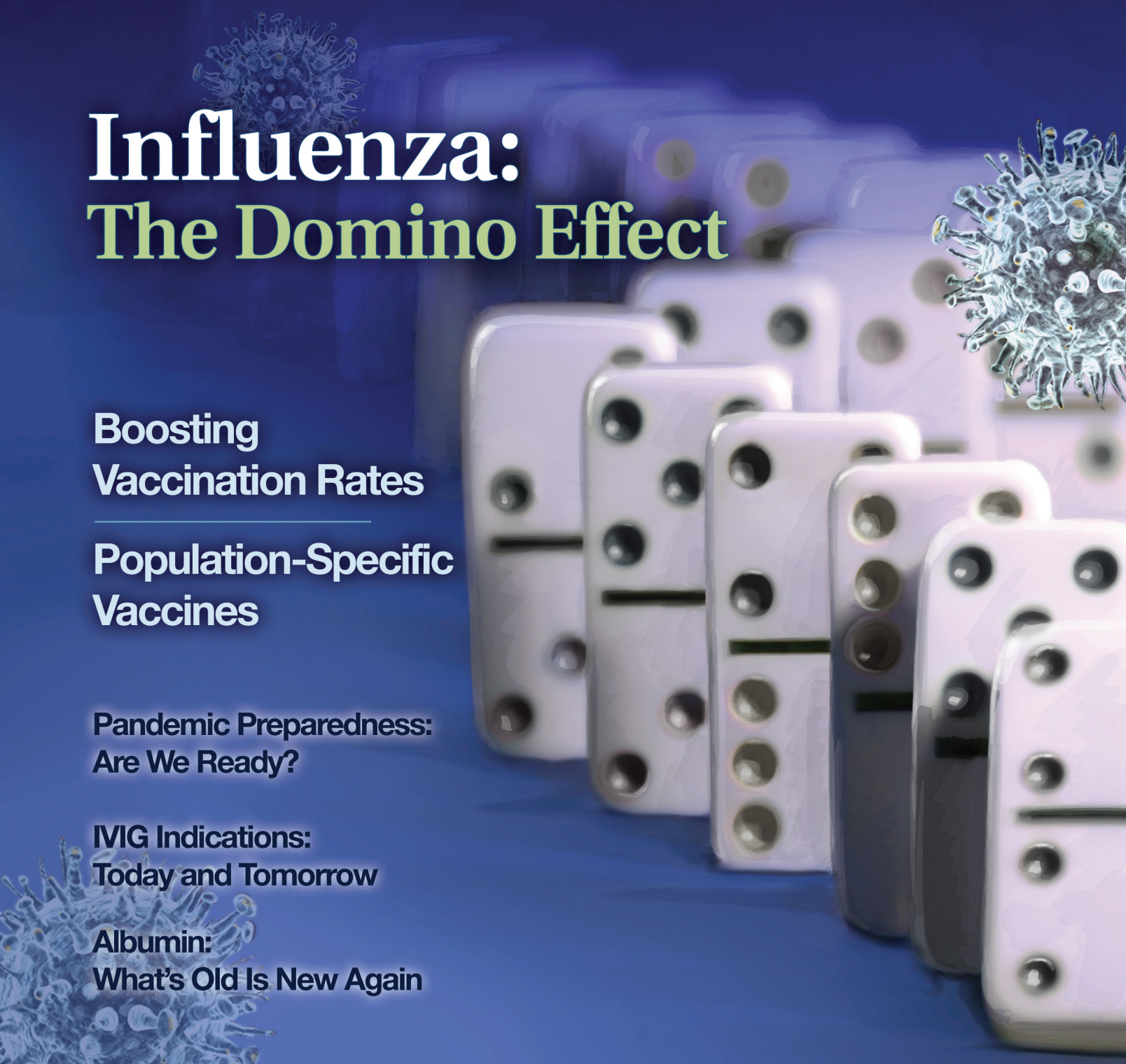
July 2009

BioSupply Trends

Special Focus: VACCINES

Quarterly



Influenza:
The Domino Effect

Boosting Vaccination Rates

Population-Specific Vaccines

Pandemic Preparedness: Are We Ready?

IVIG Indications: Today and Tomorrow

Albumin: What's Old Is New Again

PRODUCT CATALOG INSIDE!

To order FLUVIRIN® for the 2009-10 influenza season through FFF Enterprises, go to: **www.MyFluVaccine.com** or call **800-843-7477**. For any technical questions regarding FLUVIRIN or any of our pipeline products, please contact our Medical Information department at **800-244-7668.**

Your Foremost Partner in Preventing Influenza

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Influenza Virus Vaccine
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Novartis Vaccines

The demand for influenza vaccine is growing. You can be confident when you partner with a global industry leader.

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> Investment in a global manufacturing network to ensure reliable supply

A 10+ year commitment to developing and distributing vaccines worldwide

FLUVIRIN® subunit influenza vaccine is a leading product in the US and is licensed for sale in 8 countries:

> Approximately 300 million doses of FLUVIRIN manufactured to date
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The world's second-largest manufacturer of influenza vaccine

> More than $1 billion in production investments including a new site in the US scheduled to be operational in 2011
> Recipient of a $486 million grant for flu cell culture production from US HHS

Leader in supporting US government public health preparations

> Awarded the largest US government contract to supply H1N1 antigen and adjuvant

A robust, wide-ranging influenza vaccine pipeline

> AGRIFLU™ thimerosal-free (prefilled syringe) vaccine for 18+ year-olds submitted in the US
> Other next-generation seasonal and pandemic vaccines currently in Phase II/Phase III trials

A trailblazer in research and innovation

> First company to improve flu vaccine efficacy with an adjuvant
> First company to produce a cell culture–based influenza vaccine

Nationally recognized for award-winning marketing initiatives

> CDC-recognized programs aimed at educating children, parents, and teachers on the importance of flu vaccination
> A variety of educational programs in doctor's offices, retail pharmacies, and corporations

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Important Safety Information

Serious allergic reactions, including anaphylactic shock, have been observed in people receiving FLUVIRIN® Influenza Virus Vaccine. FLUVIRIN vaccine should not be administered to individuals with a history of systemic hypersensitivity reaction to eggs or egg proteins or other components of FLUVIRIN vaccine, including thimerosal, or to anyone who has had a life-threatening reaction to previous influenza vaccination. In clinical trials, the most common adverse events in adults were headache, fatigue, injection site reactions (pain, mass, redness, and induration), and malaise. These adverse events were generally mild/moderate and transient. Vaccination with FLUVIRIN vaccine may not protect all individuals who are susceptible to influenza. Immunocompromised persons, including individuals receiving immunosuppressive therapy, may have a reduced immune response to FLUVIRIN vaccine. If Guillain-Barré syndrome has occurred within 6 weeks of receipt of prior influenza vaccine, the decision to use FLUVIRIN vaccine should be based on careful consideration of the potential benefits and risks. All people, including those who are pregnant, nursing, and/or taking other medications, should consult their healthcare providers before receiving FLUVIRIN vaccine.

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Cambridge, Massachusetts 02139 USA. NVDFLU119— JUN09

NOVARTIS VACCINES

BioSupply Trends Quarterly

July 2009

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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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BioSupply Trends Quarterly has a circulation of 50,000, with an approximate readership of more than 150,000 decision-makers who are comprised of general practice physicians, hospital and clinic chiefs of staff and buyers, pharmacy managers and buyers, specialist physicians and other healthcare professionals.

For information about advertising in *BioSupply Trends Quarterly*, you may request a media kit from our Advertising Specialist: Trudie Mitschang, (800) 843-7477 x1340, tmitschang@fffenterprises.com.

Publisher's Corner

IT IS WITH great pride that I watch this first issue of *BioSupply Trends Quarterly* go to print. I often have to remind myself that in addition to our biopharmaceutical distribution company and specialty pharmacy, we are also publishers. Our first magazine, *IG Living*, which was created as a comprehensive resource for immune globulin patients and their healthcare providers, just celebrated its third anniversary in March of this year.

This newest publishing endeavor, *BioSupply Trends Quarterly*, comes in response to the positive feedback from our customers who have come to rely on our BioSupply Trends bi-weekly e-newsletter. We envision this magazine to be an expanded resource for up-to-date news, trends, perspectives and leading indicators. It is our hope that you will find valuable and timely information, insights and resources in each of our themed issues.

As this first issue goes to print, the media are rife with news of a new influenza strain circulating the globe, and pandemic preparedness is once again at the forefront of people's minds. That our inaugural issue's theme is "vaccines" is purely a coincidence, decided long before the first H1N1 (swine) flu newscast. Yet, there is little in the biopharmaceutical world more topical at the moment than vaccines. And if there are hidden blessings to be found in the current scenario, one may be the light this scare is shining on the importance of vaccination in preventing debilitating and sometimes deadly disease.

The questions are still numerous, and answers are slow, yet steady. Will this new H1N1 strain mutate to become more virulent and deadly as has happened in past pandemics? When manufacturers produce a new vaccine, will it be effective if the virus does mutate? Will the new virus be more dangerous than the seasonal flu that already claims 30,000 to 40,000 lives each year in the U.S. alone and more than half a million worldwide? Who will get the new vaccine? And, how should healthcare providers prepare for seasonal influenza vaccination with the new H1N1 vaccine in the pipeline? Our H1N1 update addresses these and other questions, and includes the most up-to-date information as this issue goes to print. Specifically, our cover feature, Influenza: The Domino Effect, delivers a new slant on who should get vaccinated, with an up-close look at "herd protection," the concept of vaccinating the strongest to protect the weak.

Our articles about increasing vaccination rates and the recommendations and requirements for population-specific vaccines take a broader look at getting people vaccinated in today's fragmented environment. And, yet another article focuses on this newest H1N1 pandemic. Are we ready?

Beyond vaccines, it's exciting to read that a potentially transformative new product on the cutting edge of clinical research is not really new: It's human albumin, and it may reduce the toll of both stroke and sepsis. There is also promising research about new indications for immune globulin that, while potentially transformational, could create new supply challenges in the already tight plasma market. Our BioResearch and BioResources sections will provide you with timely journal research updates, as well as links to governmental and disease-state websites. And, our BioDashboard presents at-a-glance information concerning product availability and reimbursement rates.

It is our sincere hope that *BioSupply Trends Quarterly* becomes a publication you look forward to receiving, and that you find informative and useful. We welcome your feedback, comments and suggestions. Please write to us at: editor@BSTQuarterly.com. ❖

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

Creative Director
Sheryl Perez

Artistic Director
Allan Bean

Graphic Artists
Allan Bean
Ben Drolet

Advertising Specialist
Trudie Mitschang

Contributing Writers
Chris Ground
Trudie Mitschang
Amy Scanlin, MS
Jim Trageser
Michelle Vogel, MPA

Proofreader
Jackie Logue

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

Comparative Effectiveness Research Council Appointed

A NEWLY CREATED, 15-member council has been appointed by the U.S. Department of Health and Human Services (HHS) to coordinate comparative effectiveness and related health services research. This research provides information on the relative strengths and weaknesses of various medical interventions, and will give clinicians and patients valid information to make decisions that will improve the performance of the U.S. healthcare system.

Authorized by the American Recovery and Reinvestment Act of 2009, the Federal Coordinating Council on Comparative Effectiveness Research will assist the agencies of the federal government, including HHS and the departments of Veterans Affairs and Defense, as well as others, in these efforts. Funds appropriated by the Recovery Act include $300 million for the Agency for Healthcare Research and Quality, $400 million for the National Institutes of Health and $400 million for allocation at the discretion of the Secretary of Health and Human Services to support comparative effectiveness research. The council will provide input on priorities for the latter $400 million fund appropriation, and public input will help to shape the council's recommendations. The council will not recommend clinical guidelines for payment, coverage or treatment.

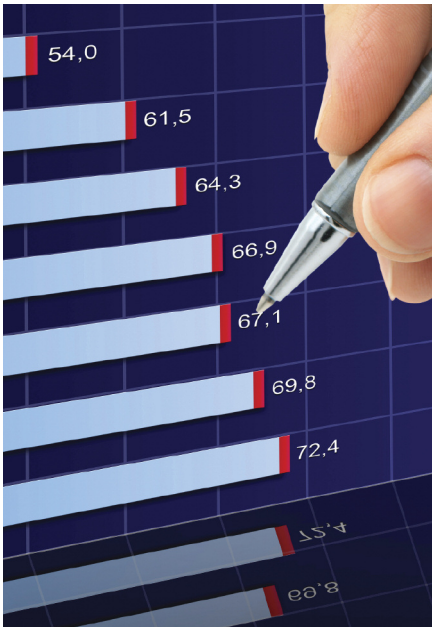
Although the Obama administration stressed that this new council will help improve healthcare at a public meeting on April 14, it has raised controversy among patient communities and providers, especially in the rare disease populations. Many are calling comparative effectiveness, "cost effectiveness" — or a tool for the government to ration care. At the HHS Advisory Committee on Blood Safety and Availability meeting held April 30, 2009, several groups raised their concerns. The hemophilia community strongly opposed "cost effectiveness research." The Alliance for Plasma Therapies, on the other hand, took a different viewpoint, since the organization represents patients who rely on intravenous immune globulin (IVIG) for treatment, and the majority of IVIG use is considered off-label for those patients. Since IVIG is effectively used to treat so many different rare diseases in the autoimmune and neurological communities, with evidence that supports the use, the Alliance considers comparative effectiveness research a tool that could, if used properly, help patients obtain and maintain insurance coverage for IVIG. ❖

IVIG Access Act of 2009 Introduced

On April 22, 2009, 18 patient advocacy and healthcare professional groups joined with Reps. Steve Israel (D-N.Y.), Kevin Brady (R-Texas) and Allyson Schwartz (D-Pa.) to introduce H.R. 2002, the IVIG Medicare Patient Access Act of 2009. This act is designed to restore access to intravenous immune globulin (IVIG) for all patients in all sites of care. More specifically, the legislation grants the Secretary of Health and Human Services authority to update the payment for IVIG based on new or existing data; reviews current physician infusion complexity codes for IVIG; makes whole the current Part B home infusion benefit for patients with a primary immunodeficiency diagnosis, allowing coverage for related items and services; and requires MedPAC to review IVIG payment and provide recommendations within a two-year period for any additional payment changes to improve access to IVIG.

The legislation is similar to the legislation (S. 701) introduced in March by Senators Kerry (D-Mass.) and Alexander (R-Tenn.). The patient organizations and professional societies endorsing both bills include the Alliance for Plasma Therapies; American Academy of Asthma, Allergy and Immunology; American Autoimmune Related Diseases Association; American Partnership for Eosinophilic Disorders; A-T Children's Project; Clinical Immunology Society; Foundation for Peripheral Neuropathy; GBS/CIDP Foundation International; Immune Deficiency Foundation; Infusion Nurses Society; International Pemphigus and Pemphigoid Foundation; Jeffrey Modell Foundation; The Myositis Association; National Patient Advocate Foundation; The Neuropathy Association; Neuropathy Action Foundation; Patient Services Inc.; and Platelet Disorder Support Association. ❖

Biovigilance Network Begins Data Collection



The U.S. Biovigilance Network, established in the fall of 2008, will, for the first time on a nationwide basis, collect and analyze data to identify trends and recommend best practices to reduce adverse reactions and incidents associated with blood transfusion and related biological therapies. Ultimately, the analyses of this data will enhance patient safety; protect donor health; make better use of blood, tissue, organs and cellular products; and reduce healthcare costs.

Major anticipated outcomes of the network include improving patient outcomes and donor health; reducing risk for hospitals, collection centers and others participating in transfusion and transplantation; reducing costs of transfusion and transplantation by eliminating errors and waste where possible; improving the policies, processes and procedures for transfusing blood and transplanting tissue, organs and cellular products; identifying threats that adversely affect patients and donors and designing interventions to mitigate them; improving quality for participating facilities through benchmarking; and developing evidence-based responses to support community efforts addressing public health concerns of the federal government.

The U.S. Biovigilance Network is a public/private collaboration with shared responsibilities for program development, management, operation and funding. The federal government, through the Department of Health and Human Services, including the Centers for Disease Control and Prevention, has committed more than $1 million toward startup costs, and has provided the platform for initial surveillance efforts through its National Healthcare Safety Network. The network has secured an additional $1.3 million in private contributions to fund the initial expenses, and is seeking an additional $1.7 million to complete development and implement the program. ❖

MICHELLE VOGEL, *MPA, is executive director for the Alliance for Plasma Therapies, Washington, D.C. She can be reached at (888) 331-2196 or mvogel@plasmaalliance.org.*

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IMPORTANT SAFETY INFORMATION

Anaphylaxis, encephalitis including death, meningitis, neuroparalytic events such as encephalitis, transient paralysis, Guillain-Barré Syndrome, myelitis, and retrobulbar neuritis; and multiple sclerosis have been reported to be temporally associated with the use of RabAvert.

The most commonly occurring adverse reactions are injection site reactions, such as injection site erythema, induration and pain; flu-like symptoms; arthralgia; dizziness; lymphadenopathy; nausea; and rash.

History of anaphylaxis to the vaccine or any of the vaccine components constitutes a contraindication to preexposure vaccination with this vaccine. In the case of postexposure prophylaxis, if an alternative product is not available, vaccination should proceed with caution and close observation. A patient's risk of acquiring rabies must be carefully considered before discontinuing vaccination.

NOVARTIS VACCINES

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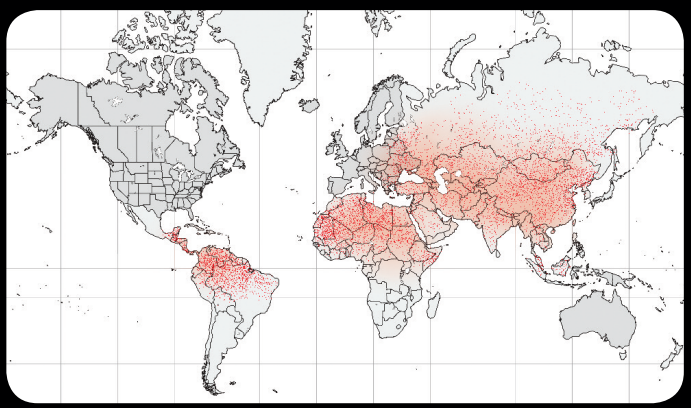
THE CDC RECOMMENDS PREEXPOSURE VACCINATION FOR:

- Persons whose activities bring them into frequent contact with rabies virus or potentially rabid animals, such as:
  - Veterinarians and their staff
  - Animal handlers
  - Rabies researchers
  - Certain laboratory workers
- Some international travelers if they are likely to come into contact with animals in areas where dog or other animal rabies is enzootic, and immediate access to appropriate medical care, including rabies vaccine and immune globulin, could be limited[1]

Geographic distribution of rabies hazards[2]:



North Africa	widespread
Central, East, & West Africa	widespread, epidemic level
Tropical South America	widespread, epidemic level
East Asia	widespread
Southeast Asia	widespread
South Asia	widespread, epidemic level
Middle East	widespread
Eastern Europe & Northern Asia	widespread

Epidemic: The occurrence of more cases of disease than expected in a given area or among a specific group of people over a particular period of time.

TO PLACE AN ORDER FOR EITHER PRE- OR POSTEXPOSURE PROPHYLAXIS, PLEASE CONTACT:

FFF Enterprises: **800-843-7477**

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References

1. Centers for Disease Control and Prevention Web site. Rabies vaccine supply situation. http://www.cdc.gov/RABIES/news/RabVaxupdate.html. Accessed April 21, 2009.
2. Centers for Disease Control and Prevention Web site. Travelers' Health - Yellow Book. http://wwwn.cdc.gov/travel/yellowBookCh3-IntroGoalsLimitations.aspx#14. Accessed April 21, 2009.

Manufactured by: Novartis Vaccines and Diagnostics GmbH & Co KG, Marburg, Germany.

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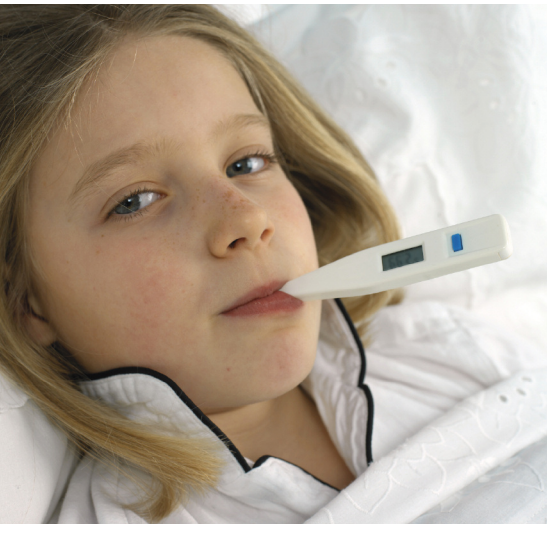
Government

CDC Recommends Child Flu Vaccine

While the CDC updated its recommendations for vaccinating children against the flu at the end of 2008, this coming flu season marks the CDC's deadline. According to the new recommendations, children ages 6 months to 18 years should be vaccinated annually with the influenza immunization no later than the 2009-2010 flu season.



Healthcare organizations' customers should be provided with the following guidelines: Children under the age of 9 and receiving the flu vaccine for the first time should be given two doses scheduled at least four weeks apart. Healthy children ages 2 and older should receive a nasal-spray vaccine. The exception to this is children under 5 years old who have recurrent wheezing and chronic health problems, who should receive the flu injection. While the flu vaccine has not been approved for children under 6 months of age, this population does have the highest rate of hospitalization due to the flu, so it is especially important that household members and caregivers are vaccinated.

According to the CDC, the flu vaccine is not contraindicated for children with mild illnesses with or without fever, mild upper-respiratory infection symptoms or allergic rhinitis. However, children and adults who are seriously ill with a fever should wait until they recover before being vaccinated. ❖

Supplier

CSL and Talecris Terminate Merger

Due to pressure from U.S. antitrust regulators, Australian-based CSL Ltd. and U.S. rival Talecris Biotherapeutics Holdings Corp. have terminated their $3.1 billion merger agreement.

The deal was made last August in an effort by CSL, which also makes vaccines, to boost its presence in the biotherapeutics industry. However, the U.S. Federal Trade Commission (FTC) challenged the acquisition, saying it would substantially reduce competition in U.S. markets for four plasma-derivative protein therapies. In response, CSL offered to sell approximately 25 collection centers accounting for 5 percent of U.S. volume, as well as two branded plasma products that treat hemolytic disease in newborns and patients with emphysema.

CSL's chief executive Dr. Brian McNamee cited the costs and distractions of a battle with the FTC as the reason to terminate the merger agreement. "We are disappointed that the U.S. Federal Trade Commission resolved to block the transaction," said McNamee. "As we have previously stated, we fundamentally disagree with the FTC case." CSL will pay Talecris a $75 million breakup fee, however the plasma supply contract signed in connection with the merger agreement remains in effect. ❖

Supplier

Octapharma Launches Research Grants

In celebration of the company's 25th anniversary, Octapharma AG has launched the first-ever grants program available to researchers based in the U.S. The program will support clinical or pre-clinical research focusing on human protein therapies in coagulation disorders, immunology, intensive care and emergency medicine.

"Octapharma is committed to supporting clinical and pre-clinical research projects that promote excellence in patient care and provide valuable information to the medical and patient community that may translate to better management of disease and improvement in patient safety," said Octapharma USA President Flemming Nielsen. "We have seen that there are tremendous unmet medical needs throughout the U.S., and we hope the grants program will advance Octapharma's primary objective — helping patients enjoy the best possible quality of life."

Grant applications will be accepted online only at www.octapharmagrants.com, and all grant requests will be evaluated every six months (in April and October) by the Octapharma 25th Anniversary Grants Committee. ❖

Did You Know?

From coffee shops to conference rooms, pandemic preparedness is a hot topic. Our thought-provoking article, Pandemic Preparedness: Are We Ready?, provides an up-to-the-minute look at the H1N1 pandemic. See pages 22-25!

Supplier

Blood Clotting Drug Approved by FDA

RiaSTAP, the first and only treatment of acute bleeding episodes in patients with congenital fibrinogen deficiency, including afibrinogenemia and hypofibrinogenemia, has been approved by the FDA. The drug is a purified fibrinogen concentrate. Fibrinogen, or Factor 1, is a protein needed to form a blood clot. According to a release submitted by CSL Behring, manufacturer of RiaSTAP, "Fibrinogen levels in plasma determine the potential clotting ability and activity in the body. Diminished concentrations of fibrinogen limit the body's ability to form a clot."

Approval of RiaSTAP was based on a phase II prospective, open-label pharmacokinetic and safety study. Results from the study showed that "median fibrinogen plasma antigen levels and median fibrinogen plasma activity levels reached a maximum within 30 minutes (antigen) to one hour (activity) post-infusion and decreased continuously afterward."

Congenital fibrinogen deficiency is a rare, potentially life-threatening bleeding disorder that affects an estimated one person per million, with an estimated prevalence in the U.S. of approximately 300 patients. "The FDA approval of RiaSTAP underscores CSL Behring's ongoing commitment to addressing the unmet needs of patients with rare and serious bleeding disorders," said Robert Lefebvre, general manager and vice president of CSL Behring's U.S. commercial operations. ❖

Supplier

Phase II IVIG Study Begins for Alzheimer's

Following promising results from its pilot study, Octapharma AG is starting its phase II clinical trial of its Octagam 10% for mild to moderate Alzheimer's disease. The phase II double-blind, randomized, multicenter, placebo-controlled trial, which will study 56 subjects of both genders ages 50 to 85 years old who have mild to moderate Alzheimer's disease, will document parameters of safety, tolerability and specific surrogate parameters of efficacy of different doses of Octagam 10%.

