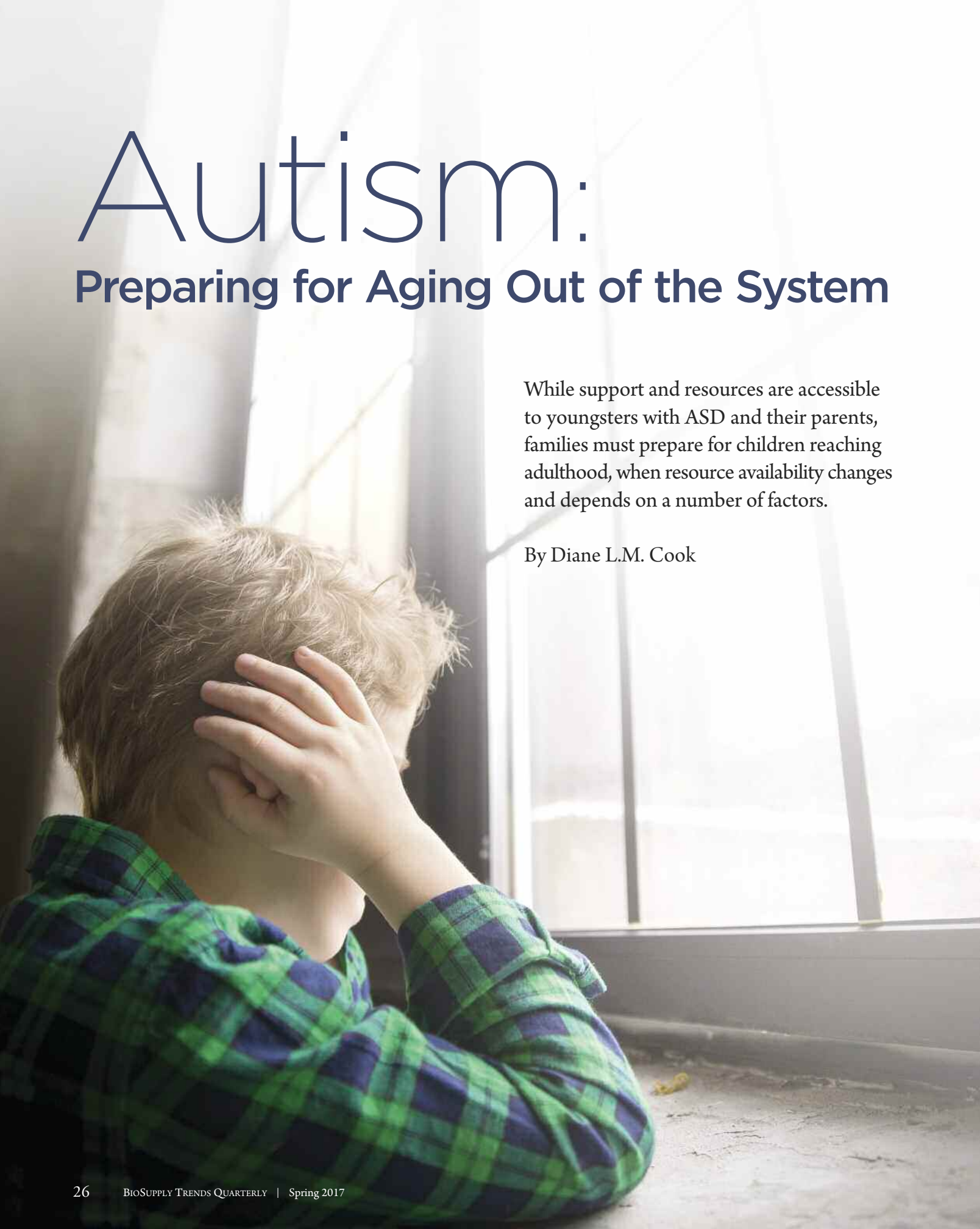
DANA HENRY is a writer and editor in the Midwest who specializes in science, medicine and health.

References

1. Health Resources and Services Administration. Quality Improvement. Accessed at www.hrsa.gov/quality/toolbox/508pdfs/qualityimprovement.pdf.
2. National Institutes of Health. HSRIC: Quality. Accessed at www.nlm.nih.gov/hsrinfo/quality.html.
3. American Academy of Family Physicians. Basics of Quality Improvement. Accessed at www.aafp.org/practice-management/improvement/basics.html.
4. Duke University School of Medicine. What Is Improvement? Contrasting QI and QA. Accessed at patientsafetyed.duhs.duke.edu/module_a/introduction/contrasting_qi_qa.html.
5. Duke University School of Medicine. What Is Quality Improvement? Accessed at patientsafetyed.duhs.duke.edu/module_a/introduction/introduction.html.
6. Batalden P and Davidoff F. What Is "Quality Improvement" and How Can It Transform Healthcare? *BMJ Quality and Safety*, 2007;16:2-3. Accessed at qualitysafety.bmj.com/content/16/1/2.full.
7. Conduent. 10 Common Mistakes in Healthcare Provider Process Improvement. Accessed at www.conduent.com/insights/healthcare-provider-solutions/process-improvement.
8. HIT Consultant. Why Unstructured Data Holds the Key to Intelligent Healthcare Systems. Accessed at hitconsultant.net/2015/03/31/tapping-unstructured-data-healthcares-biggest-hurdle-realized.
9. LeSueur D. 5 Reasons Healthcare Data Is Unique and Difficult to Measure. HealthCatalyst. Accessed at www.healthcatalyst.com/5-reasons-healthcare-data-is-difficult-to-measure.
10. Hayes C, Batalden P, and Goldmann D. A "Work Smarter, Not Harder" Approach to Improving Healthcare Quality. *BMJ Quality and Safety*, 24(2), 100–102. Accessed at qualitysafety.bmj.com/content/24/2/100.full.
11. Hughes R. Tools and Strategies for Quality Improvement and Patient Safety. In *Patient Safety and Quality: An Evidence-Based Handbook for Nurses* (1146–1168). Rockville, MD: Agency for Healthcare Research and Quality, U.S. Department of Health and Human Services. Accessed at www.ncbi.nlm.nih.gov/books/NBK2682.
12. Lachman P. Expert Interview: Peter Lachman, Key Ingredients for Quality Improvement, Oct. 9, 2015. Accessed at www.youtube.com/watch?v=fzBqZZoIJUE.
13. Parker J. 10 Keys for Successful Process Improvement Programs (Part 1). EnFocus Solutions. Accessed at enfocussolutions.com/10-keys-for-successful-process-improvement-programs-part-1.
14. Duke University School of Medicine. What Is Quality Improvement? Methods of Quality Improvement. Accessed at patientsafetyed.duhs.duke.edu/module_a/methods/methods.html.
15. Glasgow J. Introduction to Lean and Six Sigma Approaches to Quality Improvement. Agency for Healthcare Research and Quality. Accessed at www.qualitymeasures.ahrq.gov/expert/expert-commentary/32943/introduction-to-lean-and-six-sigma-approaches-to-quality-improvement.
16. Institute for Healthcare Improvement. Plan-Do-Study-ACT (PDSA) Worksheet. Accessed at www.ihi.org/resources/pages/tools/plandostudyactworksheet.aspx.
17. The W. Edwards Deming Institute. PDSA Cycle. Accessed at deming.org/management-system/pdsacycle.

Autism:

Preparing for Aging Out of the System



While support and resources are accessible to youngsters with ASD and their parents, families must prepare for children reaching adulthood, when resource availability changes and depends on a number of factors.

By Diane L.M. Cook

THE PREVALENCE OF AUTISM spectrum disorder (ASD) has increased exponentially over the last decade. In 2012, the Centers for Disease Control and Prevention's Autism and Developmental Disabilities Monitoring Network estimated ASD prevalence was 14.6 per 1,000 8-year-old children. Approximately 82 percent of those children had a previously documented ASD diagnosis or education classification given by a community healthcare provider.

The *Diagnostic and Statistical Manual of Mental Disorders (DSM-5)* defines ASD as a neurodevelopmental disorder characterized by persistent deficits in social communication and interaction and restricted, repetitive patterns of behavior, interests or activities. Some individuals diagnosed with ASD also present with intellectual or language impairment. A diagnosis of ASD can be associated with a known medical or genetic condition or environmental factors. *DSM-5* segregates ASD into three levels of severity: level 1 – requiring support, level 2 – requiring substantial support, and level 3 – requiring very substantial support.

While federal and state governments provide support and resources for children with ASD to help them with early and correct diagnoses, healthcare and education, once they turn 21, most states no longer provide these same resources, as they are said to have "aged out" of the system. Unfortunately, this happens at the same time they are transitioning into adulthood, which is challenging enough. Factor in a cognitive disability such as ASD, and it is even more overwhelming. Practitioners try to help, but much more needs to be done.

A survey conducted by Kaiser Permanente titled "A Mixed Methods Study of Physician Knowledge and Experience with Autism in Adults" concluded: "Most adult healthcare providers recognized basic autism characteristics, but reported not having adequate skills and tools to care for this growing population of adult patients. Provider training, resources and improvements in the transition from pediatrics to adult medicine are essential to support the delivery of adequate and effective healthcare to adults with ASD."

Prior to children turning age 21, pediatricians and family physicians can help guide individuals with ASD or parents of children with ASD in the transition to adulthood. Availability of assistance will depend on where an individual is on the spectrum, the state in which they reside and whether they live in an urban or rural setting.

IEPs and ITPs

Two tools at the federal level, used for students with ASD to ensure they receive the best possible education and experience a smooth transition into adulthood, are an individualized education program (IEP) and individual transition plan (ITP).

An IEP is a document that tailors education to the individual student to provide the maximum benefit. It outlines the child's special education plan (goals for the school year), services needed to help the child meet those goals and a method for evaluating the student's progress.

An ITP is a document that prepares students for life after high school. It should be written by the time a student is 16 years old. Each student's plan is highly individualized and includes planning for further education and/or training, employment, income, living arrangements, leisure time and participating in the community. However, it should be noted that an ITP is only a starting point for individuals with ASD transitioning into adulthood, and it is only useful for individuals diagnosed with ASD when they were school-aged children. Individuals diagnosed with ASD as adults won't have an ITP.

Prior to children turning age 21, pediatricians and family physicians can help guide individuals with ASD or parents of children with ASD in the transition to adulthood.

"In many school systems, ITPs are done extremely well with a thorough evaluation and seamless connections to adult services for such things as vocational rehabilitation and financial and housing assistance," says Ellen Arnold, EdD, an educational consultant and special educator who develops and teaches short courses and seminars for persons with autism. "However, in other school districts, it has become a meaningless piece of paper. It may provide information, but no one has worked directly with the student to make sure she/he knows the resources available and how to access them."

In addition, says Dr. Arnold, because an IEP and ITP are void upon completion of high school, if students with ASD want to continue on to postsecondary education, they have to renegotiate a new contract with their current institution, whether it be a university, college, trade school or employer. "In helping persons

with ASD transition into adulthood, the most common challenges they face are a loss of automatic supports provided by the schools, concern others have about their social isolation, inadequate preparation for independent living, and employers who don't understand their unique characteristics and needs, so their job security might be compromised," adds Dr. Arnold.

A myriad of [resources] exist both at the federal and state level, as well as not-for-profit organizations, to assist with post-secondary education, employment, housing and community living, and financial, medical, social and life skills training.

With or without an ITP, pediatricians and family physicians can recommend resources to parents of children and adults with ASD to help them transition into adulthood. A myriad of these exist both at the federal and state level, as well as not-for-profit organizations, to assist with postsecondary education, employment, housing and community living, and financial, medical, social and life skills training.

Autism Speaks

Autism Speaks is a U.S. organization focused on improving the transition of individuals with ASD into adulthood, increasing global understanding and acceptance of ASD, acting as a catalyst for research and breakthroughs and ensuring access to reliable information and services throughout a person's lifespan. Through Autism Speaks' online toolkits and other resources, the organization reaches more than 50,000 adults each year.

Autism Speaks' website is a treasure trove. For students still in school, there is a link to an IEP guide created by a team of lawyers at Goodwin Procter LLP to help families understand the IEP process. The 26-page guide contains an IEP timeline and clearly lays out the steps to take throughout the IEP process. The guide also includes tips, resources and answers to frequently asked questions.

Three new tools were recently launched for adults to help their transition into adulthood. *Is It Autism and If So, What Next?: A Guide for Adults* is a toolkit designed to help adults who suspect they might have ASD, as well as those recently diagnosed with the disorder. *A Parent's Guide to Employment for Adults with Autism Spectrum Disorders* includes advice on how parents can help their adult child find and keep employment. And, *Community-Based Skills Assessment: Developing a Personalized Transition Plan* uses both a criterion-based observation and an interview-based process to measure the individual's knowledge, skills and behaviors.

Two educational resources were also recently launched. The Brian and Patricia Kelly Postsecondary Scholarship Fund and the *Postsecondary Educational Opportunities Guide* are designed to help young adults with ASD and their families explore various educational opportunities beyond high school.

In addition, Autism Speaks established two new networking groups on LinkedIn to connect members of the community to specific adult-related issues: Autism Employment Network and Housing and Residential Supports Network.

There are also two extensive resource databases on the organization's website that cover all areas related to transitioning into adulthood. In the Resource Guide, users can select the state in which they live to view a listing of resources. And, in the Resource Library, users can browse the latest books, magazine articles, education manuals, software and more.

According to Donna Murray, PhD, vice president and head of clinical programs and autism treatment network at Autism Speaks, pediatricians and family physicians can help parents of children with ASD in their journey into adulthood: "I would suggest to start the discussion of transition early — including transition to adult medical providers. Compile a file of medications and past and current issues with a list of supports (strategies) that would make a visit more successful. This will help the individual with ASD [become] more independent during an adult medical visit and provide necessary information (both

Autism Spectrum Disorder Resources

- Autism and Developmental Disabilities Monitoring Network: www.cdc.gov/ncbddd/autism/addm.html
- Autism Speaks: www.autismspeaks.org/family-services/adults
- Autism Society: www.autism-society.org
- Autism Source: www.autismsource.org
- Medicaid and Medicaid Waivers: www.medicaidwaiver.org
- Supplemental Security Income: www.ssa.gov/disabilityssi/ssi.html

medical and behavioral) to the adult provider. Also, I would recommend a 'handoff' so the current provider is somewhat available for consult."

Autism Society

The Autism Society is a U.S. grassroots organization created to increase public awareness about the day-to-day issues of individuals across the spectrum, advocate for appropriate services for individuals of every age, and provide the latest information regarding treatment, education, research and advocacy. Catherine Medovich, an information and referral specialist at Autism Society, says the organization helps parents build a network of support so they do not have to reinvent the wheel when the time comes to transition their child into adulthood.

