July 2013

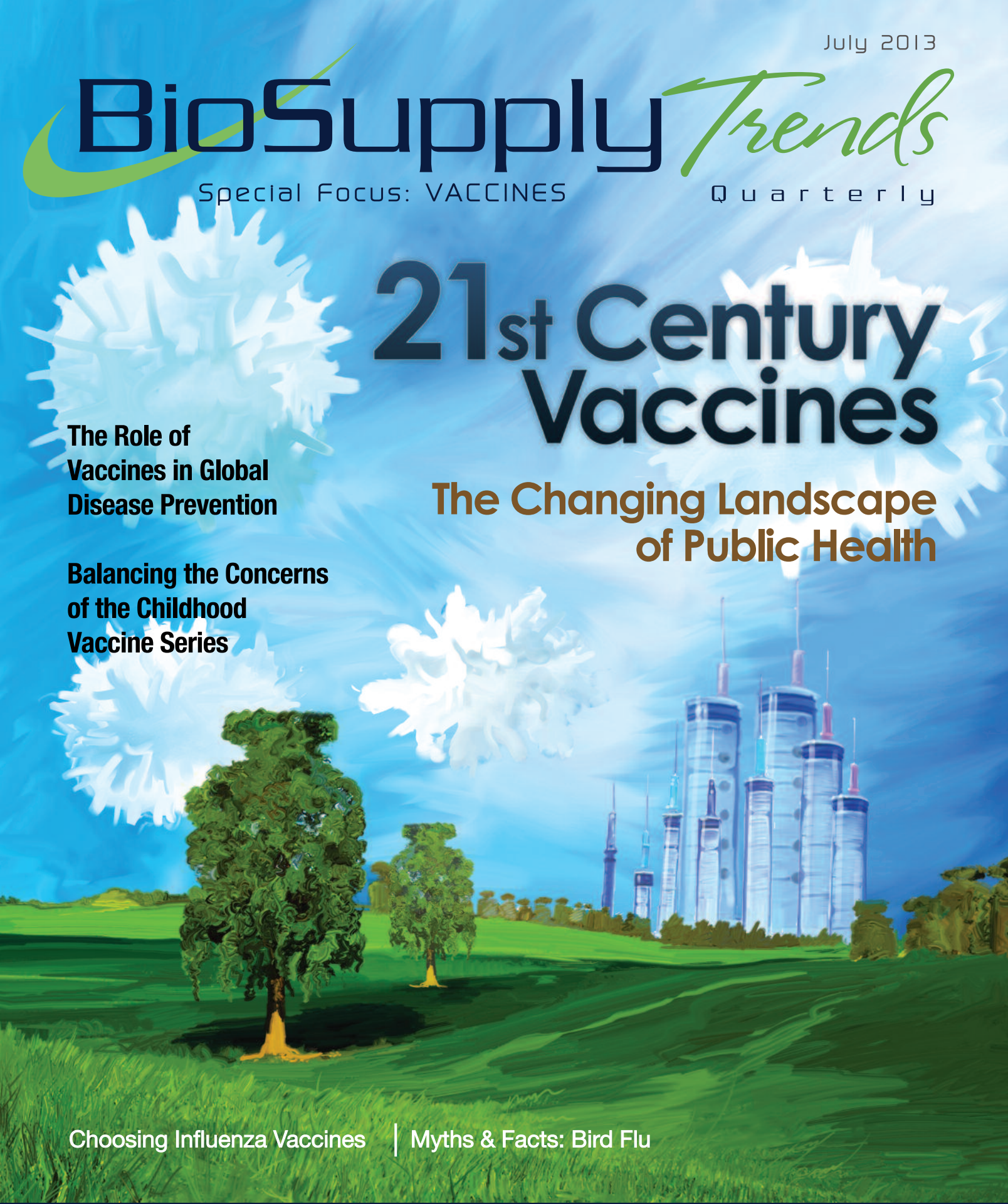
BioSupply Trends
Special Focus: VACCINES
Quarterly

21st Century Vaccines

The Changing Landscape of Public Health

The Role of Vaccines in Global Disease Prevention

Balancing the Concerns of the Childhood Vaccine Series



Choosing Influenza Vaccines | Myths & Facts: Bird Flu

Hydroxyethyl Starch: The Verdict Is In — Page 50

Flublok®

Influenza vaccine

Pure Simple Effective

No antibiotics

No eggs

No influenza virus

No latex

No formaldehyde

No thimerosal (mercury derivative) or other preservatives

Protein Sciences CORPORATION

Flublok (Influenza Vaccine)
Sterile Solution for Intramuscular Injection
Initial U.S. Approval: 2013

BRIEF SUMMARY OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Flublok safely and effectively. See full prescribing information for Flublok available at www.Flublok.com.

INDICATIONS AND USAGE

Flublok is a vaccine indicated for active immunization against disease caused by influenza virus subtypes A and type B contained in the vaccine. Flublok is approved for use in persons 18 through 49 years of age.

DOSAGE AND ADMINISTRATION

A single 0.5 mL dose for intramuscular injection.

DOSAGE FORMS AND STRENGTHS

A sterile solution for injection supplied in 0.5mL single dose vials.

CONTRAINDICATIONS

Severe allergic reaction (e.g., anaphylaxis) to any component of the vaccine.

WARNINGS AND PRECAUTIONS

If Guillain-Barré syndrome has occurred within 6 weeks of receipt of a prior influenza vaccine, the decision to give Flublok should be based on careful consideration of potential benefits and risks.

ADVERSE REACTIONS

In adults 18 through 49 years of age, the most common (≥10%) injection-site reaction was pain (>37%); the most common (≥10%) solicited systemic adverse reactions were headache (>15%), fatigue (>15%) and myalgia (>11%).

To report SUSPECTED ADVERSE REACTIONS, contact Protein Sciences Corporation at 1-888-855-7871 or VAERS at 1-800-822-7967 or www.vaers.hhs.gov.

USE IN SPECIFIC POPULATIONS

- Safety and effectiveness of Flublok have not been established in pregnant women, nursing mothers, children, or adults 50 years of age and older.
- A pregnancy registry is available for Flublok. Contact: Protein Sciences Corporation by calling 1-888-855-7871.

Issued: December 2012

Manufactured by:
Protein Sciences Corporation
1000 Research Parkway
Meriden, CT 06450
(203)686-0800 • www.proteinsciences.com

www.Flublok.com

BioSupply Trends Quarterly

July 2013

Features

Special Focus: Vaccines

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

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The New Age of Vaccines

IN THE 20TH century, vaccines virtually changed the landscape of public health. In the 21st century, it is anticipated that vaccines will play an equally significant role, addressing issues that include increased life expectancy, emerging infections and childhood mortality in developing countries. In this, our fourth anniversary issue of *BioSupply Trends Quarterly*, we look at the vaccines market on many fronts.

Since the year 2000, the global vaccines market has nearly tripled — largely attributed to advances made in the first decade of this century. But as our article "The Role of Vaccines in Global Disease Prevention" examines, some diseases have continued to represent a global health challenge. Fortunately, with new manufacturing technology, partnerships between the public and private sectors and new funding avenues, expanding immunization coverage is putting developing countries on more equal footing with industrialized nations.

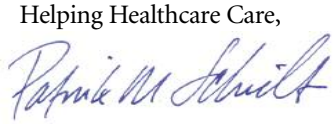
Strides in vaccines research and technology also are providing better protection against many childhood diseases. As our article "The Childhood Vaccine Series: Balancing Health, Safety and Stakeholder Concerns" illustrates, many diseases are dwindling and being eradicated, eliminating the need for some required immunizations, while other diseases are resurfacing due to parental concerns about the growing number of vaccines on the CDC's recommended list and their safety. The healthcare community is addressing these concerns through reduced exposure to the number of antigens in vaccines, as well as with the development of new combination vaccines that will reduce the number of needle sticks a child receives. It is hoped that these changes will put vaccine safety fears to rest and increase timely vaccination coverage.

Few areas of vaccine development have experienced the explosive growth occurring within the field of influenza vaccines. Today, some 13 influenza vaccines are on the market, with more on the horizon. In our article "Choosing Influenza Vaccines," we look at the quest by manufacturers to make influenza vaccines that will provide increased protection with multi-strain and egg-free formulations. This year alone, new quadrivalent and cell-based vaccines have been introduced, and more are undoubtedly in the pipeline. These new vaccines boast several advantages: It is estimated that had they been previously available, quadrivalent influenza vaccines could have saved thousands of lives during the last decade. And, in the event of a pandemic, cell-based vaccines can be manufactured quicker, allowing for a faster response to possible shortages. The good news is we are more prepared for a pandemic outbreak than we ever have been. And, it is predicted that within the next decade, a universal flu vaccine could be developed that will provide even greater protection and reduce vaccination to every five to 10 years as opposed to annually.

Finally, we take a look at a topic at the forefront of public health concerns. The current bird flu in China is raising fear that a new avian flu pandemic could arise, mimicking the Spanish flu of 1918 that killed millions. In reality, the risk of a deadly pandemic is minor. To put the risk in perspective, our article "Myths and Facts: Bird Flu" explains the misconception by many about how the flu virus mutates and spreads, as well as sheds light on how the World Health Organization and governments around the world are preparing for such an event.

As always, we hope you enjoy this issue of *BioSupply Trends Quarterly* and find the content educational and insightful. We welcome your comments.

Helping Healthcare Care,



Patrick M. Schmidt
Publisher

BioSupply Trends Quarterly

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

Publisher
Patrick M. Schmidt

Editor
Ronale Tucker Rhodes, MS

Assistant Editor
Cheryl Brooks

Artistic Director
Allan Bean

Graphic Artists
Allan Bean
Ben Drolet

Advertising Director
Cheryl Brooks

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

CMS Reverses Decision to Cut Medicare Advantage Rates

In April, the Centers for Medicare & Medicaid Services (CMS) reversed its decision to cut Medicare Advantage payments to insurers by 2.2 percent in 2014 and instead agreed to give them a 3.3 percent increase. The decision came after a lobbying campaign from lawmakers, insurers and trade associations, particularly America's Health Insurance Plans (AHIP). AHIP released a report conducted by actuarial consulting firm Oliver Wyman that showed had the rates been cut by 2.2 percent, the average Medicare Advantage beneficiary's premium would have risen $50 to $90 higher each month with a possible reduction in benefits.

"By being responsive to the more than 160 members of Congress from both parties who raised concerns about the impact of the proposed payment rate on seniors, CMS has taken an important step to help stabilize Medicare Advantage at a time when the program is facing significant challenges," said AHIP President and CEO Karen Ignagni. "We are currently reviewing the final rate announcement and will continue to work with policymakers in both parties to strengthen this critically important part of Medicare." ❖

Congress to Review Advance-Care Planning Legislation

Congress is reviewing the Personalize Your Care Act, bipartisan legislation introduced by Rep. Earl Blumenauer of Oregon, to provide Medicare and Medicaid coverage for voluntary advance-care planning consultations. The proposed law will offer families the tools to manage end-of-life decisions by providing advance-care planning meetings every five years or in the event of a change in health status. The bill also will provide grants to states to establish or expand Physician Orders for Life Sustaining Treatment (POLST) programs, and it ensures that a patient's electronic health records display his or her current POLST or advance directive form.

"Families need the tools and ability to work with healthcare providers to determine and express their wishes for care in the event that they no longer have the capacity to make decisions," said Blumenauer. "This legislation gives providers the necessary time, space and funding to conduct complex discussions with patients so they can be appropriately cared for. These consultations will ensure that an individual's values and goals for care are identified, understood and respected." ❖

Government Partners with States to Offer Health Insurance Exchanges

With only 17 states and Washington, D.C., currently signed up to run their own health insurance exchanges beginning in October, the majority of states will participate in federal government-run partnerships with the help of a grant program. That includes seven states that have signed up for partnerships. This means the Department of Health and Human Services, at least for the first year or two, will handle the technical side of things — like building the complex IT systems and helping people to sign up for coverage. And the state partners will maintain their traditional control over their health insurance markets. Partnership states can either run consumer assistance programs or oversee health plans in the exchange, or both. Whether states elect to run their own marketplaces or choose to partner with the federal government, health insurers will still be required to follow the new rules that fall under the Affordable Care Act's coverage and consumer protection requirements. ❖

24 States Have Selected Benchmark Insurance Plans

According to a study from the Commonwealth Fund, 24 states and Washington, D.C., have selected a benchmark insurance plan that will determine what health insurance providers must cover in health plans sold in state exchanges and individual and small-group markets. As part of the Patient Protection and Affordable Care Act, these benchmark insurance plans must offer an essential health benefits package that covers 10 broad categories, including prescription drugs, pediatric and maternity care, emergency services, and substance-abuse and mental health services. If a state does not choose a benchmark plan by the Oct. 1 deadline, the federal government will designate the largest small-group plan in the state as the benchmark. Because the study found that 19 states chose existing small-group plans, which are the typical employer-based plans for businesses with fewer than 50 employees, the majority of states will have the most widely purchased small-group plans as the foundation for their essential benefits package. ❖

Feds to Provide 100 Percent Funding for New Medicaid Beneficiaries

In March, the U.S. Department of Health and Human Services (HHS) announced a final rule that provides funding for states that expand Medicaid. Effective Jan. 1, 2014, the federal government will pay 100 percent of the cost of Medicaid to adults under 65 years of age with an income of up to 133 percent of the federal poverty level (approximately $15,000 for a single adult in 2012) who are defined as newly eligible, and who are enrolled in the new eligibility group. These payments will be in effect through 2016, phasing down to a permanent 90 percent matching rate by 2020. The rule also provides information about the availability of an increased Federal Medical Assistance Percentage (FMAP) for certain adults who are not newly eligible.

The rule builds on several years of work that HHS has done to support and provide flexibility to states' Medicaid programs ahead of the 2014 expansion, including 90 percent matching rate for states to improve eligibility and enrollment systems; more resources and flexibility for states to test innovative ways of delivering care through Medicaid; more collaboration with states on audits that track down fraud; and specifically outlining ways states can make Medicaid improvements without going through a waiver process. ❖

ACA Helps 105 Million Americans Receive Free Preventive Care

In the three years the Affordable Care Act (ACA) has been in effect, approximately 71 million Americans in private health insurance plans received coverage for at least one free preventive healthcare service such as a mammogram or flu shot in 2011 and 2012 because of the Act. Additionally, an estimated 34 million Americans in traditional Medicare and Medicare Advantage plans have received at least one preventive service such as an annual wellness visit at no out-of-pocket cost because of the healthcare law. Taken together, this means about 105 million Americans with private health plans and Medicare beneficiaries have been helped by the ACA's prevention coverage improvements.

"Preventing illnesses before they become serious and more costly to treat helps Americans of all ages stay healthier," said U.S. Department of Health and Human Services Secretary Kathleen Sebelius. "No longer do Americans have to choose between paying for preventive care and groceries." ❖

CARLA SCHICK *is a staff writer for* BioSupply Trends Quarterly *magazine.*

Correction

Risk of PML with TYSABRI Incorrectly Reported

In the article titled "Research Development for Multiple Sclerosis," published in the January 2013 issue of *BioSupply Trends Quarterly*, we incorrectly reported on the risk of progressive multifocal leukoencephalopathy with the immunomodulatory drug TYSABRI. Following is the corrected information:

The anti-JCV antibody test for those taking the immunomodulatory TYSABRI (natalizumab) indicates whether there is a risk of progressive multifocal leukoencephalopathy (PML), a rare brain infection caused by the JC virus, which can be fatal or cause severe

disability, and is characterized by progressive damage or inflammation of the white matter of the brain. Those testing positive for anti-JCV antibodies and taking TYSABRI less than 25 months have either a less-than-one-in-1,000-chance of developing PML if there was no prior immunosuppressant use, or a two-in-1,000-chance if there was prior immunosuppressant use. For those testing positive and taking TYSABRI between 25 months and 48 months, the risk of developing PML is either five-in-1,000 if there was no prior immunosuppressant use, or 11-in-1,000 if there was prior immunosuppressant use. Those who test negative are at significantly lower risk for developing PML, as presence of the JC virus is necessary for the development of PML. ❖

Vaccines

New "Flab Jab" Reduces Body Weight

Researchers from Braasch Biotech in South Dakota have developed an obesity vaccine that stimulates the immune system to attack a hormone that promotes slow metabolism and weight gain. The "flab jab" uses a modified form of somatostatin, a peptide protein molecule that functions as a hormone. In both mice and humans, somatostatin suppresses growth hormones that boost metabolism and cause weight loss. The vaccine "flags up" somatostatin so that it is seen as a potential threat by the immune system, and it causes the body to generate antibodies that neutralize the peptide.

In tests, obese mice fed a high fat diet saw a 10 percent drop in body weight four days after receiving the jab. In addition, the vaccine reduced body weight without affecting normal levels of growth hormones, and its effects did not significantly reduce cumulative food consumption, which was confirmed by residual anti-somatostatin antibodies in mouse plasma at the study's end. Two slightly different versions of the vaccine were studied. Both produced a sustained 10 percent reduction in body weight after booster injections were administered after three weeks. The slimming effect was not seen in a matched group of 10 untreated mice. Although the mice received large amounts of the vaccine, a recent unpublished study in pigs suggested it was effective at much lower doses.

Further research will look at the vaccine's effects in obese pigs and dogs before moving on to human trials. If the vaccine passes further safety trials, scientists believe it could provide a revolutionary new weapon against obesity. According to the lead researcher, Dr. Keith Haffer: "This study demonstrates the possibility of treating obesity with vaccination. Although further studies are necessary to discover the long-term implications of these vaccines, treatment of human obesity with vaccination could provide physicians with a drug- and surgical-free option against the weight epidemic."

The findings were reported in the *Journal of Animal Science and Biotechnology*. ❖

Research

Grifols Launches New IVIG Alzheimer's Trial

Grifols has launched a new study into methods of treatment for Alzheimer's disease. Known as the AMBAR (Alzheimer management by amyloid removal) study, it will investigate combined treatment using albumin plasmapheresis and intravenous immunoglobulin (IVIG) at different doses. The researchers will attempt to find synergies between the two treatments in order to reduce the frequency and volume of plasmapheresis, ultimately making the treatment experience more pleasant for patients and easier for medical professionals to administer.

AMBAR is expected to last two years and will be directed by Dr. Merce Boada, clinical head of the neurology service at the Vall d'Hebron Hospital in Barcelona. According to Dr. Boada, the study "opens up new prospects and hopes in dealing with an illness where success involves maintaining the quality of life of these patients." ❖

Research

Short Course of IVIG Slows Early Alzheimer's

Results from a new study in patients with early Alzheimer's disease showed a short course of intravenous immune globulin (IVIG) slows the disease's progression. Conducted at the Sutter Neuroscience Institute in Sacramento, Calif., the study hopes to replicate results of an earlier Phase 2 trial of IVIG in Alzheimer's disease patients, but with a lower total dose of IVIG. In that trial, mild to moderate Alzheimer's patients who received IVIG infusions every two to four weeks, beginning with a six-month randomized phase and continuing with a one-year open-label extension, experienced reduced brain atrophy and a near halt in their cognitive decline.

In this new study, patients with early Alzheimer's disease who received five doses of IVIG showed significantly less brain atrophy after one year than a placebo group. One-year results from the first 28 patients in a planned two-year, placebo-controlled trial showed a 5.7 percent reduction from baseline in MRI-measured ventricular brain volume among the 14 receiving IVIG, compared with an 8.76 percent decline in the 14 assigned to placebo infusions. A total of 52 patients with mild cognitive impairment attributed to Alzheimer's disease were enrolled in the study, although two dropped out before completing the eight-week course of IVIG therapy. Of the remaining 50 patients, the last to enroll had just recently finished dosing.

Because IVIG is derived from human donor plasma and is extremely scarce, production capabilities for all current suppliers could not begin to provide enough for all patients with mild to moderate Alzheimer's disease — let alone the even larger population with mild cognitive impairment — should the treatment prove to be effective. Therefore, if a short-term dosing regimen is as effective as continuing therapy, it would stretch the existing supplies to cover a greater number of patients. The eight-week, five-dose schedule used in the new study is the same as that already used in several other neurological applications and could reasonably be expected to be beneficial, said Shawn Kile, MD, of Sutter Neuroscience Institute. ❖

Medicines

New Boxed Warning Added to Immune Globulin Products

The U.S. Food and Drug Administration (FDA) has instructed manufacturers to add information to the current boxed warning in the labeling of all intravenous immune globulin (IVIG) products, and add a similar standardized boxed warning for all subcutaneous and intramuscular IG products, which highlights the risk of thrombosis and includes recommendations to mitigate that risk.

While all human IG products already contain some information related to the risk of thrombosis in the current Warnings and Precautions sections of their labels, analysis of a large health claims-related database and postmarketing adverse event reports strengthened the evidence for an association between administration of these products and the risk of thrombosis.

The new boxed warning identifies certain risk factors for thrombosis and offers specific recommendations to mitigate this risk, including ensuring adequate hydration and administering product at the minimum practicable rate of infusion. ❖

Medicines

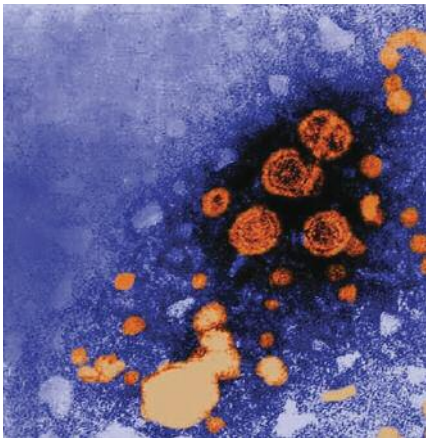
FDA Grants Expanded Indication Approval for CSL Behring's Corifact

The U.S. Food and Drug Administration (FDA) has approved an expanded indication for CSL Behring's Corifact, factor XIII (FXIII) concentrate (human) to include the perioperative management of surgical bleeding in adult and pediatric patients with congenital FXIII deficiency. In 2011, Corifact became the first and only FXIII concentrate approved in the U.S. for the routine prophylactic treatment of congenital FXIII deficiency. The expanded indication is based on use of Corifact in perioperative situations as part of both a 12-month, prospective, open-label, multi-center efficacy and safety study, as well as a nine-year investigator-initiated clinical study. In total, 20 patients received perioperative management with FXIII with neither treatment-related adverse events nor investigator-assessed serious adverse events.

Corifact, an intravenous infusion given approximately every 28 days, is a fibrin-stabilizing factor concentrate that provides both A- and B-subunits to protect against FXIII deficiency. It is packaged as lyophilized powder in a single-use vial with high stability and a long shelf life of up to six months at room temperature and 24 months when refrigerated. Corifact also has a low infusion volume, which can help reduce administration time. ❖

Diseases

Hepatitis B Exceeds Two Million in U.S.



A new study published in *Hepatology* finds that the prevalence of chronic hepatitis B virus (HBV) infection in the U.S. may be as high as 2.2 million cases. According to the study, the higher prevalence of chronic HBV can be attributed to foreign-born persons who were infected in their country of origin prior to arrival in the U.S. Emigrants from Asia and Africa, where infection with hepatitis B is highly endemic, represent close to 70 percent of the 1.32 million foreign-born persons living with chronic HBV in the U.S. in 2009.

In the study, researchers systematically reviewed the world's medical literature for HBV seroprevalence rates from 1980 to 2010. They identified 256 disease prevalence surveys for emigrants from 52 countries and 1,797 surveys for the general populations of 98 countries for use in the meta-analysis. Individuals with lower or higher risk of chronic HBV than the general population and groups not likely to emigrate were excluded. Analysis determined that between 1.04 million and 1.61 million (1.32 million estimate) foreign-born persons were living with chronic hepatitis B in the U.S. in 2009.

Chronic HBV is a major health burden that experts say affects up to 400 million individuals worldwide, with up to 25 percent at risk of premature mortality due to primary liver cancer and end-stage liver disease if the infection is left untreated. In the U.S., the Centers for Disease Control and Prevention estimates that in 2006 there were 800,000 to 1.4 million persons living with chronic HBV. However, previous reports may underestimate the true burden of chronic HBV because individuals in the U.S. who are institutionalized, homeless and foreign-born "at risk" populations are underrepresented on national health surveys. "There is a wide discrepancy in the current estimates of the chronic HBV burden in the U.S.," explains lead author Dr. Kris Kowdley, director of the Liver Center of Excellence at Virginia Mason Medical Center in Seattle, Wash. "Understanding the ethnic and cultural populations affected by chronic hepatitis B will provide more accurate estimates and help to develop programs for prevention, earlier diagnosis and access to care for those at greatest risk." ❖

Vaccine Update

Initial results from a Phase 1 trial of the world's first HIV vaccine has shown no adverse effects while significantly boosting immunity. The vaccine, which is called SAV001-H and is being developed by a team of scientists at Western's Schulich School of Medicine & Dentistry in Canada, is based on a gentically modified, dead virus. If all continues to go well, the vaccine could be commercially available in five years. ❖

Research

New Method Developed for Forecasting Flu Outbreaks

A computer model for predicting flu outbreaks weeks in advance has been developed by researchers at Columbia University and the National Center for Atmospheric Research. The model incorporates techniques used in weather prediction to forecast flu outbreaks up to seven weeks in advance, raising the possibility of flu forecasts that might one day help guide such decisions about when to increase vaccine production, close schools, better staff hospitals, etc. "Flu forecasting has the potential to significantly improve our ability to prepare for and manage the seasonal flu outbreaks that strike each year," said Irene Eckstrand, a program director at the National Institutes of Health.

To develop the model's formula, researchers used data from the Google Flu Trends project, which estimates outbreaks based on the number of flu-related search queries in a given region, as well as findings from a previous study that found wintertime U.S. flu epidemics tended to occur following very dry weather.

A practical use of the model is likely at least a year away, according to Dr. John Sinnott, director of the University of South Florida's Health Division of Infectious Disease and International Medicine. The findings were reported on in the Nov. 28, 2012, edition of the *Proceedings of the National Academy of Sciences*. ❖

One of these medicines is fake.
Can *you* tell which?

In today's global environment, it doesn't matter if you live in the United States, Europe, Asia, or Africa—**everyone is at risk from unsafe drugs.** Counterfeit drugs defraud consumers and deny patients therapies that can alleviate suffering and save lives. Unfortunately, in some cases, these drugs have caused great harm and fatalities.

Join Us For Interchange 2013

THE PARTNERSHIP FOR SAFEMEDICINES INTERCHANGE 2013

On October 24, The Partnership for Safe Medicines will host a conference with leading drug safety experts to discuss the latest information about the dangers of counterfeit drugs.

When
Thursday, October 24, 2013

Where
The Newseum
Washington, D.C.

Contact
Sarah Imber Safdar
(703) 679-SAFE
Sarah@SafeMedicines.org

To learn more about the Interchange 2013, please visit www.SafeMedicines.org.

The Partnership for SAFEMEDICINES

Together, we can protect the safety of our prescription drugs.

Vaccines

CDC Rolls Out Vaccine Tracking System

The Centers for Disease Control and Prevention (CDC) has officially initiated a national roll-out of its Vaccine Tracking System (VTrckS). VTrckS is a critical component of the Vaccine Management Business Improvement Project, which is the CDC's centralized application for managing vaccine orders and distribution of Vaccines for Children (VFC). The VFC program, a proven national initiative to reduce the impact of vaccine preventable diseases, provides vaccines at no cost to eligible children, thereby ensuring everyone has the opportunity to be vaccinated regardless of an ability to pay.