The study will be conducted in eight centers in Germany and the U.S. The primary outcome measure will be changes in an Alzheimer's disease-related serum biomarker in each arm. Secondary outcome markers will include cognitive, functional and global clinical outcome measures, as well as several additional plasma and cerebrospinal fluid biomarkers. Morphological and functional brain imaging markers will be used to assess disease progression and response to therapy. ❖

Healthcare

Pharmacists Profit from Consultations

With profit margins declining on medications, consultations are becoming a new way for pharmacists to make additional revenue. According to the April 15, 2009, *Kaiser Daily Health Policy Report*, "Under existing

CMS guidelines, insurers that offer Medicare Advantage (MA) plans are required to pay pharmacies for the meetings with patients, during which they discuss the importance of taking the proper medications at the appropriate times. MA beneficiaries with at least $4,000 worth of annual drug costs are eligible for the consultations at no cost." This means that some pharmacists are now earning up to $160 for a one-hour consultation with patients.

And, it's going to get more lucrative. In 2010, new Centers for Medicare & Medicaid Services (CMS) guidelines will expand the consultation benefit to more MA patients. "Under the revised guidelines, MA plans will be required to review their member rolls on a quarterly basis to identify eligible members for the program," says the report. "In addition, health plans will be prohibited from restricting access to the benefit to members with a high number of chronic health conditions and medications, and the annual drug cost limit will be reduced from $4,000 to $3,000." In 2010, pharmacists will be paid $50 to review a beneficiary's medications and make recommendations to their physician, and they will receive additional payments if they recommend a less-costly, therapeutic equivalent to the patient. ❖

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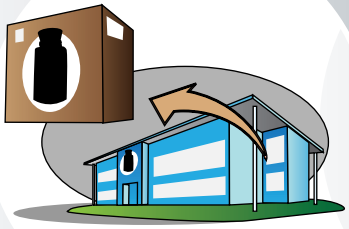
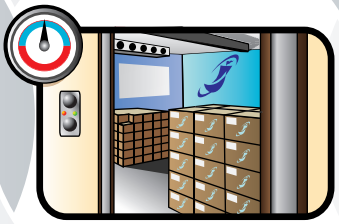


1

PURCHASING

Products are purchased only from the manufacturer – never from another distributor or source.



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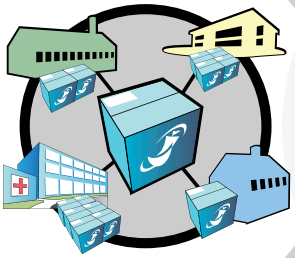

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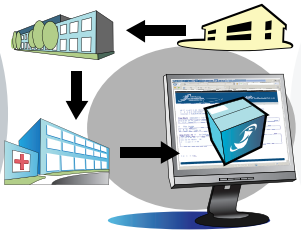

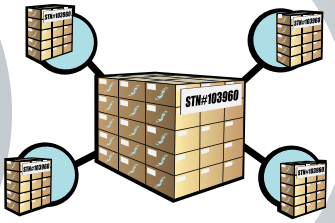

5

DELIVERY
Products are delivered only to certified healthcare providers with a DEA license and only to the address on the license.

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7

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8

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Lot-Track™, another FFF service, provides accurate product lot tracking and recall notification within four hours.

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The 8 Critical Steps to Guaranteed Channel Integrity assure that patient safety, product efficacy and fair pricing are maintained throughout our safe channel. From purchasing to storage and delivery, these best practices maintain the strength of each link in the chain,
with patient welfare at the center of every decision.

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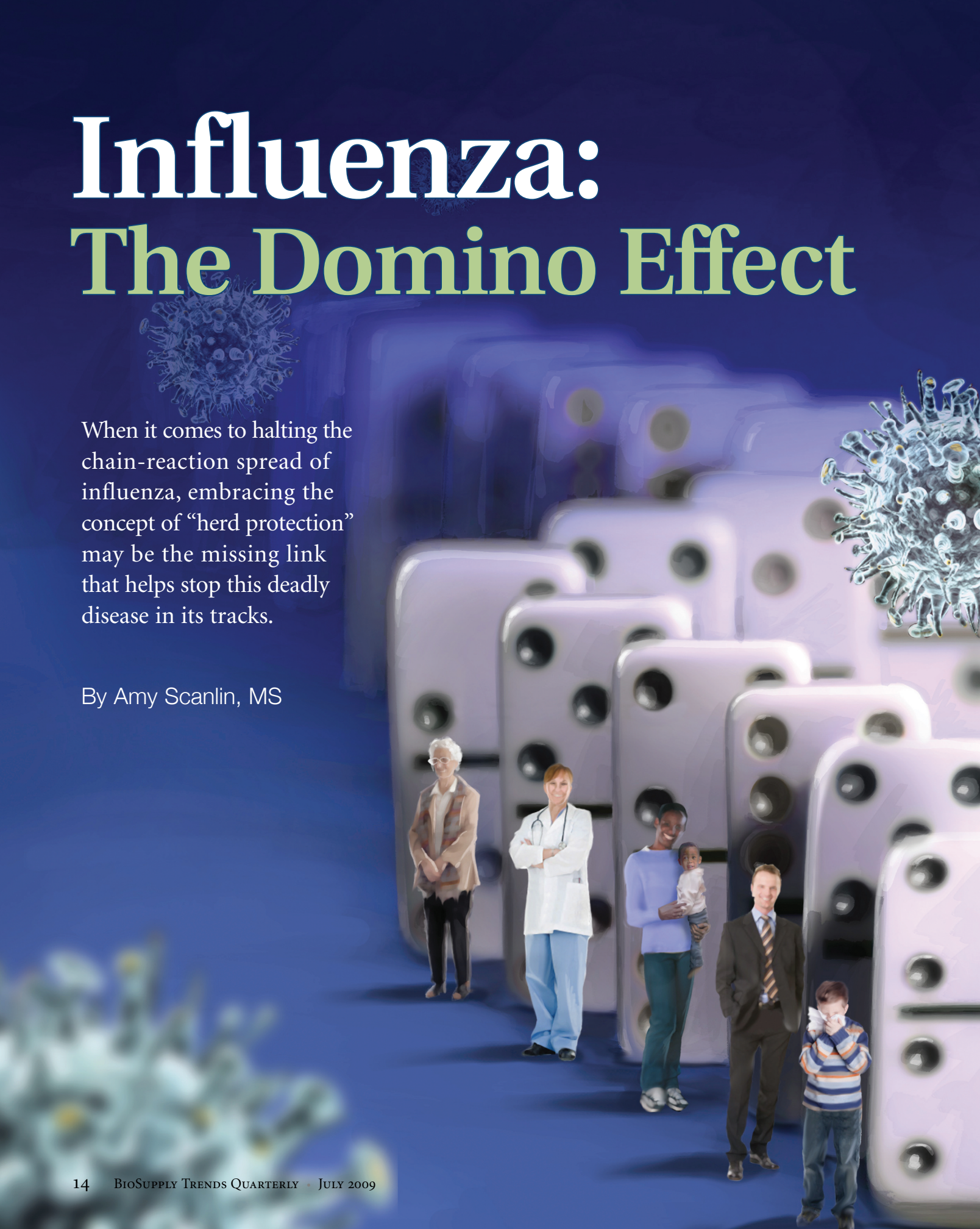
Influenza: The Domino Effect

When it comes to halting the chain-reaction spread of influenza, embracing the concept of "herd protection" may be the missing link that helps stop this deadly disease in its tracks.

By Amy Scanlin, MS



Tom is a healthy, active 38-year-old. A top sales rep for a large pharmaceutical company, Tom spends a lot of time on the road cultivating leads and contacts. While preparing to go on a business trip, Tom notices his throat is a bit scratchy and he feels achy. He knows it's flu season, but he's unconcerned and unvaccinated; he never gets sick. Before leaving for the airport, he kisses his wife and children and takes some extra vitamin C, just in case.

As it turns out, Tom beats the odds and never comes down with a full-blown case of the flu. However, he manages to infect his 11-year-old son, who in turn infects six classmates, three teachers and a janitor. He also infects a dozen or more people seated near him on the plane, including an elderly couple and a newborn. Since those infected remain symptom-free for at least 48 hours, they go on to infect dozens of people in their communities as well. Thanks to the domino effect, a flu epidemic is now in full swing.

Each year, influenza affects from 5 percent to 20 percent of the population, claiming 30,000 to 40,000 lives and requiring hospitalization of more than 200,000 in the U.S. alone. Globally, the death rate exceeds 500,000. And, a study conducted by the Centers for Disease Control and Prevention (CDC) found that there is an upward trend in the rates of flu incidence.[1] The death rate between 1972 and 1992 doubled in just 20 years — an especially alarming trend considering in 1997, flu vaccine coverage had reached 65 percent of those most vulnerable. The intensity of flu epidemics is also increasing. In the 1970s and 1980s, the average length of an epidemic period was 8 to 10 weeks. Today, it is closer to 16 to 18 weeks.[2] All of this begs several questions: As health practitioners, is our current vaccination plan working? If so, why does the flu continue to spread so quickly? Is there a better way?

Adopting Herd Protection to Halt the Spread

For years, the main thrust of flu vaccination campaigns has focused on the very young and the elderly. This emphasis may be misplaced since the immune systems of the old and infirm don't always respond efficiently to the flu vaccine, nor are these populations usually responsible for spreading the virus. That's why some suggest that a better tactic may be to focus vaccination efforts on healthcare workers, school-age children and working adults — those who consistently come in contact with others and are more likely to infect others. Embracing this concept, called "herd protection," has its roots in the idea that you protect the weakest members of a flock by strengthening the defenses of its strongest members and, in doing so, bolster the herd's communal defenses.

Paul Glezen, MD, Baylor College of Medicine, Houston, Texas, is one of a growing number of physicians who subscribe to the idea of herd protection with regard to vaccinations for the flu virus. Glezen argues that focusing vaccination efforts on the very young and old, which has been the current recommendation, is less effective because these people, while most susceptible to the effects of the flu, are not in contact with mass numbers of the population, and, ironically, may not respond as well to the vaccine. According to Glezen, herd protection is a well-established concept and a reasonable approach to a systematic immunization program.[3]

Another benefit of the approach is that school-age kids and working adults, because of their need to congregate in schools and the workplace, are accessible populations for rapid deployment of the flu vaccine and, in turn, offer the greatest chance for success for the vaccination to actually reduce the incidence of flu in a community.

This concept, called "herd protection," has its roots in the idea that you protect the weakest members of a flock by strengthening the defenses of its strongest members and, in doing so, bolster the herd's communal defenses.

There are many examples of herd protection working. In a Japanese study from 1977 to 1987, it was mandatory for school-age kids to get the flu vaccine. Most households in Japan at that time were three-generation households and the flu vaccine was not given to the elderly or high-risk. Japan saw a reduction in flu-related mortality of 35,000 to 47,000 per year.[4] Incidentally, after 1987, due to parental concerns about the vaccine being mandatory, the program was ceased and the

What Is the Flu?

Two flu virus types, influenza A and B, cause the yearly seasonal flu epidemics, and because they mutate, or undergo "antigenic drift," finding the right flu vaccine for the flu season's mutation is challenging at best. The World Health Organization coordinates the development of the contents of the vaccine each year, selecting the most likely strains of the virus to be in circulation the next year.

In a brief and simplistic explanation, influenza A is divided into subsets, H1N1 and H3N2, and these subsets along with the influenza B virus make up the yearly vaccine. A newer strain A(H1N2), identified by the World Health Organization and Geneva Public Health Laboratory Service in 2002, appears to have formed as the A(H1N1) and A(N1N2) virus strains' genes realigned. Its H1 protein structure is similar to that seen in the A(H1N1), and the N2 protein is similar in structure to the A(H3N2).[7]

Influenza C virus also causes respiratory illness; however, it is not thought to cause epidemics. Therefore, the flu vaccine only protects against the A and B viruses, including the newer strain of A(H1N2) because of its structural similarity to A(H1N1) and A(H3N2).

The flu spreads from person to person, respiratory system to respiratory system by respiratory droplet particles through sneezing, coughing, touching something on which a droplet has fallen, etc. Once infected, the time before outward symptoms is, on average, two days. However, both adults and children can spread the flu to others even before they feel signs of infection. While the duration of the flu lasts only three to five days, the persistent cough can linger for a few weeks.[8] The flu typically sees its peak infection in January, though flu season in North America is considered to begin in October, and vaccinations are recommended to begin in September. It is estimated that roughly 40 percent of the population has flu antibodies by the end of the year.

Those most affected by influenza are those with the weakest immune systems, the very young, the very old and those with a disease that would make them at higher risk. Interestingly, however, those most susceptible to the ravages of the flu are typically not the ones most frequently infected by it. Because of the flu's ability to spread easily in large groups of people, schools, places of business and anywhere large numbers of people congregate are the most likely sources of the flu, and those populations are the most likely to be infected.

death rates from the flu reverted back to pre-program levels within a few years.

In the U.S., an ongoing program in Temple, Texas, near Austin, is also proving the herd protection strategy a most effective one. Starting in 2001, school-age children have been receiving the yearly LAIV flu vaccine, and preliminary data from the 2005-2006 school year showed almost no incidents of influenza. In the 2008-2009 school year, Temple, Texas, has so far escaped the flu again, while nearby cities have had large outbreaks that resulted in school closures, hospitalizations and even deaths.

Vaccinations for Healthcare Professionals

The recommendation of vaccinations for healthcare professionals (HCPs) and those in training is also part of herd protectionism. HCPs are in close contact with those with decreased immunity — the sick, the young, the old — and even when they have subclinical presentation of the influenza virus, they can spread it. With most on the front line of patient care sharing the physician's Hippocratic oath: "Do no harm," it is puzzling to learn that nearly 60 percent of American healthcare workers fail to get an annual flu shot. "I'd like to think we [HCPs] get vaccinated because it is the right thing to do," says Dr. Andrew Eisenberg, medical director at the Iron Mountain Medical Center, Madisonville, Texas. "We have an obligation to not get patients sick. The mortality and morbidity rates are less at hospitals where vaccination of workers is mandatory."

Aside from the economic implications of death, an influenza epidemic can wreak havoc on the U.S economy.

Fifteen states have regulations regarding vaccination of HCPs in long-term care facilities, six states require that healthcare facilities offer influenza vaccination to HCPs, and four states require that HCPs either receive influenza vaccination or indicate a religious, medical or philosophical reason for not being vaccinated.[5]

While U.S. statistics regarding healthcare worker immunization are well below the goals established by Healthy People 2010,[6] international statistics are even less encouraging. In England, only 14 percent of healthcare workers were immunized before the 2008-09 flu season. An article published in the

London Times Online states that the Royal College of General Practitioners in England recently called for hospital doctors, general practitioners, nurses and other staff to have compulsory flu shots or risk being banned from patient contact.

USA Today reported that the National Foundation for Infectious Diseases cites several cases of flu outbreaks that suggest a likely link between healthcare workers and patients. These include:

- 19 babies in a neonatal intensive care unit in Ontario, Canada, were infected in 2000; one died. Healthcare workers, only 15 percent of whom were immunized, were the likely source.
- 65 residents of a nursing home in New York got the flu during the 1991-1992 flu season, and two died. Only 10 percent of healthcare workers had been vaccinated before the outbreak, according to a report by the CDC.

And in England, *The London Times* reported that at Royal Liverpool University Hospital, nearly 100 patients caught the flu in late 2008, including those on high-dependency wards treating blood diseases and kidney problems.[5]

Vaccinations: Changing Perceptions of Who and How

The CDC's Advisory Committee on Immunization Practices (ACIP) makes best practice recommendations for administering the flu vaccine. Among those recommendations are:

- The annual vaccination is to be administered to all children ages 5 to 18 years.
- The annual vaccination of all children ages 6 months through 4 years (59 months) will continue to be a primary focus of vaccination efforts because these children are at higher risk for influenza complications compared with older children.

Despite the availability of vaccines, healthcare workers consistently fall short of immunization goals.

- Either trivalent, inactivated influenza vaccine or live, attenuated influenza vaccine (LAIV) will be used when vaccinating healthy persons ages 2 through 49 years.

While it is nearly universally accepted that we will never be rid of the flu virus, we can do a better job of helping our population build antibodies to protect against it. "In my view, we have not done a very good job of vaccinating, and the biggest problem that I see is mixed messaging," says Eisenberg. "We've developed rules and procedures as to who is most at risk and [who] should be vaccinated, but everyone is at risk of catching this disease. The success of our vaccination strategy will hinge on getting a large penetration of the population immunized."

Many choose not to get the flu vaccine, and young healthy adults are chief among them because they feel they are not at high risk, that the vaccine doesn't work and/or they think that getting the flu vaccine will make them sick. Clearly, more education, communication and effort are needed to help dispel some of these common myths surrounding vaccination to ensure it is more widely embraced through our culture.

Improving Access and Distribution — Just Part of the Solution

More companies than ever are making flu vaccines, and there are also more distribution outlets from physician offices and retail pharmacy outlets, to schools and the workplace. If utilized, this ample supply and the ability to protect large

Home of the

In planning for the flu season ahead, experience matters:

CSL BIOTHERAPIES: AN UNWAVERING COMMITMENT TO INFLUENZA PREVENTION

CSL Biotherapies of Melbourne, Australia, with U.S. headquarters in King of Prussia, Pennsylvania, marked over 40 years of experience in the influenza vaccine market. During those years, the prominence of CSL Biotherapies in the marketplace has grown dramatically. **Our company now operates one of the world's largest influenza vaccine production centers for global markets, licensing and marketing flu vaccines in 27 countries.**

This heritage underpins our strong commitment to the safety, quality and reliability that are so critical to customers of influenza vaccines worldwide. **In 2002, this commitment was reflected in the total removal of the mercury-derived preservative thimerosal from the flu vaccine manufacturing process. In addition, latex is no longer used in vaccine containers.**

CSL Biotherapies' recognized scientific expertise in the early prediction of influenza strain changes allows rapid improvement of vaccine production to ensure prompt delivery to market. Since flu season comes to the Southern Hemisphere months before hitting the Northern Hemisphere, we annually bring prior experience to bear in providing many of the antigens found in the Northern Hemisphere presentation of our influenza virus vaccine. In Summer 2009, CSL Biotherapies will further accelerate access to U.S. vaccine customers by opening a syringe fast-filling line in its state-of-the-art facility in Kankakee, Illinois.

We are extremely proud of our standing as a reliable supplier of influenza vaccine to the United States and other countries throughout the Northern Hemisphere. **However, at CSL Biotherapies, we understand that our commitment to flu prevention does not stop at delivering quality vaccines.** We also offer patient advocacy and educational support to help spread the word about and underscore the importance of influenza vaccination. Our team is very passionate about its role in providing this service.

Much remains to be done to improve vaccine access, increase vaccination awareness, counter misinformation about flu vaccines, and further prevent the spread of influenza with the weapons we have at hand.

Flu Fighters

Our support to the National Foundation for Infectious Diseases (NFID) produced a **Best Practices Report, "Immunizing Healthcare Personnel Against Influenza,"** which has become an invaluable reference for healthcare organizations.

Likewise, we developed **"Season Pass," a program designed to help colleges/universities find ways to improve flu immunization rates on campus.** Such efforts are beginning to bear fruit. In the 2008-2009 flu season, for example, a 70% increase in immunizations over the previous year was seen at Arizona State University*. This level of increase indicates that providing information related to the benefits of influenza vaccination, and providing convenient access to vaccines services is a strong recipe for reinforcing a wellness attitude among students and improving vaccination rates on campus.

More recently , **"Flu-Free and a Mom-to-Be,"** a consumer campaign developed by the National Women's Health Resource Center (NWHRC) and the Association of Women's Health, Obstetric and Neonatal Nurses (AWHONN) through an educational grant provided by CSL Biotherapies, has been selected by the National Influenza Vaccine Summit to receive the 2009 Immunization Excellence Award for Best Corporate Campaign. This prestigious award recognizes individuals and organizations that have made extraordinary contributions toward improving influenza vaccination rates in their communities. **This campaign is the first of its kind to help emphasize the importance of immunizing pregnant women.**

The CSL Biotherapies team will continue to focus on the timely delivery of high-quality flu vaccines and relevant educational programs to create a positive vaccination experience for consumers and healthcare providers. Through such efforts, we are convinced that we can help stem the spread of influenza throughout the world, preserving health and saving lives.

To learn more about CSL Biotherapies and our seasonal influenza vaccine activities in the United States, please visit us online at www.cslbiotherapies-us.com.

*Markus A. L., Director of Health Services, Arizona State University, Tempe, Arizona. Influenza Vaccination: Challenges for Adolescent and College Healthcare. *Medscape Infectious Diseases* – Posted 01/15/2008.

CSL BIOTHERAPIES 1968-2008 40 years In Influenza Vaccines Production

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Preparing Your Practice for the Next Epidemic

How will you prepare for the next epidemic or pandemic? You must identify the critical staff necessary to run your business, and the goods and services necessary for the functioning of your business during the epidemic. Will you use ancillary contract workers should your staff become infected?

Planning for the flu season, from the perspective of business, is critical. A good resource for this is the "Business Pandemic Influenza Planning Checklist" found at www.pandemicflu.gov/plan/workplaceplanning/businesschecklist.html. It includes a checklist for healthcare provider offices, hospitals and long-term care facilities, as well as resources for the insurance industry.

The following is a sampling of the checklist for healthcare facilities in preparation for an impending flu outbreak taken from the website pandemicflu.gov:

1. Influenza pandemic emergency management training is implemented (including identifying a point person to assess preparedness and a committee with at least one representative from each department).
2. Responsibility has been assigned for following influenza-related health advisories (federal and state) to share with the committee.
3. A system is in place to monitor and review incoming influenza patients treated at the facility.
4. A line of communication has been established with the public health department, as well as other healthcare facilities, including points of contact, telephone numbers, fax numbers and email addresses.
5. A plan is in place to manage triage of patients, determine who should have limited contact, etc.
6. A specific waiting room is established for those with pandemic-like symptoms, away from other non-flu patients.

numbers of people in a short amount of time has the ability to reduce our rates of infection. Says Eisenberg, "Even if we can get 60 percent vaccinated, we'll protect that 40 percent who either shouldn't or won't be vaccinated."

It's important to remember that seasonality is a misnomer when it comes to the flu, because the flu is always circulating throughout the globe year-round, mutating, infecting and, in many cases, killing those who are not vaccinated or treated in time. Accurate diagnosis is also necessary if we are to effectively win the battle against the flu virus. "We have a diagnostic problem," says Eisenberg, referring to the U.S.'s ability to determine whether a person has the flu and, if so, what strain they have. "Our tests are sensitive but not too specific, and we don't have a great test to determine the strain. Many can have a relatively mild case of the flu, though not be identified as having it because they confuse the flu with something else." Misdiagnosis is a problem because as people are sent home from emergency rooms and doctors' offices, they are inadvertently spreading the flu when they should be isolating themselves.

Vaccination of the Fittest for the Survival of All

We live in a uniquely egocentric time. For many, looking out for "number one" is a way of life that is rarely questioned. When it comes to influenza control, however, a "live and let live" mentality translates to: "Infect and allow to infect." Better to reorient the national consciousness so the strong and active segments of the population step up to be immunized to protect themselves, and give indirect protection to the vulnerable. This shift may offer the most efficient and effective use of the influenza vaccine. And with the threat of a pandemic ever looming, our very survival may depend on it. ❖

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AMY SCANLIN, *MS, is a freelance writer specializing in medical and fitness writing.*

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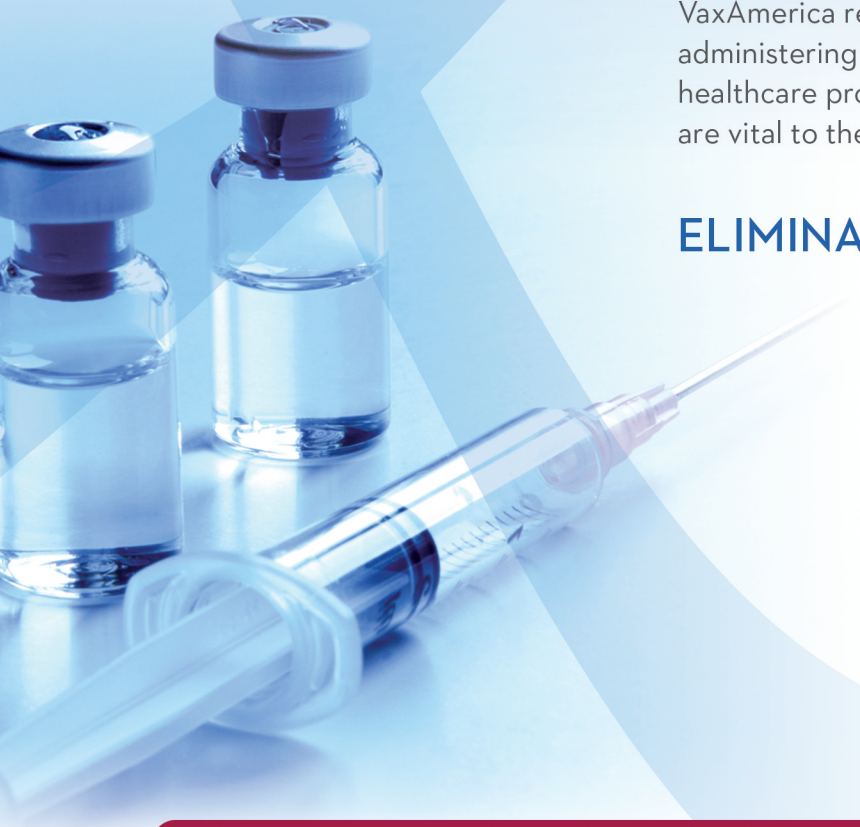

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Pandemic Preparedness: Are We Ready?

