SUMMER 2015

biosupply trends

QUARTERLY

Special Focus: **VACCINES**

The Vaccination Gap

Closing In on the Decline

The Debate Over Mandatory Childhood Vaccines

Education and Storytelling to Address Vaccine Fears

HPV Vaccine: The Untapped Potential

The Escalating Diabetes Epidemic

Myths & Facts: Autism

Measles Makes a Comeback — Page 59

Half the volume
Twice the factor*

ALPHANATE® (antihemophilic factor/von Willebrand factor complex [human]) is now available in a **2000 IU FVIII vial** with a reconstitution volume of only **10 mL**.

*That's **TWICE** the amount of factor of the largest vial available for other FVIII/VWF products,[1-4] so patients may require:

- **Less volume**
- **Less time**
- **Fewer syringes**

Isn't it time you tried ALPHANATE?

Learn more at **alphanate.com**

Alphanate®
Antihemophilic Factor/von Willebrand Factor Complex (Human)

Indications

ALPHANATE® (antihemophilic factor/von Willebrand factor complex [human]) is indicated for:

- Control and prevention of bleeding in patients with hemophilia A
- Surgical and/or invasive procedures in adult and pediatric patients with von Willebrand disease (VWD) in whom desmopressin (DDAVP®) is either ineffective or contraindicated. It is not indicated for patients with severe VWD (Type 3) undergoing major surgery

Important Safety Information

ALPHANATE is contraindicated in patients who have manifested life-threatening immediate hypersensitivity reactions, including anaphylaxis, to the product or its components.

Anaphylaxis and severe hypersensitivity reactions are possible. Should symptoms occur, treatment with ALPHANATE should be discontinued, and emergency treatment should be sought.

Development of activity-neutralizing antibodies has been detected in patients receiving FVIII containing products. Development of alloantibodies to VWF in Type 3 von Willebrand disease (VWD) patients has been occasionally reported in the literature.

Thromboembolic events may be associated with AHF/VWF Complex (Human) in VWD patients, especially in the setting of known risk factors.

Intravascular hemolysis may be associated with infusion of massive doses of AHF/VWF Complex (Human).

Rapid administration of a FVIII concentrate may result in vasomotor reactions.

Plasma products carry a risk of transmitting infectious agents, such as viruses, and theoretically, the Creutzfeldt-Jakob disease (CJD) agent, despite steps designed to reduce this risk.

The most frequent adverse events reported with ALPHANATE in >5% of patients are respiratory distress, pruritus, rash, urticaria, face edema, paresthesia, pain, fever, chills, joint pain, and fatigue.

Please see brief summary of ALPHANATE full Prescribing Information on adjacent page.

You are encouraged to report negative side effects of prescription drugs to the FDA.
Visit www.fda.gov/medwatch, or call 1-800-FDA-1088.

References: 1. ALPHANATE® (antihemophilic factor/von Willebrand factor complex [human]) Prescribing Information. Grifols. **2.** CSL Behring. Humate P Package Insert. August 2013; **3.** Octapharma. Wilate Package Insert. January 2012; **4.** Kedrion. Koate-DVI Package Insert. August 2012.

For more information: **Grifols Biologicals Inc.**
Tel. 888-GRIFOLS (888-474-3657)

Grifols Biologicals Inc.
5555 Valley Boulevard, Los Angeles, 90032 CA - USA Tel. 888-GRIFOLS (888 474 3657)
www.grifols.com

GRIFOLS

ALPHANATE®

Antihemophilic Factor/von Willebrand Factor Complex (Human)

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Alphanate safely and effectively. See full prescribing information for Alphanate.

ALPHANATE (ANTIHEMOPHILIC FACTOR/VON WILLEBRAND FACTOR COMPLEX [HUMAN])

Sterile, lyophilized powder for injection.

Initial U.S. Approval: 1978

----------INDICATIONS AND USAGE ----------

Alphanate is an Antihemophilic Factor/von Willebrand Factor Complex (Human) indicated for:

- Control and prevention of bleeding in patients with hemophilia A.
- Surgical and/or invasive procedures in adult and pediatric patients with von Willebrand Disease in whom desmopressin (DDAVP) is either ineffective or contraindicated. It is not indicated for patients with severe VWD (Type 3) undergoing major surgery.

----------DOSAGE AND ADMINISTRATION ----------

For Intravenous use only.

Alphanate contains the labeled amount of Factor VIII expressed in International Units (IU) FVIII/vial and von Willebrand Factor:Ristocetin Cofactor activity in IU VWF:RCo/vial.

Hemophilia A: Control and prevention of bleeding episodes

- Dose (units) = body weight (kg) x desired FVIII rise (IU/dL or % of normal) x 0.5 (IU/kg per IU/dL).
- Frequency of intravenous injection of the reconstituted product is determined by the type of bleeding episode and the recommendation of the treating physician.

von Willebrand Disease: Surgical and/or invasive procedure in adult and pediatric patients except Type 3 undergoing major surgery

- Adults: Pre-operative dose of 60 IU VWF:RCo/kg body weight; subsequent doses of 40-60 IU VWF:RCo/kg body weight at 8-12 hour intervals post-operative as clinically needed.
- Pediatric: Pre-operative dose of 75 IU VWF:RCo/kg body weight; subsequent doses of 50-75 IU VWF:RCo/kg body weight at 8-12 hour intervals post-operative as clinically needed.

----------DOSAGE FORMS AND STRENGTHS ----------

- Alphanate is a sterile, lyophilized powder for intravenous injection after reconstitution, available as 250, 500, 1000, 1500 and 2000 IU FVIII in single dose vials.

----------CONTRAINDICATIONS ----------

- Patients who have manifested life-threatening immediate hypersensitivity reactions, including anaphylaxis, to the product or its components.

----------WARNINGS AND PRECAUTIONS ----------

- Anaphylaxis and severe hypersensitivity reactions are possible. Should symptoms occur, treatment with Alphanate should be discontinued, and emergency treatment should be sought.
- Development of activity-neutralizing antibodies has been detected in patients receiving FVIII containing products. Development of alloantibodies to VWF in Type 3 VWD patients has been occasionally reported in the literature.
- Thromboembolic events may be associated with AHF/VWF Complex (Human) in VWD patients, especially in the setting of known risk factors.
- Intravascular hemolysis may be associated with infusion of massive doses of AHF/VWF Complex (Human).
- Rapid administration of a FVIII concentrate may result in vasomotor reactions.
- Plasma products carry a risk of transmitting infectious agents, such as viruses, and theoretically, the Creutzfeldt-Jakob disease (CJD) agent, despite steps designed to reduce this risk.

----------ADVERSE REACTIONS----------

The most frequent adverse events reported with Alphanate in > 5% of patients are respiratory distress, pruritus, rash, urticaria, face edema, paresthesia, pain, fever, chills, joint pain and fatigue.

To report SUSPECTED ADVERSE REACTIONS, contact Grifols Biologicals Inc. at 1-888-GRIFOLS (1-888-474-3657) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------USE IN SPECIFIC POPULATIONS----------

- Pregnancy: No human or animal data. Use only if clearly needed.
- Pediatric Use: Hemophilia A - Clinical trials for safety and effectiveness have not been conducted. VWD - Age had no effect on PK.

GRIFOLS

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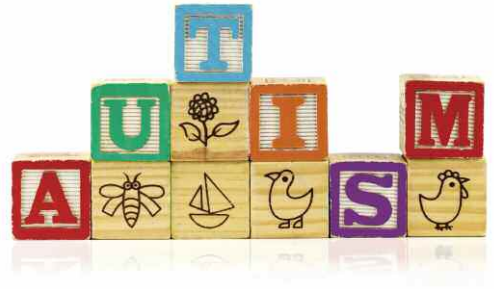
Summer 2015

Features

Special Focus: Vaccines



Up Front

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About BioSupply Trends Quarterly
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Addressing Declining Vaccination Rates

HAILED AS ONE of the most important advancements in the history of medicine, vaccines have saved the lives of hundreds of thousands of children and prevented hundreds of millions of childhood illnesses. Vaccines have been recommended for children since the 1940s, but it wasn't until 1995 that the official recommended immunization schedule for children appeared. Over the years, this schedule has evolved as vaccines have been added, removed and replaced due to the development of vaccines for new diseases and the success of vaccines in eradicating diseases.

A scant number of parents today are aware of a time when a startling number of children died before vaccines were developed. Consequently, a "vaccination gap" has resulted in fewer children receiving the recommended immunizations, and diseases that were once considered all but eliminated are reemerging. Now, with the recent measles outbreak at Disneyland, concerns about unvaccinated children possibly infecting others have stirred debate over whether vaccines should be mandatory and if religious and personal belief exemptions should be permitted. As new laws being proposed in nearly every state are challenged, our article "Mandatory Childhood Vaccines: The Debate" explores the constitutional foundation for requiring vaccines and the arguments from both sides.

As we note in our article "Measles Makes a Comeback," the measles outbreak at Disneyland infected 117 people — most of whom were unvaccinated — from 20 states and the District of Columbia. Prior to that, measles had been declared eliminated in the U.S. since the year 2000. With so little present-day experience with the disease, we share tips from the American Osteopathic Association for recognizing the signs of measles. These tips could have been useful for the families whose children were infected during the Disneyland outbreak, as well as for the healthcare professionals who treated them. In "Measles: A Patient's Perspective," we interviewed the parent of one of those children: the mother of 4-month-old Mobius, who had received his first round of vaccines before a family trip to Disneyland in mid-January. Although Mobius showed all the signs of measles, it was days before he was tested and still five days after testing until he was diagnosed.

Among the most recent additions to the recommended vaccines list is the three-dose HPV vaccination series. Although these cancer-preventing vaccines have led to declines in the disease in countries throughout the world, data released in 2014 showed that only 57 percent of girls and 34 percent of boys in the U.S. had completed the vaccine series. Our article "HPV Vaccine: A Dose of Untapped Potential" explains how the vaccines protect and why rates of vaccination are so low, including parents' concerns over the vaccines' safety and their belief that their children are too young to be exposed.

Despite the overwhelming historical proof of vaccines' success in reducing illness and death, an opposition element, "anti-vaxxers," dates back to the early 1900s. Currently, this small minority's opposition varies from a right to personal liberties, to religion and concerns about safety based on misinformation and anti-vaccine propaganda. Their objections pose a particular dilemma for healthcare providers: how to convince anti-vaxxers to vaccinate their children. Possible solutions are addressed in our article "Education and Storytelling: An Antidote to Parental Fears About Vaccine Safety."

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

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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.

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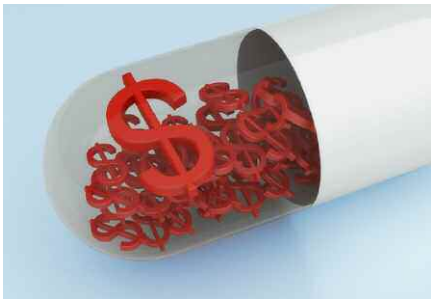
Pricing and Policies for Biosimilars Are Announced



The Centers for Medicare and Medicaid Services (CMS) plans to begin paying for biosimilars through its Part B, Part D and state coverage policies by this summer, according to a question-and-answer document released in April. As with standard drugs, coverage determinations will be based on the manufacturer's wholesale acquisition cost and the average sales price of the biosimilar. Medicare will pay 106 percent of the wholesale cost of the product until the average sales price can be determined, at which time coverage will be set at the average sales price plus 6 percent of the average price for the reference product.

The reimbursement codes for biosimilars, which are different than for their reference products, were expected to be released July 1, with reimbursements applying retroactively to the biosimilar's U.S. Food and Drug Administration's approval date — the first of which came in March for Sandoz's Zarxio (filgrastim-sndz). According to the Biotechnology Industry Organization, the distinct codes are a positive step because they recognize that biosimilars are not inherently identical to their reference products and will ensure CMS reimburses for them properly.

More guidelines will be released as necessary. The current policy documents can be accessed at www.fdanews.com/04-03-15-CMSbiosimilars.pdf. ❖

HHS Initiative Addresses Opioid-Related Drug Overdose, Death and Dependence

The U.S. Department of Health and Human Services has launched a $133 million initiative to reduce prescription opioid and heroin-related overdose, death and dependence. The initiative will focus on three priority areas:

1) Providing training and educational resources, including updated prescriber guidelines, to assist health professionals in making informed prescribing decisions and address the over-prescribing of opioids. This includes teaching medical professionals how and when to prescribe opioids by working with lawmakers on bipartisan legislation requiring specific training for safe opioid prescribing and establishing new opioid prescription guidelines for chronic pain; supporting data sharing for safe prescribing by facilitating prescription drug monitoring programs (PDMPs) and health information technology integration and further adoption of electronic prescribing practices; and increasing investments in state-level prevention interventions, including PDMPs, to track opioid prescribing and support appropriate pain management.

2) Increasing use of naloxone, as well as continuing to support the development and distribution of the lifesaving drug, to help reduce the number of deaths associated with prescription opioid and heroin overdose. This includes supporting the development, review and approval of new naloxone products and delivery options; promoting state use of Substance Abuse Block Grant funds to purchase naloxone; and implementing the Prescription Drug Overdose grant program for states to purchase naloxone and train first responders on its use.

3) Expanding the use of Medication-Assisted Treatment (MAT), a comprehensive way to address the needs of individuals that combines the use of medication with counseling and behavioral therapies to treat substance use disorders. This includes launching a grant program in FY2015 to improve access to MAT services through education, training and purchase of MAT medications for treatment of prescription opioid and heroin addiction; and exploring bipartisan policy changes to increase use of buprenorphine and develop the training to assist prescribing.

On March 6, the Centers for Disease Control and Prevention launched the Prescription Drug Overdose Prevention for States program to provide state health departments with resources to enhance their PDMPs and advance innovative prevention efforts. The funding will support approximately 16 states. ❖

HHS Contracts with BioCryst to Develop New Ebola Drug

The U.S. Department of Health and Human Services' Office of the Assistant Secretary for Preparedness and Response (ASPR) has awarded approximately $12 million to BioCryst Pharmaceuticals for the advanced development of a promising experimental drug for Ebola, including preparing for large-scale manufacturing of the drug and conducting related studies. BioCryst's drug, BCX4430, is a small molecule that prevents the Ebola virus from reproducing in the body. In non-human primate studies, the drug was effective against Ebola virus and Marburg virus, indicating that it may be useful as a broad spectrum antiviral drug.

With product development funding from the National Institutes of Health, BioCryst currently is conducting Phase I safety studies of BCX4430 in healthy volunteers. If these studies show the drug is safe, it could become one of the possible treatments tested for efficacy in clinical studies. While the studies are underway, the ASPR's Biomedical Advanced Research and Development Authority (BARDA) will support the company's ongoing efforts to improve manufacturing processes and scale up production in facilities in the United States. This work will help to increase product yield, reduce process steps and increase the scalability of manufacturing so that thousands of doses can be made with consistent product quality.

BCX4430 is the first small molecule drug to treat Ebola that BARDA has supported. If it proves to be safe and efficacious, BARDA could consider purchasing it under Project BioShield for the U.S. Strategic National Stockpile. ❖

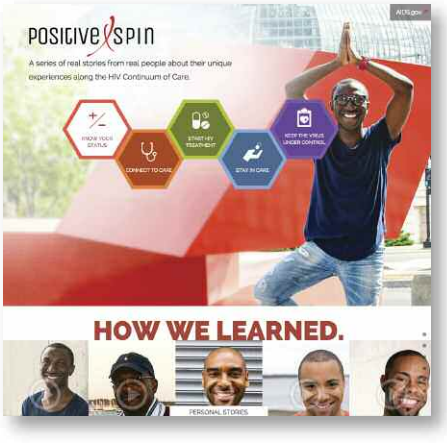
Medicare Rights Center Addresses Enrollment Pitfalls

The Medicare Rights Center has released a new *Medicare Snapshot: Stories from the Helpline* that addresses Medicare enrollment pitfalls and outlines needed improvements, including better notice for newly eligible Medicare beneficiaries, enhanced support for employers and other messengers, streamlined Medicare enrollment periods and expanded avenues for recourse. "Too frequently, individuals mistakenly delay or decline Part B enrollment because they are unaware of their rights and obligations," said Joe Baker, president of the Medicare Rights Center. "For those who fail to enroll in Part B in a timely manner, possible consequences include gaps in coverage, lifetime premium penalties and disruptions in accessing needed care. Costly and disruptive Medicare enrollment mistakes are increasingly common and deserve the attention of federal lawmakers."

The Medicare Snapshot also offers consumers advice. For assistance, beneficiaries and caregivers can visit Medicare Rights' informational website at www.medicareinteractive.org, or they can call the national helpline at (800) 333-4114. *Medicare Snapshot: Stories from the Helpline* is available at www.medicarerights.org/medicare-snapshot-april-2015.

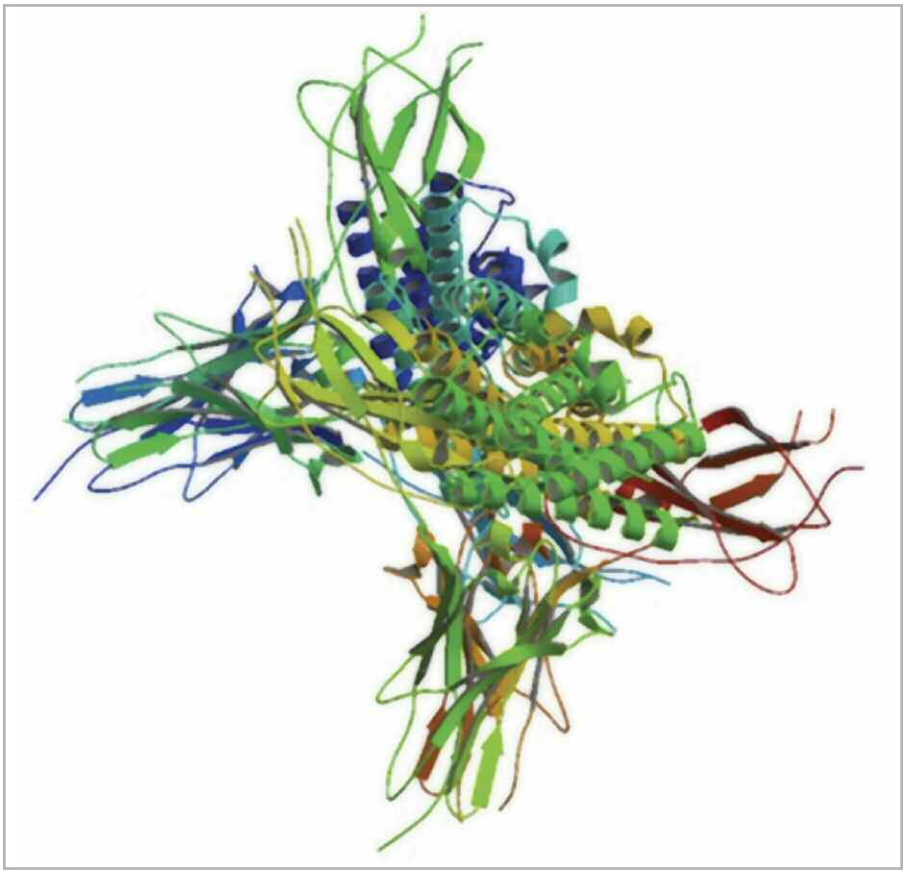
HHS Launches Digital HIV Educational Tool

Positive Spin, a comprehensive digital educational tool that uses personal storytelling to promote the importance of getting people with HIV into treatment, has been released by the U.S. Department of Health and Human Services. It features the personal experiences of five HIV-positive gay black men who have successfully navigated the HIV care continuum, from diagnosis to treatment and, ultimately, to viral suppression. Black gay and bisexual men are disproportionately affected by the domestic HIV epidemic. According to the Centers for Disease Control and Prevention, black men account for almost one-third (31 percent) of all new HIV infections in the U.S., and young black gay and bisexual men now account for more new infections than any other subgroup of gay and bisexual men by race/ethnicity and age. Federal, state and local agencies use data on the HIV care continuum to identify gaps in HIV services, develop strategies to improve engagement in care, determine how best to prioritize and target available resources, and monitor progress in their response to HIV.



Positive Spin was developed by AIDS.gov with input from federal agencies, healthcare professionals, persons living with HIV and community-based HIV organizations. It is available at https://positivespin.hiv.gov. ❖

Biosimilars Debut in the U.S.



Model, structure of filgrastim, European-Bioinformatics Institute (Wikipedia)

In light of the angst and hand-wringing over the soaring costs of biologic drugs that are alleged to be contributing to the unsustainability of biologic treatments, the U.S. Food and Drug Administration (FDA) approval of the first biosimilar in the U.S. was welcome news to many.

A biosimilar product is one that has shown it is highly similar to an already approved biological product, known as a reference product. In addition to similarity, a biosimilar must show it has no clinically meaningful differences in terms of safety and effectiveness from the reference product. Only minor differences in clinically inactive components are allowable.

Practices that understand this class of products, make definitive preparations and understand the payers' options for using them can potentially benefit their patients and their bottom line. But changes in patient and provider education programs will most likely be needed.

The Biosimilar Distinction

Biosimilars are distinct from generics. The active ingredients of generics are identical to the small molecule reference products because generic manufacturers can follow a specific formulation or recipe. This is not possible with biologic products that tend to have very large molecule structures leading to much higher development complexity for biosimilars, which renders biosimilars unique to each manufacturer and cell line.

In 2013, the top-eight best-selling biologics accounted for almost $63 billion in sales. These included Humira, Remicade, Rituxan, Enbrel, Lantus, Avastin, Herceptin and Neulasta. Lantus's patent expired in 2014; Neulasta's will expire in 2015. Humira's and Rituxan's will expire in 2016; Remicade's will expire in 2018; Avastin's and Herceptin's will expire in 2019; and Enbrel's will expire in 2028.[1]

Just as generic drugs introduced to market upon the expiration of the branded product brought choice of a less-expensive alternative, so too will biosimilar products introduced to market upon the expiration of the branded biologic product. But unlike generics, biosimilars will likely be priced at only a 20 percent to 40 percent discount compared with reference biologics. This is because biosimilar development is much more complex and costly largely due to the fact that they require far more clinical and nonclinical testing and a longer development period. Still, this is a significant potential savings given the total costs associated with biologics.

Biosimilars submitted to FDA for approval may be newly minted biologic products developed by U.S.-based pharmaceutical companies, or they may be biologic products already approved and used in other countries. Interestingly, the long-awaited U.S. move to ICD-10 classifications for diseases will make use of this comparative data considerably easier, since the rest of the world has been using this classification for many years.

The First U.S. Biosimilar

The first and only (at this time) biosimilar product in the U.S. — Zarxio (filgrastim-sndz) for the treatment of

infection in certain cancer patients undergoing chemotherapy — was approved by FDA on March 6. This product is a biosimilar version of Amgen Inc.'s Neupogen (filgrastim) and is the first U.S. biosimilar approved through an accelerated pathway authorized by the Affordable Care Act (ACA). The ACA amends the Public Health Service Act to create an abbreviated licensure pathway for biological products that are demonstrated to be "biosimilar" to or "interchangeable" with an FDA-licensed biological product.

At this early point, the actual market arrival and initial cost, as well as the final name for Zarxio (filgrastim-sndz), remain unclear. As of now, the "filgrastim" component defines the biologic and "sndz" defines the manufacturer. But two other decisions still need to be made by FDA: whether biosimilars can share the same nonproprietary names as their reference drugs, and what data FDA needs to determine that a biosimilar can be deemed interchangeable. The latter will take into account whether there are subtle differences with the terms "biosimilarity" and "interchangeability." This designation will determine the steps a pharmacy needs to take to fill the prescription or provide the drug upon receipt of a physician order. State regulations also play a role, and several are adding guidance to their regulations. ❖

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.*

Reference

1. Biologics Still on Top in Best-Selling Drugs in 2013. The Cell Culture Dish, March 13, 2014. Accessed at cellculturedish.com/2014/03/top-ten-biologics-2013-us-pharmaceutical-sales-2.

Payment for Biosimilars

The Centers for Medicare and Medicaid Services (CMS) issued a special edition of *MLN Matters* to answer some of the many reimbursement questions that arose after FDA approval of the first biosimilar product in the U.S.:

Question: How will a healthcare professional who administers this product get reimbursed under Medicare Part B?

Answer: Medicare Part B payment for newly approved drugs and biologicals is available once the product is approved by FDA. CMS will incorporate biosimilars that are approved under the abbreviated biological approval pathway into the average sales price (ASP) payment methodology, and issue additional guidance as necessary. Initially, once the manufacturer's wholesale acquisition cost (WAC) is available, Medicare will pay 106 percent of the WAC for the product until ASP information is available. Once ASP information is available for this biosimilar product, Medicare payment will equal the ASP for the biosimilar product plus 6 percent of the ASP for the reference product.

Question: How soon will CMS be releasing coding information related to Part B reimbursement?

Answer: CMS anticipated including the approved biosimilar in the next quarterly Healthcare Common Procedure Coding System (HCPCS) tape release, appearing in the claims processing system on July 1, effective retroactively to the FDA approval date.

Question: Will CMS be assigning unique codes to each biosimilar released?

Answer: CMS will create a separate code to distinguish the biosimilar from the reference biological. CMS is considering policy options for coding of additional biosimilars, and will release further guidance in the future.

Question: Will use of a distinguishing identifier to biological products make it harder to achieve Medicare reimbursement?

Answer: Distinguishing identifiers will have no bearing on coding and payment.

Question: How will CMS address providing access to biosimilars through Medicare Part D?

Answer: Although coverage for filgrastim will generally be provided through Part B, it could also be covered under Part D in certain circumstances (for example, nursing homes or intermediate care facilities for individuals with intellectual disabilities). CMS will be releasing guidance to plans confirming that biosimilars approved by FDA will be subject to existing rules for prescription drugs under Part D.

Reference

Questions and Answers About Biosimilar Products. *MLN Matters* Number: SE1509. Accessed at www.cms.gov/Outreach-and-Education/Medicare-Learning-Network-MLN/MLNMattersArticles/Downloads/SE1509.pdf.

Manufacturer News

Grifols Invests in Alkahest to Develop Plasma-Based Products

Grifols, a global healthcare company and producer of plasma therapies, has made a major equity investment in Alkahest, a privately held biopharmaceutical company, to work together to develop novel plasma-based products for the treatment of cognitive decline in aging and disorders of the central nervous system (CNS), including Alzheimer's. Alkahest was founded upon the pioneering work of Dr. Tony Wyss-Coray and other leading scientists at Stanford University who demonstrated that factors in the blood of young animals were able to restore mental capabilities in old animals. In their study published online in the May 4, 2014, edition of *Nature Medicine*, the scientists characterized important molecular, neuroanatomical and neurophysiological changes in the brains of old mice that shared the blood of young mice. Alkahest is now conducting clinical studies to determine if this promising data in animals can be translated to humans.

Grifols has acquired 45 percent of the equity of Alkahest for $37.5 million. In addition, Grifols will provide another payment of $12.5 million and fund the development of plasma-based products, which may be commercialized by Grifols. "The investment and collaboration of Alkahest will expand our research and development in fields that address one of the major unmet medical needs of this century and extend our footprint in one of the world's leading centers for biomedical innovation," said Victor Grifols, president and CEO of Grifols. "Alkahest's research activities are an extension of Grifols' long commitment to identify and develop significant therapies from human plasma for cognitive and other CNS disorders."

For more information on Grifols' research, see the article "Saving the Aging Brain: Grifols Attacks Alzheimer's Disease Head-On" in the Winter 2015 issue of *BioSupply Trends Quarterly* at www.BSTQuarterly.com. ❖

Research

Study Shows No Link Between Autism and Measles Vaccine

A recent study found no link between the measles vaccine and autism. In the study, data on 95,000 children and their older siblings, including almost 2,000 with an older sibling with autism spectrum disorder (ASD), were examined to assess risk among those already at higher likelihood of developing autism because of a family connection. They found "no harmful association between the MMR [measles, mumps, rubella] vaccine receipt and ASD even among children already at high risk for ASD," according to study authors, led by Anjali Jain of the Lewin Group, a healthcare consulting firm.

The study, which was funded by the National Institutes of Health and the Department of Health and Human Services, used claims data from a large commercial health plan, the Optum Research Database, part of insurer UnitedHealth. It illuminated reluctance among some parents to immunize their children if an older sibling has been diagnosed with autism. Research has

shown that a child has a higher likelihood of developing autism if he or she has an older sibling with ASD. In the study, among kids whose siblings didn't have autism, the MMR vaccination rate was 84 percent at age 2 and 92 percent at age 5. For kids with older siblings with autism, the vaccination rates were lower: 73 percent at age 2 and 86 percent at age 5. This data is particularly concerning because the vaccination rates drop below the 92 percent to 95 percent thought to be required for herd immunity.

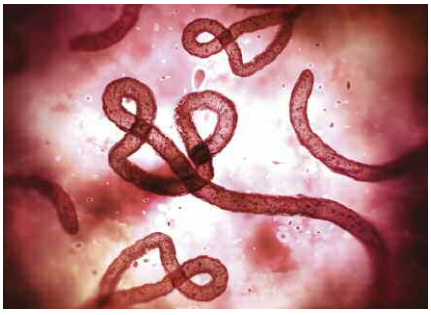
"The only conclusion that can be drawn from the study is that there is no signal to suggest a relationship between MMR and the development of autism in children with or without a sibling who has autism," explains Dr. Bryan King, a researcher at Seattle Children's Autism Center and the University of Washington. "Taken together, some dozen studies have now shown that the age of onset of ASD does not differ between vaccinated and unvaccinated children, the severity of course of ASD does not differ between vaccinated and unvaccinated children, and now the risk of ASD recurrence in families does not differ between vaccinated and unvaccinated children."