"Although some people with ASD who are transitioning into adulthood will have support from their parents and their ITP," says Medovich, "there are others we often refer to as the 'square-one phone calls.' These are typically phone calls from parents who did not receive a diagnosis for their child when they were young and, therefore, their child did not receive any support or resources throughout their school years. These parents or caregivers have to immediately become familiar with the appropriate agencies, new terminology and who they can call to obtain necessary services for their loved one with ASD."

Medovich says she also receives phone calls from adults who have "inherited" their adult sibling with ASD after one or both parents have died or moved into a care facility, leaving them responsible for their sibling's day-to-day care. "There is lots of information on autism, but you have to know where to look for it. At the Autism Society, we like to empower people with the tools they need to navigate the vast amount of information available," says Medovich. "Support and resources can vary greatly state by state, so it is important to research what your state offers before looking outside your state for help."

Individuals can locate resources for adults with ASD by visiting the Autism Society free online referral database at www.autismsource.org. On the homepage, click on "click here to search." Individuals can search within categories that are of interest such as "Community Supports for Adults." The database produces results based on ZIP code, city, county or category. Searches can also be conducted with a keyword or phrase such as "therapeutic" or "day services." In addition, the database can locate the nearest Autism Society affiliate in a region, many of which have initiatives that specifically focus on adult issues and may offer support groups for adults with autism.

Medovich, the mother of a 25-year-old son who has ASD, says her son moved out of their family home two years ago, into a place of his own and is currently employed. "Even though my son has an education, his own place and a job, there is always something to deal with when you are a parent of a child who has ASD," she says. "Right now, I'm dealing with some employment issues my son is experiencing. He is also dealing with social isolation, and he would really like to make some friends."

Life Course Outcomes Research Program (LCORP)

The LCORP at the A.J. Drexel Autism Institute at Drexel University produces research that informs policy and services at the community and national levels about ways to improve the quality of life for persons with autism. According to the LCORP's National Autism Indicators Report: Transition into Young Adulthood — 2015:

- ***Transition planning:*** 58 percent of youth with autism had a transition plan in place by the federally required age.
- ***The services cliff:*** Approximately 26 percent of young adults on the autism spectrum received no services that could help them become employed, continue their education or live more independently.
- ***Adult outcomes and disconnection:*** More than one-third of young adults with autism were disconnected during their early 20s, meaning they never got a job or continued education after high school.
- ***Health, mental health and healthcare:*** 60 percent of youth with autism had at least two health or mental health conditions.
- ***Postsecondary education:*** Only 36 percent of young adults on the autism spectrum ever attended postsecondary education of any kind between high school and their early 20s. Of those who continued their education, 70 percent attended a two-year college at some point. Approximately 40 percent of those who disclosed their disability to their postsecondary school received accommodations or some type of help.
- ***Employment:*** 58 percent of young adults on the autism spectrum worked for pay outside the home between high school and their early 20s. Those who got jobs tended to work part time in low-wage jobs. However, approximately 90 percent of youth with autism who had a job during high school also had a job during their early 20s, compared with only 40 percent of those who did not work during high school.
- ***Living arrangements:*** Only one in five young adults on the autism spectrum ever lived independently (away from parents without supervision) between high school and their early 20s.

Supplemental Security Income (SSI)

SSI is a federal income supplement program designed to help persons with disabilities meet their basic needs for food, clothing and shelter. SSI payments are made monthly to disabled people who have low income and few resources. Whether a person qualifies for SSI benefits is determined by the amount of income earned, and qualifying amounts differ from state to state. The

basic SSI amount is the same nationwide, which is $733 per individual. However, many states provide additional money.

SSI benefits are also available to persons with ASD who live in certain types of institutions. And, if a person is approved for SSI benefits, they might also be able to receive assistance from Medicaid, the Supplemental Nutrition Assistance Program and other social services.

Medicaid and Medicaid Waivers

Medicaid, a joint state and federal entitlement program, provides medical assistance to persons with low incomes. If a person receives benefits under the SSI program and they are eligible for Medicaid, a state might pay Medicaid premiums and, in some cases, other Medicaid expenses such as deductibles and coinsurance.

A technique to help with completing tasks on the transition roadmap is scaffolding.

Medicaid waivers, which are not available in all states and usually have lengthy waiting lists, are provided to persons with ASD. The funds can be used for residential placement, day programs, case management, community-based instruction, and respite and medication management.

To determine if Medicaid waivers are available, go to www.medicaidwaiver.org and click on the name of the state where the person resides. The link will provide a list of available programs and services to assist people with disabilities in that state.

Transition Roadmaps and Scaffolding

According to Dr. Arnold, transitioning into adulthood can be frustrating and create a lot of anxiety for individuals with ASD. To lessen the stress, creating a transition roadmap can help individuals with ASD learn coping skills so they can adapt to new situations and opportunities with ease. "A transition roadmap is a visually decorated map to help individuals with ASD plan ahead for important transitions such as going to a new school, starting a new job or moving into a new home," explains Dr. Arnold. "It will assist them in plotting the course from where they are now to where they are going, giving them an idea of what to expect along the way."

A technique to help with completing tasks on the transition roadmap is scaffolding. Scaffolding, says Dr. Arnold, is breaking a task into chunks that can be modeled and rehearsed. This involves lots of practice, performing tasks with changed variables, relying on peers for help and, ultimately, performing tasks alone. The more tasks that are scaffolded ahead of time, the smoother the transition will be.

Because transitions are very hard, Dr. Arnold suggests not making too many changes at once. Think small baby steps, she says. Analyze all parts of their life that will be different, and then have the individuals experience each part separately until mastered. For example, teach individuals with ASD how to use a public laundry when they are still living at home so they will know how to do laundry when they are in college or living on their own. Teach them how to handle money at a very young age so by the time they have a job and have their own credit card, they already know how to manage bank accounts and how to budget.

New locations for work or school should be visited several times so they become familiar with landmarks, maps and the environs long before they start. Take pictures of places and people so they can be reviewed over and over again until they become familiar. A good practice is for individuals to write a social story for each location or event. "Social stories are short vignettes that we read and write with individuals with ASD to help them understand what to expect, what specifically to say, how to act and how to react in a variety of conversational or social settings," explains Dr. Arnold.

An Increasing Need

As more and more children are diagnosed with ASD, many as young as 2 years old, new information is becoming available about the disorder. However, the need for additional data that address ASD challenges has become increasingly important, especially resources that help individuals with ASD transition into adulthood to become independent and pursue their dreams. ❖

DIANE L.M. COOK, B. Comm., is a Canadian freelance magazine writer with over 330 articles published in several trade journals, including *Oilweek, Oilsands Review, Alberta Construction Magazine* and *Canadian Lawyer.*

Resources

1. DSM-5 Diagnostic Criteria — Social (Pragmatic) Communication Disorder 315.39 (F80.89) and Autism Spectrum Disorder 299.00 (F84.0): psychiatry.org/patients-families/autism/what-is-autism-spectrum-disorder?_ga=1.183021926.1133117589.1483468934
2. U.S. Department of Education — The Individuals with Disabilities Education Act (IDEA) Part B — Individualized Education Program (IEP) and Individual Transition Plan (ITP): idea.ed.gov
3. Social Security — Supplemental Security Income (SSI): www.ssa.gov/disabilityssi/ssi.html
4. Medicaid and Medicaid Waivers: www.medicaidwaiver.org

Making a Difference in Our Patients' Lives...

Specialty Solutions in Chronic Care
- Immune Globulin Intravenous
- Immune Globulin Subcutaneous
- Antihemophilic Factors

NuFACTOR has the distinction of carrying all U.S.-approved immune globulin products. We are committed to exceptional customer service, product and patient safety, and secure product availability and affordability. Excellence is our standard, and we've earned the most respected name in homecare. Our customers know we care about them, and that makes all the difference.

NuFACTOR Specialty Pharmacy has earned the Joint Commission Gold Seal of Approval

urac ACCREDITED Specialty Pharmacy Expires 03/01/2018

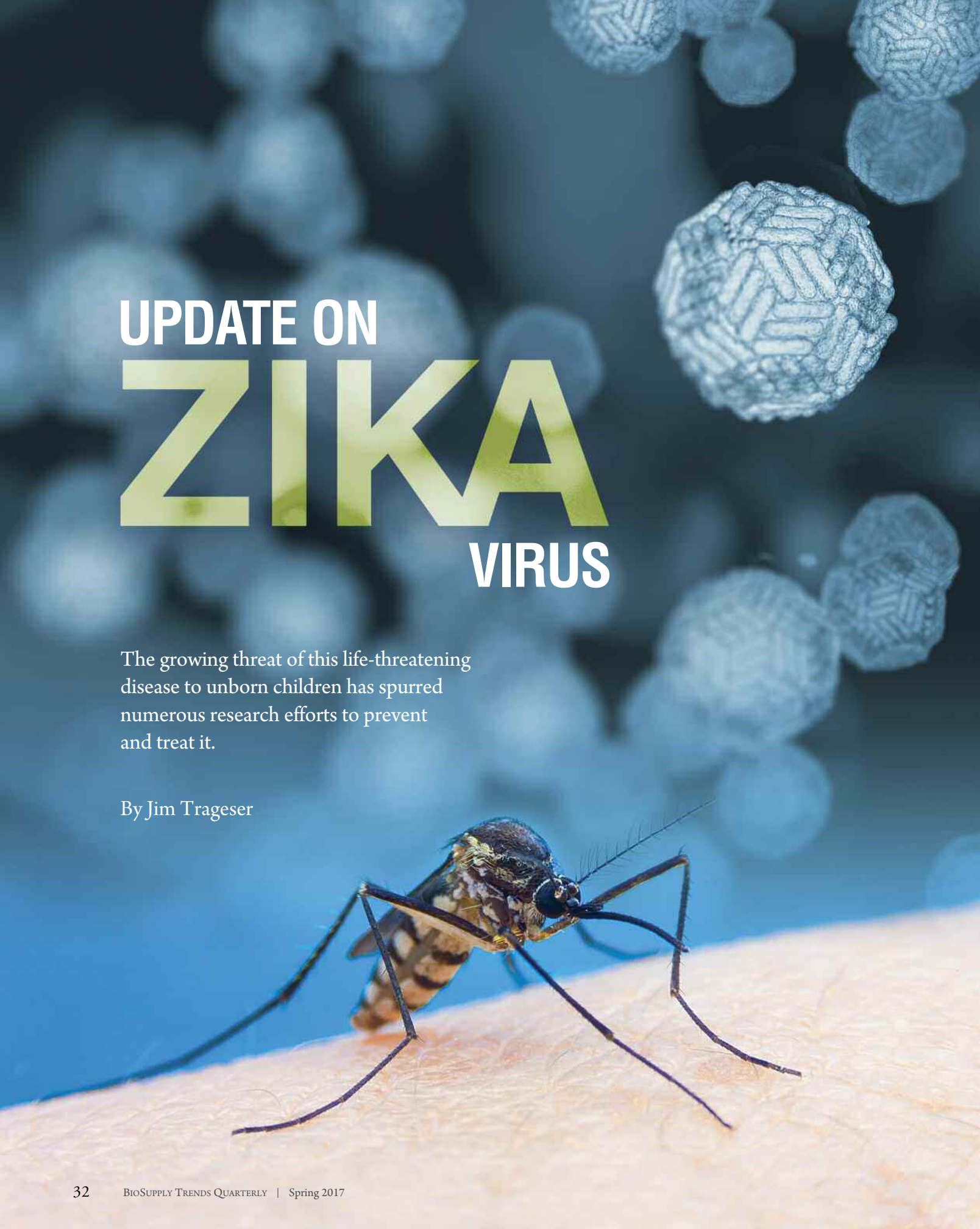
(800) 323-6832
www.NuFACTOR.com

NuFACTOR Specialty Pharmacy

UPDATE ON ZIKA VIRUS

The growing threat of this life-threatening disease to unborn children has spurred numerous research efforts to prevent and treat it.

By Jim Trageser



TODAY, ZIKA STANDS alongside Ebola and drug-resistant bacteria as one of the most frightening diseases threatening our faith in modern technology's triumph over nature. Like earlier diseases such as polio and smallpox that once terrified entire populations, Zika stokes our most primal fears because it threatens the most vulnerable: the developing child during pregnancy. An expectant mother who is infected with Zika can pass the virus along to her child, causing the development of serious, debilitating and even life-threatening birth defects.[1]

On Feb. 1, 2016, WHO had declared Zika outbreaks in Brazil and French Polynesia a public health emergency of international concern.[2] Thereafter, popular media coverage of Zika exploded when an epidemic occurred during the Rio Olympic Games in summer 2016. On the eve of the games, some health officials warned athletes and spectators to avoid the area due to risk of infection, while others reassured the public the risk was negligible. (Afterward, the World Health Organization [WHO] reported there were no infections of Zika during the Olympic Games.[3])

What Is Zika?

There are two main strains of the Zika virus: Asian and African.[4] Zika virus is a member of the same family of flaviviruses that cause dengue, West Nile and yellow fevers, and Japanese encephalitis. It is named for a region in Uganda, where it was first isolated in monkeys in 1947 by researchers studying yellow fever.[5] The first human infection was noted five years later, and the first case outside of Africa was reported in Indonesia 11 years after that.[6]

Zika virus was originally and is still primarily transmitted by mosquitoes of two Aedes species: albopictus and aegypti.[1] Since its discovery, Zika has spread beyond its original tropical habitats in equatorial Africa and Asia and is now in the United States, southern Asia and the South Pacific.[7] Today, more than 75 nations have reported a Zika outbreak.[3] However, it remained relatively unknown outside specialist circles until a series of outbreaks in 2007.[6]

The Centers for Disease Control and Prevention (CDC) reports that in 2015 and 2016, slightly fewer than 5,000 Americans were reported to have contracted Zika, and only 219 of those contracted it in this country; the rest were infected while traveling abroad.[8] However, health officials in Brazil estimate 1.5 million of Brazil's 206 million population have had Zika. And even in the U.S. Caribbean territories, the number of those who have been infected is about 36,000.[9]

Transmission of Zika

Both strains of Zika are fairly fragile and cannot exist outside of a host. For instance, the virus cannot be spread via airborne transmission or casual contact, or through food. Instead, Zika spreads when mosquitoes bite someone infected with the virus, and then pass the virus to others they bite afterward. In addition, it can spread through unprotected sexual activity with an infected person — even in the absence of any symptoms, as was illustrated by a Maryland woman who contracted the disease from her partner in 2016 when he returned from a trip to the Dominican Republic.[10]

There has been at least one reported case of laboratory-acquired infection, which occurred when a researcher accidentally pricked herself with a needle and became infected.[11] On another front, public health agencies are exploring whether Zika may spread through blood transfusions or organ transplants; however, as of this writing, no confirmed cases have been reported in the U.S. In March 2016, the U.S. Food and Drug Administration (FDA) approved an experimental test to screen blood donations for Zika virus.[12]

Today, more than 75 nations have reported a Zika outbreak.