By Ronale Tucker Rhodes, MS

Though widespread enough to reach pandemic levels, the H1N1 flu has not yet shown the deadly markings of some past pandemics that have appeared with mild spring beginnings only to return with a virulence in the winter. Is this the ultimate blessing in disguise, affording us the much-needed time for preparedness?

Imagine the scenario: Tens of millions dead, many of them young adults struck down in their prime. Hospitals and emergency rooms overrun with the sick and seriously ill. An already faltering economy on the verge of collapse due to closures of businesses, services and public transportation — not just in certain cities, states or regions, but globally. While these borrowed-from-the-box office images seem surreal, for many working behind the scenes of the H1N1 (swine) flu scare, they represent a very serious threat. Our society has been overdue for a pandemic; it wasn't if, but when. And although predicting a pandemic is highly speculative at best, what we do know is this: Historically, pandemics have started with relatively mild new flu strains in the spring, only to return with a vengeance in the fall and winter when viruses peak.

Lessons Learned

While not all new strains with pandemic markings reach their potential (many begin in the spring only to fizzle out), the world has experienced three other influenza pandemics to date. And while this number may seem low, pandemics take a heavy toll on society, shutting down economies, creating panic and, oftentimes, killing millions. So, when a new outbreak occurs, the World Health Organization (WHO) and government entities quickly step in at the epidemic, or pre-pandemic stage, to assess pandemic likelihood, minimize the spread of disease and inform and educate the public about the likelihood of another pandemic in the making. Though this level of attention causes widespread panic, the lessons of the past coupled with the short window of time between spring and fall provide a

much needed period for preparedness. With all of the uncertainties surrounding this current H1N1 pandemic period, the blessing is in the times we live in. It is a new world since the previous pandemics, with instantaneous communication, advances in vaccine capability and production, and the availability of antivirals to minimize illness and mortality rates.

From Epidemic to Pandemic

The outbreak of the H1N1 flu virus has brought considerable attention to the terms epidemic and pandemic. Despite the statement by Dr. Richard Besser, MD, previous acting director for the Centers for Disease Control and Prevention (CDC), that it means less what we call this new flu outbreak than what we do about it, many are wondering what the difference is between the two terms.

An epidemic occurs when new cases of a disease appear during a given period at a rate that substantially exceeds what is expected. When an epidemic gets out of hand, it's called a pandemic. Briefly, the requirement for a pandemic classification is the disease is so new that the population has no antibodies to protect against it. A pandemic has two nuances: geographical spread and incidence rate. A pandemic spreads rapidly, can become global and can be extremely deadly.

History of Flu Pandemics

The flu pandemic of 1918, known as the Spanish flu, was the deadliest outbreak of all time. It was particularly prevalent in young men at military training camps and on troop ships for World War I. When our military traveled overseas, they took the flu virus with them. It became known as the Spanish flu because of the press it received in that country during the war. While the Spanish flu was an H1N1 strain, it was an avian flu and different from the current H1N1 flu strain.

That pandemic struck mostly healthy young adults, although it was also particularly severe for the very young (those younger than 5 years) and very old (those older than 65 years) whose mortality is most vulnerable to the virus. Experts estimate that between 30 million and 100 million people died from the Spanish flu, but 50 million is the most often quoted figure. To put this in perspective, the Spanish flu killed more people than all previous outbreaks of the plague (Black Death) and more than the number of people who died in World War II.

In 2008, a study conducted by scientists at the National Institutes of Health (NIH) determined that most of those who died from the 1918 pandemic succumbed to bacterial pneumonia after their lungs were weakened by the influenza virus. "In essence," says study co-author Anthony S. Fauci, MD, "the virus landed the first blow, while bacteria delivered the knockout punch."[1]

A second pandemic occurred in 1957. Known as the Asian flu due to its origin in China, it was an H2N2 strain. During this pandemic, there were two waves: The first affected mostly children and the second affected the elderly. Approximately two million individuals around the world died from the Asian flu.

The next pandemic was in 1968 and was called the Hong Kong flu. While the first occurrence of this flu was detected in Hong Kong, it spread globally and killed approximately one million people, mostly the elderly. This pandemic is considered to be the mildest of all.

Flu Pandemic Scares

While there have been many flu outbreaks that have come close to being classified as pandemics, the most memorable (especially in light of the current outbreak) was another swine flu in 1976 that began in New Jersey. In that outbreak, hundreds of soldiers at Fort Dix fell ill. Of those, there were 13 severe illnesses and one death: a healthy soldier who died within 24 hours of contracting the flu. When two additional cases were reported in Virginia, the nation became alarmed and the federal government created an emergency inoculation program under which 40 million Americans were given vaccines. The inoculation program was discontinued when it was determined that several hundred of those vaccinated had developed Guillain-Barré syndrome. Fortunately, not even an epidemic developed.

When an epidemic gets out of hand, it's called a pandemic.

A more recent outbreak occurred in 2006, and was known as the bird flu. That flu, an H5N1 strain that originated in parts of Asia where people and poultry live in close quarters, spread globally. Particularly alarming about this virus was the overall mortality rate of approximately 60 percent. That is far more lethal than the worst pandemic, which had a 2.5 percent to 6 percent mortality rate. The seasonal flu has only a 0.1 percent mortality rate, causing approximately 36,000 deaths annually. The good news about the bird flu was that it didn't spread easily from one person to the next, making it easier to control. To combat the bird flu, tens of millions of infected birds were killed.

While many outbreaks of new flu strains have been kept at bay, thus preventing an epidemic or pandemic, there is still a threat potential. In the instance of the H5N1 strain, it is possible for one minor mutation to remove the barrier to transmission, thus causing it to spread from person to person more quickly.

Identifying a New Threat

How is it determined if a new flu virus strain is a threat? There are two primary characteristics of a disease: pathogenicity and virulence.[2] If a virus readily causes disease and is easily spread, it is considered pathogenic. The severity of the symptoms from the virus determines its virulence.

In the 1918 Spanish flu pandemic, the virus spread easily from person to person and the symptoms were severe, resulting in millions of deaths, which means it was highly pathogenic and highly virulent. On the other hand, the H5N1 bird flu, while it was highly pathogenic with a high mortality rate, it spread poorly from person to person, making it mildly virulent.

Pandemic Checklist

Structure your facility for planning and decision making:

1. Create a committee to specifically address pandemic influenza preparedness.
2. Assign responsibility to a person for coordinating preparedness planning.
4. Assign members to the planning committee.
5. Establish a point of contact.

Develop a written pandemic influenza plan:

1. Specify the circumstances under which the plan will be activated.
2. Describe the organizational structure that will be used to operationalize the plan.
3. Define responsibilities of key personnel that will execute the plan.
4. Develop a simulation exercise to test the effectiveness of the plan.

Elements of an influenza pandemic plan:

1. Surveillance plan
2. Communication plan
3. Education and training plan
4. Triage and admission plan
5. Facility access plan
6. Occupational health plan
7. Vaccine and antiviral use plan

Sources

Centers for Disease Control and Prevention Medical Offices and Clinics Pandemic Influenza Planning Checklist. Accessed at http://www.pandemicflu.gov/plan/healthcare/medical.html.

HHS Pandemic Influenza Plan Supplement 3 Healthcare Planning. Accessed at http://www.hhs.gov/pandemicflu/plan/sup3.html#app2.

When a new virus arises, these characteristics are identified by health experts to determine the threat potential.

The New Strain: H1N1 Flu

The newest flu strain, H1N1, is causing alarm worldwide, and the CDC, WHO and other health departments are taking steps to educate and protect populations, as well as diagnose outbreaks.

H1N1 flu occurs when people handle (but not eat) infected pigs, though the incidence of infection passing from person to person is growing. This new flu is a mixture of swine viruses and elements of human and bird flu. It has symptoms very similar to the seasonal flu, with severity also ranging from mild to severe. Thankfully, the seasonal flu season is pretty much over, and the B strain was the primary strain at the end of the season. That allows us to assume at this point that anything that tests positive for influenza A is the H1N1 flu, says Paul Glezen, MD, Baylor College of Medicine, Houston, Texas.

Only the CDC and state labs can formally confirm the infection of H1N1 flu. In May, the CDC began distributing a PCR diagnostic test kit to detect the H1N1 virus. The test kits were shipped to all states in the U.S. and Puerto Rico, as well as internationally. This increase in testing capacity has resulted in an increase in the number of reported confirmed cases in this country, which will provide a more accurate picture of the burden of disease.

Equally important to diagnosing the H1N1 flu is determining how best to protect people from it. "The swine flu seen in the 1930s is very similar in structure to the flu pandemic of 1918," says Glezen. "Right now, we are trying to determine how different is this strain." A pig has a short lifespan, which doesn't leave a lot of time for mutation, explains Glezen. "We need to know if we have any pre-existing immunity to this flu. Many of us in 1976 had the swine flu vaccination. Do we have any antibodies to this strain? Maybe the answer is we have none. That would be a bad pandemic."

An internal report prepared by researchers at the CDC's Influenza Division and Immunization Service Division, may provide some insight about antibodies to the strain. Titled "Lessons Learnt from the 1976 Swine Flu Outbreak," the research looked at whether prior infection or vaccination with the human H1N1 virus offers protection against the swine flu.[3] Researchers found that prior antibodies from circulating H1N1 strains at the time of vaccination in subjects were critical for a satisfactory immune response to vaccination with the 1976 swine influenza vaccine. Those subjects who had prior experience from circulating strains had good serological response after a single dose of vaccine, while those who did not have prior experience would require a second dose to achieve adequate immunization.

Based on the findings of this report, Luke Noll, a vaccine specialist for FFF Enterprises, Inc., Temecula, Calif., says "it may be likely that at least some of the population who received

the 1976 swine influenza vaccine, or who may have experienced circulating human H1N1 strains, may have a better immune response after a single dose of a newly created H1N1 vaccine, whereas others will likely require two doses of vaccine to achieve a satisfactory immune response."

It is possible for a future influenza pandemic to unfold in a manner similar to the outbreak in 1918.

Planning for an Influenza Pandemic

Researchers at the National Institute of Allergy and Infectious Diseases (NIAID) recommend that preparations for diagnosing, treating and preventing bacterial pneumonia should be among the highest priorities in influenza pandemic planning.[4] Right now, the CDC and WHO are continuing to monitor on a daily basis the impact the H1N1 flu is having on the U.S. and international populations. According to Dr. Anne Schuchat, director of the National Center for Immunization and Respiratory Diseases, H1N1 flu "activity seems to be declining in the nation as a whole, but there are some areas where illness is ongoing."[5] In the U.S., cases are confirmed in all 50 states, and the global situation is increasing. With the southern hemisphere now in its flu season, the CDC and WHO are keeping a close watch on that region to guage what effect the H1N1 flu might have on regions where the flu season occurs in the fall.

Younger people between the ages of 5 and 24 years are those who have been most affected by the H1N1 flu. This is different than what is normally seen with seasonal influenza during which the elderly have the highest hospitalization rates.[5] Tests have revealed what scientists suspected was the reason for this: People in their 60s and older have signs of greater immunity to the H1N1 flu virus because they have been exposed to other viruses in the past that are more similar to the H1N1 virus than recent seasonal flu viruses. However, it is still too early to tell how safe older people actually are from the new infection.[6]

Because the H1N1 flu has spread widely, the WHO has upgraded the pandemic flu stage alert from phase 5 to phase 6 — a full pandemic. Yet, Schuchat cautions that designation of a pandemic alert level only suggests that the virus has spread widely, and not that the virus is more severe than has been described in news reports.[5] "The phasing at WHO is an indicator of spread and not of severity," explains Schuchat. In addition, she adds, "the pandemic alert level [is] a reflection of epidemiologic changes in other parts of the world, not here in the Americas where we … already have had extensive community spreads."

The first steps have been taken to develop a candidate vaccine virus for the H1N1 strain. According to Schuchat, the CDC has provided that virus to a number of manufacturers to produce pilot lots of vaccines that can be tested to see whether they would be safe and provide cinical protection. However, she said, the decision about whether or not to use a vaccine and how to use it has not and won't be made until more information is known about the disease and how the vaccine performs in clinical testing. Those are the intensive efforts that the CDC plans to make over the summer months. In the meantime, whether the vaccine is needed or not, the CDC has begun efforts to plan for immunization.

"At this time," says Noll, "the research and study by the CDC is ongoing, and the experts will determine the path that we must take to remain healthy from seasonal influenza and/or this novel H1N1 strain this upcoming season. Whether we need to receive one, two or three vaccinations this upcoming season is yet to be decided. Surely, we will know the answer soon."

Only Time Will Tell

It is possible for an influenza pandemic to unfold in a manner similar to the outbreak in 1918, say researchers at the NIAID.[1] But, scientists have learned a lot over the years from previous pandemics. And, as witnessed by the recent actions by the various government agencies, the U.S. is prepared to act aggressively and to take bold action to minimize the effect on people's health. So, for now, this pandemic is not out of hand. But, as previous influenza outbreaks have shown, it is possible to see an initial outbreak early on, only to be followed by a more serious outbreak of that strain when flu season strikes. It is imperative, then, that we be prepared. ❖

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

Giving Vac

cination Rates a Boost

As nearly obsolete diseases start staging a comeback and potential pandemics loom, it's time to explore new practice and delivery models to boost vaccination rates across population lines.

By Trudie Mitschang

When most people think of infectious diseases, maladies such as colds, influenza and even STDs come to mind. But few of us today have a solid frame of reference for diseases like mumps, measles or whooping cough, believing incidents to be rare or even obsolete. Unfortunately, this false sense of security and resulting complacency can lead to increased vulnerability when it comes to potential new outbreaks.

In 2006, the United States experienced its first mumps epidemic in 20 years. The outbreak was believed to have started on a college campus in Iowa. Later, infected airline passengers spread the disease to regions around the country. Eventually, the Centers for Disease Control and Prevention (CDC) documented more than 3,000 confirmed, probable and suspected cases of mumps in at least a dozen states.

Other diseases like measles have recently become more prevalent in Europe, as parents skip the vaccination due to autism concerns, a problem American public health officials have been dealing with for several years. In the last two years alone, more than 12,000 Europeans have contracted measles, according to a *Lancet* study, and many of them have been children.

Speaking at an international seminar in the Czech Senate, Zsuzsanna Jakab, director, European Centre for Disease Prevention and Control (ECDC), highlighted the importance of vaccines as one of the most important and effective tools for the prevention of infectious diseases in the EU, but cautioned that more work is needed to counter negative perceptions of vaccines. "As people think some infectious diseases are no longer a threat, they are more likely to question the value and safety of vaccination," Jakab said.

Currently, nearly 95 percent of the 50,000 Americans who die every year from vaccine-preventable diseases are adults.

A Generation-Spanning Concern

From a public health perspective, statistics show that stagnant vaccination rates are an issue impacting children and adults alike. The CDC currently recommends vaccinations from birth through adulthood to provide a lifetime of immunity.[1] Unfortunately, few adults follow through with vaccinations as recommended, leaving them potentially at risk for unnecessary illness or even death. And since the healthcare model for adults in the U.S. is based primarily on acute care, many practitioners are either understocked with vaccines or not adequately trained on vaccination schedules for adult patients. In addition, for healthcare providers, there are valid concerns about possible financial losses due to excess vaccine inventory, or the high price tag associated with storing temperature- and time-sensitive vaccines.

Currently, nearly 95 percent of the 50,000 Americans who die every year from vaccine-preventable diseases are adults.[2] Hundreds of thousands more are hospitalized annually. And while these cases represent worst-case scenarios, millions of others become ill, miss work or school and pass their infections on to others. The situation is a frustrating one for those in the healthcare profession; with so many safe and effective vaccines available, finding new and effective ways to address public concern, misinformation and apathy is essential.

"At the adult level, our current healthcare model does not stress preventive care," says Litjen (L.J.) Tan, MS, PhD, director, medicine and public health at the American Medical Association. "We need to help providers become vaccinators by giving them the information, tools and resources necessary to succeed."

While safety concerns get a lot of press when it comes to stagnant childhood vaccination rates, cost can be a factor as well. One possible reason is that vaccines are funded by a patchwork of public and private sources. While some private health insurance plans cover recommended vaccines for children, an increasing number of plans require patients to pay out of pocket for many of them. Unfortunately, the vaccines, especially newly recommended ones, can be very pricey.

"I think we have to develop a comprehensive strategy for communicating directly and honestly with parents," adds Tan. "We need to train providers to engage with parents and address their concerns. Often, it is a time and staffing issue; in some cases, having a dedicated nurse practitioner on staff to offer vaccine consultations can help boost a practice's vaccine rates."

Understanding the Challenges

Vaccination barriers exist at all levels in the public and private sectors and among healthcare providers and delivery systems. Some key areas that could benefit from a communications and delivery booster shot include:

Boosting Awareness. Many adults, including healthcare workers, are unaware of the need to vaccinate adults. There may also be a lack of awareness regarding specific diseases vaccines are designed to prevent, such as meningitis, shingles and chickenpox. In other instances, patients may be somewhat aware of the need for vaccines, but have unanswered questions about safety and effectiveness that keep them from being immunized. For healthcare providers, having information readily available and being prepared to answer questions about various vaccines is a critical first step in increasing vaccination rates across population lines.

Boosting Influence. Healthcare providers play a significant role when it comes to influencing a patient's decision to be vaccinated. A National Foundation for Infectious Diseases (NFID) survey reported that 87 percent of respondents claimed they were more likely to be vaccinated at a doctor's recommendation, while only 41 percent said they would ask for a vaccine if their doctor did not bring it up. Unfortunately, many providers lack the resources to maintain an adequate supply of vaccine on hand and may be less-than-knowledgeable about vaccine guidelines, both deterrents to turning the tide on stagnant immunization rates. Looking at new and innovative business models and proactively planning vaccine clinics are two ways providers can reap the potential rewards within the vaccination market.

A New Distribution Model for Vaccine Supply and Delivery

"Easy" is not a word that comes readily to mind when you think about vaccine distribution and administration. Stocking vaccines, especially those that require specialized storage, are costly or have multiple dosage requirements, can pose a challenge for healthcare providers. But thanks to a new and increasingly popular distribution model, perceptions may be changing.

VaxAmerica, a nationwide network of care sites, makes vaccine distribution and administration — even for difficult-to-get vaccines — easy, convenient and cost-effective for patients, healthcare providers and health insurers.

"VaxAmerica solves many of the issues that often make it difficult or costly for healthcare providers to stock vaccines, and for patients to receive the preventive vaccines that are an investment in long-term health," says Nancy Creadon, vice president, VaxAmerica, Inc.

Launched in 2008, VaxAmerica offers access, choice and cost savings for patients and their healthcare providers. With its just-in-time delivery model, inventory costs and the risks associated with long-term storage are a thing of the past. VaxAmerica also offers direct billing, so there are no up-front costs, and healthcare providers still receive an administration fee for service. Network referrals offer an additional benefit to providers.

With a system that ensures the availability of hard-to-get vaccines — as well as the delivery of each therapy's required dose — VaxAmerica promises a long-term health solution for disease prevention that warrants a closer look. For more information, go to **www.VaxAmerica.com**.

Boosting Infrastructure. With the exception of the influenza vaccination, there has been little emphasis on creating an infrastructure within the healthcare system to achieve consistently high immunization rates in adults. Issues surrounding distribution, supply and demand, delivery, availability and storage all combine to sabotage even the best-laid plans for a vaccination clinic.

Fighting the Flu: A Season-Long Approach

In 2007, the CDC began emphasizing the need to offer the influenza vaccine and schedule immunization clinics throughout the influenza vaccination season (October into January and beyond). This is an important message for practitioners, and one that has yet to be thoroughly embraced. A cross-sectional survey sent to a national, random sample of internists and general practitioners before this change in recommendation revealed that 43 percent of the respondents stopped vaccinating in December, and only 27 percent continued vaccinating into February and beyond. Furthermore, 43 percent of the physicians indicated that they were either neutral or hesitant to vaccinate after the onset of influenza activity in their community.[3]

Thinking Outside the Clinic: Exploring Non-Traditional Settings

According to a CDC-sponsored survey,[4] the most common locations where patients received their influenza vaccine during the 2005-2006 season were physicians' offices (39 percent), the workplace (17 percent) and community health clinics (10 percent). Providing influenza vaccination services at "non-traditional" sites that offer extended hours, are easily accessible or are frequently visited (e.g., grocery and other stores, malls, pharmacies, senior centers, churches) can increase access for those who might otherwise go unvaccinated. Other non-traditional settings where vaccine might be provided include adult day-care centers, casinos, bingo halls, major transit points, airports and polling stations on election days. Drive-through vaccination programs may also be a feasible alternative.

Thinking outside the "clinic" is essential if practitioners hope to boost vaccination rates. For one thing, traditional set-

A Measure of Certainty in Uncertain Times

When it comes to flu vaccine orders, doctors and other vaccine providers face a number of uncertainties each year. From not knowing if their vaccine will arrive in time for scheduled flu clinics, to concerns about having leftover inventory at the end of the vaccination season, those on the front lines of patient care are often caught in the middle of a risky business scenario.

Through its MyFluVaccine program, FFF Enterprises, Inc., has set out to eliminate the risks associated with increasing flu vaccination rates for healthcare providers. Launched in 2006, MyFluVaccine first set out to address the uncertainty of when orders will arrive by giving healthcare providers the ability to choose the exact date they wish to receive their flu vaccine with the certainty of knowing it will arrive on time. "Our customers told us that they would often lose patients to whatever facility received its vaccine first," adds Chris Ground, senior vice president, FFF Enterprises. "MyFluVaccine gives these providers the ability to select specific delivery dates for their vaccine, which allows them to plan vaccination clinics with the confidence of knowing their flu vaccine will arrive on time. It's revolutionized the industry."

New for 2009, MyFluVaccine has revolutionized the industry yet again with Return Guarantees — from 25 percent to 100 precent depending on the manufacturer and presentation — removing yet another barrier in the quest to increase vaccination rates.

"Being prepared to vaccinate is a major part of the battle against the flu," says Patrick M. Schmidt, chief executive officer, FFF Enterprises. "However, for those on the front line, the worry of having excess inventory at the end of the vaccination season may be a reason for cautious ordering." By removing the risk of leftover inventory, providers can order adequate quantities with the peace of mind of knowing leftover quantity is returnable.

Some additional ways that MyFluVaccine has made the vaccine risk-reward ratio more appealing to healthcare providers: No prepayment requirement and a low price guarantee, so that providers can order without worry that prices may move favorably downward late in the ordering season.

In addition to its easy ordering portal, the MyFluVaccine website provides news, updates, resources and clinic planning tools. For more information, visit **www.MyFluVaccine.com**.

tings such as clinics and doctors' offices may not offer sufficient infrastructure to handle increased demand. Development of alternative sites can also help establish the infrastructure that will be necessary to address increased vaccine demand in the event of an influenza pandemic.

Practice-Proven Methods: A Look at Successful Case Studies

Utilizing a season-long approach helped one practice in Clarks Summit, Pa., achieve high vaccination rates. With one physician and two nurses on staff, the practice takes a multipronged communication approach, routinely repeating its strong recommendation for vaccination at all visits during the influenza vaccination season. Educational posters placed in the waiting room urge annual vaccination. Vaccine-only clinics are offered weekly during the influenza vaccination season.[5]

A private pediatric group practice (12 pediatricians; 26,000 patients) in Nashville, Tenn., combines many interventions, with a goal of immunizing all children in recommended categories and any other patient desiring vaccines.[6] Parents are educated about vaccination for preventable diseases at all well and sick visits. A patient reminder is mailed in September. During the influenza season, the practice's on-hold message includes information about influenza vaccination, which also can be found on the practice's website. To streamline vaccine delivery, multiple vaccine clinic days are offered, with nurses administering vaccine according to a standing order; the clinics allow for 10 appointments per hour. The vaccination program is evaluated at the end of every season, potential areas for improvement are discussed, and adjustments are made.

During the 2007-2008 influenza season, Arizona State University increased influenza vaccination among students, faculty and staff by 41 percent (from 2,343 to 3,980 vaccine doses), compared with the previous year.[7] The improved vaccination rate occurred despite an increase in price from $10 per vaccination in 2006 to $18 for students and $20 for employees in 2007. A multifaceted program included convenient access to vaccinations and increasing demand through education and giveaways. Vaccine was made available during two week-long events at the student union. In addition, nurses visited residence halls. Education and awareness were enhanced through signage, advertising in the student newspaper and radio station, and free T-shirts given to persons who were vaccinated.

What Providers Can Do: A Strategies and Tools Checklist

After conducting a systematic review of published studies that looked at the effectiveness of various population-based

approaches to increasing vaccination coverage for routinely recommended vaccines, the Task Force on Community Preventive Services and a diverse team of experts at the CDC identified a number of effective approaches.* Among them:

• **Client Reminder/Recall Systems**: Reminding members of a target population that vaccinations are due (reminders) or late (recall). Delivery method: telephone calls, letters or postcards.

• **Assessment and Feedback for Providers**: Retrospectively evaluating the performance of providers in delivering one or more vaccinations to a client population, and providing data back to providers. Delivery method: surveys, chart reviews, payment reviews.