The study was published April 21 in *The Journal of the American Medical Association*. ❖

Tirrell M. Autism Shown to Have No Link to Measles Vaccine. CNBC, April 21, 2015. Accessed at www.cnbc.com/id/102605133.

Research

GSK Ebola Shot Is Safe and Provokes an Immune Response



Results from a human trial of GlaxoSmithKline's Ebola vaccine show it is safe and generates an immune response. In the early stage Phase I trial primarily designed to test safety, 60 healthy volunteers were given the vaccine in Britain between Sept. 17 and Nov. 18. The volunteers received one of three doses: low, medium or high. Data from 28 days after vaccination showed the shot was safe at these doses with only mild side effects. "The safety profile is pretty much as we'd hoped, and the immune responses are OK, but not great," said Adrian Hill, who led the work at Oxford's Jenner Institute. "People typically experienced mild symptoms that lasted for one or maybe two days such as pain or reddening at the injection site, and occasionally people felt feverish." However, the antibody response was weaker than was found in a trial of the same Ebola vaccine in macaque monkeys, in which the animals were also found to be protected. According to Hill, the lower antibody levels, together with a lower response detected in the immune system's T cells, suggest that a booster may be needed. ❖

Medicines

Novo Nordisk Launches Novoeight for Hemophilia A in the U.S.

Novo Nordisk has launched Novoeight (antihemophilic factor [recombinant]) in the U.S. for people living with hemophilia A. Compared with other recombinant factor VIII products, Novoeight offers purity through a five-step purification process and enhanced portability. It can also be kept at the highest storage temperature for the longest period of time (up to 86 degrees Fahrenheit for 12 months). And, it can be kept at that temperature for up to four hours after reconstitution, giving it the longest postreconstitution storage time. The product was shown to be safe and effective in clinical trials with zero inhibitors confirmed in 213 previously treated patients with hemophilia A.

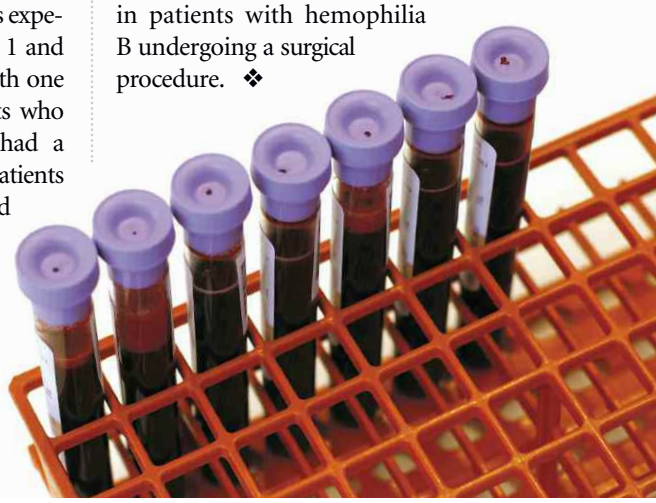
The U.S. Food and Drug Administration approved Novoeight for use in adults and children with hemophilia A for the control and prevention of bleeding, perioperative management and routine prophylaxis to prevent or reduce the frequency of bleeding episodes based on results from the guardian trials, one of the largest and most comprehensive clinical trial programs of a recombinant factor VIII to date. Ninety-one percent of bleeds experienced by patients in the guardian 1 and guardian 3 trials were controlled with one or two doses of Novoeight. Patients who took Novoeight prophylactically had a median of 3.1 bleeds per year. Patients from those trials who continued prophylaxis with Novoeight in a safety extension trial had a median of 1.7 bleeds per year. The most common adverse reactions were injection site reactions (2.3 percent), increased hepatic enzymes (1.4 percent) and pyrexia (0.9 percent). ❖

Medicines

FDA Accepts BLA for CSL's rIX-FP for Hemophilia B Patients

CSL Behring's Biologics License Application for the marketing authorization of its long-acting fusion protein linking recombinant coagulation factor IX with recombinant albumin (rIX-FP) has been accepted for review by the U.S. Food and Drug Administration. When approved, rIX-FP will provide hemophilia B patients with a long-acting treatment option with dosing intervals up to 14 days. CSL engineered rIX-FP to extend the half-life of recombinant factor IX through genetic fusion with recombinant albumin due to its long physiological half-life, as well as its good tolerability profile, low potential for immunogenic reactions and a well-known mechanism of clearance.

CSL's BLA is based on the results from the Phase II/III study in the PROLONG-9FP program, which compared the change in frequency of spontaneous bleeding events between on-demand treatment and a weekly prophylaxis regimen in patients ages 12 to 61 years who develop inhibitors against factor IX. The study evaluated multiple prophylaxis regimens, including seven-day and 14-day intervals. A sub-study evaluated the prevention and control of bleeding in patients with hemophilia B undergoing a surgical procedure. ❖



Infectious Disease Guidelines

Pediatrics Academy Updates Measles Recommendations

In response to the national measles outbreak, the American Academy of Pediatrics has released updated measles guidelines on its website. The new guidelines from the Academy's *Red Book: 2015 Report of the Committee on Infectious Diseases* weren't scheduled for publication until May, but the academy made the chapter available online earlier to give clinicians immediate access to the updated recommendations. Following are highlights of the changes to the guidelines:

• Any of the following constitutes evidence of immunity to measles: 1) documentation of age-appropriate vaccination with a live measles virus-containing vaccine (one dose for preschool-aged children, two doses for children in kindergarten through 12th grade), 2) laboratory evidence of immunity, 3) laboratory confirmation of disease or 4) birth before 1957.

• Clinicians can administer immune globulin either intramuscularly or intravenously within six days of exposure to prevent or modify measles response in people who lack evidence of measles immunity.

• The measles, mumps and rubella vaccine is recommended for everyone older than 12 months who is infected by HIV, except those who have evidence of severe immunosuppression. And, HIV-infected children who are exposed to measles should be given immune globulin prophylaxis, depending on their immune status and measles vaccine history.

• For healthcare personnel, including students who may be in contact with patients with measles, immunization programs should be implemented. And, birth before 1957 isn't a guarantee of measles immunity; therefore, facilities should consider vaccination of unimmunized healthcare personnel who lack laboratory evidence of immunity who were born before 1957.

• Immunodeficiency and immunosuppressed patients exposed to measles can best be managed with previous knowledge of patients' immune status.

• Children should receive measles vaccination prior to treatment with biological response modifiers such as tumor necrosis factor antagonists.

• Susceptible patients with immunodeficiencies should receive immune globulin after measles exposure.

• Live-virus measles vaccines are not recommended for immunocompromised patients with disorders associated with increased severity of viral infections (except people with HIV who do not have evidence of severe immunosuppression).

• Immunization is not recommended for at least a month after a patient has finished a high-dose course of corticosteroids such as prednisone.

To view the updated chapter online, go to redbook.solutions.aap.org/DocumentLibrary/2015RedBookMeasles.pdf. ❖

Research

Shingles Vaccine Developed That Is 97 Percent Effective

GlaxoSmithKline has developed a new shingles vaccine that is 97 percent effective in adults ages 50 years to 70 years, the main group affected by the virus. In the study reported on in the *New England Journal of Medicine*, only six out of 7,698 patients given the new vaccine became infected with shingles over a three-year period compared with more than 200 people in a similar-sized control group who were not given the vaccine.

Shingles is a skin rash that causes painful blisters around the body caused by the virus responsible for chickenpox, which 95 percent of people get before they are adults. The virus is protected by the immune system until it is reactivated, an event more likely to occur in people over age 50 when their T cell immunity wanes. The new vaccine stimulates those T cells. "We didn't expect that degree of efficacy," said Tony Cunningham, one of the scientists involved in the vaccine and the chief scientist at the Westmead Millennium Institute for Medical Research in Australia. "This is the first big success for this type of strategy." The world's first shingles vaccine, Zostavax, offers protection in only about 50 percent of the population. The new vaccine now needs regulatory approval before it becomes available for patients. ❖

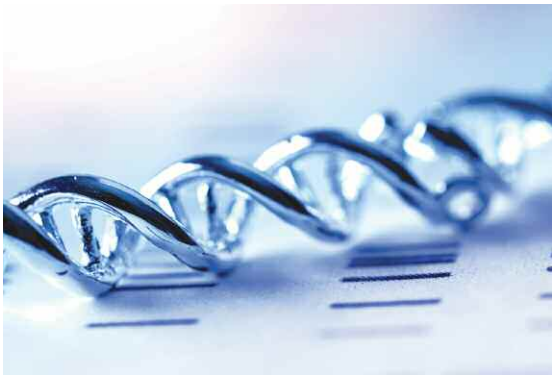
Phillips N. GlaxoSmithKline Develop Shingles Vaccine that Is 97 Per Cent Effective in Adults. *The Sydney Morning Herald*, April 28, 2015. Accessed at www.smh.com.au/technology/sci-tech/glaxosmithkline-develop-shingles-vaccine-that-is-97-per-cent-effective-in-adults-20150428-1mvb7y.html.

Research

Immune Disorders Genetic Missing Link Found

An international team of researchers has identified a gene that may be a missing link between overactive and underactive immune activity, and that may also play a key role in autoimmune diseases. In the study, scientists searched for genetic differences between 778 patients with common variable immunodeficiency (CVID) and 11,000 control patients, all from the U.S., U.K., Germany, Sweden and Norway. In 2011, Hakon Hakonarson, MD, PhD, director of the Center for Applied Genomics at The Children's Hospital of Philadelphia, and colleagues had discovered that CVID was linked to the HLA-related gene region on chromosome 6p21, which the current study confirmed. That gene region codes for the HLA (human leukocyte antigen) complex, a well-known group of proteins that helps recognize invading microorganisms. However, in this study, the investigators additionally found a robust, novel candidate for a risk gene in CVID: the CLEC16A gene region on chromosome 16p13.13. "This is the first risk susceptibility gene for CVID identified by a genome-wide association study that does not code for the HLA complex," said Dr. Hakonarson, adding that the CLEC16A gene region offers a very compelling target for understanding CVID.

In the current study, the international research team showed that mice with reduced activity in the corresponding animal gene had lower levels of B cells, the immune cells that are depleted in the human disease. In addition, previous genetic studies by Dr. Hakonarson and other researchers found that changes in CLEC16A raised the risk of type 1 diabetes, inflammatory bowel disease and other autoimmune disorders. "The biological mechanisms that cause disease symptoms in CVID are still unclear," said Dr. Hakonarson, "but this study may suggest that altered function in CLEC16A and its associated proteins may represent a 'missing link' between



immunodeficiency and autoimmunity in CVID. This may offer new opportunities for eventually designing more effective treatments."

The study was published in the April 20 online edition of *Nature Communications*. ❖

Gene Therapy Shows Promise for Rare Immune Disorder. HealthDay, April 22, 2015. Accessed at consumer.healthday.com/diseases-and-conditions-information-37/misc-diseases-and-conditions-news-203/gene-therapy-immune-disorder-jama-release-batch-1707-698535.html.

Reimbursement

Octapharma USA Launches Co-Pay Program for Wilate

Octapharma USA has launched the Octapharma Co-Pay Assistance Program available to von Willebrand's disease patients who are currently receiving Wilate (von Willebrand factor/coagulation factor VIII complex [human]) or have a prescription to begin therapy. The new program offers eligible patients a maximum of $6,000 annually for co-pay, co-insurance and deductible expenses associated with their treatment without regard for their ability to pay. Patients must have third-party commercial insurance to participate in the program.

"We realize that patient out-of-pocket expenses associated with healthcare can sometimes be daunting; therefore, Octapharma has committed to support a program specifically designed to supplement these costs," said Octapharma USA President Flemming Nielsen. To enroll in the program, eligible patients should contact the Octapharma Support Center at (800) 554-4440. The program is not available to patients who are covered under Medicaid, Medicare, MediGap, VA, DOD, Tricare or any other state or federal medical or pharmaceutical benefit program or pharmaceutical assistance program. Patients must be residents of the U.S. ❖

People and Places in the News

ACQUISITION

Novo Nordisk has signed an agreement with **Janssen Biotech Inc.** for Janssen to acquire an exclusive global license to further develop and commercialize a clinical program focused on therapy within autoimmune diseases. ❖

Medicines

FDA Finalizes Guidance Documents on Biosimilars

The U.S. Food and Drug Administration (FDA) has finalized three guidance documents outlining its expectations for biosimilars. The first is a question-and-answer document outlining how FDA interprets the Biological Price Competition and Innovation Act, including its provisions on exclusivity, biosimilarity and interchangeability. Some of the high-level expectations for biosimilars include:

• Biosimilars may be formulated differently than the drug they reference in an application, but must be supported by data indicating that such differences are minor and do not result in "meaningful differences" in safety, purity and potency.

• Differences in the delivery device or container system may also be acceptable as long as differences in the delivery do not result in clinically meaningful differences and do not employ a different route of administration.

• A biosimilar product may be approved for some of the strengths for which a reference product has obtained approval. It does not need to obtain licensure for all strengths.

• Sponsors may rely on comparative animal or clinical data using a non-U.S.-licensed product to support an indication of biosimilarity. "However, as a scientific matter, analytical studies and at least one clinical pharmacokinetic (PK) study and, if appropriate, at least one pharmacodynamic (PD) study, intended to support a demonstration of biosimilarity must include an adequate comparison of the proposed biosimilar product directly with the U.S.-licensed reference product unless it can be scientifically justified that such a study is not needed."

The second document details the quality factors companies need to take into account when characterizing a biosimilar product. Specifically, the document states: "Sponsors should use appropriate analytical methodology that has adequate sensitivity and specificity to detect and characterize differences between the proposed product and the reference product." In addition, it states that companies are required by law "to include data supporting the analytical similarity of the proposed biosimilar product to the reference product."

The third document explains FDA's recommended approach for demonstrating biosimilarity using scientific data. According to the document: "As a scientific matter, analytical studies and at least one clinical PK study, and if appropriate, at least one PD study, intended to support a demonstration of biosimilarity for purposes of section 351(k) of the PHS Act must include an adequate comparison of the proposed biosimilar product directly with the U.S.-licensed reference product unless it can be scientifically justified that such a study is not needed." And, it states that FDA encourages a "stepwise approach": "At each step, the sponsor should evaluate the extent to which there is residual uncertainty about the biosimilarity of the proposed product and identify next steps to try to address that uncertainty."

The documents can be downloaded at www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM444661.pdf, www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291134.pdf and www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291128.pdf. ❖

Research

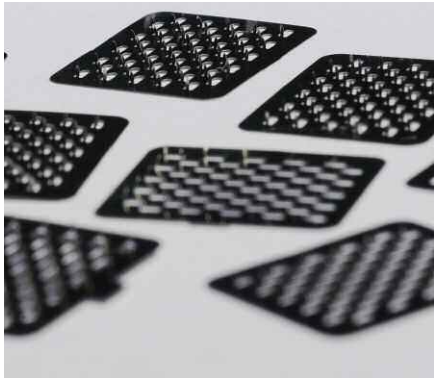
New Anti-Aging Drug Could Improve Seniors' Immune Systems

A new experimental drug could boost the immune system in older adults by as much as 20 percent, as well as help them to delay other aging effects. In a recent study, more than 200 seniors received either rapamycin, an mTOR inhibitor, or a placebo over a few weeks, after which they were given a flu shot. Participants who received the experimental version of rapamycin had 20 percent more antibodies to fight the flu, as well as lowered levels of white blood cells linked to age-related immune decline.

Dr. Nir Barzilai, anti-aging expert at the Institute for Aging Research in New York City, said that the study was a "watershed" juncture for anti-aging research. Rapamycin was previously tested and proven successful in counteracting aging effects in mice and other mammals, and this new study is one of the first to prove that rapamycin delays the aging process in humans, too. In addition to aging-related effects (such as diseases), the drug could also improve everything about aging. The researchers hope that the new drug will help them develop immune-boosting drugs for aging people, but more study and clinical tests are required. ❖

Vaccine

Scientists Develop Needle-Free Measles Vaccine



Scientists at Georgia Institute of Technology have developed a needle-free vaccine against measles that the Centers for Disease Control and Prevention (CDC) is calling a "game-changer." The vaccine, administered via a stick-on patch that is an inch square and is covered with tiny, dissolvable needles that soak into the skin in minutes, doesn't have to be kept at a constant cool temperature, and it doesn't need to be administered by anyone with special training. The hope is to be able to mail these vaccines to people to self-administer or to send them to minimally trained technicians to give them to people living in hard-to-reach areas.

The researchers had been working to develop a microneedle patch against influenza when CDC helped them come up with a formula against measles. "It took some work," said Mark Prausnitz, a professor of biomolecular engineering at Georgia Tech, who is leading the vaccine patch team. "The additives that we put into the vaccine had to be different." Measles is made using a live, but weakened, vaccine, so it took some "tinkering" to make a formula that would keep that virus viable on the patch instead of in a vial full of liquid. But, in animal tests, the needle-free vaccine worked well, and the team says it now needs to test it in people.

"Microneedle technology could move the Global Vaccine Action Plan forward by leading to improved protection against other diseases, including polio, influenza, rotavirus, rubella, tuberculosis and others," said a spokesperson for CDC. "CDC is also collaborating with Georgia Tech to see if microneedles could be used to administer inactivated polio vaccine." ❖

Fox M. New Measles Vaccine Is Needle-Free. NBC News, April 27, 2015. Accessed at www.nbcnews.com/health/health-news/new-measles-vaccine-needle-free-n349251.

Technology

New Method to Alleviate Shortage of Plasma Therapies

Plasma Tech Biopharmaceuticals has developed a new and innovative method to extract plasma proteins from pooled human plasma samples in order to alleviate the potential shortage of available plasma-based therapies. Currently, the Cohn Cold fractionation process has been the most common protocol for plasma protein extraction since its inception in the 1940s, with an extraction rate of 7 percent from blood (with plasma concentration of 1.8 grams to 3.5 grams per liter). The new method, called the Optimized Plasma Process, increases the yield by ten-fold, recovering almost 70 percent of plasma. The technique is expected to be helpful for increasing the availability of plasma therapies to treat immune disorders, autoimmune disease, neuropathies and a host of other diseases currently being researched. ❖

Accessed at lungdiseasenews.com/2015/04/20/novel-plasma-protein-extraction-technology-to-improve-access-to-plasma-for-copd-other-disease-treatments.

Research

Parkinson's Gene Is Linked to Lung Cancer

Researchers have identified a Parkinson's gene that is associated with lung cancer. The researchers, located at the Medical College of Wisconsin (MCW) and the Genetic Epidemiology of Lung Cancer Consortium, identified the gene using whole exome sequencing, which showed a link between a mutation in PARK2, a gene associated with early-onset Parkinson's disease, and familial lung cancer. They first sequenced the exomes (protein coding region of the genome) of individuals from a family with multiple cases of lung cancer, and then studied the PARK2 gene in additional families affected by lung cancer. Their findings showed a significant association between the PARK2 mutation and the families with multiple cases of lung cancer.

"These results implicate this specific mutation as a genetic susceptibility factor for lung cancer, and provide an additional rationale for further investigations of this gene and this mutation for evaluation of the possibility of developing targeted therapies against lung cancer in individuals with PARK2 variants," said Ming You, MD, PhD, the Joseph F. Heil Jr. professor of oncogenesis at MCW and director of the MCW Cancer Center. ❖

Live Life Fully

Gammaplex®

Immune Globulin Intravenous (Human), 5% Liquid

Gammaplex is proven protection

> In 50 patients with PID*, no serious acute bacterial infections were reported during a 12-month trial with Gammaplex[1]

> In 35 patients with ITP† given two days of treatment with Gammaplex, 83% achieved platelet counts ≥50 x 10^9/L by day 9 of the trial[2]

Gammaplex infusion rate can be increased every 15 minutes as tolerated[1,3]

Gammaplex is a pure IVIG product with favorable product characteristics[4]

> Low IgA content
> Low percentage of aggregates
> Viscosity similar to plasma

* PID = primary immunodeficiency
† ITP = immune thrombocytopenic purpura

In clinical studies, the most common adverse reactions with Gammaplex were headache, pyrexia, vomiting, fatigue, pain, nausea, hypertension, chills and myalgia.

For more information visit **www.gammaplex.com**

Please see the Brief Summary of Prescribing Information, including boxed warning, on accompanying page.

IMPORTANT SAFETY INFORMATION

Gammaplex® (immune globulin intravenous [human], 5% liquid) is indicated for the replacement therapy in adults with primary humoral immunodeficiency (PI). This includes, but is not limited to, the humoral immune defect in common variable immunodeficiency, X-linked agammaglobulinemia, congenital agammaglobulinemia, Wiskott-Aldrich syndrome and severe combined immunodeficiencies.

Gammaplex is also indicated for the treatment in adults with chronic immune thrombocytopenic purpura (ITP).

Thrombosis may occur with immune globulin products, including Gammaplex. Risk factors may include: advanced age, prolonged immobilization, hypercoagulable conditions, history of venous or arterial thrombosis, use of estrogens, indwelling central vascular catheters, hyperviscosity and cardiovascular risk factors. Thrombosis may occur in the absence of known risk factors.

Renal dysfunction, acute renal failure, osmotic nephrosis, and death may occur in predisposed patients who receive immune globulin intravenous (IGIV) products, including Gammaplex.

Patients predisposed to renal dysfunction include those with any degree of pre-existing renal insufficiency, diabetes mellitus, age greater than 65, volume depletion, sepsis, paraproteinemia, or patients receiving known nephrotoxic drugs. Renal dysfunction and acute renal failure occur more commonly in patients receiving IGIV products containing sucrose. Gammaplex does not contain sucrose.

For patients at risk of thrombosis, renal dysfunction or acute renal failure, administer Gammaplex at the minimum dose and infusion rate practicable. Ensure adequate hydration in patients before administration. Monitor for signs and symptoms of thrombosis and assess blood viscosity in patients at risk for hyperviscosity.

Gammaplex is contraindicated in patients who have had a history of anaphylactic or severe systemic reactions to human immune globulin; an hereditary intolerance to fructose and in infants and neonates for whom sucrose or fructose tolerance has not been established; and IgA deficient patients with antibodies to IgA and a history of hypersensitivity.

Thrombotic events may occur following treatment with immune globulin products, including Gammaplex. Monitor patients with known risk factors for thrombotic events; consider baseline assessment of blood viscosity for those at risk of hyperviscosity.

In patients at risk of developing acute renal failure, monitor renal function, including blood urea nitrogen (BUN), serum creatinine and urine output. Hyperproteinemia, increased serum viscosity, and hyponatremia may occur in patients receiving IGIV therapy.

Aseptic meningitis syndrome (AMS) may occur infrequently with IGIV treatment. AMS usually begins within several hours to 2 days following IGIV treatment. Discontinuation of IGIV treatment has resulted in remission of AMS within several days without sequelae. AMS may occur more frequently in association with high doses (2 g/kg) and/or rapid infusion of IGIV.

Hemolysis and hemolytic anemia can develop subsequent to IGIV treatments. Patient risk factors that may be associated with development of hemolysis include high dose (>2 g/kg), non-O blood group, and underlying inflammatory state. Noncardiogenic pulmonary edema may occur in patients following IGIV treatment (i.e. transfusion-related acute lung injury [TRALI]). Monitor patients for pulmonary adverse reactions (TRALI). If TRALI is suspected, test product and patient's serum for anti-neutrophil antibodies.

Gammaplex is made from human plasma and may contain infectious agents, e.g. viruses and, theoretically, the Creutzfeldt-Jakob disease agent. No cases of transmission of viral diseases or CJD have been associated with the use of Gammaplex.

In clinical studies, the most common adverse reactions with Gammaplex were headache, pyrexia, vomiting, fatigue, pain, nausea, hypertension, chills and myalgia.

Serious adverse reactions observed in clinical trial subjects with PI were thrombosis and chest pain. Serious ARs observed in clinical trial subjects with ITP were headache, vomiting and dehydration.

Please refer to the Gammaplex Prescribing Information for full prescribing details.

REFERENCES

1. Moy JN, Scharenberg AM, Stein AR, et al. *Clin Exp Immunol.* 2010;162:510-515.
2. Dash CH, et al. *PLoS ONE.* 2014;9(6):e96600.
3. Gammaplex® (Immune Globulin Intravenous [Human], 5% Liquid) Prescribing Information. Raleigh, NC: BPL Limited. 2014.
4. Data on file, BPL: December 2011

bpl
Bio Products Laboratory
a commitment for life

For product information and inquiries, please call **(866) 398-0825** or email BPLinfo@LashGroup.com

December 2014 US/Gx/1214/0020 Printed in USA

Gammaplex®

Immune Globulin Intravenous (Human), 5% Liquid

BRIEF SUMMARY

CONSULT FULL PRESCRIBING INFORMATION FOR COMPLETE PRODUCT INFORMATION

WARNING: THROMBOSIS, RENAL DYSFUNCTION and ACUTE RENAL FAILURE

Thrombosis may occur with immune globulin products, including Gammaplex. Risk factors may include: advanced age, prolonged immobilization, hypercoagulable conditions, history of venous or arterial thrombosis, use of estrogens, indwelling central vascular catheters, hyperviscosity and cardiovascular risk factors. Thrombosis may occur in the absence of known risk factors. Renal dysfunction, acute renal failure, osmotic nephrosis, and death may occur in predisposed patients who receive immune globulin intravenous (IGIV) products, including Gammaplex. Patients predisposed to renal dysfunction include those with any degree of pre-existing renal insufficiency, diabetes mellitus, age greater than 65, volume depletion, sepsis, paraproteinemia, or patients receiving known nephrotoxic drugs. Renal dysfunction and acute renal failure occur more commonly in patients receiving IGIV products containing sucrose. Gammaplex does not contain sucrose. For patients at risk of thrombosis, renal dysfunction or acute renal failure, administer Gammaplex at the minimum dose and infusion rate practicable. Ensure adequate hydration in patients before administration. Monitor for signs and symptoms of thrombosis and assess blood viscosity in patients at risk for hyperviscosity.

INDICATIONS AND USAGE

Primary Humoral Immunodeficiency (PI) - Gammaplex is an Immune Globulin Intravenous (Human), 5% Liquid indicated for replacement therapy in adults with primary humoral immunodeficiency (PI). Chronic Immune Thrombocytopenic Purpura (ITP) - Gammaplex is indicated for the treatment of adults with chronic immune thrombocytopenic purpura (ITP) to raise platelet counts.

CONTRAINDICATIONS

Gammaplex is contraindicated in patients who have had an anaphylactic or severe systemic reaction to the administration of human immune globulin. Gammaplex is contraindicated in patients with hereditary intolerance to fructose, also in infants and neonates for whom sucrose or fructose tolerance has not been established. Gammaplex is contraindicated in IgA-deficient patients with antibodies to IgA and a history of hypersensitivity.

WARNINGS AND PRECAUTIONS

Renal Dysfunction / Failure:

Acute renal dysfunction/failure, osmotic nephropathy, and death may occur upon use of human IGIV products. Ensure that patients are not volume depleted before administering Gammaplex. Periodic monitoring of renal function and urine output is particularly important in patients judged to be at increased risk of developing acute renal failure. Assess renal function, including measurement of blood urea nitrogen (BUN) and serum creatinine, before the initial infusion of Gammaplex and at appropriate intervals thereafter. If renal function deteriorates, consider discontinuing Gammaplex.

Thrombotic Events:

Thrombosis may occur following treatment with immune globulin products, including Gammaplex. Risk factors may include: advanced age, prolonged immobilization, hypercoagulable conditions, history of venous or arterial thrombosis, use of estrogens, indwelling central vascular catheters, hyperviscosity and cardiovascular risk factors. Thrombosis may occur in the absence of known risk factors. Consider baseline assessment of blood viscosity in patients at risk for hyperviscosity, including those with cryoglobulins, fasting chylomicronemia / markedly high triacylglycerols (triglycerides), or monoclonal gammopathies. For patients at risk of thrombosis, administer Gammaplex at the minimum dose and infusion rate practicable. Ensure adequate hydration in patients before administration. Monitor for signs and symptoms of thrombosis and assess blood viscosity in patients at risk for hyperviscosity.

Hypersensitivity:

Severe hypersensitivity reactions may occur. In case of hypersensitivity, discontinue Gammaplex infusion immediately and institute appropriate treatment. Medications such as epinephrine should be available for immediate treatment of acute hypersensitivity reactions. Gammaplex contains trace amounts of IgA (<10 µg/mL). Patients with known antibodies to IgA may have a greater risk of developing potentially severe hypersensitivity and anaphylactic reactions. Gammaplex is contraindicated in patients with antibodies against IgA and a history of hypersensitivity reaction.

Hyperproteinemia, Increased Serum Viscosity, and Hyponatremia:

Hyperproteinemia, increased serum viscosity, and hyponatremia may occur in patients receiving IGIV therapy. It is critical to clinically distinguish true hyponatremia from a pseudohyponatremia that is associated with or causally related to hyperproteinemia with concomitant decreased calculated serum osmolality or elevated osmolar gap, because treatment aimed at decreasing serum free water in patients with pseudohyponatremia may lead to volume depletion, a further increase in serum viscosity, and a possible predisposition to thrombotic events.

