SUMMER 2017

biosupply trends
QUARTERLY

SPECIAL FOCUS:
VACCINES

Vaccine Supply

Mitigating the Impact of Shortages

ADULT VACCINE RECOMMENDATIONS:
Young, Old and Compromised

PREVENTING SHINGLES:
A New Highly Effective Vaccine

INFLUENZA PANDEMICS:
Combating the Rising Costs

Myths and Facts: Varicose Veins p.40

8 Critical Steps

Purchasing

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

Storage

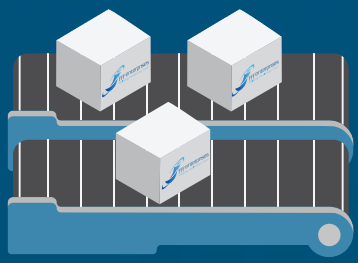
We store and transport viable protein compounds that are sensitive to temperature variations. Temperature controlled, monitored 24/7, and supported with backup generators in the event of power loss.

Specialty Packaging

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

Interactive Allocation

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



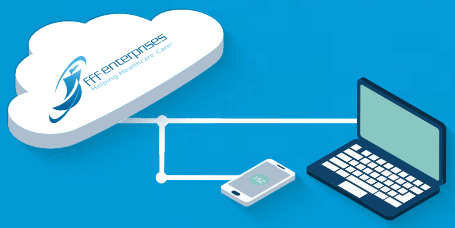
To Guaranteed Channel Integrity™

Delivery

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

Methods of Delivery

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



Verification

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

Tracking

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

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

FFF enterprises
Helping Healthcare Care®

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Since 1988

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Features

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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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Continued Discoveries About Lifesaving Vaccines

More than two centuries since the invention of the first vaccine, a great deal is still being uncovered about lifesaving sera. Some discoveries in just the past six months include researchers learning how maternal pertussis booster vaccine can provide greater protection against whooping cough in newborns, and how the influenza vaccine reduces the risk of flu-associated death by half among children with high-risk medical conditions and by two-thirds among healthy children (p.11).

Additionally, new vaccines continue to proliferate around the world. In March, researchers in India developed a new less-expensive vaccine to protect against the deadly rotavirus. This heat-stable vaccine that doesn't require refrigeration offers great hope for the thousands of children who die from the disease in sub-Saharan Africa (p.10). And, as we discuss in our article "Coming Soon: A Highly Effective New Vaccine to Prevent Shingles," a new high-potency shingles vaccine is now under review by the U.S. Food and Drug Administration and could be available later this year. Results from two clinical trials show a dramatic reduction in the risk of developing shingles and debilitating post-herpatic neuralgia in adults aged 50 years and older.

Yet, while the number of vaccines continues to grow, shortages do occur. In fact, since 2000, the U.S. has experienced a series of shortages of vaccines that protect against a variety of diseases. In our article "Vaccine Supply in the U.S.: Understanding and Combating Shortages," we review the reasons behind these shortages and what remedies are being taken. To ensure adequate future supplies, the Centers for Disease Control and Prevention monitors supply across the country, allocates distribution of vaccine to public and private sectors, and incentivizes manufacturers to continue to develop vaccines when it often costs more to produce them than they can recoup.

On the flip side of this topic is the troubling number of adults in the U.S. who do not receive recommended vaccines, despite their availability. As our article "Adult Vaccines: A Needed Boost" reveals, approximately 42,000 U.S. adults die from vaccine-preventable diseases each year. Yet, each year, the number of adults vaccinated fails to increase. Reasons for nonvaccination range from lack of awareness or perceived value to inadequate recommendations by healthcare providers and insurance reimbursement. With growing concern, many hospitals and clinics have stepped in at the grassroots level to increase awareness and make vaccines easier to get. And, state and federal organizations are doing their part by implementing plans and campaigns. Perhaps, if people understood the risks nonvaccination poses for both themselves and others, compliance would rise and preventable deaths would decrease.

Influenza is one of the principal causes of these deaths, especially during pandemics. The last pandemic, the Swine flu of 2009-2010, was responsible for 12,469 deaths in the U.S. As we explain in our article "The Rising Costs of Flu Pandemics," it is predicted the costs of the next severe-strain pandemic will increase exponentially. But, it is hoped that initiatives that focus on surveillance, management and preparedness, as well as funding established by organizations across the world to assist low-income countries, will reduce these costs to avert such a disaster in the future.