The states of Louisiana, Mississippi and West Virginia are the first three states to volunteer to work with the CDC to implement and test this VTrckS system. All three went live with electronic ordering the first week in May, and all three utilize the Scientific Technologies Corp. (www.stchome.com) immunization registry, which includes a vaccine-ordering module. VTrckS integration allows the state registries to ensure their provider communities have a single point for managing patient immunizations, including determining what immunization is next required for their patients, ordering vaccines, managing vaccines and reducing waste. ❖

Vaccines

Experts Provide New Global Vaccines Access Recommendations

Vaccine experts from the International Federation of Pharmaceutical Manufacturers & Associations (IFPMA) and the Biotechnology Industry Organization have authored a peer-reviewed article, "Delivering the Promise of the Decade of Vaccines: Opportunities and Challenges in the Development of High-Quality New Vaccines," that provides recommendations for improving global access to and use of high-quality, safe and effective vaccines. The article offers proven approaches to achieving equitable and sustained access to vaccines, including insights on achieving the Decade of Vaccines' goal of 90 percent global vaccine coverage by 2020; addressing the four As of vaccines access — availability, affordability, adoption and alliances; and increasing awareness, predictable demand and sustainable financing to support vaccines access and innovation.

According to the article's authors, accelerating vaccine access and innovation, especially in the developing world, requires a mix of "push" mechanisms that stimulate research and development through grants and investment tax credits, and "pull" mechanisms such as donor guarantees of vaccine purchases and government programs that promote vaccine uptake through increased awareness of vaccines' health benefits. "Global health stakeholders from civil society and the public and private sectors share responsibility for achieving the goals of the Decade of Vaccines," said Eduardo Pisani, IFPMA director general. "This report applies industry learnings and expertise that contributed to several past health successes such as dramatically reduced measles-related deaths and eradication of smallpox. With greater public awareness and access to innovative vaccines, great strides can be made toward preventing other leading communicable and noncommunicable diseases."

The Decade of Vaccines initiative was launched in 2010 to assemble key stakeholders from the global health community in an effort to reduce vaccine-preventable illnesses. The article was published in the April 18 edition of the journal *Vaccine*. ❖

Did You Know?

"Thirty-six percent of adults have only basic or below-basic skills for dealing with health material. This means that 90 million Americans can understand discharge instructions written only at a fifth-grade level or lower. About 52 percent have intermediate skills: They can figure out what time a medication should be taken if the label says "take two hours after eating." Twelve percent are deemed proficient because they can search a complex document and find the information necessary to define a medical term."

— 2006 study by the U.S. Department of Education

Research

Shingles Vaccine May Be Safe for Autoimmune Disease Patients

A recent study conducted at the University of Alabama at Birmingham shows that the shingles vaccine appears to be safe and effective for those suffering from autoimmune diseases. In the study, data were collected on more than 460,000 Medicare patients who had one of several rheumatic or immune-mediated diseases. Of those, more than 18,600 patients with rheumatoid arthritis, psoriasis, psoriatic arthritis, ankylosing spondylitis (an inflammation of the spine) or inflammatory bowel disease received the shingles vaccine. In the 42 days following vaccination, there were no cases of shingles, including among the more than 600 who were taking so-called anti-tumor necrosis factor biologics to treat their other conditions. And, there was only one case of shingles seen among all the patients during that time. More than 42 days after being vaccinated, 138 patients did develop shingles, which is in the range of the effectiveness of the vaccine. After two years of follow-up, the investigators concluded that the vaccine reduces the risk of shingles in these patients. That conclusion also was based on accounting for the type of immune disease, treatment and the use of arthritis drugs and steroids.

Because the shingles vaccine is a live vaccine, the U.S. Food and Drug Administration and other organizations say the vaccine should not be used in patients taking immunosuppressive drugs including all biologic agents and some nonbiologics because these patients may develop shingles from the vaccine virus strain. "A live attenuated vaccine reduces [shingles] risk by 70 percent and 51 percent among immunocompetent individuals 50 to 59 years and 60 years and older in two randomized, blinded trials, respectively," the researchers wrote. And, "the risk of [shingles] is elevated by one-and-a-half to two times in patients with rheumatic and immune-mediated diseases such as rheumatoid arthritis and Crohn's disease. This increase has been attributed to both the underlying disease process and treatments for these conditions."

According to Dr. Bruce Hirsch, an attending physician in infectious diseases at North Shore University Hospital in Manhasset, N.Y., who was not involved in the study, "The findings are reassuring for a very specific group of patients." However, the study does not address the vaccine in patients who have weakened immune systems related to other causes, Hirsch said. And, he cautions that the vaccine does have some risks and there is no long-term data on its effectiveness in these patients. "I don't consider this study to be completely definitive," Hirsch said. "The book isn't closed, but I am cautiously optimistic. The vaccine seems to be safe, and these kinds of patients are able to handle the vaccine and get a benefit from it."

The study was published on Jul. 4, 2012, in the *Journal of the American Medical Association*. ❖

Medicines

FDA Orders New Boxed Warning for Hydroxyethyl Starch

The U.S. Food and Drug Administration (FDA) has determined that hydroxyethyl starch (HES) solutions should not be used in critically ill adult patients, including patients with sepsis and those admitted to the intensive care unit (ICU). Data analyzed from numerous randomized controlled trials (RCTs), meta-analyses and observational studies document that HES use is associated with increased mortality and/or renal injury requiring renal replacement therapy (RRT), according to an FDA Safety Communication. The FDA has instructed manufacturers of all HES products* to add a Boxed Warning to the labeling, identifying these increased mortality and severe renal injury risks.

Based on the totality of the evidence, the FDA considers these serious adverse outcomes in critically ill adult patients, including those with sepsis and those admitted to the ICU, to be HES class effects.

Health professionals are additionally advised to avoid use of HES products in patients with pre-existing renal dysfunction and to discontinue use of HES at the first sign of renal injury or coagulopathy. As the need for RRT has been reported up to 90 days after HES administration, renal function monitoring is recommended for 90 days in all patients.

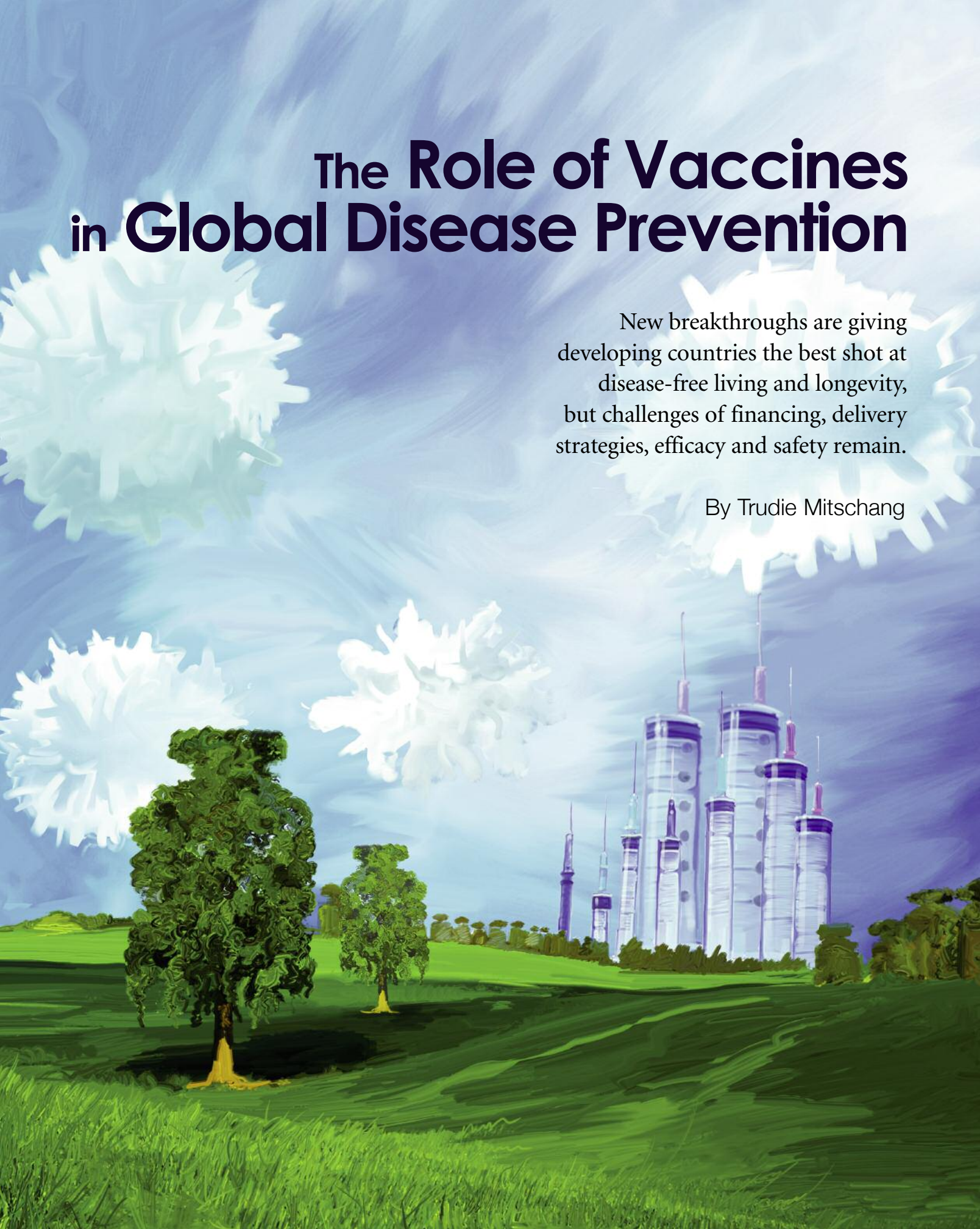
The FDA has additionally ordered manufacturers of HES solutions to add new safety information to the Warning and Precautions Section of the package insert, identifying the risk of excess bleeding in patients undergoing open heart surgery in association with cardiopulmonary bypass. A meta-analysis of 18 RCTs reviewed by the agency found that increased bleeding occurred irrespective of molecular weight or degree of molar substitution. Again, the FDA indicated that it considers excess bleeding in this particular treatment setting to be a HES class effect. ❖

*HESPAN (6% HES 450/0.7 in Sodium Chloride Injection; B. Braun Medical Inc.), Hetastarch (6%) in 0.9% Sodium Chloride Injection (generic equivalent to HESPAN; Teva Pharmaceuticals USA), HEXTEND (6% HES 450/0.7 in physiological solution; BioTime Inc.) and Voluven (6% HES 130/0.4 in normal saline; Fresenius Kabi USA, LLC).

The Role of Vaccines in Global Disease Prevention

New breakthroughs are giving developing countries the best shot at disease-free living and longevity, but challenges of financing, delivery strategies, efficacy and safety remain.

By Trudie Mitschang



The year is 2020, and the state of the global health landscape is vastly different from the one we see today. Polio and measles have been virtually eradicated worldwide, as have neonatal and maternal tetanus cases. The widespread use of vaccines against pneumococcal, rotavirus, meningococcal and HPV disease have inspired new and more ambitious international health and immunization guidelines, revolutionizing the state of the vaccine marketplace. Perhaps most significantly, breakthrough vaccines have been introduced to combat even the most lethal diseases, including malaria, tuberculosis and HIV/AIDS. Sound like a utopian pipe dream? Perhaps not.

Aggressive growth within the vaccine industry in recent years has resulted in significant achievements, especially when it comes to increasing immunization access in developing countries. Industry analysts predict that by 2020, manufacturers in developing countries may have acquired the capacity to make their own state-of-the-art vaccines tailored to meet their specific needs. Such a contribution to the global vaccine supply could put many of those countries on more equal footing with their industrialized counterparts when it comes to infectious disease control and prevention.

A Surge in Vaccine Development

The first decade of this century has been touted as the most productive in the history of vaccine development. New lifesaving vaccines have been introduced for meningococcal meningitis, rotavirus diarrheal disease, avian influenza caused by the H5N1 virus, pneumococcal disease and cervical cancer caused by human papillomavirus (HPV). According to the World Health Organization (WHO), the next 10 years will spur an increased demand for some of these newer vaccines, especially in developing countries. New vaccine delivery systems are also anticipated, as devices that use needles may largely be replaced with innovative approaches such as aerosol formulations sprayed in the nose (already available in an influenza vaccine) or lungs.[1]

Since the year 2000, the vaccine market has almost tripled, exceeding $17 billion in global revenue by mid-2008, and making the vaccine industry one of the fastest growing sectors of industry.[1] Most of this expansion has come from sales in industrialized countries of newer, costlier vaccines, which account for more than half of the total value of vaccine sales worldwide. There are also a large number of candidate vaccines in the late stages of research and development — more than 80, according to recent unpublished data. Furthermore, about 30 of these candidates aim to protect against diseases for which no vaccines are currently available.[2]

According to a report by WHO, the surge in new vaccine development can be largely attributed to three key factors: the use of innovative manufacturing technology; growing support from public-private product development partnerships; and new funding resources and mechanisms. At the same time, the industry has seen significant growth in the capacity of manufacturers in developing countries to contribute to the supply of traditional childhood vaccines. Since 2000, the demand for these vaccines has grown steadily in an effort to meet the needs sparked by several major initiatives to combat polio, measles and neonatal and maternal tetanus. Currently, there are seven vaccines recommended for distribution and use in developing countries:

- DTP, for diphtheria, tetanus and pertussis
- BCG, for tuberculosis
- measles
- polio
- yellow fever
- hepatitis B
- Haemophilus influenzae type b (Hib)

Expanding immunization coverage for basic vaccines is a proven, cost-effective method for saving lives in the developing world. Globally, increased access to vaccinations has saved more than 20 million children and is widely considered one of the most significant successes in public health. For example, the death rate due to childhood measles has declined 75 percent since the year 2000, while measles immunization rates have increased to 82 percent worldwide since 1990.[3] Polio vaccine rates have also seen dramatic increases, thanks in part to the Global Polio Eradication Initiative (GPEI); incidence of the disease went from 350,000 cases in 1988 to 1,652 cases in 2008.[4]

Currently, there are seven vaccines recommended for distribution and use in developing countries.

Envisioning a World Without Polio

In 1988, polio was endemic in 125 countries, resulting in close to 1,000 incidents of paralysis per day.[4] That same year, the World Health Assembly (WHA) passed a resolution calling for global eradication of the disease. The GPEI, an international partnership, was initiated to achieve that goal by 2018, and to date, polio eradication efforts have resulted in several landmark successes. For instance, India, long regarded as the nation

facing the greatest challenges to eradication, was removed from the list of polio-endemic countries in February 2012. And, outbreaks in previously polio-free countries were nearly all stopped. Currently, a plan is in place to boost vaccination coverage in Nigeria, Pakistan and Afghanistan, the three remaining polio endemic countries, to levels needed to stop polio transmission. Despite the successes, outbreaks in recent years in China and West Africa due to importations from Pakistan and Nigeria, respectively, highlight the continued threat of resurgence. By some estimates, failure to eradicate polio could lead within a decade to as many as 200,000 paralyzed children a year worldwide.[5] "Polio eradication is at a tipping point between success and failure," said Dr. Margaret Chan, director-general of WHO. "We are in emergency mode to tip it toward success — working faster and better, focusing on the areas where children are most vulnerable."[6]

Once achieved, polio eradication would generate net benefits of $40 billion to $50 billion globally by 2035, with the bulk of savings in the poorest countries, calculated based on investments made since the GPEI was formed and savings from reduced treatment costs and gains in productivity. "We know polio can be eradicated, and our success in India proves it," said Kalyan Banerjee, president of Rotary International, a global humanitarian service organization. "It is now a question of political and societal will. Do we choose to deliver a polio-free world to future generations, or do we choose to allow 55 cases this year to turn into 200,000 children paralyzed for life, every single year?"[6]

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Immunizing the "Meningitis Belt"

Meningococcal meningitis occurs in small clusters throughout the world and accounts for a variable proportion of epidemic bacterial meningitis. The largest burden of meningococcal disease occurs in an area of sub-Saharan Africa comprising 26 countries and known as the "meningitis belt," which stretches from Senegal in the west to Ethiopia in the east.[7]

In 2001, PATH, an international nonprofit organization, and WHO partnered to create the Meningitis Vaccine Project to develop, test, produce and provide vaccines that prevent meningococcal disease in the meningitis belt. In 2010, the project launched a new vaccine called MenAfriVac using an innovative vaccine-development model involving partners with expertise in technology, materials and manufacturing located on four continents. The vaccine was produced at one-tenth the cost of a typical new vaccine, costing less than 50 cents a dose. It also signified the first time a vaccine was designed specifically for Africa and became the first vaccine ever introduced in Africa prior to reaching any other continent.[7]

According to published materials, MenAfriVac has several advantages over existing polysaccharide vaccines: It induces a higher and more sustainable immune response against group A meningococcus; it reduces the carriage of the bacteria in the throat and, thus, its transmission; it is expected to confer long-term protection not only for those who receive the vaccine, but on family members and others who would otherwise have been exposed to meningitis; it is available at a lower price than other meningococcal vaccines; and it is expected to be particularly effective in protecting children under 2 years of age, who do not respond to conventional polysaccharide vaccines.

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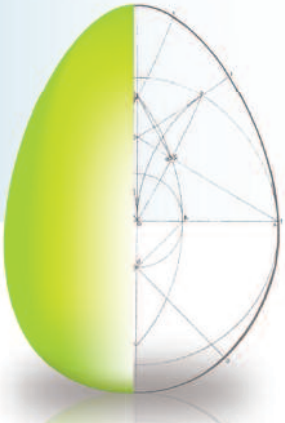

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Important Safety Information

Privigen is indicated as replacement therapy for patients with primary immunodeficiency (PI) associated with defects in humoral immunity, including but not limited to common variable immunodeficiency (CVID), X-linked agammaglobulinemia, congenital agammaglobulinemia, Wiskott- Aldrich syndrome, and severe combined immunodeficiencies. Privigen is also indicated to raise platelet counts in patients with chronic immune thrombocytopenic purpura (ITP).

WARNING: Use of Immune Globulin Intravenous (IVIg) products, particularly those containing sucrose, have been associated with renal dysfunction, acute renal failure, osmotic nephropathy, and death. Privigen does not contain sucrose. Administer Privigen at minimum rate practicable in patients at risk of renal dysfunction or acute renal failure. At-risk patients include those with preexisting renal insufficiency, diabetes mellitus, volume depletion, sepsis, or paraproteinemia; over 65 years of age; or receiving known nephrotoxic drugs. See full prescribing information for complete boxed warning.

Privigen is contraindicated in patients with history of anaphylactic or severe systemic reaction to human immune globulin, in patients with hyperprolinemia, and in IgA-deficient patients with antibodies to IgA and history of hypersensitivity.

Monitor patient vital signs throughout infusion of Privigen. In cases of severe hypersensitivity or anaphylactic reactions, discontinue administration and institute appropriate medical treatment. In patients at risk for developing renal failure, monitor urine output and renal function, including blood urea nitrogen and serum creatinine. Thrombotic events have occurred in patients with risk factors; consider baseline assessment of blood viscosity for those at risk of hyperviscosity. Patients could experience increased serum viscosity, hyperproteinemia or hyponatremia; infrequently, aseptic meningitis syndrome (AMS) may occur (most often with high doses and/or rapid IVIg infusion).

Hemolysis that is either intravascular or due to enhanced red blood cell sequestration can develop subsequent to treatment with Privigen. Closely monitor patients for hemolysis and hemolytic anemia. Risk factors for hemolysis include non-O blood group, underlying inflammation, and high doses. Carefully consider relative risks and benefits before prescribing high-dose regimen for chronic ITP in patients at increased risk of thrombosis, hemolysis, acute kidney injury or volume overload.

Monitor patients for pulmonary adverse reactions and signs of transfusion-related acute lung injury (TRALI).

Privigen is derived from human plasma. The risk of transmission of infectious agents, including viruses and, theoretically, the Creutzfeldt-Jakob disease (CJD) agent, cannot be completely eliminated.

In clinical studies of patients being treated with Privigen for PI, the most serious adverse reaction was hypersensitivity (one subject). Adverse reactions observed in >5% of subjects with PI were headache, pain, nausea, fatigue, chills, vomiting, joint swelling/effusion, pyrexia, and urticaria.

In clinical studies of patients being treated with Privigen for chronic ITP, the most serious adverse reactions were AMS (one subject) and hemolysis (eight subjects). Adverse reactions seen in >5% of subjects with chronic ITP were headache, pyrexia/hyperthermia, positive DAT, anemia, vomiting, nausea, increases in conjugated and unconjugated bilirubin, hyperbilirubinemia, and increased blood lactate dehydrogenase.

Treatment with Privigen might interfere with a patient's response to live virus vaccines and could lead to misinterpretation of serologic testing.

Please see brief summary of full prescribing information on following pages.

1020 First Avenue, PO Box 61501, King of Prussia, PA 19406-0901 USA
www.CSLBehring-us.com www.Privigen.com PVG10-11-0014a 6/2012

CSL Behring

BRIEF SUMMARY OF PRESCRIBING INFORMATION

Privigen®, Immune Globulin Intravenous (Human), 10% Liquid

Before prescribing, please consult full prescribing information, a brief summary of which follows. Some text and references refer to full prescribing information.

WARNING: ACUTE RENAL DYSFUNCTION/FAILURE

- **Use of Immune Globulin Intravenous (IGIV) products, particularly those containing sucrose, have been reported to be associated with renal dysfunction, acute renal failure, osmotic nephropathy, and death.[1] Patients at risk of acute renal failure include those with any degree of pre-existing renal insufficiency, diabetes mellitus, advanced age (above 65 years of age), volume depletion, sepsis, paraproteinemia, or receiving known nephrotoxic drugs (*see* *Warnings and Precautions [5.2]*). Privigen does not contain sucrose.**
- **For patients at risk of renal dysfunction or failure, administer Privigen at the minimum infusion rate practicable (*see* *Dosage and Administration [2.3]*, *Warnings and Precautions [5.2]*).**

4 CONTRAINDICATIONS

- Privigen is contraindicated in patients who have a history of anaphylactic or severe systemic reaction to the administration of human immune globulin.
- Privigen is contraindicated in patients with hyperprolinemia because it contains the stabilizer L-proline (*see Description [11]*).
- Privigen is contraindicated in IgA-deficient patients with antibodies to IgA and a history of hypersensitivity (*see Warnings and Precautions [5.1]*).

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity

Severe hypersensitivity reactions may occur (*see Contraindications [4]*). In case of hypersensitivity, discontinue the Privigen infusion immediately and institute appropriate treatment. Medications such as epinephrine should be available for immediate treatment of acute hypersensitivity reactions.

Privigen contains trace amounts of IgA (≤25 mcg/mL) (*see Description [11]*). Individuals with IgA deficiency can develop anti-IgA antibodies and anaphylactic reactions (including anaphylaxis and shock) after administration of blood components containing IgA. Patients with known antibodies to IgA may have a greater risk of developing potentially severe hypersensitivity and anaphylactic reactions with administration of Privigen. Privigen is contraindicated in patients with antibodies against IgA and a history of hypersensitivity.

5.2 Renal Dysfunction/Failure

Acute renal dysfunction/failure, osmotic nephropathy, and death may occur with the use of IGIV products, including Privigen. Ensure that patients are not volume depleted and assess renal function, including measurement of blood urea nitrogen (BUN) and serum creatinine, before the initial infusion of Privigen and at appropriate intervals thereafter.

Periodic monitoring of renal function and urine output is particularly important in patients judged to be at increased risk of developing acute renal failure.[1] If renal function deteriorates, consider discontinuing Privigen. For patients judged to be at risk of developing renal dysfunction because of pre-existing renal insufficiency, or predisposition to acute renal failure (such as those with diabetes mellitus or hypovolemia, those who are overweight, those who use concomitant nephrotoxic medicinal products, or those who are over 65 years of age), administer Privigen at the minimum rate of infusion practicable (*see Boxed Warning*, *Dosage and Administration [2.3]*).

5.3 Thrombotic Events

Thrombotic events may occur following treatment with IGIV products, including Privigen.[2-4] Patients at risk include those with a history of atherosclerosis, multiple cardiovascular risk factors, advanced age, impaired cardiac output, coagulation disorders, prolonged periods of immobilization, and/or known/ suspected hyperviscosity.

Because of the potentially increased risk of thrombosis, consider baseline assessment of blood viscosity in patients at risk for hyperviscosity, including those with cryoglobulins, fasting chylomicronemia/ markedly high triacylglycerols or monoclonal gammopathies. For patients judged to be at risk of developing thrombotic events, administer Privigen at the minimum rate of infusion practicable *(see Dosage and Administration [2.3]).*

5.4 Hyperproteinemia, Increased Serum Viscosity, and Hyponatremia

Hyperproteinemia, increased serum viscosity, and hyponatremia may occur following treatment with IGIV products, including Privigen. The hyponatremia is likely to be a pseudohyponatremia, as demonstrated by a decreased calculated serum osmolality or elevated osmolar gap. It is critical to distinguish true hyponatremia from pseudohyponatremia, as 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 thromboembolic events.[5]

5.5 Aseptic Meningitis Syndrome (AMS)

AMS may occur infrequently following treatment with Privigen (*see Adverse Reactions [6]*) and other human immune globulin products. Discontinuation of treatment has resulted in remission of AMS within several days without sequelae.[6] AMS usually begins within several hours to 2 days following IGIV treatment.

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 are frequently positive with pleocytosis up to several thousand cells per cubic millimeter, predominantly from the granulocytic series, and with 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.

5.6 Hemolysis

Privigen 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.[7-9] Delayed hemolytic anemia can develop subsequent to Privigen therapy due to enhanced RBC sequestration, and acute hemolysis, consistent with intravascular hemolysis, has been reported.[10] Cases of severe hemolysis-related renal dysfunction/failure or disseminated intravascular coagulation have occurred following infusion of Privigen.

The following can be associated with risk of hemolysis: high doses (eg, ≥ 2 g/kg), whether given either as a single administration or divided over several days; non-0 blood group; and underlying inflammatory state.[11,12] Hemolysis has been reported following administration of IGIV for indications including ITP AND PI.

Monitor patients for clinical signs and symptoms of hemolysis. If these are present after a Privigen infusion, perform appropriate confirmatory laboratory testing. If transfusion is indicated for patients who develop hemolysis with clinically compromising anemia after receiving IGIV, perform adequate cross-matching to avoid exacerbating on-going hemolysis.

5.7 Transfusion-Related Acute Lung Injury (TRALI)

Noncardiogenic pulmonary edema may occur following treatment with IGIV products, including Privigen.[11] 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 and anti-human leukocyte antigen (HLA) antibodies in both the product and the patient's serum.

TRALI may be managed using oxygen therapy with adequate ventilatory support.

5.8 Volume Overload

Carefully consider the relative risks and benefits before prescribing the high dose regimen (for chronic ITP) in patients at increased risk of thrombosis, hemolysis, acute kidney injury, or volume overload.

5.9 Transmissible Infectious Agents

Because Privigen is made from human blood, it may carry a risk of transmitting infectious agents (e.g., viruses and, theoretically, the Creutzfeldt-Jakob disease [CJD] agent). The risk of infectious agent transmission has been reduced by screening plasma donors for prior exposure to certain viruses, testing for the presence of certain current virus infections, and including virus inactivation/removal steps in the manufacturing process for Privigen.

Report any infection thought to be possibly transmitted by Privigen to CSL Behring Pharmacovigilance at 1-866-915-6958.