Aseptic Meningitis Syndrome (AMS):

AMS may occur with IGIV treatment. AMS usually begins within several hours to 2 days following IGIV treatment. Discontinuation of IGIV treatment has resulted in remission of AMS within several days without sequelae. AMS is characterized by the following signs and symptoms: severe headache, nuchal rigidity, drowsiness, fever, photophobia, painful eye movements, nausea, and vomiting. Cerebrospinal fluid (CSF) studies frequently reveal pleocytosis up to several thousand cells per cubic millimeter, predominantly from the granulocytic series, and elevated protein levels up to several hundred mg/dL, but negative culture results. Conduct a thorough neurological examination on patients exhibiting such signs and symptoms, including CSF studies, to rule out other causes of meningitis. AMS may occur more frequently in association with high doses (2 g/kg) and/or rapid infusion of IGIV.

Hemolysis:

Gammaplex may contain blood group antibodies that can act as hemolysins and induce *in vivo* coating of red blood cells (RBCs) with immunoglobulin, causing a positive direct antiglobulin test (DAT) (Coombs' test) result and hemolysis. Delayed hemolytic anemia can develop subsequent to IGIV therapy due to enhanced RBC sequestration and acute hemolysis, consistent with intravascular hemolysis, has been reported. The following risk factors may be associated with the development of hemolysis following IGIV administration: high doses (e.g., ≥2 g/kg), given either as a single administration or divided over several days, and non-O blood group. Closely monitor patients for clinical signs and symptoms of hemolysis, particularly patients with risk factors noted above. If clinical signs and symptoms of hemolysis or a significant drop in hemoglobin or hematocrit have been observed, perform confirmatory laboratory testing. If transfusion is indicated for patients who develop hemolysis with clinically compromising anemia after receiving IGIV, perform adequate cross-matching.

Transfusion-related Acute Lung Injury (TRALI):

Noncardiogenic pulmonary edema may occur in patients following IGIV treatment. TRALI is characterized by severe respiratory distress, pulmonary edema, hypoxemia, normal left ventricular function and fever. Symptoms typically appear within 1 to 6 hours following treatment. Monitor patients for pulmonary adverse reactions. If TRALI is suspected, perform appropriate tests for the presence of anti-neutrophil antibodies in both the product and the patient's serum. TRALI may be managed using oxygen therapy with adequate ventilatory support.

Volume Overload:

Carefully consider the relative risks and benefits before prescribing the high dose regimen (for chronic ITP) in patients at increased risk of volume overload.

Transmissible Infectious Agents:

Because Gammaplex is made from human blood, it may carry a risk of transmitting infectious agents, e.g., viruses, the variant Creutzfeldt-Jakob disease (vCJD) agent and, theoretically, the Creutzfeldt-Jakob disease (CJD) agent. No cases of transmission of viral diseases or CJD have been associated with the use of Gammaplex. All infections suspected by a physician possibly to have been transmitted by this product should be reported by the physician or other healthcare providers to **BPL Inc. 1-866-398-0825**. Before prescribing Gammaplex, the physician should discuss the risks and benefits of its use with the patient.

Laboratory Tests:

After infusion of immunoglobulin, the transitory rise of the various passively transferred antibodies in the patient's blood may yield positive serological testing results, with the potential for misleading interpretation. Passive transmission of antibodies to erythrocyte antigens (e.g., A, B, and D) may cause a positive direct or indirect antiglobulin (Coombs') test. Clinically assess patients with known renal dysfunction, diabetes mellitus, age greater than 65, volume depletion, sepsis, paraproteinemia, or those receiving nephrotoxic agents, and monitor as appropriate (BUN, serum creatinine, urine output) during therapy with Gammaplex. Consider baseline assessment of blood viscosity in patients at risk for hyperviscosity, including those with polycythemia, cryoglobulins, fasting chylomicronemia/markedly high triglycerides, or monoclonal gammopathies. Consider measuring hemoglobin or hematocrit at baseline and approximately 36 to 96 hours post infusion in patients at higher risk of hemolysis. If signs and/or symptoms of hemolysis are present after an infusion of Gammaplex, perform appropriate laboratory testing for confirmation. If TRALI is suspected, perform appropriate tests for the presence of anti-neutrophil antibodies in both the product and patient's serum.

ADVERSE REACTIONS

Serious adverse reactions (ARs) observed in clinical trial subjects with primary humoral immunodeficiency (PI) were thrombosis and chest pain. Serious ARs observed in clinical trial subjects with immune thrombocytopenic purpura (ITP) were headache, vomiting and dehydration. The most common ARs observed in the PI clinical trial were headache (18 subjects, 36%), pyrexia (8 subjects, 16%), fatigue (6 subjects, 12%), nausea (6 subjects, 12%), hypertension (3 subjects, 6%), chills (3 subjects, 6%), myalgia (3 subjects, 6%), pain (4 subjects, 8%), and vomiting (3 subjects, 6%). The most common ARs observed in the chronic ITP clinical trial were headache (12 subjects, 34%), vomiting (8 subjects, 23%), nausea (5 subjects, 14%), pyrexia (5 subjects, 14%), pruritus (2 subjects, 6%) and arthralgia (2 subjects, 6%).

Clinical Trials Experience:

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Treatment of Primary Humoral Immunodeficiency:

In a multicenter, open-label, non-randomized clinical trial, 50 subjects with PI received doses of Gammaplex ranging from 279 to 799 mg/kg every 21 days (mean dose 465 mg/kg) or 28 days (mean dose 458 mg/kg), for up to 12 months. Twenty-four subjects (48%) had an AR at some time during the clinical trial that was considered product-related. The total number of ARs during infusion or within 72 hours of infusion was 237 (a rate of 0.34 ARs per infusion). The percentage of Gammaplex infusions with one or more ARs within 72 hours of infusion was 21%. The upper bound of the 1-sided 97.5% confidence interval for this percentage was 24%, which was below the pre-specified upper limit of 40% for this safety endpoint. The most common ARs observed in this clinical trial were headache (18 subjects, 36%), fatigue (6 subjects, 12%), nausea (6 subjects, 12%), pyrexia (6 subjects, 12%), pain (4 subjects, 8%), hypertension (3 subjects, 6%), chills (3 subjects, 6%), myalgia (3 subjects, 6%) and vomiting (3 subjects, 6%). Two subjects experienced serious ARs (thrombosis and chest pain). Forty-seven of the 50 subjects enrolled in this clinical trial had a negative direct antiglobulin test (DAT) at baseline. Of these 47 subjects, 4 (9%) developed a positive DAT at some time during the clinical trial. However, no subjects showed evidence of hemolytic anemia.

Table 1: Adverse Reactions (ARs*) Occurring in >5% of Subjects with PI

Adverse Reactions	Subjects (%) PI [n=50]	Infusions (%) PI [n=703]
Headache	18 (36%)	53 (7.5%)
Pyrexia	7 (14%)	10 (1.4%)
Sinusitis	8 (16%)	9 (1.3%)
Fatigue	6 (12%)	9 (1.3%)
Nausea	6 (12%)	7 (1.0%)
Nasal Congestion	5 (10%)	3 (0.4%)
Pain	4 (8%)	5 (0.7%)
Vomiting	3 (6%)	3 (0.4%)
Chills	3 (6%)	5 (0.7%)
Hypertension	3 (6%)	4 (0.6%)
Insomnia	3 (6%)	3 (0.4%)
Muscle spasms	3 (6%)	2 (0.3%)
Myalgia	3 (6%)	3 (0.4%)
Upper respiratory tract infection	3 (6%)	5 (0.7%)

**Adverse Reactions (ARs) are defined as treatment emergent adverse events which met any of the following criteria: (a) adverse events which began during an infusion of Gammaplex or within 72 hours of the end of an infusion, (b) adverse events considered by the investigator or sponsor to have been possibly, probably, or definitely related to administration of Gammaplex, (c) adverse events for which the investigator's causality assessment was either missing or indeterminate.*

Treatment of Chronic Immune Thrombocytopenic Purpura:

In a multicenter, open-label, non-randomized clinical trial, 35 subjects with chronic immune thrombocytopenic purpura were treated with a nominal dose of 1,000 mg/kg on each of two consecutive days (total dose 2,000 mg/kg). Doses of Gammaplex ranged from 482 to 1149 mg/kg on an infusion day. The median total dose per subject was 2035 mg/kg. All 35 subjects received at least one infusion of clinical trial drug, and all but one subject completed the first course of treatment. Twenty-four subjects (69%) reported at least one AR (103 in total); the most commonly reported being headache (12 subjects, 34%), vomiting (8 subjects, 23%), nausea (5 subjects, 14%), pyrexia (5 subjects, 14%), pruritus (2 subjects, 6%), dehydration (2 subjects, 6%) and arthralgia (2 subjects, 6%). Three subjects experienced a total of five serious ARs. Of the five serious ARs, one subject had three concurrently (vomiting, dehydration and headache) and two subjects each had one serious AR (headache). One of these latter two subjects discontinued from the clinical trial because of the severe headache. Table 2 lists the ARs in more than 5% of subjects. Based on a review of clinical and laboratory data, 4/35 subjects (11%) with drops in hemoglobin exceeding 2 g/dL following administration of Gammaplex were considered to have experienced suspected treatment-emergent hemolysis. Milder treatment-emergent hemolysis could not be excluded for an additional 7 subjects, giving a total of 11 of 35 subjects (31%) for whom hemolysis could not be excluded (not including an additional two subjects who lacked follow-up testing for hemolysis, so their hemolysis status was considered unassessable).

Table 2: Adverse Reactions (ARs) Occurring in >5% of Subjects with ITP

Adverse Reactions	Subjects (%) ITP [n=35]	Infusions (%) ITP [n=94]
Headache	12 (34%)	15 (16%)
Vomiting	8 (23%)	9 (9.6%)
Nausea	5 (14%)	5 (5.3%)
Pyrexia	5 (14%)	7 (7.4%)
Pain	2 (6%)	2 (2.1%)
Abdominal pain upper	2 (6%)	2 (2.1%)
Nausea	6 (12%)	7 (1.0%)
Nasal Congestion	5 (10%)	3 (0.4%)
Gastritis	2 (6%)	2 (2.1%)
Contusion	2 (6%)	2 (2.1%)
Arthralgia	2 (6%)	2 (2.1%)
Cough	2 (6%)	2 (2.1%)
Anemia	2 (6%)	1 (1.1%)
Ecchymosis	2 (6%)	3 (3.2%)
Pruritus	2 (6%)	2 (2.1%)
Dehydration	2 (6%)	2 (2.1%)
Hypertension	2 (6%)	1 (1.1%)
Neck pain	2 (6%)	1 (1.1%)

**Adverse Reactions (ARs) are defined as treatment emergent adverse events which met any of the following criteria: (a) adverse events which began during an infusion of Gammaplex or within 72 hours of the end of an infusion, (b) adverse events considered by the investigator or sponsor to have been possibly, probably, or definitely related to administration of Gammaplex, (c) adverse events for which the investigator's causality assessment was either missing or indeterminate.*

In neither of the above trials was there evidence of transmission of HBV, HCV, HIV and parvovirus B19.

Postmarketing Experience: *Because adverse reactions are voluntarily reported post-approval from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to product exposure.*

In addition to the adverse reactions identified in clinical studies, the following adverse reactions have been identified during postmarketing use of Gammaplex: ***Infusion reactions:*** Dizziness, back pain, flushing; ***Respiratory:*** Pulmonary embolism, dyspnea; ***Cardiovascular:*** Myocardial infarction; ***Integumentary:*** Rash, urticarial. The following adverse reactions have been identified during post-marketing use of intravenous immune globulins: ***Infusion reactions:*** hypersensitivity (e.g., anaphylaxis), headache, diarrhea, tachycardia, fever, fatigue, dizziness, malaise, chills, flushing, urticaria or other skin reactions, wheezing or other chest discomfort, nausea, vomiting, rigors, back pain, myalgia, arthralgia, and changes in blood pressure; ***Renal:*** Acute renal dysfunction/failure, osmotic nephropathy; ***Respiratory:*** Apnea, Acute Respiratory Distress Syndrome (ARDS), TRALI, cyanosis, hypoxemia, pulmonary edema, dyspnea, bronchospasm; ***Cardiovascular:*** Cardiac arrest, thromboembolism, vascular collapse, hypotension; ***Neurological:*** Coma, loss of consciousness, seizures, tremor, aseptic meningitis syndrome; ***Integumentary:*** Stevens-Johnson syndrome, epidermolysis, erythema multiforme, dermatitis (e.g., bullous dermatitis); ***Hematologic:*** Pancytopenia, leukopenia, hemolysis, positive direct antiglobulin (Coombs') test; ***Gastrointestinal:*** Hepatic dysfunction, abdominal pain; ***General/Body as a Whole:*** pyrexia, rigors

DRUG INTERACTIONS: Transitory rise of the various passively transferred antibodies in the patient's blood after infusion of immunoglobulin may yield positive serological testing results, with the potential for misleading interpretation. Passive transmission of antibodies to erythrocyte antigens (e.g., A, B, and D) may cause a positive direct or indirect antiglobulin (Coombs') test. Passive transfer of antibodies may transiently interfere with the immune response to live virus vaccines such as measles, mumps, rubella and varicella. Inform the immunizing physician of recent therapy with Gammaplex so that appropriate measures may be taken.

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Mandatory Childhood Vaccines: The Debate

By Kevin O'Hanlon

Recent events have re-energized the ongoing debate about mandatory vaccines for children in the U.S. It remains to be seen which side of the controversy will prevail.

If most medical experts had their way, people would treat getting vaccines as routinely as making a trip to the grocery store. And, generally, most Americans do. Millions of adults get annual influenza shots and vaccines for shingles and a variety of other ailments. And the majority of parents comply with the Centers for Disease Control and Prevention (CDC) recommended immunization schedule for their children. But news stories about a measles outbreak originating in Disneyland late last year have rekindled the debate about the risks of children getting — or not getting — the recommended vaccines, and whether they should be mandated.

The American Academy of Pediatrics, the American Academy of Family Physicians, CDC and other organizations all urge protecting children with recommended vaccinations. Why? The statistical benefits of vaccines are indisputable. Between 1994 and 2014, for example, an estimated 732,000 American children were saved from death and 322 million cases of childhood illnesses were prevented due to vaccination, according to CDC. In addition, hospitalizations avoided and lives saved through vaccination will save nearly $295 billion in direct costs and $1.38 trillion in total societal costs.[1]

History of Vaccines

While vaccines are at the forefront of modern medicine, their creation dates back more than 10 centuries. There is evidence that the Chinese used a smallpox inoculation as early as 1000 A.D., and inoculations were later used in Turkey and parts of Africa.[2]

The first use of vaccine promotion in the United States occurred in 1721, when a Puritan minister named Cotton Mather promoted vaccination as a response to smallpox.[3] Vaccination, as practiced today, came into being when Edward Jenner, an English physician and scientist, created the first smallpox vaccine using cowpox (a bovine disease similar to smallpox) and vaccinated an 8-year-old boy in 1796. Jenner's innovation was tweaked over the next 200 years and eventually led to the eradication of smallpox.[2,3]

Louis Pasteur's 1885 rabies vaccine was the next to make an impact on human disease. And as bacteriology grew, new developments followed, including vaccines against anthrax, diphtheria, cholera, plague, tetanus, tuberculosis and typhoid. By the mid-20th century, through the use of viruses grown in laboratories, there was a rapid increase in discoveries and innovations, including the creation of vaccines for polio. Researchers also targeted common childhood diseases such as measles, mumps and rubella. Today, innovative techniques drive vaccine research, with recombinant DNA technology and delivery techniques leading scientists in new directions. In addition, disease targets have expanded, and some vaccine research is focusing on noninfectious conditions such as addiction and allergies.[2]

Herd Immunity

Ideally, a population must reach so-called "herd immunity" (or community immunity) for vaccines to be most effective. When a "critical portion" of a population is vaccinated against a contagious disease such as influenza, measles, mumps, rotavirus and pneumococcal disease, an outbreak is unlikely to occur, and most members of the community will be protected. Even those not eligible for certain vaccines — infants, pregnant women or immunocompromised individuals — get some protection because the spread of contagious disease is contained.[4]

Eventually, herd immunity can lead to the eradication of diseases. For instance, today, there is no evidence of naturally occurring smallpox transmission anywhere in the world, which eliminated the need for children to be vaccinated against it. The last case of smallpox in the United States was in 1948, and the last case in the world was reported in 1977 in Somalia.[5]

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Without herd immunity, though, it is possible for the incidences of diseases to rise. Measles is an excellent example. Until measles vaccines became common in the early 1960s, as many as four million Americans each year were diagnosed with the disease, and as many as 500 died. For the past four years, the reported incidence of measles in the U.S. has been less than one case per million, with only 86 cases reported to CDC in 2000. Last year, however, there were a total of 644 measles cases in 27 states — the largest number since 2000.[6]

Healthy People 2020, an initiative of the U.S. Department of Health and Human Services, has set a national baseline goal of 90 percent for preschooler MMR (measles, mumps and rubella) vaccinations. According to the initiative, reaching a national immunization rate above 91 percent has helped reduce measles rates by 99 percent. Achieving even higher vaccination rates would protect even more individuals and increase herd immunity protection for the wider community.

Mandating Vaccinations

Today, the CDC recommendation is that children receive 10 vaccines in 28 doses between birth and age 6. There is no federal mandate requiring that children get vaccinations, but all 50 states require children to receive them before they attend

public schools (although the required vaccinations vary). Of those, all except Mississippi and West Virginia allow parents to request religious exemptions. Other states allow medical, religious and philosophical/personal belief exemptions.[7]

The first school vaccination requirement was enacted in the 1850s in Massachusetts to prevent smallpox transmission. By the beginning of the 20th century, nearly half of the states had requirements for children to be vaccinated before they entered school. By 1963, 20 states, the District of Columbia and Puerto Rico had such laws, with a variety of vaccines mandated. However, enforcement was uneven.[8]

The constitutional foundation for requiring vaccinations stems from a 1905 ruling by the U.S. Supreme Court in a case called Jacobson v. Massachusetts that upheld the right of states to compel vaccinations. The high court ruled that requiring smallpox vaccinations was a "reasonable" exercise of Massachusetts' police power and did not violate the liberty rights of individuals under the Fourteenth Amendment to the U.S. Constitution. Specifically, the court stated that "the police power of a state must be held to embrace, at least, such reasonable regulations established directly by legislative enactment as will protect the public health and the public safety."[9]

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R. Alta Charo, a Warren P. Knowles professor of law and bioethics at the University of Wisconsin Law School, said that, as an ethical matter, vaccination policy represents a form of "social contract" in which "our individual well-being is enhanced when everyone gives up just a little bit of autonomy.… This is done all the time. Every time you follow the traffic rules, you are participating in a social contract. And from the earliest days of our country, the role of government to protect public health has been recognized as a legitimate exercise of its powers, even when this intrudes to some extent on personal choices." Not allowing unvaccinated children to attend school, Charo said, is an attempt "to balance parental autonomy — to forgo vaccinating their kids — with the public health risks created by having too many unvaccinated children in the group, children who may contract an illness and then pass it along — either to those medically contraindicated to the vaccine, too young for the vaccine or previously vaccinated but without complete immune response.… The number of medically contraindicated kids is very low, so having just those children unvaccinated poses much less risk, but if you add all the kids whose parents have medical/philosophical objections, the numbers can get very high, and herd immunity is lost."

Fears

Vaccine opponents argue that vaccines can cause serious and sometimes fatal side effects. Indeed, CDC says all vaccines carry a risk of a life-threatening allergic reaction (anaphylaxis) in about one child per million. The rotavirus vaccination, for example, can cause intussusception (bowel blockage that can require hospitalization) in about one out of 20,000 children. The DTaP (diphtheria, tetanus and pertussis) and MMR vaccines can be associated with long-term seizures, coma, lowered consciousness and permanent brain damage — though the agency says such reaction is so rare that it is difficult to determine causation.[10]

Vaccination foes also have often said that vaccines cause autism. But despite much controversy on the topic, researchers haven't found a connection between autism and childhood vaccines. In fact, the original study that ignited the debate years ago has been debunked and retracted. Although signs of autism may appear at about the same time children receive certain vaccines such as the MMR vaccine, this is simply a coincidence.[11]

In addition to the fear of side effects from vaccines, needle phobia is a serious issue that affects about 50 million Americans and is a disorder recognized by the Americans with Disabilities Act. At least 20 percent of those suffering from needle phobia don't seek medical treatment as a result, said Heather Potters, vice chairman and chief business development officer at PharmaJet, which has developed a needle-free injector for adults ages 18 years to 64 years to get an annual vaccination against the flu. "It is estimated that over 35 percent of Americans, or 71 million people, could be positively influenced by a needle-free option due to their aversion to needles, many of whom do not get a flu shot as a result," Potters said. "Also, needle-free delivery provides a safer workplace environment. Since there is no needle, there is no chance of needlestick injuries or needle reuse when administering the flu shot. It also offers an option for healthcare workers who have an aversion or fear of needles."

On another front, vaccination opponents also counter that the immune systems of children can handle most infections. The Mayo Clinic says that natural infection "often provides more complete immunity than a series of vaccinations — but there's a price to pay for natural immunity. For example, a natural chickenpox (varicella) infection could lead to pneumonia. A natural polio infection could cause permanent paralysis. A natural mumps infection could lead to deafness. A natural Hib infection could result in permanent brain damage. Vaccination can help prevent these diseases and their potentially serious complications."[11]

Vaccination Gap

Parental oncerns over possible adverse effects of vaccinations have resulted in decreases in the number of children who have had their recommended vaccines, including MMR. Although health officials have not identified who brought measles to Disneyland, the outbreak — which spread to some 117 people from 21 states and the District of Columbia[12] — "shines a glaring spotlight on our nation's growing antivaccination movement and the prevalence of vaccination-hesitant parents," according to a study published in *The Journal of the American Medical Association*.[13]

Nationwide, 91.9 percent of children ages 19 months to 35 months have received their MMR shot, according to CDC's latest National Immunization Survey. While that is an increase from 2000, when 90.5 percent had been immunized, it is down from 2006, when the rate was 92.3 percent.[14] However, an analysis released in February by the Trust for America's Health (TFAH), using data from the National Immunization Survey, found that fewer than 90 percent of U.S. children ages 19 months to 35 months have received the recommended MMR vaccination in 17 states. New Hampshire has the highest MMR vaccination rate for preschoolers at 96.3 percent. Colorado, Ohio and West Virginia have the lowest at 86 percent. No state in the Northeast was below 90 percent, while eight states in the South, five in the West and four in the Midwest had rates below 90 percent. "It is so important that communities maintain high levels of MMR vaccination because measles is so infectious, and especially when outbreaks are occurring around them," said Litjen (L.J) Tan, MS, PhD, chief strategy officer of the Immunization Action Coalition. "To have pockets where community immunity is below 90 percent is worrisome, as they will be the ones most vulnerable to a case of measles exploding into an outbreak."[15]

"Sadly, there is a persistent preschooler vaccination gap in the United States. We're seeing now how leaving children unnecessarily vulnerable to threats like the measles can have a tragic result," said Jeffrey Levi, PhD, executive director of TFAH. "We need to redouble our national commitment to improving vaccination rates."[16]

The Public Debate

The vaccination debate has stirred emotions and even spilled over into the race for the 2016 presidential nomination. In February, Sen. Rand Paul (R-Ky.) said in interviews that most vaccines should be voluntary, adding that "many tragic cases of walking, talking, normal children … wound up with profound mental disorders after vaccines." Then, in an interview on CNBC, Paul stated: "The state doesn't own your children. Parents own the children. And it is an issue of freedom and public health."

Professor Charo stressed that requiring vaccinations is not an example of government telling people what to do solely to protect them from their own behaviors such as with motorcycle helmet laws. "The vaccine policies are about protecting the community from the individual objectors who have made themselves potential vectors of disease," she said, which is why the laws mandating vaccination are not just about protecting the children of the objecting parents. "Rather, they are about protecting all children."

Dr. Tim Jacks, an Arizona pediatrician, has spoken publicly about the need for childhood vaccines after his two children were exposed to measles — presumably by someone who was infected via the Disneyland outbreak — during a visit to Phoenix Children's Hospital. Jacks' 3-year-old daughter, Maggie, has acute lymphoblastic leukemia and a compromised immune system. In addition, his then-10-month-old son, Eli, was too young to have received his recommended first dose vaccination for MMR.

Jacks wrote an open letter first published on his family blog for Maggie: "To the parent of the unvaccinated child who exposed my family to measles: I have a number of strong feelings surging through my body right now. Towards my family, I am feeling extra protective like a papa bear. Towards you, unvaccinating parent, I feel anger and frustration at your choices … I assume you love your child just like I love mine. I assume that you are trying to make good choices regarding their care. Please realize that your child does not live in a bubble. When your child gets sick, other children are exposed. My children. Why would you knowingly expose anyone to your sick, unvaccinated child after recently visiting Disneyland? That was a boneheaded move." According to Jacks, since then, "the kids finished quarantine without incident. Eli is back to his toddler ways. Maggie has resumed her chemotherapy treatments, has lost her hair again, and is doing pretty well overall."

It's Professor Charo's opinion that a parent who refuses to vaccinate a child — without good reason — is attempting to cash in on the benefits of herd immunity provided by all the other children who endured the discomfort and minimal risk of the vaccine, but without participating in that same sacrifice of discomfort and minimal risk. "One might call this 'free-riding,'" said Charo.

Jennifer Margulis, PhD, author of *Your Baby, Your Way: Taking Charge of Your Pregnancy, Childbirth, and Parenting Decisions for a Happier, Healthier Family*, said childhood vaccinations are necessary and useful. But there is a "but," she said. "My research has revealed that the problem is not vaccines in general; it is the current American childhood vaccine schedule. Our American vaccine schedule is overpacked with vaccines, several of which are not necessary." She pointed out that the birth dose of hepatitis B is not given in Europe unless the child's mother or father is hepatitis B positive, a prostitute or an intravenous drug user. "Yet we give this unnecessary vaccine to every newborn in America," she stressed.

Margulis said vaccines should not be mandated: "Vaccines are a pharmaceutical product that carry some risk and that the consumer is required to pay for. It is not the state or federal government's place to mandate medical products. The decision about how and when a child — or an adult — should receive a medical treatment or a medical prevention should be made in the privacy of a doctor's office." According to Margulis, she has interviewed hundreds of families who have chosen to delay or forgo some vaccines — and those choices were not made lightly. "Forgoing some vaccines is a difficult choice that sometimes opens you up to ridicule, anger and hate," Margulis explained. "It is very difficult to choose not to vaccinate your children and not something American parents are doing thoughtlessly. Most parents who are referred to as 'anti-vaxxers' actually began by vaccinating their child on the recommended schedule, but their child had some kind of bad reaction to the vaccines, or some other devastating health problem that the doctors could not explain. In these cases, it was the current vaccine schedule that ended up being more harmful to their child's health than not vaccinating."

Vaccine opponents argue that vaccines can cause serious and sometimes fatal side effects.

Dr. Gregory Poland, chief of the Mayo Clinic Vaccine Research Group and American editor of the journal *Vaccine*, said that "research has repeatedly demonstrated the value of vaccines in reducing the risks and complications of infectious diseases across the population. Vaccines have improved longevity and quality of life in a safe and cost-effective manner."

The Legal Debate

Since the beginning of this year, 29 states have introduced vaccine bills, many of which would make it harder for parents to opt out of immunizing their kids based on personal or religious beliefs.[17] While many of these bills are still being considered, others have been withdrawn due to increasing opposition among individuals and organizations that are instructing members how to fight them.

Whether vaccines should be mandated is a hotly debated topic. A host of expert arguments on both sides can be read at ProCon.org (vaccines.procon.org), a nonpartisan vaccines website. In addition to expert statements, the site includes a chart of religious, medical and philosophical exemptions for vaccinations by state; a state-by-state listing of vaccinations required for public school; and an article on how deaths from measles, chickenpox, influenza and other diseases were impacted when the vaccines became available.