Expectant mothers can transmit the virus to their developing children through the placenta. But, there is no evidence of transmitting the virus to the child via breast milk, and Zika-positive mothers are encouraged to breastfeed their infants since the benefits outweigh any known risk at this time.[13]

It is also now thought that the Asian strain of Zika is responsible for all cases of congenital Zika syndrome. In fact, genome analysis shows the Zika virus most prevalent in the Americas is more closely related to the Asian strain.[14]

Both mosquito species that carry Zika are now found on all continents except Antarctica, and can be found across the southern United States, and even in the upper Midwest, as well as in American territories in the Caribbean.[15] Aedes aegypti prefers to feed on humans rather than other animals, but it is confined to tropical, subtropical and some temperate climates. Aedes albopictus will bite humans, but it prefers other animals, and it can withstand a broader range of temperatures, so it is more widespread.[13]

The risk of contracting Zika is highest when mosquitoes are most active in areas with a current outbreak. Indeed, public health experts attributed the lack of Zika infections during the Rio Olympics to the games being held during the winter season in the Southern Hemisphere, when mosquito activity is lowest.

The length of incubation of Zika is unknown, but it is

thought to range from two to 12 days. Similarly, it is not known how long the Zika virus remains in the body, although it is recognized that the immune system eventually purges it. Researchers believe Zika may remain in the semen for up to six months.[16]

Separate studies on monkeys and mice indicate that having been infected with Zika confers immunity to further infections, but researchers do not yet know how long that immunity lasts.[17]

The majority of patients infected with Zika will exhibit no symptoms.

Symptoms and Progression of Zika

The majority of patients infected with Zika will exhibit no symptoms. Researchers surveyed infected patients in Yap State — a four-island group in Micronesia where a 2007 outbreak infected an estimated 73 percent of the 7,400 residents — and found 77 percent with Zika antibodies never experienced any symptoms at all.[9]

Of those who develop symptoms, the most common are a non-itchy rash that may appear anywhere on the body, conjunctivitis, headaches, general muscle and joint pain, and fever. Symptoms will exhibit anywhere from two days to a week.[18] Most healthy adults will fully recover from a Zika infection quickly with no further complications.

A small but unknown percentage of those infected develop autoimmune disorders that attack the body's nervous system, including Guillain-Barré syndrome (GBS) and acute disseminated encephalomyelitis (ADEM).[19] GBS occurs when the body's immune system attacks the myelin lining around nerve tissue, often leading to a weakening of the arms and legs and, in severe cases, affecting the ability to breathe.[20] While the specific cause of GBS is not widely understood, it is known to be associated with a previous infection, and GBS rates have increased in areas with high numbers of Zika infections, leading researchers to believe the virus can trigger GBS.[21] When Zika migrates to the brain, it results in ADEM. Similar to GBS, the body's attempt to fight the infection instead attacks the myelin sheath that surrounds all nerve tissue (including the brain), causing it to swell. The cause of ADEM is also not yet completely understood.[22]

Pregnant women exhibit symptoms similar to other patients. While researchers believe there may be a link between miscarriage and a Zika infection, this has yet to be conclusively determined, and studies continue.[23]

The damage that can be caused by the Asian strain of Zika to a developing child is devastating: One outcome linked to Zika is microcephaly, which results in the child's brain failing to properly develop.[7] Other brain deformities associated with congenital Zika infection (also known as congenital Zika syndrome) include ventriculomegaly, polymicrogyria, cortical deformity, cerebellar deformity and intracranial calcifications, among others.[24] Researchers now believe the virus directly attacks the nascent nervous system and brain in unborn children, preventing neural progenitor cells from properly reproducing — and even killing the cells. Magnifying the problem is a recent study conducted on mice that shows the Zika virus can disrupt the blood flow from the placenta to the baby, stunting growth of the child by denying it nutrients.[25]

Researchers are also examining whether some babies infected in utero who do not develop microcephaly or other congenital Zika syndrome defects may have other, milder damage that is not immediately evident that will manifest over time.[25] However, there is no evidence yet that a child who contracts Zika after birth is at risk for microcephaly or other conditions associated with congenital Zika syndrome. It is thought, though, that the virus interacts differently with neural progenitor stem cells than with the nerve cells they differentiate into.[26]

Diagnosing Zika

Diagnosis of Zika is made by examining patients' symptoms and reviewing their travel history to determine possible exposure.[27] If either indicates possible infection and first symptoms appeared within two weeks of the examination, a physician may conduct an RNA nucleic acid test of patient bodily fluids to determine whether there is presence of Zika virus. If it has been longer than two weeks, a urine sample will be tested. If that molecular test is negative, however, or if the infection is thought to be further along, antibody testing may be warranted to ensure an accurate diagnosis. All testing options should be conducted on pregnant patients.[28]

Because of the similarity of Zika virus to other flaviviruses — dengue fever, yellow fever and West Nile — false positives are not uncommon. A recent study indicated that dengue and Zika share 54 percent identical amino acid sequences, making an accurate lab diagnosis challenging.[3] The most accurate method to differentiate between closely related viruses is a plaque-reduction neutralization test. However, currently, only a handful of laboratories around the world have the capability to perform this type of test, making it impractical for clinical use at this time.[3]

Treating Zika

There is currently no cure for Zika.[3] Treatment is the same as for any other mild viral infection: Drink plenty of fluids, get plenty of rest and address fever and aches with over-the-counter medications.

For patients who develop GBS, plasmapheresis and intravenous immune globulin (IVIG) are the two most common treatments. Plasmapheresis is a filtering process that removes antibodies from the bloodstream to reduce damage to the nervous system. IVIG is shown to help ease symptoms in most GBS patients, but it is not understood why it is effective.[29] However, a Dutch study of patients with GBS showed those receiving IVIG may be at higher risk of hypoalbuminemia, which has its own health risks, so patients on IVIG therapy should be monitored.[30]

Those who develop ADEM are treated similarly to those with multiple sclerosis (MS), a similar autoimmune disorder. (ADEM is typically a one-time outbreak, rather than a chronic outbreak that marks MS.) Intravenous methyl prednisolone is typically the first-line treatment. If unsuccessful, plasma exchange may be an option, or IVIG may be tried if there is peripheral nervous system involvement. Specific treatments will vary by patient, depending on severity and secondary conditions.[31]

Children who develop microcephaly or other congenital Zika syndrome conditions before birth are likely to face significant health and developmental challenges throughout life, including vision and hearing problems. Depending on the severity, children may also suffer seizures. A full diagnostic workup and referral to early childhood development specialists can assist in developing a comprehensive care plan for children.[32]

Children whose mothers test positive for Zika but who do not exhibit any symptoms of congenital Zika syndrome should be observed for a period of years because the full impact of Zika infection is still not fully understood.

Preventing Zika

There is no vaccination to prevent the Zika virus. Prevention efforts involve avoiding travel to areas with current Zika outbreaks, protecting oneself from mosquito bites, vector control to stop outbreaks by killing mosquitoes that transmit the virus, and using protection during sex or abstaining from sex during outbreaks.[18]

Pregnant women and women who are planning to become

pregnant, or who are open to the possibility of pregnancy, should consult the CDC's Zika Travel Information page at wwwnc.cdc.gov/travel/page/zika-travel-information to see where current Zika outbreaks have been reported. If possible, they should avoid travel to those areas.

If travel to an area with an active Zika outbreak is required, individuals are advised to protect against mosquito bites by covering as much of their body as possible with light-colored clothing, including full-length sleeves and pants, sleeping under mosquito netting, keeping doors and windows closed (or using screens), and using insect repellents containing DEET, IR3535 or picaridin (all of which are safe for use by pregnant women).[18]

Individuals should also dispose of standing water in containers because mosquitoes can breed even in a small bucket or pot. They're also advised to contact local health authorities for assistance in treating large bodies of water such as ponds, lakes and abandoned pools.

Ongoing Research

Research is being conducted to further the fight against Zika on multiple fronts: improved diagnosis, treatment of active infections and inoculations.

Diagnosis. Better lab tests are needed to ensure physicians are able to accurately differentiate between Zika infection and infection by related flaviviruses. Consequently, the National Institute of Allergy and Infectious Diseases (NIAID) is funding research to fine-tune antibodies so a cross diagnosis between these closely related infections becomes less likely.[33]

For patients who develop GBS, plasmapheresis and intravenous immune globulin (IVIG) are the two most common treatments.

At the University of Bonn in Germany, a team that developed a standardized Middle East respiratory syndrome detection test is studying methods to improve diagnosis. An initial study showed that most polymerase chain reaction tests are not sensitive to low levels of the Zika virus in bodily fluids, and since tests made by various companies look at different parts of the RNA chain, they are not uniformly consistent in detecting different strains of Zika. The team has since developed a Zika "calibrator" so companies can ensure their testing systems are able to more accurately detect Zika RNA.[34]

In February 2016, WHO extended its Ebola-oriented Emergency Use Assessment and Listing protocols to Zika research. This protocol eliminates much of the bureaucracy normally required to bring new diagnostic testing technology to market. It is intended to encourage researchers and manufacturers to expedite new technology.[3]

And, researchers at Florida Atlantic University recently received a nearly $200,000 state grant to devise a proof-of-principle for a portable field testing device similar to one the same team devised to test for HIV. This would be available for use at airports and other nonhospital settings to help control outbreaks by identifying infected patients quickly and inexpensively.[35]

Treatment. NIAID is conducting reviews of approved antiviral drugs to see if any are effective in treating Zika virus. One of the most recent and most promising was a Zika-specific test conducted with the antiviral compound BCX4430, a drug built around a small molecule that interferes with the ability of a virus to replicate its RNA.[36] It has been shown effective at blocking Ebola reproduction in laboratory settings, leading FDA to fast track the drug for human testing.[37]

Another study is examining the differences between the ways in which Asian and African strains, as well as the closely related dengue virus, affect developing neural stem cells. The study offers some promising leads into the possibility that an inhibitor targeting protein P53 may be developed to stop the virus from harming human neural progenitor cells in unborn children.[14]

Because Zika has only fairly recently become a serious health threat, research on using antivirals against other flaviviruses are further along, particularly for dengue fever. This research is being reviewed to see if it might hold promise for Zika. Two other proteins associated with flaviviruses (NS3 and NS5) are the target of a potential inhibitor to tackle dengue fever. Similar approaches have yielded effective treatment for HIV and hepatitis C. If successful, this could lead to a possible approach for Zika as well.[38]

To date, there are no approved antiviral drugs for any of the flavivirus infections,[6] and many of the original studies are more than a decade old.[39] Still, several have shown promise in early testing, and further studies on those drugs are underway.[40]

Vaccination. Multiple vaccines are currently being researched, and three have shown success in providing mice and monkeys full immunity against Zika:

- A purified inactivated virus developed by Army researchers at Walter Reed Hospital;
- An adenovirus vector-based vaccine with a fragment of Zika DNA coding developed at Beth Israel Deaconess Medical

Center in Boston (BIDMC; affiliated with Harvard Medical School); and

• A plasmid DNA vaccine, also developed at BIDMC.

Researchers have tested all three of these vaccines on either mice or monkeys, and have found that all three stimulated an effective immunity in test subjects. The next step is testing on humans.[41]

A fourth vaccine is a live-attenuated vaccine being developed from a cloned version of the virus. The cloning technology will allow for a rapid ramp-up to deployment if the vaccine proves successful.[42]

Lastly, the inactivated vaccine project at Walter Reed is based on a successful vaccine program targeting Japanese encephalitis, a related flavivirus. The Zika study, called ZPIV, is already being administered to human volunteers.[43]

Looking Ahead

Because mosquitoes that transmit Zika are found globally, and Zika is now known to also be transmitted sexually, it is likely that Zika will spread more widely from the tropics where it was first found. It may well be that travel advisories become useless in coming years if Zika becomes globally widespread.

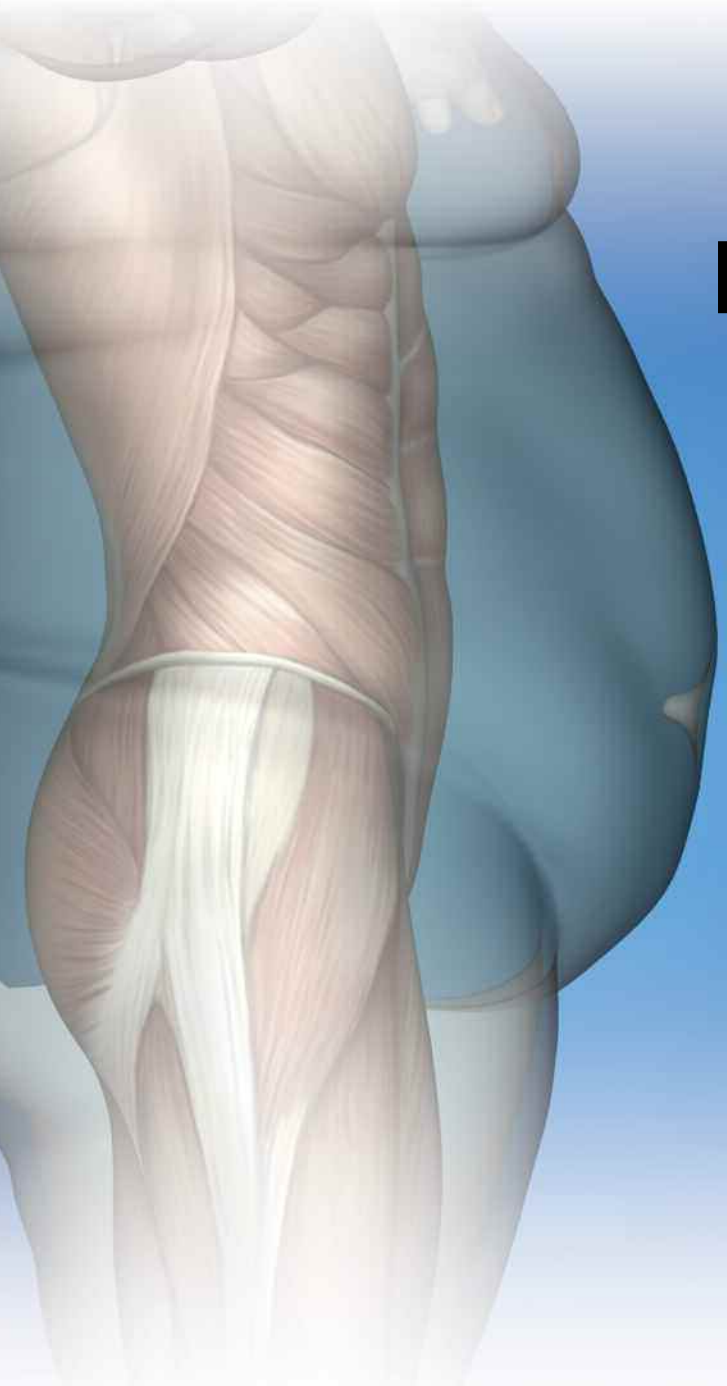
WHO, the U.S. and other governments are putting significant resources into developing a vaccine and antiviral treatment. Last year, WHO received $25 million from various donors to fight Zika,[44] the U.S. Congress allocated $350 million toward Zika,[45] and the state of Florida recently allocated $25 million.[46] It is impossible to say whether or when such vaccines or treatments will prove successful and be approved for human use, but given recent advances in producing effective vaccines for related flaviviruses, it is reasonable that these preventatives will be ready sooner than later.