5.10 Interference with Laboratory Tests

Various passively transferred antibodies in immunoglobulin preparations may lead to misinterpretation of the results of serological testing.

6 ADVERSE REACTIONS

The most serious adverse reactions observed in clinical study subjects receiving Privigen for PI was hypersensitivity in one subject. The most common adverse reactions observed in >5% of clinical study subjects with PI were headache, pain, nausea, fatigue, chills, vomiting, joint swelling/effusion, pyrexia, and urticaria.

The most serious adverse reactions observed in clinical study subjects receiving Privigen for chronic ITP were aseptic meningitis syndrome in one subject and hemolysis in two subjects. Six other subjects in the ITP study experienced hemolysis as documented from clinical laboratory data. The most common adverse reactions observed in >5% of clinical study subjects with chronic ITP were headache, pyrexia/hyperthermia, positive DAT, anemia, vomiting, nausea, hyperthermia, bilirubin conjugated increased, bilirubin unconjugated increased, hyperbilirubinemia, and blood lactate dehydrogenase increased.

6.1 Clinical Trials Experience

Because different 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 prospective, open-label, single-arm, multicenter clinical study (pivotal study), 80 subjects with PI (with a diagnosis of XLA or CVID) received Privigen every 3 or 4 weeks for up to 12 months (*see Clinical Studies [14.1]*). All subjects had been on regular IGIV replacement therapy for at least 6 months prior to participating in the study. Subjects ranged in age from 3 to 69; 46 (57.5%) were male and 34 (42.5%) were female.

The safety analysis included all 80 subjects, 16 (20%) on the 3-week schedule and 64 (80%) on the 4-week schedule. The median dose of Privigen administered was 428.3 mg/kg (3-week schedule) or 440.6 mg/kg (4-week schedule) and ranged from 200 to 888 mg/kg. A total of 1038 infusions of Privigen were administered, 272 in the 3-week schedule and 766 in the 4-week schedule

Routine premedication was not allowed. However, subjects who experienced two consecutive infusion-related adverse events (AEs) that were likely to be prevented by premedication were permitted to receive antipyretics, antihistamines, NSAIDs, or antiemetic agents. During the study, 8 (10%) subjects received premedication prior to 51 (4.9%) of the 1038 infusions administered.

Temporally associated AEs are those occurring during an infusion or within 72 hours after the end of an infusion, *irrespective of causality*. In this study, the upper bound of the 1-sided 97.5% confidence interval for the proportion of Privigen infusions temporally associated with one or more AEs was 23.8% (actual proportion: 20.8%). The total number of temporally associated AEs was 397 (a rate of 0.38 AEs per infusion), reflecting that some subjects experienced more than one AE during the observation period.

Table 2: PI Pivotal Study – Adverse Events Occurring in >5% of Subjects During a Privigen Infusion or Within 72 Hours After the End of an Infusion, *Irrespective of Causality*

Adverse Event (Excluding Infections)	Number (%) of Subjects [n=80]	Number (Rate) of Infusions with Adverse Event [n=1038]
Headache	35 (43.8)	82 (0.079)
Pain	20 (25.0)	44 (0.042)
Fatigue	13 (16.3)	27 (0.026)
Nausea	10 (12.5)	19 (0.018)
Chills	9 (11.3)	15 (0.014)
Vomiting	7 (8.8)	13 (0.013)
Pyrexia	6 (7.5)	10 (0.010)
Cough	5 (6.3)	5 (0.005)
Diarrhea	5 (6.3)	5 (0.005)
Stomach discomfort	5 (6.3)	5 (0.005)

Of the 397 temporally associated AEs reported for the 80 subjects with PI, the investigators judged 192 to be at least possibly related to the infusion of Privigen (including 5 serious, severe AEs described below). Of these, 91 were mild, 81 were moderate, 19 were severe, and 1 was of unknown severity.

Table 3: PI Pivotal Study – Adverse Reactions Occurring in >5% of Subjects, *Irrespective of Time of Occurrence*

Adverse Reaction	Number (%) of Subjects [n=80]	Number (Rate) of Infusions with Adverse Reaction [n=1038]
Headache	24 (30.0)	62 (0.060)
Pain, all types*	12 (15.0)†	26 (0.025)
Nausea	10 (12.5)	18 (0.017)
Fatigue	9 (11.3)	16 (0.015)
Chills	9 (11.3)	15 (0.014)
Vomiting	6 (7.5)	11 (0.011)

* Includes abdominal pain lower, abdominal tenderness, arthralgia, back pain, chest pain, infusion-site pain, injection-site pain, neck pain, pain, pain in extremity, and pharyngolaryngeal pain.

† Some subjects experienced more than one type of pain.

Sixteen (20%) subjects experienced 41 serious AEs. Five of these AEs (hypersensitivity, chills, fatigue, dizziness, and increased body temperature, all severe) were related to Privigen, occurred in one subject, and resulted in the subject's withdrawal from the study. Two other subjects withdrew from the study due to AEs related to Privigen treatment (chills and headache in one subject; vomiting in the other).

Seventy-seven of the 80 subjects enrolled in this study had a negative DAT at baseline. Of these 77 subjects, 36 (46.8%) developed a positive DAT at some time during the study. However, no subjects showed evidence of hemolytic anemia.

During this study, no subjects tested positive for infection due to human immunodeficiency virus (HIV), hepatitis B virus (HBV), hepatitis C virus (HCV), or B19 virus (B19V).

An extension of the pivotal study was conducted in 55 adult and pediatric subjects with PI to collect additional efficacy, safety, and tolerability data. This study included 45 subjects from the pivotal study who were receiving Privigen and 10 new subjects who were receiving another IGIV product prior to enrolling in the extension study. Subjects ranged in age from 4 to 81 years; 26 (47.3%) were male and 29 (52.7%) were female.

Subjects were treated with Privigen at median doses ranging from 286 to 832 mg/kg per infusion over a treatment period ranging from 1 to 27 months. Twelve (21.8%) subjects were on a 3-week treatment schedule with the number of infusions per subject ranging from 4 to 38 (median: 8 infusions); 43 (78.2%) subjects were on a 4-week schedule with the number of infusions ranging from 1 to 31 (median: 15 infusions). A total of 771 infusions were administered in this study.

In this study, subjects who continued from the pivotal study were permitted to receive infusions of Privigen at a rate up to 12 mg/kg/min (as opposed to the maximum of 8 mg/kg/min allowed in the pivotal study) at the discretion of the investigator based on individual tolerability. Twenty-three (51%) of the 45 subjects from the pivotal study (41.8% of the 55 subjects in the extension study) received 265 (38.4%) infusions at a maximum rate greater than the recommended rate of 8 mg/kg/min (*see Dosing and Administration [2.3]*). The median of the maximum infusion rate in this subset was 12 mg/kg/min. However, because the study was not designed to compare infusion rates, no definitive conclusions regarding tolerability could be drawn for infusion rates higher than the recommended rate of 8 mg/kg/min.

In this study, the proportion of infusions temporally associated with one or more AEs occurring during a Privigen infusion or within 72 hours after the end of an infusion was 15%. The total number of temporally associated AEs, *irrespective of causality*, was 206 (a rate of 0.27 AEs per infusion), reflecting that some subjects experienced more than one AE during the observation period.

Of the 206 temporally associated AEs reported for the 55 subjects with PI, the investigators judged 125 to be at least possibly related to the infusion of Privigen. Of these, 76 were mild, 40 were moderate, and 9 were severe.

Eleven (20%) subjects experienced 17 serious AEs, none of which were considered to be related to Privigen. Three subjects experienced AEs that were considered to be at least possibly related to Privigen: dyspnea and pancytopenia in one subject, a transient ischemic attack 16 days after the infusion in one subject, and mild urticaria in one subject, resulting in the subject's withdrawal from the study.

Treatment of Chronic Immune Thrombocytopenic Purpura

In a prospective, open-label, single-arm, multicenter clinical study, 57 subjects with chronic ITP and a platelet count of 20 x 10^9/L or less received a total of 2 g/kg dose of Privigen administered as 1 g/kg infusions daily for 2 consecutive days (*see Clinical Studies [14.2]*). Subjects ranged in age from 15 to 69; 23 (40.4%) were male and 34 (59.6%) were female.

Concomitant medications affecting platelets or other treatments for chronic ITP were not allowed. Thirty-two (56.1%) subjects received premedication with acetaminophen and/or an antihistamine.

Table 6: Chronic ITP Study – Adverse Events Occurring in >5% of Subjects During a Privigen Infusion or Within 72 hours After the End of a Treatment Cycle, *Irrespective of Causality (Two consecutive daily infusions)*

Adverse Event	Number (%) of Subjects [n=57]	Number (Rate) of Infusions With Adverse Event [n=114]
Headache	37 (64.9)	41 (0.360)
Pyrexia/hyperthermia	21 (36.8)	22 (0.193)
Nausea	6 (10.5)	6 (0.053)
Epistaxis	6 (10.5)	6 (0.053)
Vomiting	6 (10.5)	6 (0.053)
Blood unconjugated bilirubin increased	6 (10.5)	6 (0.053)
Blood conjugated bilirubin increased	5 (8.8)	5 (0.044)
Blood total bilirubin increased	4 (7.0)	4 (0.035)
Hematocrit decreased	3 (5.3)	3 (0.026)

Table 7: Chronic ITP Study – Adverse Reactions Occurring in >5% of Subjects, *Irrespective of Time of Occurrence*

Adverse Reaction	Number (%) of Subjects [n=57]	Number (Rate) of Infusions With Adverse Reaction [n=114]
Headache	37 (64.9)	52 (0.456)
Pyrexia/hyperthermia	19 (33.3)	21 (0.184)
Positive DAT	6 (10.5)	7 (0.061)
Anemia	6 (10.5)	6 (0.053)
Vomiting	5 (8.8)	6 (0.053)
Nausea	5 (8.8)	7 (0.061)
Bilirubin conjugated, increased	5 (8.8)	5 (0.044)
Bilirubin unconjugated, increased	5 (8.8)	5 (0.044)
Hyperbilirubinemia	3 (5.3)	3 (0.026)
Blood lactate dehydrogenase increased	3 (5.3)	3 (0.026)
Hematocrit decreased	3 (5.3)	3 (0.026)

Of the 149 non-serious AEs related to Privigen, 103 were mild, 37 were moderate, and 9 were severe.

Three subjects experienced three serious AEs, one of which (aseptic meningitis) was related to the infusion of Privigen.

One subject withdrew from the study due to gingival bleeding that was not related to Privigen.

Eight subjects, all of whom had a positive DAT, experienced transient drug-related hemolytic reactions, which were associated with elevated bilirubin, elevated lactate dehydrogenase, and a decrease in hemoglobin level within two days after the infusion of Privigen. Two of the eight subjects were clinically anemic but did not require clinical intervention; these cases resolved uneventfully.

Four other subjects with active bleeding were reported to have developed anemia without evidence of hemolysis.

In this study, there was a decrease in hemoglobin after the first Privigen infusion (median decrease of 1.2 g/dL by Day 8) followed by a return to near baseline by Day 29.

Fifty-six of the 57 subjects in this study had a negative DAT at baseline. Of these 56 subjects, 12 (21.4%) developed a positive DAT during the 29-day study period.

6.2 Postmarketing Experience

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

The following adverse reactions have been identified and reported during the post-approval use of IGIV products.[12]

- **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, bullous dermatitis
- *Hematologic:* Pancytopenia, leukopenia, hemolysis, positive DAT (Coombs' test)
- *Musculoskeletal:* Back pain
- *Gastrointestinal:* Hepatic dysfunction, abdominal pain
- *General/Body as a Whole:* Pyrexia, rigors

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Based on May 2012 revision

It is hoped that all 26 countries in the African meningitis belt will have introduced this vaccine by 2016. High coverage of the target age group of 1 year to 29 years has the potential to eliminate meningococcal A epidemics from this region of Africa.[7]

Fighting Measles and Rubella in Rwanda

Launched in March of this year, Rwanda's measles-rubella (MR) vaccination campaign is the beginning of an effort to vaccinate more than 700 million children under 15 years of age against these two disabling and deadly diseases. The combined MR vaccine will be introduced in 49 countries by 2020 thanks to financial support from the GAVI Alliance, a public-private partnership committed to saving children's lives and protecting people's health by increasing access to immunization in developing countries.[8] The support builds on the efforts of the Measles & Rubella Initiative (M&RI) that have helped countries to protect 1.1 billion children against measles since 2001. The initiative is a partnership of many health agencies, vaccine companies, donors and others, but it is led by the American Red Cross, the United Nations Foundation, the Centers for Disease Control and Prevention, UNICEF and WHO.

Because of this initiative, Rwanda became the first sub-Saharan African country to provide MR vaccine nationwide with GAVI support. The vaccine will stop not only the transmission of rubella from mother to child, preventing children being born with severe birth defects, but also protect children against measles, which is highly contagious. Every year, an estimated 112,000 children, mostly in Africa, South Asia and the Pacific Islands, are born with handicaps caused by their mothers' rubella infections. "Rwanda has made great strides over the past four years in child survival by introducing vaccines against leading child killers, including pneumonia and diarrhea," said Dr. Agnes Binagwaho, Rwanda's Minister of Health. "The introduction of the combined measles-rubella vaccine is one more important step to ensuring that all children in Rwanda receive the full immunization package. In our efforts to eliminate measles, we have raised measles coverage through campaigns and routine immunization to higher than 95 percent."[8]

Five other countries — Bangladesh, Cambodia, Ghana, Senegal and Vietnam — are expected to introduce the MR vaccine through vaccination campaigns with GAVI support by the end of 2013. "Investing in rubella will provide a much-needed boost to improving women's and children's health in poor countries. GAVI's support for measles-rubella campaigns will help accelerate global progress in controlling two life-threatening diseases," said Dr. Seth Berkley, GAVI Alliance CEO. "Rubella vaccine has been available since the 1970s in many parts of the world. Accelerating the introduction of rubella vaccine in developing countries will spread the benefits of the vaccine to those in most need and build on country efforts to control measles with a cost-effective combined vaccine. It brings us one step closer to ensuring that every child everywhere is fully immunized."[8]

Every year, an estimated 112,000 children, mostly in Africa, South Asia and the Pacific Islands, are born with handicaps caused by their mothers' rubella infection.

Promising Malaria Vaccine Faces Setbacks

There is currently no vaccine that offers complete protection against malaria, but hopes have been high regarding RTS,S, the

most advanced candidate malaria vaccine developed by GlaxoSmithKline (GSK). Unfortunately, in March 2013, a study published in the *New England Journal of Medicine* showed the effectiveness of the vaccine wanes over time, with the shot protecting only 16.8 percent of children over 4 years, according to trial data. The disappointing results raised further questions about whether RTS,S can make a difference in the fight against the disease, a major cause of illness and death among children in sub-Saharan Africa. Results from a separate trial last year showed the vaccine was only 30 percent effective in babies. The new data found that although RTS,S initially had a protection rate as high as 53 percent, after an average of eight months, that effectiveness faded swiftly.[9] "It was a bit surprising to see the efficacy waned so significantly over time. In the fourth year, the vaccine did not show any protection," said Ally Olotu of the Kenya Medical Research Institute (KEMRI) Wellcome Trust Research Programme in Kenya, who led the follow-up study.

Malaria, caused by a parasite carried in the saliva of mosquitoes, is endemic in more than 100 countries worldwide. According to WHO, malaria infected around 219 million people in 2010, killing some 660,000 of them. Control measures such as insecticide-treated bed nets, indoor spraying and anti-malaria drugs have helped cut malaria cases and deaths significantly in recent years, but drug resistance is growing, and experts say an effective vaccine could be a vital tool in eradicating the disease.

Phillip Bejon, another researcher at KEMRI, asserts there is still a clear benefit to the GSK vaccine. "Many of the children (in Africa) will experience multiple episodes of clinical malaria infection, but overall we found that 65 cases of malaria were averted over the four-year period for every 100 children vaccinated," he said. "We now need to look at whether offering a vaccine booster can sustain efficacy for longer."[10]

Meningitis Key Facts

- Meningococcal meningitis is a bacterial form of meningitis, a serious infection of the thin lining that surrounds the brain and spinal cord.
- The meningitis belt of sub-Saharan Africa, stretching from Senegal in the west to Ethiopia in the east, has the highest rates of the disease.
- Group A meningococcus accounts for an estimated 80 percent to 85 percent of all cases in the meningitis belt, with epidemics occurring at intervals of seven to 14 years.
- In the 2009 epidemic season, 14 African countries implementing enhanced surveillance reported 88,199 suspected cases, including 5,352 deaths, the largest number since a 1996 epidemic.
- Several vaccines are available to control the disease: a meningococcal A conjugate vaccine, C conjugate vaccines, tetravalent A, C, Y and W-135 conjugate vaccines and meningococcal polysaccharide vaccines.

Source: World Health Organization. Meningococcal Meningitis. Accessed at www.who.int/mediacentre/factsheets/fs141/en.

Addressing the Cold Chain Challenge

HIV, malaria and tuberculosis have long represented major global health challenges. Although promising research is underway to develop vaccines for these diseases, considerable hurdles remain for countries where transporting and storing live vaccines in a continuously cold environment (around 2 degrees Celsius to 8 degrees Celsius or below) is simply not possible. If a cold chain cannot be maintained for a live vaccine, there is a high risk it could become unsafe and lose effectiveness.

A recent published study by scientists at King's College London may offer promise in overcoming this hurdle. Results of the study demonstrated the ability to deliver a dried live vaccine to the skin without a traditional needle, and showed for the first time that this technique is powerful enough to enable specialized immune cells in the skin to kick-start the immunizing properties of the vaccine.[11] "We have shown that it is possible to maintain the effectiveness of a live vaccine by drying it in sugar and applying it to the skin using microneedles — a potentially painless alternative to hypodermic needles," said Dr. Linda Klavinskis from the Peter Gorer Department of Immunobiology at King's College London. "We have also uncovered the role of specific cells in the skin which act as a surveillance system, picking up the vaccine by this delivery system and kick-starting the body's immune processes."[11]

The report went on to state that the discovery opens up the possibility of delivering live vaccines in a global context, without the need for refrigeration. It could potentially reduce the cost of manufacturing and transportation, improve safety and avoid the need for hypodermic needle injection, reducing

the risk of transmitting bloodborne disease from contaminated needles and syringes. "This new technique represents a huge leap forward in overcoming the challenges of delivering a vaccination program for diseases such as HIV and malaria. But these findings may also have wider implications for other infectious disease vaccination programs, for example infant vaccinations, or even other inflammatory and autoimmune conditions such as diabetes," said Klavinskis.[11]

Today, as never before, governments have an unprecedented number of partners willing to help pay for vaccines and immunization.

A Commitment to the Future

In recent years, efforts to develop and deliver vaccines to the world's poorest countries have been on the upswing. In January 2010 at the World Economic Forum, the Bill & Melinda Gates Foundation launched the Decade of Vaccines by pledging $10 billion over 10 years to support worldwide vaccination efforts. The foundation also challenged other global partners to demonstrate their continuing commitment, with a singular goal in mind: to dramatically reduce child mortality by the end of the decade. The effort is an ambitious one, and stakeholders agree there is no easy formula for success. Achieving this goal will require a multipronged approach, including the strengthening of current health systems and immunization programs; new public-private partnerships for vaccine development; new long-term global financing mechanisms; innovative and sustainable delivery strategies; and improved advocacy and communication.

The good news is that today, as never before, governments have an unprecedented number of partners willing to help pay for vaccines and immunization. In a media release following the announcement of the Decade of Vaccines pledge, Dr. Christopher Elias, president and CEO of PATH, said: "The commitment announced by Bill and Melinda Gates will have a tremendous impact on children and families in the poorest areas of the world. PATH is committed, as is the Bill & Melinda Gates Foundation, to letting no child die from a preventable disease, and we are heartened by their continued efforts to move us one step closer toward a world where health is within reach for everyone." ❖

TRUDY MITSCHANG *is a staff writer for* BioSupply Trends Quarterly *magazine.*

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The Childhood Vaccine Series:

Balancing Health, Safety and Stakeholder Concerns

Following today's recommended childhood immunization schedule results in improved protection against at least 14 different diseases during the first years of life. As the series continues to evolve, parents and scientists alike are working to ensure the childhood series is safe, while looking for ways to make compliance even easier.

By Hillary Johnson, MHS

In January 1925, a relay of 20 mushers and 150 sled dogs raced 674 miles across the U.S. territory of Alaska. The trip along the Nenana-to-Nome Trail usually took 15 to 20 days, but on this occasion, the mushers were not afforded such luxury. Days earlier, Nome doctor Curtis Welch had frantically sent out telegrams requesting antitoxin to help curb an outbreak that had already killed two children and had the potential to nearly wipe out the remote town of 10,000 people. The culprit, diphtheria, was a highly infectious respiratory tract illness known at the time as "the strangling angel of children." Complications from toxin-producing bacteria C. diphtheriae included the growth of a leathery membrane in the pharynx, which could lead to airway obstruction, coma and death.

Government officials had located the closest supply of antitoxin — hundreds of miles away in the city of Anchorage. Because Nome had no viable roads, air service or winter-accessible ports, Alaska's Territorial Governor Scott Bone determined a dog sled relay was the best option for delivering the lifesaving drugs. Through radio and newspapers, the nation anxiously followed what became known as the Great Race of Mercy. On Feb. 2, 1925, the anchoring dog sled arrived with the antitoxin in a record-breaking five days and seven hours. Although at least five children died during the outbreak, countless additional lives were ultimately saved through antitoxin administration and quarantine. (The Great Race of Mercy would also serve as a cornerstone event for what would later become the Iditarod Trail Race we know today.)[1]

With only one case reported in 2012, and less than 60 national cases of diphtheria total since 1980,[2] a U.S. parent's most significant encounter with diphtheria today is likely through the fact sheet they receive at their child's immunization appointments. However, diphtheria was once a significant cause of illness and death in the U.S., with an average of 100,000 to 200,000 cases and 13,000 to 15,000 deaths per year reported in the 1920s.[3] Diphtheria antitoxin, first used in the U.S. in the 1890s, provided some treatment relief, but it was only helpful in neutralizing early circulating (unbound) toxins, and it was unable to assist when toxins had already fixed to the body's tissues.[4] (Thus, the incredible importance of timely administration.) Prevention through diphtheria vaccine would not be possible until its development in the 1920s and widespread use in the 1930s.[5]

Thanks to achievements in vaccine research, manufacturing and production technologies over the last century, diphtheria and many more infectious diseases are dwindling worldwide. The U.S. has significantly reduced childhood morbidity and mortality through implementation of a robust and thorough national childhood immunization program focusing on widespread routine vaccination for a standardized list of diseases. This list, as well as its recommended vaccines, continues to evolve. The program diligently works to balance children's overall health with vaccine safety and stakeholder concerns.

Getting on Schedule

The first vaccines to be routinely recommended for U.S. children included smallpox, diphtheria, tetanus and pertussis in the 1940s. In the 1950s, the nation rejoiced as the newly invented polio vaccine joined the list, and in the 1960s, measles, mumps and rubella vaccines were recommended as well. In the 1970s, thanks to successful eradication campaigns globally, the U.S. removed smallpox vaccine from the list of recommended vaccines. In the 1980s, vaccine recommendations for hepatitis B and Haemophilus influenzae type b (Hib) were also added to the list.[6]

Thanks to achievements in vaccine research, manufacturing and production technologies over the last century, diphtheria and many more infectious diseases are dwindling worldwide.

Throughout these decades, a recommended childhood schedule for vaccination was published periodically in response to new vaccine developments and changes in epidemiology. Since 1995, however, the Advisory Committee on Immunization Practices (ACIP), the American Academy of Pediatrics (AAP) and the American Academy of Family Physicians (AAFP) have initiated a review and official publication of an updated schedule annually.[7]

Addressing Parent Concerns

The U.S. childhood immunization schedule has changed significantly over the years, incorporating new vaccines as appropriate, and discontinuing outdated vaccines as technology and disease patterns evolve. The list of recommended vaccinations can appear overwhelming to the new parent, and on the surface (when compared to the list of recommendations from previous decades) has led many to wonder if today's child is receiving "too many vaccinations too soon."

In March, the *Journal of Pediatrics* published a study examining that exact question. The study not only scrutinized how many overall vaccines a child was given and the maximum number of vaccines in one day, but specifically looked at the number of antigens within each vaccine that a child would be exposed to during the first two years of life. (Antigens are the immune-stimulating substances within a vaccine that prompt a body's immune system to recognize and destroy pathogens

that contain them.) Dr. Frank DeStefano, the lead researcher and director of the Immunization Safety Office at the Centers for Disease Control and Prevention (CDC), points out that antigenic composition of some vaccines has changed over time, and a complete assessment of the antigenic content of vaccines should take into account all of the antibody-stimulating proteins and polysaccharides in each vaccine, not just the total number of shots.[8]

For example, previous whole-cell pertussis vaccines contained upwards of 3,000 bacterial proteins. But with advancements in protein purification and the specific identification of proteins responsible for evoking protective immune responses, scientists were able to develop the current purer, acellular vaccine of today, in which only four proteins are needed.[9] "Although the current vaccine schedule contains more vaccines than the schedule in the 1990s," said Dr. DeStefano, "the maximum number of antigens a child could be exposed to by 2 years of age in 2013 is 315, compared with several thousand in the late 1990s."[10]

The list of recommended vaccinations can appear overwhelming to the new parent, and on the surface has led many to wonder if today's child is receiving "too many vaccinations too soon."

In Dr. DeStefano's study, he compared 752 children without autism to 256 children with autism spectrum disorder (ASD) and examined their antigen exposure. The study concluded that for both groups, the antigen exposure was the same, however measured (in one day or over the first two years).[8] "There was no association between antigenic exposure and the development of autism," Dr. DeStefano told CNN.[11]

Addressing these parental concerns is crucial, as a recent survey found that more than 10 percent of parents are refusing or delaying vaccination, with most believing that a delay in vaccinations is safer than providing them in accordance with CDC's recommended vaccination schedule.[12]

Fewer Needles Through the Promotion of Combination Vaccines

Despite the fact that children today may actually be exposed to fewer antigenic proteins and polysaccharides in today's vaccines than 20 years ago, a needle stick is still a needle stick. Any parent who has accompanied their little one into the pediatrician's office for an immunization visit knows the torture associated with seeing them so uncomfortable. Luckily, combination vaccines are leading the way in reducing the number of needle sticks a child receives, and they have other indirect benefits as well.

Combination vaccines work by merging into a single product antigens that prevent different diseases. The first such combination was developed in 1948, when scientists merged diphtheria, tetanus and pertussis vaccines into one vaccine, called DTP.[6] Later, in 1971, scientists merged measles, mumps and rubella vaccines into one product, called MMR. There have since been new reformulations of these and other combination vaccines, all with the goal of improving the vaccine and reducing the number of injections a child receives. (In fact, today only various combination vaccines are available in the U.S. for these six diseases.)

However, reducing needle sticks is not the only rationale behind combination products. Combination vaccines may help in timely vaccination coverage by ensuring a child receives all the recommended vaccines at a particular visit (especially if there is a risk a parent may prefer a minimum number of injections, provoking them to spread out vaccinations across multiple visits). Combination vaccines also reduce the cost of stocking multiple individual products and can reduce multiple administration fees. Admittedly, the price of a new combination vaccine may not always be less than the summed cost of similar individual component vaccines, yet when taking into account both direct and indirect costs, combination products may still represent a better economic value.[13] With studies showing comparable efficacy across numerous single and combination vaccines,[14] they are a no-brainer for many parents. This appeal to parents and pediatricians alike means the occasional manufacturing delay can lead to national shortages (such as the one experienced by Sanofi Pasteur's Pentacel vaccine [a combination vaccine containing diphtheria, tetanus, pertussis, polio and Hib] in 2012 and into 2013).