With strongly held views driving both sides of the debate over mandating vaccines, this issue is far from resolved. And, in fact, it is a controversy dating back to the 1800s in this country that continues today among a variety of individuals with opposing personal beliefs. Proponents focus on the statistics of disease prevention and the common good, while opponents are more interested in preserving individual freedoms and personal choices. Not surprisingly, the collision between these factions is bound to continue with uncertain results. ❖

KEVIN O'HANLON *has been a writer and editor for 30 years, including with the Associated Press,* Cincinnati Enquirer *and* Omaha World-Herald. *He lives in Lincoln, Neb.*

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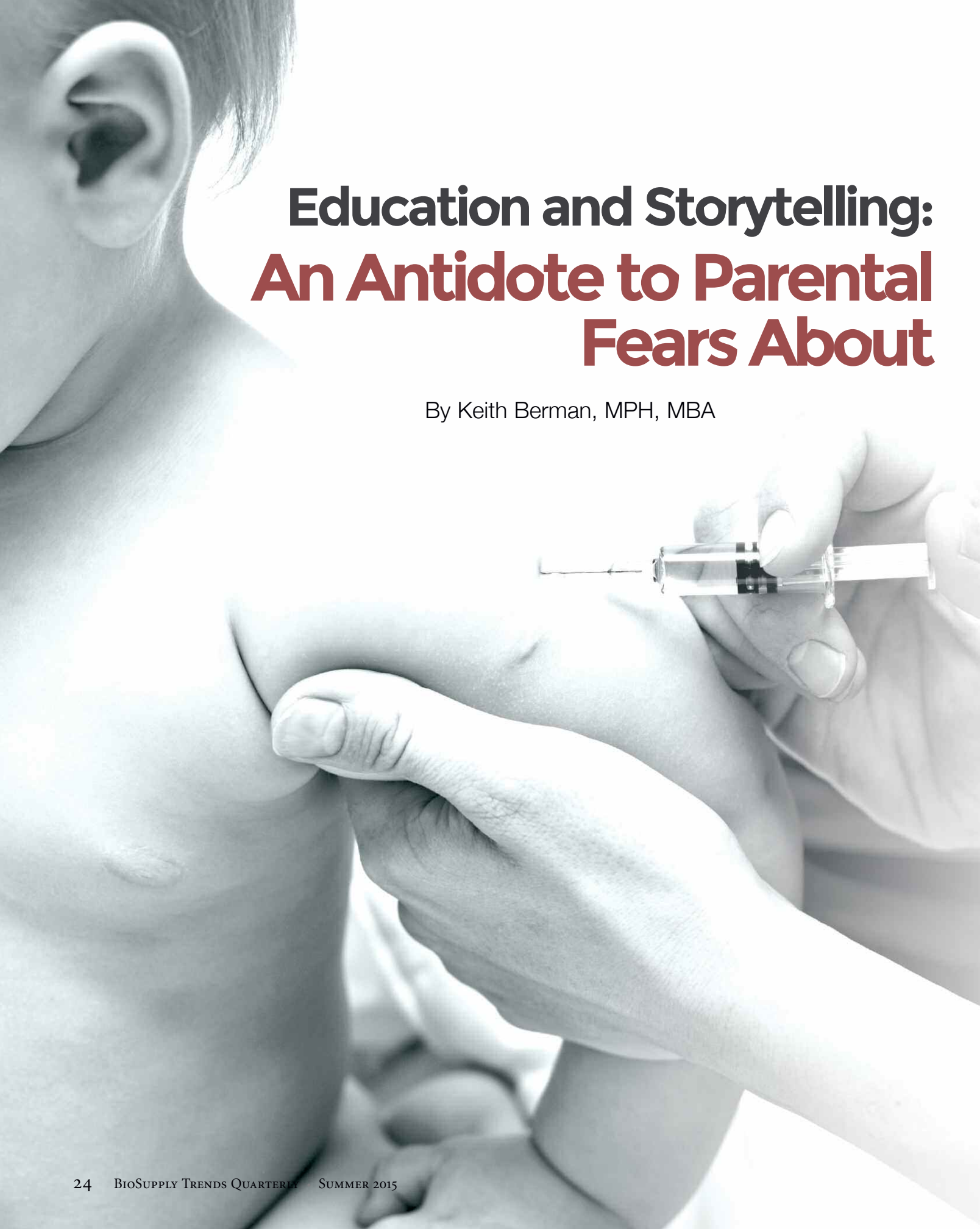
Education and Storytelling: An Antidote to Parental Fears About

By Keith Berman, MPH, MBA



Vaccine Safety

What has been will be again, what has been done will be done again; there is nothing new under the sun. — Ecclesiastes 1:9

The year was 1908 and, late in life, a wealthy 67-year-old industrialist named John Pitcairn found himself drawn to a newfound interest. Pitcairn's son Raymond had suffered an adverse reaction after receiving a childhood vaccination some years earlier. More recently, citing their religious belief in homeopathic medicine, Pitcairn and fellow church members resisted efforts by Pennsylvania health officials to vaccinate them during a local smallpox outbreak. But Pitcairn most ardently opposed vaccination for yet another reason: He believed it was wrong for government to force people to act against their will.[1]

This energetic Scottish immigrant, who had parlayed his elementary school education into a huge personal fortune in steel and railroads, knew how to make things happen. He personally bankrolled a national conference of vaccination opponents, which was held in Philadelphia in October 1908. This event served as the springboard for Pitcairn and his friend and fellow businessman Charles Higgins to cofound the Anti-Vaccination League of America.[1]

As they lobbied state legislatures to repeal compulsory vaccination laws and distributed numerous polemical pamphlets regaling readers with graphic descriptions and photographs of victims allegedly disfigured, blinded and killed by vaccination, public health authorities were busy deploying smallpox vaccine to control outbreaks. The number of reported cases of the much more deadly of two smallpox variants, variola major, fell from an average of 5,100 cases per year between 1900 and 1905 to 400 per year between 1906 and 1909; deaths plummeted from just over 800 per year to 33.[2]

By the 1920s, Pitcairn and Higgins were gone, but the effects of anti-vaccination activism by them and others lingered on. Just 10 states had compulsory vaccination laws, while 28 had none and four actively prohibited such laws. Reported smallpox case rates make it clear which side was in the right: There were 6.6 cases per 100,000 residents in the 10 states with compulsory vaccination laws, and 66.7 and 115.2 cases per 100,000 in the 28 states with no laws and prohibitions, respectively.[2] By 1930, vaccination programs had eradicated variola major, one of the most terrible scourges in human history, in the United States.

Understanding Today's "Anti-Vaxxers"

Laws and regulations created by government at the local and state levels dictate limits on how we drive, what protective gear motorcyclists must wear, at what age we can buy alcohol, and where smokers can and cannot smoke — all intrusions on personal choice justified by volumes of public health and safety research. But state laws making vaccinations compulsory for our children, whom we commit to nurture and protect, represent a unique test of our democratic process. It turns out that, much like a century ago, there are those who are simply unwilling to place their trust in government and its scientific and public health experts.

Smallpox in Illinois, 1912. Courtesy Illinois Department of Public Health

Not unlike the anti-vaccine dissidents of a century ago, people most vehemently opposed to childhood vaccination often have broader underlying reasons. Some are ideologically opposed to government mandates or restriction of personal liberties. Some have religious-based objections. Some eschew conventional medicines in favor of "natural" health treatments. And some have a blanket distrust for pharmaceutical manufacturers or the integrity of the U.S. Food and Drug Administration's (FDA) vaccine safety oversight.

But ardent "anti-vaxxers" comprise a very small minority of the millions of parents who this year will choose not to allow their children to receive their scheduled vaccines. Most are simply fearful parents who have been exposed to anti-vaccine propaganda, with its terrifying warnings and tales about children who suddenly developed any of a panoply of neurological, neurobehavioral, autoimmune and other serious disorders following vaccination.

As has been widely reported, some of the lowest childhood immunization rates are found in relatively highly educated and health-focused communities.

Unfortunately, today's band of anti-vaccination zealots have been joined by a modern-day version of the infamous snake-oil salesmen of the late 19th century. A prime example is an osteopathic physician and web entrepreneur named Dr. Joseph Mercola. Parents who stumble upon or are referred to Mercola's vast website will find astonishing anti-vaccine statements like this one:[3]

"*Vaccinations are very neurotoxic and have been associated with many neurological disorders, like encephalopathies, epilepsy, convulsions, ADD, LD, autism, mental retardation, depression, anxiety, CNS disorders, paralysis, Guillain-Barré Syndrome, nerve deafness, blindness and SIDS. The neurological disorders associated with vaccinations are diverse and numerous. Vaccinations lower IQ as well as contribute to the overt mental disorders and neurological diseases listed here.*" [A list of 17 disorders follows.]

Baseless inflammatory misinformation of this nature is the dangled bait for uninformed parents already prone to unquestioningly embrace it, but a pop-up quickly reveals this Internet huckster's real agenda: "*Here's your chance to start enjoying my high-quality natural products.*"

Disease Outbreaks: The Upshot of Declining Vaccination Rates

As has been widely reported, some of the lowest childhood immunization rates — far below the 95 percent rate commonly cited as a goal for herd immunity — are found in relatively highly educated and health-focused communities. The seeming paradox is that these are just the kinds of parents one would expect to be most enthusiastic about protecting their children from these serious childhood illnesses. But this is not the case for three related reasons:

1. *Thanks to the success of U.S. childhood immunization policy over a number of decades, parents today are typically unfamiliar with these diseases or their potential seriousness.* Prior to the availability of a measles vaccine, about 500,000 people were infected annually with measles in the U.S. Serious health complications were not uncommon, especially in children under 5 years of age. About one in every 1,000 people with measles developed brain swelling, which often led to brain damage. One to two out of 1,000 died, even with the best care.

But since the 1963 introduction of the vaccine and 1994 implementation of the Vaccines for Children program that now provides free vaccines for all children,* measles was declared eliminated in 2000, meaning that no new cases originated domestically. Few new parents have seen or heard about anyone with the measles. The same can be said for most other childhood illnesses all but eradicated by a universal childhood vaccination policy: Notwithstanding a local outbreak affecting their own community, most parents have little or no awareness of their potentially serious threats to health.

2. *Publicized toxin-disease links make it easy to stir up fears about vaccine safety.* Well-educated and more health-conscious parents tend also to be more aware that there are real causal associations between toxins created by human activity — certain plasticizers in food containers, high mercury levels in fish, chemical contaminants in the water supply — and serious diseases, including cancers. These legitimate concerns have propelled a growing market for organic and natural foods. On the flip side, this same sensitivity can readily be exploited to push baseless theories and disproven claims linking vaccine products to serious health conditions, particularly those such as autism that have no clear cause.

3. *Anti-vaccination campaigns addressing children have a powerful psychological impact.* No parent wants to be an accomplice to an action that could seriously harm his or her child. The more extreme the allegations against vaccines, the more that

*Following a 1989-1991 measles outbreak in the U.S. that infected 55,000 persons, mainly poor and uninsured children.

Table 1. CDC's Suggested Responses to Parents' Common Concerns About Vaccination[4]

Parent comment or question	Suggested health provider response
"All those people who say that the MMR vaccine causes autism must be on to something."	"Autism is a burden for many families and people want answers – including me. But well designed and conducted studies that I can share with you show that MMR vaccine is not a cause of autism."
"What are all these vaccines for? Are they really necessary?"	"I know you didn't get all these vaccines when you were a baby. Neither did I. But we were both at risk of serious diseases like Hib and pneumococcal meningitis. Today, we're lucky to be able to protect our babies from 14 serious diseases with vaccines."
"You really don't know if vaccines cause any long-term effects."	"We have years of experience with vaccines and no reason to believe vaccines cause long-term harm. I understand your concern, but I truly believe that the risk of diseases is greater than any risks posed by vaccines. Vaccines will get your baby off to a great start for a long, healthy life."

caution seems merited. And again, while anti-vaccination slogans and propaganda today echo the florid statements of a century ago, today the diseases themselves are virtually nowhere to be found — except when an isolated outbreak happens to hit.

Of course, plenty of information is available to help providers make parents aware of the risks of not immunizing their children against measles, mumps, rubella, polio, diphtheria, pertussis, tetanus and other diseases on the pediatric immunization schedule. A Centers for Disease Control and Prevention (CDC) brochure for providers titled "Talking with Parents about Vaccines for Infants" offers helpful suggested responses to common concerns expressed by parents (Table 1).[4] Materials developed by CDC in collaboration with pediatric and family practice specialty societies can be found on the Internet, downloaded and printed with just a few clicks.[5,6]

Many of these resources require parents to read fairly dry or lengthy written items. For example, another CDC document for parents headlined "If You Choose Not to Vaccinate Your Child, Understand the Risks and Responsibilities"[7] is single-spaced and two pages long. Unfortunately, some people are easily distracted, or become overwhelmed, or don't effectively absorb information when they try to read it. Others with a skeptical nature simply may not trust written materials.

That is where the healthcare provider, and the provider's relationship built over time with each family, comes in.

Taking Measure of Parents' Cognitive and Learning Styles

Ordinarily when discussing a treatment with a patient, there is a disease or condition connected to it. The patient is motivated to manage the problem, usually has no preexisting biases, and looks to the clinician as the authority. In part, childhood vaccination turns this typical interaction on its head. There is no disease present (and thus little tangible motivation). Some parents inevitably arrive with a negative frame of reference primed by exposure to alarmist misinformation about the safety of vaccines.

Fortunately, parents have already placed their trust in their child's pediatrician or family physician to do the right thing for their child's health. They are prepared to listen. The challenge for the physician and allied health staff is to try to gauge what kind of information, presented in what way, might work best. Behavioral experts have suggested a variety of preferred cognitive styles, with labels such as *denialist* ("I don't care what the data show; I don't believe the vaccine is safe"), *innumerate* ("a one-in-a-million risk sounds high"), *heuristic* ("I remember Guillain-Barré syndrome happened in 1977 after flu vaccines; that must be common, so I'm not getting a flu vaccine") *and analytical* ("I want to see the data so I can make a decision"). More basically, a CDC guidance points out that presenting too much science will frustrate some parents, while too little will frustrate others.[4]

But regardless of any given parent's cognitive leanings, educators the world over know that illustrative diagrams and stories are key to effective communication.

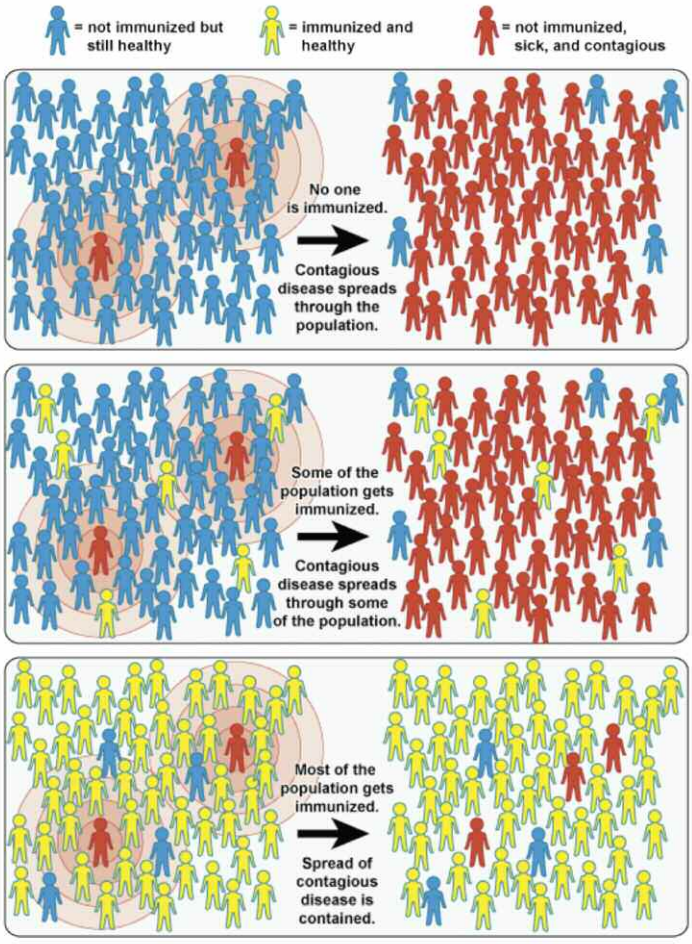
Herd Immunity Told in Graphics and Stories

There is one last "easy out" for those parents who have heard the statistics, seen the images and disease descriptions, and received the reassurances about safety, but are still hesitant. They can decide to skip vaccination for their child and rely on herd (community) immunity, betting that the protective immune resistance of other vaccinated children will act to shield their unvaccinated child from exposure. Essentially, these are vaccination "freeloaders" who want to put their faith in herd immunity to protect their child without committing to join the herd.[8] So how does one go about clarifying the importance of herd immunity while also harnessing it to persuade these parents to get on board?

Below are two focused educational tactics that may achieve this — and more. The first introduces two important considerations that parents may not have thought about: 1) the ever-present risk that infected visitors from overseas will start a community outbreak, and 2) the threat that an unvaccinated child presents to others with congenital or treatment-related immunodeficiency disorders. The second of these tactics — a story of a serious measles outbreak in Ireland — dovetails with the history of how the alleged link between measles-mumps-rubella (MMR) vaccination and autism (since disproven by a number of large studies[9,10]) came to be: Callous research fraud by a now-notorious former United Kingdom physician named Andrew Wakefield.

Present a graphic representation of herd immunity, which illustrates how it works and why herd immunity breaks down when the community vaccination rate drops significantly below 95 percent (Figure 1). The authoritative *Oxford Textbook of Public Health* defines herd immunity as "the relative protection of a population group achieved by reducing or breaking the chains of transmission of an infectious agent because most of the population is resistant to infection through immunization (or prior natural infection)."[11] Depending on the parent receiving it, a verbal characterization like this may or may not confer some idea of how herd immunity works. Herd immunity is too important a concept to trust mere words to communicate it to parents questioning the need to vaccinate their child. Coupling the words *and* a simple graphic representation of a small "herd" of human beings can serve to bring the concept to life.

Figure 1. The Principle of Herd Immunity



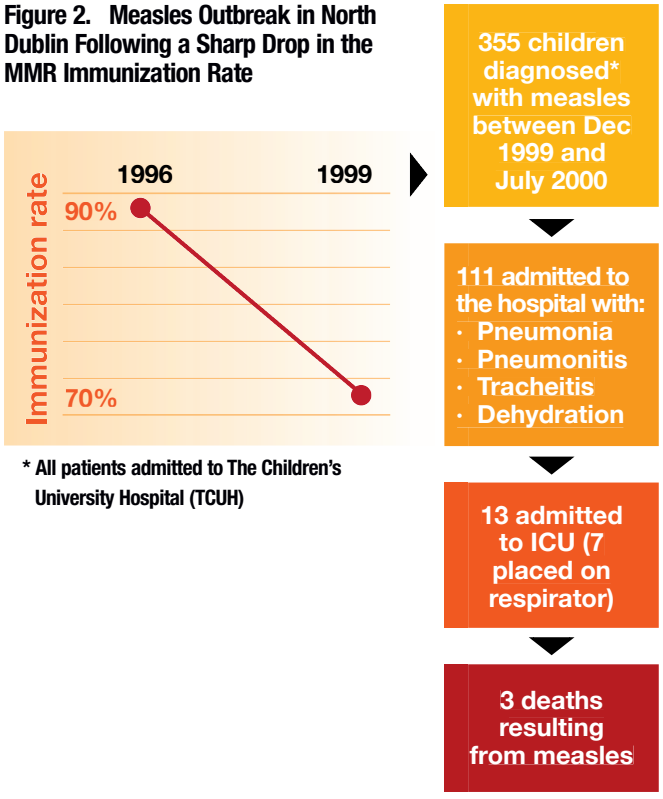
Source: National Institute of Allergy and Infectious Diseases (NIAID)[16]

Graphics similar to those in Figure 1 can be used for more than just explaining why it's so important to achieve as close to a 100 percent vaccination rate as possible. A stick figure can be circled or highlighted to represent a child with leukemia whose immune system has been weakened by chemotherapy, or a pregnant woman at risk for contracting rubella and giving birth to a baby with permanent brain or heart damage, or an elderly person in the family with diminished resistance to seasonal influenza virus. The point is that the game of hoping that herd immunity will protect one's non-vaccinated child has far higher stakes: That child who becomes infected presents a very serious threat to the health of many others with impaired defenses against the infective pathogen.

With a pen or marker, the clinician-educator can also draw a *new* stick figure just outside the "herd" that represents an infected child or adult visiting the U.S. from abroad. The measles genotype of infected persons during a well-publicized outbreak traced to Disneyland in Southern California perfectly matched the genotype circulating in 14 countries, including the Philippines, where there was a large recent outbreak.[12] This finding strongly suggests that a foreign visitor may have been the source. Foreign tourists account for a significant share of the many millions of people streaming through airports and visiting U.S. theme parks and other large public venues each year. An unvaccinated child visiting a nearby theme park may contract the infection from an international visitor and show up as usual the next week in the school classroom. With a simple drawing or a few strokes on an illustration depicting herd immunity, parents can be visually shown how disease can be propagated by children who have not received their protective vaccines. The lower the community vaccination rate, the faster and farther it can spread. A brief visually-aided presentation like this reduces the wiggle room for the parent first inclined to be a vaccine "freeloader."

Share a real story about a disease outbreak attributable to a suboptimal immunization rate. Because of the special circumstances leading up to it, an outbreak of measles that occurred in Ireland between December 1999 and July 2000 (Figure 2) is an excellent example to use. In February 1998, *The Lancet*

Figure 2. Measles Outbreak in North Dublin Following a Sharp Drop in the MMR Immunization Rate



*** All patients admitted to The Children's University Hospital (TCUH)**

published a fraudulent 12-patient case series, authored by a London gastroenterologist named Andrew Wakefield, that asserted a strong temporal association between MMR vaccination and onset of chronic enterocolitis and behavioral symptoms later diagnosed as autism. Later investigations found that Wakefield had entirely falsified the data, and had been secretly paid nearly $700,000 by personal-injury lawyers trying to make a case that the MMR vaccine was unsafe.[13]

The fraudulent Wakefield report was retracted six years later, long after the damage to public confidence about MMR vaccine safety had been done. Ireland's national MMR immunization rate fell from more than 90 percent prior to the Wakefield *Lancet* report to 79 percent two years later. In North Dublin, the epicenter of the outbreak where 355 measles cases were reported over a seven-month period, it had fallen to less than 70 percent. As summarized in Figure 2, more than 100 of these children had to be admitted to the hospital; three died from measles complications.

Healthcare Professionals: Still the Front Line

Worried by stubbornly low vaccination rates and recent measles, pertussis and other disease outbreaks, lawmakers in several states are sponsoring bills to do away with "personal belief" exemptions that allow parents to opt out of the vaccination requirement for their children to attend school.[14] Much as their predecessors did a century ago, they find themselves skirmishing every step of the way with anti-vaccination advocates. While 30 states already have laws banning personal exemptions, all but five states continue to allow religious exemptions.[15]

It is uncertain how this unending tension between the broad ideal of personal freedom and government use of mandates to protect everyone's health will play out in the future. What is certain is that each day the sun comes up, a new crop of worried parents will raise questions or flatly refuse to allow vaccinations for their children. And each day, responsible, caring healthcare professionals will listen and acknowledge the fear, consider what they know about that parent's background and thinking style, and patiently start a conversation that could, for better or ill, forever change the life of a young child. ❖

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Factor IX Complex

Compare the price of PROFILNINE to other complex concentrates

PROFILNINE is a mixture of vitamin K-dependent clotting factors IX, II, X, and low levels of VII and is stable for 3 years at room temperature (provided that the storage temperature does not exceed 25 °C [77 °F]).

Potency	Diluent Size	NDC Numbers
500 IU FIX Range	5 mL	68516-3201-1
1000 IU FIX Range	10 mL	68516-3202-2
1500 IU FIX Range	10 mL	68516-3203-2

Important Safety Information

PROFILNINE® (factor IX complex) is indicated for the prevention and control of bleeding in patients with factor IX deficiency (hemophilia B). PROFILNINE contains non-therapeutic levels of factor VII and is not indicated for use in the treatment of factor VII deficiency.

Because PROFILNINE is made from human plasma, it may carry a risk of transmitting infectious agents, eg, viruses, and, theoretically, the Creutzfeldt-Jakob disease (CJD) agent, despite steps designed to reduce this risk.

The use of factor IX concentrates has historically been associated with development of thromboembolic complications, and the use of such products may be potentially hazardous in patients undergoing surgery, in patients post surgery, in patients with known liver disease, and in patients with signs of fibrinolysis, thrombosis, or disseminated intravascular coagulation (DIC). For these patients, clinical surveillance for early signs of consumptive coagulopathy should be initiated with appropriate biological testing when administering this product. PROFILNINE should only be administered to patients when the beneficial effects of use outweigh the serious risk of potential hypercoagulation.

After repeated treatment with PROFILNINE, patients should be monitored for the development of neutralizing antibodies (inhibitors) that should be quantified in Bethesda Units (BU) using appropriate biological testing.

Hypersensitivity and allergic type hypersensitivity reactions, including anaphylaxis, have been reported for all factor IX complex concentrate products. As with intravenous administration of other plasma-derived products, the following reactions may be observed following administration: headache, fever, chills, flushing, nausea, vomiting, tingling, lethargy, hives, or manifestation of allergic reactions.

During post-approval use of PROFILNINE, cases of allergic/hypersensitivity reactions (including urticaria, shortness of breath, hypotension, and pruritus) and adverse reactions characterized by either thrombosis of disseminated intravascular coagulation (DIC) have been reported.

Do not administer PROFILNINE at a rate exceeding 10 mL/minute. Rapid administration may result in vasomotor reactions.

Please see brief summary of PROFILNINE Package Insert on adjacent page.

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Profilnine®

Factor IX Complex

Solvent Detergent Treated/Nanofiltered

BRIEF SUMMARY
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DESCRIPTION

Factor IX Complex, Profilnine®, is a solvent detergent treated, nanofiltered, sterile, lyophilized concentrate of coagulation factors IX, II, and X and low levels of factor VII. The factor II content is not more than (NMT) 150 units* per 100 factor IX units, the factor X content is NMT 100 units per 100 factor IX units, and the factor VII content is NMT 35 units per 100 factor IX units. Profilnine is intended for intravenous administration only. Each vial is a single dose container and is labeled with the factor IX potency expressed in international units. Profilnine does not contain heparin and contains no preservatives. Profilnine contains few, if any, activated factors based on results from the non-activated partial thromboplastin time (NAPTT) test.

Profilnine is prepared from pooled human plasma and purified by diethylaminoethyl (DEAE) cellulose adsorption. The risk of transmission of infective agents by Profilnine has been substantially reduced by donor selection procedures and virus screening of individual donations and plasma pools by serological and nucleic acid testing. In addition, specific, effective virus elimination steps such as nanofiltration and solvent/detergent (tri-n-butyl phosphate/TNBP) treatment have been incorporated into the Profilnine manufacturing process. Additional removal of some viruses occurs during the DEAE cellulose product purification step. The ability of the manufacturing process to eliminate virus from Profilnine was evaluated in the laboratory by intentionally adding virus to product just prior to the elimination step and monitoring virus removal. Table 1 shows the amounts of virus that can be removed by solvent detergent treatment, nanofiltration and purification by DEAE chromatography when vesicular stomatitis virus (VSV), human immunodeficiency virus-1 and 2 (HIV-1, HIV-2), parvovirus, West Nile virus (WNV), bovine viral diarrhea virus (BVDV), hepatitis A virus (HAV) and pseudorabies virus (PRV) were evaluated in these virus spiking studies. The results indicate that the solvent detergent treatment step effectively inactivates enveloped viruses and the nanofiltration step effectively removes both enveloped and non-enveloped viruses.

Table 1

			Virus Reduction (log_{10}) Process Step		
Virus	**Virus Type**	**Model For:**	1st DEAE Chromatography	Solvent-Detergent	Nanofiltration
Sindbis	Env	Hepatitis C	1.4	≥ 5.3	NT
VSV	Env	Robust enveloped viruses	NT	≥ 4.9	NT
HIV-1	Env	HIV-1	NT	≥ 12.2	≥ 6.2
HIV-2	Env	HIV-2	NT	≥ 6.0	NT
WNV	Env	WNV	NT	NT	≥ 6.6
BVDV	Env	Hepatitis C	NT	NT	≥ 4.9
Parvo[a]	Non-Env	Parvovirus B19	NT	NT	≥ 6.1
HAV	Non-Env	HAV	NT	NT	≥ 5.8
PRV	Non-Env	Hepatitis B	NT	NT	≥ 5.3

[a] Porcine, NT=Not tested, Env=enveloped

CLINICAL PHARMACOLOGY

Profilnine is a mixture of the vitamin K-dependent clotting factors IX, II, X and low levels of VII. The administration of Profilnine temporarily increases the plasma levels of factor IX, thus enabling a temporary correction of the factor deficiency.

A clinical study that evaluated twelve subjects with hemophilia B indicated that, following administration of Profilnine, the factor IX *in vivo* half-life was 24.68 ± 8.29 hours and recovery was 1.15 ± 0.16 units/dL per unit infused per kg body weight.

Administration of factor IX complex can result in higher than normal levels of factor II due to its significantly longer half-life.

INDICATIONS AND USAGE

Profilnine is indicated for the prevention and control of bleeding in patients with factor IX deficiency (hemophilia B).

Profilnine contains non-therapeutic levels of factor VII, and is not indicated for use in the treatment of factor VII deficiency.

CONTRAINDICATIONS

None known.

WARNINGS

Because Profilnine is made from pooled human plasma, it may carry a risk of transmitting infectious agents, e.g., viruses, and theoretically, the Creutzfeldt-Jakob disease (CJD) agent. Stringent procedures designed to reduce the risk of adventitious agent transmission have been employed in the manufacture of this product, from the screening of plasma donors and the collection and testing of plasma to the application of viral elimination/reduction steps such as DEAE chromatography, solvent detergent treatment and nanofiltration in the manufacturing process. Despite these measures, such products can potentially transmit disease: therefore the risk of infectious agents cannot be totally eliminated. The physician must weigh the risks and benefits of using this product and discuss these issues with the patient. Appropriate vaccination (hepatitis A and B) for patients in receipt of plasma derived factor IX complex concentrates is recommended.

The use of factor IX complex concentrates has historically been associated with the development of thromboembolic complications and the use of such products may be potentially hazardous in patients undergoing surgery, in patients post surgery, in patients with known liver disease, and in patients with signs of fibrinolysis, thrombosis or disseminated intravascular coagulation (DIC). For these patients, clinical surveillance for early signs of consumptive coagulopathy should be initiated with appropriate biological testing when administering this product. Profilnine should only be administered to patients when the beneficial effects of use outweigh the serious risk of potential hypercoagulation.

PRECAUTIONS

General

Exercise caution when handling Profilnine due to the limited risk of exposure to viral infection. Discard any unused Profilnine vial contents. Discard administration equipment after single use. Do not resterilize components. Do not reuse components.

Information for Patients

After repeated treatment with Profilnine, patients should be monitored for the development of neutralizing antibodies (inhibitors) that should be quantified in Bethesda Units (BU) using appropriate biological testing.

Hypersensitivity and allergic type hypersensitivity reactions, including anaphylaxis, have been reported for all factor IX complex concentrate products. Patients must be informed of the early symptoms and signs of hypersensitivity reaction, including hives, generalized urticaria, angioedema, chest tightness, dyspnea, wheezing, faintness, hypotension, tachycardia and anaphylaxis. Patients must be advised to discontinue use of the product and contact their physician and/or seek immediate emergency care if these symptoms occur.