• **Provider Reminder/Recall Systems**: Developing strategies to inform healthcare providers their patients are due or overdue for vaccinations. Delivery method: chart stickers, computer notification, vital sign stamps, medical record flow sheets and checklists.

Thinking outside the "clinic" is essential if practitioners hope to boost vaccination rates.

• **Standing Orders**: Establishing protocols that enable non-physician personnel to prescribe or deliver vaccinations to patients without direct physician involvement during patient visits. This is particularly effective for increasing flu and pneumococcal vaccination for adults age 65 and over. Delivery method: interaction with patients at time of visit in clinics, hospitals, nursing homes and other healthcare settings.

• **Reducing Out-of-Pocket Costs**: Providing insurance for, reducing co-payments associated with or offering free vaccinations. Delivery method: provision programs, insurance coverage or reduction of co-pays at the point of service.

• **Expanding Access**: Increasing availability of vaccinations in healthcare settings. Delivery method: increasing or changing the hours during which services are provided, reducing the distance from the client to the setting, delivering services where not previously provided (e.g., emergency rooms, in-patient clinics) or reducing administrative barriers to obtaining services within clinics (e.g., "express-lane" vaccination services).

The CDC recommends these findings be used by decision makers and clinicians in delivering and/or improving vaccine delivery.

The High Price of a Pound of Cure

At a White House summit on healthcare reform earlier this year, the administration stated that soaring medical costs present "one of the greatest threats not just to the well-being of our families ... but to the very foundation of our economy." That economic burden is only worsened when vaccine-preventable diseases are spread due to lack of awareness, apathy and misinformation. The reality is, the burden of many adult vaccine-preventable diseases in terms of cost and lives lost is high. Consider the following:

- Influenza kills an average of 36,000 people annually and is associated with more than $10 billion in costs with a moderately severe seasonal outbreak.
- Pertussis, with an estimated one to three million cases each year, can lead to pneumonia and exposure of infants, who are at greatest risk of death from pertussis.
- Pneumococcal disease, which causes pneumonia and invasive infections, kills approximately 5,000 annually.
- HPV infects more than 6 million females per year; two HPV strains included in the vaccine cause 70 percent of all cervical cancers.
- Shingles will affect one in three Americans in their lifetime. The accompanying severe pain syndrome (post-herpetic neuralgia) may last months or years after the shingles rash heals.
- Hepatitis B-related liver disease kills about 5,000 Americans and costs $700 million annually.

Clearly, finding ways to increase vaccination rates for preventable diseases across population lines can have a positive societal impact, from both a human and financial perspective. Is an ounce of prevention really worth a pound of cure? When it comes to vaccines for preventable diseases, the answer is a definitive "yes."

**These findings and conclusions are those of the authors and the Task Force on Community Preventive Services and do not necessarily represent the official position of the CDC.* ❖

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TRUDIE MITSCHANG *is a staff writer for* BioSupplyTrends Quarterly.

BRIEF SUMMARY OF PRESCRIBING INFORMATION

Vivaglobin®
Immune Globulin Subcutaneous (Human)

Manufactured by:
CSL Behring GmbH
35041 Marburg, Germany
US License No. 1765

Distributed by:
CSL Behring LLC
Kankakee, IL 60901 USA

CSL Behring

℞ **only**

Before prescribing, please consult full prescribing information, a brief summary of which follows:

INDICATIONS AND USAGE

Vivaglobin® Immune Globulin Subcutaneous (Human), is indicated for the treatment of patients with primary immune deficiency (PID).

CONTRAINDICATIONS

As with all immune globulin products, Vivaglobin® Immune Globulin Subcutaneous (Human) is contraindicated in individuals with a history of anaphylactic or severe systemic response to immune globulin preparations and in persons with selective immunoglobulin A (IgA) deficiency (serum IgA < 0.05 g/L) who have known antibody against IgA.

WARNINGS

Patients who receive immune globulin therapy for the first time, who are switched from another brand of immune globulin, or who have not received immune globulin therapy within the preceding eight weeks may be at risk for developing reactions including fever, chills, nausea, and vomiting. On rare occasions, these reactions may lead to shock. Such patients should be monitored for these reactions in a clinical setting during the initial administration of Vivaglobin® Immune Globulin Subcutaneous (Human).

If anaphylactic or anaphylactoid reactions are suspected, discontinue administration immediately. Treat any acute anaphylactoid reactions as medically appropriate.

Vivaglobin® is made from human plasma. Products made from human plasma may contain infectious agents, such as viruses, that can cause disease. Because Vivaglobin® is made from human blood, it may carry a risk of transmitting infectious agents, e.g., viruses, and theoretically, the CJD agent. The risk that such plasma-derived 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 during manufacture (see **DESCRIPTION** section for virus reduction measures). Stringent procedures utilized at plasma collection centers, plasma-testing laboratories and fractionation facilities are designed to reduce the risk of virus transmission. The primary virus reduction steps of the Vivaglobin® manufacturing process are pasteurization (heat treatment of the aqueous solution at 60°C for 10 hours) and ethanol - fatty alcohol / pH precipitation. Additional purification procedures used in the manufacture of Vivaglobin® also potentially provide virus reduction. Despite these measures, such products may still potentially contain human pathogenic agents, including those not yet known or identified. Thus, the risk of transmission of infectious agents cannot be totally eliminated. Any infections thought by a physician to have been possibly transmitted by this product should be reported by the physician or other healthcare provider to CSL Behring at 1-800-504-5434 (in the US and Canada). The physician should discuss the risks and benefits of this product with the patient.

During clinical trials, no cases of infection due to hepatitis A, B, or C virus, parvovirus B19, or HIV were reported with the use of Vivaglobin®.

PRECAUTIONS

General-Administer Vivaglobin® Immune Globulin Subcutaneous (Human), subcutaneously. **Do not administer this product intravenously.** The recommended infusion rate and amount per injection site stated under **DOSAGE AND ADMINISTRATION** should be followed. When initiating therapy with Vivaglobin®, patients should be monitored for any adverse events during and after the infusion.

Laboratory Tests - After injection of immunoglobulins, the transitory rise of the various passively transferred antibodies in the patient's blood may yield positive serological testing results, with the potential for misleading interpretation. Passive transmission of antibodies to erythrocyte antigens, e.g., A, B, D may cause a positive direct or indirect antiglobulin (Coombs') test.

Drug Interactions - Immunoglobulin administration can transiently impair the efficacy of live attenuated virus vaccines such as measles, mumps and rubella. The immunizing physician should be informed of recent therapy with Vivaglobin® Immune Globulin Subcutaneous (Human), so that appropriate precautions can be taken.

Vivaglobin® should not be mixed with other medicinal products.

Pregnancy Category C - Animal reproduction studies have not been conducted with Vivaglobin® Immune Globulin Subcutaneous (Human). It is also not known whether Vivaglobin® can cause fetal harm when administered to a pregnant woman, or can affect reproduction capacity. Vivaglobin® should be given to a pregnant woman only if clearly needed.

Pediatric Use - Vivaglobin® was evaluated in 6 children and 4 adolescents in the US and Canada study and in 16 children and 6 adolescents in the non-IND study. There were no apparent differences in the safety and efficacy profiles as compared to adult subjects. No pediatric-specific dose requirements were necessary to achieve the desired serum IgG levels. The safety and efficacy of Vivaglobin® was not studied in pediatric subjects under two years of age.

Geriatric Use - The clinical study of Vivaglobin® Immune Globulin Subcutaneous (Human), did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

ADVERSE REACTIONS

In clinical studies, administration of Vivaglobin® Immune Globulin Subcutaneous (Human), has been shown to be safe and well tolerated in both adult and pediatric subjects. Reactions similar to those reported with administration of other immune globulin products may also occur with Vivaglobin®. Rarely, immediate anaphylactoid and hypersensitivity reactions may occur. In exceptional cases, sensitization to IgA may result in an anaphylactic reaction (see **CONTRAINDICATIONS**).

Should evidence of an acute hypersensitivity reaction be observed, the infusion should be stopped promptly, and appropriate treatment and supportive therapy should be administered.

In the US and Canada clinical study, the safety of Vivaglobin® was evaluated for 15 months (3-month wash-in/wash-out period followed by 12-month efficacy period) in 65 subjects with PID. The most frequent adverse reaction was local reaction at the injection site. Table 5 summarizes the most frequent adverse events by subject reported in the clinical study, and Table 6 summarizes the most frequent adverse events by infusion.

Table 5: Most Frequent Adverse Events by Subject *Irrespective* of Causality* in the US and Canada Study

Adverse Events (≥ 10% of subjects)	**No. of Subjects (% of total)**
Adverse Events at the Injection Site	60 (92%)
Non-Injection Site Reactions	
Headache	31 (48%)
Gastrointestinal disorder	24 (37%)
Fever	16 (25%)
Nausea	12 (18%)
Sore throat	11 (17%)
Rash	11 (17%)
Allergic reaction	7 (11%)
Pain	6.7 (10%)†
Diarrhea	6.7 (10%)†
Cough increased	6.7 (10%)†

*Excluding infections

† Due to missing subject diary information, values listed are estimates.

Table 6: Most Frequent Adverse Events by Infusion *Irrespective* of Causality* in the US and Canada Study

Adverse Events (≥ 1% of infusions) (Number of Infusions: 3656)	**No. of Adverse Events** (Rate**)
Adverse Events at the Injection Site	1789 (49%)
Mild	1112 (30%)
Moderate	601 (16%)
Severe	65 (2%)
Unknown Severity	11 (< 1%)
Non-Injection Site Reactions	
Headache	159 (4%)
Gastrointestinal disorder	40.3 (1%)†

*Excluding infections

**Rate = number of reactions/infusion

†Due to missing subject diary information, values listed are estimates.

Table 7 summarizes the most frequent related adverse events by subject reported in the clinical study, and Table 8 summarizes the most frequent related adverse events by infusion.

Table 7: Most Frequent Related Adverse Events by Subject* in the US and Canada Study

Related Adverse Event (≥ 2 subjects)	**No. of Subjects (% of total)**
Adverse Events at the Injection Site	60 (92%)
Non-Injection Site Reactions	
Headache	21 (32%)
Nausea	7 (11%)
Rash	4 (6%)
Asthenia	3 (5%)
Gastrointestinal disorder	3 (5%)
Fever	2 (3%)
Skin disorder	2 (3%)
Tachycardia	2 (3%)
Urine abnormality	2 (3%)

*Excluding infections

Table 8: Most Frequent Related Adverse Events by Infusion* in the US and Canada Study

Related Adverse Event (≥ 2 AEs) (Number of Infusions: 3656)	**No. of AEs (Rate**)**
Adverse Events at the Injection Site	1787 (49%)
Non-Injection Site Reactions	
Headache	59 (1.6%)
Rash	9 (0.2%)
Nausea	9 (0.2%)
Nervousness	4 (0.1%)
Asthenia	3 (0.1%)
Gastrointestinal disorder	3 (0.1%)
Skin disorder	3 (0.1%)
Urine abnormality	3 (0.1%)
Fever	2 (0.1%)
Dyspnea	2 (0.1%)
Gastrointestinal pain	2 (0.1%)
Tachycardia	2 (0.1%)

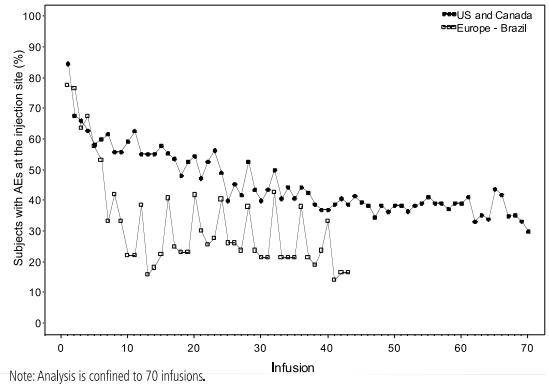
*Excluding infections

**Rate = number of reactions/infusion

In the non-IND Europe and Brazil clinical study, the safety of Immune Globulin Subcutaneous (Human), Vivaglobin® was evaluated for 10 months in 60 subjects with PID. The adverse events and their rates reported in this study were similar to those reported in the US and Canada study, with two notable exceptions for the related adverse events. These events were 59 episodes of headache (1.6%) and 2 episodes of fever (0.1%) in the US and Canada study and no episodes of headache and 18 episodes of fever (0.8%) in the Europe and Brazil study.

Local (Injection Site) Reactions - Local injection site reactions consisting of mostly mild or moderate swelling, redness and itching, have been observed with the use of Vivaglobin®. No serious local site reactions were observed. The majority of injection site reactions resolved within four days. Additionally, the number of subjects reporting local injection site reactions decreased substantially after repeated use (see Figure 1). Only three subjects in the US and Canada study and one subject in the Europe and Brazil study discontinued due to local site reactions.

Figure 1: Subjects Reporting Local Site Reactions By Infusion



Note: Analysis is confined to 70 infusions.

After administration, discard any unused solution and administration equipment in accordance with biohazard procedures.

HOW SUPPLIED

Vivaglobin® Immune Globulin Subcutaneous (Human), is supplied in single-use vials containing 160 mg IgG per mL. The following dosage forms are available:

NDC 0053-7596-03	Box of ten 3 mL vials
NDC 0053-7596-10	10 mL vial
NDC 0053-7596-15	Box of ten 10 mL vials
NDC 0053-7596-20	20 mL vial
NDC 0053-7596-25	Box of ten 20 mL vials

STORAGE

Store in the refrigerator at 2 - 8°C (36 - 46°F). Vivaglobin® Immune Globulin Subcutaneous (Human), is stable for the period indicated by the expiration date on its label. Do not freeze. Keep vials in storage box until use.

Based on April 2007 revision

In primary immunodeficiency

More patients are moving to steady levels with Vivaglobin®

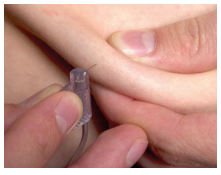
Vivaglobin® weekly infusions deliver steady serum Ig levels that protect patients against infections all month long.

Vivaglobin® is the only FDA-approved 16% Sub-Q Ig – and has been used worldwide for more than 10 years.

You can prescribe Vivaglobin® with confidence, and it is readily covered by most insurance plans.

www.vivaglobin.com

Life has its ups and downs. Ig levels don't have to.



- Vivaglobin® Sub-Q treatment is injected into the thigh, upper arm, stomach or hips on a weekly basis
- Injection-site reactions are typically mild to moderate and decrease substantially over time

Vivaglobin®

Immune Globulin Subcutaneous (Human)

Important Safety Information

Immune Globulin Subcutaneous (Human), Vivaglobin®, is indicated for the treatment of patients with primary immunodeficiency (PI).

As with all immune globulin products, Vivaglobin® is contraindicated in individuals with a history of anaphylactic or severe systemic response to immune globulin preparations and in persons with selective immunoglobulin A deficiency who have known antibody against IgA. If anaphylactic or anaphylactoid reactions are suspected, discontinue administration immediately and treat as medically appropriate.

Vivaglobin® is derived from human plasma. As with all plasma-derived products, the risk of transmission of infectious agents, including viruses and, theoretically, the Creutzfeldt-Jakob disease (CJD) agent, cannot be completely eliminated.

In clinical trials, the most frequent adverse event was injection-site reaction, consisting of mild or moderate swelling, redness, and itching. No serious local site reactions were observed, and reactions tended to decrease substantially after repeated use. Other adverse events irrespective of causality included headache, gastrointestinal disorder, fever, nausea, sore throat, and rash.

As with all immune globulin (Ig) products, patients receiving Ig therapy for the first time, receiving a new product, or not having received Ig therapy within the preceding eight weeks may be at risk for developing reactions including fever, chills, nausea, and vomiting. On rare occasions, these reactions may lead to shock. Such patients should be monitored in a clinical setting during the initial administration.

Ig administration can transiently impair the efficacy of live attenuated virus vaccines, such as measles, mumps and rubella.

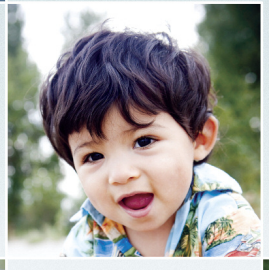
In clinical studies, administration of Vivaglobin® has been shown to be safe and well tolerated in both adult and pediatric subjects. No pediatric-specific dose requirements were necessary to achieve the desired serum IgG levels. Safety and efficacy were not studied in pediatric subjects under two years of age.

Please see brief summary of Prescribing Information on adjacent page.

Manufacturing and Distribution:
Vivaglobin® is manufactured by CSL Behring GmbH and distributed by CSL Behring LLC.

1020 First Avenue • PO Box 61501
King of Prussia, PA 19406-0901 • USA
IO#9B046 12/2008

www.vivaglobin.com



Population-Specific Vaccines

Recommendations and Requirements

Debilitating illness and death are always tragic, but when disease is preventable by a readily available vaccine, the tragedy begs the questions: Were the affected individuals and their families aware of this vaccine-preventable disease, and was the vaccine required or recommended?

By Ronale Tucker Rhodes, MS

Unfortunately, when it comes to individuals taking care of themselves, it becomes clear just how much of a reactive society we live in. Preventive care is preached, but rarely practiced. This is evident not only in lifestyle choices, but in the decision to forgo doctor visits to receive regular checkups and needed vaccinations. While the reasons are varied, part of the problem with vaccination rates is that no national immunization law exists; states enact their own laws, and those laws vary. In addition, laws pertain only to children, enacted to control the spread of infectious diseases in schools, and in some cases to young adults entering college. For teens and adults, the main problem is a lack of awareness of what is recommended for the various population age groups.

What Is Required?

Most individuals born in the U.S. are immunized against vaccine-preventable diseases in the weeks and months after birth as a result of routine immunization schedules. These "childhood immunizations consist of a series of intramuscular or subcutaneous injections or oral dosing of inactivated bacteria, toxoids, live attenuated viruses or inactive viral antigens against 14 diseases: influenza, pneumococcal, diphtheria, tetanus, pertussis, measles, mumps, rubella, polio, Haemophilus influenza b, hepatitis A and B, varicella and rotavirus. Most of the immunizations are given as combined vaccines during routine well-child checks in the first two years of life."[1]

All 50 states have laws requiring vaccination against diptheria, measles, rubella and polio prior to attendance in K-12. Washington, D.C., and 49 of the 50 states require tetanus vaccination, 44 states and D.C. require pertussis vaccination, and 48 states and D.C. require mumps vaccination. In addition, 48 states have requirements for vaccination prior to Head Start enrollment. Only 32 states have requirements for immunization prior to college attendance.[2]

Despite these laws, there still are children who do not receive these immunizations. A recent study shows that this has a lot to do with convenience and communication. The study, conducted at Columbia University Medical Center and reported on May 5, 2009, by Reuters (www.reuters.com), found that children whose parents have difficulty scheduling appointments or who have a tough time communicating with their child's doctor are more likely to be under-immunized.

Another reason for this is due to exemption for children with medical contraindications to immunizations, as well as religious and philosophical exemptions. While the numbers of students on record for exemptions is very low, data show that states with the simplest procedures for exemption had the highest rates of exemption, and there are health implications associated with those exemptions.[2] For instance, children with personal exemptions were 22 times more likely to have measles during the years 1987 through 1998, and nearly six times more likely to have pertussis.

What Is Recommended?

Because there are no laws governing immunization for adults, the number of individuals not protected against vaccine-preventable diseases is widespread. But, this is not the main reason for lack of immunization. Even if individuals were immunized as children, most don't get immunized as adults because they don't know whether they have previously been vaccinated or whether a follow-up vaccine is needed later in life. In addition, they don't know that they should ask their doctors what is recommended. According to the Centers for Disease Control and Prevention (CDC), even if individuals get vaccinated as a child, most of the vaccinations don't last forever, and they are needed again to maintain immunity. Further exacerbating this lack of awareness is that most doctors don't ask their patients if and when they've been immunized, and they fail to tell them what immunizations are needed to protect against infectious diseases.

Infectious Disease Vaccinations

All individuals require some vaccinations at intervals throughout their lives. And the case for ensuring they are up to date with these vaccines is simple: "Some of the illnesses, once contracted, do not have a cure, and all may cause tremendous health problems or even death."[3] The following vaccine-preventable diseases are those that are recommended by the major health organizations.

Influenza. Flu viruses change all the time. Flu shots are needed between September and mid-November each year to give an individual's body time to build the proper defense. The flu shot both prevents and controls the flu.

Pneumococcal disease. Pneumonia is a serious disease affecting the lungs, and the bacteria that form from this disease can attack other parts of the body, including the brain, which can cause meningitis. The CDC recommends that people over the age of 65 get the pneumococcal vaccine one time. If an individual has received this vaccine before age 65, and it has been longer than five years, the CDC recommends a second shot. Individuals ages 2 through 64 who have diabetes or chronic heart, lung, liver or kidney disorders should also get a pneumococcal vaccine.

Diphtheria, tetanus and pertussis. While tetanus is not spread from person to person, it is caused by a toxin that enters through the skin. Common signs include headache and muscle stiffness in the jaw initially, and then stiffness in the neck, difficulty swallowing, muscle spasms, sweating and fever. Diphtheria, on the other hand, is also caused by a toxin, but it can also spread from an infected person to the nose or throat of others. In some instances, it can lead to breathing problems, heart failure, paralysis and sometimes death; in others, it can cause sores on the skin that are painful, red and swollen. Pertussis (whooping cough) has recently been on the rise, and is easily spread and most dangerous in babies younger than 1 year old. In 2008, 19,000 whooping cough cases in adolescents and adults were reported to the CDC. Most children receive a combined diphtheria-tetanus-pertussis (DTP) vaccine, and adolescents and adults need a Tdap vaccine followed by a Td booster every 10 years.

Chickenpox. Also known as varicella, chickenpox is extremely contagious, spread through the air when people sneeze or cough, or through an infected person's chickenpox sores. Most children are vaccinated against chickenpox at 15 months old. People ages 13 years and older who were not vaccinated as children need two doses of the chickenpox vaccine. Once chickenpox is contracted, it is very rare but possible to get it again. It's more common for people who have had it to develop shingles later in life, caused by a reactivation of the same virus.

Measles, mumps and rubella. Most adults today are immune to measles, mumps and rubella either because they have had the diseases as children or they have been vaccinated against them. People born in or after 1957 have likely received at least one dose of the measles-mumps-rubella (MMR) vaccine. However, those born before 1957 who don't think they've been vaccinated should be, and healthcare workers and individuals who travel outside of the U.S. are advised to get a second dose.

Polio. While polio has been eliminated from the Western Hemisphere, it has not been eradicated in the rest of the world. Most children are vaccinated against polio in four different doses, the first three before 18 months of age, and the last before 6 years old. Teens who have not completed their series of polio vaccines and are not yet 18 years old are advised to complete them.

Haemophilus influenzae type b. Hib disease is caused by a bacteria and usually strikes children under 5 years old. A child can get Hib disease by being around other children or adults, as the germs spread from person to person. If the germs stay in a child's nose and throat, the child probably will not get sick. But if the germs spread into the lungs or the bloodstream, they can cause serious problems. Before the vaccine, Hib disease was the leading cause of bacterial meningitis among children

Even if individuals were immunized as children, most don't get immunized as adults because they don't know whether they have previously been vaccinated or whether a follow-up vaccine is needed later in life.

under 5 years old in the United States. All children should be immunized with the Hib vaccine. And while children over 5 years old usually do not need Hib vaccine, some older children or adults with special health conditions should get it.

Meningococcal disease. Meningitis has seen a resurgence in the U.S. Approximately 2,600 people in the U.S. are diagnosed with meningitis, and about 10 percent to 15 percent of those people die. Meningitis is a viral or bacterial infection of the fluid of a person's spinal cord and the fluid that surrounds the brain, and is spread through the exchange of respiratory and throat secretions (i.e., coughing, kissing). Symptoms include high fever, headache and stiff neck, which can develop over several hours, or they may take one to two days. Other symptoms may include nausea, vomiting, discomfort looking into bright lights, confusion and sleepiness. All teens ages 11 through 18, as well as college freshmen living in dormitories and individuals with special medical conditions, should be vaccinated against this disease. (See the related story on meningitis in this issue on page 58.)

Hepatitis A and B. Approximately 12.5 million Americans have been infected with hepatitis B virus at some point in their lifetime, and about 5,000 people die each year from hepatitis B-related liver disease.[5] The number of new infections per year is declining due to routine hepatitis B vaccination in children and adolescents. But, even if vaccinated as a child, vaccines to protect against hepatitis A and B are recommended for individuals in high-risk groups, such as healthcare workers, those who live in households and/or have sex with people with chronic hepatitis B, those with multiple sex partners, people with a recently acquired sexually transmitted disease, men who have sex with men and injecting drug users.

Rotavirus. Rotavirus is the most common cause of severe diarrhea among children, and approximately 55,000 children in the United States are hospitalized each year, while more than 600,000 children die from it annually worldwide. The disease is characterized by vomiting and watery diarrhea for three to eight days, and fever and abdominal pain occur frequently. Repeat infections can occur, but they tend to be less severe than the original infection. Three doses of the rotavirus vaccine is recommended in children at ages 2, 4 and 6 months.

Shingles. Although shingles typically occurs in adults later in life, caused by a reactivation of the chickenpox virus, adults of all ages have been known to get this disease. One dose of the shingles vaccine is recommended only for adults age 60 and over. (See the related article on shingles on page 52.)