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

Helping Healthcare Care,

Patrick M. Schmidt
Publisher

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

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CMS Delays Implementation and Expansion of Bundled Payment Programs

In March, the Centers for Medicare and Medicaid Services (CMS) issued an interim rule to delay the implementation of its bundled payment program for cardiac care, as well as for expansion of its Comprehensive Care for Joint Replacement (CJR) program. Bundled payments were to have been provided for the cardiac care models for patients who receive cardiac rehabilitation, suffer heart attacks or undergo heart surgery, and for the CJR programs for patients who undergo nonreplacement surgery following a hip fracture. In addition, the cardiac program included a provision to make updates to the CJR model, including "refinements" of the bundle's skilled nursing facility waiver. Both were slated for demonstrations beginning July 1 and ending Dec. 31, 2021. Under the interim rule, the programs are scheduled to begin Jan. 1, 2018.

"This additional three-month delay is necessary to allow time for additional review, to ensure that the agency has adequate time to undertake notice and comment rulemaking to modify the policy if modifications are warranted, and to ensure that in such a case, participants have a clear understanding of the governing rules and are not required to take needless compliance steps," reads the interim rule. This is the second time the rule's effective date has been changed. ❖

Mongan E. CMS Postpones Expansion, Implementation of Bundled Payment Programs. McNight's, March 21, 2017. Accessed at www.mcknights.com/news/cms-postpones-expansion-implementation- of-bundled-payment-programs/article/645379.

Elllison A. CMS Further Delays Major Bundled Payment Initiatives: 4 Things to Know. Becker's Hospital CFO, May 19, 2017. Accessed at www.beckershospitalreview.com/finance/cms-further-delays-major-bundled-payment-initiatives-4-things-to-know.html.

HHS Launches Webpage to Empower Patients

The U.S. Department of Health and Human Services (HHS) has launched a new page on its website that highlights regulatory and administrative actions it is taking to support a patient-centered healthcare system. The new page is part of a broader plan the current administration has to repeal and replace the Affordable Care Act.

Text on the new page reads: "Within what the law allows, HHS is taking action to stabilize the individual and small group insurance markets (the markets most affected by the ACA) so that they work better for everyone. We are going through every page of regulations and guidance related to the Affordable Care Act to determine whether or not they work for patients and whether or not they are making our health care system better."

According to HHS, new measures will be announced as soon as allowable by law, including future actions that will:

- Lower costs and increase choices by providing relief from the burdensome regulations and fostering competition in insurance markets;
- Work to ensure a stable transition period;
- Offer states greater flexibility of their Medicaid programs to meet the needs of their most vulnerable populations; and
- Increase the opportunities for patients to get the care they need when they need it. ❖

HHS Launches Webpage Highlighting Administrative Actions to Empower Patients. U.S. Department of Health and Human Services press release, March 20, 2017. Accessed at www.hhs.gov/about/news/2017/03/20/offering-states-flexibility-increase-market-stability-and-affordable-choices.html.

Drug Companies Can Be Fined for Overcharging Hospitals Under 340B Drug Discount Program

Under a new rule, the Health Resources and Services Administration (HRSA) of the Department of Health and Human Services can issue fines of up to $5,000 for each incident to drug manufacturers that knowingly and intentionally overcharge 340B hospitals for drugs purchased under the program. The rule also outlines how manufacturers estimate the ceiling price for a new covered outpatient drug. And, it requires manufacturers to offer refunds for overcharges on new drugs, rather than waiting for providers to request refunds. The agency began enforcing the new rule on April 1.

"Today's new 340B drug discount program rule should help prevent the drug industry from overcharging America's 340B health providers for lifesaving medicines," said Randy Barrett, vice president of communications for 340B Health. "It's a welcome development in light of public outrage about the unsustainable cost of prescription drugs." ❖

MacDonald I. 340B Final Rule: Feds Will Fine Drug Companies That Overcharge Hospitals. *FierceHealthcare,* Jan. 4, 2017. Accessed at www.fiercehealthcare.com/finance/340b-final-rule-feds-will-fine-drug-companies-overcharge-hospitals.

VA Rule Expands Scope of Advanced-Practice Registered Nurses

The Veterans Affairs (VA) Department has issued a rule that will allow all advanced-practice registered nurses, with the exception of certified registered nurse anesthetists, to practice to their full authority at VA facilities. Effective Jan. 14, the rule is intended to make it easier for veterans to be seen by medical professionals by increasing the number of available primary care providers. "This part of the VA's final rule will rewind the clock to an outdated model of care delivery that is not consistent with the current direction of the healthcare system," said Andrew Gurman, MD, president of the American Medical

Association. Dr. Gurman added that state law should be followed. Approximately half of states have full scope of practice laws for nurse practitioners.