Pregnancy Category C

Animal reproduction studies have not been conducted with Profilnine. It is also not known whether Profilnine can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Profilnine should be given to a pregnant woman only if clearly indicated.

Pediatric Use

Safety and effectiveness in pediatric patients below the age of 16 have not been established. However, across a well controlled half-life and recovery clinical trial in patients previously treated with factor IX concentrates for Hemophilia B, the two pediatric patients receiving Profilnine responded similarly when compared with the adult patients.

ADVERSE REACTIONS

As with other intravenous administration of other plasma-derived products, the following reactions may be observed following administration: headache, fever, chills, flushing, nausea, vomiting, tingling lethargy, hives, or manifestation of allergic reactions.

In addition, during post-approval use of Profilnine, cases of allergic/hypersensitivity reactions (including urticaria, shortness of breath, hypotension, and pruritus) and adverse reactions characterized by either thrombosis or disseminated intravascular coagulation (DIC) have been reported. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

To report SUSPECTED ADVERSE REACTIONS, contact Grifols at 1-888-GRIFOLS (1-888-474-3657) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

* Unit refers to International Unit in the labeling of Profilnine.

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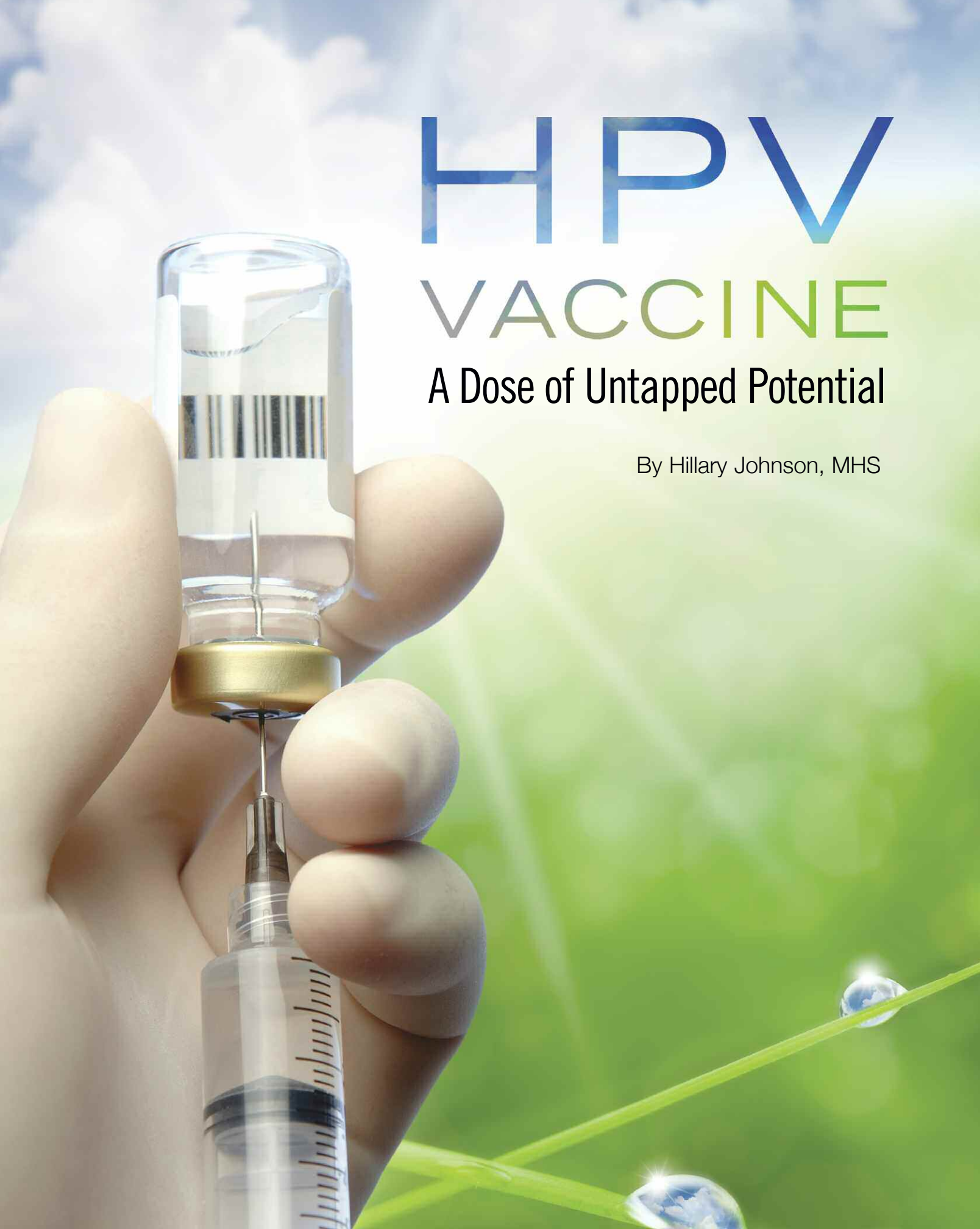

HPV VACCINE

A Dose of Untapped Potential

By Hillary Johnson, MHS

It is estimated that 79 million Americans are currently infected with human papillomavirus (HPV), and an additional 14 million HPV infections occur each year. The disease is so common, nearly everyone will be infected at some point. Approximately 26,000 new cancers each year are HPV-related, and most could be prevented with a simple three-dose series of HPV vaccine. While other countries are moving forward with successful HPV vaccination initiatives and seeing significant declines in infection in their populations, U.S. vaccination rates remain stagnantly low. With more than 4,000 preventable[1] deaths a year in the U.S., why aren't Americans getting vaccinated?

On July 23, 2014, the Centers for Disease Control and Prevention (CDC) released data from the 2013 National Immunization Survey of Teens (NIS-Teen), a very large, nationally representative survey that collects clinician-validated vaccination histories of adolescents ages 13 years to 17 years. The 2013 report summarized information on 18,264 teens and found that only 57.3 percent of girls and 34.6 percent of boys had initiated the Advisory Committee on Immunization Practices' (ACIP) recommended three-dose HPV vaccination series. And while vaccination coverage with greater than or equal to one dose of HPV vaccine had increased from 2012 (from 53.8 percent in 2012 to 57.3 percent in 2013 among adolescent girls and from 20.8 percent in 2012 to 34.6 percent in 2013 among adolescent boys), 2011 to 2012 had shown no improvements among adolescent girls at all.[2]

Admittedly, HPV vaccine is a relative newcomer to the list of ACIP routine recommendations (Merck's Gardasil was approved in 2006), and incremental entry into the market would be expected with any new vaccine. However, while CDC describes the initial uptake of HPV vaccine as good, it plateaued much sooner than expected. "We often think of about a 10 percentage point increase per year the first few years after a vaccine is recommended," says Dr. Anne Schuchat, assistant surgeon general in the U.S. Public Health Service and the director of CDC's National Center of Immunization and Respiratory Diseases. "So it was an early plateau."[3]

There are three routine vaccines targeted at adolescents, and ACIP also recommends administration of these and all age-appropriate vaccines during a single visit (typically the well-child visit at 11 or 12 years of age). These include the HPV vaccine, the Tdap vaccine that protects against tetanus, diphtheria and pertussis (whooping cough), and the meningococcal conjugate vaccine (MenACWY). With vaccine acceptance for HPV so low, but 2013 coverage estimates for Tdap and MenACWY at 86.0 percent and 77.8 percent, respectively,[4] there is clearly a disconnect among consumers and what should be considered three simultaneously recommended and administered vaccines.

A Cancer-Causing Virus

Human papillomavirus, or HPV, encompasses a group of more than 150 related viruses, each referred to as a "type" and given a number to distinguish it. Originally named for the warts (or papillomas) some HPV types cause, it was Dr. Harold zur Hausen's Nobel Prize-winning research in the 1970s that pursued the idea that HPV played a role in cervical cancer as well. We now know that approximately 40 HPV types affect the mucosal or genital regions of the body, with some types classified as high-risk and cancer-causing (most notably HPV 16 and 18 — responsible for 70 percent of cervical cancers) and some types classified as non-cancer-causing and low-risk (most notably HPV 6 and 11 — accounting for 90 percent of anal and genital warts).

There are three routine vaccines targeted at adolescents, and ACIP also recommends administration of these and all age-appropriate vaccines during a single visit.

HPV is the most common sexually transmitted infection (STI), and nearly all men and women will become infected with at least one type of HPV at some point in their lives.[5] Transmission occurs from skin-to-skin contact, and people do not need to be symptomatic to spread the virus. CDC estimates

Available HPV Vaccine Formulations

	2vHPV	4vHPV	9vHPV
Vaccine	Cervarix	Gardasil	Gardasil 9
HPV Types	16, 18	6, 11, 16, 18	6, 11, 16, 18, 31, 33, 45, 52, 58
Approved For	Females	Females and Males	Females and Males
Manufacturer	GlaxoSmithKline	Merck & Co. Inc.	Merck & Co. Inc.

more than 79 million Americans are currently infected, and 14 million new infections occur each year domestically.[6] Most often, people remain asymptomatic and will never even know they had the virus, but for those who do manifest disease, the results can be devastating.

HPV is associated with cervical, vulvar and vaginal cancers in females, penile cancer in males, and anal and oropharyngeal cancer in both males and females. HPV types 16 and 18 cause the majority (64 percent) of all HPV-associated cancers (approximately 21,300 cases annually).[7] Worldwide, 500,000 women are diagnosed each year with cervical cancer alone, and 250,000 will die of their disease.[8]

HPV vaccine is a prophylactic, or preventive, vaccine, meaning it works best before exposure.

A Cancer-Preventing Vaccine Emerges

Two companies currently have approved HPV vaccines licensed for use in the U.S.: bivalent HPV vaccine (2vHPV) called Cervarix by GlaxoSmithKline, and quadrivalent (4vHPV) and 9-valent (9vHPV) HPV vaccines by Merck & Co. called Gardasil and Gardasil 9, respectively.

HPV vaccines utilize recombinant DNA technology (meaning DNA from different species are combined together). A host plasmid is injected with a surface protein gene (L1) from HPV DNA to generate viral proteins capable of self-assembling into virus-like particles (VLPs) for each of the targeted HPV types. The HPV VLPs look superficially identical to actual HPV under the microscope, but they do not have a genome within so cannot reproduce themselves. Encountering the L1 HPV surface protein effectively mimics exposure to HPV and provokes the immune system to generate antibodies against specific types of HPV targeted in the vaccine. As a result, HPV vaccines are some of the most immunogenic vaccines available, and produce better immune response in the body than natural infection.[1]

HPV vaccine is a prophylactic, or preventive, vaccine, meaning it works best before exposure.

And, What's More, the HPV Vaccine Works

Some of the best data available on vaccine efficacy comes from Australia, where in 2007, the country began implementing a nationwide school-based 4vHPV vaccination campaign. By 2010, Australia had achieved more than 80 percent coverage for the first two doses of HPV vaccine among 12- to 13-year-old girls. The nation saw large declines (92.6 percent) in the proportion of women under 21 years of age diagnosed with genital warts during the vaccination period, consistent with vaccine-induced protection.[9] (As genital warts occur much sooner after HPV infection [on average weeks to months, as opposed to several years after infection for cancer to appear],[10] these data serve as an early indicator of potential vaccine efficacy.) Additionally promising, in 2011, no genital wart diagnoses were made among 235 women under 21 years of age who reported prior HPV vaccination. While Australia targeted only girls for vaccination in the program, researchers still noted an 81 percent decline in the proportion of men under 21 years diagnosed with genital warts during the vaccination period as well, indicating notable herd immunity at the high coverage level. No significant decline in genital wart diagnoses were seen in men and women over 30 years of age (a group not targeted for vaccination) during the study period.[9]

Australia is not alone. Published reports of declines in HPV vaccine type prevalence and anogenital warts from several other countries (including Denmark,[11] Germany[12] and New Zealand[13]) further strengthen the evidence of direct, as well as indirect, impact of the quadrivalent HPV vaccine.

U.S. Success

The U.S. has not achieved anywhere near the vaccine coverage demonstrated in the Australian study, but early data still shows an impact in disease prevention. National Health and Nutrition Examination Surveys (NHANES) data showed a 56 percent decline in prevalence of HPV 6/11/16/18 across surveyed pre- and post-vaccine era girls ages 14 years to 19 years. NHANES is conducted every two years and is considered the gold standard

on health indicators. For the survey, government health workers interviewed more than 8,000 girls and women ages 14 years to 59 years and collected vaginal swabs that were evaluated by CDC. Prior to the availability of HPV vaccination, HPV infection rates were steady among all age groups of women. The subsequent declines noted in younger, vaccinated age groups were not observed in older, unvaccinated age groups, further highlighting the vaccine's impact.[14]

Another early indicator of success can be seen in a recent study examining incidence of genital warts among U.S. service members. Researchers found that incidence rates of genital warts diagnoses markedly declined among female service members in the 4vHPV vaccine-eligible age range from 2007 (following introduction of the 4vHPV vaccine) through 2010.[15]

Too Young for STI Protection? A Taboo Topic for Parents

Many parents think HPV vaccine is not needed, or rather, not needed "yet" when it comes to STI prevention. It is a costly assumption on many levels.

The research on HPV antibody data shows that adolescents at the 11- and 12-year-old age range have much higher antibody response than do older teens or young adults.[16] This is also the ideal age for vaccination exactly because very little exposure to HPV occurs among young adolescents, and the vaccine works best prior to exposure when both boys and girls, fully vaccinated with the three-dose series, have had the time to develop the antibody protection. And while the research will continue to follow vaccinated adolescents into adulthood, there has been no evidence of waning protection over time.[16,17]

The notion of sexual activity among youth brings with it a potential rabbit hole of questions among HPV vaccine-hesitant parents. Some believe that their children are not yet at risk for STIs (and thus do not need the HPV vaccine), and some critics have expressed concern that vaccination might encourage earlier onset of risk-taking behaviors. Research has addressed both these issues.

Unfortunately, a 2012 study in the *Journal of Infectious Diseases* found that HPV was detected in 46 percent of women "prior" to their first vaginal sex.[18] This highlights the high transmissibility of HPV. Transmission can occur from intimate skin-to-skin contact, and intercourse is not required[19] (again reinforcing the need to vaccinate at a younger age prior to exposure). Luckily, contrary to some parental worries, it seems HPV vaccination is not a blank check for unsafe sexual activity. Multiple studies have shown that HPV vaccination is not associated with increased sexual activity outcomes that include pregnancy, STI testing or diagnosis, or contraceptive counseling.[20,21]

Sexual activity can be a tricky topic among providers and parents of children at such a young age. However, providers often actually overestimate parents' concerns. Missed opportunities can result from assumptions about the timing of vaccination relative to sexual activity as well.[22] CDC advises routine recommendation of HPV vaccine as "cancer" prevention rather than "STI" prevention to address this issue.

Expanding Prevention

The U.S. Food and Drug Administration approved Gardasil 9, a new 9-valent HPV vaccine, in December 2014. Marketed by Merck & Co. Inc., the vaccine targets HPV types 6, 11, 16 and 18, the types targeted by the company's quadrivalent HPV vaccine (4vHPV), as well as five additional types (31, 33, 45, 52 and 58). These five additional HPV types are responsible for an additional 10 percent of invasive HPV-associated cancers (approximately 3,400 cases annually).[1] The Advisory Committee on Immunization Practices (ACIP) has reviewed immunogenicity, efficacy and safety studies, and in February 2015 voted to allow 9vHPV for use in routine HPV vaccination. There is currently no preference among respectively approved HPV vaccine formulations for either men or women. (The recommendation is that providers should complete the three-dose series with vaccine on hand, rather than waiting for a different formulation, to ensure they do not miss a vaccination opportunity entirely.) ACIP anticipates reviewing additional clinical trial data assessing alternative dosing schedules and will likely address the question of a 9-valent booster among recipients who have already completed the three-dose series with quadrivalent or bivalent vaccine at a future date.[2]

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But, Is the HPV Vaccine Safe?

The 2013 NIS-Teen asked parents who reported they were not likely to vaccinate their teen in the 12 months after interviews, or were unsure of their vaccination plans, to identify the main reason why their teen would remain unvaccinated. Safety ranked third for girls and fifth for boys.[2] In the U.S., postlicensure vaccine safety monitoring and evaluation are conducted independently by federal agencies and vaccine manufacturers. Today, HPV is one of the best-studied vaccinations. Clinical trials studied bivalent and quadrivalent HPV vaccines in a cumulative 60,000 people.[23] Since licensure, more than 67 million doses have been distributed in the U.S., and more than one

The Celebrity Touch

Recent comments from celebrities have helped perpetuate questions of vaccine safety. During the Republican Presidential Primary in 2011, former U.S. Representative Michele Bachman was seen on NBC's "Today" show calling HPV vaccine potentially a very dangerous drug with "very dangerous side effects," including "mental retardation."[1] (The Institute of Medicine has found the vaccine is generally safe, and there is no evidence linking it to mental retardation.) More recently, talk show host Katie Couric addressed HPV vaccination on her program. Couric was accused of a lopsided presentation,[2] since the 2013 broadcast included her interview of two mothers of daughters claiming adverse health outcomes (one death) following HPV vaccination. Couric admitted no proof has linked these two health issues to HPV vaccine. Following public outcry, Couric herself wrote a response in the *Huffington Post* in which she apologized for the skewed presentation of information leaning toward anti-vaccination, and stated her own conclusions that the benefits of HPV vaccine outweighed the risks, and she had her own daughters each vaccinated against HPV.[3]

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3. Couric K. Furthering the Conversation on the HPV Vaccine. *Huffington Post*, Dec. 10, 2013. Accessed at www.huffingtonpost.com/katie-couric/vaccine-hpv-furthering-conversation_b_4418568.html.

million people have been studied in postlicensure trials.[24] No serious safety concerns have been linked to HPV vaccinations in any of these studies.[2]

The most common adverse events, or side effects, reported to the Vaccine Adverse Event Reporting System (VAERS) are considered mild and include injection-site reactions (such as pain, redness or swelling), dizziness, fainting, nausea and headache. Although considered mild, these reactions should be and are taken seriously, particularly the risk of syncope, or fainting. As a result, ACIP updated its vaccination recommendation to include information about preventing falls and possible injuries from fainting after receiving shots. Providers should share this information with their patients and have the patients remain seated and observed for 15 minutes after receiving a shot. It is also noted that HPV vaccine is one of the most painful vaccines because of its high salt concentration.

Overall, reports of adverse events to VAERS have been decreasing each year since 2008[2] and are consistent with prelicensure clinical trial data and with the 2009 published summary of the first 2.5 years of postlicensure reporting to VAERS.[2] Among serious adverse events reported, no unusual patterns or clustering has been identified that would suggest events were caused by HPV vaccine.[23] And while recent comments by celebrities have helped perpetuate the safety question in the news (see The Celebrity Touch), national safety monitoring data continue to indicate that the HPV vaccine is safe.[2]

While Rates of Vaccine Uptake Among Girls May Seem Low, Boys Have Even Further to Go

A routine recommendation of HPV vaccine for females was first published in June 2006. Recommendations for males have taken a slightly more complicated journey. ACIP first published a permissive "may be given" recommendation for 4vHPV for males in October 2009, and did not publish a full routine recommendation for boys until October 2011. Dr. Paul Offit of Children's Hospital of Philadelphia argues that this delayed recommendation for 4vHPV for boys may have led to a false public perception among some that HPV was not as important for boys. "We certainly knew even by 2006 that the [4vHPV] vaccine could prevent [HPV] infection in men," he said in a recent Association of Immunization Managers presentation. "I think what they were waiting for was data showing that it could prevent anal cancers in men, and those data came later. But you know, obviously, if a vaccine can prevent infection, it can prevent cancer. A cell can't be transformed to become cancerous if it can't be infected."[1]

About one-third of HPV-associated cancers occur in males. While cervical cancer does occur most frequently, the second most diagnosed HPV-associated cancer is oropharyngeal, almost 80 percent of which are in males.[24] HPV vaccine benefits both males and females.

Making Use of the Tools at Hand

The data show that a recommendation from a healthcare professional is strongly associated with teens getting vaccinated. While the percentage of parents who reported receiving a recommendation for HPV vaccine increased in 2013 NIS-Teen, nearly one-third of parents of girls and more than half of parents of boys reported that their child's clinician had not recommended HPV vaccine for their child.[2] One of the top five reasons parents listed for not getting the HPV vaccine for their child was that it had not been recommended to them by their teen's doctor or nurse. Other studies show similar results. A 2014 study published in *Pediatrics* listed a lack of a physician recommendation as the most common reason (44 percent) parents reported for not vaccinating their daughters.[22]

The keys to moving forward and reducing vaccine-preventable infections and cancers caused by HPV lie in improving practice

patterns and ensuring clinicians utilize every opportunity to recommend HPV vaccines and address parent questions and concerns, particularly around safety and need.

At 12,000 cases of cervical cancer and 4,000 deaths a year in the U.S., CDC estimates that maintaining current HPV vaccination levels would prevent 45,000 cases of cervical cancer and 14,000 deaths among a cohort of girls now age 13 and younger over the course of their lifetimes. However, increasing vaccination levels to 80 percent (on par with other recommended adolescent vaccines) would prevent an additional 53,000 cancers and nearly 17,000 deaths.[25]

And there are plenty of chances to do so. When a teen is in the doctor's office and receives another vaccine, but not HPV, that is a missed opportunity. CDC estimates that if every time an 11- or 12-year-old girl received another vaccine and HPV was administered as well, HPV coverage by the 13th birthday would have been 91 percent for girls.[2]

Providers have indicated they need resources to speak to their patients' parents, and CDC has produced a website full of resources in response: cdc.gov/vaccines/YouAreTheKey.

Unlike many other diseases addressed through vaccination, severe sequelae from HPV often do not appear until years or decades after exposure. This means that the pediatricians responsible for recommending and administering the HPV vaccine are not likely to be the diagnosing provider when HPV manifests into a disease like cancer. That is why it is important to take advantage of every opportunity available to educate both patients and providers on the importance of HPV vaccination. Clinicians should strongly recommend the HPV vaccine the same way and the same day they recommend and administer meningococcal conjugate and Tdap vaccines. ❖

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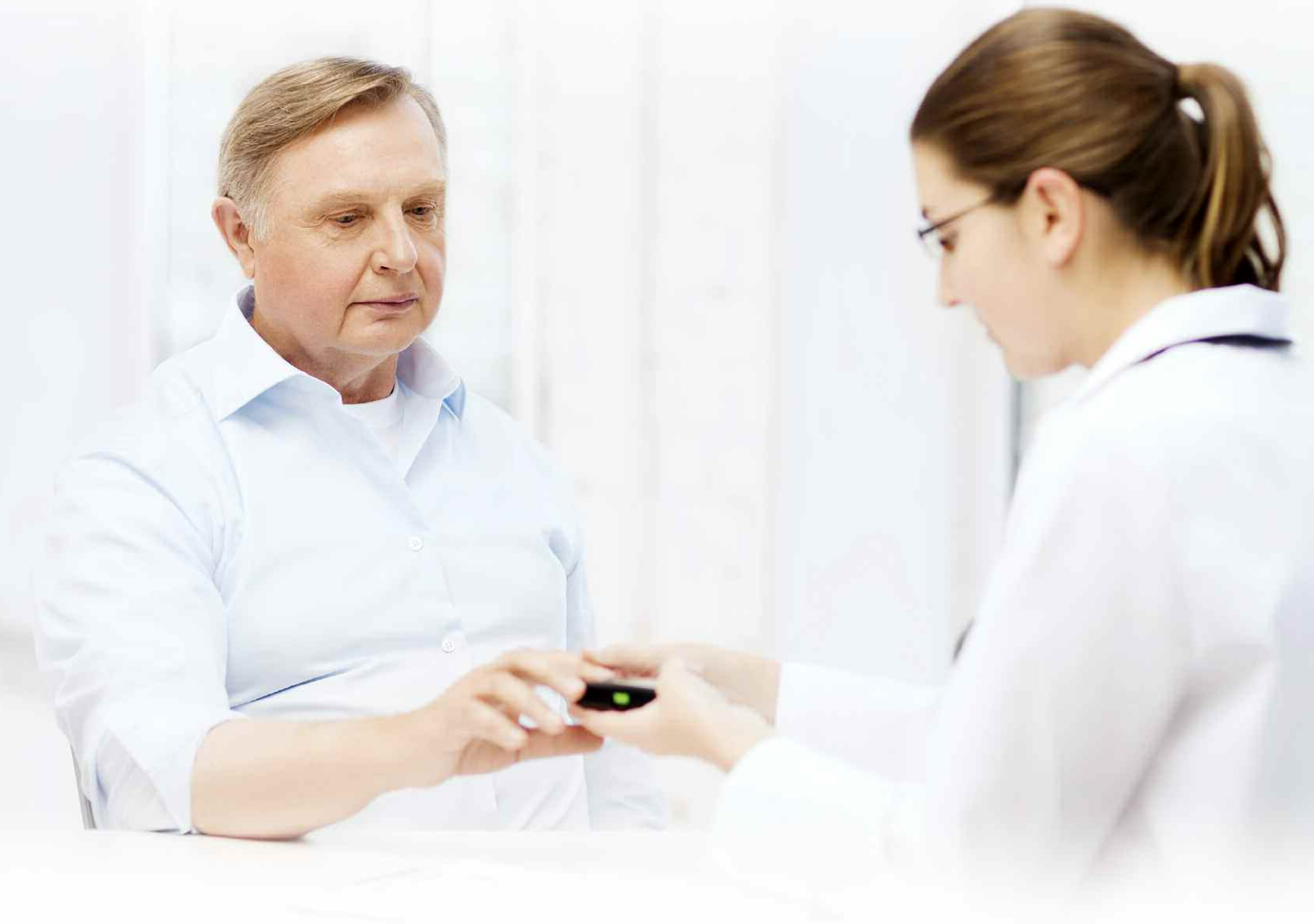
The Escalating Diabetes Epidemic

By Tina Tockarshewsky



Will the evolving therapeutic guidelines for treating diabetes, as well as managing its risks and complications, stem the tide of this costly and sometimes deadly disease?

Diabetes continues to be a complex chronic illness epidemic defined by staggering statistics expressed in millions, if not billions. According to the Centers for Disease Control and Prevention's (CDC) *2014 National Diabetes Statistics Report*, 29.1 million people (or 9.3 percent of the U.S. population) have diabetes; of these, 8.1 million are undiagnosed (27.8 percent).

Year after year, the numbers escalate exponentially. Currently, it is estimated that:

- 1.7 million new cases of diabetes are diagnosed each year (in adults 20 years or older);
- 86 million adults (greater than one in three) are pre-diabetic; and
- 15 percent to 30 percent of those with pre-diabetes will develop type 2 diabetes within five years.

The prevalence of diabetes (as well as pre-diabetes) is also increasing across age groups and races/ethnicities. Type 1 diabetes, once thought of as a childhood disease, has begun to appear in adults; type 2 diabetes, once a chronic illness of adulthood, has been trending younger into the childhood years at alarming rates. While diabetes can be found in all demographics, its presence is growing across and within races and ethnicities:

- 15.9 percent of American Indians/Alaska Natives adults
- 13.2 percent of non-Hispanic black adults
- 12.8 percent of Hispanic adults
- 9 percent of Asian-American adults

And the numbers continue to escalate.

The Cost of Diabetes

Using 2012 data, CDC estimates this diabetes epidemic costs the U.S. $245 billion in combined direct and indirect costs. Direct medical costs in 2012 were $176 billion, a number 2.3 times higher than costs for non-diabetics; indirect costs come in at an alarming $69 billion due to disability, work loss and premature death. Many of these numbers are feared to be an underestimation of the actual human and economic toll.

Case in point, only 35 percent to 40 percent of people with diabetes actually had diabetes noted on their death certificates, and approximately 10 percent to 15 percent had diabetes listed as cause of death — yet, the risk of death for those with diabetes is 50 percent greater than it is for those without diabetes. Thankfully, for those deaths reported, CDC can track diabetes-related death rates falling up to 40 percent between 1997 and 2006 as a result of progressive improvements in cardiovascular care, glucose management and lifestyle interventions.[1]

Picking Up the Pace of the Therapeutic Pipeline

The therapeutic guidelines for treating diabetes, as well as managing its risks and complications, are continually being refined as a result of research and outcomes. Diagnostic benchmarks and tools also are evolving and improving. While there have been great strides made in recognizing that disease management involves healthy lifestyle changes (such as diet and exercise regimens) in conjunction with medications, it is also well-documented that medications — and improved adherence to medication regimens — increase health outcomes, as well as reduce risks and their associated costs. According to a study published in the *American Journal of Managed Care*,[2] medication adherence by diabetes patients results in fewer diabetes-related complications, causing fewer amputations/ulcers (4 percent lower), fewer renal events (5 percent lower), less neuropathy/nerve damage (4 percent lower) and less retinopathy/eye damage (2.7 percent lower). Additionally, a study published in *Health Affairs* indicates that better medication adherence by patients could prevent more than one million emergency department visits and hospitalizations each year — an annual healthcare cost savings of $8.3 billion.[3]

Eight new classes of type 2 diabetes medications have been added by the U.S. Food and Drug Administration in the last few years.