Human papillomavirus. HPV, known to cause cervical cancer, is now believed to cause other women's cancers like vulvar and vaginal. The three-dose HPV vaccine is recommended for all females ages 11 to 26, and could be given to females as young as 9 years old.

Many organizations, including the Centers for Disease Control and Prevention, Immunization Action Coalition, American Academy of Pediatrics and most state health departments, publish immunization schedules. While some are more indepth than others, even listing medical conditions as factors, all follow the same general guidelines. Listed in Table 1 are the recommendations and requirements set forth for the different populations.

Table 1. Population-Specific Vaccine Recommendations

Vaccine	Children Ages Infant-11 Years
Influenza	
Pneumococcal conjugate (PCV)	4 doses: 2 months, 4 months, 6 months, 12-15 months
Diptheria, Tetanus and Pertussis (DTaP)	5 doses: 2 months, 4 months, 6 months, 15-18 months, 4-6 years old*
Varicella (Chickenpox)	2 doses: 12-15 months, 4-6 years
Measles, Mumps and Rubella (MMR)	2 doses: 12-15 months, 4-6 years
Polio	4 doses: 2 months, 4 months, 6-18 months, 4-6 years
Meningococcal	
Hepatitis A	2 doses: 12-23 months, 6 months apart
Hepatitis B (Hep B)	4 doses: birth, 2 months, 4 months, 6-18 months
Zoster (Shingles)	
Human papillamavirus (HPV)	
Haemophilus influenza type b (Hib)	4 doses: 2 months, 4 months, 6 months **, 12-15 months
Rotavirus (RV)	3 doses: 2 months, 4 months, 6 months **

* This dose can be given as early as 12 months if it has been 6 months since the previous dose

** Dose may not be needed depending upon type of vaccine

Keeping Up-to-Date Records

To keep current on vaccinations, physicians should stress to their patients the need to keep up-to-date vaccination records. No central repository of immunization records exists. Parents are given the only records that exist when their children are immunized, although some schools retain immunization records of children who attended, but usually for only a year or two. If an individual has served in the military, immunization records would have been required for them. Yet, again, those records are the property of the individual. Physician offices may also keep records of patients who have been vaccinated.

One way physicians can encourage patients to keep records is to provide vaccination record cards for patients to write immunizations and the dates they were received. This card should be kept in a safe place, yet a copy of the card should be made and placed in the individual's purse or wallet.

A new free service from Google — Google Health — may offer an easy solution to maintaining immunization records, as well as

and Requirements

Teens Ages 11-18	Adults Ages 19-49	Adults Ages 50-64	Adults 65 & Older
1 dose: every year after 6 months			
	1-2 doses: for cigarette smokers and/or sufferers of chronic medical conditions		1 dose: at age 65 if never been vaccinated
1 dose: 11-12 years	3 doses: if not previously vaccinated; Td booster every 10 years		
	2 doses: if not previously vaccinated		
	1 or 2 doses: if born before 1957		
1 dose: 11-12 years	1 or more doses: for high-risk occupational, medical or lifestyle groups		
	2 doses: for high-risk occupational, medical or lifestyle groups		
3 doses: if not received previously	3 doses: for high-risk occupational, medical or lifestyle groups		
			1 dose
3 doses: over 6-month period (girls only; 11-26 years)			

Note: The doses during specific age ranges are recommended. If doses are missed at those ages, they may still be given at an older age.
Sources: Immunization Action Coalition, www.immunize.org/catg.d/p4050.pdf Centers for Disease Control, www.cdc.gov/vaccines/recs/schedules/adult-schedule.htm

a complete repository for all kinds of personal health information. At www.google.com/health, it's possible to create online personal health profiles, including health conditions, medications, allergies and lab results by importing medical records from hospitals and pharmacies. Sharing health records within an approved care network is another feature, as well as browsing an online health services directory to find services that are integrated with Google Health. Competitor offerings include Microsoft's HealthVault and the Indivo project (an open-source project managed by the Children's Hospital Informatics Program).

If individuals can't locate a record of whether they've been immunized for a particular disease, "there is a blood test called the antibody titer that can detect the presence of antibodies against the disease in question. If the level of these antibodies is high enough, it is a good indication that they have immunity to the disease and do not need another vaccination."[4]

Vaccination Is a Shared Responsibility

There are many social and economic costs of vaccine-preventable diseases. While great strides have been made in the medical community to protect individuals against these diseases, everyone must do their part to ensure that vaccination rates continue to rise. According to the U.S. Department of Health and Human Services' Healthy People 2010 report on immunization and infectious diseases, vaccination rates have continued to rise among all populations. Among the Healthy People 2010 objectives are total elimination for congenital rubella syndrome, diphtheria, Haemophilus influenzae type b, measles, mumps, polio, rubella and tetanus; 41 percent improvement for pertussis; 99 percent improvement for hepatitis B; and 99 percent improvement for varicella. To accomplish this, physicians play a pivotal role by emphasizing the need for all populations to get their recommended and required vaccinations. ❖

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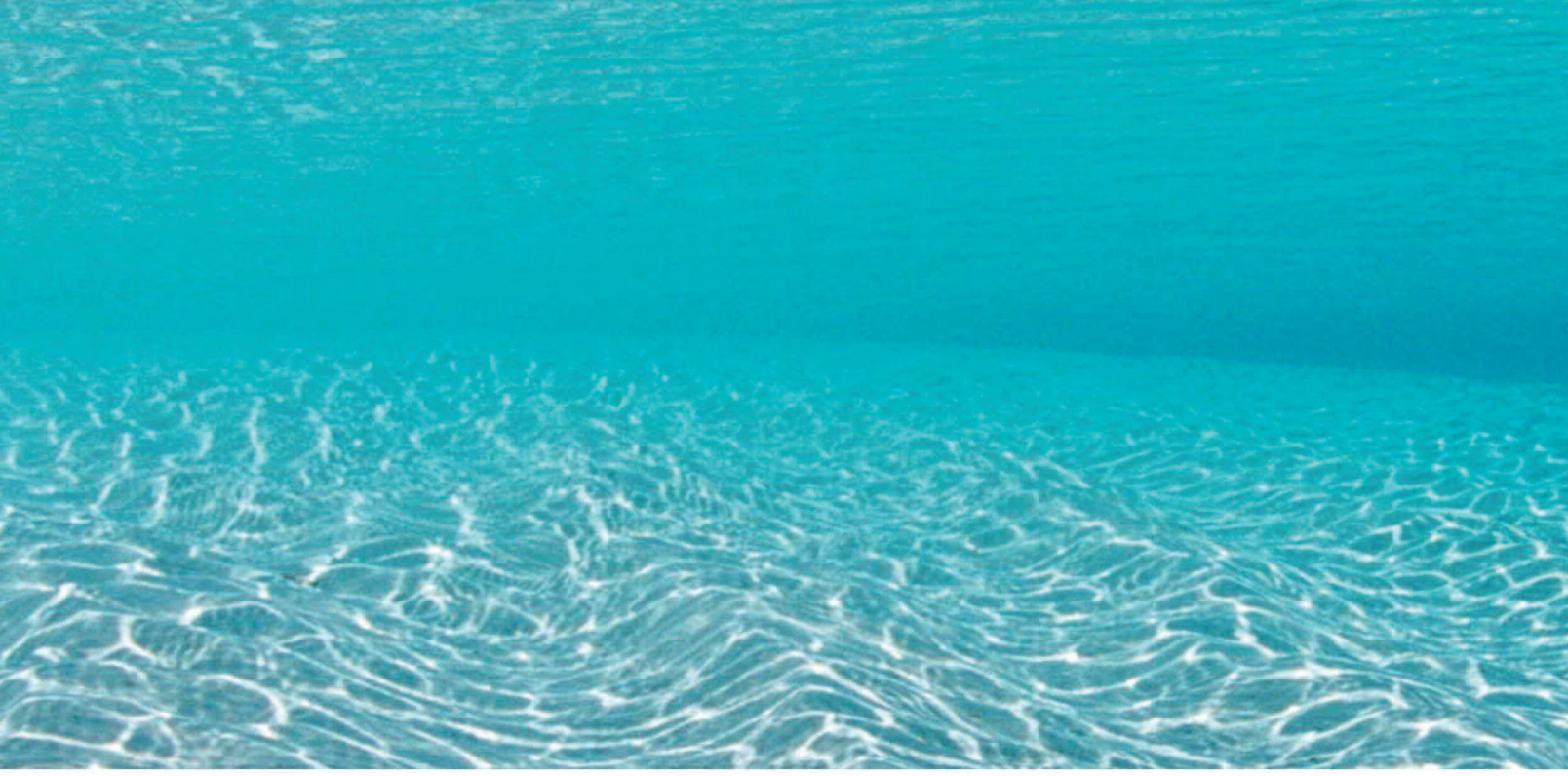
5. Centers for Disease Control and Prevention. Vaccines & Immunizations: What Would Happen If We Stopped Vaccinations? Accessed at http://www.cdc.gov/vaccines/vac-gen/whatifstop.htm.

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



HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use octagam®, Immune Globulin Intravenous (Human), safely and effectively.

OCTAGAM®
Immune Globulin Intravenous (Human) 5% Liquid Preparation

Initial U.S. Approval: 2004

RECENT MAJOR CHANGES

Warnings and Precautions - Hyperproteinemia 8/2008

WARNING: ACUTE RENAL DYSFUNCTION and RENAL FAILURE
See full prescribing information for complete boxed warning.

- **Renal dysfunction, acute renal failure, osmotic nephrosis, and death may be associated with Immune Globulin Intravenous (Human) (IGIV) products in predisposed patients.**
- **Renal dysfunction and acute renal failure occur more commonly in patients receiving IGIV products containing sucrose. octagam® 5% liquid does not contain sucrose.**
- **Administer IGIV products at the minimum concentration available and the minimum infusion rate practicable.**

INDICATIONS AND USAGE

- octagam® is an immune globulin intravenous (human), 5% liquid, indicated for treatment of primary humoral immunodeficiency (PI).

DOSAGE FORMS AND STRENGTHS

octagam® 5% liquid is supplied in 1.0 g, 2.5 g, 5 g , 10 g or 25 g single-use bottles

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

- IgA deficient patients with antibodies against IgA are at greater risk of developing severe hypersensitivity and anaphylactic reactions. Epinephrine should be available immediately to treat any acute severe hypersensitivity reactions.
- Monitor renal function, including blood urea nitrogen and serum creatinine, and urine output in patients at risk of developing acute renal failure.
- Falsely elevated blood glucose readings may occur during and after the infusion of octagam® 5% liquid with some glucometer and test strip systems.
- Hyperproteinemia, increased serum viscosity and hyponatremia 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 has been reported with octagam® 5% liquid and other IGIV treatments, especially with high doses or rapid infusion.
- Hemolytic anemia can develop subsequent to IGIV therapy due to enhanced RBC sequestration.
- IGIV recipients should be monitored for pulmonary adverse reactions (TRALI).
- The product is made from human plasma and may contain infectious agents, *e.g.* viruses and, theoretically, the Creutzfeldt-Jakob disease agent.

ADVERSE REACTIONS

Most common adverse reactions with an incidence of > 5% during a clinical trial were headache and nausea. To report SUSPECTED ADVERSE REACTIONS, contact Octapharma at 1-866-766-4860 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

DRUG INTERACTIONS

- The passive transfer of antibodies may confound the results of serological testing.
- The passive transfer of antibodies may interfere with the response to live viral vaccines.

USE IN SPECIFIC POPULATIONS

- Pregnancy: no human or animal data. Use only if clearly needed.
- In patients over age 65 or in any person at risk of developing renal insufficiency, do not exceed the recommended dose, and infuse octagam® 5% liquid at the minimum infusion rate practicable.

HOW SUPPLIED

	1g	2.5g	5g	10g	25g
Size	20ml	50ml	100ml	200ml	500ml
NDC#	67467-843-01	67467-843-02	67467-843-03	67467-843-04	67467-843-05
NDC#	68209-843-01	68209-843-02	68209-843-03	68209-843-04	

Manufactured by:
OCTAPHARMA Pharmazeutika Produktionsges.m.b.H.
Oberlaaer Strasse 235
A-1100 Vienna, Austria

Distributed by:
Octapharma USA, Inc.
121 River Street, Suite 1201
Hoboken, NJ 07030
Tel: 201-604-1130
Fax: 201-604-1131
www.octapharma.com/usa

A clear solution

IMPORTANT SAFETY INFORMATION

octagam® is contraindicated in individuals with intolerance to immunoglobulins, especially in immunoglobulin A (IgA) deficiency, when the patient has IgE mediated antibodies to IgA. Immune Globulin intravenous (Human) (IGIV) products have been reported to be associated with renal dysfunction, acute renal failure, osmotic nephrosis, and death. Other possible side effects with octagam® include: aseptic meningitis, hemolysis, transfusion-related acute lung disease (TRALI) and thrombotic events.

Immune Globulin Intravenous (Human) products have been reported to be associated with various minor reactions, such as headache, chills, backache, chest pain, fever, allergic reactions, arthralgia, dizziness, changes in blood pressure, cutaneous reactions and/or nausea and vomiting. Cases of reversible aseptic meningitis and migraine and isolated cases of reversible hemolytic anemia and reversible increases in liver function tests have been observed with octagam®. Immediate anaphylactic and hypersensitivity reactions are a remote possibility.

As with all medicines made from human plasma, the risk of spreading infectious agents, including viruses, cannot be completely eliminated.

Some types of blood glucose testing systems falsely interpret the maltose contained in octagam® as glucose. This has resulted in falsely elevated glucose readings and, consequently, in the inappropriate administration of insulin, resulting in life-threatening hypoglycemia.

See brief summary of PI on facing page.

[1]Ochs HD, Pinciaro PJ and the octagam® Study Group. octagam® 5%, an Intravenous IgG Product, is Efficacious and Well Tolerated in Subjects with Primary Immunodeficiency Diseases. *J. Clin Immunol* 2004,24;3:309-314

octagam®

Immune globulin intravenous (human)
5% liquid preparation

If you've been looking for an IGIV solution, take a look at octagam®.

octagam® has earned its reputation for safety and documented clinical efficacy[1].

To ensure tolerability[1], octagam® is carefully produced to retain as many of the characteristics of natural plasma as possible.

With over 40 million grams of octagam® infused world-wide, Octapharma is committed to helping PI patients live more active and healthier lives.

Ask your health care provider today about octagam® and find out if it could be the right solution for you.

For clinical or technical questions, please call our Medical Affairs team at 888-429-4535.

To order call FFF at 1-800-843-7477.

octapharma

For the safe and optimal use of human proteins

IG Indications:

Immune globulin is a standard of care for both FDA-approved and non-FDA-approved indications, and a growing body of research now shows promise for treating other diseases.

Immune globulin (IG) is used to treat a wide range of disorders. While the most common use of IG therapy is in treating primary immune deficiencies, its efficacy in numerous other disorders is well-documented. It is estimated that for every FDA-approved indication, there are more than 10 non-FDA-approved indications. In certain neurological and dermatological disorders, IG is considered a first-line agent. In other areas, such as renal transplant and cardiology, it has established itself as an integral part of the patient's therapy. In the future, IG may be a potentially effective treatment for diseases and conditions for which there is no cure.

However, the expansion of use of IG therapy into many newly discovered areas is complicated. The two main issues are the recurrent short supply of plasma to make IG and continual reimbursement challenges. While costs to manufacture IG continue to rise, reimbursement in many cases is below the clinician's acquisition cost of the product. And efforts to convince government and private insurance payers that higher reimbursement is necessary have been, for the most part, unsuccessful.

Production and Distribution

Five manufacturers supply IG to the U.S.: Talecris Biotherapeutics, CSL Behring, Baxter BioScience, Grifols USA and Octapharma USA. These manufacturers' products come in both liquid and powder form. Manufacturers report that they are operating near or at full capacity, which means IG availability depends upon IG sales to the rest of the world, adoption of high-yield fractionation technologies and capacity enhancements.[1] In addition, since IG is manufactured from human plasma by fractionation — a lengthy, arduous process — plasma availability is a bottleneck to increase supply levels. The fractionation process takes approximately nine months from when an individual donates plasma to when the medication is ready for use.

On- and Off-Label Indications, and Standard of Care

Marketing for IG is currently approved for five indications: primary humoral immunodeficiency; immune thrombocytopenia; chronic demyelinating polyneuropathy (CIDP); B-cell lymphocytic leukemia; and Kawasaki syndrome. While

all IG products carry an indication for primary immunodeficiency, no one product carries an indication for all five.

The number of off-label uses for IG far exceeds that of labeled indications. Although IG has been proven useful for many disease states, the likelihood of manufacturers pursuing FDA approval for already treated indications is remote given the high cost of conducting trials without the benefit of increased marketing advantages. The sometimes tenuous and limited supply of IG, combined with the high costs of treatment, require best practice standards be used when deciding to treat with IG. Some diseases commonly treated off label with IG are Guillain-Barré syndrome, polymyositis, dermatomyositis, multifocal motor neuropathy, stiff person syndrome, relapsing-remitting multiple sclerosis and pemphigus.[1]

Although there have been no controlled studies comparing one brand of IG to another, anecdotally, some patients report having fewer side effects with one product over another. IG does not come in a generic form and, therefore, brands of IG are not interchangeable. Any change in product should be monitored by a physician.[4]

Today and Tomorrow

By Ronale Tucker Rhodes, MS, and Kris McFalls

All IG products have a risk of inducing an anaphylactic reaction to IgA. While it is not known what level of IgA induces the reaction, it has been shown that IG preparations depleted of IgA (0.4 to 2.9 µg/mL) were better tolerated by a limited number of patients who reacted to preparations with higher IgA concentrations. Currently, Gammagard S/D is the only IG product available that has a low IgA level. Gammagard S/D is available in two strengths — less than 2.2 µg/mL and less than 1 µg/mL — and is typically reserved for those patients who have documented IgA deficiency and, therefore, may be at a higher risk for anaphylaxis reactions or are unable to tolerate other products.

For patients with poor venous access or for those having difficulty tolerating the side effects of intravenous immune globulin (IVIG), subcutaneous immune globulin (SCIG) may be an option. As a matter of convenience, SCIG provides patients with an infusion option that can be given independently at home. Because SCIG is administered in smaller, more frequent doses, usually once a week, patients experience more consistent trough levels rather than the peaks and valleys that come with IVIG. Vivaglobin, manufactured by CSL Behring, is currently the only FDA-approved product for subcutaneous administration.

Indications Under Current Research

Many studies are currently being conducted to look at the efficacy of IG in non-FDA-approved indications. Two specific areas that are being explored, for which IG is not used as a standard of care, include Alzheimer's and secondary recurrent miscarriage.

Alzheimer's. While IVIG use in Alzheimer's is in the early stages of investigation, it appears to have promising effects for both reducing the risk of developing Alzheimer's, as well as improving the cognitive ability of those suffering from it. Results of a study presented at the International Alzheimer's Symposium in 2008 showed that the risk of developing Alzheimer's disease and related disorders (ADRD) may be reduced by about 40 percent in patients previously treated with IVIG. In the study, a total of 847 cases treated with IVIG were compared to 84,700 untreated controls matched by age, gender and other risk factors. The proportion of patients diagnosed with dementia was 2 percent for treated cases and 4.2 percent for untreated controls. The relative risk of developing ADRD over time was 0.577 for treated patients versus controls, indicating a 42 percent lower incidence rate of dementia in patients treated with IVIG.[5]

As of early 2009, several small clinical trials have shown promising results for treating Alzheimer's with IVIG. Two studies examined the effects of IVIG in Alzheimer's disease at a mild to moderate stage of the illness. In those studies, 13 patients were treated, and while the study group was too small a number to establish conclusively whether the treatment works, IVIG was well-tolerated by the patients, and the majority showed improved cognitive ability. In addition, the first clinical study conducted at the New York-Presbyterian Hospital/Weill Cornell Medical Center suggests that IVIG may stabilize or improve cognitive function when administered over a period of a year or more. These are significant findings since other drugs on the market only work to temporarily halt or slow deterioration. A larger and more thorough Phase III clinical study is currently being developed that will involve a higher number of patients and blind studies that incorporate placebo controls to determine the usefulness of IVIG for treating Alzheimer's patients.[6]

Secondary Recurrent Miscarriage. Several clinical trials have been conducted to determine whether IVIG is an effective treatment for recurrent miscarriage. While clinical trials are

The PROOF is everywhere you look

GAMUNEX is the IGIV therapy supported by robust clinical trials

- Proven efficacy and safety in more FDA-approved indications (CIDP, PI, and ITP)* than any other liquid IGIV[1]
- The most clinically studied liquid IGIV, with >600 patients and >4100 infusions[2]

The most common drug-related adverse reactions observed at a rate ≥5% were headache, fever, chills, hypertension, rash, nausea, and asthenia (in CIDP); headache, cough, injection site reaction, nausea, pharyngitis, and urticaria (in PI); and headache, vomiting, fever, nausea, back pain, and rash (in ITP).

The most serious adverse reactions observed in clinical study subjects receiving GAMUNEX 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).

*CIDP=chronic inflammatory demyelinating polyneuropathy; PI=primary humoral immunodeficiency; ITP=idiopathic thrombocytopenic purpura.

References: 1. Data on file. Talecris Biotherapeutics, Inc. **2.** GAMUNEX® [package insert]. Research Triangle Park, NC: Talecris Biotherapeutics; 2008.

Important Safety Information—Gamunex, Immune Globulin Intravenous (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). Gamunex is contraindicated in individuals with known anaphylactic or severe systemic response to Immune Globulin (Human).

Immune Globulin Intravenous (Human) (IGIV) products have been reported to be associated with renal dysfunction, acute renal failure, osmotic nephrosis and death. Patients should be instructed to immediately report symptoms of decreased urine output, sudden weight gain, fluid retention/edema, and/or shortness of breath (which may suggest kidney damage) to their physicians.

While these reports of renal dysfunction and acute renal failure have been associated with the use of many of the licensed IGIV products, those containing sucrose as a stabilizer accounted for a disproportionate share of the total number. Gamunex does not contain sucrose. Glycine, a natural amino acid, is used as a stabilizer.

There have been reports of noncardiogenic pulmonary edema [Transfusion-Related Lung Injury (TRALI)], hemolytic anemia, and aseptic meningitis in patients administered with IGIV. 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, and/or known or suspected hyperviscosity. Hyperproteinemia, increased serum viscosity, and hyponatremia may occur in patients receiving IGIV therapy.

Gamunex is made from human plasma. As with all plasma-derived therapeutics, the potential to transmit infectious agents, such as viruses and theoretically, the Creutzfeldt-Jakob (CJD) agent that can cause disease, cannot be totally eliminated. There is also the possibility that unknown infectious agents may be present in such products.

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

Please see adjacent page for brief summary of GAMUNEX full Prescribing Information.

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immune globulin intravenous (human), 10% caprylate/chromatography purified

Talecris BIOTHERAPEUTICS

To get GAMUNEX call 1-888-MY-GAMUNEX (694-2686) USA Customer Service 1-800-243-4153 Clinical Communications 1-800-520-2807 Reimbursement *Help*line 1-877-827-3462

gamunex®

immune globulin intravenous (human), 10%
caprylate/chromatography purified

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use GAMUNEX®, Immune Globulin Intravenous (Human), 10% Caprylate/Chromatography Purified, safely and effectively. See full prescribing information for GAMUNEX.

GAMUNEX (Immune Globulin Intravenous [Human], 10% Caprylate/Chromatography Purified) 10% Liquid Preparation

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 be associated with Immune Globulin Intravenous (Human) (IGIV) products in predisposed patients.**
- **Renal dysfunction and acute renal failure occur more commonly in patients receiving IGIV products containing sucrose. GAMUNEX does not contain sucrose.**
- **Administer IGIV products at the minimum concentration available and the minimum infusion rate practicable.**

INDICATIONS AND USAGE

GAMUNEX is an immune globulin intravenous (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. Epinephrine should be 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.
- Hyperproteinemia, increased serum viscosity and hyponatremia 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 has been reported with GAMUNEX and other IGIV treatments, especially with high doses or rapid infusion.
- Hemolytic anemia can develop subsequent to IGIV therapy due to enhanced RBC sequestration.
- IGIV recipients should be monitored for pulmonary adverse reactions (TRALI).
- The product is made from human plasma and may contain infectious agents, e.g., viruses and, theoretically, the Creutzfeldt-Jakob disease agent.

ADVERSE REACTIONS

- **PI** – Most common drug related adverse reactions during clinical trials were headache and cough.
- **ITP** – Most common drug related adverse reactions during clinical trials were headache, vomiting, fever, and nausea.
- **CIDP** – Most common drug related adverse reactions during clinical trials were headache and fever.

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 interfere with the response to live viral vaccines.
- The passive transfer of antibodies may confound the results of serological testing.

USE IN SPECIFIC POPULATIONS

- In patients over age 65 or in any patient at risk of developing renal insufficiency, do not exceed the recommended dose, and infuse GAMUNEX at the minimum infusion rate practicable.
- Pregnancy: no human or animal data. Use only if clearly needed.

Talecris BIOTHERAPEUTICS

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

08939392/08939393-BS
Revised: October 2008

8 Guiding Principles for Safe, Effective and Appropriate Use of IG[4]

The American Academy of Allergy, Asthma and Immunology has outlined these eight principles to help healthcare providers appropriately provide coverage to patients with primary immunodeficiency whose lives depend upon it.

1. Indication. IVIG therapy is indicated as replacement therapy for patients with PI characterized by absent or deficient antibody production. This is an FDA-approved indication for IVIG, for which all currently available products are licensed.