Still, until the day comes that we can vaccinate against Zika, common-sense precautions should be taken to control the spread of the disease, and ongoing support will be needed for families raising children with special needs due to the effects of infection in utero. ❖

JIM TRAGESER is a freelance journalist in the San Diego area.

References

1. Centers for Disease Control and Prevention. About Zika. Accessed at www.cdc.gov/zika/about.
2. Chua A, Prat I, Nueblind CM, et al. Update on Zika Diagnostic Tests and WHO's Related Activities. *PLOS Neglected Tropical Diseases,* Feb. 2, 2017. Accessed at journals.plos.org/plosntds/article?id=10.1371/journal.pntd.0005269.
3. Tavernise S. No Zika Cases Reported During Rio Olympics, W.H.O. Says. *New York Times,* Sept. 2, 2016. Accessed at www.nytimes.com/2016/09/03/health/zika-rio-olympics.html?_r=0.
4. Haddow AD, Schuh AJ, Yasuda CY, et al. Genetic Characterization of Zika Virus Strains: Geographic Expansion of the Asian Lineage. *PLOS Neglected Tropical Diseases,* Feb. 28, 2012. Accessed at www.ncbi.nlm.nih.gov/pmc/articles/PMC3289602.
5. Cohen J. Zika's Long, Strange Trip Into the Limelight. *Science,* Feb. 8, 2016. Accessed at www.sciencemag.org/news/2016/02/zika-s-long-strange-trip-limelight.
6. Weaver SC, Costa F, Garcia-Blanco MA, et al. Zika Virus: History, Emergence, Biology, and Prospects for Control. *Antiviral Research,* Volume 130, June 2016. Accessed at www.sciencedirect.com/science/article/pii/S0166354216301206.
7. Mayo Clinic. What Is the Zika Virus, and Should I Be Worried? Accessed at www.mayoclinic.org/diseases-conditions/zika-virus/expert-answers/zika-virus/faq-20178199.
8. Centers for Disease Control and Prevention. Case Counts in the U.S. Accessed at www.cdc.gov/zika/geo/united-states.html.
9. Ross J. What You Need to Know About Zika Virus. Harvard Health Blog, Feb. 1, 2016. Accessed at www.health.harvard.edu/blog/what-you-need-to-know-about-zika-virus-201602019114.
10. Brooks R, Carlos MP, Myers RA, et al. Likely Sexual Transmission of Zika Virus from a Man with No Symptoms of Infection — Maryland, 2016. *Morbidity and Mortality Weekly Report,* Sept. 2, 2016. Accessed at www.cdc.gov/mmwr/volumes/65/wr/mm6534e2.htm.
11. Schnirring L. Needle Stick Infects Lab Worker with Zika Virus. *Center for Infections Diseases Research and Policy News,* June 9, 2016. Accessed at www.cidrap.umn.edu/news-perspective/2016/06/needle-stick-infects-lab-worker-zika-virus.
12. Thompson D. Zika Virus Transmitted Through Blood Transfusion, New Report Suggests. CBS News, Aug. 18, 2016. Accessed at www.cbsnews.com/news/zika-virus-transmitted-through-blood-transfusion-new-report-suggests.
13. Dovey D. Is Zika Contagious? Facts And Myths About How It Spreads. *Medical Daily,* Aug. 8 2016. Accessed at www.medicaldaily.com/zika-contagious-facts-and-myths-about-how-it-spreads-394198.
14. Zhang F, Hammack C, Ogden S, et al. Molecular Signatures Associated with ZIKV Exposure in Human Cortical Neural Progenitors. *Nucleic Acids Research,* Oct. 14, 2016. Accessed at academic.oup.com/nar/article-lookup/doi/10.1093/nar/gkw765.
15. Centers for Disease Control and Prevention. Potential Range in U.S. Accessed at www.cdc.gov/zika/vector/range.html.
16. Zika Virus Awareness. Transmission and Risks. Accessed at www.mygnp.com/zika-virus/transmission.
17. Fox M. New Studies Show Just How Tricky the Zika Virus Is. NBC News, June 28, 2016. Accessed at www.nbcnews.com/storyline/zika-virus-outbreak/new-studies-show-just-how-tricky-zika-virus-n600736.
18. World Health Organization. Zika Virus. Accessed at www.who.int/mediacentre/factsheets/zika/en.
19. Rettner R. Zika Virus Linked with Another Brain Disease: What's ADEM?. *LiveScience,* April 11, 2016. Accessed at www.livescience.com/54366-zika-virus-adem.html.
20. Centers for Disease Control and Prevention. Zika Virus: Health Effects and Risks. Accessed at www.cdc.gov/zika/healtheffects/index.html.
21. Cao-Lormeau VM, Blake A, et al. Guillain-Barré Syndrome Outbreak Associated with Zika Virus Infection in French Polynesia: A Case-Control Study. *The Lancet,* April 9, 2016. Accessed at www.thelancet.com/journals/lancet/article/PIIS0140-6736(16)00562-6/abstract.
22. Cara E. How Zika Virus Attacks the Body and What Happens After Infection: Everything You Need to Know, Watch For. *Medical Daily,* Aug. 4, 2016. Accessed at www.medicaldaily.com/how-zika-virus-attacks-body-and-what-happens-after-infection-everything-you-393977.
23. Centers for Disease Control and Prevention. Outcomes of Pregnancies with Laboratory Evidence of Possible Zika Virus Infection in the United States. Accessed at www.cdc.gov/zika/geo/pregnancy-outcomes.html.
24. Russell K, Oliver S, et al. Update: Interim Guidance for the Evaluation and Management of Infants with Possible Congenital Zika Virus Infection — United States, August 2016. *Morbidity and Mortality Weekly Report,* Aug. 26, 2016. Accessed at www.cdc.gov/mmwr/volumes/65/wr/mm6533e2.htm?s_cid=mm6533e2_w.
25. Healy M. Scientists Offer First Direct Proof that Zika Virus in Brazil Causes Birth Defects. *Los Angeles Times,* May 11, 2016. Accessed at www.latimes.com/science/sciencenow/la-sci-sn-zika-birth-defects-20160510-story.html.
26. Centers for Disease Control and Prevention. Zika Virus: Infants and Children. Accessed at www.cdc.gov/zika/hc-providers/infants-children/zika-microcephaly.html.
27. Centers for Disease Control and Prevention. Testing for Zika. Accessed at www.cdc.gov/zika/symptoms/diagnosis.html.
28. Centers for Disease Control and Prevention. Diagnostic Tests for Zika Virus. Accessed at www.cdc.gov/zika/hc-providers/types-of-tests.html.
29. About Guillain-Barre Syndrome. Treatment for Guillain-Barre Syndrome (GBS). Accessed at www.about-guillain-barre.com/guillain_barre_treatment#.WJLB9NcrK00.
30. Fokkink WJR, Walgaard C, Kuitwaard K, et al. Association of Albumin Levels with Outcome in Intravenous Immunoglobulin–Treated Guillain-Barré Syndrome. *JAMA Neurology,* Dec. 27, 2016. Accessed at jamanetwork.com/journals/jamaneurology/article-abstract/2594534.
31. Alexander M and Murthy JMK. Acute Disseminated Encephalomyelitis: Treatment Guidelines. *Annals of Indian Academy of Neurology,* July 2011. Accessed at www.ncbi.nlm.nih.gov/pmc/articles/PMC3152158.
32. Centers for Disease Control and Prevention. Facts About Microcephaly. Accessed at www.cdc.gov/ncbddd/birthdefects/microcephaly.html.
33. National Institute of Allergy and Infectious Diseases. Zika Virus Diagnosis. Accessed at www.niaid.nih.gov/diseases-conditions/zika-diagnosis.
34. German Center for Infection Research. Zika Virus: Optimized Tests for Reliable Diagnosis. *Science Daily,* May 12, 2016. Accessed at www.sciencedaily.com/releases/2016/05/160512102626.htm.
35. Florida Atlantic University. Device Will Rapidly, Accurately and Inexpensively Detect Zika Virus at Airports and Other Sites. *Science Daily,* Feb. 22, 2017. Accessed at www.sciencedaily.com/releases/2017/02/170222101822.htm.
36. Julander J1, Siddharthan V, Evans J, et al. Efficacy of the Broad-Spectrum Antiviral Compound BCX4430 Against Zika Virus in Cell Culture and in a Mouse Model. *Antiviral Research,* 2017 Jan;137:14-22. doi: 10.1016/j.antiviral.2016.11.003. Epub 2016 Nov 10. Accessed at www.ncbi.nlm.nih.gov/pubmed/27838352.
37. Litterman N, Lipinski C, and Ekins S. Small Molecules with Antiviral Activity Against the Ebola Virus. *F1000 Research,* Feb. 9, 2015. Accessed at www.ncbi.nlm.nih.gov/pmc/articles/PMC4335594.
38. Lescar J, Pheng LS, and Luo D. Towards the Design of Antiviral Inhibitors Against Flaviviruses: The Case for the Multifunctional NS3 Protein from Dengue Virus as a Target. *Antiviral Research,* July 2, 2008. Accessed at www.researchgate.net/profile/Julien_Lescar/publication/23143909_Towards_the_design_of_antiviral_inhibitors_against_flaviviruses_The_case_for_the_multifunctional_NS3_protein_from_Dengue_virus_as_a_target/links/0deec52e5b94f17dc8000000.pdf.
39. Wiwanitkit V. What is New in Treatment of Dengue? *Expert Review of Anti-Infective Therapy,* 2010;8(7):841-845. Accessed at www.medscape.com/viewarticle/725639_4.
40. National Institute of Allergy and Infectious Diseases. Zika Virus Treatment. Accessed at www.niaid.nih.gov/diseases-conditions/zika-treatment.
41. Beth Israel Deaconess Medical Center. Vaccine Candidates Protect Primates Against Zika Virus. Accessed at www.bidmc.org/News/PRLandingPage/2016/August/BarouchZikaNonhumanPrimates.aspx.
42. American Society for Microbiology. New Zika Clone Could Be New Model for Developing Vaccine. Accessed at www.asm.org/index.php/journal-press-releases/94511-new-zika-clone-could-be-new-model-for-developing-vaccine.
43. Harris R. Testing Begins on an Experimental Zika Vaccine with Inactivated Virus. National Public Radio, Nov. 7, 2016. Accessed at www.npr.org/sections/health-shots/2016/11/07/501015866/testing-begins-on-an-experimental-zika-vaccine-with-inactivated-virus.
44. World Health Organization. Zika: Response Funding. Accessed at www.who.int/emergencies/zika-virus/response/contribution/en.
45. Centers for Disease Control and Prevention. CDC Awards Nearly $184 Million to Continue the Fight Against Zika. Press release, Dec. 22, 2016. Accessed at www.cdc.gov/media/releases/2016/p1222-zika-funding.html.
46. Cordner S. Florida Universities, Research Institutes Receive Millions in Zika Grant Funding. WFSU, Feb. 1, 2017. Accessed at news.wfsu.org/post/florida-universities-research-institutes-receive-millions-zika-grant-funding.



MYTHS AND FACTS: OBESITY

What are the true causes of the obesity epidemic that now affects more than one-third of people globally? And, do the measures thought to prevent obesity really work?

By Ronale Tucker Rhodes, MS

OBESITY WAS ONCE considered to be simply a major public health threat. But, in 2013, the American Medical Association (AMA) at its annual meeting voted to declare obesity a chronic disease. That vote came only after impassioned debate, with many unconvinced that it met the criteria for disease. Russell Kridel, MD, then-incoming-chair of the AMA Council on Science and Public Health, was one of the dissenters: "It's more like smoking. Smoking isn't a disease. Smoking can cause disease such as lung cancer and emphysema in the same way that obesity can lead to diabetes and hypertension. We're really talking nomenclature here, not philosophy." Nevertheless, Dr. Kridel did agree that "there is no debate about the importance and urgency of addressing the problem."[1]

According to the Centers for Disease Control and Prevention (CDC), between 2011 and 2014, more than one-third (36.5 percent) of U.S. adults were obese, and more than 17 percent of youth were obese.[2] And CDC predicts these rates will rise. It estimates that 42 percent of Americans will be obese by 2030.[3] Just what factors contribute to the cause of obesity and how to reverse it are not well understood. In fact, a pervasive number of myths and presumptions about obesity need clarification — not just for those who suffer from it, but also for those who treat it.

Separating Myth from Fact

Myth: The obesity epidemic is exaggerated.

Fact: There has been criticism over the years that the number of overweight and obese individuals is overstated. The reason: It relies on body mass index (BMI) scores. But, despite arguments that BMI classifications don't account for varying factors, most organizations agree and some studies show that BMI is a reasonable indicator and the best option.