A quick "diabetes" word search on www.clinicaltrial.gov generates a listing of nearly 3,000 active clinical trials across the type 1 and type 2 chronic care and symptom management spectrum. The Pharmaceutical Research and Manufacturers of America's (PHRMA) *2014 Report on Medicines in Development: Diabetes* cites 180 new medicines in development (Phase I, II, III and applications submitted) for type 1 and type 2 diabetes and diabetes-related conditions.[4] This pipeline also includes 110 medications that may benefit older adults, of particular note since diabetes impacts 10.9 million Americans over age 65.[2]

New Therapies = New Approaches

Eight new classes of type 2 diabetes medications have been added by the U.S. Food and Drug Administration (FDA) in the last few years. The current pipeline being tested will hopefully expand the therapeutic toolkit even further by developing new medications to potentially offer:

- Improvements in glucose-dependent insulin secretion

Figure 1. Newly FDA-Approved Therapies for Improving Diabetic Care[4]

Duetact (pioglitazone/glimepiride)	a combination therapy bringing together two previously FDA-approved type 2 medications for a singular delivery that can target insulin resistance while simultaneously increasing pancreatic insulin production
Invokana (canagliflozin)	the first sodium-glucose co-transporter 2 (SGLT2) inhibitor approved for type 2, promoting excess glucose removal via urination
Farxiga (dapagliflozin)	a newer SGLT2 inhibitor for glycemic control in type 2 adults
Nesina (alogliptin)	a new DPP-4 inhibitor that improves pancreatic function to secrete insulin and manage blood glucose levels

• Diabetic nerve pain relief, including a medication to block an enzyme associated with diabetic neuropathy (nerve damage)

• Stimulation and enhancement of insulin-producing cell regeneration

• Next-generation oral treatments

• Once-weekly treatments

• Glucose regulation for type 2 by a delayed-release formulation of metformin that acts as a gut sensory modulator (GSM)

• First-in-class therapy to protect against and treat diabetic nephropathy (chronic progressive kidney disease)[4]

While the market awaits these and other trial outcomes, in February, FDA gave expanded use approval for Lucentis (ranibizumab injection) 0.3 mg as the first drug to treat diabetic retinopathy (DR) in patients with diabetic macular edema (DME). A once-a-month eye injection administered in a physician's office, Lucentis is intended for use in conjunction with other appropriate control therapies. With diabetes being the leading cause of new blindness for people ages 20 to 74 years, diabetic retinopathy is a significant diabetes complication and the most common diabetic eye disease (33 percent of diabetics older than 40 have diabetic retinopathy). Lucentis had been previously approved to treat DME, which led to two clinical studies being conducted to test the drug's safety and efficacy in treating DR with DME. Strong early evidence caused FDA to fast track the drug's approval for DR, finally offering people with diabetes access to their first retinopathy therapy.[5]

Heightened emphasis on improving quality of life for those diagnosed has yielded significant new therapies within the scope of the past two years. FDA has already approved several unique therapies to expand the clinician's toolkit for improving diabetes care (see Figure 1).

Resolving DPP-4 Concerns

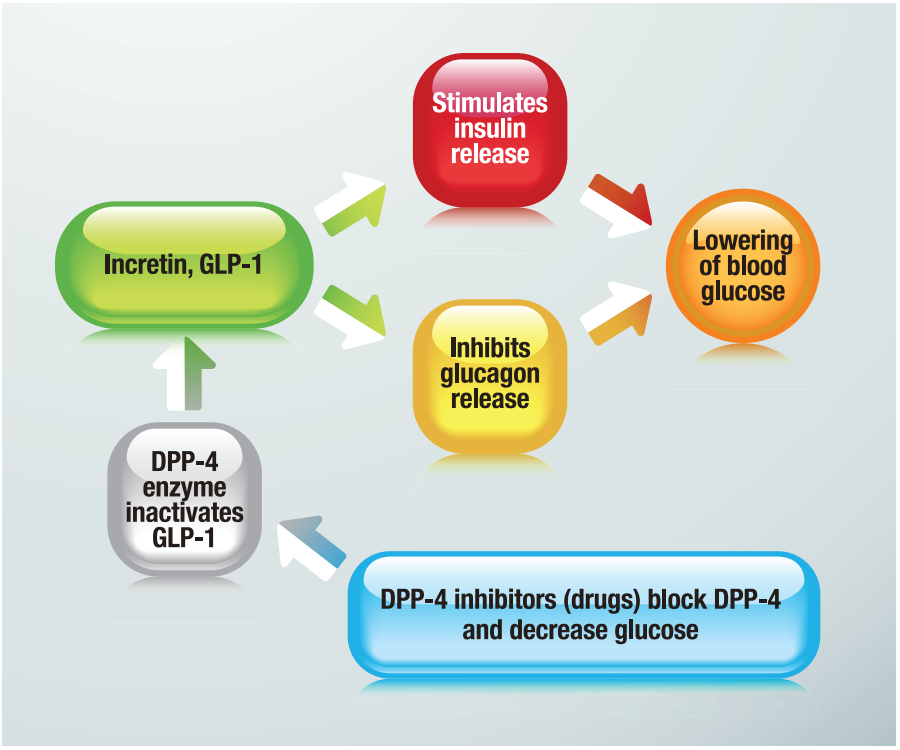
Inhibitors of dipeptidyl peptidase 4, known as DPP-4 inhibitors, are a class of oral hypoglycemics used to treat type 2 diabetes (see Figure 2). Despite their promise as newer front-line therapies, all of the DPP-4 inhibitors, like alogliptin (Nesina) and sitagliptin (Januvia), are currently receiving close examination due to cardiovascular events documented across this class of medication. Those in the diabetes field are anxiously awaiting a soon-to-be completed cardiovascular-outcomes trial for Januvia use, with results due to be presented in June at an American Diabetes Association (ADA) meeting.

Outcomes of the trial, called TECOS, are expected to be particularly telling because they specifically test Januvia, the DPP-4 inhibitor that has been available and used for the longest period of time. This trial follows on the heels of two other large DPP-4 inhibitor outcomes trial studies, Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus (SAVOR)-TIMI 53 and EXAMINE with alogliptin, both of which yielded unexpected cardiovascular events indicative of a possible increase in risk for heart failure in type 2 patients taking these medications. SAVOR-TIMI 53 results had a hazard ratio of 1.27; P = .007 for hospitalization for heart failure in patients taking saxagliptin vs. placebo, resulting in FDA announcing it would more closely review saxagliptin's heart failure rate. EXAMINE also yielded a pattern of higher heart failure hospitalization risk for diabetic patients on alogliptin. Other sitagliptin studies before TECOS have produced conflicting heart failure results. Experts still believe DPP-4 inhibitors are generally safe for diabetes patients with heart failure unless the patient has a history of advanced heart failure and concomitant renal failure. With mixed results and serious concerns documented, the June TECOS report will be significant for patients, professionals and the pharmaceutical industry alike as all try to assess the future for DPP-4 inhibitors.[6]

Do Exchanges Restrict Access to Therapies?

Access to care is a crucial part of successful diabetes treatment and management. With more therapeutic options available (and hopefully more on the horizon), medication adherence is a strong driver of health outcomes. Yet, socio-economic factors hindering diagnoses, as well as policies and provider coverage issues, may contribute to roadblocks for accessing therapies. A PHRMA analysis of 84 health insurance exchange plans in the

Figure 2. How DPP-4 Inhibitors Work



15 states with the highest expected 2014 exchange enrollment found some plans created significant barriers to access for diabetes therapies. These included the exclusion of certain types of medicines from the formulary, high co-insurance rates for some diabetes medications, and a greater likelihood for diabetes medications to face step therapy or prior authorization challenges in the exchanges (compared with employer or benchmark plans).

With co-insurance of more than 40 percent required for antidiabetics 21 percent of the time and more than 40 percent for insulins 16 percent of the time, resulting annual out-of-pocket costs for patients could be from $195 to $1,150 for antidiabetics and $600 to $4,000 for insulins. Variations in plans from state to state not only risk inconsistencies in care, but the analysis showed that the states anticipated to have the highest exchange enrollments do not cover many diabetes medications: Nine of these top 15 states cover less than 60 percent of single-source diabetes medicines on the market, with plans in Georgia, Indiana and Ohio, N.Y., in particular covering, on average, less than half of the single-source medicines available.[7]

Modifications to Care Management and New Standards of Care

The base of knowledge for improvements in clinical care for diabetes continues to expand. Because cardiovascular disease (CVD) is the primary cause of death associated with diabetes and the leading contributor to diabetes costs, its risks of heart attacks and stroke become a critical part of the overall management and prevention treatment plan for people with diabetes. Of all the common diabetes comorbidities leading to CVD risk, hypertension management has been shown to be one of the strongest areas for health improvements.

In the Feb. 10 issue of *JAMA*, researchers show that blood pressure-lowering treatment for type 2 patients results in a lower CVD risk, fewer heart disease events and improvements in mortality rates. People with diabetes, on average, have higher blood pressure (BP) levels; however, there currently exists a debate over which patients warrant BP-lowering therapy and which BP targets to use for benchmarking. In the *JAMA* article, researchers note that every 10 mmHg lower systolic BP demonstrated a lower risk of mortality, CVD events, heart attacks, stroke, albuminuria (excess protein in the urine) and diabetic retinopathy. Although there were proportional health gains realized for most outcomes when the systolic BP level was brought to 140 mmHg, the data reported that bringing the level down further to below 130 mmHg provided even lower risk for stroke, retinopathy and albuminuria. This possibly indicates that people at high risk for these complications could greatly benefit from the BP reduction.[8]

Because of the chronic care complexities of managing diabetes, in 2012, ADA published a consensus document reviewing all relevant literature to provide clinical practice recommendations. That document has been subsequently updated in the recent January "Standards of Medical Care in Diabetes — 2015." While broken down into 14 areas of focus, the document is meant to be viewed in its entirety for evidence-based and expert opinions on best practices and guidelines for care.

In acknowledging the complexities, the document offers the following strategies for improving care:

- "A patient-centered communication style that incorporates patient preferences, assesses literacy and numeracy, and addresses cultural barriers to care should be used;
- Treatment decisions should be timely and founded on evidence-based guidelines that are tailored to individual patient preferences, prognoses, and comorbidities;
- Care should be aligned with components of the Chronic

Care Model (CCM) to ensure productive interactions between a prepared proactive practice team and an informed activated patient; and,

• When feasible, care systems should support team-based care, community involvement, patient registries, and decision support tools to meet patient needs."[9]

The standards stress that inherent to these strategies are three themes clinicians, policymakers and advocates need to be mindful of: patient centeredness, diabetes across the life span and advocacy for people with diabetes.

Access to care is a crucial part of successful diabetes treatment and management.

Practicing patient centeredness recognizes that recommendations are, indeed, just recommendations: The clinician needs to consider the particular needs and risks for each individual patient when developing individualized plans of care. Diabetes across the life span acknowledges the challenge of managing and coordinating care between clinical teams as patients transition through different stages of their lives (including all stages of pregnancy). It also recognizes that diabetes is trending younger, and concedes that many older adults are living longer with chronic diabetes — a demographic for which there is a lack of clinical trial evidence to help guide therapy use. Advocacy promotes the need to help patients access lifestyle improvements that can prevent diabetes or help with quality of life for those diagnosed. Especially since lifestyle factors like weight management, physical activity and smoking cessation can have huge health impacts — and socioeconomic factors can become barriers to diagnosis, care and access to these programs — advocacy becomes critical to connect patients with programs that can directly impact their health.

In updating the 2015 standards, several key revisions are worth noting because they reflect new research and changes in expert opinion:

• *Classification and diagnosis of diabetes:* For obese Asian-Americans, the body mass index cutoff point for screening for pre-diabetes and type 2 diabetes changed to 23 kg/m2 (vs. 25 kg/m2), reflecting current evidence that this population (vs. the general population) is at a greater risk for diabetes at lower BMI levels.

• *Foundations of care: Education, nutrition, physical activity, smoking cessation, psychosocial care and immunization:*

-Given new evidence that all people, including those with diabetes, should limit the amount of time they are sedentary to be less than 90 minutes spent sitting, the physical activity section encourages patients to break up extended amounts of sedentary time.

-With the increasing popularity of e-cigarettes, the standards point out that e-cigarettes are not considered a smoking alternative or cessation tool.

-Immunization guidelines now reflect CDC guidelines for PCV13 and PPSV23 vaccinations in older adults.

• *Glycemic targets:* ADA recommendations for pre-meal blood glucose targets are now 80 mg/dL to 130 mg/dL, rather than 70 mg/dL to 130 mg/dL as a result of new data comparing actual average glucose levels with A1C targets.

• *Cardiovascular disease and risk management:* To reflect evidence from randomized clinical trials, the recommended goal for diastolic blood pressure management was changed from 80 mmHg to 90 mmHg for most people with diabetes and hypertension. Statins treatment and lipid monitoring recommendations were adjusted to treatment initiation (and initial statin dose) being driven by risk status rather than LDL cholesterol level. Lipid screening profile is recommended at diabetes diagnosis, at initial medical evaluation and/or at age 40, and periodically after that.

• *Microvascular complications and foot care:* Foot examinations during every clinical visit are encouraged, especially for those with insensate feet, foot deformities or history of foot ulcers, to identify those at high risk for foot-related complications.

• *Children and adolescents:* With new evidence indicating the importance of tight glycemic control in children and adolescents with diabetes, a target of A1C of less than 7.5 percent is recommended for all pediatric age groups, with individualization still being encouraged.

• *Management of diabetes in pregnancy:* A newly added section addressing pregnancy provides recommendations from pre-conception through delivery regarding care and diabetes management.[9]

Initial Evaluation and Diabetes Management Planning

The standards also extensively address the many diabetes complications and comorbidities. Some of the recommendations include screening, as appropriate, those with type 1 diabetes for autoimmune diseases (e.g., thyroid dysfunction, celiac disease), plus encouragement to assess for common co-morbid conditions (e.g., depression, obstructive sleep apnea, fatty liver disease, fractures, cancer, cognitive impairment, low testosterone in men, periodontal disease and hearing impairment) that may complicate diabetes management.

Not included in the standards is a new study released Jan. 8 in *Diabetes Care* citing the possibilities of using a procedure called corneal confocal microscopy (CCM) to predict diabetic peripheral neuropathy (DPN). Researchers used CCM to

assess deficits in corneal nerve fiber length (CNFL) in 90 non-neuropathic type 1 patients over the course of four years and then assessed who did and did not develop DPN. They found that the receiver operator characteristic curve could be used to determine measures of neuropathy to predict DPN. While CCM has been previously used in assessing DPN, the researchers were pleased to discover the ability of CCM to predict DPN, which expanded the diagnostic capabilities of this novel ophthalmic marker.[10] "Confocal microscopy (CCM) holds great potential as a diagnostic tool for peripheral neuropathy in clinical trials," concurs A. Gordon Smith, MD, director of the University of Utah's Peripheral Neuropathy Clinic and Cutaneous Innervation Laboratory and vice chair of research for the department of neurology. "With diabetic peripheral neuropathy, the biggest challenge for research and developing treatments is that the focus continues to be primarily symptomatic for pain rather than focusing on disease alteration. For this reason, we're looking at the expansion of lifestyle interventions to address painful diabetic peripheral neuropathy."

The University of Utah team has recently published findings in both the *Annals of Neurology* (January 2015) and the *Annals of Clinical and Translational Neurology* (October 2014) linking exercise directly to possible disease modifications for DPN.[11,12] Exercise was found to increase cutaneous nerve density in diabetic patients without neuropathy, plus exercise resulted in the clear ability for cutaneous axons to regenerate following controlled denervation, with the exercise actually enhancing nerve regeneration rates.

Early diabetic neuropathy involves the loss of unmyelinated axons; this causes pain, numbness and progressive deterioration of intraepidermal nerve fiber density (IENFD). The Utah team found that when patients with type 2 diabetes — but without neuropathy — were given therapeutic interventions of either lifestyle counseling or weekly exercise for one year, the exercise cohort demonstrated significant increase in distal leg IENFD, yet the counseling cohort remained the same. Not only does this indicate that damage to unmyelinated axons could be prevented in pre-diabetic conditions, it also demonstrated that IENFD may become a useful biomarker for future clinical trials assessing prevention.

In yet another approach to tracking IENFD involvement, a study of the unmyelinated cutaneous axons was conducted using the premise that these axons are not only susceptible to physical and metabolic injury, but they also are very capable of rapid regeneration. Metabolic syndrome served as the test since it demonstrates reduced baseline IENFD and cutaneous regeneration comparable to rates seen in diabetes. A short but intense six-month exercise program designed to improve glucose, insulin and lipid metabolism resulted in a clear increase in the ability of cutaneous axons to regenerate following controlled denervation. Reduced A1C levels were the primary identifiable individual metabolic result of the exercise intervention, and most strongly correlated with the enhanced regenerative capacity of the axons. Because the study showed significant regeneration after only a short period of exercise intervention, the promise of exercise to prevent and treat diabetic nerve damage and associated pain is highly encouraging.

A Hopeful Future for Managing Diabetes

Just as the diabetes numbers continuously evolve, so, too, does the rate of research and development to stem the tide of the diabetes epidemic. The significant amount of work being done across the field and the improvements in care and treatment are also harbingers of a more hopeful future in managing this complex chronic illness. Still, bringing this epidemic under control and seeking prevention for millions from diabetes' path of destruction and death is critical. Progress is being made, but time will tell whether that progress can outpace the diabetes juggernaut. ❖

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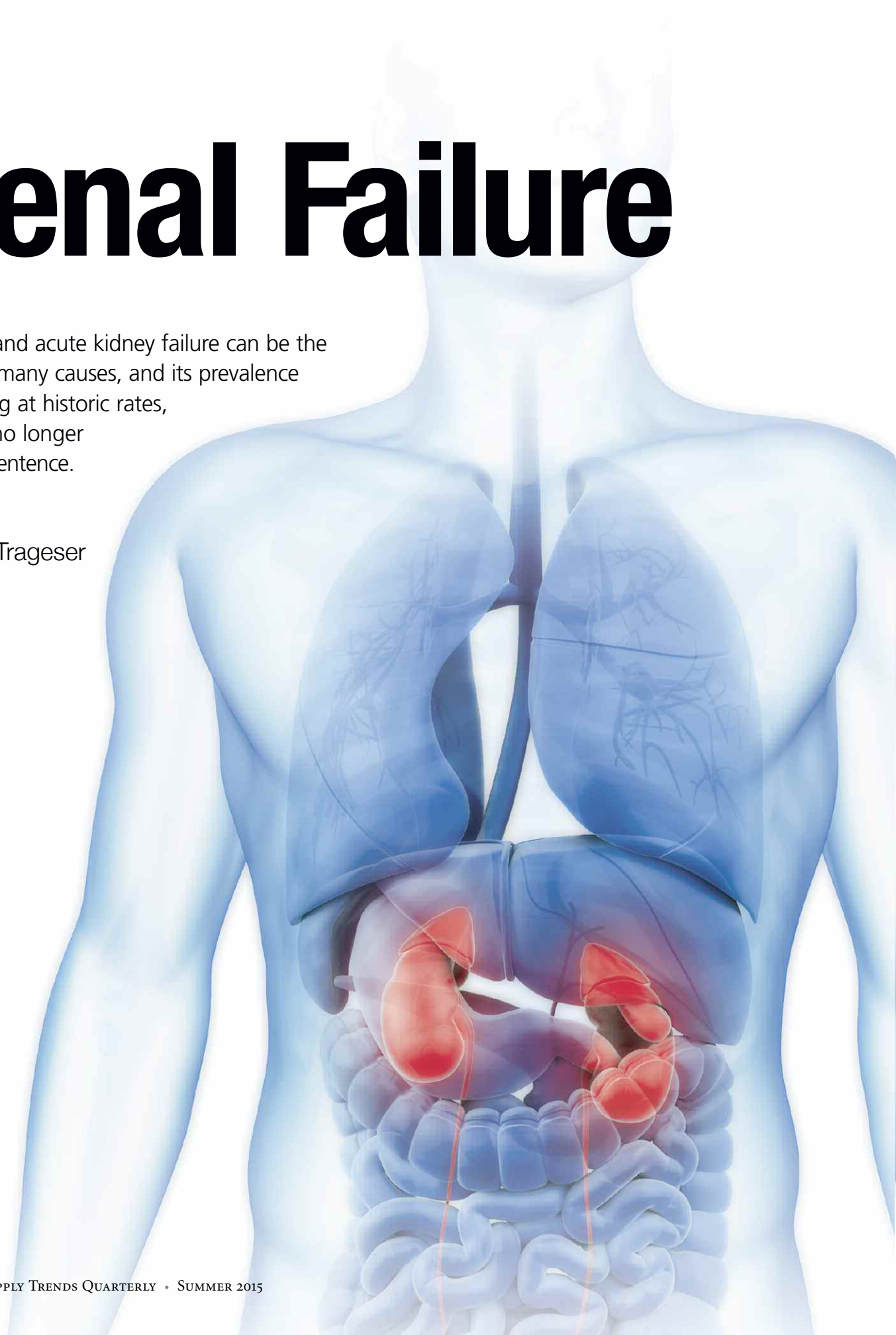
Renal Failure

Chronic and acute kidney failure can be the result of many causes, and its prevalence is growing at historic rates, but it is no longer a death sentence.

By Jim Trageser



Engineers like to speak of "mission critical" components in various systems — components so key to the overall operation that their failure can cause the entire system to become unstable or halt. The human body has quite a few mission critical components: the brain, the heart, the liver and the kidneys. If any of these stop working, life ceases.

Nature utilizes a concept engineers refer to as "redundancy" — components that are repeated in the system for safety so that if one fails, the rest can continue to function and keep the system operating. The lungs are a prime example of redundancy in the human body. Kidneys are another, with their role in clearing the bloodstream of toxins. If one is damaged, the other can continue functioning. Unfortunately, most of the non-traumatic causes of renal failure are likely to affect both kidneys.

What Is Renal Failure?

The medical community classifies kidney failure into two general categories: chronic kidney disease (CKD) and acute kidney disease. Both describe a condition in which the ability of one or both kidneys to effectively filter the blood has been weakened, leading to a buildup of toxins in the body.[1]

Chronic kidney failure is a slow-developing condition that can exist for years before it is detected. It is generally caused by other health issues such as diabetes or hypertension.[2]

Acute kidney failure can develop over the course of days or even hours. It is most often the result of traumatic injury to the kidneys (from an auto accident, for instance) or other sudden health emergency: a heart attack, liver failure, infection.[3] End-stage renal disease (ESRD) occurs when the kidneys are irreversibly damaged, requiring dialysis and/or transplant. This can result from either chronic or acute kidney failure when the kidneys have 10 percent or less of healthy function.[4]

The Centers for Disease Control and Prevention reports that kidney failure is the No. 9 cause of death in the United States, with some 47,000 patients dying from kidney failure in 2013.[5] A total of 3.9 million people were diagnosed with kidney disease that year in the United States (about 1.7 percent of the total population). Other studies indicate that up to 20 million adults (one in 10) have undiagnosed kidney disease.[6]

Causes of Renal Failure

Kidney disease and failure can be brought on by many different conditions, from cancer to infection. However, the vast majority of cases are attributed to diabetes and hypertension. In the United States, diabetes alone accounts for 44 percent of all cases of kidney failure, while hypertension causes about 28 percent.[6]

Other top causes in the U.S. include glomerulonephritis (an inflammation of the glomeruli, the tiny filters that remove waste from the bloodstream), kidney infections, lupus and other autoimmune diseases, kidney stones, polycystic kidney disease (a hereditary disease in which cysts develop on the kidneys, impairing their function), overuse of some pain medications, and abusing illegal drugs.[6] Physical trauma — a kidney being punctured or severely bruised by an accident, sports, etc. — can also trigger kidney disease or failure.

Symptoms of Renal Failure

The onset of kidney disease can manifest through a variety of symptoms, no matter the underlying cause:[7]

- Changes in urine output
- Nausea and/or vomiting
- Swelling due to fluid retention
- Fatigue
- Chest pain
- Confusion
- Changes in sleeping patterns

Of course, these symptoms may also indicate other conditions as well. And in many cases, kidney disease will have no symptoms and is only detected through lab tests — sometimes lab tests looking for other conditions.[7,8] Unfortunately, at this point, there may already be serious, permanent damage to kidney function before the disease is diagnosed.

Diagnosing Renal Failure

Several tools can be used to make a formal diagnosis of kidney disease:

• Urine tests: Lab tests of a urine sample can look for excessive levels of proteins, blood and/or sugar. High protein levels can indicate that the kidneys are not functioning properly, while high blood sugar levels can help detect underlying causes of low kidney function such as diabetes.[9]

• Blood tests: The results of blood sample tests can show elevated levels of creatinine and urea nitrogen, toxins that are removed from the bloodstream by healthy kidneys.[9]

• Imaging: Both ultrasounds and CT scans can reveal physical abnormalities in the kidneys, or kidney stones.[9]

• Biopsy: Kidney tissue can be tested for infecting organisms, high protein levels or other symptoms or causes of kidney disease. It may also be prescribed in cases where a transplanted kidney is not doing well.[10]

The Centers for Disease Control and Prevention reports that kidney failure is the No. 9 cause of death in the United States.

Treating Renal Failure

Once a positive diagnosis of kidney disease has been made, treatment options depend on the amount of damage to the kidneys, whether that damage is permanent and the underlying cause of the disease. While treating the root cause of the kidney dysfunction is the only way to halt or at least slow the advance of the damage to the kidneys, physicians also need to address patient symptoms to relieve pain and stress.

Symptomatic relief may include:

• Diuretics to reduce swelling due to fluid retention[11]

• Iron or hormone treatments to treat anemia; erythropoietin is a common hormone supplement used to treat anemia associated with CKD[10]

• Calcium or vitamin D supplements to prevent bone damage[11]

• Drugs to control the potassium levels in the blood; sodium polystyrene sulfonate (often sold as Kayexalate or Kionex) is commonly prescribed if potassium levels are high (which can cause irregular heartbeat or muscle weakness)[12]

Diabetes causes kidney damage when high sugar levels cause the kidneys to filter more blood than normal, increasing the wear and tear on the glomeruli, which are specialized capillaries. As these tiny filters wear out, the kidneys become less effective, leaving more waste in the bloodstream.

Despite the sobering statistics, kidney disease is not inevitable with diabetes. Diabetics can prevent or slow the advance of kidney disease by carefully regulating their blood sugar levels and controlling their blood pressure. Weight control, avoiding alcohol and tobacco, and regular exercise are all key components of controlling diabetes-related hypertension (or any hypertension). Some physicians prescribe a low-protein diet, as that seems to slow the progression of kidney disease by lessening the amount of work for the kidneys.[13]

A class of drugs known as ACE inhibitors (angiotensin-converting enzyme inhibitors) is also often used in conjunction with one or more of the above approaches. These drugs not only lower blood pressure by blocking release of an enzyme that constricts blood vessels, but also seem to preserve kidney function in ways other blood pressure medications do not.[14] The literature indicates that researchers are not entirely clear as to why this works, but studies show that there is a clear benefit to using ACE inhibitors for diabetics with CKD.

Hypertension can lead to kidney disease by slowly stretching out the glomeruli. As the glomeruli enlarge, their ability to filter out toxins while leaving healthy cells and nutrients in the bloodstream becomes compromised. For those with hypertension linked to diabetes, these effects compound the damage done by blood sugar levels associated with diabetes. But even in cases where high blood pressure is not related to diabetes, the treatment is the same: improved diet and exercise and, if necessary, a regimen of hypertension medication — generally ACE inhibitors.

Lupus can cause kidney disease when the body's immune system attacks the kidneys, causing inflammation of the glomeruli and a related structure called the nephron — a condition known as glomerulonephritis that prevents the kidneys from effectively filtering the blood. Glomerulonephritis is very common in lupus patients, with up to 40 percent of adults and 67 percent of children developing kidney disease. Kidney disease associated with lupus may be treated with prednisone or other corticosteroids to reduce swelling and restore kidney function.[15] These medications may be supplemented by or even replaced by immunosuppressive drugs such as cyclophosphamide (Cytoxan), azathioprine (Imuran), cyclosporin A and mycophenolate mofetil (CellCept). To complicate matters, other medications used to treat lupus can create side effects that mimic the symptoms of CKD. And, long-term use of nonsteroidal anti-inflammatory drugs or aspirin to treat the symptoms of lupus can lead to CKD.

Glomerulonephritis has many causes besides lupus: Strep throat can lead to the development of glomerulonephritis, as

can Goodpasture's syndrome, Wegener's granulomatosis and polyarteritis nodosa. When glomerulonephritis develops from one of these causes, it is generally considered an acute kidney disease. In each of these diseases, the underlying cause must be addressed in order to treat the kidney disease.