Since 1999, the ACIP has generally recommended the use of licensed combination vaccines over separate injections of their equivalent component vaccines whenever possible[13] (an exception being the first dose of MMRV [measles, mumps, rubella and varicella], discussed below). Licensed combination vaccines can be used whenever a patient is due for one or more of the components within the combination, provided the

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Never administer HyperRHO S/D Full Doses intravenously. Inject only intramuscularly. Never administer to the neonate.

Rh_0(D) Immune Globulin (Human) should be given with caution to patients with a history of prior systemic allergic reactions following the administration of human immunoglobulin preparations. Such persons have increased potential for developing antibodies to IgA and could have anaphylactic reactions to subsequent administration of blood products that contain IgA.

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A large fetomaternal hemorrhage late in pregnancy or following delivery may cause a weak mixed field positive DU test result. If there is any doubt about the mother's Rh type, she should be given Rh_0(D) Immune Globulin (Human). A screening test to detect fetal red blood cells may be helpful in such cases.

If more than 15 mL of D-positive red blood cells are present in the mother's circulation, more than a single dose of HyperRHO S/D Full Dose is required. Failure to recognize this may result in the administration of an inadequate dose.

Although systemic reactions to human immunoglobulin preparations are rare, epinephrine should be available for treatment of acute anaphylactic symptoms.

Administration of live virus vaccines (eg, MMR) should be deferred for approximately 3 months after Rh_0(D) Immune Globulin (Human) administration.

HyperRHO S/D Full Doses should be given in pregnant women only if clearly needed because animal reproduction studies have not been conducted.

Reactions to Rh_0(D) Immune Globulin (Human) are infrequent in Rh_0(D)-negative individuals and consist primarily of slight soreness at the site of injection and slight temperature elevation. While sensitization to repeated injections of human immunoglobulin is extremely rare, it has occurred.

Elevated bilirubin levels have been reported in some individuals receiving multiple doses of Rh_0(D) Immune Globulin (Human) following mismatched transfusions. This is believed to be due to a relatively rapid rate of foreign red cell destruction.

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Reference: 1. HyperRHO® S/D Full Dose (Rh_0[D] immune globulin [human]) [package insert]. Research Triangle Park, NC: Grifols Inc; 2012.

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1. The mother must be Rh_O(D) negative and must not already be sensitized to the Rh_O(D) factor.
2. Her child must be Rh_O(D) positive, and should have a negative direct antiglobulin test (see PRECAUTIONS).

If Hyper**RHO** S/D Full Dose is administered antepartum, it is essential that the mother receive another dose of Hyper**RHO** S/D Full Dose after delivery of an Rh_O(D) positive infant.

If the father can be determined to be Rh_O(D) negative, Hyper**RHO** S/D Full Dose need not be given.

Hyper**RHO** S/D Full Dose should be administered within 72 hours to all nonimmunized Rh_O(D) negative women who have undergone spontaneous or induced abortion, following ruptured tubal pregnancy, amniocentesis or abdominal trauma unless the blood group of the fetus or the father is known to be Rh_O(D) negative. If the fetal blood group cannot be determined, one must assume that it is Rh_O(D) positive, and Hyper**RHO** S/D Full Dose should be administered to the mother.

Transfusion

Hyper**RHO** S/D Full Dose may be used to prevent isoimmunization in Rh_O(D) negative individuals who have been transfused with Rh_O(D) positive red blood cells or blood components containing red blood cells.

CONTRAINDICATIONS

None known.

WARNINGS

HyperRHO S/D Full Dose is made from human plasma. Products made from human plasma may contain infectious agents, such as viruses, and, theoretically, the Creutzfeldt-Jakob Disease (CJD) agent that can cause disease. The risk that such products will transmit an infectious agent has been reduced by screening plasma donors for prior exposure to certain viruses, by testing for the presence of certain current virus infections, and by inactivating and/or removing certain viruses. Despite these measures, such products can still potentially transmit disease. There is also the possibility that unknown infectious agents may be present in such products. Individuals who receive infusions of blood or plasma products may develop signs and/or symptoms of some viral infections, particularly hepatitis C. ALL infections thought by a physician possibly to have been transmitted by this product should be reported by the physician or other healthcare provider to Grifols Therapeutics Inc. [1-800-520-2807].

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Rh_O(D) Immune Globulin (Human) should be given with caution to patients with a history of prior systemic allergic reactions following the administration of human immunoglobulin preparations.

The attending physician who wishes to administer Rh_O(D) Immune Globulin (Human) to persons with isolated immunoglobulin A (IgA) deficiency must weigh the benefits of immunization against the potential risks of hypersensitivity reactions. Such persons have increased potential for developing antibodies to IgA and could have anaphylactic reactions to subsequent administration of blood products that contain IgA.

As with all preparations administered by the intramuscular route, bleeding complications may be encountered in patients with thrombocytopenia or other bleeding disorders.

PRECAUTIONS

General

A large fetomaternal hemorrhage late in pregnancy or following delivery may cause a weak mixed field positive D^u test result. If there is any doubt about the mother's Rh type, she should be given Rh_O(D) Immune Globulin (Human). A screening test to detect fetal red blood cells may be helpful in such cases.

If more than 15 mL of D-positive fetal red blood cells are present in the mother's circulation, more than a single dose of Hyper**RHO** S/D Full Dose is required. Failure to recognize this may result in the administration of an inadequate dose.

Although systemic reactions to human immunoglobulin preparations are rare, epinephrine should be available for treatment of acute anaphylactic reactions.

Drug Interactions

Other antibodies in the Rh_O(D) Immune Globulin (Human) preparation may interfere with the response to live vaccines such as measles, mumps, polio or rubella. Therefore, immunization with live vaccines should not be given within 3 months after Rh_O(D) Immune Globulin (Human) administration.

Drug/Laboratory Interactions

Babies born of women given Rh_O(D) Immune Globulin (Human) antepartum may have a weakly positive direct antiglobulin test at birth.

Passively acquired anti-Rh_O(D) may be detected in maternal serum if antibody screening tests are performed subsequent to antepartum or postpartum administration of Rh_O(D) Immune Globulin (Human).

Pregnancy Category C

Animal reproduction studies have not been conducted with Hyper**RHO** S/D Full Dose. It is also not known whether Hyper**RHO** S/D Full Dose can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Hyper**RHO** S/D Full Dose should be given to a pregnant woman only if clearly needed.

Pediatric Use

Safety and effectiveness in the pediatric population have not been established.

ADVERSE REACTIONS

Reactions to Rh_O(D) Immune Globulin (Human) are infrequent in Rh_O(D) negative individuals and consist primarily of slight soreness at the site of injection and slight temperature elevation. While sensitization to repeated injections of human immune globulin is extremely rare, it has occurred. Elevated bilirubin levels have been reported in some individuals receiving multiple doses of Rh_O(D) Immune Globulin (Human) following mismatched transfusions. This is believed to be due to a relatively rapid rate of foreign red cell destruction.

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other combination components are not contraindicated for that dose in the series.[15] For example, some combination vaccines such as Pediarix (DTaP-IPV-HepB) mean a child may receive an extra dose of hepatitis B vaccine in their childhood series, but CDC has not found this to be harmful.[16]

Pediarix and Pentacel, addressing a maximum of five diseases each, remain the most comprehensive combination vaccines approved within the U.S. at this time, although some areas of the world are examining hexavalent options as well. (In developing countries, where disease rates are often greater, cold storage may be limited and children have fewer opportunities for vaccination, combination vaccines are more than a convenience, they are a necessity.)

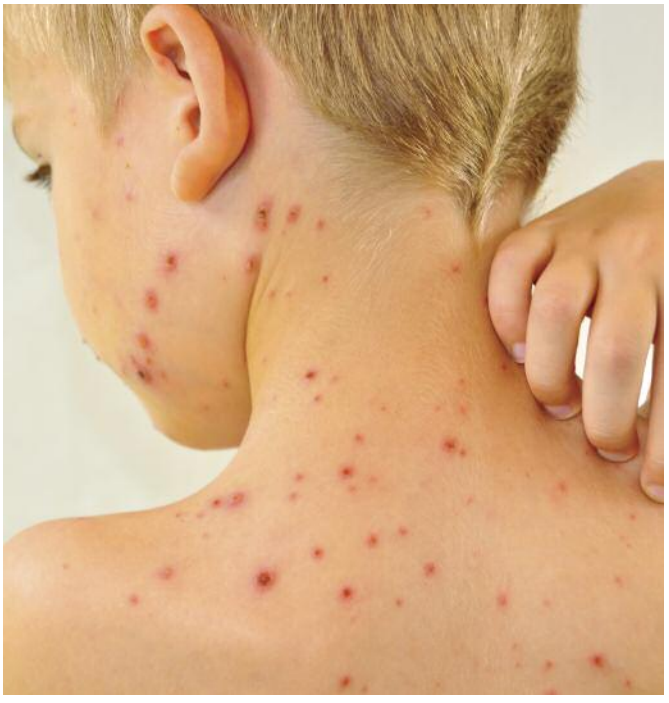
MMRV Returns as an Option

It was not too long ago that varicella (more commonly known as chicken pox) was a standard childhood disease. So recently, in fact, that some parents today first learn there is a chicken pox vaccine at their child's 12-month immunization appointment. Occasionally, a parent may even wonder if the vaccine is necessary. After all, they survived childhood chicken pox, didn't they? (CDC generally considers most people born in the U.S. before 1980 likely to have had varicella at some point.)[17]

Prior to the varicella vaccine, approximately four million cases of varicella occurred annually. What many parents don't realize, however, is that before the vaccine, 150,000 to 200,000 of those varicella cases developed complications, 10,000 required hospitalization and 100 people would die each year.[18] (Not to mention that varicella infection leaves you vulnerable to shingles, an incredibly painful skin rash, later in life.) The varicella vaccine first became licensed in 1995 as a single antigen vaccine, and then joined with the MMR vaccine to form the combination MMRV vaccine in 2005.

It was not too long ago that varicella (more commonly known as chicken pox) was a standard childhood disease.

Supplies of combination MMRV became temporarily unavailable due to manufacturing constraints (unrelated to efficacy or safety) in 2007 and did not widely return to the market until 2012. In the interim, the ACIP examined post-licensure data and concluded that children aged 12 months to 23



months receiving the combination vaccine had an increased risk for febrile seizures (this was not the case for older children). As a result, the ACIP now recommends use of separate MMR and varicella vaccines for children aged 12 months to 47 months, and use of the combination vaccine MMRV for children aged 4 years to 6 years.[19] This recommendation exemplifies a responsive immunization system that follows the data and responds accordingly as needed.

Pertussis on the Rise Across the U.S.

Reports of soaring whooping cough incidence dominated the news in 2012. With more than 41,000 cases of pertussis reported nationally,[20] the U.S. has not seen such record-breaking numbers since the 1950s.[21] Pertussis, commonly known as whooping cough, is an infection in which the bacteria attach to the cilia of the respiratory system. The bacteria produce toxins that paralyze the cilia, preventing the respiratory tract from clearing away pulmonary secretions. Classic symptoms for pertussis include a pronounced "whooping cough" as patients experience difficulty breathing and attempt to expel the thick mucus from their throat and lungs.[22] Pertussis can affect people of any age, but can be particularly severe in infants and young children.

Recent pertussis outbreaks highlight the challenges associated with an immunization program that must balance both risk of disease and concerns about safety. CDC believes waning immunity and recent changes in pertussis vaccine formulation

are likely contributing to the outbreaks. New data are showing that immunity in children vaccinated with the current acellular pertussis vaccine formulation may wane more rapidly than in children vaccinated with the previous whole-cell pertussis vaccine formulation phased out in the 1990s.[23]

Following the recommended childhood vaccination schedule is still one of the most effective ways to protect your child against disease.

At the time the ACIP recommended the switch, whole-cell pertussis vaccines were associated with higher rates of minor and transient adverse events (or side effects) such as pain, swelling and fever, as well as some rare, but serious neurologic side effects.[9] While not all studies were consistent in linking the vaccine to the more severe neurological problems, the U.S. elected to switch to an acellular pertussis vaccine with a better safety profile.[24] Now, as the first generation of children solely vaccinated with acellular pertussis vaccine completes their childhood series, scientists are better able to examine potential gaps in immunity coverage.

It is important to note that waning immunity is not only just associated with pertussis vaccination; studies show that even if individuals are directly infected with Bordetella pertussis, they do not develop lifelong immunity and would be susceptible to pertussis again later in life.[22] But with the acellular pertussis vaccine, we may have sacrificed stronger immunity for a safer vaccine.[9] Researchers are currently examining the impact of the acellular vaccine series, and parents should not be surprised if an enhanced booster dose schedule for adolescents and adults appears in the next few years to combat this waning immunity.

Strategies to Protect Our Infants

Although symptoms for pertussis may be milder in adults than in infants and young children, adults are still the most common sources of infection in children; thus, adults and children should both be vaccinated. And when it comes to the smallest of infants, this is particularly important. Of the 18 pertussis-related deaths in 2012, most occurred in infants too young to be vaccinated.[20] Previous strategies to protect this vulnerable age group have centered around "cocooning," or the idea that you create a circle of protection by vaccinating the primary caregivers around an infant. But in light of the national outbreaks and new safety and immunogenicity data, the ACIP published additional guidelines in February recommending that pregnant women receive a Tdap (tetanus, diphtheria and acellular pertussis combination vaccine) with *each* pregnancy.[25]

This recommendation is particularly significant, and the ACIP examined many factors when considering this step (previous recommendations have indicated only one lifetime Tdap for all individuals). The idea is to protect infants when they are most vulnerable (in the first few months of life before vaccination). This is achieved indirectly by ensuring the mother is protected, and directly by maximizing transplacental maternal antibodies transferred to the infant. Data now indicate that by vaccinating a mother during pregnancy, we can prevent more hospitalizations and deaths than by vaccinating after pregnancy. They have even found the best stage of pregnancy (between 27 weeks and 36 weeks gestation) to ensure maximum antibody transfer. Because a mother's antibodies will gradually wane, this new recommendation for each pregnancy ensures that subsequent infants also achieve high levels of protection.

The Safest Bet Is Timely Vaccination

Following the recommended childhood vaccination schedule is still one of the most effective ways to protect children against

disease. Admittedly, no vaccine is perfect. Yet even in the occasional case of "breakthrough disease" (the scenario in which a pathogen still manages to break through a vaccinated person's immune system defenses), the vaccinated patient often experiences less severe disease symptoms than their unvaccinated counterparts.

The Institute of Medicine found no evidence that the current childhood immunization schedule is unsafe.

In January, the Institute of Medicine (IOM) published a report titled *The Childhood Immunization Schedule and Safety, Stakeholder Concerns, Scientific Evidence, and Future Studies*. Through analysis of available research, current monitoring systems and stakeholder input, the IOM found no evidence that the current childhood immunization schedule is unsafe. In fact, "rather than exposing children to harm, following the complete immunization schedule is strongly associated with reducing vaccine-preventable diseases."[26] As the number of diseases preventable through vaccination continues to expand, innovations such as combination vaccines are making compliance with the childhood vaccine series even easier. ❖

HILLARY JOHNSON, *MHS, has a graduate degree in health sciences from the Johns Hopkins Bloomberg School of Public Health and has worked in STD and HIV prevention both domestically and in Africa. She is currently an epidemiologist with the Massachusetts Department of Public Health's Immunization Program.*

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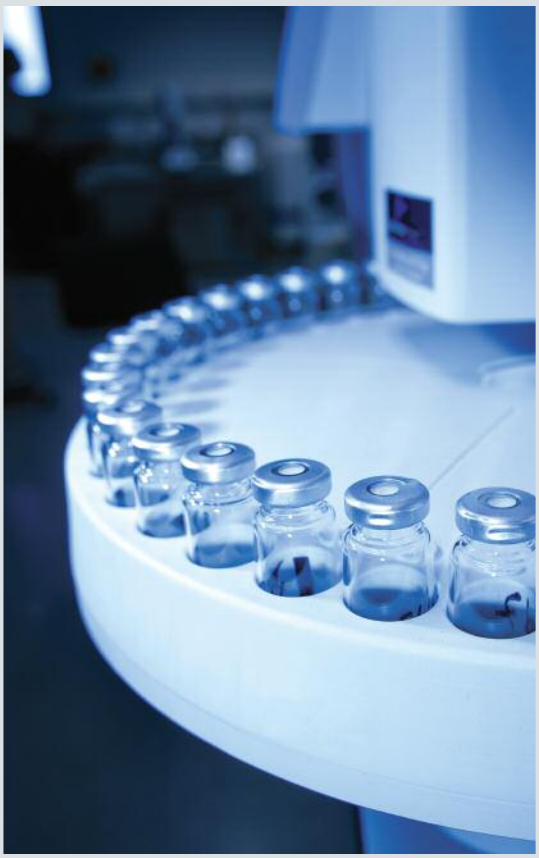
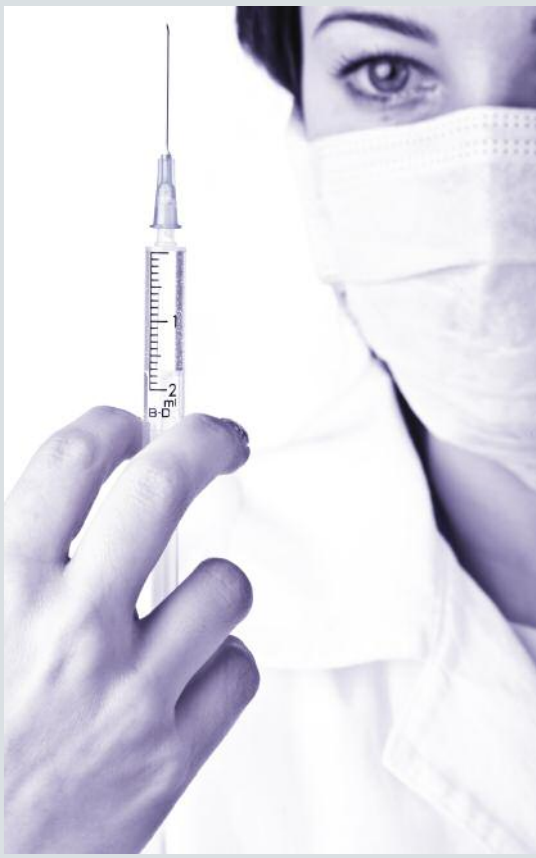



Choosing Influenza Vaccines

With the advent of new products with new manufacturing processes and added protection, the number of available influenza vaccine presentations has risen to 13. Which ones to choose for your patients can be simplified with a look at the pros and cons of the new compared with the traditional.

By Ronale Tucker Rhodes, MS

Choosing which influenza vaccines to administer to your patients these days is more complicated than it used to be. In just the past year, five new vaccines have been approved by the U.S. Food and Drug Administration (FDA), and there are reports of even more coming to market as we begin the 2013-2014 flu season. Instead of replacing the current ones, almost all of these vaccines are just being added to the list, making purchasing decisions more complex.

Manufacturers are on a quest to make vaccines that will provide more protection, but in doing so, both patients and healthcare providers are confused about which ones best suit their needs. For instance, what are the advantages of an egg-based or cell-culture vaccine? Do four strains in the quadrivalent inactivated vaccines (IIV4s) really provide that much more protection than the three strains included in the trivalent inactivated vaccines (IIV3s)? What about whether the vaccines and/or vaccine packaging contain additives? And, let's not forget that the new vaccines cost more. Are the added protections in the new vaccines really worth that additional cost?

What Vaccines Have Been Available

Prior to this year, nine influenza vaccines have been available, including FluLaval and Fluarix (GlaxoSmithKline), Afluria (Merck/CSL), Fluvirin and Agriflu (Novartis Vaccines), Fluzone, Fluzone Intradermal and Fluzone High-Dose (Sanofi Pasteur) and FluMist (MedImmune). All of these vaccines are IIV3, with the exception of FluMist, a live-attenuated influenza vaccine (LAIV4). It is the only one that has been completely replaced by a new quadrivalent formulation for the 2013-2014 flu season. All of these vaccines are produced annually according to the formulation identified by the FDA and the World Health Organization (WHO) that contains the isolated influenza virus strains thought most likely to be circulating and causing illness among people during the upcoming flu season. The differences among these vaccines range from how they are manufactured, how they are packaged, the age groups for which they are indicated, the number of doses required, the route of administration, and whether the vaccines contain preservatives or other additives. See Table 1 for specifications for each of these vaccines.

The Challenges of Influenza Vaccine Production

For years, the most troublesome issues surrounding influenza vaccines include the manufacturing process and the identified vaccine strains' potential protective benefit. To address these issues, many manufacturers have been researching ways of producing flu vaccines using new methods, and the FDA and WHO have continued to struggle to predict the correct virus strains to include in the vaccines, achieving a match with the circulating strains just five out of 10 years during the decade beginning with the 2001-2002 flu season.

Furthermore, there are several problems with the 60-year-old production method that requires the strains of the influenza vaccines be grown in fertilized chicken eggs, which can take up to six months. In the event of a pandemic, such as the potential one that occurred in 2003 with the re-emergence of the H5N1 bird flu and the actual pandemic that occurred in 2009 with the H1N1 swine flu, the egg-based production method cannot supply enough influenza vaccine to adequately protect the public. It became especially worrisome that the U.S. would have a sufficient supply when in 2004, the U.S. flu vaccine supplies were devastated by contamination at a plant in Liverpool, England, underscoring the need for the U.S. to have its own manufacturing capabilities, says Robin Robinson, director of the U.S. Biomedical Advanced Research and Development Authority (BARDA), a part of the U.S. Department of Health and Human Services (HHS). Should a pandemic occur, the fear was that other countries might be tempted to commandeer all flu vaccines made within their own borders, leaving the U.S. without enough vaccines. "We needed to develop new vaccines using modern technologies that would make not only more vaccine available sooner, but also make it more effective," explains Robinson.[1] Added to these issues are the inherent problems with the manufacturing process, plus egg-related complications. At every step of the process, there is risk of contamination, and in some years, certain flu strains have refused to grow readily in eggs. And, people with severe allergic reaction (anaphylaxis) to eggs can't get a flu shot. Notably, eggs happen to be one of the most common food allergens; in the U.S., more than 600,000 people have egg allergies.[2]

Manufacturers are on a quest to make vaccines that will provide more protection, but in doing so, both patients and healthcare providers are confused about which ones are best.

To combat these issues, in 2006, the HHS provided more than $1 billion in contracts to six manufacturers to develop cell-culture-based flu vaccine technology in the U.S. Then, in 2009, when it was difficult to grow vaccine to respond to the H1N1 swine flu pandemic, the HHS granted Novartis nearly $500 million to build the first U.S. facility capable of producing cell-based vaccine for seasonal and pandemic flu in the U.S. (Novartis footed the additional $1 billion price tag.) Also in 2009, the HHS awarded a five-year, $147 million investment to Protein Sciences, which was investigating a recombinant

vaccine that is grown inside insect cells.[1] With cell-culture-based and recombinant production techniques, influenza vaccines can be produced easier and faster — within weeks — for seasonal or pandemic influenza. And, because the vaccine is grown in sterile, controlled environments, the risk of potential impurities is significantly reduced.[3]

The other most troublesome issue concerns the vaccines' effectiveness. In some years, influenza vaccines protect only 50 percent to 70 percent of people who receive them. According to the Centers for Disease Control and Prevention's mid-season vaccine effectiveness (VE) estimates published on Feb. 21, 2013, the 2012-2013 VE for protecting against having to go to the doctor because of flu illness was 56 percent for all age groups. When broken down by age groups, the VE against flu A and B viruses ranged from 27 percent in people 65 and older, to 64 percent in children aged 6 months to 17 years.

There are several problems with the 60-year-old egg-based production method.

Predicting which strains of the virus to include in the influenza vaccines is difficult at best, not only because the virus mutates from year to year but the number of influenza subtypes A and type B that can be selected for inclusion is limited. IIV3s help protect against the two A virus strains most common in humans and the B strain expected to be predominant in a given year. But, since the year 2000, two influenza B lineages (Victoria and Yamagata) have co-circulated to varying degrees each season. Various degrees of mismatch have occurred between the B lineage included in IIV3s and the B lineage that actually circulated, causing an increased risk of influenza-related morbidity across all age groups. "Trivalent influenza vaccines have helped protect millions of people against flu, but in six of the last 11 flu seasons, the predominant circulating influenza B strain was not the strain that public health authorities selected," says Dr. Leonard Friedland, vice president and head of GlaxoSmithKline North America Vaccines Clinical Development and Medical Affairs.[4]

Adding a second B strain to the seasonal vaccine had been discussed for years. The problem with doing this, however, was the lack of adequate manufacturing capacity to produce IIV4s that still allowed manufacturers to make enough doses to meet projected demand. "From the 2001-2002 through the 2005-2006 flu seasons, fewer than 100 million doses of seasonal flu vaccine were produced and distributed in the U.S.," says Keith Berman, founder of Health Research Associates. "But since 2005-2006, flu vaccine manufacturing capacity has dramatically expanded — a direct byproduct of avian and swine flu outbreaks that prompted the U.S. government to help industry improve preparedness for a potential global flu pandemic." Over the last two flu seasons, manufactured doses of influenza vaccines have outpaced market demand, and "for the first time, the vaccines industry finds itself with the capacity to inoculate many millions more eggs to produce large stocks of IIV4 without jeopardizing its ability to make enough doses to satisfy market demand," adds Berman.[5]

The benefit of adding a second B lineage to influenza vaccines is "essentially a matter of chance," says Berman. However, as an example of how it could make a difference, in the 2007-2008 flu season, B viruses accounted for 29 percent of all flu infections. Unfortunately, WHO and FDA virologists picked the wrong B lineage: the Victoria lineage vs. the Yamagata lineage. Had they added the Yamagata lineage that was identified in 98 percent of the flu cases with a B virus infection, the CDC estimates that nearly one million flu illnesses and 484 deaths could have been averted. The next year also serves as an example. In the 2008-2009 flu season, officials picked the wrong lineage again. Had both B lineages been included in the influenza vaccines, the CDC estimates that 169 lives could have been saved.[5]

Widespread avoidance of the influenza vaccination remains yet another issue. On average, the number of people who get a flu shot each year hovers in the 40 percent range.[6] The reasons vary, but mainly it's due to misconceptions that the flu shot causes the flu, that the flu shot causes unwanted side effects, that it doesn't work and, for many, it's a fear of needles. While the first three reasons are known to be myths, a fear of needles is all too real. Which is why the HHS is now focusing on a universal vaccine that could be given every five to 10 years, much like a tetanus shot. The universal vaccine also would protect against most types of flu, including seasonal varieties and the highly mutated kinds that cause pandemics.[1]

A final issue surrounding influenza vaccines are additives that are introduced into the vaccines through the manufacturing process. These additives include thimerosal, antibiotics and latex — all of which may cause problems in individuals with allergies to them. Thimerosal is a mercury-containing organic compound that has been widely used since the 1930s as a preservative in vaccines to help prevent potentially life-threatening contamination with harmful microbes. Because public concerns about the use of thimerosal in vaccines and other products have been raised, the FDA is working with manufacturers to reduce or eliminate thimerosal from vaccines. Most influenza vaccines have very low, trace or no thimerosal levels.[7]

Certain antibiotics, including neomycin, polymyxin B,

streptomycin and gentamicin, also may be used in making inactivated influenza virus vaccines to help prevent bacterial contamination during manufacturing. Antibiotics used in vaccine production are present in some vaccines, but they are reduced to very small or undetectable amounts during subsequent purification steps. And, the very small amounts of antibiotics contained in vaccines have not been clearly associated with severe allergic reactions.[8]

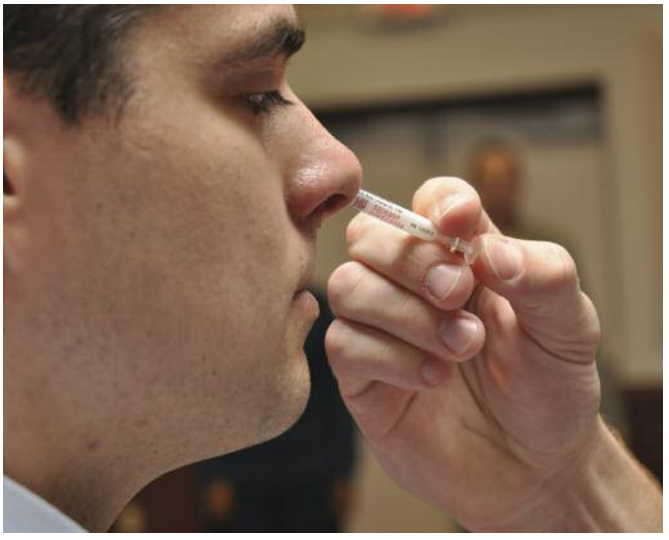
Some influenza vaccine packaging, including syringes, plungers and vial stoppers, may contain latex, to which some people are allergic. According to the 2011 general recommendations on immunization by the Advisory Committee on Immunization Practices: "If a person reports a severe (anaphylactic) allergy to latex, vaccines supplied in vials or syringes that contain natural rubber should not be administered unless the benefit of vaccination outweighs the risk for a potential allergic reaction. In these cases, providers should be prepared to treat patients who are having an allergic reaction. For latex allergies other than anaphylactic allergies (e.g., a history of contact allergy to latex gloves), vaccines supplied in vials or syringes that contain dry natural rubber or rubber latex may be administered."[9]

What's New in Influenza Vaccines

As a result of the HHS response to the two most troublesome issues surrounding influenza vaccines, five new vaccines have entered the market for the 2013-2014 flu season, more are planned for this season, and even more are on the horizon.