In 1998, the National Institutes of Health lowered the overweight threshold for BMI to match international guidelines, as well as to "help primary care providers address weight management as a pathway to promoting the health of their patients."[4,5] The move added 30 million Americans who were previously in the "healthy weight" category to the "overweight" category, more than doubling the size of the category.[4] According to the book *An Epidemic of Obesity Myths* published in 2005, this meant that actors Tom Cruise, Sylvester Stallone and Mel Gibson, as well as baseball players Sammy Sosa and Barry Bonds and boxer Mike Tyson, were technically obese.[6]

CDC acknowledges there are clinical limitations of BMI that need to be considered. For instance, "factors such as age, sex, ethnicity and muscle mass influence the relationship between BMI and body fat. And, BMI doesn't distinguish between excess fat, muscle or bone mass, nor does it provide any indication of the distribution of fat among individuals."[7] Because muscle weighs more than fat, individuals who are muscular can fall into the overweight status, even if their fat levels are low. And, "BMI doesn't tease apart different types of fat, each of which can have different metabolic effects on health. BMI cannot take into consideration, for example, where the body holds fat" such as in the belly or under the skin (visceral fat), according to an article in the journal *Science*. The problem with this is that relatively thin people who are considered healthy by BMI standards can have high levels of visceral fat, putting them at higher risk of developing health problems related to weight gain.[8]

Yet, while there are better ways to measure body fat, they are also a lot more expensive, eliminating them as an everyday option. And, while it has been suggested that doctors rely not just on BMI but also hormones and biomarkers in the blood or urine to better understand the processes that may contribute to obesity and chronic disease, until such tests become available, BMI is still the most useful indicator of overweight and obesity.[8]

Moreover, the growing prevalence of obesity is clear due to an abundance of observational and experimental data, both among adults and children.[9] Worldwide, the rate of obesity has nearly doubled since 1980, with just over 200 million adult men and just under 300 million adult women obese, accounting for 39 percent of all adults.[10] "With the continuing rise in obesity and limited treatment efficacy, options for averting a poor public health outcome seem to rest either on the hope that scientists are wrong in their projections or speedy investment in the development of more effective public health measures to deal with it," say Robert W. Jeffrey, PhD, professor of epidemiology and community health at the University of Minnesota School of Public Health, and Nancy E. Sherwood, PhD, a research investigator for HealthPartners Research Foundation. "We think the second option [is] a more prudent scientific and policy choice."[9]

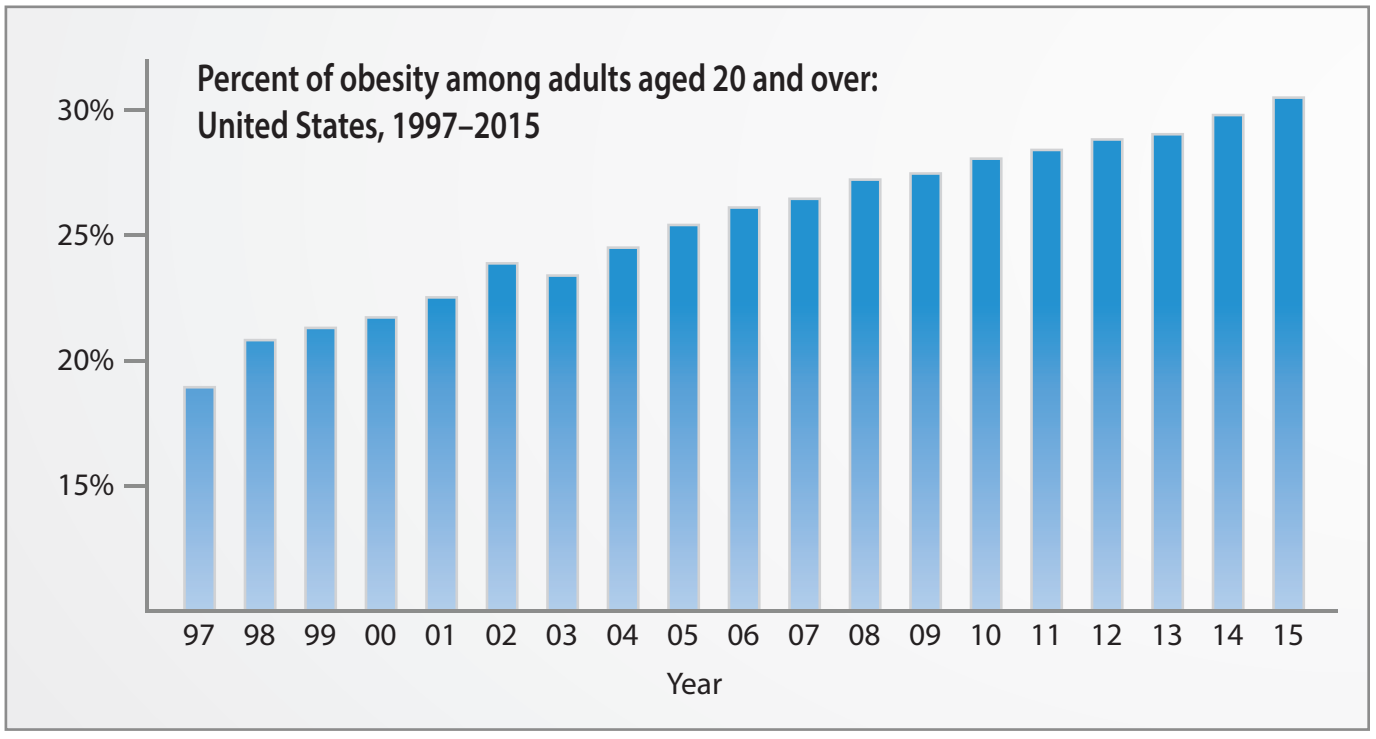
Myth: Obesity is genetic.

Fact: Obesity is rarely caused by genes; however, some people may be genetically predisposed to obesity. According to the Harvard School of Public Health, researchers have identified certain rare instances in which obesity seems to be caused solely by genetic mutations.[11] To date, studies have identified more than 30 candidate genes on 12 chromosomes associated with BMI.[12] But even people who carry genes associated with obesity don't become overweight, and vice versa, because weight is also influenced by lifestyle factors.[11]

CDC acknowledges there are clinical limitations of BMI that need to be considered.

In 2013, two studies found mutations in genes that could explain weight gain, but the mutations account for only less than 5 percent of obesity in society. In a mouse study conducted at Boston Children's Hospital, researchers found that mutations in the Mrap2 gene led the animals to eat less initially but still gain about twice as much weight as they normally would. When their appetites returned, the mice continued to gain weight even though they were fed the same number of calories as a group of control mice. They determined the mice were simply sequestering fat rather than breaking it down for energy. Like people, mice contain two copies of the Mrap2 gene. Mice with just one defective copy experienced significant weight gain, but not as much as mice with two defective copies.[12]

The second study conducted at the University College London divided a group of 359 healthy men of normal weight by the FTO gene status, the majority of whom had low-risk versions of the gene, while 45 had mutations linked to greater appetite and caloric consumption. To determine how the altered



genes were affecting appetite, the researchers measured levels of the hunger hormone ghrelin before and after meals. Those with the mutated FTO gene did not show the same drop in ghrelin levels to signify they were full as did the men with the low-risk FTO gene.[12]

Myth: A person can be obese and healthy.

Fact: Despite reports to the contrary, studies show that a person cannot be obese and healthy. In one study conducted at Columbia University's Mailman School of Public Health in 2013, researchers found that overweight and obesity were associated with 18.2 percent of all deaths among adults from 1986 through 2006 in the U.S. Previous estimates established the obesity-related death rate at only approximately 5 percent. In addition, the study showed that the more recent the birth year, the greater effect obesity has on mortality rates. And, contrary to claims made in public health literature, obesity is not protective in the elderly.[13]

A second study in 2014 of more than 14,000 men and women aged 30 to 59 years found that those who were obese had more plaque buildup in their arteries, putting them at greater risk for heart disease and stroke than people of normal weight. In the study, researchers at Kangbuk Samsung Hospital Total Healthcare Center in Seoul, Korea, scanned the hearts of 14,828 people who had no apparent risk factors for heart disease to look for buildup of calcium plaque in the heart arteries. They found that obese people had a higher prevalence of atherosclerosis of the heart arteries than people of normal weight, which if not managed, can lead to heart attack and sudden cardiac death, among other heart conditions. "There has long been debate about the relative importance to health of fitness versus fatness. The argument has been made that if one is fit, fatness may not be a significant health concern," said David Katz, MD, MPH, FACPM, FACP, FACLM, director of the Yale University Prevention Research Center. "Excess body fat can increase inflammation, one of the key factors contributing to heart disease, and other chronic diseases as well."[14]

And yet another study conducted in 2016 found that overweight and obesity are associated with higher all-cause mortality and mortality related to coronary heart disease (CHD), stroke, respiratory disease and cancer. In the study, researchers from the Global BMI Mortality Collaboration investigated the association between BMI and mortality in 3,951,455 people from 189 studies in multiple countries. Analysis was limited to individuals who were never-smokers, did not have preexisting chronic disease and who survived the first five years of follow-up. Of these, 385,879 died during the study period. There was a nonlinear association between BMI and mortality for each major cause of death in each major region included in the study, with BMI greater than 25 showing a strong positive correlation with CHD, stroke and respiratory disease mortality, and a moderate positive correlation with cancer mortality.[15]

Myth: A calorie in *is/is not* a calorie out.

Fact: Whether a calorie is a calorie when it comes to weight loss has been a considerable source of debate. According to the "calories in, calories out" mindset, obesity is simply a matter of eating too many calories. A pound of fat is 3,500 calories, so if a person eats 500 calories less than they burn every day, after a week, a pound of fat will have been lost. But, it does appear that while calories do matter, not all calories are equal. It's just not very well understood.

A calorie is a measure of energy. According to Kris Gunnars, BSc, a nutrition researcher and CEO and founder of Authority Nutrition, "On a molecular level, the body functions with an enormously complex set of chemical reactions. These chemical reactions require energy, which is where calories step in." Different foods have different effects on the body and go through different metabolic pathways before they're turned into energy. "Some foods can cause hormone changes that encourage weight gain, while other foods can increase satiety and boost the metabolic rate," says Gunnars. For instance, when fructose enters the liver from the digestive tract, it can be turned into glucose and stored as glycogen. But, if the liver is full of glycogen, it can be turned into fat. Consumed in excess, it can cause insulin resistance, which drives fat gain. Fructose also doesn't impact satiety, and it doesn't lower the hunger hormone ghrelin. On the other hand, Gunnars explains, about 30 percent of calories from protein will be spent on digesting it because the metabolic pathway requires energy. In addition, protein may increase levels of fullness and boost the metabolic rate. Increased protein levels may also be used to build muscle, which burns calories around the clock.[16]

One study showed that diets high in protein and/or low in carbohydrate produced greater weight loss, but "neither macronutrient-specific differences in the availability of dietary energy nor changes in energy expenditure could explain these differences in weight loss."[17] Another study concluded that the body may use calories from low-carbohydrate diets less efficiently than those from low-fat diets, with greater weight loss as a result. In that study, a group of obese volunteers lost 10 percent to 15 percent of their weight by reducing their calorie intake to 60 percent of estimated needs with a carefully controlled diet for 12 years. They were then fed enough calories to maintain their newly reduced body weight through either a low-fat, low-glycemic index (low in readily absorbed sugars and simple starches) or a very-low-carbohydrate diet. Those on the very-low-carbohydrate (very-high-fat) diet burned between 100 and 300 calories more per day than those on the low-fat (high-carbohydrate) diet. The researchers, however, didn't determine the source of the energy loss, but the results implied that very-low-carbohydrate diets result in more calories wasted in metabolism.[18]

But, despite studies showing a calorie in is not just a calorie out, the jury is out on this. According to Malden Nesheim, emeritus professor of nutrition at Cornell University, and Marion Nestle, a professor of nutrition, food studies and public health at New York University, "Most studies that find significant differences in weight loss in people eating different proportions of protein, fat or carbs rarely last more than six months. Longer-term studies of a year or more seldom show clear advantages of low-carb diets." And, they say, "Most scientific reviews conclude that a diet of any composition will lead to weight loss if it reduces calories sufficiently."[18]

Myth: Slow, gradual weight loss, rather than rapid weight loss, leads to long-term results.

Fact: Actually, more rapid and greater initial weight loss has been associated with lower body weight at the end of long-term follow-up. A meta-analysis conducted in 2010 that compared rapid weight loss with slower weight loss found that people with rapid weight loss early on were not more likely to gain back the pounds than people who lost weight gradually.[19]

Myth: Setting unrealistic goals defeats weight-loss goals.

Fact: While this is a reasonable hypothesis, studies show that setting unrealistic goals does not interfere with weight-loss outcomes. In one study of 314 women whose average age was 51 years, researchers examined whether having a weight-loss experience that lived up to expectations was related to maintenance in a group that successfully lost weight. At study entry, participants had lost 19 percent of their body weight, yet 86 percent of participants were currently trying to lose more weight. Further losses of 13 percent of body weight were needed to reach self-selected ideal weights, with heavier participants wanting to lose more. While the weight loss-related benefits participants achieved did not live up to their expectations, it did not affect subsequent weight maintenance outcomes.[20]

Whether a calorie is a calorie when it comes to weight loss has been a considerable source of debate.

Myth: Making small, sustained changes in diet and exercise will lead to greater and longer-term weight loss.

Fact: This, again, relies on the "calorie in, calorie out" theory. While it seems to make sense that cutting or burning 3,500 calories over time leads to a pound of weight lost, over the long

term, it's much more complex due to individual variability that affects changes in body composition, as well as balance of food and type of exercise. Studies show that you can't apply the 3,500-calorie rule when modifications are made over long-term periods because it was derived from short-term experiments performed mostly in men on very-low-energy diets. One study found that people who gradually lost weight over a long period of time only lost about 20 percent as much as would be expected: just 10 pounds, rather than 50, after walking a mile every day for five years.[19,21]

> The types of physical education classes offered in the U.S. have not been shown to reduce or prevent obesity.

Myth: Physical education classes reduce obesity in children.

Fact: The types of physical education classes offered in the U.S. have not been shown to reduce or prevent obesity. Three different studies that focused on an increase in the number of days children attended physical education classes found that the effects on BMI were inconsistent across sexes and age groups.[19] One, a meta-analysis of 26 studies, found that school-based physical activity interventions have a positive impact on four of nine outcome measures: duration of physical activity, television viewing, VO_2 max and blood cholesterol. However, these interventions had no effect on leisure time physical activity rates, systolic and diastolic blood pressure, BMI and pulse rate.[22]

Dispelling the Myths Now

Most would not deny that obesity is a serious health problem all over the world. Termed "globesity," the problem is most acute in prosperous countries. In fact, the U.S. has the distinction of being the world's fattest nation. But, obesity is also a problem in low- and middle-income countries, and governments worldwide recognize this.

In 2011, the World Health Organization (WHO) made a political declaration committed to advancing the implementation of the "WHO Global Strategy on Diet, Physical Activity and Health," which introduced policies and actions aimed at promoting healthy diets and increasing physical activity in the entire population. WHO also developed the "Global Action Plan for the Prevention and Control of Noncommunicable Diseases [NCD] 2013-2020." Known as the "Global Action Plan," it will "contribute to progress on nine global NCD targets to be attained by 2025, including a 25 percent relative reduction in premature mortality from NCDs by 2025 and a halt in the rise of global obesity to match the rates of 2010." In 2016, the World Health Assembly published a report titled the "Commission on Ending Childhood Obesity" that included six recommendations to "address the obesogenic environment and critical periods in the life course to tackle childhood obesity."[23]

Yet, even with global efforts, many myths and misconceptions continue to spread, contributing to the rising rates of obesity. Aimed at understanding this epidemic, studies indicate that curbing obesity works best at the individual level, on a case-by-case basis, starting with an understanding of obesity's factual causes and preventive measures. Unfortunately, it's just not as simple as calories in/calories out. ❖

RONALE TUCKER RHODES, MS, is the editor of *BioSupply Trends Quarterly*.