Post-streptococcal glomerulonephritis is caused by an untreated strep infection. It generally manifests about two weeks after a throat infection, and three to four weeks after a skin infection. It will usually subside on its own in a few weeks to a month. Antibiotics should be used to kill off any remaining streptococcal bacteria, and diuretics can help relieve any swelling from fluid retention. However, corticosteroids and other anti-inflammatory medications generally are ineffective.[16]

Goodpasture's syndrome is an autoimmune disease of unknown cause, in which the immune system produces anti-glomerular basement membrane (GBM) antibodies that attack a collagen that helps make up the glomeruli. It can be successfully treated with corticosteroids, immunosuppressives such as cyclophosphamide to lower the number of antibodies being created and, in severe cases, plasmapheresis, which removes the GBM antibodies from the patient's blood supply.[17]

Wegener's granulomatosis is a rare inflammation of the blood vessels that results in restricted blood flow that damages the kidneys. While the cause is presently unknown, research indicates it is likely an autoimmune disorder.[18] It is treated with prednisone and other corticosteroids, along with immunosuppressives — cyclophosphamide (Cytoxan), azathioprine (Azasan, Imuran) or methotrexate (Rheumatrex, Trexall) — which help stop the body's attack on itself.[19]

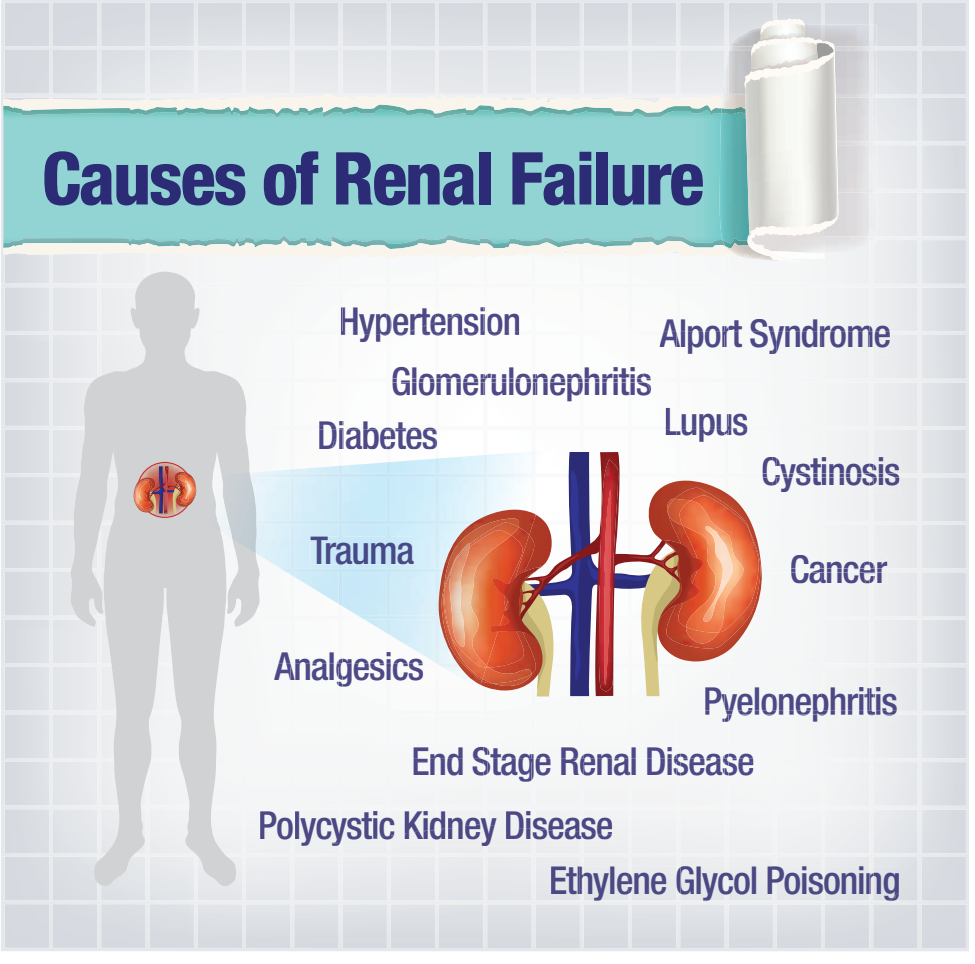
Polyarteritis nodosa is an inflammation of the arteries, the cause of which is presently unknown. However, it can be effectively treated with high doses of corticosteroids in most cases. More severe cases can be treated with immunosuppressives.[20]

Glomerulonephritis can also be chronic, developing slowly. It is known to run in families and to not have a definable cause in some patients. This chronic form often takes years to show symptoms. There is no specific treatment for chronic glomerulonephritis; however, dietary restrictions (limiting intake of salt, protein and potassium) can help, as can controlling hypertension.[21]

Polycystic kidney disease (PKD) is a hereditary condition in which benign cysts grow in and on the kidneys. There is no cure. Keeping hypertension under control is critical — usually with ACE inhibitors. Pain from the cysts may be treated with acetaminophen. If the pain becomes unbearable, or if the cysts obstruct blood vessels or other organs, surgery may become necessary. Most patients with PKD will eventually progress to ESRD and need dialysis or transplant.[22]

Cystinosis is a genetic disease that causes an intracellular buildup of the amino acid cystine.[23] The condition is successfully treated with Cysteamine, which removes the cystine from cells.[24]

Alport syndrome is a genetic disease that leads to kidney disease due to the lack of a needed protein to make collagen.[25] Without collagen, the glomeruli that serve as filters are not



replaced or repaired as needed, and they lose their ability to effectively filter the blood. There is no cure, but the progression of the disease can be slowed by carefully controlling blood pressure.

Cancer can originate in the kidneys (kidney cancer) or spread to the kidneys from another malignancy. The American Cancer Society reports that renal cancer is one of the 10 most common forms of cancer for both men and women.[26] In adults, the most common form is renal cell carcinoma. Young children are more prone to a type of malignancy called Wilms' tumor. Treatment will depend on how advanced the cancer is, the specific form of cancer, where on the kidney it is located and the age of the patient. Strategies include surgery, radiation and chemotherapy — often a combination of these. Depending on how renal performance is affected, dialysis may also be part of the treatment.

Once a positive diagnosis of kidney disease has been made, treatment options depend on the amount of damage to the kidneys, whether that damage is permanent and the underlying cause of the disease.

Pyelonephritis is an infection of the urinary tract that, if left untreated, can cause scarring in the kidneys, potentially leading to kidney failure. While many bacteria and viruses can cause pyelonephritis, the most common culprit is E. coli.[27] Treatment generally consists of a round of antibiotics with bed rest and plenty of fluids.

Some **analgesics** can cause chronic interstitial nephritis (a swelling of the tubules that return water and nutrients to the bloodstream after filtering) if used long term. Ibuprofen and naproxen are among them. And high doses of aspirin taken for a long time can also lead to this condition. (Low doses of daily aspirin used to prevent heart attacks are safe.)[28]

Ethylene glycol poisoning can bring about kidney failure in a matter of hours. Patients suspected of ingesting ethylene glycol, a common ingredient in automotive antifreeze, should immediately be sent to the nearest emergency room, where their stomach can be pumped and, in many cases, they will be hooked up to a dialysis machine to remove the poison from the bloodstream.[29] Illegal street drugs, including heroin, phencyclidine (PCP) and MDMA (3,4- methylenedioxymethamphetamine), can also damage or destroy kidney function.[30] As there is no other treatment to restore kidney function in cases of poisoning, the kidneys will either heal with time, or the damage is irreversible.

Trauma to the kidneys can occur in a variety of settings, from sports injuries to car accidents to battlefield wounds. Advances in treatment mean there are options beyond surgical removal of a damaged kidney. For example, embolization and endourologic stenting to control bleeding are both nonsurgical methods of treatment. As always, though, the specific nature and severity of the injuries will determine the correct treatment path.

ESRD occurs when kidneys have less than 10 percent of normal function left. At this point, the body needs assistance ridding itself of toxins. There are two treatments for ESRD: transplant and dialysis. Due to demand, wait times for a donor kidney can stretch into years. And due to underlying health or lifestyle issues, some patients are not candidates for transplant.

In transplant, the healthy kidney of a donor — living or deceased — is matched for compatibility. In general, the existing kidneys are kept in place, and the new kidney is placed adjacent to them. Antirejection drugs are prescribed to prevent the patient's immune system from attacking the foreign organ.

There are two types of dialysis. Hemodialysis uses a tube to run the blood supply through the dialysis machine, artificially performing the work of the kidneys to remove toxins. Peritoneal dialysis uses a tube to pump a solution into the abdominal cavity to absorb waste products, which can then be withdrawn and disposed of.[11]

Preventing Renal Failure

Many cases of kidney disease are preventable. While nearly three-quarters of kidney disease in the United States is linked to diabetes or hypertension, neither condition makes kidney disease an inevitability.

Kidney damage that leads to kidney disease and failure can be prevented through good health maintenance: avoiding smoking and alcohol (or drinking in moderation), avoiding illegal street drugs, keeping blood pressure under control and avoiding overreliance on analgesics. Even if these steps do not prevent kidney damage due to diabetes or other underlying health issues (lupus, hypertension), they will help relieve the stress on the kidneys and slow the progression of kidney disease.

Ongoing Research

Currently, much research is concentrated on multiple fronts to develop better technologies and treatments for kidney disease.

Benjamin Freedman, a researcher at Brigham and Women's Hospital and Harvard Medical School, is working with adult stem cells of patients with polycystic kidney disease to study

the cellular-level nature of PKD to see if treatments can be developed — or perhaps even a cure.[31] The hope is that Freedman's research will lead to a method of taking kidney cells from PKD patients, then genetically engineering those cells to be free of the genetic mutation that causes PKD before reintroducing them into the patient's kidneys.

Kidney damage that leads to kidney disease and failure can be prevented through good health maintenance.

Dr. Marta Christov from Massachusetts General Hospital is working on new methods of removing phosphorus from the body to help slow skeletal and vascular damage in those suffering from CKD.[32]

Another researcher at Mass General, Dr. Sahir Kalim, is conducting research to improve the efficiency of dialysis so that it more closely mirrors the work done by healthy kidneys. Even the best dialysis machines today remove too many amino acids and miss too many metabolites.[33]

And Dr. Martina McGrath, at Brigham and Women's Hospital in Boston, is exploring new strategies to further reduce rejection of transplanted kidneys. Currently, she is studying how suppressing production of the TIM-4 molecule can help block rejection of transplanted organs.[34]

Looking Ahead

While the research is promising and holds out hope, the reality is that for the foreseeable future, kidney disease is going to be with us. In fact, one recent study showed that early-stage chronic kidney disease is being diagnosed at historic rates.[35] But, there are more treatments available than ever before to alleviate patient pain, to slow the disease's progression and to provide effective treatment at every stage of the disease. What was once a death sentence is now a manageable condition — no small accomplishment at all. ❖

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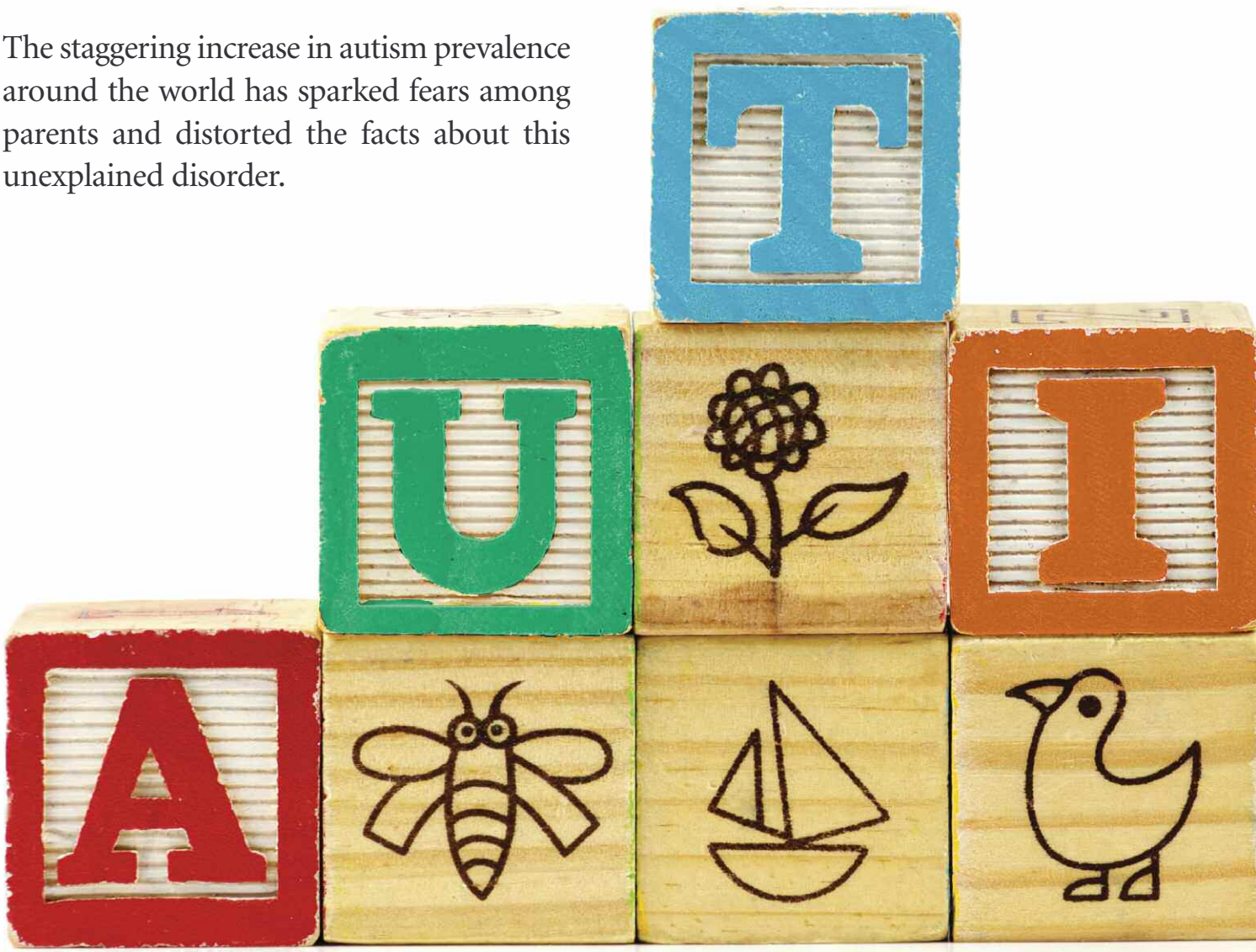
Myths and Facts:

By Ronale Tucker Rhodes, MS

The staggering increase in autism prevalence around the world has sparked fears among parents and distorted the facts about this unexplained disorder.



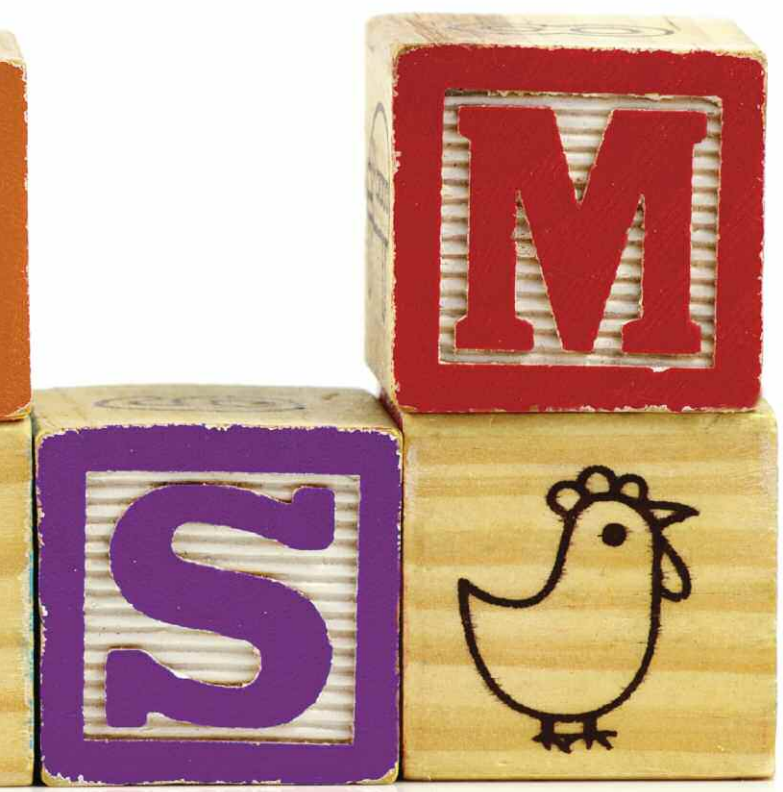
In 2014, there were almost four million births in the U.S.[1] Today, one in every 68 of these births is identified as having autism spectrum disorder (ASD)[2] (an increase from one in 110 in 2009 and one in 150 a decade ago). This equates to a staggering 159 children born with the disorder each day. It occurs in all racial, ethnic and socioeconomic groups and in boys five times more often than girls.[3] At a cost of $60,000 a year on average per family, there is no medical detection or cure for it.[2]

In fact, autism is the fastest-growing developmental disorder in the U.S., affecting an estimated 1.5 million children and adults.[4] Yet, despite its growing prevalence, it is not a new disorder. Scientist Leo Kranner first described autism in 1943, but the earliest description of a child now known to have had autism was written in 1799.[5] Why more children are being born with autism has created fear among many parents. And this fear has resulted in fallacies that are harmful for both autistic children and their families.

Separating Myth from Fact

Myth: More kids have autism today than ever before.

Fact: While it's true that there has been a significant surge in diagnoses of autism (increasing nearly 1,800 percent from 1992 to 2008), experts question whether there is actually a higher incidence of the disorder or if there is just increased public awareness of autism symptoms, more media attention and better diagnostic tools.[6] "It could be that we're just finding it more often," said Dr. Jeffrey Skowron, regional clinical director for Autism Intervention Specialists in Worcester, Mass. "Families are looking for the signs more, and they have better access to pediatricians, clinicians and psychologists who are better able to diagnose them." What should really be said, he adds, is that more people are *diagnosed* with autism today than ever before.[7]



The increase in autism prevalence is also attributed by some experts to the redefinition of autism, which includes a wider range of disorders on the spectrum.[6] That redefinition occurred in May 2013, when the National Institutes of Health published the fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5), which is widely used to diagnose mental health conditions in North America. In this edition, all autism disorders were merged into one umbrella diagnosis of ASD.[8]

A decade ago, autism was thought of as a single rare and distinct condition made familiar by Dustin Hoffman's portrayal of an autistic adult in *Rain Man*. "Hoffman did a beautiful job of looking autistic, and he did everything we associate with this disorder," said Catherine Lord, PhD, a nationally recognized expert on autism from the University of Michigan. "But he showed us about 10 out of the 12 or so behaviors associated with autism, including echolalia, idiosyncratic speech, verbal and behavioral rituals, preoccupations, unusual sensory responses, as well as difficulties with eye contact, facial expressions and gestures that are common to almost all individuals with autistic spectrum disorder. Most children and adults do not have all, or even most, of these behaviors."

As clinicians and researchers came to realize that autism is part of a spectrum of disorders, the diagnostic framework was fundamentally changed, as was treatment and prognosis. "Children were previously diagnosed as autistic only at the extreme of these behaviors, and usually when they were already over 6 years of age, when fewer successful treatments are available," said Janice Ware, PhD, associate director of the Developmental Medicine Center at Boston Children's Hospital. "Therefore, many professionals hesitated to diagnose a child as autistic."[4]

A study conducted in Denmark appears to confirm the increase in autism is due to redefinition. In the study, researchers found that most of the increase (60 percent) can be attributed to changes in diagnostic criteria and the inclusion of out-of-hospital diagnoses. In 1994, the diagnostic criteria used by clinicians to establish psychiatric diagnoses were changed. "This meant that autism was recognized as a range of disorders — which is why we today call it ASD — but it also

meant changes in the specific symptoms that form the basis of an autism diagnosis," said lead researcher Stefan Hansen from the section for biostatistics in the Department of Public Health at Aarhus University. Then, in 1995, the national health registries in Denmark also began including diagnoses made outside of hospitals; prior to that, only diagnoses made in hospitals were reported. In the study, the researchers collected data on almost 700,000 children born in Denmark from 1980 through 1991. The kids were followed from birth until autism was diagnosed, or until they died or emigrated, or until the end of 2011, whichever came first. Almost 4,000 children from that group were diagnosed with an ASD, most of whom were diagnosed after the diagnostic criteria and inclusion of outpatient diagnoses occurred. Of course, there is still 40 percent of the increase that is unexplained, acknowledged Hansen.[9]

The increase in autism prevalence is also attributed by some experts to the redefinition of autism, which includes a wider range of individuals on the spectrum.

Myth: Autism is a disease.

Fact: Autism is not a disease; it is a collection of behaviors or symptoms, which makes it a syndrome. While the underlying pathology or physical issues related to it are not well understood, Dr. Skowron believes it is like a disorder of the brain.[7] Studies of people with autism have revealed abnormalities in brain structure and neurotransmitter levels.[5] In fact, autism appears to be caused during very early brain development; however, the most obvious signs and symptoms tend to emerge between 2 years and 3 years of age. The disorder can be associated with intellectual disability, difficulties in motor coordination and attention, and physical health issues such as sleep and gastrointestinal disturbances.[8]

Myth: All autistic individuals are affected the same by the disorder.

Fact: As the name implies, ASD is vast, and the symptoms can manifest in a variety of ways. Indeed, every autistic individual is unique. Many have exceptional abilities in visual skills, music and academic skills. About 40 percent have average to above average intellectual abilities, and they take pride in their distinctive abilities and "atypical" ways of viewing the world. On the other side of the spectrum are individuals who have significant disability and are unable to live independently. About 25 percent of individuals are nonverbal but can learn to communicate using other means.[8]

Myth: Autistics are violent.

Fact: It's very unusual for individuals with autism to act violently out of malice or to pose any danger to others. However, if violent acts do arise, it is typically due to sensory overload or emotional distress.[5] Mostly, autistic individuals act out or have what are known as meltdowns usually as expressions of frustration with themselves or situations, but their actions don't equate to violence against other people.[10]

The connection between autism and violence stems from recent news stories, including the shooting at Sandy Hook Elementary School in Newtown, Conn., in 2012. It was claimed that Adam Lanza, the shooter, was diagnosed with autism or Asperger syndrome, causing many to believe that the diagnosis was the cause for his violent actions. But, according to a statement from the Autism Society, "There is absolutely no evidence or any reliable research that suggests a linkage between autism and planned violence. To imply or suggest that some linkage exists is wrong and is harmful to more than 1.5 million law-abiding, nonviolent and wonderful individuals who live with autism each day." Peter Bell, executive vice president for programs and services for Autism Speaks, and the father of a son with autism, maintains that, by definition, people with a diagnosis of autism or Asperger syndrome are not inclined to commit an act of violence; the likelihood of that happening would be no different than the rest of the population.[11]

A 2008 study shows that violent acts — such as the one committed by Lanza — appear to be due to autism plus a psychiatric disorder. The study by scientists at King's College London found that 70 percent of their young autistic subjects had at least one co-morbid disorder such as childhood anxiety disorder, depressive disorder, oppositional defiant and conduct disorder or ADHD. Forty-one percent had two or more co-morbid disorders. And, in a 2008 literature review of 17 papers describing Asperger syndrome, the researchers found that "an overwhelming number of violent cases had co-existing psychiatric disorders at the time of committing the offence"— 84 percent, to be precise. They also couldn't rule out personality disorders such as anti-social personality disorder in the remaining subjects.[12]

Myth: Individuals with autism aren't able to have relationships with others.

Fact: While many autistic individuals have difficulty with social interaction, they can have close relationships, fall in love and have children. In addition, those with autism feel as much, if not more, empathy as others, although they may express it in ways that are harder to recognize.[5] Many autistics are easily

overwhelmed by emotions of those around them. It is often assumed that autistic people want to be isolated, but isolating them to protect them can be very harmful.[10]

Myth: Individuals with autism have savant abilities.

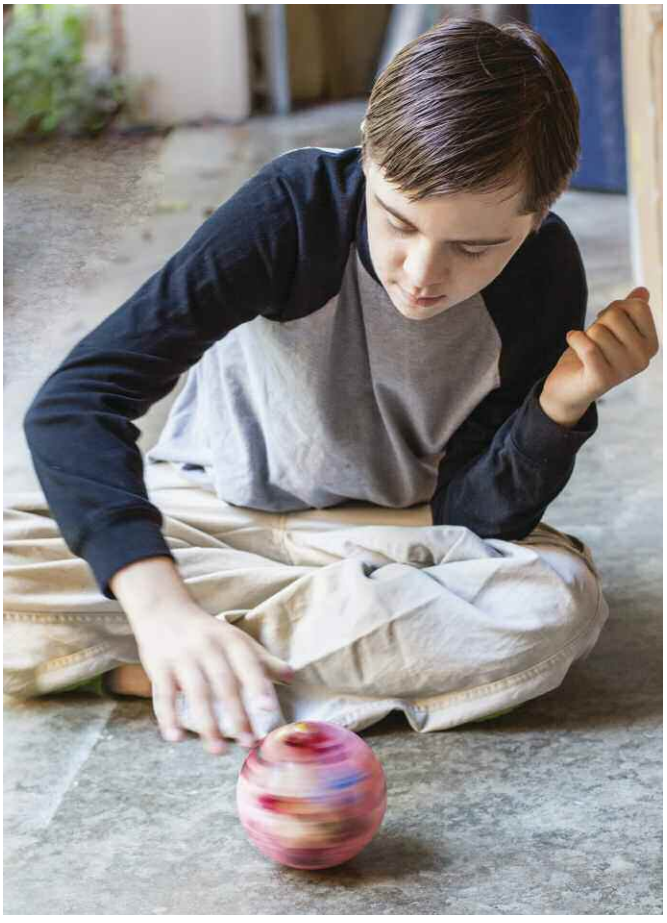
Fact: Some savants are autistic, but not everyone who is autistic is a savant. While there is a higher prevalence of savant abilities among those with autism, only about 10 percent exhibit savant abilities. Some even have what is known as "splinter skills," meaning they perform above average in one or two areas.[5]

Myth: Autism is caused by poor parenting.

Fact: In the 1950s, it was assumed that autism was caused by emotionally distant or cold mothers, who were referred to as "refrigerator mothers." Today, research is revealing answers about the cause of autism, and it is now known that parenting has nothing to do with it.[5] In fact, there is no one cause of autism, just as there is no one type of autism. Instead, what has been learned so far is that, in most cases, it's a combination of genetics and environmental factors that influence early brain development. During the past five years, scientists have identified a number of rare gene changes, or mutations, associated with autism. And, when there is a genetic predisposition, nongenetic or environmental stresses further increase a child's risk of autism. There is clear evidence of a number of risk factors for autism both before and during birth, including advanced age of parents at the time of conception, maternal illness during pregnancy and certain difficulties during birth, most notably those that cause periods of oxygen deprivation to the baby's brain.[8]

There are also other genetic risk factors. Among identical twins, if one child has autism, then the other will also have the disorder about 36 percent to 95 percent of the time. In non-identical twins, if one has autism, the other is affected less than 31 percent of the time. Parents who have a child with autism have a 2 percent to 18 percent chance of having a second child with autism. And, people who have certain genetic or chromosomal conditions are more likely to have autism. For instance, about 10 percent of children with autism also have Down syndrome, fragile X syndrome and tuberous sclerosis.[13]

Recently, the link between autoimmunity and autism has been identified. In one study at the Center for Autoimmune and Musculoskeletal Disorders at The Feinstein Institute for Medical Research in Long Island, N.Y., researchers found that one in 10 women who have a child with autism has anti-brain antibodies. These antibodies don't harm the brains of the women who produce them because of the blood-brain barrier, a filter that prevents most molecules from entering the brain. However, the immature blood-brain barrier of a developing fetus may let them through, allowing them to damage the brain and perhaps cause autism. In the study, the researchers screened blood plasma samples from 2,431 mothers enrolled



in the Simons Simplex Collection, a registry of families with one child affected by autism and unaffected parents and siblings. They found that plasma from 260 of the women, or 10.5 percent, reacts strongly with the mouse brain tissue, a signal that the blood contains anti-brain antibodies. Samples from 318 mothers enrolled in a different autism registry, the Autism Genetic Resource Exchange, were also sampled, finding that 28, or 8.8 percent, of them also have anti-brain antibodies. In contrast, among a group of 653 controls drawn from the general population of women of childbearing age in New York City, only 17, or 2.6 percent, carry the autism-linked antibodies. This means the prevalence of these antibodies is about four times greater among mothers of children with autism than among controls. This is the largest survey yet on the prevalence of these anti-brain antibodies.[14]

In another study, researchers investigated whether autoimmune disorders and autism have a common genetic basis. They looked at the genomes of individuals in 941 families that have more than one child with autism, 3,000 individuals with an autoimmune disorder (ankylosing spondylitis, multiple sclerosis, rheumatoid arthritis or Crohn's disease) and 4,500

controls. First, they identified all the single nucleotide polymorphisms (SNPs) — alterations to single DNA base pairs — associated with each disorder, and then they compared the SNPs associated with autism and those linked to autoimmune disease. They found a strong correlation between gene variants in individuals with autism and in those with ankylosing spondylitis or multiple sclerosis. Specifically, autism-associated SNPs increase the likelihood of developing ankylosing spondylitis, whereas they appear to protect against multiple sclerosis. They also found that autoimmune thyroid disease is slightly associated with an increased risk of autism. However, there was no association between autism and Crohn's disease or rheumatoid arthritis.[15]

In April, a study showed that autism risk could be related to diabetes in the prenatal environment. The study, using the Kaiser-Permanente database, looked at whether the risk for ASD increased among offspring of mothers with type 2 diabetes during pregnancy, and, for those mothers who develop gestational diabetes, whether the time of onset during the pregnancy influences that risk or provides clues about critical periods of vulnerability. Of the 322,323 children studied, 3,388 were diagnosed with ASD, including 2,963 unexposed, 115 exposed to preexisting maternal type 2 diabetes, and 310 exposed to gestational diabetes. The unadjusted incidences were 1.77, 3.26 and 2.14 per 1,000, respectively. More than 99 percent of infants who were exposed to maternal diabetes in utero did not develop ASD. However, in adjusted analyses, the authors found an increased risk in the subgroup of children exposed to gestational diabetes at 26 weeks or earlier. The hazard ratio for preexisting type 2 diabetes was 1.21 and for gestational diabetes at 26 weeks or earlier 1.42. This suggests the timing for this environmental exposure is isolated to early pregnancy. As more women of child-bearing age are obese, understanding the effect of insulin and maternal diabetes on pregnancy outcomes is important.[16]

Recently, the link between autoimmunity and autism has been identified.