2. Diagnoses. There are a large number of PI diagnoses for which IVIG is indicated and recommended. Many have low total levels of IgG, but some have a normal level with documented specific antibody deficiency.

3. Frequency of IVIG treatment. IVIG is indicated as continuous replacement therapy for primary immunodeficiency. Treatment should not be interrupted once a definitive diagnosis has been established.

4. Dose. IVIG is indicated for patients with primary immunodeficiency at a starting dose of 400 to 600 mg/kg every three to four weeks. Less frequent treatment, or use of lower doses, is not substantiated by clinical data.

5. IgG trough levels. IgG trough levels can be useful in some diagnoses to guide care, but are not useful in many and should not be a consideration in access to IVIG therapy.

6. Site of care. The decision to infuse IVIG in a hospital, hospital outpatient, community office or home-based setting must be based upon clinical characteristics of the patient.

7. Route. Route of immunoglobulin administration must be based upon patient characteristics. The majority of patients are appropriate for intravenous and a subset for subcutaneous therapy.

8. Product. IVIG is not a generic drug, and IVIG products are not interchangeable. A specific IVIG product needs to be matched to patient characteristics to ensure patient safety. A change of IVIG product should occur only with the active participation of the prescribing physician.

still ongoing, one particular study consisted of a systematic review of randomized controlled trials, comparing all dosages of IVIG to a placebo or an active control. The study looked at eight trials involving 442 women that evaluated IVIG therapy used to treat recurrent miscarriage. The findings showed that, overall, IVIG did not significantly increase the odds ratio of live birth when compared with a placebo for treatment of recurrent miscarriage. However, there was a significant increase in live births following IVIG use in women with secondary recurrent miscarriage, while those with primary miscarriage did not experience the same benefit.[7]

Plasma Supply

Although plasma is not currently in short supply and IG medicines are not depleted, the United States has experienced shortages in the past. For instance, in 2007, the shortfall of supply relative to demand was about 14 percent, and this was probably underestimated because existing demand is often suppressed by hospital protocols and reimbursement problems.[2] In a survey of public hospitals, approximately 50 percent indicated they could not purchase enough IG to meet all patient needs. As a result, 56 percent reported they had implemented a protocol to prioritize and monitor use of IG in their facilities. In addition, a survey of 310 hospital pharmacy directors conducted by the Immune Deficiency Foundation found that 27 percent of hospitals had instituted criteria for prioritizing IG use.

A more serious shortage occurred in 1998 when scarcity forced doctors to cut dosages for some patients, postpone treatment for others or switch brands, which all affect patients differently.[3] The shortage occurred due to a combination of events, including a recall of plasma products that carried a theoretical but unproven risk of transmitting a fatal, little-understood disease; the discovery of serious violations of manufacturing standards among makers of plasma products, which prompted a demand for improvements that slowed production; an increase by manufacturers in overseas shipments of the drug by about 2 percentage points, to almost 19 percent of the total available; and the discovery of uses for the drug for other illnesses, which significantly increased demand.

In 2007, manufacturers estimated annual IG demand growth between 6 percent and 8 percent, but healthcare providers predicted demand to fall between 10 percent and 15 percent annually.[2] Should the number of diseases approved by the FDA to be treated by IG continue to increase, and the number of plasma fractionation plants fail to keep up with that demand, another shortage could become a reality.

Medicare Reimbursement

Many patient groups and physicians have reported problems to the U.S. Department of Health and Human Services regarding access under current Medicare reimbursement levels. These problems include increased difficulty in acquiring IVIG,

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Discover information about dosing and transitioning from lyophilized products at:

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Please see adjacent Brief Summary of Prescribing Information including boxed warning.

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BRIEF SUMMARY OF PRESCRIBING INFORMATION

CSL Behring

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

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 AND ACUTE RENAL FAILURE

Immune Globulin Intravenous (Human) (IGIV) products have been reported to be associated with renal dysfunction, acute renal failure, osmotic nephrosis, and death.[1] Patients predisposed to acute renal failure include patients with any degree of pre-existing renal insufficiency, diabetes mellitus, age greater than 65, volume depletion, sepsis, paraproteinemia, or patients receiving known nephrotoxic drugs. In such patients, IGIV products should be administered at the minimum rate of infusion practicable. While these reports of renal dysfunction and acute renal failure have been associated with the use of many of the licensed IGIV products, those containing sucrose as a stabilizer accounted for a disproportionate share of the total number. Privigen® does not contain sucrose. *(See Dosage and Administration [2.4] and Warnings and Precautions [5.1] for important information intended to reduce the risk of acute renal failure.)*

4 CONTRAINDICATIONS

Privigen® is contraindicated in patients who have had an anaphylactic or severe systemic reaction to the administration of human immune globulin.

Because it contains the stabilizer L-proline, Privigen® is contraindicated in patients with hyperprolinemia.

Privigen® is contraindicated in individuals with selective IgA deficiency because they can develop antibodies to IgA and anaphylactic reactions (including anaphylaxis and shock) after administration of blood components containing IgA. Privigen® contains trace amounts of IgA (*see Description [11]*).

5 WARNINGS AND PRECAUTIONS

5.1 Acute Renal Dysfunction and Acute Renal Failure

Patients should not be volume depleted prior to the initiation of the infusion of Privigen®. Periodic monitoring of renal function and urine output is particularly important in patients judged to have a potential increased risk of developing acute renal failure. Renal function, including measurement of blood urea nitrogen (BUN) and serum creatinine, should be assessed before the initial infusion of Privigen® and at appropriate intervals thereafter. For patients judged to be at risk of developing renal dysfunction, Privigen® should be administered at the minimum rate of infusion practicable (*see Dosage and Administration [2.2, 2.3]*). If renal function deteriorates, consider discontinuing Privigen®. (*See Patient Counseling Information [17.1]*.)

5.2 Aseptic Meningitis Syndrome (AMS)

AMS has been reported to occur infrequently with Privigen® and other IGIV treatments. The syndrome usually begins within several hours to 2 days following IGIV treatment. AMS is characterized by signs and symptoms including 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. Patients exhibiting such signs and symptoms should receive a thorough neurological examination, 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. Discontinuation of IGIV treatment has resulted in remission of AMS within several days without sequelae.[2] (*See Patient Counseling Information [17.2]*.)

5.3 Hemolysis

IGIV products can contain blood group antibodies that may act as hemolysins and induce *in vivo* coating of red blood cells (RBCs) with immunoglobulin, causing a positive direct antiglobulin reaction and, rarely, hemolysis.[3-5] Hemolytic anemia can develop subsequent to IGIV therapy due to enhanced RBC sequestration (extravascular hemolysis) or intravascular RBC destruction (intravascular hemolysis).[6]

Hemolysis, possibly intravascular, occurred in two subjects treated with Privigen® in the ITP study. These cases resolved uneventfully. Six other subjects experienced hemolysis in the ITP study as documented from clinical laboratory data.

IGIV recipients should be monitored for clinical signs and symptoms of hemolysis (*see Patient Counseling Information [17.3]*). If signs and/or symptoms of hemolysis are present after IGIV infusion, appropriate confirmatory laboratory testing should be performed. If transfusion is indicated for patients who develop hemolysis with clinically compromising anemia after receiving IGIV, adequate cross-matching should be performed to avoid exacerbating on-going hemolysis.

5.4 Transfusion-related Acute Lung Injury (TRALI)

There have been reports of noncardiogenic pulmonary edema in patients administered IGIV.[7] TRALI is characterized by severe respiratory distress, pulmonary edema, hypoxemia, normal left ventricular function, and fever and typically occurs within 1 to 6 hours following transfusion. IGIV recipients should be monitored for pulmonary adverse reactions (*see Patient Counseling Information [17.4]*). Patients with TRALI may be managed using oxygen therapy with adequate ventilatory support.

If TRALI is suspected, appropriate tests should be performed for the presence of antineutrophil antibodies in both the product and the patient's serum.

5.5 Thrombotic Events

Thrombotic events have been reported with Privigen® and other IGIV treatments.[8-10] Patients at risk may include those with a history of atherosclerosis, multiple cardiovascular risk factors, advanced age, impaired cardiac output, hypercoagulable disorders, prolonged periods of immobilization, and/or known or suspected hyperviscosity. The potential risks and benefits of IGIV should be weighed against those of alternative therapies in all patients for whom IGIV administration is being considered.

Because of the potentially increased risk of thrombosis, baseline assessment of blood viscosity should be considered in patients at risk of hyperviscosity, including those with cryoglobulins, fasting chylomicronemia/markedly high triacylglycerols (triglycerides), or monoclonal gammopathies.

5.6 Transmissible Infectious Agents

Privigen® is made from human plasma. Products made from human plasma may contain infectious agents, e.g., 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 during manufacturing through pH 4 incubation, depth filtration, and virus filtration (*see Description [11]*).

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. 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 CSL Behring at 1-800-504-5434. (*See Patient Counseling Information [17.5].*)

5.7 Interference With Laboratory Tests

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. Passive transmission of antibodies to erythrocyte antigens (e.g., A, B, and D) may cause a positive direct or indirect antiglobulin (Coombs') test.

5.8 Interference With Live Virus Vaccines

Immunoglobulin administration may transiently impair the efficacy of live virus vaccines such as measles, mumps, and rubella. The immunizing physician should be informed so that appropriate measures may be taken (*see Drug Interactions [7.1], Patient Counseling Information [17.6]*).

6 ADVERSE REACTIONS

The most serious adverse reaction observed in clinical study subjects receiving Privigen® for PI was hypersensitivity in one subject. The most serious adverse reactions observed in 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. (*See Warnings and Precautions [5.2, 5.3]*).

The most common adverse reactions observed in subjects with PI were headache, pain, nausea, fatigue, and chills. The most common adverse reactions observed in subjects with chronic ITP were headache, pyrexia/hyperthermia, and anemia.In general, reported adverse reactions to Privigen® in subjects with either PI or chronic ITP were similar in kind and frequency to those observed with other IGIV products.

6.1 Clinical Studies Experience

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

Treatment of Primary Immunodeficiency

In a prospective, open-label, single-arm, multicenter clinical study, 80 subjects with PI received median doses of Privigen® ranging from 200 to 888 mg/kg every 3 weeks (median dose 428.3 mg/kg) or 4 weeks (median dose 440.6 mg/kg) for up to 12 months (*see Clinical Studies [14.1]*).

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 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 Immune Globulin Intravenous (Human), 10% Liquid Privigen® infusions with temporally associated AEs was 23.8% (actual proportion: 20.8%). This is below the target of 40% for this safety endpoint.[11] The total number of temporally associated AEs was 397 (a rate of 0.38 AEs per infusion).

Table 1 lists the temporally associated AEs that occurred in more than 5% of subjects within 72 hours after the end of a Privigen® infusion, *irrespective of causality*.

Table 1: Temporally Associated Adverse Events* (TAAEs) in >5% of Subjects With PI Within 72 Hours After the End of a Privigen® Infusion, *Irrespective of Causality*

TAAE	No. Subjects Reporting TAAE (% of Subjects [n=80])	No. TAAEs Reported (as % Rate of Infusions [n=1038])	No. Infusions With TAAE (% of Infusions [n=1038])
Headache	35 (43.8)	90 (8.7)	82 (7.9)
Pain	20 (25.0)	51 (4.9)	44 (4.2)
Fatigue	13 (16.3)	29 (2.8)	27 (2.6)
Nausea	10 (12.5)	22 (2.1)	19 (1.8)
Chills	9 (11.3)	15 (1.4)	15 (1.4)
Vomiting	7 (8.8)	13 (1.3)	13 (1.3)
Pyrexia	6 (7.5)	11 (1.1)	10 (1.0)
Cough	5 (6.3)	5 (0.5)	5 (0.5)
Diarrhea	5 (6.3)	5 (0.5)	5 (0.5)
Stomach discomfort	5 (6.3)	5 (0.5)	5 (0.5)

*Excluding infections.

Of the 397 temporally associated AEs reported for the 80 subjects with PI, the investigators judged 192 to be related to the infusion of Privigen® (including 5 serious, severe AEs described below). Of the 187 non-serious AEs related to the infusion of Privigen®, 91 were mild, 81 were moderate, 14 were severe, and 1 was of unknown severity. The most common temporally associated AEs judged by the investigators to be "at least possibly" related to the infusion were headache (29% of subjects), pain (14% of subjects), nausea (11% of subjects), fatigue (11% of subjects), and chills (11% of subjects).Sixteen subjects (20%) experienced 41 serious AEs. Five of these were related severe AEs (hypersensitivity, chills, fatigue, dizziness, and increased body temperature) that 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® (chills and headache in one subject; vomiting in the other).

Seventy-seven of the 80 subjects enrolled in this study had a negative direct antiglobulin test (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).

Treatment of Chronic Immune Thrombocytopenic Purpura

In a prospective, open-label, single-arm, multicenter clinical study, 57 subjects with chronic ITP received a 2 g/kg dose of Privigen® administered daily as two 1 g/kg intravenous infusions for 2 consecutive days (*see Clinical Studies [14.2]*).

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 2 lists the temporally associated AEs that occurred in more than 5% of subjects with chronic ITP within 72 hours after the end of a treatment cycle (two consecutive infusions) with Privigen®, *irrespective of causality*.

Table 2: Temporally Associated Adverse Events (TAAEs) in >5% Subjects With Chronic ITP Within 72 hours After the End of a Treatment Cycle* With Privigen®, *Irrespective of Causality*

TAAE	No. Subjects Reporting TAAE (% of Subjects [n=57])	No. TAAEs Reported (as % Rate of Infusions [n=114])	No. Infusions With TAAE (% of Infusions [n=114])
Headache	37 (64.9)	48 (42.1)	41 (36.0)
Pyrexia/hyperthermia	21 (36.8)	23 (20.2)	22 (19.3)
Nausea	6 (10.5)	8 (7.0)	6 (5.3)
Epistaxis	6 (10.5)	8 (7.0)	6 (5.3)
Vomiting	6 (10.5)	7. (6.1)	6 (5.3)
Blood unconjugated bilirubin increased	6 (10.5)	6 (5.3)	6 (5.3)
Blood conjugated bilirubin increased	5 (8.8)	5 (4.4)	5 (4.4)
Blood total bilirubin increased	4 (7.0)	4 (3.5)	4 (3.5)
Hematocrit decreased	3 (5.3)	3 (2.6)	3 (2.6)

* Two consecutive daily infusions.

Of the 183 temporally associated AEs reported for the 57 subjects with chronic ITP, the investigators judged 150 to be related to the infusion of Privigen® (including the one serious AE described below). Of the 149 non-serious AEs related to the infusion of Privigen®, 103 were mild, 37 were moderate, and 9 were severe. The most common temporally associated AEs judged by the investigators to be "at least possibly" related to the infusion were headache (65% of subjects) and pyrexia/hyperthermia (35% of subjects).

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, which 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.

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

The following mild to moderate reactions may occur with the administration of IGIV products: headache, diarrhea, tachycardia, fever, fatigue, dizziness, malaise, chills, flushing, skin reactions, wheezing or chest tightness, nausea, vomiting, rigors, back pain, chest pain, myalgia, arthralgia, and changes in blood pressure. Immediate hypersensitivity and anaphylactic reactions are also a possibility. The following adverse reactions have been identified and reported during the postapproval use of IGIV products.[12]

- *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
- *Integumentary:* Stevens-Johnson syndrome, epidermolysis, erythema multiforme, bullous dermatitis
- *Hematologic:* Pancytopenia, leukopenia, hemolysis, positive direct antiglobulin (Coombs') test
- *General/Body as a Whole:* Pyrexia, rigors
- *Musculoskeletal:* Back pain
- *Gastrointestinal:* Hepatic dysfunction, abdominal pain

Because postmarketing reporting of adverse reactions is voluntary and 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. Evaluation and interpretation of these postmarketing reactions is confounded by underlying diagnosis, concomitant medications, pre-existing conditions, and inherent limitations of passive surveillance.

Manufactured by:
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Bern, Switzerland
US License No. 1766

Distributed by:
CSL Behring LLC
Kankakee, IL 60901 USA

Based on January 2008 version.

IG Products and Indications

Product	Manufacturer	On-Label Indications
Carimune NF	CSL Behring	Primary immunodeficiency (PIDD) Immune thrombocytopenia (ITP)
Flebogamma DIF 5%	Grifols	Primary humoral immunodeficiency
Gammagard Liquid	Baxter Healthcare Corp.	Treatment of primary immunodeficiency disorders associated with defects in humoral immunity
Gammagard S/D	Baxter Healthcare Corp.	Primary immune disease (PIDD) B-cell chronic lymphocytic leukemia Immune thrombocytopenia purpura (ITP) Kawasaki syndrome
Gamunex	Talecris	Primary immunodeficiency (PIDD Chronic demyelinating polyneuropathy (CDP) Immune thrombocytopenia (ITP)
Octagam	Octapharma	Primary humoral immunodeficiency
Privigen	CSL Behring	Primary immunodeficiency (PIDD) Immune thrombocytopenia (ITP)
Vivaglobin	CSL Behring	Primary immunodeficiency (PIDD)

switching from administration in a physician's office to a hospital outpatient facility, fewer treatments due to difficulty acquiring IVIG and switching among IVIG products.[2]

An anonymous survey conducted by the American Academy of Allergy, Asthma and Immunology (AAAAI) revealed that more than 95 percent of AAAAI's member physicians feel that current reimbursement standards present a health risk to their patients with primary immunodeficiencies.[4] In another survey by the Immune Deficiency Foundation, 26 percent of Medicare patients and 10 percent of other patients experienced adverse health outcomes due to problems with IVIG access.

Access problems are often attributed to the reduction in Medicare reimbursement rates for IG, a consequence of the average sales price (ASP) methodology, introduced in the Medicare Modernization Act of 2003 (MMA), for Part B covered drugs that are not paid on a cost or prospective payment basis. The ASP methodology is based on quarterly drug pricing data submitted to the Centers for Medicare and Medicaid Services (CMS) by drug manufacturers. The lag time inherent in this approach means that the payment rate in a quarter is based on the ASP from two quarters prior. In a rising price environment, some healthcare providers are paying more, sometimes substantially more, than the ASP plus 6 percent, and therefore, are not fully reimbursed.[2]

Conclusion

The future of IG does look promising for its ability to treat a host of disease states. However, for treatment to truly be effective for a growing number of patients, equal effort will need to be given to finding solutions to the supply and reimbursement issues as is given to the testing of the product to spread its reach. ❖

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RONALE TUCKER RHODES, *MS, is the editor of* BioSupply Trends Quarterly *magazine, and Kris McFalls is the patient advocate for* IG Living *magazine, written or patients who depend upon immune globulin products and their healthcare providers.*

Helping Healthcare Care

"If your actions inspire others to dream more, learn more, do more and become more, you are a leader."

— John Quincy Adams

BY TRUDIE MITSCHANG

AS THE FOUNDER and chief executive officer of FFF Enterprises, Inc., Patrick M. Schmidt has spent the past 21 years inspiring others in the healthcare industry to put the needs of patients first. His company's motto, "helping healthcare care," has been the driving force behind every business decision and, according to Schmidt, the secret of his success.

Like many great American achievement stories, Schmidt's has humble beginnings. After a career as a pro football player, Schmidt just wanted to make a little extra money while at UCLA prior to beginning his planned career as a football coach. FFF Enterprises was founded in 1988 with $100 and a vision to distribute patient examination gloves. Today, the company's annual sales exceed $1 billion, and its influence has been felt far and wide. In an industry like biopharmaceuticals with a distribution channel that was once rampant with unstable pricing, ill-managed shortages and unpredictable product allocation, Schmidt saw an opportunity to make a positive change that would have lasting ramifications. Almost from the start, he set out to secure the biopharmaceutical supply chain and thereby minimize the risk of counterfeits for manufacturers, distributors and customers. By all accounts, his mission has been a successful one.

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Today, FFF is recognized as the most trusted distributor of biopharmaceuticals, plasma products and vaccines in the nation.

"Our customers recognize the value of channel integrity to their patients and their bottom lines," says Schmidt. "As we continue developing our channel, we expect that responsibility, safety and trust will become the driving values throughout the industry."

When it comes to leadership, a reputation for integrity is an essential component behind any individual or company with designs on blazing new trails. Knowing that achieving Guaranteed Channel Integrity for his company was dependent on engendering the trust of manufacturers and customers, FFF sought out committed partners who shared the vision, and found them. FFF also developed innovative technologies such as the Verified Electronic Pedigree™ (VEP) system, which electronically displays the chain of custody for every product it ships, and the LotTrack™ service, which tracks products by lot number and provides recall notification to those affected. Schmidt's foresight also led to the development of a best practices business model dubbed "The 8 Critical Steps to Guaranteed Channel Integrity™." Today, FFF is recognized as the most trusted distributor of biopharmaceuticals, plasma products and vaccines in the nation, serving more than 80 percent of U.S. hospitals and supplying the nation's leading non-acute care group purchasing organizations.

Another example of FFF's quality commitment is epitomized by its specialty pharmacy subsidiary, NuFACTOR, which was established to provide IVIG, coagulation factors and vaccines directly to patients. The ability to have a direct and often profound impact on the quality of life of a patient in need is what truly motivates Schmidt. In addition, innovative programs such as MyFluVaccine and VaxAmerica have provided revolutionary approaches to vaccination, removing barriers for healthcare providers, patients and health plans in providing and receiving the preventive vaccines that are vital to long-term health and wellness.

myths and facts: shingles

Understanding the shingles virus can help patients dodge this painful and sometimes debilitating condition.

By Jim Trageser

Many misconceptions exist about whether an individual can get shingles, why and at what age, and how it is treated and/or prevented. Medical providers have no doubt felt frustrated by the lack of basic understanding patients have about shingles. These common myths and facts surrounding the disease should help clear up any confusion.

Myth: I can't get shingles because I had chickenpox as a child.

Fact: Nearly every general practitioner or geriatrician has heard the disbelief in the voice of a patient diagnosed with shingles who proclaims, "But I can't have shingles; I had chickenpox as a child!"

Shingles is a painful rash caused by the same virus, the varicella-zoster virus (VZV), that causes chickenpox. Having chickenpox provides a patient with a lifetime immunity from another chickenpox outbreak, but it doesn't prevent them from getting shingles. In fact, it's little more than the first step in getting shingles, as VZV can reactivate years or decades later as herpes zoster, or shingles. So, if an individual has had chickenpox, they can get shingles at any time, without warning.

Preventing chickenpox through vaccination is one approach to minimizing the risk of developing shingles. The childhood chickenpox vaccine is now in wide use in the developed world, which may eventually make shingles far less common than is true today. But the vaccine wasn't introduced in the United States until 1995 — meaning there are hundreds of millions of Americans who already had chickenpox as children and are at risk of developing shingles later in life. The Immunization Action Coalition reports that some 90 percent of American adults have had chickenpox, and some 30 percent of them will develop shingles at some point in life.[1]

If you've had chickenpox, you can get shingles at any time, without warning.

Initial studies seem to indicate that while the varicella, or chickenpox, vaccine reduces the rate of shingles eventually developing, it doesn't seem to eliminate the incidence of shingles altogether. Because the chickenpox vaccine is a live, attenuated vaccine, some people will develop chickenpox — although generally a mild form — from the vaccine itself and thus be susceptible to developing shingles down the road.[2] With or without receiving the varicella vaccine, some patients may have had a case of chickenpox so mild, they never knew they had it.

So while future generations may endure a far lower incidence of shingles, for the foreseeable future, it's a disease medical professionals are going to be treating on a regular basis.

Myth: Shingles affects only older adults.

Fact: While it isn't known exactly what triggers an outbreak of shingles, age is likely a contributing factor. Young people can and do get shingles, but it is more common in the elderly — and more likely to be severe, meaning more painful and lasting longer than in a young person.

It is estimated that in the United States, one million cases of shingles occur every year, and an individual's risk of getting shingles increases with age. (See the Rate of Shingles by Age Group graph.) Of those cases, almost half will occur in people 60 years of age or older. And, as the population ages, the number of cases of shingles is likely to increase.[3]

Myth: Shingles is not a serious condition.

Fact: While generally not a serious condition, shingles can be incapacitatingly painful during its several-week run as a painful blistering rash that can appear anywhere on the body. Prior to the rash, individuals typically feel burning, itching or tingling in the area where the rash will form. A few days later, a blistering rash appears on the skin, typically on only one side of the body, and lasting up to 30 days.

For most people, the pain associated with the rash lessens as it heals. But, for some, shingles may lead to long-term pain that can last for months or even years. Because the rash inflames nerve endings themselves, traditional analgesics are often ineffective in providing relief. And even after the shingles infection has abated, a condition called postherpetic neuralgia (PHN) in the affected nerve tissue can result in lingering pain for years — pain often more difficult to treat than that of the shingles infection itself.

But while shingles typically isn't dangerous, the incidence of serious complications from shingles itself increases with a patient's age. Potential complications include scarring, bacterial skin infections, decrease or loss of vision or hearing, paralysis on one side of the face, muscle weakness, allodynia (pain from a source that would not normally cause pain — such as a slight breeze over the skin or the touch of clothing on the skin) and, as mentioned, PHN, which is long-term nerve pain. In addition, blindness (if the shingles outbreak covers an eye) and even encephalitis leading to death, have been attributed to shingles.

Myth: Shingles can't be treated; it just has to be endured.