References

1. Frellick M. AMA Declares Obesity a Disease. Medscape, June 19, 2013. Accessed at www.medscape.com/viewarticle/806566.
2. Ogden CL, Carroll MD, Fryar CD, and Flegal KM. Prevalence of Obesity Among Adults and Youth: United States, 2011–2014. NCHS Data Brief, No. 219, November 2015. Accessed at www.cdc.gov/nchs/data/databriefs/db219.pdf.
3. Thaik CM. The Psychology of Obesity. *Psychology Today*, June 20, 2013. Accessed at www.psychologytoday.com/blog/the-heart/201306/the-psychology-obesity.
4. Wilson S. The History of BMI. How Stuff Works. Accessed at health.howstuffworks.com/wellness/diet-fitness/weight-loss/bmi4.htm.
5. Nainggolan L. New Obesity Guidelines: Authoritative 'Roadmap' to Treatment. Medscape, Nov. 12, 2013. Accessed at www.medscape.com/viewarticle/814202.
6. An Epidemic of Obesity Myths. "Overweight" and "Obese" Celebrities and Sports Stars. Accessed at www.obesitymyths.com/myth1.1.htm.
7. Centers for Disease Control and Prevention. Body Mass Index: Considerations for Practitioners. Accessed at www.cdc.gov/obesity/downloads/BMIforPactitioners.pdf.
8. Sifferlin A. Why BMI Isn't the Best Measure for Weight (or Health). *Time*, Aug. 26, 2013. Accessed at healthland.time.com/2013/08/26/why-bmi-isnt-the-best-measure-for-weight-or-health/.
9. Jeffrey RW and Sherwood NE. Is the Obesity Epidemic Exaggerated? No. *British Medical Journal*, 2008 Feb 2; 336(7638): 245. Accessed at www.ncbi.nlm.nih.gov/pmc/articles/PMC2223031.
10. Harvard School of Public Health. Obesity Trends. Accessed at www.hsph.harvard.edu/obesity-prevention-source/obesity-trends.
11. Legg TJ. Obesity: When Is It Genetic? Healthline, June 6, 2016. Accessed at www.healthline.com/health/obesity-when-it-genetic#Overview1.
12. Sifferlin A. New Genes IDd in Obesity: How Much of Weight is Genetic? *Time*, July 19, 2013. Accessed at healthland.time.com/2013/07/19/news-genes-idd-in-obesity-how-much-of-weight-is-genetic/.
13. Laidman J. Obesity's Toll: 1 in 5 Deaths Linked to Excess Weight. Medscape, Aug. 15, 2013. Accessed at www.medscape.com/viewarticle/809516.
14. Reinberg S. Is Healthy Obesity a Myth? WebMD, April 30, 2014. Accessed at www.webmd.com/diet/news/20140430/is-healthy-obesity-a-myth#1.
15. Rodriguez T. Obesity Associated with Increased Mortality Risk. Endocrinology Advisor, July 14, 2016. Accessed at www.endocrinologyadvisor.com/obesity/mortality-higher-in-obesity/article/509605.
16. Gunnars K. Why "Calories In, Calories Out" Doesn't Tell the Whole Story. Authority Nutrition. Accessed at authoritynutrition.com/debunking-the-calorie-myth.
17. Buchholz AC and Schoeller DA. Is a Calorie a Calorie? *American Journal of Clinical Nutrition*, May 2004, vol. 79 no. 5 899S-906S. Accessed at ajcn.nutrition.org/content/79/5/899S.full.
18. Nasheim M and Nestle M. Is a Calorie a Calorie? PBS, Sept. 20, 2012. Accessed at www.pbs.org/wgbh/nova/body/is-a-calorie-a-calorie.html.
19. Casazza K, Fontaine KR, Astrup A, et al. Myths, Presumptions, and Facts About Obesity. *New England Journal of Medicine*, 2013; 368:446-454. Accessed at www.nejm.org/doi/pdf/10.1056/NEJMsa1208051.
20. Gorin AA, Pinto AM, Tate DF, et al. Failure to Meet Weight Loss Expectations Does Not Impact Maintenance in Successful Weight Losers. *Obesity*, 2007;15:3086–3090. Accessed at www.academia.edu/19007386/Failure_to_Meet_Weight_Loss_Expectations_Does_Not_Impact_Maintenance_in_Successful_Weight_Losers_.
21. Friedman LF. 7 Common Myths About Obesity and Weight Loss. Business Insider, Nov. 30, 2015. Accessed at www.businessinsider.com/obesity-weight-loss-exercise-science-2015-11.
22. Dobbins M, DeCorby K, Robeson P, Husson H, and Tirilis D. School-Based Physical Activity Programs for Promoting Physical Activity and Fitness in Children and Adolescents Aged 6-18 (Review). *Evidenced-Based Child Health: A Cochrane Review Journal*, 4: 1452–1561 (2009). Accessed at www.academia.edu/6212587/Cochrane_review_School-based_physical_activity_programs_for_promoting_physical_activity_and_fitness_in_children_and_adolescents_aged_6-18.
23. World Health Organization. Obesity and Overweight. Accessed at www.who.int/mediacentre/factsheets/fs311/en.

Help **BioSupply Trends Quarterly** *Go Green*

Join our campaign to reduce unnecessary paper consumption!

Here's how you can help: If you can forgo receiving a hard copy of the magazine and utilize the digital version instead, go to **www.BSTQuarterly.com** and click on Go Green to sign up for the electronic version and opt out of the print version.

The Benefits of Going Digital for You!

- Enjoy **early online access** to every new issue
- **Print individual articles** to keep or share with colleagues and care providers
- **Easily share articles** instantly on Social Media
- **Read the issues anywhere** at any time on all of your digital devices (smartphone, computer, iPad, tablet)
- Quickly **access all published articles**

Fibrin Sealants: *When More Is Needed to Stop the Bleeding*

Fibrin sealant appears to be a significant adjunct to meticulous surgical technique, potentially providing faster, safer and more effective patient care.

— William D. Spotnitz, MD

By Keith Berman, MPH, MBA

SURGEONS RELY every day on sutures, staples, collagen pads, gelatin sponges and other simple hemostats to stop or control bleeding in the operating room. But sometimes these methods aren't up to the task, or it takes too much time to achieve hemostasis. Depending on the procedure, difficult-to-control operative bleeding can cause a host of problems: prolonged operative time, impaired visualization of the surgical field, increased need for blood transfusions, increased re-operative risk and treatment failure.

Decades ago, the need was recognized for a material that could be topically applied to effectively stop or control bleeding, and in certain surgical settings — vascular anastomosis suture lines and dural graft placement, for example — to provide air and fluid tightness as well. The ideal product would need to be biocompatible and biodegradable, highly adhesive to various tissues, flexible yet possess adequate tensile strength and, very importantly, not induce inflammation, foreign body reactions, tissue necrosis or extensive fibrosis.[1]

At that time, it was recognized that the one product that could meet all of these criteria comes from ourselves: a concentrate of human fibrinogen and thrombin combined at the bleeding site directly or

by spray applicator to both mimic and enhance the natural clotting cascade. Fibrin sealants were first conceptualized in the early 1940s,[2,3] but early experimental agents prepared from plasma turned out to have suboptimal adhesive properties due to its naturally low fibrinogen level.[4] A much higher fibrinogen concentration was needed for a fibrin-based biological adhesive to have the strength and tissue sealing properties required for difficult-to-control bleeds.

This technical barrier was finally solved as refinements to the original Cohn plasma fractionation process enabled manufacturers to highly concentrate specific plasma proteins, including fibrinogen and thrombin, on an industrial scale. In 1998, the U.S. Food and Drug Administration (FDA) approved Baxter's TISSEEL, the first of four commercially available fibrin sealants that now include EVICEL (Ethicon), RAPLIXA (Mallincrodt) and ARTISS (Baxter), a novel slower-acting fibrin sealant (Table 1).

Fibrin Sealant Indications: From Narrow to Broad

Fibrin sealants — often referred to as "fibrin glue" in clinical literature — are used today in an extraordinary range of procedures, from diffuse mediastinal bleeding in cardiac surgery to bleeding from cut liver surfaces, adhesion of split thickness skin grafts, and oozing from vascular graft suture anastomoses. But to secure initial marketing approval from FDA and later expand the labeled indications for their products in these diverse surgical settings, manufacturers had to work through the inherent challenges of designing well-controlled, adequately powered patient trials for different types of surgeries, and defining appropriate clinical endpoints in each of them to document the benefits of fibrin sealants compared to conventional options to achieve hemostasis.

"Fibrin sealants — often referred to as "fibrin glue" in clinical literature — are used today in an extraordinary range of procedures."

TISSEEL was first approved for use as an adjunct to hemostasis in cardiopulmonary bypass surgeries or for splenic injuries resulting from abdominal trauma, when control of bleeding by conventional techniques (e.g., suture, ligature, cautery) were ineffective or impractical.* EVICEL was initially licensed specifically for use in vascular surgery. But today, after FDA review of completed Phase III clinical studies across multiple surgical applications, these products, as well as RAPLIXA, are now broadly labeled for use as an adjunct to hemostasis when control of bleeding by standard techniques (such as suture, ligature or cautery) is ineffective or impractical.

However, the production of fibrin sealants is much more resource-intensive and complex than are conventional

Table 1. Licensed Fibrin Sealant Products

Supplier	Product	Delivery Form(s)	Presentations	Active Ingredients
Baxter	TISSEEL	Freeze-Dried Frozen	2 mL, 4 mL, 10 mL	Fibrinogen (Human) Thrombin (Human) Aprotinin (Synthetic)**
Ethicon	EVICEL	Frozen	2 mL, 4 mL, 10 mL	Fibrinogen (Human) Thrombin (Human)
Mallincrodt	RAPLIXA	Powder	0.5 g, 1 g, 2 g vials	
Baxter	ARTISS	Frozen	2 mL, 4 mL, 10 mL	

** *Aprotinin is a fibrinolysis inhibitor*

* *TISSEEL is also indicated as an adjunct in the closure of colostomies.*

products used to control bleeding, and thus they are also more costly. Fibrinogen and thrombin are purified from screened donor plasma in highly controlled manufacturing processes, subjected to viral clearance steps, frozen, lyophilized or spray-dried, and delivered using an array of devices customized for different surgical applications. So while suture, pads, sponges and other conventional products used to control surgical bleeding can generally be used without restriction, fibrin sealants tend to be used more judiciously in the cost-conscious hospital operating room setting.

> Many years after the first products were introduced in the late 1990s, the need for fibrin sealants continues to increase.

Uses and Clinical Benefits of Fibrin Sealants

Fortunately, in deciding when and in which types of surgeries it may be justified to use a fibrin sealant to manage hard-to-control bleeding, surgeons can refer to an extensive and growing body of published clinical experience. Below are findings from selected studies of some of the most common surgical applications of fibrin sealant products.

Bleeding anastomoses in vascular surgery procedures. In a single-blind Phase III trial, 175 adult patients undergoing vascular surgical procedures with suture hole bleeding were randomized to use of a fibrin sealant delivered with a gelatin sponge, or to the gelatin sponge alone. Procedures included arterial bypass (81 percent), arteriovenous graft formation (9 percent) and endarterectomy (9 percent). The mean time to hemostasis (TTH) was two minutes in the fibrin sealant arm versus four minutes in the control arm ($P < 0.002$). Similar reductions in TTH were also observed in patients receiving concomitant antiplatelet agents, anticoagulants or both.[5]

Fibrin sealant was evaluated in a Phase III randomized trial of fibrin sealant against gauze pads to control persistent anastomotic suture hole bleeding following placement of peripheral ePTFE vascular grafts, specifically arterio-arterial bypasses and arterio-venous shunts for dialysis access. In 44 of 70 patients (62.9 percent), a single application of fibrin sealant achieved suture line hemostasis within four minutes that was maintained until surgical closure, against 22 of 70 (31.4 percent) in the control patients ($P < 0.0001$).[6]

Mediastinal bleeding in cardiac surgeries. Diffuse mediastinal bleeding during open-heart surgery is exacerbated by multiple factors, including heparin anticoagulation and hypothermia. Difficult-to-control bleeding is especially problematic in reoperative cardiac surgery ("redo") or emergency resternotomy. One large trial in this challenging surgical setting randomly assigned 333 patients to receive fibrin sealant or a conventional topical hemostatic agent when required during the operation.[7] The success rate for fibrin sealant in controlling bleeding within five minutes of application was 92.6 percent, compared with only a 12.4 percent success rate with conventional topical agents ($P < 0.001$). Fibrin sealant also rapidly controlled 82 percent of bleeding episodes not initially controlled by conventional agents. Additionally, the emergency resternotomy rate following redo operations was significantly lower in the fibrin sealant group (5.6 percent) than in a non-matched historical control group (10 percent) ($P < 0.0089$).

Bleeding in liver resection surgery. Because the liver is highly vascular and the cut surface is friable, bleeding can be persistent and difficult to control despite the use of such conventional hemostatic techniques as heat cautery or argon beam coagulation. A number of serious postoperative complications are associated with prolonged bleeding in liver surgery.

A prospective trial randomized 121 undergoing hepatic resection to treatment with fibrin sealant administered by a spray applicator or standard topical hemostatic agents, used singly or in combination.[8] The primary endpoint was time to hemostasis, and secondary outcomes included intraoperative blood loss and occurrence of complications, defined as reoperation for any reason, development of abdominal fluid collections, or bilious appearance of drained fluid for at least one day.

The mean time to hemostasis for the 116 evaluable patients was 282 seconds for the fibrin sealant group, compared with 468 seconds with standard agents ($P = 0.06$). While intraoperative blood loss was similar between the two groups, postoperatively, the percentage of patients with complications was 17.2 percent in the fibrin sealant group, about half the

36.5 percent complication rate in the control group (P = 0.02).

Bleeding in urological surgery. Bleeding control can be very difficult to achieve with conventional hemostats in partial or radical nephrectomy, prostatectomy and cystectomy. Investigators randomized 53 patients undergoing these and other urologic surgeries to use of EVICEL fibrin sealant or an absorbable hemostat. A significantly higher percentage of patients who received fibrin sealant achieved the primary endpoint of hemostasis at 10 minutes than those who received absorbable hemostat (96.4 percent [27/28] versus 72.0 percent [18/25]; relative risk [RR] = 1.34; P = 0.013). A lower overall incidence of treatment failure was also observed for patients who received fibrin sealant versus absorbable hemostat: 3.6 percent [1/28] versus 28.0 percent [7/25], respectively (RR = 0.13; P = 0.013).[9]

Fixation of skin grafts and skin flaps. Hematoma or seroma and poor graft adherence are frequent adverse outcomes with the use of sutures or staples to affix autologous skin grafts in burn patients, or skin flaps in cosmetic surgeries such as facelift or abdominoplasty. A number of comparative studies with commercial or single-donor fibrin sealants have documented various benefits compared to point fixation techniques, including reduced hematoma or seroma formation risk, reduced time to hemostasis, reduced transfusion requirements in patients with more extensive thermal injury and improved graft adherence with use of fibrin sealants compared to point fixation techniques.[10,11,12,13,14]

To allow surgeons more time to position the skin graft, Baxter developed ARTISS, a novel fibrin sealant whose human thrombin component is intentionally formulated at a very low concentration (2.5 to 6.5 IU/mL compared to 400 IU/mL or higher for other fibrin sealants). This product reformulation extends the fibrinogen polymerization time and gives the surgeon up to 60 seconds to manipulate and better position the graft or flap, while preserving the ability of this fibrin sealant to improve surface adherence to the wound bed and thus reduce "dead space" that results in increased risk of hematoma and seroma formation.