Myth: Vaccines cause autism.

Fact: The idea that vaccines cause autism is perhaps one of the biggest myths about the disorder. This myth arose when an article published in the British medical journal *The Lancet* claimed a link between the measles-mumps-rubella (MMR) vaccine, gastrointestinal disease and autism. The article was written by an unknown British scientist, Andrew Wakefield, and 12 colleagues, and it was later found that the research had many problems: 1) There were more authors than subjects. The study was based on only 12 children from the hospital where Wakefield was working. 2) Subsequent analysis of the methodology, which should have been done during the peer review process, revealed that Wakefield cherry-picked the patients for the study. 3) The study stated that the kids developed cognitive problems a few days after the vaccine, but a simple investigation of hospital records revealed that, in several cases, parents reported problems before the vaccine. 4) Wakefield was getting money from lawyers planning on suing vaccine makers, and he owned a patent on an alternative to the MMR vaccine. Ten of the other 12 authors formally retracted their interpretation of the results in 2004, and the journal later retracted the article.[17]

Although the fear about a possible link between vaccines and autism persists, there is no evidence that supports the association. "Parents may make the association because it is often at around age 2 that we are now able to diagnose autism. This is a difficult diagnosis and we all search for reasons why. This also happens to be when many immunizations occur," said Dr. Leonard Rappaport, director of the Developmental Medicine Center at Boston Children's Hospital. "But given that there is absolutely no scientific evidence of this connection, we, as physicians, worry this may become an excuse for not having immunizations, which makes a child vulnerable to a host of other problems."[4]

The most recent study that disproved the link between vaccines and autism was published in the April 21 edition of the *Journal of the American Medical Association*. In the study, researchers evaluated two questions: Does the incidence of ASD differ in younger siblings of affected children who are immunized with MMR versus those who are not? And, for the population as a whole, does the incidence of ASD vary as a function of MMR immunization status? They found that of 95,727 children with older siblings who were included in the study, 1,929 had an older sibling with ASD and 994 children had ASD diagnosed. The relative risk of ASD at age 2 years was 0.76 for children with older siblings with ASD and 0.91 for children with older siblings without ASD. The study authors wrote that they found "no harmful association between MMR vaccine receipt and ASD even among children already at higher risk for ASD."[16,18]

Myth: Children can't be diagnosed with autism until after age 4.

Fact: On average, the age of diagnosis in the U.S. has remained stalled at 4.5 years.[19] However, research has shown that a diagnosis at age 2 can be reliable, valid and stable. And, studies have shown that parents of children with ASD notice a developmental problem before their child's first birthday, including vision and hearing problems in the first year and

differences in social, communication and fine motor skills at 6 months of age.[3]

Diagnosing autism can be difficult. One study that looked at the medical records of more than 2,700 children with autism at age 8 found a significant connection between age of diagnosis and how many symptoms were displayed. Children who displayed only seven of 12 recognized autism symptoms were diagnosed more than four years later, on average, than kids with all 12 symptoms. The median age at diagnosis was 8.2 years for children with seven symptoms and 3.8 years for those with all 12 symptoms.[20]

Diagnosing ASD involves two steps: developmental screening and comprehensive diagnostic evaluation. Developmental screen tests will indicate if children are learning basic skills when they should or if they are having delays. These tests should be conducted during regular well-child visits at 9 months, 18 months and 24 or 30 months. All kids should also be screened specifically for ASD during regular well-child visits at 18 months and 24 months. And, additional screening is recommended if a child is at high risk for developmental problems or ASD.[21] Several screening instruments have been developed to quickly gather information about a child's social and communicative development within medical settings, including the Checklist of Autism in Toddlers (CHAT), the modified Checklist for Autism in Toddlers (M-CHAT), the Screening Tool for Autism in Two-Year-Olds (STAT) and the Social Communication Questionnaire (SCQ) (for children 4 years of age and older). During the last few years, screening instruments have been devised to screen for Asperger syndrome and higher functioning autism. The Autism Spectrum Screening Questionnaire (ASSQ), the Australian Scale for Asperger Syndrome and, the most recent, the Childhood Asperger Syndrome Test (CAST) are some of the instruments that are reliable for identification of school-age children with Asperger syndrome or higher functioning autism.[22]

During a comprehensive diagnostic evaluation, a physician will review a child's behavior and development, as well as provide hearing and vision screening, genetic testing, neurological testing and other medical testing.[21]

Myth: Treatment for autism turns kids into robots.

Fact: While some say that behavioral therapy, which is the recommended treatment for autism, is highly impersonal and turns kids into robots, Dr. Skowron doesn't believe that is true. "It seems very personal to me," he says. "Based on the needs of the kids, you form a strong bond with the person. The families play a big role in the treatment, and they can have a great effect on the treatment of the child."[7]

Scientific studies have shown that using early intensive behavioral intervention improves learning, communication and social skills in young children with autism. There are several types of comprehensive behavioral early intervention: the Lovaas Model based on applied behavior analysis (ABA), the Early Start Denver Model, Floortime, Pivotal Response Therapy and Verbal Behavior Therapy.[23] With ABA, an intense behavioral intervention designed to improve the functioning and communication of children with ASD, a therapist works with the child directly, usually one-on-one, on specific behaviors for up to 30 hours per week. Research on ABA outcomes has shown significant improvement that lasts over time in the functioning of autistic children. Floortime is a more child-directed form of therapy that is more interactive. Some therapists use a purely ABA or a purely Floortime approach, while others use a combination of the two tailored to each child's needs.[4]

But, intervention isn't always limited to behavioral therapy. Some kids also require antipsychotic medications to treat severe symptoms of autism, which can include anxiety, depression or obsessive-compulsive disorder,[7] and others require medicines to treat additional medical conditions such as sleep disturbance, seizures and gastrointestinal distress.[23] How much and which types of treatment are best will depend on the child's unique needs.

Myth: There is a cure for autism.

Fact: According to the National Institute for Neurological Disorders and Stroke, there is no cure for ASD. Some individuals "can learn to compensate with autism in very effective ways to the point that other people might not even know," explains Dr. Skowron. "But whatever physical problems are in the brain of that person, those will remain throughout the person's life."[7]

On average, the age of diagnosis in the U.S. has remained stalled at 4.5 years.

There are some children who reach "best outcome" status, meaning they have scored within normal ranges on tests for IQ, language, adaptive functioning, school placement and personality, but they still have mild symptoms on some personality and diagnostic tests. In addition, there is growing evidence that suggests a small minority of persons with autism can move off of the autism spectrum. Theories about why this happens include the possibility of an initial misdiagnosis, the possibility that some children mature out of certain forms of autism and the possibility that successful treatment can, in some instances, produce outcomes that no longer meet the criteria for an autism diagnosis.[23]

What is now known for sure is that intensive early intervention is critical for producing significant improvement in autism symptoms. "There is an important window for success during early childhood," says Ware. "We now know that with early diagnosis, treatment and support, children with ASD can make strides never believed possible, even a decade ago."[4]

Dispelling the Myths Now

In 2011, the total societal costs for caring for children with ASD were over $9 billion. On average, medical expenditures for children and adolescents with ASD are 4.1 to 6.2 times greater than for those without ASD.[3] Unfortunately for most families dealing with this disorder, most insurance companies exclude autism from the coverage plan, and only half of the 50 states currently require coverage for treatments of ASD.[24]

With the growing rate of autistic diagnoses, it's more important than ever to identify what the actual prevalence rate is in the U.S. According to Michael Rosanoff, Autism Speaks' director for public health research, the method that the Centers for Disease Control and Prevention (CDC) uses is likely underestimating the ASD prevalence. Currently, CDC's surveillance system, called the Autism and Developmental Disabilities Monitoring (ADDM) Network, consists of 14 communities across the country that are meant to represent the U.S. as a whole. Within this network, CDC researchers examine educational and medical records of 8-year-olds for diagnoses of ASD based on the assumption that most children who have autism will be diagnosed by this age. But, says Rosanoff, this indirect, records-based approach misses children who have autism but have not been diagnosed and/or are not receiving appropriate medical or educational services. And, he adds, when we underestimate prevalence, we underestimate the needs of individuals with autism and their families. An Autism Speaks study found that direct screening of schoolchildren with autism produces a markedly higher prevalence estimate than does CDC's indirect method.[25]

CDC is continuing to monitor rates among grade-schoolers, but it is considering changes due to the recent overhaul of the criteria used to diagnose the disorder. With an investment of more than $20 million over four years, CDC is enhancing tracking at the eight ADDM sites and will launch two new sites. It is also expanding its national autism monitoring to include preschoolers at six of its sites. And, the ADDM staff will conduct research aimed at better understanding why prevalence has increased dramatically over recent years, and it will conduct education and outreach activities in local communities. "It's vitally important to monitor changes in the average age of diagnosis to see if we're identifying and getting services to kids earlier," said Rosanoff. "It's also crucial to maintain ongoing monitoring of prevalence over time and among different groups to better understand why prevalence is increasing and why we see differences among communities."[19]

Indeed, the question concerning why the prevalence of ASD is rising will help to make earlier diagnoses and put early intervention strategies into place. It is also at the heart of quieting the fears and dispelling the fallacies about this tragic disorder. ❖

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

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Measles: A Patient's Perspective

BY TRUDIE MITSCHANG

This California family thought a trip to Disneyland would be the perfect way to celebrate their new baby. Unfortunately, the Loops came home with much more than the happy memories they had hoped for.

Ariel Loop gave birth to her son, Mobius, in the fall of 2014. Knowing it was flu season, she vaccinated herself during pregnancy and kept her baby in the house until after his second round of vaccines. Mobius contracted measles at Disneyland in mid-January, but it took almost five days to confirm the diagnosis.

ARIEL LOOP IS a registered nurse who lives with her husband, Chris, and young son, Mobius, in Southern California. Perhaps because she works in healthcare, Ariel was concerned about the risks of flu and whooping cough, especially since Mobius was born a month early in the middle of fall 2014. The cautious mom kept her infant inside for the first two months of his life, just to be safe. "I made sure to get a Tdap and flu shot myself while pregnant in hopes of passing a bit of protection to the baby, who would spend some of the cold and flu season otherwise completely unprotected," says Ariel. "We kept him almost entirely at home until after his first round of vaccines at two months. We were counting down the days until we'd be able to start getting out with him."

In January 2015, the young family decided they were ready for their first big outing. As longtime Disneyland annual passholders, Ariel and Chris felt "the Happiest Place on Earth" was the perfect setting to introduce Mobius to the world. Sadly, that seemingly harmless decision turned into a harrowing ordeal for the couple when their baby became one of the hundreds of people who were exposed to measles while visiting the Disney theme park. "It's hard to wrap my head around the fact that the very first time my 4-month-old son got sick, it was with the measles," says Ariel. "Actually, we were not there during the initial outbreak, but it appears that Mobius contracted measles at Disneyland when we visited in mid-January."

Getting the Diagnosis

The days before Mobius's rash appeared, his parents say he seemed just a little off, but they were not concerned until he began rubbing his eyes nonstop. Because he had no outward symptoms yet, the couple took Mobius out with family and friends multiple times in the days preceding his diagnosis, not realizing how contagious he was. "Unbeknownst to us, we exposed hundreds of people to measles," explains Ariel. "This fact weighs heavy on my heart; although Mobius was too young to be vaccinated, I know this all could have been prevented had the person who infected him gotten vaccinated."

Mobius's temperature was just over 102 for several days, and refused to budge despite the medication and cool baths. Doctors ran three sets of tests on him: blood and nasal swabs in the ER, and then the health department came in and collected urine. The tests from the hospital came back first, but Ariel says it still took almost five days to confirm the diagnosis of measles. For Ariel, watching her son suffer through this serious infection was a mother's worst nightmare. "It was traumatizing to feel my infant son's entire body rattle as he breathed. While he was able to fight through the infection, it worries me to think of the repercussions an even more widespread resurgence of measles could cause."

The Ongoing Vaccine Debate

As a parent and as a nurse, Ariel says she understands that people on both sides of the vaccination debate are doing what they feel is best for their children. She notes that there are so many personal decisions that parents make — cloth diapers vs. disposable, breast milk vs. formula — but none have an impact on the community at large like vaccination decisions. "I know not everyone agrees with me, but I think not vaccinating your child due to fear of an incredibly rare side effect amounts to not wearing a seat belt because of the minute chance it may cause more harm than good," explains Ariel. "It's easy to feel comfortable because diseases like measles aren't ones we personally see every day, but if this trend of delaying or skipping vaccines continues, diseases that were close to being gone will make a comeback. In fact, they already have. And my son is living proof." ❖

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

Measles Makes a Comeback

BY TRUDIE MITSCHANG

The measles resurgence is introducing a whole new generation of physicians to a once-eradicated and potentially deadly disease.

BEFORE THE WIDESPREAD use of vaccines in the 1960s, most pediatricians were well-acquainted with the symptoms of measles. When patients presented with a fever and other flu-like symptoms, doctors knew to check their patients' throats for the spray of telltale spots that indicated a measles infection. The disease was so commonplace that many people expected to get it, and according to the World Health Organization, 2.6 million deaths annually were attributed to measles in the years preceding the development of the vaccine.[1]

Today, 145,000 people die of measles each year, most because they lack access to the vaccine, with only a small percentage of fatalities occurring in the United States. The recent measles outbreak that began in Southern California, however, has alarmed public health officials and serves as a reminder that if large segments of the population continue to avoid vaccination, a full-blown epidemic is not only possible but probable.

Measles Vaccine: A Brief History

The measles, mumps and rubella vaccine (MMR) was introduced in the United States in 1968. A decade later, the Centers for Disease Control and Prevention set a goal to eliminate measles from the United States by 1982. By 1981, the number of reported measles cases was 80 percent less compared with the previous year; however, a 1989 measles outbreak among vaccinated school-aged children prompted the Advisory Committee on Immunization Practices, the American Academy of Pediatrics and the American Academy of Family Physicians to recommend a second dose of MMR vaccine for all children. Following the implementation of that initiative, reported measles cases declined even further. Measles was declared eliminated (absence of continuous disease transmission for greater than 12 months) from the United States in 2000.[2]

The recent measles outbreak that originated in Disneyland has health officials alarmed. Initial exposures at the park happened in December 2014, according to the California Department of Public Health, but an additional outbreak was linked to theme park attendees in January. From Jan. 1 to May 29, 173 people from 21 states and the District of Columbia were reported to have measles, 117 of whom were part of the outbreak linked to Disneyland.[3]

Measles: Recognizing the Signs

In the wake of recent outbreaks of measles, many physicians are being tasked with identifying symptoms of a disease they may have never seen outside of a textbook. The American Osteopathic Association offers the following tips to physicians who want to be prepared should a measles outbreak occur in their community:[4]

• Familiarize yourself with the signs and symptoms of measles, as well as vaccination recommendations for the disease. Measles symptoms include a bad cough, red eyes, a rash on the face and a fever of 102 or 103 degrees Fahrenheit. People who become infected are contagious for two to three days before they start showing symptoms.

• Train your front office staff to listen for mentions of potential measles symptoms. Patients who mention these symptoms should be asked appropriate follow-up questions and flagged so they can be given appropriate care when they visit your practice. While at home, measles patients should drink plenty of liquids and take ibuprofen as needed. Also remind staff of the necessity of vaccines in preventing disease. Whatever their personal beliefs, staff should not discourage vaccinations when interacting with patients.

• Because measles is highly contagious, it may be wise to bring patients who could be infected through the back door and straight into an exam room, rather than having them wait in the waiting room and risk exposing other patients. This practice is especially important in pediatric practices, since infants must be between 12 months and 15 months old before receiving the MMR vaccine. As an alternative, the patient and anyone accompanying them should be advised to wear a face mask in the waiting room and common areas.

• Secretions from measles patients, like a sneeze, remain active for two hours. After treating a patient with measles, clean the exam room with Lysol, and wait two hours before using the waiting room for other patients. ❖

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

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100% Efficacy in Pivotal Trial of Recombinant von Willebrand Factor Used to Treat Severe von Willebrand Disease

The efficacy of Baxter International's investigational recombinant von Willebrand factor (rVWF) was rated "excellent" (96.9%) or "good" (3.1%) for treatment of 192 bleeding events in 22 patients with severe von Willebrand disease who were enrolled in a Phase 3 clinical trial. This multi-center, open-label trial was designed to assess the safety, efficacy and pharmacokinetics of this highly purified rVWF (BAX 111) among patients aged 18 years to 65 years.

On-study bleeding events were treated with 40-60 IU/kg of BAX 111; major bleeds were treated with up to 80 IU/kg. Initial bleeds were treated together with recombinant factor VIII, and subsequently alone if hemostatic factor VIII levels were maintained. The median number of infusions required to treat bleeding events was one, and most events (81.8%) were resolved with a single infusion. No patients developed inhibitors or binding antibodies. There were six nonserious adverse events (AEs) considered causally related to the product; two related serious AEs (chest discomfort and increased heart rate) occurred in one patient.

The investigators concluded that the trial met its primary efficacy endpoint, defined by the number of patients who achieved treatment success for control of bleeding episodes. Baxter submitted a biologics license application to the U.S. Food and Drug Administration for approval of BAX 111 in late 2014.

Gill JC, Castaman G, Windyga J, et al. Efficacy and safety of a recombinant von Willebrand factor for bleed treatment in patients with severe von Willebrand disease. Oral presentation: 2015 Scientific Symposium of the Hemostasis and Thrombosis Research Society (New Orleans, LA), April 17, 2015.

IVIG Monotherapy Mediates Improvement in CLE

A single-center proof-of-concept study was conducted to learn whether intravenous immunoglobulin (IVIG) can control acute cutaneous lupus erythematosus (CLE) and thus replace current systemic immunosuppressive therapy that causes severe side effects and adverse reactions. IVIG was administered to 16 patients who tried and failed various systemic treatments for CLE at 500 mg/kg/day on four consecutive days, up to a total of 2 g/kg/month for three months. The subjects were monitored for a possible relapse for an additional six months without any drug treatment.

Cumulative results revealed an overall improvement in both objective and subjective measures of disease activity. The CLE Disease Area and Severity Index (CLASI-A) score dropped from a baseline defined as 100 percent, and remained in the range of approximately 70 percent until the last visit. Three patients had a temporary flare of CLE symptoms, but recovered within a month from the relapse. There were no serious side effects or adverse events. The investigators concluded that IVIG monotherapy for CLE was associated with 1) a rapid and persistent decrease in disease activity, 2) steady improvement in patients' quality of life assessed by Skindex-29 scores, 3) a low relapse rate, and 4) relapses that were mild and of short duration. As healing was maintained for months after IVIG treatment, the investigators also raised the possibility that "IVIG triggered molecular events … that continued to unfold after the end of therapy."

Ky C, Swasdibutra B, Khademi S, et al. Efficacy of intravenous immunoglobulin monotherapy in patients with cutaneous lupus erythematosus: results of proof-of-concept study. Dermatol Reports *2015 Mar 16;7(1):5804.*

Four-Factor Prothrombin Complex Superior to Plasma for Rapid VKA Reversal

In results from a Phase 3b trial in 168 patients needing urgent reversal of acquired coagulation factor deficiency induced by vitamin K antagonist (VKA) therapy, 78 patients (90 percent) treated with CSL Behring's four-factor prothrombin complex concentrate (Kcentra; 4F-PCC) achieved effective hemostasis, compared with 61 patients (75 percent) treated with plasma. 4F-PCC demonstrated both noninferiority and superiority compared with plasma for this primary endpoint.

A co-primary endpoint — rapid reduction of the International Normalized Ratio (INR) to ≤1.3 at 0.5 hours after the end of infusion — was achieved in 48 patients (55 percent) treated with 4F-PCC vs. eight patients (10 percent) treated with plasma. The safety profile of 4F-PCC was generally similar to plasma, with 56 percent and 60 percent experiencing adverse events, respectively. While thromboembolic adverse events (7 percent vs. 8 percent) and late bleeding events (3 percent vs. 5 percent) were also similar, just three patients (3 percent) receiving 4F-PCC experienced fluid overload or similar cardiac events, compared with 11 patients (13 percent) of patients receiving plasma therapy.

The investigators concluded that 4F-PCC is noninferior and superior to plasma for rapid INR reversal and effective hemostasis in patients needing VKA reversal for urgent surgical or invasive procedures.

Goldstein JN, Refaai MA, Milling TJ, et al. Four-factor prothrombin complex concentrate versus plasma for rapid vitamin K antagonist reversal in patients needing urgent surgical or invasive interventions: a phase 3b, open-label, non-inferiority, randomized trial. Lancet *2015 Feb 26 [Epub ahead of print].*

BioResources

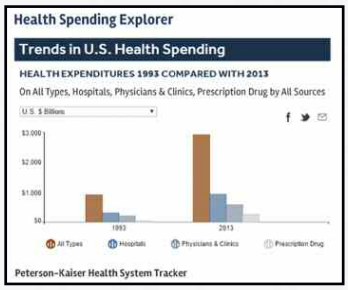
Recently released resources for the biopharmaceuticals marketplace.

Guide to International Pharma Regulation: 2015 Edition

Author: U.S. Food and Drug Administration

This guide is a compilation of more than 150 reports highlighting changes from 2014 on regulatory topics, including the European Medicines Agency's (EMA) clinical trials transparency initiative; the European Union's (EU) clinical trials regulations; India's clampdown on conduct of clinical trials, patient protections and compensation; Canada and the EU's major trade compact; the latest guidance and changes to the EMA's pharmacovigilance requirements; the new track and trace requirements in Brazil and the U.S.; and dozens more key topics in pharma regulation worldwide.

www.fdanews.com/products/category/101/product/48928-print-edition---fdanews-guide-to-international-pharma-regulation---2015-edition



Health Spending Explorer

Developer: Kaiser Family Foundation

A new interactive tool on the Peterson-Kaiser Health System Tracker allows users to analyze the most up-to-date data on U.S. health spending and then build, display and share the charts they create. Developed by analysts at the Kaiser Family Foundation, the Health Spending Explorer helps users examine five decades worth of numbers documenting expenditures by federal and local governments, private insurers and individuals on 15 categories of health services, including hospitals, physicians and clinic care and prescription drugs. The data, which spans from 1960 to 2013, is drawn from the National Health Expenditure Account, and will be updated with each new data release. Examples of questions that the data can answer include:

- How much did the U.S. spend on health services in billions of dollars inflation-adjusted in 1993 vs. 2013?
- What was out-of-pocket per capita spending on hospitals, dental care, physicians and clinic services and prescription drugs in 2009 and 2013?
- What percentage of the country's total health expenditures was represented by prescription drug spending each year from 1960 to 2013?

A short video tutorial on how to use the tool is also available.

www.healthsystemtracker.org

Informed Consent for Clinical Trials: A Regulatory Reference Guide

Author: U.S. Food and Drug Administration

This new guide has been completely updated for 2015. The 300-plus page guide contains all the information to ensure federal standards are met. New for this edition are:

- Guidance on Important Considerations for When Participation of Human Subjects in Research is Discontinued
- Informed Consent Requirements in Emergency Research
- Obtaining and Documenting Informed Consent of Subjects Who Do Not Speak English
- Human Subject Regulations Decision Charts
- The Challenge of Informed Consent

www.fdanews.com/products/49398-informed-consent-for-clinical-trials-2015-a-regulatory-reference-guide

Mastering New Reporting Rules for Clinicaltrials.gov

Author: U.S. Food and Drug Administration

This report helps to ensure that regulatory affairs and clinical trial management teams are ready and compliant with the new rules that affect how drugmakers report the details of clinical trials on ClinicalTrials.gov. Included is information on how to stay on top of deadlines for making initial, interim and final reports (including when the deadline for making changes is 15 days and when it's 30 days); knowing when and how to delay reports and still stay in compliance; understanding how much data must be reported about adverse events, partial results and compassionate use program details; and determining how much detail about the statistical significance of data must be reported.

www.fdanews.com/products/49184-mastering-new-reporting-rules-for-clinicaltrialsgov

IVIG Reimbursement Calculator

Medicare Reimbursement Rates
Rates are effective July 1, 2015, through September 30, 2015.

Product	Manufacturer	HCPCS	ASP+6% (before sequestration)	ASP + 4.3%* (after sequestration)
BIVIGAM	Biotest Pharmaceuticals	J1556	$78.02	$76.76
CARIMUNE NF	CSL Behring	J1566	$64.50	$63.46
FLEBOGAMMA 5% & 10% DIF	Grifols	J1572	$69.50	$68.39
GAMMAGARD LIQUID	Baxter	J1569	$77.57	$76.32
GAMMAGARD S/D (Low IgA)	Baxter	J1566	$64.50	$63.46
GAMMAKED	Kedrion	J1561	$79.60	$78.33
GAMMAPLEX	Bio Products Laboratory	J1557	$73.06	$71.89
GAMUNEX-C	Grifols	J1561	$79.60	$78.33
OCTAGAM 5% & 10%	Octapharma	J1568	$77.33	$76.09
PRIVIGEN	CSL Behring	J1459	$76.56	$75.34

*Reflects 2% sequestration reduction applied to 80% Medicare payment portion as required under the Budget Control Act of 2011.

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IVIG/SCIG Reference Table

Product	Manufacturer	Indication	Size
BIVIGAM Liquid, 10%	Biotest Pharmaceuticals	IVIG: PI	5 g, 10 g
CARIMUNE NF Lyophilized	CSL Behring	IVIG: PI, ITP	6 g, 12 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%	Baxter	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)	Baxter	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%	Baxter	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

2015-2016 Influenza Vaccine

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

Manufacturer	Product	Presentation	Age Group	Code
bioCSL	AFLURIA (IIV3)	5 ML multi-dose vial	5 years and older*	90658/Q2035
		0.5 ML prefilled syringes, 10-BX		90656
GlaxoSmithKline	FLULAVAL QUADRIVALENT (IIV4)	5 ML multi-dose vial	3 years and older	90688
	FLUARIX QUADRIVALENT (IIV4)	0.5 ML prefilled syringes, 10-BX		90686
MedImmune	FLUMIST QUADRIVALENT (LAIV4)	0.2 ML live virus intranasal spray	2–49 years	90672
Novartis Vaccines	FLUCELVAX (ccIIV3)	0.5 ML prefilled syringes, 10-BX	18 years and older	90661
	FLUVIRIN (IIV3)	5 ML multi-dose vial	4 years and older	90658/Q2037
		0.5 ML prefilled syringes, 10-BX		90658
Protein Sciences	FLUBLOK (RIV3)	0.5 ML single-dose vials, 10-BX	18 years and older	90673
Sanofi Pasteur	FLUZONE (IIV3)	5 ML multi-dose vial	6 months and older	Q2038
	FLUZONE QUADRIVALENT (IIV4)	5 ML multi-dose vial	6 months and older	90688
		0.25 ML prefilled syringes, 10-BX	6-35 months	90685
		0.5 ML prefilled syringes, 10-BX	36 months and older	90686
		0.5 ML single-dose vials, 10-BX		90686
	FLUZONE INTRADERMAL QUADRIVALENT (IIV4)	0.1 ML prefilled microinjection, 10-BX	18-64 years	90630
	FLUZONE HIGH-DOSE (IIV3)	0.5 ML prefilled syringes, 10-BX	65 years and older	90662

IIV3 Egg-based trivalent inactivated injectable
ccIIV3 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.

8 Critical Steps

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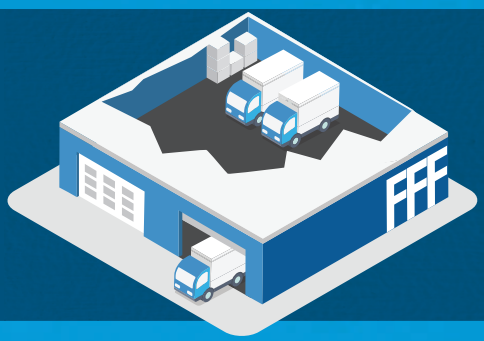
Storage

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.

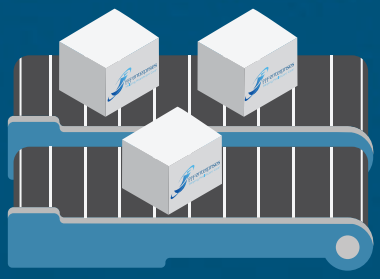


Specialty Packaging

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.



Nearly 27 counterfeit-free years

Since 1988

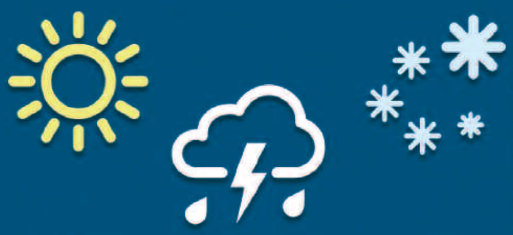
To Guaranteed Channel Integrity™

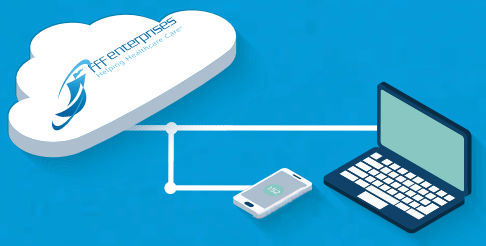
Delivery

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

FFF's Verified Electronic Pedigree™ (VEP) system allows customers to easily verify online the pedigree of pharmaceuticals purchased through FFF Enterprises.

Tracking

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®

BioSupply Trends Quarterly
41093 County Center Drive
Temecula, CA 92591-9815

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