In February 2012, the FDA approved the first LAIV4, FluMist Quadrivalent, manufactured by MedImmune. The vaccine is approved for individuals aged 2 years through 49 years, and it contains four strains of the influenza virus: two A strains and two B strains. Like the LAIV FluMist (which has been removed from the market for the new flu season), the LAIV4 contains weakened forms of the virus strains and is administered as a nasal spray. The safety and effectiveness of FluMist Quadrivalent is supported by studies conducted previously for the LAIV FluMist, as well as three new clinical studies conducted in the U.S. involving 4,000 children and adults, that demonstrated that the immune responses were similar between FluMist and FluMist Quadrivalent. Reported adverse reactions also were similar, including runny or stuffy nose in both children and adults and headache and sore throat in adults.[10]

Then, in December 2012, a second IIV4 was approved by the FDA. Fluarix Quadrivalent, manufactured by GlaxoSmithKline, is the first intramuscular vaccine to protect against four influenza strains, and it is approved for individuals aged 3 years and older. In clinical trials, the most common adverse reactions in adults were pain at the injection site, muscle aches, headache and fatigue. In children between 3 years and less than



6 years, the most common adverse reactions were drowsiness, irritability and loss of appetite. And, in children 6 years to less than 18 years, the most common systemic adverse reactions were fatigue, muscle aches, headache, arthralgia and gastrointestinal symptoms.[11]

Last month, the FDA approved Sanofi Pasteur's Fluzone Quadrivalent for use in children 6 months and older, adolescents and adults. It is the first IIV4 option for children as young as 6 months. The vaccine comes in preservative-free, prefilled syringes and single-dose vials for intramuscular administration. In clinical trials, the most common local and systemic adverse reactions were pain, erythema and swelling at the vaccination site; myalgia; malaise; headache; and fever. In some young children, the vaccine also caused irritability, crying and drowsiness.

In January, the FDA approved the first two new influenza vaccines using non-egg-based technologies, making flu vaccines available to the hundreds of thousands of individuals allergic to eggs, as well as providing an easier methodology of producing influenza vaccines at a faster rate both for seasonal influenza and in the event of a flu pandemic.

Novartis' Flucelvax is manufactured using MDCK cell-culture technology, and it is approved for individuals 18 years and older. The ccIIV3 vaccine is produced through four steps. First, the seed stocks for three influenza viruses are produced. Then, the virus is propagated in cells that are expanded and inoculated with the influenza viruses and allowed to replicate over several days. The virus is then isolated, inactivated and purified by removing the influenza-antigen components. Finally, the virus is formulated by combining the antigen components into one vaccine. In seven controlled studies of Flucelvax, the rates of serious adverse events were collected for 21 days in two studies

Table 1. Influenza Vaccine Comparison Chart

Manufacturer	Vaccine	Presentation	Route of Administration	Manufacturing Technology	Age Group
GlaxoSmithKline	FluLaval	5 mL 10-dose vial	Injectable	Egg-based	18 years and older
GlaxoSmithKline	Fluarix	0.5 mL prefilled syringe	Injectable	Egg-based	3 years and older
Merck/CSL	Afluria	0.5mL prefilled syringe and 5 mL 10-dose vial	Injectable	Egg-based	5 years and older (ACIP recommends 9 years and older)
Novartis Vaccines	Fluvirin	0.5 mL prefilled syringe and 5 mL 10-dose vial	Injectable	Egg-based	4 years and older
Novartis Vaccines	Agriflu	0.5 mL prefilled syringe	Injectable	Egg-based	18 years and older
Sanofi Pasteur	Fluzone	0.25 mL and 0.5 mL prefilled syringes and 0.5 mL single-dose vial	Injectable	Egg-based	6 months and older
Sanofi Pasteur	Fluzone Interdermal	0.1 mL prefilled micro-injection system	Injectable	Egg-based	18-64 years old
Sanofi Pasteur	Fluzone High-Dose	0.5 mL prefilled syringe	Injectable	Egg-based	65 years and older
Sanofi Pasteur	Fluzone Quadrivalent	0.25 mL and 0.5 mL prefilled syringes and 0.5 mL single-dose vial	Injectable	Egg-based	6 months and older
Sanofi Pasteur	Fluzone	5 mL 10-dose vial	Injectable	Egg-based	6 months and older
GlaxoSmithKline	Fluarix Quadrivalent	0.5 mL prefilled syringes	Injectable	Egg-based	3 years and older
MedImmune	FluMist Quadrivalent	0.2 mL prefilled single-use sprayer	Intranasal spray	Egg-based	2-49 years
Novartis Vaccines	Flucelvax	0.5 mL prefilled syringe	Injectable	Cell-culture	18 years and older
Protein Sciences	Flublok	0.5 mL single-dose vial	Injectable	Recombinant	18-49 years

and for six to nine months in five studies. Subjects were divided into three groups, one that received Flucelvax, the other that received a U.S.-licensed comparator vaccine and a third that received a placebo. In each of these groups, the rate of all serious adverse events among adults 18 through 64 years of age was 1 percent. The rate of serious adverse events among adults 65 years of age and older was 4 percent in both groups that received Flucelvax and those that received a U.S.-licensed comparator vaccine. Flucelvax contains no additives or preservatives.[12]

Protein Science's Flublok is manufactured using an insect virus (baculovirus) expression system and recombinant DNA technology. The recombinant production process involves programming insect cells grown in steel tanks to produce large amounts of a particular protein, known as hemagglu-

No. of Doses	Thimerosal	Latex	Antibiotics
1	Yes	No	No
1 or 2	No	Yes	Yes
1	No (syringe); Yes (vial)	No (syringe); No (vial)	Yes
1 or 2	Yes (syringe) Yes (vial)	Yes (syringe); No (vial)	Yes
1	No (syringe)	Yes (syringe)	Yes
1 or 2	No (syringe) No (vial)	No (syringe); No (vial)	No
1	No	No	No
1	No	No (syringe); No (vial)	No
1 or 2	No	No	No
1 or 2	Yes	No	No
1 or 2	No	Yes	Yes
1 or 2	No	No	Yes
1	No	Yes	No
1	No	No	No

tinin. The majority of antibodies that prevent influenza virus infection are directed against hemagglutinin. The RIV3 is designed to protect against the H1N1, H3N2, both A strains and one B strain of the influenza virus, and it is approved for people between the ages of 18 and 49. In a study of 2,300 people, the vaccine was found to be 44.6 percent effective against all strains of the flu. Flublok's safety evaluation was conducted in a study of about 2,500 people who were vaccinated with Flublok. The most common side effects included muscle aches, headache, fatigue and pain in the area the shot was administered. This vaccine also contains no additives or preservatives.[13]

While both the cell-culture-based and recombinant technologies are new to flu vaccine production, they are used to make vaccines that have been approved by the FDA to prevent other infectious diseases. See Table 1 for specifications for each of these vaccines, as well as the quadrivalent vaccines.

These five new vaccines are not the only result of HHS efforts. Novartis Vaccines also is developing egg-based and cell-culture-based quadrivalent products.[5] And, two other genetically engineered flu vaccines also are under development. One by Novavax uses bits of genetic material grown in caterpillar cells called "virus-like particles" that mimic a flu virus. The other is being developed by VaxInnate Corp. In 2011, the HHS awarded VaxInnate a five-year, $196 million grant to make a vaccine that combines a bacterial protein called flagellin, a potent stimulator of the immune system, with a very small portion of hemagglutinin. VaxInnate's flu vaccine is in mid-stage clinical trials. Both of these vaccines are expected to be available in the latter part of the decade.[1]

It's not known how soon a universal influenza vaccine could be made available. However, while several teams have tried and failed to produce such a vaccine, scientists at the National Institute of Allergy and Infectious Disease (NIAID), a part of the National Institutes of Health (NIH), and others are making good progress, according to Dr. Anthony Fauci, director of the NIAID. Dr. Fauci and Dr. Gary Nabel, former head of NIH's Vaccine Research Center who recently joined Sanofi Pasteur as chief science officer, showed that a portion of the flu virus that is usually hidden from the immune system may be the key. Most vaccines target proteins on the bulb portion of the hemagglutinin part of the flu virus, which mutates from year to year. But, the stem portion, which contains proteins that are structurally hidden from the immune system, don't change much from virus to virus. A genetically engineered vaccine could overcome that by presenting only the stem proteins to the immune system. Phase I studies have begun in people to test for safety and whether the vaccine can create an appropriate immune response. Novartis Vaccines and BARDA will be handling the manufacturing of the vaccine.[1]

Weighing the Cost vs. the Benefit

The new cell-culture-based vaccines and quadrivalents do come with an additional cost, and many question whether the added expense is worth choosing these vaccines for patients over the less-expensive ones that are on the market. The answer to that question lies in the safety and effectiveness of the new vaccines. Of course, as recent entries on the market,

no data from annual influenza infection rates are available yet to prove their safety and efficacy. And, it is possible that not everyone needs to be inoculated with the new vaccines. But those who have allergies to eggs now can receive a flu shot, potentially adding 600,000 to the ranks of people protected from the influenza virus. And, considering the challenge of choosing the correct B lineage to include in the trivalent seasonal influenza vaccine, the chances of individuals gaining more protection from including both B lineages in the quadrivalent cannot be argued. This extra protective edge could be especially important for high-risk populations most susceptible to succumbing from influenza.

In January, the FDA approved the first two new influenza vaccines using non-egg-based technologies, making flu vaccines available to the hundreds of thousands of individuals allergic to eggs.

Added protection also can positively influence the high cost to society caused by influenza. A recent study examined the additional influenza cases that a quadrivalent may have averted during the past decade (influenza seasons 1999 through 2009) to determine the potential cost-savings a quadrivalent may provide. The researchers divided influenza cases into three categories: those who were infected without requiring hospitalization, those who required hospitalization and survived, and those who were hospitalized and died. They also divided the quadrivalent into different price premiums of $5, $15, $30 and $120 more than a trivalent. These translated to a median of $3.1 billion societal cost savings and a median of $292 million third-party payer cost savings during the decade if the quadrivalent were used instead of the trivalent and priced equally to the trivalent. Over the decade, 2,684,145 total cases were averted with a quadrivalent vaccine. From the third-party payer perspective, a $120 premium would have saved $11 per case and a $0 premium would have saved $109 per case across the decade. Cost savings per case across the decade from the societal perspective ranged from $1,163 ($0 premium) to $1,041 ($120 premium). The cost per case tended to increase as premiums decreased, resulting in less cost savings. The researchers concluded that "adding an additional B strain to the seasonal influenza vaccine could reap substantial cost savings for society and third-party payers, even if the quadrivalent enjoyed a significant price premium over the trivalent."[14]

Currently, less than half of the U.S. population gets a flu shot each year, despite the grim statistics that influenza affects from 5 percent to 20 percent of the population, claiming a range of 3,000 to 49,000 lives and requiring hospitalization of more than 200,000 suffering from influenza-associated illnesses. Without at least 90 percent of the population becoming vaccinated, herd immunity, which provides sufficient protection to stop the spread of disease, cannot be achieved. If the goal is to increase the numbers of individuals vaccinated against the often-deadly influenza virus, perhaps the greatest hope to boost vaccination rates lies with the improvements offered by the new vaccines. ❖

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

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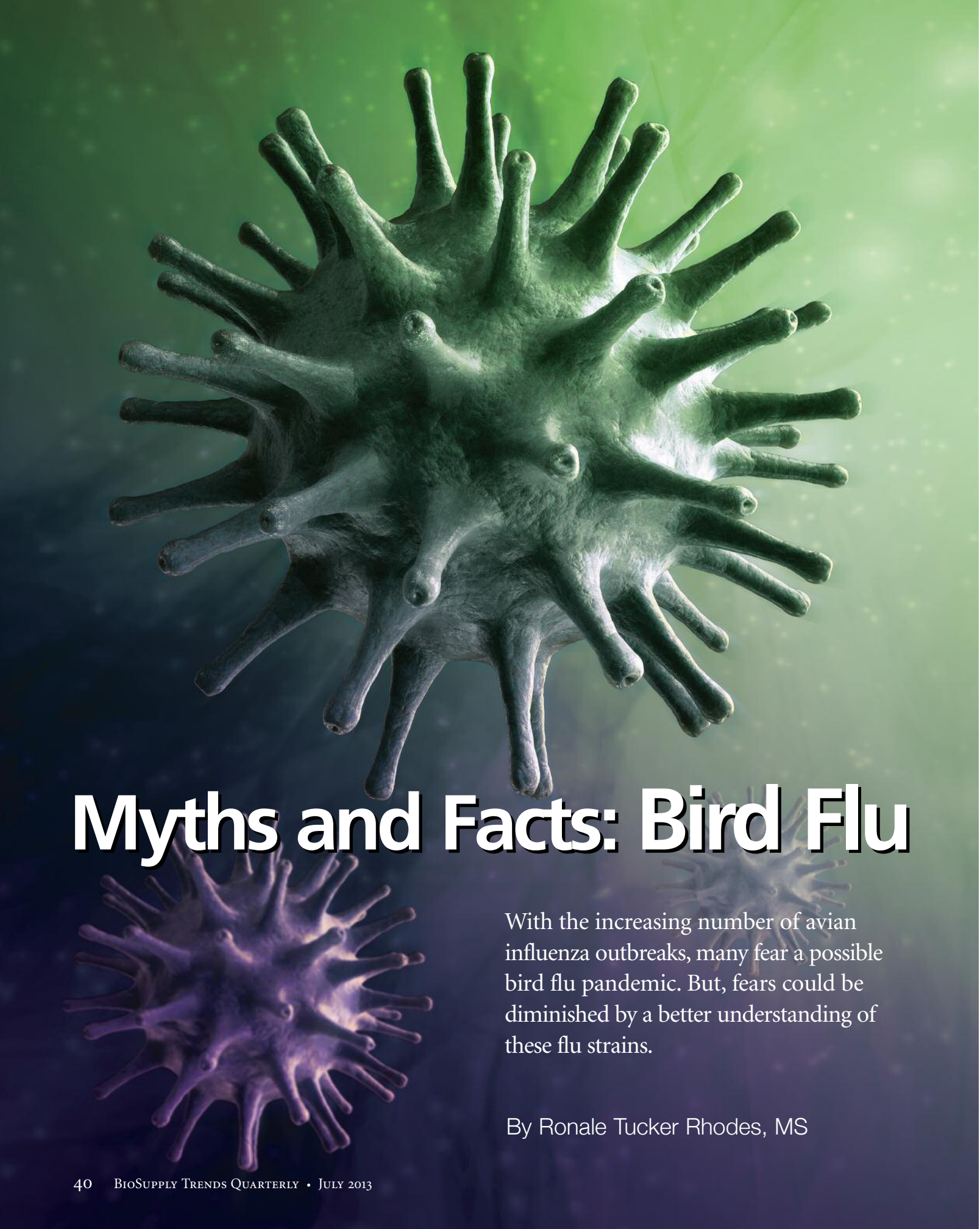

Myths and Facts: Bird Flu

With the increasing number of avian influenza outbreaks, many fear a possible bird flu pandemic. But, fears could be diminished by a better understanding of these flu strains.

By Ronale Tucker Rhodes, MS

The bird flu has struck again, this time in China, with the number of infections and deaths increasing weekly. What's worrisome is that this strain of the bird flu is one that has not previously been detected in humans.[1] Add this strain to the recurring and ever mutating ones that have been reported since 1997 (the year in which a strain was unusually severe), and it's no wonder many fear that this flu virus, also known as avian influenza, could mutate into a deadly pandemic similar to the Spanish flu that occurred in 1918. But, while health officials throughout the world are keeping a close eye on outbreaks and making preparations in the event of a pandemic, most believe that the likelihood of a disastrous pandemic is very small. Indeed, most people's fear could be quelled by clearing up the many misconceptions about the avian influenza virus.

Separating Myth from Fact

Myth: The avian influenza viruses are the same as the human influenza viruses.

Fact: While the avian influenza viruses and most human influenza viruses are type A viruses (human viruses are also types B and C), there are substantial genetic differences between the subtypes that typically infect both people and birds. Influenza viruses are divided into subtypes based on the two proteins, hemagglutinin (H) and neuraminidase (N), that they have on their surfaces. There are 16 recognized H types and nine N types, and these are known to occur in a number of different combinations. Avian influenza virus subtypes are restricted to H5, H7 and H9 viruses, all of which can be partnered with any one of nine N proteins. Therefore, there are potentially nine different forms of each subtype (e.g., H5N1, H5N9, H7N1, H9N9). These combinations of bird flu viruses infect birds.[2,3] And, while it is possible for humans to be infected through contact with birds, the spread from person to person has been very rare to date.[4]

Myth: All bird flu viruses are the same.

Fact: The three avian influenza subtypes — H5, H7 and H9 — vary in several ways. As mentioned, each has potentially nine different subtypes. The viruses also can be distinguished as low pathogenic (LPAI) or high pathogenic (HPAI) strains based on the viruses' genetic features and the severity of the illness they cause in poultry. The H5 and H7 viruses can be distinguished as both LPAI and HPAI, whereas the H9 virus is documented only as an LPAI strain. It is possible for humans to be infected by all three, but the severity of the infections vary. H5 infections have been documented among humans, and they sometimes cause severe illness and death. H7 infections in humans are rare, but they can occur among persons who have direct contact with infected birds, and symptoms typically include conjunctivitis and/or upper-respiratory symptoms. At least three H9 infections in humans have been confirmed.[2]

Myth: The bird flu is relatively rare.

Fact: The bird flu actually dates back to 1918 with the Spanish flu, which was the first major flu pandemic of the 20th century that killed an estimated 20 million to 40 million people. In 2005, researchers at the Armed Forces Institute of Pathology in Rockville, Md., reconstructed the genetic code of the deadly Spanish flu and found that the virus strain developed in birds and was similar to today's bird flu.[5] After that, the Asian flu was a category two flu pandemic outbreak of avian influenza that originated in China in early 1956 lasting until 1958.[6]

Today, avian influenza outbreaks among poultry occur worldwide from time to time. According to the World Organization for Animal Health (OIE) reporting criteria for Notifiable Avian Influenza in commercial poultry, since 1997, the United States has experienced 17 incidents of H5 and H7 LPAI and one incident of HPAI that was restricted to one poultry farm. The first HPAI in the U.S. occurred in 2004. This was an outbreak of avian influenza H5N2 that infected a flock of 7,000 chickens in south-central Texas. However, there was no report of transmission to humans.[7]

The bird flu actually dates back to 1918 with the Spanish flu.

Other countries have experienced much greater avian influenza activity. In 1997, an H5N1 outbreak infected chickens and humans in Hong Kong. It was the first time an avian influenza virus had ever been found to transmit directly from birds to humans. During this outbreak, 18 people were hospitalized, six of them died and 1.5 million chickens were killed to remove the source of the virus. In 1999, two cases of H9N2 in Hong Kong were confirmed in children. In 2003, two cases of H5N1 infections occurred among members of a Hong Kong family that traveled to China. H7N7 infections among poultry workers and their families were confirmed in the Netherlands during an outbreak among poultry, with more than 80 cases reported and one patient dying. Also that year, a child was infected with H9N2 in Hong Kong.[8] In 2004, the H5N1 virus resurfaced, infecting and killing 32 people in Thailand and Vietnam. Another mild virus infected a couple of poultry workers in Canada, and two more mild forms, H5N2 and H5N6, were discovered. In 2005, the bird flu infected 64 in Asia, 42 in Vietnam, 13 in Thailand, five in Indonesia and four in Cambodia. In August of the same year, the bird flu was found in Tibet, Siberia, Russia, Turkey, Romania, Croatia, Canada and Kazakhstan.[9] And, as mentioned, this year, a new

H7N9 strain has infected hundreds and killed dozens.

Myth: Bird flu viruses are highly contagious toward humans.

Fact: Despite the large number of people in the world who have contact with poultry every day, human cases of bird flu remain rare. Since 2003, only approximately 600 people have been infected with an avian influenza virus. Direct contact with poultry poses the highest risk. However, indirect exposure to bird feces also poses a risk. Therefore, contact with unwashed eggs from sick birds or water contaminated by poultry feces poses a potential risk of disease. There also is a theoretical risk that laboratory workers who handle the avian flu virus could become infected. Human-to-human spread of bird flu has occurred only in isolated cases. It is possible that caring for a person infected with bird flu can be a risk factor.[10]

It's difficult for the bird flu virus to infect human cells, but there is a possibility that mutations like antigenic shifts may reduce such difficulties. The concern is that the virus, if given enough opportunities, may change by reassortment with human influenza viruses or by some other mechanism into a form that is highly infectious for humans and spreads easily from person to person. Such a change could mark the start of a pandemic (a global outbreak in humans).[3]

Myth: People can contract the bird flu by eating poultry and eggs.

Fact: Precautions should be taken to eat only animal products from healthy animals. This is true for humans and other animals. However, even in areas experiencing outbreaks of HPAI, poultry and poultry products can be safely consumed if they are properly cooked and handled during food preparation. Avian influenza is not transmitted through cooked food, and to date, there is no evidence to indicate anyone has become infected following the consumption of properly cooked poultry or poultry products.[3]

Myth: The bird flu is a death sentence.

Fact: While the rate of death due to the bird flu is high, not all people who contract the bird flu die. Bird flu causes a very aggressive form of pneumonia (acute respiratory distress syndrome, or ARDS) that is often fatal. Many cases of bird flu occur in people who are poor, live in rural areas in underdeveloped countries, and do not have access to modern intensive care units or antiviral therapy.[10] It is the highly pathogenic form of the avian influenza virus that poses a death threat, and the H5N1 virus is often, but not always, deadly. In the 505 confirmed cases of avian influenza virus from 2003 to 2010, 300 have died, which corresponds to a 60 percent mortality rate.[11]

Myth: There is a vaccine to protect against the bird flu.

Fact: While there is one vaccine approved by the U.S. Food and Drug Administration to prevent infection with the H5N1 influenza virus strain — the one that has caused the largest outbreak of bird flu — the vaccine isn't available to the public.

Instead, the U.S. government is stockpiling it in the Centers for Disease Control and Prevention's (CDC) Strategic National Stockpile and will distribute it in the event of an outbreak. The vaccine is approved for adults ages 18 to 64 and is made from inactivated viruses and does not contain any live viruses. It has been shown to stimulate the immune system to make antibodies against the bird flu virus that could presumably protect a person from the bird flu. But, it is not known if it would be effective against any newly mutated strains.[10,12]

With the recent outbreak of the H7N9 avian influenza virus, experts around the world began talking daily about if and when to start making a vaccine. Shortly thereafter, the CDC announced it had begun making a seed vaccine against H7N9 based on the genetic sequences of the virus that China posted on public databanks.[13]

Myth: Without being vaccinated, there is no way to prevent the bird flu.

Fact: People can prevent the bird flu by avoiding contact with sick poultry originating in countries known to be affected by the virus. As of 2011, Egypt has the most reported cases to date. Prevention also includes poultry safety measures such as destroying flocks when sick birds are identified and vaccinating healthy flocks. Because the bird flu can spread to any area of the world by migrating birds, proper handling and cooking of poultry and eggs is recommended to kill bird flu viruses. For those caring for or in close contact with an infected patient, masks and other respiratory protection should be used. Those individuals also may be prescribed oseltamivir (Tamiflu) in an attempt to prevent infection.[10]

Myth: The same tests to diagnose the human flu are used to diagnose the bird flu.

Fact: While routine tests for human influenza A will be positive in patients with the bird flu, they are not specific for the avian virus. Instead, a specific diagnosis requires specialized tests. Culture and polymerase chain reaction (PCR) tests can detect the virus in sputum. PCR tests detect nucleic acid from the influenza A virus. Both tests are conducted in laboratories that have an appropriate biosafety reference certification. In the U.S., local health departments and the CDC can provide access to specialized testing. Unfortunately, the tests must be conducted during and after infection with the bird flu to detect antibodies against the virus. This means one sample must be taken at the onset of the disease and another sample must be taken several weeks later; therefore, the results are not available until the patient has recovered or died.[10]

Myth: Antivirals aren't effective against the bird flu.

Fact: Antivirals are recommended if they are taken within two days after the appearance of symptoms. However, according to the Mayo Clinic, many influenza viruses have become resistant to the effects of a category of antiviral drugs that includes amantadine and rimantadine. Therefore, health officials recommend the use of oseltamivir (Tamiflu) and possibly zanamivir (Relenza) instead.[14]

Myth: There is a real threat of a bird flu pandemic.

Fact: Many experts believe that the world is overdue for a global influenza pandemic that is as deadly as the Spanish flu. That's why scientists are working to determine which viruses might spark pandemics. Evidence of the 1918 Spanish flu strain mutations in the H5N1 virus suggests the ability of strains to jump directly to humans from other animals without having to first combine with a flu strain already adapted to humans. In addition, the century's other great pandemics of 1957 and 1968 were sparked by hybrid flu viruses (human influenzas that acquired some genes from an avian source), which suggests that pandemics can form in more than one way.[5]

So far, however, the bird flu viruses, including H5N1, have not triggered a pandemic in humans because they don't spread easily among mammals, and some scientists believe they never will. To spread easily from one person to another, a virus would have to become airborne, or develop the ability to spread via tiny droplets that people spray out of their mouths and noses when they cough and sneeze, which is how other flu viruses spread.