In a Phase III rhytidectomy study, a "split-face" design was used in each of 75 patients to evaluate flap adherence and reduction of dead space with ARTISS plus standard of care on one side and standard of care alone on the other side. Drainage volume in subjects treated with ARTISS was 7.7 ± 7.4 mL versus 20.0 ± 11.3 mL for the standard-of-care group (P < 0.0001). A total of seven hematoma or seroma events occurred in five subjects on the ARTISS side versus 17 hematomas/seromas in 17 patients on the standard-of-care side.[15]

Evidence, Experience and Usage Grow

Many years after the first products were introduced in the late 1990s, the need for fibrin sealants continues to increase. Between 2010 and 2015, demand by U.S. surgeons for fibrin sealant products climbed almost 50 percent, according to the Marketing Research Bureau.[16] This impressive growth in usage shouldn't come as a surprise. Hundreds of new studies — case reports, clinical trials and meta-analyses — were published over that same five-year period, adding to the thousands that preceded them. As more published evidence documenting their efficacy and safety accumulates, there is more interest in fibrin sealants as a standard option to achieve hemostasis or fluid-tight membranous sealing.

But, appropriately, surgeons tend to be conservative when considering significant changes to their standard practices. It can take time for an entirely new treatment approach to something as important as surgical hemostasis to be seriously considered, and more time for the surgeon to evaluate that new treatment in his or her own hands in the operating room. But in applications as diverse as head and neck surgery, hip and knee arthroplasty, mandibular third molar wound closure and anastomotic leakage following colorectal surgery, more surgeons each day discover for themselves the power of this potent concentrate of nature's own solution to vascular bleeding. ❖

KEITH BERMAN, MPH, MBA, is the founder of Health Research Associates, providing reimbursement consulting, business development and market research services to biopharmaceutical, blood product and medical device manufacturers and suppliers. Since 1989, he has also served as editor of *International Blood/Plasma News*, a blood products industry newsletter.

References

1. Radosevich M, Goubran HA and Burnouf T. Fibrin sealant: scientific rationale, production methods, properties, and current clinical use. *Vox Sang* 1997;72:133-43.
2. Young JZ, Medawar PB. Fibrin sutures of peripheral nerves: measurement of the rate of regeneration. *Lancet* 1940;ii:126-8.
3. Seddon HJ, Medawar PB. Fibrin sutures of human nerves. *Lancet* 1942;ii:87-92.
4. Tidrick RT, Warner ED. Fibrin fixation of skin transplants. *Surgery* 1944;15:90-95.
5. Gupta N, Chetter I, Hayes P, et al. Randomized trial of a dry-powder, fibrin sealant in vascular procedures. *J Vasc Surg* 2015 Nov;62(5):1288-95.
6. Saha SP, Muluk S, Schenk W, et al. A prospective randomized study comparing fibrin sealant to manual compression for the treatment of anastomotic suture-hold bleeding in expanded polytetrafluoroethylene grafts. *J Vasc Surg* 2012 Jul;56(1):134-41.
7. Rousou J, Levitsky S, Gonzelez-Lavin L, et al. Randomized clinical trial of fibrin sealant in patients undergoing resternotomy or reoperation after cardiac operations. A multicenter study. *J thorac Cardiovasc Surg* 1989 Feb; 97(2):194-203.
8. Schwartz M, Madariaga J, Hirose R, et al. Comparison of a new fibrin sealant with standard topical hemostatic agents. *Arch Surg* 2004 Nov;139(11):1148-54.
9. Albala DM, Riebman JB, Kocharian R, et al. Hemostasis during urologic surgery: fibrin sealant compared with absorbable hemostat. *Rev Urol* 2015;17(1):25-30.
10. Nervi C, Gamelli RL, Greenhalgh DG, et al. A multicenter clinical trial to evaluate the topical hemostatic efficacy of fibrin sealant in burn patients. *J Burn Care Rehabil* 2001 Mar-Apr;22(2):99-103.
11. McGill V, Kowal-Vern A, Lee M, et al. Use of fibrin sealant in thermal injury. *J Burn Care Rehabil* 1997 Sep-Oct;18(5):429-34.
12. Stuart JD, Kenney JG, Lettieri J, et al. Application of single-donor fibrin glue to burns. *J Burn Care Rehabil* 1988 Nov-Dec;9(6):619-22.
13. Killion EA, Hyman CH, Hatef DA, et al. A systematic examination of the effect of tissue glues on rhytidectomy complications. *Aesthet Surg J* 2015 Mar;35(3):229-34.
14. Lee JC, Teitelbaum J, Shajan JK, et al. The effect of fibrin sealant on the prevention of seroma formation after postbariatric abdominoplasty. *Can J Plast Surg* 2012 Fall;20(3):178-80.
15. Hester TR, Shire JR, Nguyen DB, et al. Randomized, controlled, phase 3 study to evaluate the safety and efficacy of fibrin sealant VH S/D 4 s-apr (Artiss) to improve tissue adherence in subjects undergoing rhytidectomy. *Aesthet Surg J* 2013 May;33(4):487-96.
16. Personal communication with Patrick Robert (The Marketing Research Bureau, Inc., Orange, CT).

As a journalist, Nick Brown was used to travel stints in foreign countries and even contracting the occasional travel bug. But, in early 2016, Brown was shocked when an assignment in Puerto Rico led to a health-threatening infection with the Zika virus.

Zika Virus: *A Patient's Perspective*

By Trudie Mitschang

IT COULD HAVE been a bad case of the flu, with symptoms that included a painful sore throat, unrelenting fever and night sweats. Reuters journalist Nick Brown was on assignment in Puerto Rico, and while his symptoms were troubling, they were hardly an immediate cause for alarm. A seasoned traveler, Brown remained unconcerned, even as the symptoms escalated to include joint pain, a genital rash and a persistent throbbing ache behind his eyes. As the symptoms came and went, increasing in severity over time, it was Brown's mother who correctly guessed he'd contracted the Zika virus. Brown recounted his experience and eventual diagnosis in a September 2016 interview with Reuters. "Initially, I laughed off her 'Internet diagnosis' as the overwrought worries of a long-distance mom," Brown recalled. "But I agreed to see my long-time physician during a visit home in late June, and after listening to my symptoms and learning I'd been working in San Juan, my physician arranged to have my blood sent for screening. Eight days later, we learned my mother was correct. I had contracted Zika."[1]

A Growing Global Concern

Zika has made headlines in recent years, and to date, hundreds of thousands of people are estimated to have been infected since it was first detected in Brazil in early 2014.

Zika is spread mostly by the bite of an infected Aedes species mosquito. But, an unusual attribute of Zika (and of special concern to Brown) is that it can also be transmitted through sexual intercourse, a highly uncommon concern with mosquito-borne viruses. While many people experience no notable symptoms, Zika poses a particular threat to pregnant women, since it can penetrate the womb and infect unborn children with a birth defect called microcephaly. In adults, it has been linked to Guillain-Barré syndrome (GBS), a rapid-onset muscle weakness that causes temporary paralysis. Although research is ongoing, to date, Zika has no vaccine or treatment.

Puerto Rico, the island where Brown was infected, has been hit especially hard by the Zika virus. As of this writing, more than 38,000 infections have been reported in the region, including more than 3,000 among pregnant women and at least 12 cases of microcephaly.[2]

"As a journalist and a patient, I've had access to some of the brightest minds studying Zika. But the virus has confounded experts at the highest levels and launched a global race to understand its risks,"[1] said Brown.

A Look at Life After Zika

Brown's case was puzzling to doctors, both for its rarity and because of the way his symptoms came and went during the three weeks following his initial infection. But, for Brown, there were more pressing personal concerns: the risk of sexually transmitting the virus to his wife, Julie, and the potential threat of developing GBS. "My wife and I are both in our early 30s, and have had to consider how dangerous my bout with Zika could be to our plans to have children someday," he explained. "Our most intimate decisions were suddenly affected by the uncertainty surrounding Zika."[1]

With more questions than answers about his long-term prognosis, Brown agreed to join a Centers for Disease Control and Prevention (CDC) study gauging how long Zika can be spread through semen and urine. As one of 140 participants, he was required to provide monthly semen samples and detailed sexual activity updates via FedEx shipments and email. "I endured the embarrassment in exchange for a $50 Visa gift card for each sample, and, more importantly, for the chance to learn and to contribute to science," he explained.

After waiting for months to get results, in December, Brown learned the study he participated in revealed he no longer tested positive for Zika. As of this interview, he says his health outlook is a good one. "Overall, my health is good and my life is totally normal, although I've developed a lot of minor skin-related symptoms that I never had before. I seem to be more prone to rashes and skin irritations. I was diagnosed with mild rosacea and find myself scratching a lot. I have no idea if these are related to Zika," he said. "As for family planning, my wife and I are both content to take the CDC's word that I am Zika-free, and we don't plan to have kids for a couple of years. So, in that sense, all is well." ❖

References

1. Brown N. For One Zika Patient, Lingering Symptoms and Few Answers. Reuters.com, Sept. 12, 2016. Accessed at www.reuters.com/article/us-health-zika-patient-insight-idUSKCN11I0AT.
2. Puerto Rico Department of Health. Surveillance of Zika. Accessed at www.salud.gov.pr/Estadisticas-Registros-y-Publicaciones/Pages/VigilanciadeZika.aspx.

Zika Virus:
A Physician's Perspective

BRIAN FOY, MD, works with vectors and vector-borne pathogens, and his research spans both basic and applied biology. Dr. Foy's undergraduate training at Notre Dame was in medical entomology, anthropology and ecology, and his graduate school training at Tulane was in molecular and cellular biology, immunology and tropical medicine research. Dr. Foy's expertise as a researcher prepared him for many forays outside the U.S., but what it could not prepare him for was exposure to the Zika virus during a 2008 trip to Senegal. Upon his return, the doctor unknowingly passed the virus to his wife, making the Colorado couple the first known case of sexually acquired Zika in the United States. As a physician, researcher and now a patient, Dr. Foy offers unique insights into the search to find a vaccine for this potentially dangerous and highly contagious illness.

BSTQ: Tell us about your background in Zika research.

Dr. Foy: Prior to my fateful trip to Senegal, I had done a lot of research on arbovirus infections in mosquitoes, mostly with Sindbis, o'nyong-nyong, dengue and West Nile viruses. On that trip, of course, my graduate student and I came down with symptoms that seemed to me at the time to be the result of an arbovirus infection, and then my wife became ill with very similar symptoms about a week after my symptoms arose. Following that, I spent two years following up that now well-documented report, and eventually discovered that we had all been infected with Zika virus. Subsequently, I obtained some isolates of Zika virus, began doing some simple experiments in the lab and wrote a grant to the National Institutes of Health to get funding to study Zika virus sexual transmission, but that first grant was rejected. After a report in 2015 described the 2013 Tahiti outbreak confirmed our supposition that Zika virus could be sexually transmitted, I rewrote my grant, and it was recently funded. In addition, my wife and I have donated our blood to several research groups that needed it for diagnostics and therapeutics research.

BSTQ: Have you or your wife had any lingering health problems since your infection?

Dr. Foy: My arthralgia lasted longer than any other of my symptoms — at least a month. My wife's symptoms were worse than mine, and not only did she have long-term arthralgia in her wrists and thumb joints, to this day, she has lingering aching and weakness in those joints that she ascribes to being infected with Zika virus.

BSTQ: Where is the greatest risk of infection in the U.S.?

Dr. Foy: If by mosquitoes, most of the risk is concentrated in South Florida and Gulf Coast states on the U.S. mainland. Outside of the mainland, Puerto Rico is obviously a hotspot for Zika virus mosquito transmission, and Hawaii is at risk. If through sex, that could be anywhere an infected traveler travels.

BSTQ: Are there any research breakthroughs on the horizon?

Dr. Foy: I'm particularly interested in research that is looking at why microcephaly cases seemed to be so prevalent in the northeast of Brazil relative to other highly infected areas (South Pacific islands, parts of Colombia, Puerto Rico, etc.). Was it simply that there was an unfortunate confluence of many pregnant women in the region where there was a large outbreak of a new virus and people didn't yet know it could infect fetuses? Or were there/are there other important risk factors that we don't yet understand? Similarly, data from lab studies are showing that previous exposure and antibody-based immunity to other flaviviruses, like dengue viruses, can enhance Zika virus infection in cells. The big question is how much this influences disease presentation in communities that have many dengue immune people.

BSTQ: What is your research focused on?

Dr. Foy: Currently, we are working to understand Zika virus sexual transmission. I have also been working with my colleagues and publishing papers to understand Zika virus transmission in mosquitoes, and developing Zika virus diagnostic assays.

BSTQ: Where are we in terms of developing a vaccine?

Dr. Foy: I'm no expert on this, but it seems to me from the news and scientific reports that early Zika virus vaccine studies are very promising, and human vaccine trials are imminent. ❖

TRUDIE MITSCHANG is a contributing writer for *BioSupply Trends Quarterly* magazine.