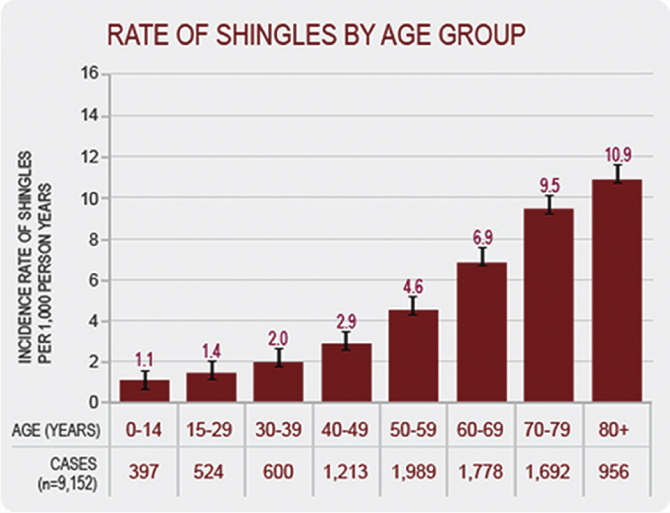
Fact: For the vast majority of human history, a case of the shingles was something patients had no option but to endure. Given that shingles is rarely life-threatening, the best advice physicians could dispense to their patients with shingles was to grit their teeth and bear it. And "bear it" is the operative phrase.

But, the release of the first generation of antiviral medications in the 1980s gave medical providers their first real tool to

effectively treat shingles. Historically, viral infections could be prevented through vaccination, but not treated after a patient was infected.

Coincidentally, shingles is closely related to other human herpesviridae, like herpes simplex I and II, the viruses that cause cold sores and genital herpes — the latter of which provided a potentially lucrative patient base for any effective treatments that might be introduced to market. Acyclovir was developed to fight genital herpes, but because varicella is so similar in how it replicates in a host cell, the antivirals developed to fight genital herpes (by preventing them from replicating themselves) turned out to also be effective against shingles.

Acyclovir (sold under the brand names of Acivir, Cyclovir, Herpex and Zovirax) is effective at shortening the duration of a shingles outbreak (much as it is effective at shortening a genital herpes outbreak). However, it has not been shown to eliminate the incidence of the post-shingles PHN, or to significantly diminish the pain during a shingles outbreak.



Graph reprinted from www.shinglesinfo.com. Copyright Merck & Co., Inc.

Myth: There is no vaccine to prevent shingles.

Fact: While this was true before 2006, pharmaceutical manufacturer Merck was granted permission in that year to market its shingles vaccine, Zostavax, to patients 60 and older, and now real relief from a debilitating disease is at hand.

Like the varicella vaccine administered in childhood to prevent chickenpox, the Zostavax vaccine is an attenuated, live inoculation, which means patients are given a weakened strain of the virus to allow their bodies to build up their own immunity naturally with little risk of developing a full-blown case of shingles. Zostavax is administered only to those who are at least 60 years old and have had chickenpox. It is not, however, recommended for those who have a variety of medical conditions. And, patients who have never had chickenpox should still get the varicella vaccine. In the near future, Zostavax may be indicated for adults ages 50 to 59. Currently, a large, phase III study to evaluate the safety and efficacy of Zostavax in that age group is ongoing, and Merck anticipates filing for this new indication in 2010.

About Zostavax

Information for patients unsure about the Zostavax vaccine is available from both the Food and Drug Administration (www.fda.gov/cber/products/zostavax.htm) and the CDC (www.cdc.gov/vaccines/vpd-vac/shingles/default.htm).

Zostavax has been shown to prevent shingles in half the patients given it, and to reduce the incidence of postherpetic neuralgia by two-thirds.[4] Paul Richards, a public affairs specialist in the Food and Drug Administration's Center for Biologics Evaluation and Research, says that the most common adverse reactions to the Zostavax vaccine have been "redness, pain and tenderness, swelling at the site of injection of the vaccine and headache."

Because the risks of the Zostavax vaccine are so low, and patients' quality of life can be so dramatically impacted by a case of shingles, the Centers for Disease Control and Prevention has recommended that all patients age 60 and older who have had chickenpox be given the Zostavax vaccine. ❖

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JIM TRAGESER *edits the film, religion and books sections for a daily newspaper in the San Diego, Calif., area, and has contributed to two reference books on the blues.*

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When thrombotic risk is high in hereditary antithrombin deficiency

Proceed Safely

When it comes to treating patients with hereditary antithrombin deficiency, Thrombate III is the proven therapy to prevent thromboembolic events in high-risk situations, such as[1]:

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- Obstetrical procedures (including childbirth)
- Acute thromboembolism

And the long-term safety experience with Thrombate III is unmatched[1,2]:

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- Pasteurized to inactivate viruses, with no confirmed case of virus transmission
- Purified to remove proinflammatory antibodies and cytokines

To order, call Talecris USA Customer Service at **1-800-243-4153** or visit **www.thrombate.com**.

For technical questions, call Talecris Clinical Communications at **1-800-520-2807** or visit **www.thrombate.com**.

Thrombate III—treating hereditary antithrombin deficiency for more than 16 years.

References: 1. Thrombate III [prescribing information]. Research Triangle Park, NC: Talecris Biotherapeutics, Inc.; 2008. **2.** Data on file, Talecris Biotherapeutics, Inc., 1988. **3.** Scott GR, Robinson MJ, Wilczek J, Berson MR. *FDA Drug and Device Product Approvals.* Springfield, VA: Division of Drug Information Resources, OM, CDER, US Dept of Health and Human Services, Public Health Service; 1991;14(2):333.

Important Safety Information

Thrombate III is indicated for the treatment of patients with hereditary antithrombin deficiency in connection with surgical or obstetrical procedures or when they suffer from thromboembolism. In clinical studies with Thrombate III, the most common side effects were dizziness, chest tightness, nausea, and a foul taste in the mouth. The anticoagulant effect of heparin is enhanced by concurrent treatment with Thrombate III in patients with hereditary AT-III deficiency. Thus, in order to avoid bleeding, reduced dosage of heparin is recommended during treatment with Thrombate III.

Thrombate III is made from human plasma. As with all plasma-derived therapeutics, the potential to transmit infectious agents, such as viruses and theoretically, the Creutzfeldt-Jakob (CJD) agent that can cause disease, cannot be totally eliminated. 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.

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

Talecris BIOTHERAPEUTICS

Thrombate III® antithrombin III (human)

Printed in USA May 2009 TH48-0509

THROMBATE III®
Antithrombin III (Human)

BRIEF SUMMARY
CONSULT PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION

FOR INTRAVENOUS USE ONLY

DESCRIPTION
Antithrombin III (Human), THROMBATE III® is a sterile, nonpyrogenic, stable, lyophilized preparation of purified human antithrombin III.

THROMBATE III is prepared from pooled units of human plasma from normal donors by modifications and refinements of the cold ethanol method of Cohn. When reconstituted with Sterile Water for Injection, USP, THROMBATE III has a pH of 6.0–7.5, a sodium content of 110–210 mEq/L, a chloride content of 110–210 mEq/L, an alanine content of 0.075–0.125 M, and a heparin content of not more than 0.004 unit/IU AT-III. THROMBATE III contains no preservative and must be administered by the intravenous route. In addition, THROMBATE III has been heat-treated in solution at 60°C ± 0.5°C for not less than 10 hours.

Each vial of THROMBATE III contains the labeled amount of antithrombin III in international units (IU) per vial. The potency assignment has been determined with a standard calibrated against a World Health Organization (WHO) antithrombin III reference preparation.

The manufacturing process was investigated for its capacity to decrease the infectivity of an experimental agent of transmissible spongiform encephalopathy (TSE), considered as a model for the vCJD and CJD agents.

An individual production step in the THROMBATE III manufacturing process has been shown to decrease TSE infectivity of that experimental model agent. The TSE reduction step is the Effluent I to Effluent II + III fractionation step (6.0 logs). These studies provide reasonable assurance that low levels of CJD/vCJD agent infectivity, if present in the starting material, would be removed.

CLINICAL PHARMACOLOGY
Antithrombin III (AT-III), an alpha$_2$-glycoprotein of molecular weight 58,000, is normally present in human plasma at a concentration of approximately 12.5 mg/dL and is the major plasma inhibitor of thrombin. Inactivation of thrombin by AT-III occurs by formation of a covalent bond resulting in an inactive 1:1 stoichiometric complex between the two, involving an interaction of the active serine of thrombin and an arginine reactive site on AT-III. AT-III is also capable of inactivating other components of the coagulation cascade including factors IXa, Xa, XIa, and XIIa, as well as plasmin.

The neutralization rate of serine proteases by AT-III proceeds slowly in the absence of heparin, but is greatly accelerated in the presence of heparin. As the therapeutic antithrombotic effect in vivo of heparin is mediated by AT-III, heparin is ineffective in the absence or near absence of AT-III.

The prevalence of the hereditary deficiency of AT-III is estimated to be one per 2000 to 5000 in the general population. The pattern of inheritance is autosomal dominant. In affected individuals, spontaneous episodes of thrombosis and pulmonary embolism may be associated with AT-III levels of 40%–60% of normal. These episodes usually appear after the age of 20, the risk increasing with age and in association with surgery, pregnancy and delivery. The frequency of thromboembolic events in hereditary antithrombin III (AT-III) deficiency during pregnancy has been reported to be 70%, and several studies of the beneficial use of Antithrombin III (Human) concentrates during pregnancy in women with hereditary deficiency have been reported. In many cases, however, no precipitating factor can be identified for venous thrombosis or pulmonary embolism. Greater than 85% of individuals with hereditary AT-III deficiency have had at least one thrombotic episode by the age of 50 years. In about 60% of patients thrombosis is recurrent. Clinical signs of pulmonary embolism occur in 40% of affected individuals. In some individuals, treatment with oral anticoagulants leads to an increase of the endogenous levels of AT-III, and treatment with oral anticoagulants may be effective in the prevention of thrombosis in such individuals.

In clinical studies of THROMBATE III conducted in 10 asymptomatic subjects with hereditary deficiency of AT-III, the mean in vivo recovery of AT-III was 1.6% per unit per kg administered based on immunologic AT-III assays, and 1.4% per unit per kg administered based on functional AT-III assays. The mean 50% disappearance time (the time to fall to 50% of the peak plasma level following an initial administration) was approximately 22 hours and the biologic half-life was 2.5 days based on immunologic assays and 3.8 days based on functional assays of AT-III. These values are similar to the half-life for radiolabeled Antithrombin III (Human) reported in the literature of 2.8–4.8 days.

In clinical studies of THROMBATE III, none of the 13 patients with hereditary AT-III deficiency and histories of thromboembolism treated prophylactically on 16 separate occasions with THROMBATE III for high thrombotic risk situations (11 surgical procedures, 5 deliveries) developed a thrombotic complication. Heparin was also administered in 3 of the 11 surgical procedures and all 5 deliveries. Eight patients with hereditary AT-III deficiency were treated therapeutically with THROMBATE III as well as heparin for major thrombotic or thromboembolic complications, with seven patients recovering. Treatment with THROMBATE III reversed heparin resistance in two patients with hereditary AT-III deficiency being treated for thrombosis or thromboembolism.

During clinical investigation of THROMBATE III, none of 12 subjects monitored for a median of 8 months (range 2–19 months) after receiving THROMBATE III, became antibody positive to human immunodeficiency virus (HIV-1). None of 14 subjects monitored for ≥ 3 months demonstrated any evidence of hepatitis, either non-A, non-B hepatitis or hepatitis B.

INDICATIONS AND USAGE
THROMBATE III is indicated for the treatment of patients with hereditary antithrombin III deficiency in connection with surgical or obstetrical procedures or when they suffer from thromboembolism.

Subjects with AT-III deficiency should be informed about the risk of thrombosis in connection with pregnancy and surgery and about the inheritance of the disease.

The diagnosis of hereditary antithrombin III (AT-III) deficiency should be based on a clear family history of venous thrombosis as well as decreased plasma AT-III levels, and the exclusion of acquired deficiency.

AT-III in plasma may be measured by amidolytic assays using synthetic chromogenic substrates, by clotting assays, or by immunoassays. The latter does not detect all hereditary AT-III deficiencies.

The AT-III level in neonates of parents with hereditary AT-III deficiency should be measured immediately after birth. (Fatal neonatal thromboembolism, such as aortic thrombi in children of women with hereditary antithrombin III deficiency, has been reported.)

Plasma levels of AT-III are lower in neonates than adults, averaging approximately 60% in normal term infants. AT-III levels in premature infants may be much lower. Low plasma AT-III levels, especially in a premature infant, therefore, do not necessarily indicate hereditary deficiency. It is recommended that testing and treatment with THROMBATE III of neonates be discussed with an expert on coagulation.

CONTRAINDICATIONS
None known.

WARNINGS
THROMBATE III is made from human plasma. Products made from human plasma may contain infectious agents, such as viruses and theoretically, the Creutzfeldt-Jakob (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 Talecris Biotherapeutics, Inc. [1-800-520-2807].

The physician should discuss the risks and benefits of this product with the patient, before prescribing or administering it to a patient.

The anticoagulant effect of heparin is enhanced by concurrent treatment with THROMBATE III in patients with hereditary AT-III deficiency. Thus, in order to avoid bleeding, reduced dosage of heparin is recommended during treatment with THROMBATE III.

PRECAUTIONS
General
1. Administer within 3 hours after reconstitution. Do not refrigerate after reconstitution.
2. Administer only by the intravenous route.
3. THROMBATE III, once reconstituted, should be given alone, without mixing with other agents or diluting solutions.
4. Product administration and handling of the needles must be done with caution. Percutaneous puncture with a needle contaminated with blood can transmit infectious virus including HIV (AIDS) and hepatitis. Obtain immediate medical attention if injury occurs.

   Place needles in sharps container after single use. Discard all equipment including any reconstituted THROMBATE III product in accordance with biohazard procedures.

The diagnosis of hereditary antithrombin III (AT-III) deficiency should be based on a clear family history of venous thrombosis as well as decreased plasma AT-III levels, and the exclusion of acquired deficiency.

Laboratory Tests
It is recommended that AT-III plasma levels be monitored during the treatment period. Functional levels of AT-III in plasma may be measured by amidolytic assays using chromogenic substrates or by clotting assays.

Drug Interactions
The anticoagulant effect of heparin is enhanced by concurrent treatment with THROMBATE III in patients with hereditary AT-III deficiency. Thus, in order to avoid bleeding, reduced dosage of heparin is recommended during treatment with THROMBATE III.

Pregnancy Category B
Reproduction studies have been performed in rats and rabbits at doses up to four times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to THROMBATE III. It is not known whether THROMBATE III can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Pediatric Use
Safety and effectiveness in the pediatric population have not been established. The AT-III level in neonates of parents with hereditary AT-III deficiency should be measured immediately after birth. (Fatal neonatal thromboembolism, such as aortic thrombi in children of women with hereditary antithrombin III deficiency, has been reported.)

Plasma levels of AT-III are lower in neonates than adults, averaging approximately 60% in normal term infants. AT-III levels in premature infants may be much lower. Low plasma AT-III levels, especially in a premature infant, therefore, do not necessarily indicate hereditary deficiency. It is recommended that testing and treatment with THROMBATE III of neonates be discussed with an expert on coagulation.

ADVERSE REACTIONS
In clinical studies involving THROMBATE III, adverse reactions were reported in association with 17 of the 340 infusions during the clinical studies. Included were dizziness (7), chest tightness (3), nausea (3), foul taste in mouth (3), chills (2), cramps (2), shortness of breath (1), chest pain (1), film over eye (1), light-headedness (1), bowel fullness (1), hives (1), fever (1), and oozing and hematoma formation (1). If adverse reactions are experienced, the infusion rate should be decreased, or if indicated, the infusion should be interrupted until symptoms abate.

CAUTION
℞ only

U.S. federal law prohibits dispensing without prescription.

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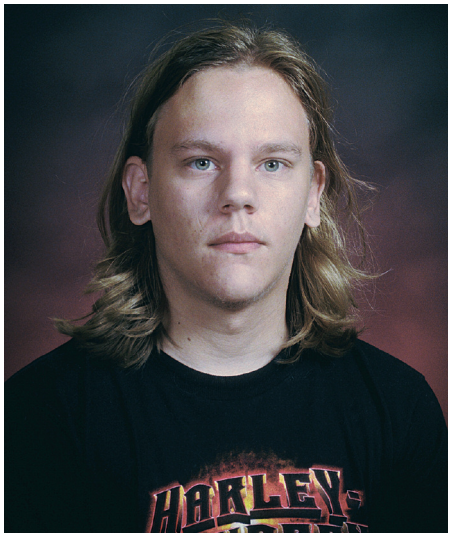
08938503-BS

When the Laughter Dies

Following the tragic loss of their son, the Knutter family copes by spreading the word about meningococcal meningitis in hopes of boosting awareness and vaccination rates.

by TRUDIE MITSCHANG



ALEX KNUTTER HAD a keen sense of humor. Friends say the outgoing 17-year-old high school senior could make you laugh, even when the joke was on you. He had a talent for sketching, often filling notebooks with his artistic creations. Boisterous in the way of teenage boys, Alex also had a vivid imagination and gregarious personality — even in a crowded room, his was the voice that carried. He had good friends, a loving family and a bright future. As it turns out, one thing Alex did not have was a meningococcal vaccination. It was the one thing that might have saved his life.

On Friday, Feb. 23, 2007, Alex became ill. Although he seemed healthy for the better part of the day, at 7:30 that evening he complained of a headache and flu-like symptoms. His parents, Jeff and Donna, recall suggesting he take some Tylenol and rest. But by the next morning Alex's condition had worsened; he'd vomited much of the night and seemed strangely disoriented and unresponsive. That's when Donna began to suspect something was seriously wrong.

"So much of what happened is a blur," she says. "I remember calling 911 and telling my husband to do CPR. I remember it taking way too long for the ambulance to arrive. I remember the police asking lots of questions and I remember letting the dog out because she was going crazy. I remember praying."

Alex was rushed to the hospital, and in a matter of hours, the situation turned from worrisome to dire. Donna and Jeff were stunned when a hospital chaplain suggested calling family members; the rapidly unfolding events seemed impossible to comprehend. Doctors wanted to transfer Alex to Children's Hospital in Milwaukee, but were unable to do so unless his condition stabilized. Despite their best efforts, Alexander John Knutter passed away at 10:36 a.m. on Feb. 24, 2007, a victim of meningococcal meningitis. He died just 16 hours after he first displayed symptoms.

Meningococcal disease strikes about 3,000 Americans each year and is responsible for approximately 300 deaths annually. About 10 percent of people who develop meningococcal meningitis die, and another 10 percent suffer severe complications including hearing and limb loss and mental retardation. At a glance, those numbers can seem relatively small, which may partially account for the widespread lack of awareness about the disease and its vaccine. Of course, those numbers are not small to the parents, grandparents and friends of those whose lives are cut tragically short by a merciless disease that preys on infants, teens and young adults. Those statistics are anything but insignificant to Donna and Jeff Knutter.

"As we were making funeral arrangements for our son, we learned for the first time that there was a vaccine that could have prevented his death," says Jeff. "We couldn't understand, given the swiftness and severity of this disease, why the immunization was not required, why no one had ever talked with us about it."

Donna agrees. "We were up-to-date on all scheduled vaccinations, and had we been aware of this deadly disease, we would have protected Alex against it. We are now

Meningococcal Meningitis

A 5K walk was held in the Knutters' community on April 25 to commemorate World Meningitis Awareness Day and in remembrance of their son, Alex.

learning everything we can about all forms of meningitis; we want to do whatever we can to prevent another family from having to go through this nightmare."

Today, the Knutters devote much of their time to spreading the word about the importance of having children and teens immunized against meningitis. On April 25 of this year, they organized a 5K walk in their community to commemorate World Meningitis Awareness Day. The walk drew 135 participants and raised more than $10,000. "We spread the word wherever we can, anyplace people will listen," says Jeff. "We really want to educate people about how devastating this disease can be."

For any family, the loss of a child leaves an empty place at the table and a profound emptiness in the heart. For the Knutters, though, it is their home's newfound silence that resonates the loudest. "Every day we miss his smile and the sound of his laughter in the house; it's just so quiet now," Donna says. "It constantly reminds us how important it is for doctors to provide vaccine information to their patients. Ultimately, parents have to make their own decisions, but they should at least be given the choice. If we had been given that choice, Alex would be alive today." ❖

TRUDIE MITSCHANG, *is a staff writer for* BioSupplyTrends Quarterly.

What Can Healthcare Providers Do?

Familiarizing yourself with the facts about meningococcal meningitis is the first step to becoming an advocate for change. Passing on critical information to patients is essential so that families can make informed choices about the decision to vaccinate. Here are some frequently asked questions:

What is meningococcal meningitis?

Meningococcal disease is a rare but potentially fatal bacterial infection. The disease is expressed as either meningococcal meningitis, an inflammation of the membranes surrounding the brain and spinal cord, or meningococcemia, the presence of bacteria in the blood.

What causes meningococcal meningitis?

Meningococcal disease is caused by the bacterium Neisseria meningitidis, a leading cause of meningitis and septicemia (or blood poisoning) in the United States.

How is it spread?

Meningococcal disease is transmitted through the air via droplets of respiratory secretions and direct contact with an infected person.

What are the symptoms?

The early symptoms include fever, severe headache, stiff neck, rash, nausea, vomiting and lethargy, and may resemble the flu.

Who is at risk?

Although meningococcal disease rates are highest in infants, rates begin to rise again in early adolescence and peak between the ages of 15 and 24.

Who should be vaccinated?

The Advisory Committee on Immunization Practices (ACIP) to the Centers for Disease Control and Prevention (CDC) has recommended that children ages 11 to 12 and teens entering high school, as well as college freshmen living in dormitories, receive meningococcal vaccine.

Is the vaccine effective?

The meningococcal vaccine has been shown to provide protection against the most common strains of the disease, including serogroups A, C, Y and W-135.

Is the vaccine safe?

The bacterial meningitis vaccine is safe, effective and generally well-tolerated. The vaccination is given in one injection.

What is the duration of protection?

The duration of the Menactra meningococcal vaccine's efficacy is expected to be eight years, possibly longer.

For more information

National Meningitis Foundation: www.nmaus.org
Meningitis Angels: www.meningitis-angels.org

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Albumin on the Cutting Edge

BY CHRIS GROUND

DESPITE AN EXCELLENT emergency care system, ischemic stroke remains a leading cause of death in the U.S. More than one in five survivors faces serious long-term disability. Many would-be neuroprotective drugs have been tested in clinical trials with the hope of limiting the damage to brain tissue. None has worked.

Then there is severe sepsis, an even more efficient killer that will claim the lives of roughly one-third of its 750,000 victims this year. This complex infection-induced syndrome has managed to outflank a long list of conceptually appealing experimental agents: antioxidants, antibodies targeting endotoxin and cytokines, vasoregulators, anti-inflammatory agents. All of them have fallen short.

So it may surprise many that, after all the years and billions of research dollars spent on failed drug candidates, doctors could soon have a single, effective new treatment to reduce the terrible toll of both stroke and sepsis. Interestingly, however, this potentially transformative new product isn't really new: It's human albumin.

Albumin Through History

Albumin was developed in the laboratory of a Harvard chemist named Edwin J. Cohn on the eve of the U.S. entry into World War II. The first inventory of 50 bottles of purified albumin was airlifted to Honolulu to treat the severely burned and wounded just days after the December 1941 bombing of Pearl Harbor. Since then, albumin has been within reach of military surgeons in every U.S. armed conflict, including Iraq and Afghanistan. It is credited with saving thousands of lives.

Over the last six decades, albumin has been administered to millions of hospitalized patients to restore blood volume, boost blood pressure and combat dangerous edema. Yet prior to a landmark 1999 trial in which its use cut mortality and renal impairment by roughly threefold in patients with cirrhosis and bacterial peritonitis, it had never been evaluated in a large-scale clinical trial.

Now — a mere 68 years since it emerged from Cohn's lab in Cambridge — this simple plasma protein finds itself back on the center stage of critical care medicine.

Albumin as a Neuroprotective Agent After Stroke

In a 2001 study, human albumin proved remarkably effective in protecting the brains of rats given experimental strokes. Against a saline comparison group, high-dose 25 percent albumin reduced infarct size by two-thirds. Instead of 11 percent brain swelling, the albumin-infused animals had zero. Neurological function was significantly improved.

Then, a 2006 pilot human safety trial suggested a strong neuroprotective benefit in stroke patients who received the highest albumin doses, especially those who also got thrombolytic therapy.

Based on these findings, more than 80 study sites are now actively enrolling 1,100 stroke patients in the pivotal National Institutes of Health-sponsored ALIAS (Albumin in Acute Stroke) trial. Similar to thrombolytic dosing within three hours, subjects must get their high-dose albumin or saline placebo infusion within five hours of the onset of stroke symptoms.

Will some mix of albumin's well-known hemodilution, antioxidant, anti-adhesion and anti-inflammatory properties reduce disability or even save lives of stroke victims? When the ALIAS trial finishes in a couple of years, we'll have our answer.

Albumin Takes on Severe Sepsis and Septic Shock

Albumin has been used for decades to temporarily restore blood pressure in patients with established septic shock. But now, a network of 27 French hospitals is going a big step further.

Starting within hours of the onset of shock, 800 patients will receive three daily infusions of either saline or concentrated albumin. By late next year, we should learn whether albumin supplementation translates into fewer deaths, fewer days on ventilator and dialysis, fewer hospital days and fewer nosocomial infections.