This has happened, but it is rare. In 2009, the H1N1 swine flu became airborne and caused a mild pandemic. Viruses like H5N1 and H1N1 are mutating all the time. If H5N1 were by chance to acquire some of the properties of H1N1, then it would spread more easily in mammals. One way it could do this is by accumulating chance mutations; another way is by swapping genes with other viruses, for instance while co-infecting an intermediate host (known as genetic reassortment).[15]

Since 2003, only approximately 600 people have been infected with an avian influenza virus.

One study shows how this might happen. In a new experiment, scientists induced five genetic changes in the H5N1 virus, transforming it into a type capable of airborne transmission between mammals. The scientists first changed three amino acid molecules of H5N1 in a way they believed would boost the virus's affinity for human hosts, and then infected ferrets with the mutated virus. They then swabbed the noses

3000*

*US deaths from flu have ranged from 3000 to about 49,000 per year.[1]
—*CDC*

Help protect your patients during the 2013-14 flu season. Order **FLUVIRIN® (Influenza Virus Vaccine)** today.

Order FLUVIRIN® now and help protect your patients for the 2013-2014 flu season.

In 2009, 28,000 men died from prostate cancer[2] and more than 40,000 women from breast cancer.[3] And while influenza may not seem like a serious disease, each year it causes 3000 to 49,000 flu-associated deaths.[1]

The ACIP recommendation for annual influenza vaccination now includes all persons aged 6 months and older.[4] FLUVIRIN is indicated for persons 4 years of age and older.

Novartis Vaccines is committed to providing seasonal flu vaccine doses on time. In fact, in 2012, Novartis Vaccines completed the shipping of more than 36 million seasonal flu vaccine doses ahead of schedule, allowing for early and convenient administration.

Make sure you have your supply of vaccine ready for the next flu season. Contact FFF Enterprises today at 800-843-7477 or visit www.myfluvaccine.com.

Indication

FLUVIRIN vaccine is an inactivated influenza virus vaccine indicated for active immunization of persons 4 years of age and older against influenza disease caused by influenza virus subtypes A and type B contained in the vaccine.

FLUVIRIN vaccine is not indicated for children less than 4 years of age because there is evidence of diminished immune response in this age group.

Important Safety Information

FLUVIRIN® (Influenza Virus Vaccine) should not be administered to anyone with known systemic hypersensitivity reactions to egg proteins (egg or egg products), or to any component of FLUVIRIN,® or who has had a life-threatening reaction to previous influenza vaccinations.

If Guillain-Barré syndrome has occurred within 6 weeks of receipt of prior influenza vaccine, the decision to give FLUVIRIN® should be based on careful consideration of the potential benefits and risks.

If FLUVIRIN® is administered to immunocompromised persons, including individuals receiving immunosuppressive therapy, the expected immune response may not be obtained.

Prior to administration of any dose of FLUVIRIN,® the healthcare provider should review the patient's prior immunization history for possible adverse events, to determine the existence of any contraindication to immunization with FLUVIRIN® and to allow an assessment of benefits and risks. Appropriate medical treatment and supervision must be available to manage possible anaphylactic reactions following administration of the vaccine.

The tip caps of the FLUVIRIN® prefilled syringes may contain natural rubber latex which may cause allergic reactions in latex sensitive individuals.

Vaccination with FLUVIRIN® may not protect all individuals. In clinical trials, the most common adverse events in adults were headache, fatigue, injection site reaction (pain, mass, redness, and induration), and malaise.

Please see brief summary of the Fluvirin Prescribing Information on the following pages.

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Influenza Virus Vaccine
Fluvirin®

FLUVIRIN® (Influenza Virus Vaccine)
Suspension for Intramuscular Injection
2012-2013 Formula
Initial US Approval: 1988

BRIEF SUMMARY: Please see package insert for full prescribing information.

1 INDICATIONS AND USAGE

FLUVIRIN® is an inactivated influenza virus vaccine indicated for immunization of persons 4 years of age and older against influenza virus disease caused by influenza virus subtypes A and type B contained in the vaccine [see DOSAGE FORMS AND STRENGTHS (3) in the full prescribing information].

FLUVIRIN® is not indicated for children less than 4 years of age because there is evidence of diminished immune response in this age group.

4 CONTRAINDICATIONS

4.1 Hypersensitivity

Do not administer FLUVIRIN® to anyone with known history of severe allergic reactions (e.g., anaphylaxis) to egg proteins (eggs or egg products), or to any component of FLUVIRIN®, or who has had a life-threatening reaction to previous influenza vaccinations.

5 WARNINGS AND PRECAUTIONS

5.1 Guillain-Barré Syndrome

If Guillain-Barré syndrome has occurred within 6 weeks of receipt of prior influenza vaccine, the decision to give FLUVIRIN® should be based on careful consideration of the potential benefits and risks.

5.2 Altered Immunocompetence

If FLUVIRIN® is administered to immunocompromised persons, including individuals receiving immunosuppressive therapy, the expected immune response may not be obtained.

5.3 Preventing and Managing Allergic Reactions

Prior to administration of any dose of FLUVIRIN®, the healthcare provider should review the patient's prior immunization history for possible adverse events, to determine the existence of any contraindication to immunization with FLUVIRIN® and to allow an assessment of benefits and risks. Appropriate medical treatment and supervision must be available to manage possible anaphylactic reactions following administration of the vaccine.

The tip caps of the FLUVIRIN® prefilled syringes may contain natural rubber latex which may cause allergic reactions in latex sensitive individuals.

5.4 Limitations of Vaccine Effectiveness

Vaccination with FLUVIRIN® may not protect all individuals.

6 ADVERSE REACTIONS

6.1 Overall Adverse Reaction Profile

Serious allergic reactions, including anaphylactic shock, have been observed in individuals receiving FLUVIRIN® during postmarketing surveillance.

6.2 Clinical Trial Experience

Adverse event information from clinical trials provides a basis for identifying adverse events that appear to be related to vaccine use and for approximating the rates of these events. However, because clinical trials are conducted under widely varying conditions, the adverse reaction rates observed in the clinical trials of a vaccine cannot be directly compared to rates in the clinical trials of another vaccine, and may not reflect rates observed in clinical practice.

Adult and Geriatric Subjects

Safety data were collected in a total of 2768 adult and geriatric subjects (18 years of age and older) who have received FLUVIRIN® in 29 clinical studies since 1982.

In 9 clinical studies since 1997, among 1261 recipients of FLUVIRIN®, 745 (59%) were women; 1211 (96%) were White, 23 (2%) Asian, 15 (1%) Black and 12 (1%) other; 370 (29%) of subjects were elderly (≥65 years of age). All studies have been conducted in the UK, apart from a study run in the US in 2005-2006 where FLUVIRIN® was used as a comparator for an unlicensed vaccine.

After vaccination, the subjects were observed for 30 minutes for hypersensitivity or other immediate reactions. Subjects were instructed to complete a diary card for three days following immunization (i.e. Day 1 to 4) to collect local and systemic reactions (see Tables 2 and 3). All local and systemic adverse events were considered to be at least possibly related to the vaccine. Local and systemic reactions mostly began between day 1 and day 2. The overall adverse events reported in clinical trials since 1998 in at least 5% of the subjects are summarized in Table 4.

TABLE 2
Solicited Adverse Events in the First 72-96 Hours After Administration of FLUVIRIN® in Adult (18-64 years of age) and Geriatric (≥65 years of age) Subjects.

	1998-1999*§		1999-2000*§		2000-2001*§	
	18-64 yrs	≥ 65 yrs	18-64 yrs	≥ 65 yrs	18-64 yrs	≥ 65 yrs
	N = 66	N = 44	N = 76	N = 34	N = 75	N = 35
Local Adverse Events						
Pain	16 (24%)	4 (9%)	16 (21%)	-	9 (12%)	-
Mass	7 (11%)	1 (2%)	4 (5%)	-	8 (11%)	1 (3%)
Inflammation	5 (8%)	2 (5%)	6 (8%)	-	7 (9%)	1 (3%)
Ecchymosis	4 (6%)	1 (2%)	3 (4%)	1 (3%)	4 (5%)	-
Edema	2 (3%)	1 (2%)	1 (1%)	2 (6%)	3 (4%)	1 (3%)
Reaction	2 (3%)	-	2 (3%)	-	4 (5%)	1 (3%)
Hemorrhage	-	-	1 (1%)	-	-	-
Systemic Adverse Events						
Headache	7 (11%)	1 (2%)	17 (22%)	3 (9%)	4 (5%)	-
Fatigue	3 (5%)	2 (5%)	4 (5%)	1 (3%)	3 (4%)	-
Malaise	2 (3%)	1 (2%)	2 (3%)	1 (3%)	1 (1%)	-
Myalgia	1 (2%)	-	2 (3%)	-	-	-
Fever	1 (2%)	-	1 (1%)	-	-	-
Arthralgia	-	1 (2%)	-	1 (3%)	-	-
Sweating	-	-	3 (4%)	-	1 (1%)	1 (3%)

	2001-2002*^		2002-2003*^		2004-2005*^	
	18-64 yrs	≥ 65 yrs	18-64 yrs	≥ 65 yrs	18-64 yrs	≥ 65 yrs
	N = 75	N = 35	N = 107	N = 88	N = 74	N = 61
Local Adverse Events						
Pain	12 (16%)	1 (3%)	14 (13%)	7 (8%)	15 (20%)	9 (15%)
Mass	4 (5%)	1 (3%)	-	-	-	-
Ecchymosis	2 (3%)	-	3 (3%)	3 (3%)	2 (3%)	1 (2%)
Edema	2 (3%)	1 (3%)	6 (6%)	2 (2%)	-	-
Erythema	5 (7%)	-	11 (10%)	5 (6%)	16 (22%)	5 (8%)
Swelling	-	-	-	-	11 (15%)	4 (7%)
Reaction	-	-	2 (2%)	-	-	-
Induration	-	-	14 (13%)	3 (3%)	11 (15%)	1 (2%)
Pruritus	-	-	1 (1%)	-	-	-
Systemic Adverse Events						
Headache	8 (11%)	1 (3%)	12 (11%)	9 (10%)	14 (19%)	3 (5%)
Fatigue	1 (1%)	1 (3%)	-	-	5 (7%)	2 (3%)
Malaise	3 (4%)	-	3 (3%)	4 (5%)	1 (1%)	1 (2%)
Myalgia	3 (4%)	-	5 (5%)	3 (3%)	8 (11%)	1 (2%)
Fever	-	-	-	1 (1%)	-	-
Arthralgia	-	-	2 (2%)	-	1 (1%)	-
Sweating	3 (4%)	1 (3%)	-	2 (2%)	-	-
Shivering	-	-	-	1 (1%)	-	-

Results reported to the nearest whole percent; Fever defined as >38°C
– not reported
* Solicited adverse events in the first 72 hours after administration of FLUVIRIN®
§ Solicited adverse events reported by COSTART preferred term
^ Solicited adverse events reported by MEDDRA preferred term

TABLE 3
Solicited Adverse Events in the First 72 Hours After Administration of FLUVIRIN® in Adult Subjects (18-49 years of age).

	2005-2006 US Trial FLUVIRIN® N = 304
Local Adverse Events	
Pain	168 (55%)
Erythema	48 (16%)
Ecchymosis	22 (7%)
Induration	19 (6%)
Swelling	16 (5%)
Systemic Adverse Events	
Headache	91 (30%)
Myalgia	64 (21%)
Malaise	58 (19%)
Fatigue	56 (18%)
Sore throat	23 (8%)
Chills	22 (7%)
Nausea	21 (7%)
Arthralgia	20 (7%)
Sweating	17 (6%)
Cough	18 (6%)
Wheezing	4 (1%)
Chest tightness	4 (1%)
Other difficulties breathing	3 (1%)
Facial edema	-

Results reported to the nearest whole percent
– not reported

TABLE 4
Adverse Events Reported by at least 5% of Subjects in Clinical Trials since 1998

	1998-1999§		1999-2000§		2000-2001§	
	18-64 yrs	≥ 65 yrs	18-64 yrs	≥ 65 yrs	18-64 yrs	≥ 65 yrs
	N = 66	N = 44	N = 76	N = 34	N = 75	N = 35
Adverse Events						
Fatigue	8 (12%)	2 (5%)	8 (11%)	2 (6%)	5 (7%)	-
Back pain	4 (6%)	3 (7%)	-	-	-	-
Cough increased	2 (3%)	2 (5%)	-	-	-	-
Ecchymosis	4 (6%)	1 (2%)	4 (5%)	1 (3%)	5 (7%)	-
Fever	3 (5%)	-	-	-	-	-
Headache	12 (18%)	5 (11%)	22 (29%)	5 (15%)	14 (19%)	2 (6%)
Infection	3 (5%)	2 (5%)	-	-	-	-
Malaise	4 (6%)	4 (9%)	4 (5%)	1 (3%)	-	-
Migraine	4 (6%)	1 (2%)	-	-	-	-
Myalgia	4 (6%)	1 (2%)	-	-	-	-
Sweating	5 (8%)	1 (2%)	-	-	-	-
Rhinitis	3 (5%)	1 (2%)	-	-	5 (7%)	2 (6%)
Pharingitis	6 (9%)	1 (2%)	10 (13%)	-	6 (8%)	-
Arthralgia	-	-	-	2 (6%)	-	-
Injection site pain	16 (24%)	4 (9%)	16 (21%)	-	9 (12%)	-
Injection site ecchymosis	4 (6%)	1 (2%)	-	-	4 (5%)	-
Injection site mass	7 (11%)	1 (2%)	4 (5%)	-	8 (11%)	1 (3%)
Injection site edema	-	-	1 (1%)	2 (6%)	-	-
Injection site inflammation	5 (8%)	2 (5%)	6 (8%)	-	7 (9%)	1 (3%)
Injection site reaction	-	-	-	-	4 (5%)	1 (3%)

	2001-2002^		2002-2003^		2004-2005^	
	18-64 yrs	≥ 65 yrs	18-64 yrs	≥ 65 yrs	18-64 yrs	≥ 65 yrs
	N = 75	N = 35	N = 107	N = 88	N = 74	N = 61
Adverse Events						
Fatigue	5 (7%)	4 (11%)	11 (10%)	8 (9%)	4 (5%)	2 (3%)
Hypertension	-	-	1 (1%)	4 (5%)	-	-
Rinorrhea	-	-	2 (2%)	5 (6%)	-	-
Headache	20 (27%)	2 (6%)	35 (33%)	18 (20%)	12 (16%)	1 (2%)
Malaise	6 (8%)	1 (3%)	13 (12%)	8 (9%)	-	-
Myalgia	4 (5%)	1 (3%)	10 (9%)	4 (5%)	-	-
Sweating	3 (4%)	3 (9%)	2 (2%)	5 (6%)	-	-
Rhinitis	4 (5%)	-	-	-	-	-
Pharingitis	-	-	-	-	6 (8%)	-
Arthralgia	-	-	5 (5%)	4 (5%)	-	-
Sore throat	4 (5%)	1 (3%)	5 (5%)	4 (5%)	-	-
Injection site pain	13 (17%)	3 (9%)	14 (13%)	7 (8%)	6 (8%)	2 (3%)

(continued)

TABLE 4
Adverse Events Reported by at least 5% of Subjects in Clinical Trials since 1998

	2001-2002^		2002-2003^		2004-2005^	
	18-64 yrs	≥ 65 yrs	18-64 yrs	≥ 65 yrs	18-64 yrs	≥ 65 yrs
	N = 75	N = 35	N = 107	N = 88	N = 74	N = 61
Adverse Events						
Injection site ecchymosis	4 (5%)	1 (3%)	4 (4%)	4 (5%)	-	-
Injection site erythema	5 (7%)	2 (6%)	11 (10%)	5 (6%)	4 (5%)	-
Injection site mass	4 (5%)	1 (3%)	-	-	-	-
Injection site edema	-	-	6 (6%)	2 (2%)	4 (5%)	1 (2%)
Injection site induration	-	-	14 (13%)	3 (3%)	7 (9%)	-

Results reported to the nearest whole percent; Fever defined as >38°C
– not reaching the cut-off of 5%
§ Solicited adverse events reported by COSTART preferred term
^ Solicited adverse events reported by MEDDRA preferred term

Adults (18 to 64 years of age)
In adult subjects, solicited local adverse events occurred with similar frequency in all trials. The most common solicited adverse events occurring in the first 96 hours after administration (Tables 2 and 3) were associated with the injection site (such as pain, erythema, mass, induration and swelling) but were generally mild/moderate and transient. The most common solicited systemic adverse events were headache and myalgia.

The most common overall events in adult subjects (18-64 years of age) were headache, fatigue, injection site reactions (pain, mass, erythema, and induration) and malaise (Table 4).

Geriatric Subjects (65 years of age and older)
In geriatric subjects, solicited local and systemic adverse events occurred less frequently than in adult subjects. The most common solicited local and systemic adverse events were injection site pain, and headache (Tables 2 and 3). All were considered mild/moderate and were transient.

The most common overall events in elderly subjects (≥65 years of age) were headache and fatigue.

Only 11 serious adverse events in adult and geriatric subjects (18 years and older) have been reported to date from all the trials performed. These serious adverse events were a minor stroke experienced by a 67 year old subject 14 days after vaccination (1990), death of an 82 year old subject 35 days after vaccination (1990) in very early studies; death of a 72 year old subject 19 days after vaccination (1998-1999), a hospitalization for hemorrhoidectomy of a 38 year old male subject (1999-2000), a severe respiratory tract infection experienced by a 74 year old subject 12 days after vaccination (2002-2003), a planned transurethral resection of the prostate in a subject with prior history of prostatism (2004-2005), two cases of influenza (2005-2006), a drug overdose (2005-2006), cholelithiasis (2005-2006) and a nasal septal operation (2005-2006). None of these events were considered causally related to vaccination.

Clinical Trial Experience in Pediatric Subjects
In 1987 a clinical study was carried out in 38 'at risk' children aged between 4 and 12 years (17 females and 21 males). To record the safety of FLUVIRIN®, participants recorded their symptoms on a diary card during the three days after vaccination and noted any further symptoms they thought were attributable to the vaccine. The only reactions recorded were tenderness at the site of vaccination in 21% of the participants on day 1, which was still present in 16% on day 2 and 5% on day 3. In one child, the tenderness was also accompanied by redness at the site of injection for two days. The reactions were not age-dependent and there was no bias towards the younger children.

Three clinical studies were carried out between 1995 and 2004 in a total of 520 pediatric subjects (age range 6 - 47 months). Of these, 285 healthy subjects plus 41 'at risk' subjects received FLUVIRIN®. No serious adverse events were reported.

FLUVIRIN® should only be used for the immunization of persons aged 4 years and over.

6.3 Postmarketing Experience
The following additional adverse reactions have been reported during postapproval use of FLUVIRIN®. 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 vaccine exposure. Adverse events described here are included because:
a) they represent reactions which are known to occur following immunizations generally or influenza immunizations specifically; b) they are potentially serious; or c) the frequency of reporting.

- *Body as a whole:* Local injection site reactions (including pain, pain limiting limb movement, redness, swelling, warmth, ecchymosis, induration), hot flashes/flushes; chills; fever; malaise; shivering; fatigue; asthenia; facial edema.
- *Immune system disorders:* Hypersensitivity reactions (including throat and/or mouth edema). In rare cases, hypersensitivity reactions have lead to anaphylactic shock and death.
- *Cardiovascular disorders:* Vasculitis (in rare cases with transient renal involvement), syncope shortly after vaccination.

- *Digestive disorders:* Diarrhea; nausea; vomiting; abdominal pain.
- *Blood and lymphatic disorders:* Local lymphadenopathy; transient thrombocytopenia.
- *Metabolic and nutritional disorders:* Loss of appetite.
- *Musculoskeletal:* Arthralgia; myalgia; myasthenia.
- *Nervous system disorders:* Headache; dizziness; neuralgia; paraesthesia; confusion; febrile convulsions; Guillain-Barré Syndrome; myelitis (including encephalomyelitis and transverse myelitis); neuropathy (including neuritis); paralysis (including Bell's Palsy).
- *Respiratory disorders:* Dyspnea; chest pain; cough; pharyngitis; rhinitis.
- *Skin and appendages:* Stevens-Johnson syndrome; sweating; pruritus; urticaria; rash (including non-specific, maculopapular, and vesiculobulbous).

6.4 Other Adverse Reactions Associated with Influenza Vaccination
Anaphylaxis has been reported after administration of FLUVIRIN®. Although FLUVIRIN® contains only a limited quantity of egg protein, this protein can induce immediate hypersensitivity reactions among persons who have severe egg allergy. Allergic reactions include hives, angioedema, allergic asthma, and systemic anaphylaxis [see CONTRAINDICATIONS (4)].

The 1976 swine influenza vaccine was associated with an increased frequency of Guillain-Barré syndrome (GBS). Evidence for a causal relation of GBS with subsequent vaccines prepared from other influenza viruses is unclear. If influenza vaccine does pose a risk, it is probably slightly more than 1 additional case/1 million persons vaccinated.

Neurological disorders temporally associated with influenza vaccination such as encephalopathy, optic neuritis/neuropathy, partial facial paralysis, and brachial plexus neuropathy have been reported.

Microscopic polyangiitis (vasculitis) has been reported temporally associated with influenza vaccination.

7 DRUG INTERACTIONS

7.1 Concomitant Administration with Other Vaccines
There are no data to assess the concomitant administration of FLUVIRIN® with other vaccines. If FLUVIRIN® is to be given at the same time as another injectable vaccine(s), the vaccines should always be administered at different injection sites.

FLUVIRIN® should not be mixed with any other vaccine in the same syringe or vial.

7.2 Concurrent Use with Immunosuppressive Therapies
Immunosuppressive therapies, including irradiation, antimetabolites, alkylating agents, cytotoxic drugs, and corticosteroids (used in greater than physiologic doses), may reduce the immune response to FLUVIRIN®.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy
Pregnancy Category C: Animal reproduction studies have not been conducted with FLUVIRIN®. It is also not known whether FLUVIRIN® can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. FLUVIRIN® should be given to a pregnant woman only if clearly needed.

8.3 Nursing Mothers
It is not known whether FLUVIRIN® is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when FLUVIRIN® is administered to a nursing woman.

8.4 Pediatric Use
The safety and immunogenicity of FLUVIRIN® have not been established in children under 4 years of age.

The safety and immunogenicity of FLUVIRIN® have been established in the age group 4 years to 16 years. The use of FLUVIRIN® in these age groups is supported by evidence from adequate and well controlled studies of FLUVIRIN® in adults that demonstrate the immunogenicity of FLUVIRIN® [see ADVERSE REACTIONS (6) and CLINICAL STUDIES (14) in the full prescribing information].

8.5 Geriatric Use
Since 1997, of the total number of geriatric subjects (n = 397) in clinical studies of FLUVIRIN®, 29% were 65 years and over, while 2.1% were 75 years and over.

Antibody responses were lower in the geriatric population than in younger subjects. Adverse events occurred less frequently in geriatric subjects (≥65 years) than in younger adults. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. [See ADVERSE REACTION (6) and CLINICAL STUDIES (14) in the full prescribing information].

16 STORAGE AND HANDLING

16.2 Storage and Handling
Store FLUVIRIN® refrigerated between 2° and 8°C (36° and 46°F).

Do not freeze. Discard if the vaccine has been frozen.

Store in the original package to protect from light.

Do not use after the expiration date.

Between uses, return the multidose vial to the recommended storage conditions.

FLUVIRIN® is a registered trademark of Novartis Vaccines and Diagnostics Limited.

Manufactured by: Novartis Vaccines and Diagnostics Limited, Speke, Liverpool, UK
An affiliate of: Novartis Vaccines and Diagnostics, Inc.,
350 Massachusetts Avenue, Cambridge, MA 02139 USA
1-877-683-4732

of the infected ferrets and used virus samples from their bodies to infect another round of ferrets. At each stage, they took tissue samples from the ferrets to see how H5N1 was evolving. After 10 passages, the scientists found the virus had acquired the ability to transmit from animal to animal, which suggests that "in humans, it would take a low number of transmission for the mutations to accumulate," said the study's co-author. Five mutations gave the virus the ability to jump from ferret to ferret: three of the initial amino-acid changes, plus two that emerged through evolutionary selection in the animals' bodies.[4]

Much of the focus of H5N1 research has been to investigate how easy it might be for H5N1 to mutate into a readily transmissible form, and if so, which genes would be involved. This information can help researchers know what changes to look out for in emerging strains when assessing pandemic risk.[15]

Much of the focus of H5N1 research has been to investigate how easy it might be for H5N1 to mutate into a readily transmissible form.

It is impossible to calculate the risk of a human pandemic of bird flu, but for it to emerge naturally, too many circumstances would have to coincide, making it unlikely for it to happen. As scientists from the St. Petersburg Influenza Research Institute point out: For a pandemic bird flu to occur, the epidemics of human and avian influenza must happen simultaneously and at the same place. And, it would be necessary for two related viruses to multiply in one and the same cell, which would have to result in not a weak mutation, but a powerful biotic mutation that would enable it to develop and multiply aggressively.[16]

Myth: In the event of a pandemic, the government won't be ready to respond.

Fact: The World Health Organization (WHO) and governments around the world are working in conjunction to develop pandemic response plans. These plans include monitoring local health conditions, reporting suspected instances of bird flu infection within 24 hours, developing plans for access to healthcare systems, containment of transmission of the bird flu, allocation of medications, and coordination of information with other health authorities. Governments also are coordinating efforts related to monitoring bird populations.

To prepare for an outbreak, the WHO has established a global, rapid deployment stockpile of three million treatment packs of antiviral medications, designated for use as a means of short-term containment in areas experiencing confirmed human-to-human transmission.[17]

Dispelling the Myths Now

Undoubtedly, the frequency of avian influenza outbreaks in the past several years, the way the viruses are mutating to create new strains and the lethality of many of these viruses are concerning. But compared with the human strains of the flu virus that kill thousands of people throughout the world each year, the bird flu is a minor threat. Scientists worldwide are devoted to studying the risks of a potential bird flu pandemic and, in the chance one does occur, they are making preparations to protect the public. ❖

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

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Alphanate®

Antihemophilic Factor/von Willebrand Factor Complex (Human)

FACTORS FOR HEALTH

The Power of FVIII/VWF Complex

Convenient Room Temperature Storage

First FVIII/VWF product in the US stable for 3 years, up to the expiration date printed, when stored at or below 77°F (25°C). Do not freeze.

Please see brief summary of Alphanate® Full Prescribing Information below.

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Alphanate Antihemophilic Factor/von Willebrand Factor Complex (Human) safely and effectively. See Full Prescribing Information for Alphanate.

ALPHANATE (ANTIHEMOPHILIC FACTOR/VON WILLEBRAND FACTOR COMPLEX [HUMAN])
Sterile, lyophilized powder for injection

For Intravenous Use Only

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.