2017 Comprehensive Review for Family Physicians

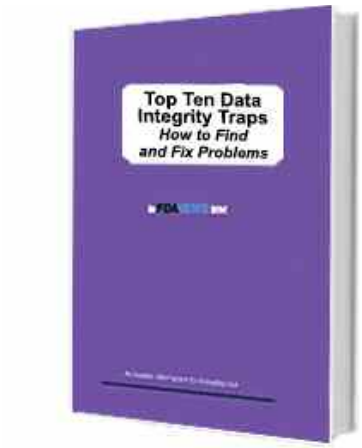
Author: Audio Digest

Audio Digest has developed the 2017 Comprehensive Review for Family Physicians, which brings together lectures developed specifically for the field of family medicine, along with specific lectures that family physicians have found invaluable. These handpicked 447 lectures are grouped into 30 topics based on feedback from hundreds of physicians. Each topic is set up as a distinct playlist for easier access. A sampling of topics includes cardiovascular diseases, infectious diseases, pediatric and adolescent medicine, digestive system diseases, mental and behavioral health, cancer, musculoskeletal diseases and nervous system diseases. Each lecture is CME-certified.

lp.audio-digest.org/Promotions/16/9/E/168ifmhp00?cid=ldi-homelp-email-comprev_p-fm_wk-20160905

Top Ten Data Integrity Traps: How to Find and Fix Problems

Author: U.S. Food and Drug Administration



This report helps to ensure manufacturing and lab data are reliable. It shows where most data integrity problems occur and helps create a plan to weed and keep them out. Included is information on the 10 areas to watch for data integrity violations: quality culture, batch records, manufacturing floor, raw versus recorded data, lab equipment, analytical documentation, document control, lab control procedures, material management and personnel.

www.fdanews.com/products/53463-top-ten-data-integrity-traps-how-to-find-and-fix-problems

PDR Drug Information Handbook — 2018 Edition

Author: PDR Network

This second edition of the *PDR Drug Information Handbook* provides professionals in healthcare an accurate, up-to-date and easily accessible guide for the most commonly prescribed drugs. Based on U.S. Food and Drug Administration-approved prescribing information, PDR's staff of pharmacists has developed concise monographs that highlight the most important information on each drug, including its approved use; dosages; interactions with other drugs, food and alcohol; side effects; safety information; and more. Clear, straightforward patient considerations outline essential information for proper assessment and monitoring, as well as counseling and drug administration guidance. In addition, this edition includes dozens of up-to-date product comparison and reference tables, reflecting the latest information and current practice standards.

www.ecampus.com/2018-pdr-drug-information-handbook-unknown/bk/9781563638428

GCP Questions, FDA Answers

Author: U.S. Food and Drug Administration (FDA)

In this report, FDA news' staff has culled through hundreds of questions submitted to the FDA's Office of Good Clinical Practice and curated more than 175 of the most relevant responses — segmented by category. Intended for the clinical trial professional, it includes information on how to conduct safe, effective, compliant trials that can win FDA approval. It also sheds light on some of the most difficult and important topics in clinical trial research, including dealing with protocol deviations; investigator responsibilities; communicating with trial subjects; inspections of clinical investigators and sites; monitoring investigators; submitting information to ClinicalTrials.gov; good documentation practices; laboratory certification; randomization procedures and unblinding; IND waivers; and recruitment advertising.

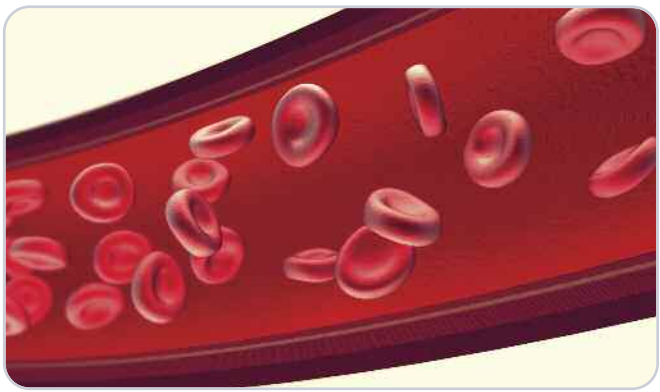
www.fdanews.com/products/53444

Reduced Mortality with Use of Four-Factor Prothrombin Complex Concentrates vs. FFP for Warfarin Reversal: Meta-Analysis

Coagulation factor replacement with either prothrombin complex concentrate (PCC) or fresh frozen plasma (FFP) are treatment options for urgent reversal of warfarin in patients who experience major bleeding or need urgent surgery, but the optimal reversal strategy is unclear based on clinically relevant outcomes. Canadian investigators conducted a systematic review of the clinical literature through December 2015, and identified five randomized clinical trials and eight observational studies for evaluation.

PCC use was associated with a significant reduction in all-cause mortality compared to FFP (odds ratio [OR], 0.56; 95% confidence interval [CI], 0.37 to 0.84; P = 0.006). Removing studies considered to have a high risk of bias did not importantly change this finding (OR, 0.59; CI, 0.39 to 0.89). Studies utilizing four-factor PCC accounted for 98% of the weight of evidence for this significant mortality difference.

PCC use additionally was more likely to achieve normalization of the international normalized ratio (INR) (OR, 10.80; CI, 6.12 to 19.07), resulted in a shorter time to INR correction (mean difference -6.50 hours; CI, -9.75 to -3.24) and was associated



with a lower risk of posttransfusion volume overload compared to FFP (OR, 0.27; CI, 0.13 to 0.58). There was no significant difference in the risk of thromboembolism following administration of PCC or FFP (OR, 0.91; CI, 0.44 to 1.89).

Chai-Adisaksopha C, Hillis C, Siegal DM, et al. Prothrombin complex concentrates versus fresh frozen plasma for warfarin reversal: A systematic review and meta-analysis. Thromb Haemost *2016 Oct 28;116(5):879-90.*

Topical Use of Fibrin Sealant Can Reduce Blood Loss and Need for Transfusion in Total Knee and Hip Arthroplasty

To assess the safety and effectiveness of topical administration of fibrin sealants on postoperative blood loss and blood requirements in patients undergoing total hip arthroplasty (THA) and total knee arthroplasty (TKA), Chinese investigators searched electronic medical databases through February 2016 to identify randomized clinical trials (RCTs) for inclusion in a meta-analysis. Evaluated outcomes included transfusion requirements, total blood loss, length of hospital stay and occurrence of infection. A total of 19 RCTs enrolling 1,489 patients (405 hip and 1,084 knee replacements) were included.

Results of the meta-analysis indicated that topical administration of a fibrin sealant can decrease the need for transfusion (relative risk [RR], 0.33; 95% confidence interval [CI], 0.28 to 0.40; P < 0.001), decrease total blood loss (mean difference [MD], -138.25 mL, CI, -203.49 to -75.00 mL), decrease blood drainage loss (MD, -321.44 mL; CI, -351.96 to -290.92 mL; P <0.001) and shorten the length of hospital stay (MD, -0.98 days; CI, -1.35 to -0.62 days; P < 0.001). There was no evidence of an increased risk of infection with use of fibrin sealants (RR, 0.87; CI, 0.33 to 2.27; P = 0.775). The investigators concluded that topical use of fibrin sealant can effectively reduce the need for transfusions, total blood loss and volume of postsurgical drainage without increasing the risk of infection.

Li J, Li HB, Zhai XC, et al. Topical use of fibrin sealant can reduce the need for transfusion, total blood loss and the volume of drainage in total knee and hip arthroplasty: A systematic review and meta-analysis of 1489 patients. Int J Surg *2016 Dec;36(Pt A):127-37.*

Medicare IVIG/SCIG Reimbursement Rates

Rates are effective April 1, 2017, through June 30, 2017

Product	Manufacturer	HCPCS	ASP + 6% (before sequestration)	ASP + 4.3%* (after sequestration)
CARIMUNE IVIG	CSL Behring	J1566	$65.28	$64.23
FLEBOGAMMA IVIG	Grifols	J1572	$60.35	$59.38
GAMMAGARD SD IVIG	Shire	J1566	$65.28	$64.23
GAMMAPLEX IVIG	Bio Products Laboratory	J1557	$83.23	$81.90
OCTAGAM IVIG	Octapharma	J1568	$72.17	$71.02
PRIVIGEN IVIG	CSL Behring	J1459	$77.73	$76.49
CUVITRU SCIG	Shire	J3490 / J3590 / J7799	**	**
HIZENTRA SCIG	CSL Behring	J1559	$98.26	$96.68
HYQVIA SCIG	Shire	J1575	$129.56	$127.48
GAMMAGARD LIQUID IVIG/SCIG	Shire	J1569	$80.86	$79.57
GAMMAKED IVIG/SCIG	Kedrion	J1561	$67.86	$66.77
GAMUNEX-C IVIG/SCIG	Grifols	J1561	$67.86	$66.77

* Reflects 2% sequestration reduction applied to 80% Medicare payment portion as required under the Budget Control Act of 2011.
** CUVITRU does not yet have Medicare rates.

Calculate your reimbursement online at www.FFFenterprises.com.

IVIG/SCIG Reference Table

Product	Manufacturer	Indication	Size
CARIMUNE NF Lyophilized	CSL Behring	IVIG: PI, ITP	6 g, 12 g
CUVITRU Liquid, 20%	Shire	SCIG: PI	1 g, 2 g, 4 g, 8 g
FLEBOGAMMA 5% DIF Liquid	Grifols	IVIG: PI	2.5 g, 5 g, 10 g, 20 g
FLEBOGAMMA 10% DIF Liquid			5 g, 10 g, 20 g
GAMMAGARD LIQUID 10%	Shire	IVIG: PI, MMN SCIG: PI	1 g, 2.5 g, 5 g, 10 g, 20 g, 30 g
GAMMAGARD S/D Lyophilized, 5% (Low IgA)	Shire	IVIG: PI, ITP, CLL, KD	5 g, 10 g
GAMMAKED Liquid, 10%	Kedrion	IVIG: PI, ITP, CIDP SCIG: PI	1 g, 5 g, 10 g, 20 g
GAMMAPLEX Liquid, 5%	Bio Products Lab	IVIG: PI, ITP	5 g, 10 g, 20 g
GAMUNEX-C Liquid, 10%	Grifols	IVIG: PI, ITP, CIDP SCIG: PI	1 g, 2.5 g, 5 g, 10 g, 20 g, 40 g
HIZENTRA Liquid, 20%	CSL Behring	SCIG: PI	1 g, 2 g, 4 g, 10 g
HYQVIA Liquid, 10%	Shire	SCIG: PI	2.5 g, 5 g, 10 g, 20 g, 30 g
OCTAGAM Liquid, 5%	Octapharma	IVIG: PI	1 g, 2.5 g, 5 g, 10 g
OCTAGAM Liquid, 10%		IVIG: ITP	2 g, 5 g, 10 g, 20 g
PRIVIGEN Liquid, 10%	CSL Behring	IVIG: PI, ITP	5 g, 10 g, 20 g, 40 g

CIDP Chronic inflammatory demyelinating polyneuropathy
CLL Chronic lymphocytic leukemia
ITP Immune thrombocytopenic purpura
KD Kawasaki disease
MMN Multifocal motor neuropathy
PI Primary immune deficiency disease

2016-2017 Influenza Vaccine

Administration Codes: G0008 (Medicare plans)
Diagnosis Code: V04.81

Manufacturer	Product	Presentation	Age Group	Code
TRIVALENT				
SEQIRUS	AFLURIA (IIV3)	5 ML multi-dose vial	5 YEARS AND OLDER*	90658/Q2035
		0.5 ML prefilled syringe, 10-BX		90656
SEQIRUS	FLUVIRIN (IIV3)	5 ML multi-dose vial	4 YEARS AND OLDER	90658/Q2037
		0.5 ML prefilled syringe, 10-BX		90656
SEQIRUS	FLUAD (aIIV3)	0.5 ML prefilled syringe, 10-BX	65 YEARS AND OLDER	90653
PROTEIN SCIENCES	FLUBLOK (RIV3)	0.5 ML single-dose vial, 10-BX	18 YEARS AND OLDER	90673
SANOFI PASTEUR	FLUZONE HIGH-DOSE (IIV3)	0.5 ML prefilled syringe, 10-BX	65 YEARS AND OLDER	90662
QUADRIVALENT				
SEQIRUS	FLUCELVAX (ccIIV4)	0.5 ML prefilled syringe, 10-BX	4 YEARS AND OLDER	90674
GSK	FLUARIX (IIV4)	0.5 ML prefilled syringe, 10-BX	3 YEARS AND OLDER	90686
GSK	FLULAVAL (IIV4)	0.5 ML single-dose syringe	6 MONTHS AND OLDER	90686
		5 ML multi-dose vial	6 MONTHS AND OLDER	90688
MEDIMMUNE	FLUMIST** (LAIV4)	0.2 ML live virus intranasal spray	2-49 YEARS	90672
SANOFI PASTEUR	FLUZONE (IIV4)	5 ML multi-dose vial	6-35 MONTHS	90687
			3 YEARS AND OLDER	90688
		0.5 ML prefilled syringe, 10-BX	3 YEARS AND OLDER	90686
		0.5 ML single-dose vial, 10-BX		90686
SANOFI PASTEUR	FLUZONE PEDIATRIC (IIV4)	0.25 ML prefilled syringe, 10-BX	6-35 MONTHS	90685
SANOFI PASTEUR	FLUZONE INTRADERMAL (IIV4)	0.1 ML prefilled microinjection, 10-BX	18-64 YEARS	90630

aIIV3 MF59-adjuvanted trivalent inactivated injectable
IIV3 Egg-based trivalent inactivated injectable
ccIIV4 Cell culture-based trivalent inactivated injectable
IIV4 Egg-based quadrivalent inactivated injectable
LAIV4 Egg-based live attenuated quadrivalent nasal spray
RIV3 Recombinant hemagglutinin trivalent injectable

* Age indication per package insert is ≥5 years; however, the Advisory Committee on Immunization Practices recommends Afluria not be used in children aged 6 months through 8 years because of increased reports of febrile reactions in this age group. If no other age-appropriate, licensed inactivated seasonal influenza vaccine is available for a child aged 5-8 years who has a medical condition that increases the child's risk for influenza complications, Afluria can be used; however, providers should discuss with the parents or caregivers the benefits and risks of influenza vaccination with Afluria before administering this vaccine.

Afluria may be used in persons aged ≥9 years.

** As of June 22, 2016, the CDC's ACIP voted against using the live attenuated influenza vaccine (LAIV), also known as nasal spray, during the 2016-2017 flu season. According to the CDC, data from the U.S. Influenza Vaccine Effectiveness Network showed a 3 percent vaccine effectiveness (VE) in study participants between 2 years and 17 years of age. This 3 percent estimate means no protective benefit could be measured, compared to traditional flu shots (IIV), which demonstrated a 63 percent VE against any flu virus among children 2 years to 17 years of age.

Replenish *and* Fulfill *your* Inventory *on-* Demand

Find out how our RFID-enabled inventory management solutions can impact your pharmacy.

FFF enterprises
Helping Healthcare Care®

Verified Inventory Program-Consignment™

Reduces Carrying Costs
Enables Continuous Monitoring
Automates Replenishment

Spend less time managing inventory and more time focusing on patient care.

To get started, email VIPManager@fffenterprises.com or call (800) 843-7477 ext. 1142

take control of your flu vaccine supply

with MyFluVaccine.com easy online ordering

YOU PICK THE DELIVERY DATE » Conveniently secure YOUR best delivery date(s)

YOU PICK THE QUANTITY » Choose from a broad portfolio of products

WE SAFELY DELIVER » Count on FFF's secure supply channel with Guaranteed Channel Integrity™

MyFluVaccine™
A PROGRAM OF FFF ENTERPRISES

YOU PICK THE DATE • YOU PICK THE QUANTITY • WE DELIVER

TO ORDER | MyFluVaccine.com | 800.843.7477