An Italian research team is casting a wider net. A total of 1,350 patients with severe sepsis or septic shock will be given either a salt solution or concentrated albumin. But in this case, albumin will be dosed on a daily basis to maintain its serum concentration above a minimum threshold — for as long as the patient remains in the ICU.

Could simple sustained albumin therapy reduce hospital stays or actually save the lives of severe sepsis patients? While suggestive evidence from older studies abounds, these larger trials may settle the question.

Albumin and the Future of Healthcare

Albumin has patiently waited its turn while more exotic therapeutic candidates were pushed to the front of the research pipeline.

Now the most versatile blood protein that nature could create has returned to do battle. ❖

CHRIS GROUND *is the senior vice president of national accounts at FFF Enterprises, Inc., specialty provider of vaccines, plasma products and other biopharmaceuticals.*

BioDashboard

CALCULATOR

IVIG Reimbursement Calculator

Product	Manufacturer	HCPCS	Reimbursement Rates: Hospital Outpatient ASP+4% (per gram)	Reimbursement Rates: Physician Office ASP+6% (per gram)
CARIMUNE NF	CSL	J1566	$60.618	$61.786
FLEBOGAMMA DIF	Grifols	J1572	$72.55	$73.952
GAMMAGARD LIQUID	Baxter	J1569	$75.752	$77.214
GAMMAGARD S/D	Baxter	J1566	$60.618	$61.786
GAMUNEX	Talecris	J1561	$72.379	$73.772
OCTAGAM	Octapharma	J1568	$74.074	$75.50
PRIVIGEN	CSL	J1459	$68.854	$70.19

Rates are effective July 1, 2009 through September 30, 2009.

REFERENCE TABLES

IG Reference Table

Product	Size	Manufacturer	Indications
CARIMUNE NF (Lyophilized)	3 g, 6 g, 12 g	CSL	PIDD, ITP
FLEBOGAMMA 5% DIF (Liquid)	0.5 g, 2.5 g, 5 g, 10 g, 20 g	Grifols	PIDD
GAMMAGARD LIQUID (10%)	1 g, 2.5 g, 5 g, 10 g, 20 g	Baxter	PIDD
GAMMAGARD S/D (Lyophilized, 5% or 10%)	2.5 g, 5 g, 10 g	Baxter	PIDD, ITP, CLL, KD
GAMUNEX (Liquid, 10%)	1 g, 2.5 g, 5 g, 10 g, 20 g	Talecris	PIDD, ITP, CIDP
OCTAGAM (Liquid, 5%)	1 g, 2.5 g, 5 g, 10 g, 25 g	Octopharma	PIDD
PRIVIGEN (Liquid, 10%)	5 g, 10 g, 20 g	CSL	PIDD, ITP
VIVAGLOBIN (Liquid, 16%)	3 mL, 10 mL, 20 mL	CSL	PIDD

CIDP Chronic inflammatory demyelinating polyneuropathy – Immune mediated peripheral nervous system demyelinating disorder causing pain and weakness of limbs and resulting in paralysis or gradual muscle deterioration and/or motor sensory dysfunction due to the presence of anti-neuroblastoma cell line (NBL) antibodies.

CLL Chronic lymphocytic leukemia – A deficit or imbalance in the number of white and red blood cells that invade the bone marrow – leaving the patient at high risk of serious infections. [Causes include radiation and/or chemotherapeutic agents, exposure to toxic substances, etc. Accounts for 30% of all childhood cancers and commonplace in elderly patients.]

ITP Idiopathic thrombocytopenic purpura – Low platelets – Diminished or absent clotting ability – [Platelets are the "plugs" that form to prevent excessive bleeding – Purpura is hemorrhaging into the skin and other organs leaving visible brown or purple spots.]

KD Kawasaki disease – Mucocutaneous lymph node syndrome – Inflammation of the coronary arteries (pediatric form of vasculitis).

PIDD Primary immune deficiency – Low and insufficient antibodies leaving deficient persons vulnerable to chronic infectious diseases. [Congenital hypogammaglobulinemia, common variable immunodeficiency, agammaglobulinemia, etc.]

Influenza Vaccine Reference Table

Administration Code: G0008 Diagnosis Code: V04.81

Product	Size	CPT Code Descriptors	CPT Code
FLUZONE Pediatric	0.25 mL PFS	Influenza virus vaccine, split virus, preservative-free, for children 6-35 months of age, for intramuscular use	90655
FLUZONE	0.5 mL 10 SDV 0.5 mL PFS	Influenza virus vaccine, split virus, preservative-free, for use in individuals 3 years of age and above, for intramuscular use	90656
FLUZONE	5 mL 10 DS VIAL	Influenza virus vaccine, split virus, for children 6-35 months of age, intramuscular use	90657
AFLURIA	5 mL 10 DS VIAL PFS 0.5 mL	Influenza virus vaccine, split virus, for use in individuals 3 years of age and above, intramuscular use	90658
FLUVIRIN	5 mL 10 DS VIAL PFS 0.5 mL LUER LOCK		
FLUZONE	5 mL 10 DS VIAL		

BioResources

The following websites provide useful information about vaccine-preventable diseases.

Allied Vaccine Group
The Allied Vaccine Group is comprised of websites dedicated to presenting valid scientific information about the sometimes confusing subject of vaccines. It is intended to be the portal of vaccines, including scientific research and the pros and cons of research results.
www.vaccines.org

Centers for Disease Control and Prevention
Part of the Department of Health and Human Services, this CDC site section provides information about specific vaccine-preventable diseases, immunization schedules, common questions, recommendations and guidelines and more.
www.cdc.gov/vaccines

The Children's Hospital of Philadelphia Vaccine Education Center
The Children's Hospital of Philadelphia's Vaccine Education Center provides complete, up-to-date and reliable information about vaccines for parents and healthcare professionals. Videos, informational tear sheets and information on every vaccine are included.
www.chop.edu/consumer/jsp/division/generic.jsp?id=75697

Faces of Influenza
The American Lung Association's Faces of Influenza campaign offers a variety of ready-to-use tools that healthcare professionals can customize for their patients, for the community and for reporters.
www.facesofinfluenza.org

Families Fighting Flu
FFF was established for the children who die each year due to the influenza virus. The non-profit organization, made up of families and healthcare practitioners, is dedicated to educating people about the severity of influenza and the importance of vaccinating children against the flu every year.
www.familiesfightingflu.org

FDA Center for Biologics and Research
The Center for Biologics Evaluation and Research regulates vaccine products. Its vaccine page outlines the vaccine approval process, lists vaccines licensed for immunization and distribution in the U.S., provides safety information and more.
www.fda.gov/cber/vaccines.htm

Hepatitis Foundation International
HFI provides up-to-date news, research, support and educational information, as well as motivational messages for patients, educators and the healthcare community.
www.hepfi.org

Immunization Action Coalition
This site provides vaccination information for healthcare professionals, as well as case reports, personal testimonies and newspaper and journal articles about people who have suffered or died from vaccine-preventable diseases.
www.immunize.org/reports

Meningitis Research Foundation
This foundation funds research to prevent meningitis and septicaemia, and promotes education and awareness to reduce death and disability, and gives support to people affected.
www.meningitis.org

National Network for Immunization Information
This special project for the Infectious Diseases Society of America, the Pediatric Infectious Diseases Society, the American Academy of Pediatrics and the American Nurses Association provides up-to-date, science-based facts about vaccines and immunization for healthcare professionals, the media and the public.
www.immunizationinfo.org

Parents of Kids with Infectious Diseases
PKIDs is a parent group whose highest priority is to seek the best care for their own children and to prevent other children from being harmed by infectious diseases.
www.pkids.org

Pertussis.com
This site provides information about pertussis (commonly known as whooping cough) to help parents and healthcare providers understand why whooping cough has been on the rise in the U.S., and to learn how to prevent this infectious disease.
www.pertussis.com

ShinglesInfo.com
This site provides information about the risk, symptoms and potential complications of shingles. The Helpful Tools section allows individuals to download more information, test their knowledge with the Shingles Quiz, and print a list of questions for healthcare professionals.
www.shinglesinfo.com

VaccinePlace.com
Developed to offer healthcare consumers and professionals helpful information on vaccines and the diseases they prevent, the site provides information on the history of vaccines, the latest information on vaccine safety, recent immunization schedules and answers to frequently asked questions.
www.vaccineplace.com

BioResearch

Summaries of up-to-date clinical research published in medical journals internationally.

SCIG Is Alternative Option to IVIG

Short-term administration of subcutaneous immunoglobulin (SCIG) is as safe and effective as infusion of intravenous immunoglobulin (IVIG) for the treatment of multifocal motor neuropathy. This is according to a team of Danish researchers who tested equivalent doses of either SCIG or IVIG in nine patients, and then crossed each patient over to the other treatment.

Both treatments were equally effective in improving strength in affected muscles. Similarly, patients reported no differences in their perceived quality of life in questionnaire responses. One patient infused with SCIG experienced sustained erythema and edema at the injection site for a few weeks; all other adverse effects during SCIG therapy were mild and transient. The investigators proposed that SCIG is a feasible alternative option to IVIG for treatment of multifocal motor neuropathy, adding the advantage of flexibility to the treatment schedule.

Harbo, T, Andersen, H, Hess, A, et al. Subcutaneous versus intravenous immunoglobulin in multifocal motor neuropathy: A randomized, single-blinded cross-over trial. European Journal of Neurology, *2009, Feb 19. [Epub ahead of print]*

IVIG Use Controls Sjögren's Pain

Noting that severe neuropathic pain associated with Sjögren's syndrome is often not relieved by conventional treatments, Japanese researchers treated five Sjögren's patients affected by painful sensory neuropathy with intravenous immunoglobulin (IVIG) to learn if IVIG might be effective. Patients were dosed with 0.4 g/kg/day for five days.

All five patients reported "remarkable improvement" in neuropathic pain following IVIG therapy, with an average 73.4 percent reduction from days two to 14 following treatment. This observed clinical improvement persisted for two to six months. The authors of this report have recommended further evaluation of IVIG for this condition in a controlled, blinded study.

Morozumi, S, Kawagashira, Y, Iijima, M, et al. Intravenous immunoglobulin treatment for painful sensory neuropathy associated with Sjögren's syndrome. Journal of Neurological Sciences, *2009, Apr 15;279(1-2):57-61.*

Low IgG Levels Lead to Septic Shock

A team of Belgian investigators assessed the time course of gamma-globulin concentrations in 21 patients with septic shock, to learn whether there is a relationship to disease severity and outcome. Of 16 patients (76 percent) with hypogammaglobulinemia at admission, 12 (57 percent) had low IgG concentrations (<650 mg/dL), nine had low IgM and two had low IgA concentrations. The two patients who had low levels of all three gamma globulins both died from refractory shock within two days.

All six deaths occurred in the patients with low IgG concentrations (6/12 vs. 0/9 in patients with gamma globulin levels in the normal range). Patients with low IgG concentrations were indistinguishable from those with normal IgG levels at baseline, but had fewer vasopressin-free days and more frequently developed acute lung injury (ALI) or acute respiratory distress syndrome (ARDS) (10/12 vs. 3/9, p=0.02). The authors suggested that "patients with low IgG concentrations may represent a logical target group to study the effects of immunoglobulin supplementation in septic shock."

Taccone, FS, Stordeur, P, De Backer, D, et al. Gamma-globulin levels in patients with community-acquired septic shock. Shock, *2009, Mar 13. [Epub ahead of print]*

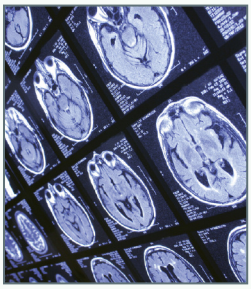
Combining Albumin with Frusemide Proves Effective

The co-administration of 20% human albumin with the loop diuretic drug frusemide (furosemide) was more effective in inducing diuresis, weight loss and natriuresis (salt excretion through the kidneys) than frusemide alone in hypoalbuminemic children with nephrotic syndrome, according to investigators at the All India Institute of Medical Sciences in New Delhi.

In a randomized cross-over trial involving 16 children with nephrotic syndrome and refractory edema, the addition of 1g/kg of 20% albumin over four hours to IV frusemide resulted in a median urine volume of 3.27 ml/kg per hour,

versus 1.33 with frusemide only (p=0.01). The median daily sodium excretion was 58 versus 30 mEq, respectively (p=0.08), and weight loss was 5.2 percent versus just 0.8 percent (p=0.006). The authors proposed that supplemental albumin works primarily by increasing the delivery of frusemide to the renal tubules.

Dharmaraj, R, Hari, P, Bagga, A. Randomized cross-over trial comparing albumin and frusemide infusions in nephrotic syndrome. Pediatric Nephrology, *2009, Apr;24(4):775-82.*

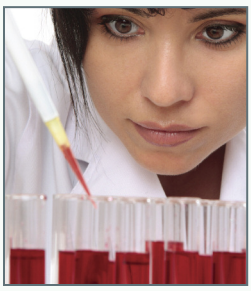


Stroke with IVIG Use Related to Risk Factors

When four or more cardiovascular risk factors are present, the risk of stroke and other thromboembolic (TE) events following administration of IVIG increased sharply in this comparison of 19 IVIG-treated patients who experienced a TE event against age-matched controls. No single risk factor increased the risk of a TE event, but the presence of four or more risk factors significantly elevated the odds (odds ratio = 10.50; 95% confidence interval: 1.91, 57.58). Specific risk factors included coronary artery disease, high blood pressure, previous stroke or arterial thrombosis, diabetes, high cholesterol level and cigarette use.

The Wake Forest University investigators acknowledged that the confidence intervals for their study were very wide, so that the actual degree of increased risk associated with four or more cardiovascular risk factors is difficult to predict. They suggested nevertheless that "clinicians prescribing IVIG should carefully consider the risk of stroke and myocardial infarction in elderly patients with multiple cardiovascular risk factors."

Caress, JB, Hobson-Webb, L, Passmore, LV, et al. Case-control study of thromboembolic events associated with IV immunoglobulin. Journal of Neurology, *2009, Mar;256(3):339-42.*



Guidelines Developed for Treatment of AHA

Based on their collective clinical experience, an international group of hemophilia experts has developed a set of practice guidelines for treating acquired hemophilia A (AHA). AHA is a rare disorder characterized by autoantibodies directed against circulating factor VIII. While patients typically present with spontaneous bleeding and an isolated prolonged aPTT, they can present without any bleeding symptoms; thus an isolated prolonged aPTT should always be investigated.

Recommended first-line therapy for control of acute bleeding related to AHA includes bypassing agents such as recombinant activated factor VII (rVIIa) or activated prothrombin complex concentrate (APCC). Corticosteroids or combination therapy with corticosteroids and cyclophosphamide is recommended to eradicate the autoantibody and thereby reduce subsequent bleeding risk; rituximab is a suggested second-line therapy if this fails. As no comparative studies exist to support treatment recommendations, treatment guidance must rely on the experience and expertise of specialists in the field.

Huth-Kühne, A, Baudo, F, Collins, P, et al. International recommendations on the diagnosis and treatment of patients with acquired hemophilia A. Haematologica, *2009, Apr;94(4):566-75*

sanofi pasteur

The vaccines division of sanofi-aventis Group

To order Fluzone vaccine, please call FFF Enterprises at **1-800-843-7477**
or visit **www.MyFluVaccine.com.**

Indication

Fluzone vaccine is indicated for active immunization in persons 6 months of age and older against influenza virus types A and B contained in the vaccine.

Safety Information

The most common local and systemic adverse reactions to Fluzone vaccine include soreness at the vaccination site that can last up to 2 days, pain, and swelling; fever, malaise, and myalgia. Other adverse reactions may occur. Influenza vaccine should not be administered to anyone with a history of hypersensitivity to any vaccine component, including eggs, egg products, or thimerosal (the only presentation that contains thimerosal is the multi-dose vial). Fluzone vaccine should not be administered to individuals who have a prior history of Guillain-Barré syndrome (GBS). Vaccination with Fluzone vaccine may not protect all individuals.

Before administering Fluzone vaccine, please see brief summary of full Prescribing Information on following page.

Fluzone vaccine is manufactured and distributed by Sanofi Pasteur Inc.

sanofi pasteur. Discovery Drive, Swiftwater, Pennsylvania 18370. www.sanofipasteur.us

Influenza Virus Vaccine Fluzone®

2008-2009 Formula

Flu

℞ only

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

INDICATIONS AND USAGE

Fluzone® is an inactivated influenza virus vaccine indicated for active immunization in persons 6 months of age and older against influenza disease caused by influenza virus subtypes A and type B contained in the vaccine.

DOSAGE AND ADMINISTRATION

Preparation for Administration Inspect Fluzone vaccine syringes and vials visually for particulate matter and/or discoloration prior to administration. If either of those conditions exists, the vaccine should not be administered. Shake the syringe and single-dose vials well before administering the vaccine and shake the multi-dose vial each time before withdrawing a dose of vaccine.

Recommended Dose and Schedule

Children Children 6 through 35 months of age who have not previously been vaccinated with an influenza vaccine should receive two 0.25 mL doses, one on day 1 followed by another 0.25 mL dose at least 1 month later.[1] Children 6 through 35 months of age who have been previously vaccinated with two doses of any influenza vaccine should receive only one 0.25 mL dose.[1] Children 36 months through 8 years of age who have not previously been vaccinated with influenza vaccine should receive two 0.5 mL doses, one on day 1 followed by another 0.5 mL dose at least 1 month later. Children 36 months through 8 years of age who have been previously vaccinated with two doses of any influenza vaccine should receive only one 0.5 mL dose.[1] Children 9 years of age and older should receive a single 0.5 mL intramuscular dose.[1]

Adults Fluzone vaccine should be administered as a single 0.5 mL intramuscular dose preferably in the deltoid muscle. The vaccine should not be injected into the gluteal region or into areas where there may be a major nerve trunk.

DOSAGE FORMS AND STRENGTHS

Fluzone vaccine is a sterile suspension for intramuscular injection. Each 0.25 mL dose of Fluzone vaccine contains a total of 22.5 micrograms (µg) of influenza virus hemagglutinin and each 0.5 mL dose contains a total of 45 µg of influenza virus hemagglutinin from the 3 influenza virus strains in the vaccine.

CONTRAINDICATIONS

Do not administer Fluzone vaccine to anyone with a known severe hypersensitivity to egg proteins or any component of the vaccine or life-threatening reactions after previous administration of any influenza vaccine. (See **WARNINGS AND PRECAUTIONS**)

WARNINGS AND PRECAUTIONS

Guillain-Barré Syndrome Recurrence of Guillain-Barré syndrome (GBS) has been temporally associated with the administration of influenza vaccine. Fluzone vaccine should be administered to individuals who have a prior history of Guillain-Barré syndrome only based on careful consideration of the potential benefits and risks.

Altered Immunocompetence If Fluzone vaccine is administered to immunocompromised persons, including those receiving immunosuppressive therapy, the immune response may be diminished.

Preventing and Managing Allergic Reaction Appropriate medical treatment and supervision must be available to manage possible anaphylactic reactions following administration of the vaccine.

Limitations of Vaccine Effectiveness Vaccination with Fluzone vaccine may not protect all recipients.

ADVERSE REACTIONS

Adverse event information from clinical trials provides the 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, adverse event rates observed in the clinical trials of a vaccine cannot be directly compared to rates in the clinical trial of another vaccine, and may not reflect the rates observed in practice.

Clinical Trial Experience

Adults and Geriatrics In placebo-controlled studies among adults, the most frequent side effect of vaccination is soreness at the vaccination site (affecting 10%-64% of patients) that lasts <2 days, local pain and swelling. These local reactions typically are mild. Fever, malaise, myalgia, and other systemic symptoms can occur following vaccination and most often affect persons who have had no prior exposure to the influenza virus antigens in the vaccine (eg, young children). These reactions begin 6-12 hours after vaccination and can persist for 1-2 days. Placebo-controlled trials demonstrate that among older persons and healthy young adults, administration of split-virus influenza vaccine is not associated with higher rates of systemic symptoms (eg, fever, malaise, myalgia, and headache) when compared with placebo injections.[1]

Children The 2003-2004 formulation of Fluzone vaccine was studied in 19 children 6 to 23 months of age and in 12 children 24 to 36 months of age, given in 2 doses one month apart. Local reactions and systemic events were solicited for 3 days after each dose. Most local and systemic reactions were mild. The proportions of local and systemic reactions in children were similar to the proportions in adults. No reported local or systemic reaction required a therapeutic intervention other than analgesics.[2]

Post-Marketing Experience The following additional events have been reported during post-approval use of Fluzone vaccine. Because these events 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.

Blood and Lymphatic System Disorders: Thrombocytopenia, lymphadenopathy

Immune System Disorders: Anaphylaxis, other allergic/hypersensitivity reactions (including urticaria, angioedema)

Nervous System Disorders: GBS, convulsions, myelitis (including encephalomyelitis and transverse myelitis), facial palsy (Bell's palsy), optic neuritis/neuropathy, brachial neuritis, syncope (shortly after vaccination), dizziness, paresthesia

Vascular Disorders: Vasculitis, vasodilation/flushing

Respiratory, Thoracic and Mediastinal Disorders: Dyspnea, pharyngitis, rhinitis

Skin and Subcutaneous Tissue Disorders: Stevens-Johnson syndrome

General Disorders and Administration Site Conditions: Fever, pain, pruritis, asthenia/fatigue, pain in extremities, chest pain

Other Adverse Events Associated with Influenza Vaccines Anaphylaxis has been reported after administration of influenza vaccines. Although Fluzone vaccine 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**)

DRUG INTERACTIONS

Concomitant Administration with Other Vaccines Fluzone vaccine should not be mixed with any other vaccine in the same syringe or vial. If Fluzone vaccine is to be given at the same time as another injectable vaccine(s), the vaccine(s) should always be administered at different injection sites.

Immunosuppressive Therapies If Fluzone vaccine is administered to immunosuppressed persons or persons receiving immunosuppressive therapy, immunologic response may be diminished.

USE IN SPECIFIC POPULATIONS

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

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

Pediatric Use Safety and effectiveness of Fluzone vaccine in children below the age of 6 months have not been established. The immune response and safety of Fluzone vaccine was evaluated in 31 children between the ages of 6-26 months. (See **ADVERSE REACTIONS**, **CLINICAL STUDIES**)

Geriatric Use Immune response to Fluzone vaccine in subjects older than 65 years of age may be lower when compared to immune responses in younger subjects. (See **CLINICAL STUDIES**)

NON-CLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility Fluzone vaccine has not been evaluated for carcinogenic or mutagenic potential, or for impairment of fertility.

CLINICAL STUDIES

Immunogenicity in the Adult and Geriatric Population In an observational study of the immunogenicity of Fluzone vaccine in a geriatric population (median age: 72.0 range: 61 to 86 years of age) compared with younger adults (median age: 38.0 range: 19 to 59 years of age; racial distribution was 2 Asian, 11 Black, 106 Caucasian, and 2 other; no gender data were available), the following results were obtained using a single-dose of the year 1999-2000 formulation of Fluzone vaccine. (See Table 1.) Antibody levels were obtained on the day of and just prior to vaccination and approximately 21 days after vaccination.[3]

Table 1: Geometric Mean Titer (GMT) and Percentage (%) Achieving an HI Titer ≥1:40 or Greater (N = 58-62) in Adults and the Elderly

	ANTIGEN		PRE-VACCINE GMT	POST-VACCINE GMT (% TITER ≥40)
A (H3N2)	**Cohort 1999**	Young (N=60) Elderly (N=61)	16.6 20.1	53.1 (72) 58.2 (70)
	Cohort 2000	Young (N=58) Elderly (N=62)	18.6 18.1	72.7 (79) 49.7 (68)
A (H1N1)	**Cohort 1999**	Young (N=60) Elderly (N=61)	11.1 12.2	35.6 (49) 26.5 (38)
	Cohort 2000	Young (N=58) Elderly (N=62)	8.9 6.7	39.5 (54) 16.0 (23)
B	**Cohort 1999**	Young (N=60) Elderly (N=61)	14.4 9.9	41.4 (38) 19.4 (10)
	Cohort 2000	Young (N=58) Elderly (N=62)	9.4 7.4	21.5 (38) 9.9 (11)

N = Number of participants

Immunogenicity in Children In a study using 2 doses of Fluzone vaccine (2003-2004) in 31 healthy children 6-36 months of age (3 Black, 23 Caucasian, 2 Hispanic, and 3 other; 15 were male and 16 were female), the following immunogenicity results were obtained on day 0 before vaccination and approximately 14 days after dose number 2. (See Table 2)

Table 2: Geometric Mean Titer (GMT) and Percentage (%) Achieving an HI Titer of 1:40 in Children

ANTIGEN	PRE-VACCINE GMT	POST-DOSE 2 GMT (% TITER ≥40)
A (H3N2)	7.7	52.9 (77.4)
A (H1N1)	6.5	52.9 (77.4)
B	5.2	27.3 (48.4)

STORAGE AND HANDLING

Store all Fluzone vaccine presentations refrigerated at 2° to 8°C (35° to 46°F). **DO NOT FREEZE**. Discard if vaccine has been frozen. Between uses, return the multi-dose vial to the recommended storage conditions at 2° to 8°C (35° to 46°F).

Do not use after the expiration date shown on the label.

REFERENCES

1. Centers for Disease Control and Prevention. Prevention and Control of Influenza: Recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR 2007;56(RR06):1-54. **2.** Sanofi Pasteur Inc. Data on file, 071107. **3.** Hannoun C, et al. Immunogenicity and protective efficacy of influenza vaccination. Virus Res 2004;103:133-138.

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