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 have 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.
- Labor and Delivery: No human or animal data. Use only if clearly needed.
- Nursing Mothers: No human or animal data. Use only if clearly needed.
- Pediatric Use: Clinical trials for safety and effectiveness in pediatric hemophilia A patients have not been conducted. The hemostatic efficacy of Alphanate has been studied in 20 pediatric subjects with VWD 18 years of age and under. Based on the data from a subset of these subjects, age had no effect on the pharmacokinetics of VWF:RCo.
- Geriatric Use: No human or animal data. Use only if clearly needed.

For more information: **Grifols Inc.**
Customer Service: 888 325 8579 Fax: 323 441 7968

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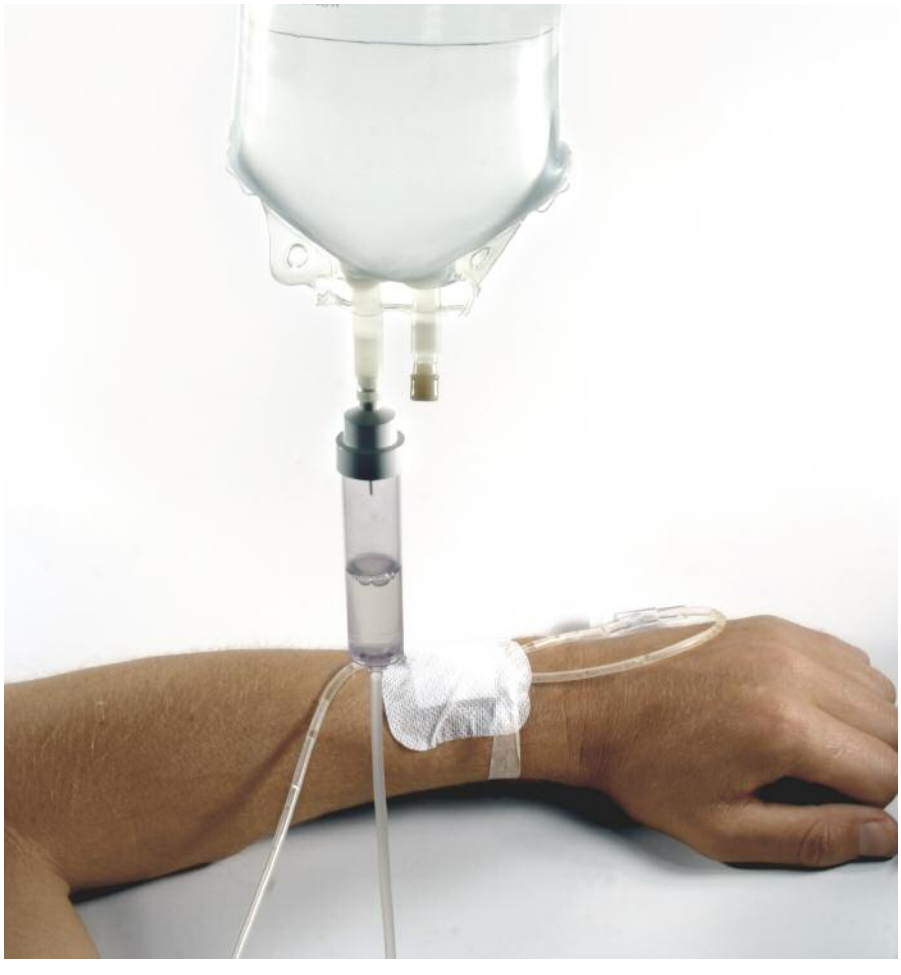
Hydroxyethyl Starch in Critically Ill Patients: The Verdict Is In

Fluid is a drug.

— Lakhmir Chawla, MD, Associate Professor of Anesthesiology and Critical Care Medicine, George Washington University School of Medicine



BY KEITH BERMAN, MPH, MBA

TWENTY-FIVE YEARS ago, an eye-catching double-page advertisement ran in medical journals, trumpeting that "Albumin & PPF* are no safer or more effective than Hespan (hetastarch)… they're simply double the price." Messages like this promoting Hespan and other 6 percent hydroxyethyl starch products strongly resonated at that time with hospitals eager to take advantage of a relatively cheap resuscitative colloid solution available in essentially unlimited supply.

Decades and millions of infusions later, a surge of recent evidence from well-designed prospective trials and meta-analyses has swept away the presumption that starch products, including Hespan, Hextend and Voluven, are safe in critically ill patients who require volume resuscitation. Clinical specialists and drug regulators are now left to ponder the missteps that led to untold numbers of serious complications and deaths over so many years. But, in essence, it boils down to

** Plasma protein fraction (a human plasma-based product in which albumin accounts for about 88 percent of total protein content)*

a failure at the outset to ask the right questions and demand answers.

Not Looked For, Not Found

Hespan, a synthetic maize-derived starch product featuring high molecular weight and molar substitution ratios (450/0.7),** was licensed in 1972 for "treatment of hypovolemia when plasma volume expansion is desired." Hespan was promoted as an effective, lower-cost alternative to human albumin. The U.S. Food and Drug Administration (FDA) approved the product based on a handful of very small clinical studies, conducted in a variety of treatment settings, comparing it to albumin; unsurprisingly, no differences in safety or efficacy were detected in these underpowered trials.

By the 1990s, numerous reports had described adverse effects of Hespan and other starches on coagulation function. Yet, curiously, in the absence of any large-scale clinical studies to assess its safety, roughly one-half of starch products purchased in the U.S. were being administered in lieu of human albumin or crystalloids to patients undergoing cardiopulmonary bypass (CPB) surgeries — a surgical population at particularly high risk for surgical bleeding complications.[1]

Finally in 2002, several published look-back studies[2,3,4] documenting excessive hemorrhage in CPB surgery patients switched to starch from albumin were brought to the attention of the FDA.[5] A year later, the FDA added specific warnings against use of licensed starch products in this surgical population. A very recent meta-analysis of 18 small clinical trials confirmed that, compared with albumin, starch-based colloids increased postoperative bleeding by 33.3 percent, increased red blood cell transfusions by 28.4 percent, and more than doubled the risk of reoperation; all findings were highly significant.[6]

Newer Starch Product, Same Old Toxicities

Tinkering with starch crosslinking chemistry to try to reduce its effects on coagulation function, several manufacturers came up with starch solutions featuring a lower mean molecular weight and reduced molar substitution ratios. In particular, 200/0.4-0.5 (pentastarch) and 130/0.38-0.45 products are thought to interfere less with coagulation function than the older 450/0.7 products, including Hespan and Hextend. These and other synthetic colloids have significantly displaced the use of albumin in European intensive care settings.

Renal function impairment appears to be associated with starches of varying molecular weights, plainly implying a class effect.

In 2007, a 130/0.4 starch product (Voluven) was approved in the U.S. with a very broad indication — "treatment and prophylaxis of hypovolemia" — and an adult dosage limit two-and-one-half times higher than Hespan or Hextend. The basis for that approval included a U.S. elective orthopedic surgery study randomizing just 100 patients to Voluven or conventional 450/0.7 starch, and three small non-U.S. studies evaluating Voluven against pentastarch products not licensed for use in the U.S. for treatment of hypovolemia.[7] Estimated blood loss was not different between Voluven and older starch groups in the U.S. trial. But, inexplicably, the study design permitted doses exceeding 3,000 mL — twice the recommended dose limit for Hespan and other 450/0.7 starch products. Unsurprisingly, three cases of serious coagulopathy occurred in the 450/0.7 arm.

One might question why the pivotal U.S. licensing study evaluated Voluven against Hespan at upper dosage limits far above the 1,500 mL recommended limit in the Hespan labeling and known to induce coagulopathy. Or why, given the investigators' interest in testing Voluven at doses up to 3,500 mL for a 70 kg adult, regulators did not insist on a comparison against 5% human albumin, the body's natural circulating colloid that, of course, is not coagulopathic (apart from a dilutional effect) at any dose.

Fortunately, not one but two well-designed and adequately powered trials published last year finally put Voluven and its class of 130/0.4 starch products to the test. The Crystalloid Versus Hydroxyethyl Starch Trials (CHEST) in Australia and New Zealand randomized a heterogeneous mix of 7,000 intensive care unit (ICU) patients to receive fluid resuscitation with Voluven or saline.[8] The relative risk (RR) of requiring renal replacement therapy (RRT) was 1.21 in the Voluven arm versus the saline control arm; serum creatinine was persistently elevated, implying a progressive

** *450 refers to a mean molecular size of 450 kD, and 0.7 refers to molar substitution (the percentage of hydroxyethyl groups substituted per glucose monomer)*

Table 1. Key Clinical Outcomes in a Trial Comparing 130/0.4 Hydroxyethyl Starch (HES) and Ringer's Acetate in 798 Subjects with Severe Sepsis

Outcome	130/0.4 HES (N = 398)	Ringer's Acetate (N = 400)	Relative Risk (95% CI)	P Value
Dead at day 90 (%)	201 (51%)	172 (43%)	1.17 (1.01-1.36)	0.03
Severe bleeding	38 (10%)	25 (6%)	1.52 (0.94-2.48)	0.09
Use of renal replacement therapy	87 (22%)	65 (16%)	1.35 (1.01-1.80)	0.04

Adapted from Perner A, et al. Hydroxyethyl starch 130/0.4 versus Ringer's acetate in severe sepsis. New Engl J Med 2012 Jul 12;367(2):124-34.[9]

reduction in creatinine clearance and more severe acute kidney injury. Remarkably, these findings occurred in the context of a massive study in which a mean of just 526 mL and 626 mL of Voluven and saline were respectively administered in the first four days.

A more tightly focused Scandinavian 6S trial randomized 798 patients with severe sepsis to receive either a 130/0.4 starch product or Ringer's acetate.[9] At 90 days, 51 percent of those assigned to starch had died, as compared with 43 percent of those assigned to Ringer's (RR, 1.17, P = 0.03). Starch administration was also associated with significantly increased risk of RRT and a strong trend toward increased severe bleeding risk (Table 1).

This same group's meta-analysis of studies of 130/0.4 starches used in sepsis, published earlier this year, confirmed its findings. In a predefined analysis of five trials with low risk of bias, the risk of requiring RRT was higher in the starch group (RR, 1.36; P = 0.009), as were risks of needing red blood cell transfusion and experiencing serious adverse events.[10]

Yet another systematic review and meta-analysis published this year documented increased risks of renal complications and mortality associated with administration of a spectrum of starch products in critically ill patients (Table 2).[11] The authors carefully excluded a number of discredited studies by German anesthesiologist Dr. Joachim Boldt, who for years was a tireless proponent of newer-generation starch solutions. Much of this man's prolific body of starch-related clinical research was retracted in 2011 after the discovery of systematic scientific misconduct.[12]

Renal function impairment appears to be associated with starches of varying molecular weights, plainly implying a class effect.[13] That stands to reason: Both higher and lower molecular weight 130/0.4 starches are taken up and stored in cells throughout the body. It tends to concentrate in the kidneys, which is thought to be a factor in the increased risk of acute kidney injury versus crystalloids.

Table 2. Findings from a Meta-Analysis of Studies Comparing Hydroxyethyl Starch (HES) to Crystalloids, Albumin or Gelatin in Critically Ill Patients

Outcome	Trials	Patients	Risk Ratios all Favoring Control Fluid Over HES	95% Confidence Interval
Mortality	28	10,290	1.09	1.02 to 1.17
Acute renal failure	5	8,725	1.27	1.09 to 1.47
Use of renal replacement therapy	10	9,258	1.32	1.15 to 1.50
Red cell transfusion	5	1,482	1.42	1.15 to 1.75

Adapted from Zarychanski R, et al. Association of hydroxyethyl starch administration with mortality and acute kidney injury in critically ill patients requiring volume resuscitation. A systematic review and meta-analysis. JAMA 2013 Feb 20;309(7):678-88.[10]

Albumin Resuscitation for Sepsis: A Closer Look

Some favor colloid solutions in sepsis resuscitation for their ability to obtain rapid and lasting circulatory stabilization. Many others prefer use of crystalloids, arguing that evidence for superiority of more costly colloids is lacking. Results from the landmark 2004 Saline Versus Albumin Fluid Evaluation (SAFE) trial would appear to support the former fluid choice. In a subset of 1,218 ICU severely septic patients randomized to albumin or saline, a strong mortality trend favored albumin (RR, 0.87; P=0.07). At that time, it was pointed out that if this finding is robust, more than one of every 10 lives of septic ICU patients now lost could be saved simply by resuscitating them with 5% albumin instead of saline.[14]

Seven years later, the SAFE investigators decided to take a closer look at their findings. Conducting multivariate regression analysis adjusting for baseline factors in 919 patients with complete baseline data, the adjusted odds ratio for death for albumin versus saline was 0.71 (95% confidence interval, 0.52-0.97; P = 0.03).[15]

This mortality difference favoring albumin should not come as a surprise. A landmark Spanish trial more than 10 years ago found that plasma volume expansion with albumin in addition to antibiotic treatment yielded a nearly three-fold lower in-hospital death rate than antibiotic alone (10 percent versus 29 percent; P = 0.01) in patients with cirrhosis and spontaneous bacterial peritonitis (SBI). Closely matching this was a dramatic renal protective effect: 10 percent in the albumin arm suffered renal impairment versus 33 percent of patients in the antibiotic-only arm.[16] The investigators pointed out that cirrhosis with SBI has many features of the sepsis syndrome; albumin may be protecting kidneys by enhancing circulatory function. But they also suggested that the beneficial effects of this multifunctional protein could involve other mechanisms as well, such as inhibition of apoptosis and scavenging of reactive oxygen species.[13]

Colloids and Crystalloids: Time to Think Anew

For resuscitation of patients with sepsis, the verdict is in: Hydroxyethyl starch products increase the risk of acute kidney injury and death. A logical question that follows is whether *operative patients at meaningful risk for developing sepsis* should be administered a starch product when the physician decides that colloid resuscitation is appropriate.

At last, well-designed and adequately powered clinical trials are revealing why resuscitative fluids — including crystalloids — should be thought of as drugs. Today, for critical care patients in particular, the fluid chosen for a specific patient can and should be the one for which the best available evidence points to the most benefit and the least harm.

If albumin is the resuscitative fluid you prefer for some patients, you may also appreciate knowing that frustrating supply shortages and pricing instability are things of the distant past. Since the late 1990s, a dramatic expansion in plasma supply and processing capacity — driven by surging demand for intravenous immunoglobulin — has created a structural, long-term surplus capacity to produce 5% and 25% albumin. The inflation-adjusted price of albumin has fallen by nearly one-half since the mid-1990s, and has consistently remained in good supply for more than a decade.[1]

It may be worthwhile to have a conversation with your critical care pharmacist about your resuscitative fluid strategy, as a wealth of important new information invites us all to think anew about the age-old colloid-crystalloid debate. ❖

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

Lyme Disease: A Patient's Perspective

Regina Weichert thought she was cured of Lyme disease, but then suffered a relapse that led to years of illness before finding a physician who specializes in an alternative approach to testing for disease.

BY TRUDIE MITSCHANG

Regina Weichert suffered for years from the effects of Lyme disease but finally found a successful treatment from a doctor who utilized an out-of-the-box approach.

AT 50, Regina Weichert is a graduate student at New York University's Heyman Center of Fundraising and Philanthropy, working toward an MS in fund-raising and grant-making. Her journey with Lyme disease began in 2004, when an afternoon walk on Martha's Vineyard led to a tick bite that changed the course of her life. "My guess is a tick latched on after a walk through dune grass one day. Chilmark, the town where I lived, is a Lyme epicenter. They have documented that 40 percent of the population has had Lyme, but given the fact that about 50 percent of blood tests are inaccurate, the real number is probably much higher than that."

Weichert never found the tick or developed the telltale "bull's-eye" rash characteristic of Lyme disease, instead experiencing fatigue and unusual headaches. A few days later, a 103-degree Fahrenheit fever sent her to the ER, where it was confirmed she had a tick-borne illness. A10-day course of doxycycline failed to relieve her symptoms, and follow-up Western blot and ELISA testing returned positive for Borrelia burgdorferi, the bacterial agent of Lyme disease.

Frightened, Weichert sought help from an infectious disease specialist at Brigham and Women's Hospital in Boston. At the time, she was still on high-dose doxycycline (400 mg twice a day), and she was advised to stay on it as long as possible. "After several months of doxy, I felt something recede within me, and thought I was better," she says. "My doctors redid the blood tests and said the Borrelia levels now indicated that my infection was gone."

Unfortunately, her battle with Lyme was far from over. Six months later, Weichert experienced new and troubling symptoms, including kidney aches, intense fatigue and abdominal swelling and pain. She consulted with at least half a dozen doctors, and she was repeatedly misdiagnosed with stress or depression. Then, five years after her original diagnosis, Weichert heard about an alternative practitioner in Manhattan who used the French ACMOS testing method to diagnose various disease states. After undergoing a series of treatments, including IVs, UVB and neural therapy, Weichert remained ill, and she began an online search for other alternative Lyme disease treatments. That search led her to Dietrich Klinghardt, MD, PhD, medical director of the Klinghardt Academy. Intrigued by his unique treatment protocol and his successful track record treating Lyme disease patients, she scheduled an appointment.

"Meeting Dr. Klinghardt was life-changing," she says. "He used the kinesiology Autonomic Response Testing to assess me and various labs to diagnose me. I had several chronic infections: one in my jawbone from an old wisdom tooth extraction; chronic strep; parasites; and high levels of mercury toxicity. He did not test me for Lyme right away because my immune system was so low. Later on, we ran blood tests, and I tested positive for both Lyme and Babesia."

Weichert's treatment regimen included natural therapies interspersed with pharmaceutical drugs such as antiparasitics. The recovery period was difficult, and she says it was well over a year before she sensed real improvement. "In 2008,

I was so sick I could barely walk a block," says Weichert. "I had a lot of pain, cognitive impairment and fatigue. I couldn't hold a job. By 2012, I was well enough to begin a graduate program, and I will graduate in 2014. I am beginning a job hunt this summer, and recent lab work showed my white blood cell count was in the normal range for the first time in about 15 years! My immune markers are substantially up, and my inflammation level is way down — my body has been healing, cell by cell."

Weichert credits Dr. Klinghardt with saving her life and is thankful for his "out-of-the-box" treatment approach, compassion and humor. "He's not frightened of the illness, and he doesn't give up, but rather meets patients as the individuals that they are. His style as a doctor is to teach — he teaches people how to be healthy, and provides a new way of looking at and living life. It's a blessing to be his patient." ❖

TRUDIE MITSCHANG *is a staff writer for* BioSupply Trends Quarterly.

What Patients Wish Physicians Knew About Lyme Disease

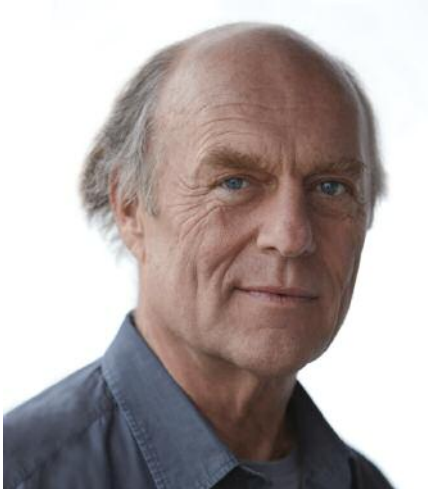
By Regina Weichert

- There's a serious problem with diagnostic testing. Studies show that 44 out of 100 Lyme tests give false negative results. The physicians who initially diagnosed me certainly were not aware of this data.
- If patients have odd symptoms for which no cause can be found, suspect that it may be a tick-borne illness. There are 100 symptoms of Lyme, and it can affect every system and organ in the body. Physicians need to become more familiar with those 100 symptoms.
- I would encourage physicians to listen to and believe their patients. Understand that if you are dealing with a patient with Lyme, they are most likely experiencing real trauma from the illness itself, which is an internal "invader," coupled with a lack of understanding from the medical profession, their families, friends and society at large. Also, be extra kind to people with Lyme — they need your compassion because the illness is so demoralizing.
- Pay attention to detoxification pathways. Your patients will be constantly experiencing die-off, and it's good to know if their ability to detoxify is normal or impaired. Recommend as much detox support as possible, both supplementation and physical methods (colonics, saunas, baths, etc.).
- Understand that the recovery process can be both lengthy and nonlinear. But if you don't give up on your patients, and they don't give up their protocol, recovery is possible.
- I encourage the medical community to advocate for updated diagnostic guidelines, better medical education about Lyme, more government funding of research for a test and a cure, and insurance coverage of long-term Lyme.

Lyme Disease: A Physician's Perspective

Lyme disease is the most common vector-borne disease in the U.S. — by some estimates, it is now more prevalent than AIDS.

BY TRUDIE MITSCHANG



Dr. Dietrich Klinghardt, whose practice treats mostly late-stage Lyme patients after treatment has failed under the care of other healthcare practitioners, uses a systemic and local approach to treatment.

LYME DISEASE is often called the "great imitator"; it can be difficult to diagnose and even more challenging to treat. We spoke with Dietrich Klinghardt, MD, PhD, medical director of the Klinghardt Academy, founder of the American Academy of Neural Therapy and lead clinician at the Sophia Health Institute in Woodinville, Wash. Internationally known for his successful treatment of chronic pain and illness, Dr. Klinghardt combines nonsurgical orthopedic medicine with immunology, endocrinology, toxicology, neural therapy and energy psychology. His unique approach has led to particular success with Lyme disease.

BSTQ: In your opinion, why is Lyme disease so difficult to diagnose?

Dr. Klinghardt: The biggest problem is we do not have an appropriate lab test, just a number of tests with a significant level of false negatives. After more than 100 years of tuberculosis, we still do not have a practical in-office way to diagnose tuberculosis with an appropriate lab test either, even though the illness is on the rise again. We have an insufficient skin test and the X-ray, which shows the illness when it is too late. With that in mind, there is nothing unusual about not having an appropriate microbiological test for Lyme. We are hoping the new culture test will be a success.

BSTQ: What are the main obstacles facing Lyme disease patients?

Dr. Klinghardt: In many cases, it's a complex chronic illness affecting many body subsystems (hormones, joints, brain and CNS, gut, immune system). To clear the Lyme biotoxins (similar to botulism), our detox pathways have to be genetically sound and not overloaded with other toxins such as insecticides, lead, etc.

BSTQ: What are some common myths about Lyme disease?

Dr. Klinghardt: First, that it can be treated by giving two capsules of doxycycline in the evening and you will be cured in the morning (published a few years ago on the front page of most major U.S. newspapers). Second, that it does not exist (published and discussed online on Medscape). And, third, that it's a psychological problem (it is not).

BSTQ: How does your treatment approach differ from conventional treatment?

Dr. Klinghardt: My preferred approach is both systemic and local: ozone injections to affected joints, restoration of gut microflora, systemic antimicrobial treatment and restoring immune competence. I use a combination of antimicrobial herbs in liposomal form and apheresis (blood filtration for immune complexes). For a few months, I prescribe a fat-free diet (microbes embedded in biofilm depend on fatty acids for nutrition). And, I include removal techniques for biotoxins and man-made toxins. After each biological intervention, we look at mobilized psychological issues and deal with them as well. I do use antibiotics if I run out of other options.

BSTQ: What is your success rate?

Dr. Klinghardt: The average patient in my office has seen and failed with 23 other healthcare practitioners, so I am mostly dealing with late-stage Lyme patients who have been therapy-resistant. We get most patients better, back into their life and a significant number well.

BSTQ: Can Lyme disease be cured?

Dr. Klinghardt: There is a difference between having the presence of the microbes and having the illness. The illness can be cured. I do not believe that in most cases we can establish a sterile tissue and blood environment. That is consistent with the current collective experience. The goal is to get the immune system of the patient back in the driver's seat, not to sterilize the body.

BSTQ: What do you see in the pipeline in terms of treatment breakthroughs for this disease?

Dr. Klinghardt: Apheresis — filtering the blood for immune complexes, microbes and toxins as an adjunctive treatment. Currently it is only fully available in Germany. ❖

TRUDIE MITSCHANG *is a staff writer for* BioSupply Trends Quarterly.

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Inspirational Leadership

"A leader's first responsibility is to set the vision and inspire the team to carry it out."

— Ronald J. Sokol, MD, Professor and Vice Chair of Pediatrics, University of Colorado School of Medicine

BY TRUDIE MITSCHANG

BILIARY ATRESIA IS a rare, incurable and potentially fatal disease causing blockage of the bile ducts and affecting only infants. Even with surgical intervention to reroute the intestine to drain bile from the liver, 80 percent of all children diagnosed with biliary atresia require a liver transplant before they reach adulthood. These dire statistics are not lost on Dr. Ronald J. Sokol, professor and vice chair of pediatrics at the University of Colorado School of Medicine and Children's Hospital Colorado, whose life work revolves around the research and treatment of childhood liver diseases and other pediatric disorders.

Sokol is a man who wears many hats, but embraces his multiple callings with confidence. Among his numerous endeavors, he serves as director and principal investigator of the Colorado Clinical and Translational Sciences Institute at University of Colorado Denver, funded by the National Institutes of Health. He is also the chair of the Steering Committee of the NIH-supported Childhood Liver Disease Research and Education Network (ChiLDREN), a collaborative team of doctors, nurses, scientists and research coordinators at 16 medical facilities and patient support organizations focused on improving the lives of children and families dealing with rare liver diseases. ChiLDREN also receives funding from the Cystic Fibrosis Foundation, the Alpha One Foundation and the Alagille Syndrome Alliance. A review of his career accomplishments shows Sokol has much to be proud of, but what fuels his passion these days is his role as the lead investigator for a NIH-funded study on biliary atresia using intravenous immune globulin (IVIG). "Over the last five years, a focus has been the potential impact of anti-inflammatory therapy in biliary atresia patients," says Sokol. "IVIG has been used to successfully treat a number of other autoimmune diseases, and it is proposed that it may have similar positive anti-inflammatory effects when used post-surgery in biliary atresia patients. This study has the potential to break new ground in terms of the long-term prognosis of these patients and might delay or even eliminate the need for a future liver transplant."

Sokol has a history of leading research teams to identify scientific breakthroughs.

Dr. Ronald Sokol's life work revolves around the research and treatment of childhood liver diseases and other pediatric disorders.

Sokol says ChiLDREN just completed a clinical trial that tested another drug's ability to reduce inflammation in post-surgery biliary atresia patients, noting the IVIG trial will be much more targeted. This early phase clinical trial aims to enroll 29 patients over a 12-month to 18-month period. All patients will participate in the testing, with no placebos. The groundwork for the study began

several years ago, and Sokol leads efforts to secure funding, which led to a partnership with FFF Enterprises, in Temecula, Calif. "A colleague had worked with FFF and encouraged us to reach out to them since they are the country's largest distributor of IVIG," says Sokol. "I met Patrick Schmidt, FFF's chief executive officer, earlier this year when he paid a visit to Children's Hospital Colorado in Denver. While here, he had the opportunity to meet a family whose infant was recently diagnosed with biliary atresia. I think the experience was very moving for him, and fueled his decision to provide funding for this important study."

A Team Approach to Leadership

As a physician and researcher, Sokol is known for his commitment to leading by example. He is quick to stress that, by definition, good leadership is only as strong as the team behind it. "A leader's first responsibility is to set the vision and inspire the team to carry it out," he says. "Especially when you face obstacles, you need to empower people so that they feel excited and rewarded for their efforts. I currently hold several leadership roles, and I try to always be mindful of those principles."

Sokol adds that he draws his motivation first and foremost from his role model. Dr. Arnold Silverman was one of the first pediatric gastroenterologists in the nation, and Sokol says it was Dr. Silverman's style of practicing medicine that inspired him toward professional excellence. Still, with so many balls in the air, Sokol says finding a balance and managing work flow can be a challenge. "I received good advice from a former chair of mine," says Sokol. "He said the method he uses to get everything done is simply tackling one thing at a time. Of course, in these days of multitasking that may not be as easy as it sounds, but it's a philosophy that still helps me when things get hectic."

Working in any pediatric specialty puts you in touch with families at a very vulnerable time in their lives. The nature of Sokol's work, especially in the IVIG study, puts him in direct contact with the youngest and most vulnerable of patients: infants. "Although biliary atresia is rare, my heart goes out to the children and families suffering with this awful disease — I could not imagine what it is like to have a newborn diagnosed with it," he says. "The families inspire me every day to use my resources and abilities to try and improve the outcomes for these patients."

Leading Research, Now and in the Future

Sokol has a history of leading research teams to identify scientific breakthroughs. A number of years ago, children with liver disease commonly developed ataxia, a nervous system disorder causing them to lose balance, strength and mobility. Sokol was tasked with finding out the cause of the puzzling condition. At the time, there was some indication that a vitamin E deficiency might be linked, and after completing a study and working with the U.S. Food and Drug Administration, it was determined that treating patients with a novel liquid form of vitamin E could actually reverse the debilitating symptoms. "This was a very gratifying accomplishment," says Sokol. "Vitamin E supplementation with this novel preparation is now the standard treatment in the U.S. for children presenting with cholestatic liver diseases to prevent vitamin E deficiency and ataxia symptoms."

As he looks to the future, Sokol plans to focus his attention on gaining new insights and leading change in the area of treatment protocols for childhood liver diseases.

As he looks to the future, Sokol plans to focus his attention on gaining new insights and leading change in the area of treatment protocols for childhood liver diseases. On a personal note, he is committed to ensuring the ChiLDREN research network that he chairs remains funded, and is also looking forward to providing future investigators with the tools and inspiration needed to blaze new trails within this challenging field. "We actually have a program in our network that is focused on training and supporting the next generation of clinical researchers," explains Sokol. "We want to guarantee that we have a pipeline in place that will foster significant medical breakthroughs for generations of future families." ❖

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Intravenous Immunoglobulin Sharply Reduces Relapse Rate in a Series of Patients with Neuromyelitis Optica

With the objective of evaluating the safety and tolerability of intravenous immune globulin (IVIG) as a treatment for neuromyelitis optica (NMO), a team of Spanish investigators administered IVIG (0.7 g/kg body weight for three days) every two months to eight patients meeting Wingerchuk's revised diagnostic criteria for the disorder. Five patients had relapsing optic neuritis with or without myelitis, and three had recurrent longitudinally extensive transverse myelitis. The mean age of onset was 20.5 years (range 7 years to 31 years).

Following 83 total infusions (range 4 to 21 per patient) and a mean follow-up time of 19.3 months (range 6 to 39 months), only a few minor adverse events had occurred: headache in three patients and a mild cutaneous eruption in a single patient. The relapse rate decreased from a mean of 1.8 attacks in the previous year to 0.006 attacks during follow-up ($P = 0.01$). The Expanded Disability Status Scale (EDSS) score fell from 3.3 ± 1.3 to 2.5 ± 1.5 ($P = 0.04$).

The investigators concluded that treatment with IVIG is safe and well-tolerated, and it may be used as a treatment alternative for NMO spectrum disorders.

Magraner MJ, Coret F, Casanova B. The effect of intravenous immunoglobulin on neuromyelitis optica. Neurologia *2013Mar;28(2):65-72.*

Use of Hydroxyethyl Starch in Sepsis Patients Increases Risk of Renal Replacement Therapy, Transfusion, Serious Adverse Events

Newer hydroxyethyl starch (HES) products with molecular weight of 130kDa and substitution ratios ranging from 0.38 to 0.45 (130/0.38-0.45) have been claimed to be safer than higher molecular weight (200/0.5-0.6) HES products, which were shown to cause acute kidney injury in two randomized trials in patients with sepsis. Danish investigators conducted a systematic review and meta-analysis of randomized trials to assess the effects of 130/0.38-0.45 HES products versus crystalloid of human albumin on mortality, kidney injury, bleeding and serious adverse events on patients with sepsis.

Nine trials that randomized a total of 3,456 patients with sepsis were included. Six trials studied Voluven 6% HES 130/0.4 in saline (Fresenius Kabi), and the other three trials evaluated other or unspecified 130/0.4-0.42 HES products. Two trials compared HES against 20% albumin, while the remaining trials used crystalloid as a comparator. Overall, HES versus crystalloid or albumin did not affect the relative risk of death (1.04, 95 percent confidence interval, 0.89 to 1.22), but in predefined analysis of four trials with low risk of bias, the relative risk of death was 1.11 (1.00 to 1.23, 0.95 to 1.29). Renal replacement therapy was used more in patients receiving HES (1.36, 1.08 to 1.72). More patients in the HES groups were transfused with red blood cells (1.29, 1.13 to 1.48) and had serious adverse events (1.30, 1.02 to 1.67).

The investigators concluded that use of HES 130/0.38-0.45 increased the requirement for renal replacement therapy and transfusion with red blood cells, and resulted in more serious adverse events in patients with sepsis.

Haase N, Perner A, Hennings L, et al. Subcutaneous Hydroxyethyl starch 130/0.38-0.45 versus crystalloid or albumin in patients with sepsis: systematic review with meta-analysis and trial sequential analysis. BMJ *2013 Feb 15;346:f839.*

IVIG and Rituximab Desensitization for Renal Transplantation Is Cost-Effective and May Improve Survival

A desensitization protocol using intravenous immune globulin (IVIG) and rituximab has been used for a number of years to allow renal transplantation in highly sensitized (HS) patients, defined as having panel reactive antibody (PRA) >80 percent. A series of 207 HS patients who were desensitized using IVIG and rituximab between July 2006 and December 2011 were compared with age, end-stage renal disease etiology and PRA-matched patients remaining on dialysis only during the study period. Costs and outcomes of desensitization were compared with dialysis.

Of the 207 treated patients, 146 proceeded to transplant. At 48 months, patient and graft survival by Kaplan-Meier were 95 percent and 87.5 percent, respectively. The total three-year cost for patients treated with the desensitization protocol was $219,914 per patient, compared with $238,667 per patient treated with dialysis. Overall, estimated patient survival at the end of three years was 96.6 percent for patients in the desensitization arm of the model, compared with 79.0 percent for the matched group of patients remaining on dialysis during the study period.

The investigators concluded that desensitization with IVIG and rituximab yields financial savings and an estimated 17.6 percent greater probability of three-year survival versus dialysis alone. These benefits of desensitization, however, are limited by organ availability and allocation policies.

Vo AA, Petrozzino J, Yeung K, et al. Efficacy, outcomes, and cost-effectiveness of desensitization using IVIG and rituximab. Transplantation *2013 Mar 27;95(6):852-8.*

BioResources

Recently released resources for the biopharmaceuticals marketplace.

Countering the Problem of Falsified and Substandard Drugs

Author: Institute of Medicine of the National Academies

At the request of the U.S. Food and Drug Administration, the Institute of Medicine convened a committee charged with assessing the global public health implications of falsified, substandard and counterfeit pharmaceuticals to help jump-start international discourse about this problem. In the committee's report, *Countering the Problem of Falsified and Substandard Drugs*, the committee narrowly defines the term "counterfeit" to mean a drug that infringes on a registered trademark and centers its attention on substandard and falsified drugs, problems of public health consequence. The report lays out a plan to invest in quality to improve public health.

www.iom.edu/Reports/2013/Countering-the-Problem-of-Falsified-and-Substandard-Drugs.aspx

Dietary Supplement Inspections: A Comprehensive Guide to FDA Focus Areas and Expectations

Author: U.S. Food and Drug Administration

Dietary Supplement Inspections spells out how to cope with this new era of enforcement, with tips and how-to strategies to prepare for inspections and avoid GMP violations cited in 483s and warning letters. It provides an overview of essential references to cope with tough new levels of FDA scrutiny, plus specifics including how to avoid the most common GMP violations cited in 483s and warning letters; how to prepare for inspections; inspection hot spots — areas the FDA is likely to scrutinize most closely; how FDA inspections will change in coming years; and more. The guide originated as an FDANews webinar featuring Dean Cirotta, vice president of EAS Consulting Group, and William Ment, senior consultant to EAS Consulting Group.

www.fdanews.com/store/product/detail?productId=42629&hittrk=13319&utm_source=MagnetMail&utm_medium=email&utm_term=rrhodes@igliving.com&utm_content=BDIET - 13319 - 3/19/13 - DD/DR-NO/MBDR/MDR&utm_campaign=Supplement Makers%3A

Online Health Career Center for Physicians

eHealthCareers.com is a new online job search platform for physicians. New jobs are posted each day from more than 400 industry-leading medical journals. Physicians can enter their resumés, sign up for job alerts and browse jobs by specialty. Also included are articles and videos about the healthcare workplace.

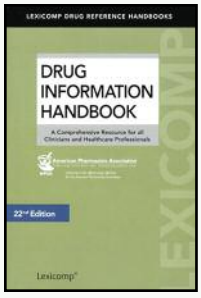
www.ehealthcareers.com

Handbook of Nonprescription Drugs, 17th Edition

Author: Daniel L. Krinsky, et al.

Thoroughly updated and revised, this handbook provides accessible information on nonprescription drug pharmacotherapy, nutritional supplements, medical foods, nondrug and preventive measures, and complementary and alternative therapies. The 17th edition helps practitioners develop or improve problem-solving and critical-thinking skills needed to assess and triage a pharmacy patient's medical complaints. It includes 52 peer-reviewed chapters providing updated content on over-the-counter (OTC) medications and complementary therapies, prescription to OTC conversions, FDA revised or final rules, FDA safety and label warnings, therapeutic issues and controversies, treatment or prevention guidelines, OTC drug withdrawals from the market, updated product tables with examples of specific nonprescription products, and references. Disease-oriented chapters contain new and revised case studies, treatment algorithms that outline triage and treatment, comparisons of self-treatment options, patient education boxes, product selection guidelines, and dosage and administration guidelines. A new chapter, "Self-Care Components of Selected Chronic Diseases," addresses the self-care needs of patients with asthma, diabetes mellitus, hypertension, heart failure, dyslipidemia and osteopenia/osteoporosis. Each chapter features a key points section at the end that summarizes critical information.

portal.pharmacist.com/Source/Orders/index.cfm?section=Shop_APhA&task=3&CATEGORY=OTC&PRODUCT_TYPE=SALES&SKU=9781582121604



Drug Information Handbook 22nd Edition

Author: American Pharmacists Association

The handbook follows a user-friendly, dictionary-like format, providing clinicians with fast access to clear, concise Lexicomp drug information. It covers more than 5,500 medications and features 41 new monographs and hundreds of updates to existing content. Each monograph encompasses up to 39 fields of information, including detailed content on dosage, drug interactions and adverse reactions. Supplementing the drug information is a comprehensive appendix offering charts, tables, treatment guidelines and therapy recommendations, and a Pharmacologic Category Index listing all drugs within their unique pharmacologic class.

webstore.lexi.com/Drug-Information-Handbook

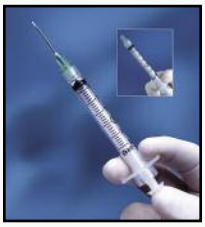
BioProducts

New products in the marketplace.

Bioneedles

Bioneedles are biodegradable, hollow, implantable needles that are filled with vaccine and dissolve in the body within minutes — delivering necessary inoculation and requiring no cleanup or disposal of needles. Using a material that is quickly biodegradable, capable of holding any type of vaccine and able to withstand high-speed injection, the Bioneedle creators have addressed the major problems of needle-based injections: the transportation of needles, syringes and vaccine around the world that presents a serious logistics problem; the deterioration of vaccines over time; the requirement for them to be stored in temperature-controlled locations; and the dangerous problem of needlesticks and improper waste disposal, which can easily transmit disease. The Bioneedle is inserted into a patient using an ultra portable hand-held applicator. Once beneath the skin, the needle dissolves and releases a vaccine. There is no waste product, and a medical professional is not required to deliver injection or dispose of the used needle. Though the Bioneedle is still in early stages of development, the idea won the 2012 Katerva Award for its "pinnacle of recognition for global sustainability excellence."

Gijsbert van de Wijdeven, www.launch.org/innovators/gijsbert-van-de-wijdeven



BD Integra Retracting Syringes

BD Integra's retracting syringes allow for single-handed activation. The needle is housed inside the syringe after activation, eliminating the potential for needlestick injury. It features a detachable needle, BD PrecisionGlide needle technology and a lightweight spring that reduces the needle retraction speed. Benefits include low waste space and dosing accuracy.

BD Integra, (201) 847-6800,
www.bd.com/hypodermic/products/integra

New Flu Vaccines

The newly FDA-approved Flucelvax by Novartis is manufactured to protect patients ages 18 years and older from the flu. Its manufacturing process is similar to that used in egg-based manufacturing; however, the virus strains are grown in mammalian cells, its production occurs in a closed, sterile, controlled environment that considerably reduces the risk of potential impurities, and it has no impurities, preservatives such as thimerosal, or antibiotics.

Flublok, manufactured by Protein Sciences Corp., is newly approved by the FDA for individuals 18 years and older and contains the elements necessary to help fend off three flu viruses, including H1N1 and H3N2. It is produced by programming insect cells grown in steel tanks to produce large amounts of a particular flu virus protein, known as hemagglutinin, which allows for more rapid production, making more of the vaccine available more quickly in the event of a pandemic.

For more information about both of these vaccines, see page 35.

Novartis, (877) 683-4732, flucelvax.com
Protein Sciences Corp., www.flublok.com

New Plasma Product Indications

The Fenwal Alyx and Amicus plasma collection systems have received clearance from the U.S. Food and Drug Administration to hold plasma up to 24 hours before freezing. The systems already are cleared to collect fresh frozen plasma, which is frozen within eight hours. The Fenwal Alyx system is a portable cell separation device used to collect two units of red cells, or red cells and plasma from qualified donors. The Amicus separator is an advanced cell separation device with multiple component collection and therapeutic protocols, and is cleared for use with the Fenwal InterSol platelet additive solution, which replaces a portion of the plasma stored with platelets, allowing the plasma to be used for other therapeutic purposes. The new indication will provide blood centers more flexibility to collect plasma on mobile blood drives and to process additional plasma for transfusion.

Fenwal Inc., (800) 333-6925, www.fenwalinc.com

IVIG Reimbursement Calculator

Medicare Reimbursement Rates*
Rates are effective July 1, 2013 through September 30, 2013.

Product	Manufacturer	HCPCS	ASP+6% (per gram)
BIVIGAM	Biotest Pharmaceuticals	**	**
CARIMUNE NF	CSL Behring	J1566	$61.32
FLEBOGAMMA 5% & 10% DIF	Grifols	J1572	$71.89
GAMMAGARD LIQUID	Baxter BioScience	J1569	$78.34
GAMMAGARD S/D (Low IgA)	Baxter BioScience	J1566	$61.32
GAMMAKED	Kedrion	J1561	$77.94
GAMMAPLEX	Bio Products Laboratory	J1557	$73.89
GAMUNEX-C	Grifols	J1561	$77.94
OCTAGAM	Octapharma	J1568	$63.15
PRIVIGEN	CSL Behring	J1459	$73.20

* Hospital outpatient and physician office settings
** Refer to Bivigam Coverage and Reimbursement Guide at www.bivigam.com/clientuploads/pdfs/BivigamReimbursementGuide.pdf

Calculate your reimbursement online at www.FFFenterprises.com.

IVIG/SCIG Reference Table

Product	Indication	Size	Manufacturer
BIVIGAM Liquid, 10%	IVIG: PIDD	5 g, 10 g	Biotest Pharmaceuticals
CARIMUNE NF Lyophilized	IVIG: PIDD, ITP	3 g, 6 g, 12 g	CSL Behring
FLEBOGAMMA 5% & 10% DIF Liquid	IVIG: PIDD	0.5 g, 2.5 g, 5 g, 10 g, 20 g	Grifols
GAMMAGARD LIQUID 10%	IVIG: PIDD, MMN SCIG: PIDD	1 g, 2.5 g, 5 g, 10 g, 20 g, 30 g	Baxter BioScience
GAMMAGARD S/D Lyophilized, 5% (Low IgA)	IVIG: PIDD, ITP, CLL, KD	5 g, 10 g	Baxter BioScience
GAMMAKED Liquid, 10%	IVIG: PIDD, ITP, CIDP SCIG: PIDD	1 g, 2.5 g, 5 g, 10 g, 20 g	Kedrion
GAMMAPLEX Liquid, 5%	IVIG: PIDD	5 g, 10 g	Bio Products Laboratory
GAMUNEX-C Liquid, 10%	IVIG: PIDD, ITP, CIDP SCIG: PIDD	1 g, 2.5 g, 5 g, 10 g, 20 g	Grifols
HIZENTRA Liquid, 20%	SCIG: PIDD	5 mL, 10 mL, 20 mL	CSL Behring
OCTAGAM Liquid, 5%	IVIG: PIDD	1 g, 2.5 g, 5 g, 10 g, 25 g	Octapharma
PRIVIGEN Liquid, 10%	IVIG: PIDD, ITP	5 g, 10 g, 20 g, 40 g	CSL Behring

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

2013-2014 Influenza Vaccine

Administration Codes: G0008 (Medicare plans) 90471 (non-Medicare plans) **Diagnosis Code:** V04.81

Product	Size	When Administered to Indicated Age Group	Code
FLUZONE INTRADERMAL	0.1 mL microinjection	Influenza virus vaccine, split virus, preservative free, for intradermal use	90654
FLUZONE Pediatric	0.25 mL prefilled syringe	Influenza virus vaccine, trivalent, split virus, preservative free, when administered to children 6-35 months of age, for intramuscular use	90655
AFLURIA	0.5 mL prefilled syringe	Influenza virus vaccine, trivalent, split virus, preservative free, when administered to individuals 3 years of age and older, for intramuscular use	90656
FLUARIX	0.5 mL prefilled syringe		
FLUVIRIN	0.5 mL prefilled syringe		
FLUZONE	0.5 mL single-dose vial		
FLUZONE	0.5 mL prefilled syringe		
FLUZONE	5 mL multi-dose vial	Influenza virus vaccine, trivalent, split virus, when administered to children 6-35 months of age, for intramuscular use	90657
FLUCELVAX	0.5 mL prefilled syringe	Influenza virus vaccine, derived from cell cultures, subunit, preservative and antibiotic free, for intramuscular use	90661
FLUZONE HIGH-DOSE	0.5 mL prefilled syringe	Influenza virus vaccine, split virus, preservative free, enhanced immunogenicity via increased antigen content, for intramuscular use	90662
FLUMIST QUADRIVALENT	0.2 mL nasal spray	Influenza virus vaccine, quadrivalent, live, intranasal use, when administered to individuals 2-49 years of age	90672
FLUBLOK	0.5 mL single-dose vial	Influenza virus vaccine, trivalent, derived from recombinant DNA (RIV3), hemagglutnin (HA) protein only, preservative and antibiotic free, for intramuscular use	90673
FLUARIX QUADRIVALENT	0.5 mL prefilled syringe	Influenza virus vaccine, quadrivalent, split virus, preservative free, when administered to individuals 3 years of age and older, for intramuscular use	90686
AFLURIA	5 mL multi-dose vial	Influenza virus vaccine, trivalent, split virus, when administered to individuals 3 years and older, for intramuscular use	Q2035
FLULAVAL			Q2036
FLUVIRIN			Q2037
FLUZONE			Q2038

GAMUNEX®-C

Immune Globulin Injection (Human) 10% Caprylate/Chromatography Purified

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use GAMUNEX®-C safely and effectively. See full prescribing information for GAMUNEX-C.

GAMUNEX-C, [Immune Globulin Injection (Human) 10% Caprylate/Chromatography Purified]

Initial U.S. Approval: 2003

WARNING: ACUTE RENAL DYSFUNCTION and FAILURE

See full prescribing information for complete boxed warning.

- **Renal dysfunction, acute renal failure, osmotic nephrosis, and death may occur with immune globulin intravenous (IGIV) products in predisposed patients.**
- **Renal dysfunction and acute renal failure occur more commonly in patients receiving IGIV products containing sucrose. GAMUNEX-C does not contain sucrose.**
- **For patients at risk of renal dysfunction or failure, administer GAMUNEX-C at the minimum concentration available and the minimum infusion rate practicable.**

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

GAMUNEX-C is an immune globulin injection (human) 10% liquid indicated for treatment of:

- Primary Humoral Immunodeficiency (PI)
- Idiopathic Thrombocytopenic Purpura (ITP)
- Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)

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

- Anaphylactic or severe systemic reactions to human immunoglobulin
- IgA deficient patients with antibodies against IgA and a history of hypersensitivity

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

- IgA deficient patients with antibodies against IgA are at greater risk of developing severe hypersensitivity and anaphylactic reactions. Have epinephrine available immediately to treat any acute severe hypersensitivity reactions.
- Monitor renal function, including blood urea nitrogen, serum creatinine, and urine output in patients at risk of developing acute renal failure.
- GAMUNEX-C is not approved for subcutaneous use in ITP patients. Due to a potential risk of hematoma formation, do not administer GAMUNEX-C subcutaneously in patients with ITP.
- Hyperproteinemia, with resultant changes in serum viscosity and electrolyte imbalances may occur in patients receiving IGIV therapy.
- Thrombotic events have occurred in patients receiving IGIV therapy. Monitor patients with known risk factors for thrombotic events; consider baseline assessment of blood viscosity for those at risk of hyperviscosity.
- Aseptic Meningitis Syndrome (AMS) has been reported with GAMUNEX-C and other IGIV treatments, especially with high doses or rapid infusion.
- Hemolytic anemia can develop subsequent to IGIV therapy due to enhanced RBC sequestration. Monitor patients for hemolysis and hemolytic anemia.
- Monitor patients for pulmonary adverse reactions (transfusion-related acute lung injury [TRALI]).
- Volume overload
- GAMUNEX-C is made from human plasma and may contain infectious agents, e.g., viruses and, theoretically, the Creutzfeldt-Jakob disease agent.
- Passive transfer of antibodies may confound serologic testing.

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

- **PI** – The most common adverse reactions (≥5%) with intravenous use of GAMUNEX-C were headache, cough, injection site reaction, nausea, pharyngitis and urticaria. The most common adverse reactions (≥5%) with subcutaneous use of GAMUNEX-C were infusion site reactions, headache, fatigue, arthralgia and pyrexia.
- **ITP** – The most common adverse reactions during clinical trials (reported in ≥5% of subjects) were headache, vomiting, fever, nausea, back pain and rash.
- **CIDP** – The most common adverse reactions during clinical trials (reported in ≥5% of subjects) were headache, fever, chills, hypertension, rash, nausea and asthenia.

To report SUSPECTED ADVERSE REACTIONS, contact Talecris Biotherapeutics, Inc. at 1-800-520-2807 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

- The passive transfer of antibodies may transiently interfere with the response to live viral vaccines, such as measles, mumps and rubella. Passive transfer of antibodies may confound serologic testing.

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

- Pregnancy: no human or animal data. Use only if clearly needed.
- Geriatric: In patients over 65 years of age do not exceed the recommended dose, and infuse GAMUNEX-C at the minimum infusion rate practicable.

Talecris BIOTHERAPEUTICS

Talecris Biotherapeutics, Inc.
Research Triangle Park, NC 27709 USA
U.S. License No. 1716

08939771/08939782-BS
Revised: October 2010

gamunex®-C
immune globulin injection (human), 10%
caprylate/chromatography purified

Evidence based. Patient proven.

Product Features

FDA approved indications[1]:

- Chronic inflammatory demyelinating polyneuropathy (CIDP)
- Primary immunodeficiency (PI) for both IV and SC administration
- Idiopathic thrombocytopenic purpura (ITP)

Product properties[1]:

- No sugar
- Optimal pH of: (4.0-4.5)
- IgA content: average of 46µg/mL
- Only trace amounts of sodium
- Close to physiologic osmolality: (258 mOsm/kg)

Easy to use[1]:

- Latex-free packaging
- Tamper-evident vials (cap overwrap)
- Vials available in 1, 2.5, 5, 10, and 20 g
- Long 3-year shelf life; room temperature storage*

* Up to 6 months at any time during 36-month shelf life.

Important Safety Information

Gamunex-C, Immune Globulin Injection (Human), 10% Caprylate/Chromatography Purified, is indicated for the treatment of primary humoral immunodeficiency disease (PI), idiopathic thrombocytopenic purpura (ITP), and chronic inflammatory demyelinating polyneuropathy (CIDP).

Renal dysfunction, acute renal failure, osmotic nephrosis, and death may occur with immune globulin intravenous (IGIV) products in predisposed patients. Patients predisposed to renal dysfunction include those with any degree of preexisting 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. Gamunex-C does not contain sucrose. For patients at risk of renal dysfunction or failure, administer Gamunex-C at the minimum concentration available and the minimum infusion rate practicable.

Gamunex-C is contraindicated in individuals with acute severe hypersensitivity reactions to Immune Globulin (Human). It is contraindicated in IgA deficient patients with antibodies against IgA and history of hypersensitivity.

Gamunex-C is not approved for subcutaneous use in patients with ITP or CIDP. **Due to the potential risk of hematoma formation, Gamunex-C should not be administered subcutaneously in patients with ITP.**

Hyperproteinemia, increased serum viscosity, and hyponatremia may occur in patients receiving IGIV therapy.

Thrombotic events have been reported in association with IGIV. Patients at risk for thrombotic events may include those with a history of atherosclerosis, multiple cardiovascular risk factors, advanced age, impaired cardiac output, coagulation disorders, prolonged periods of immobilization and/or known or suspected hyperviscosity.

There have been reports of noncardiogenic pulmonary edema [Transfusion-Related Acute Lung Injury (TRALI)], hemolytic anemia, and aseptic meningitis in patients administered with IGIV. The high dose regimen (1g/kg x 1-2 days) is not recommended for individuals with expanded fluid volumes or where fluid volume may be a concern.

Gamunex-C is made from human plasma. Because this product is made from human plasma, it may carry a risk of transmitting infectious agents, e.g., viruses, and, theoretically, the Creutzfeldt-Jakob disease (CJD) agent.

After infusion of IgG, 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.

In clinical studies, the most common adverse reactions with Gamunex-C were headache, fever, chills, hypertension, rash, nausea, and asthenia (in CIDP); headache, cough, injection site reaction, nausea, pharyngitis, and urticaria with intravenous use (in PI) and infusion site reactions, headache, fatigue, arthralgia and pyrexia with subcutaneous use (in PI); and headache, vomiting, fever, nausea, back pain, and rash (in ITP).

The most serious adverse reactions in clinical studies were pulmonary embolism (PE) in one subject with a history of PE (in CIDP), an exacerbation of autoimmune pure red cell aplasia in one subject (in PI), and myocarditis in one subject that occurred 50 days post-study-drug infusion and was not considered drug related (in ITP).

Please see adjacent page for brief summary of Gamunex-C full prescribing information.

1. GAMUNEX-C package insert. Research Triangle Park, NC: Grifols Therapeutics Inc.; 2010.

For more information: **Grifols, Inc.**
Customer Service: 888 325 8579 Fax: 323 441 7968

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

GRIFOLS

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