Certified registered nurse anesthetists were excluded after opposition by the American Society of Anesthesiologists, which believes a physician anesthesiologist should always be present in the emergency room in case of a medical emergency. Physician anesthesiologists receive between 12 years and 14 years of education, including medical school and between 12,000 hours and 16,000 hours of clinical training, in contrast with about half the education and almost 2,500 hours of clinical training for nurse anesthetists. ❖

Dickson V. VA Finalizes Rule That Expands Scope of Nurse Practice. *Modern Healthcare,* Dec. 14, 2016. Accessed at www.wvha.org/Media/NewsScan/2016/December/12-14-2016-VA-finalizes-rule-that-expands-scope-of.aspx.

New Educational Initiative Introduced to Raise Awareness of Chronic Care Management

Connected Care is a new educational initiative to raise awareness of the benefits of chronic care management (CCM) services for Medicare beneficiaries with multiple chronic conditions and to provide healthcare professionals with support to implement CCM programs. It is a nationwide effort within fee-for-service Medicare that includes a focus on racial and ethnic minorities, as well as rural populations, who tend to have higher rates of chronic diseases.

According to the Centers for Medicare and Medicaid Services (CMS), which launched the initiative with the Federal Office of Rural Health Policy at the Health Resources and Service Administration, "two-thirds of Medicare beneficiaries have two or more chronic conditions, and one-third have four or more chronic conditions. Many healthcare professionals are providing these patients with chronic care management, non-face-to-face services such as reviewing test results or coordinating with other providers, but are not aware of the separate payments under the Medicare Physician Fee Schedule and are not receiving the full separate payments that are now available for CCM services under Medicare Part B."

The initiative includes new resources to educate patients and healthcare professionals, including:

- A toolkit for healthcare professionals with detailed information about CCM and resources to help providers implement CCM;
- A partner toolkit that includes downloadable resources and suggested activities to get involved in the Connected Care initiative; and
- Patient education resources, including a poster and postcard that can be used in a clinical or community setting.

All resources are available online at go.cms.gov/ccm and can be ordered at no cost. ❖

Connected Care: New Educational Initiative to Raise Awareness of Chronic Care Management. Centers for Medicare and Medicaid Services press release, March 15, 2017. Accessed at www.cms.gov/Newsroom/MediaReleaseDatabase/Press-releases/2017-Press-releases-items/2017-03-15.html.

Drug Pricing Reform and Cost Containment

With the cost of medications in hospitals, outpatient areas, physician offices and at home surging at an unprecedented rate, the emphasis is on drug pricing reform and cost management. But choosing and using expensive products wisely and judiciously is often perceived by some as limiting choice or rationing, eliciting a pushback against restrictions in product use or cost sharing.

While drug breakthroughs greatly benefit those who need them, costs can be prohibitive. Today, immunotherapies are in the limelight as wonder drugs for a number of disease states. According to the research firm GlobalData, the "global market for cancer immunotherapies alone is expected to grow more than four-fold globally to $75.8 billion by 2022 from $16.9 billion in 2015." In addition, a news report by Reuters states that competition between next-generation cancer drugs "is not reining in prices," with some medications costing more than $250,000 each year. Even for a patient with the highest level of insurance coverage, a modest copayment of 10 percent would translate to an annual out-of-pocket expenditure of $25,000.

Drug Pricing

Myriad factors ultimately contribute to the list price of a product. For one, the complicated and convoluted nature of providing healthcare in the U.S., with its multiple administrative and management layers, contributes to high pricing. It is often a tussle between who controls and manages the dollars spent. The words "control" and "manage" in any capacity translate into a cost that is added on to the product itself before it ultimately reaches the patient.

Obviously, a number of basics contribute to the baseline cost of a drug. Years of expensive research and discovery, development and the arduous and lengthy process of clinical studies seeking to meet the requirements of U.S. Food and Drug Administration approval consume vast amounts of capital. Following that comes manufacturing the product in a manner that can be brought to scale in a rigidly controlled environment.

> When faced with growing expenses that loom larger than the budget to pay for them, cost containment and cost management quickly gain traction with both healthcare providers and payers.

Simultaneously, other teams are tasked with pricing the product, creating marketing strategies and determining distribution channels. Data analytics plays a major role in determining the value of a new drug and in setting price. So does who the decision maker is. Currently, the key decision maker is moving away from physician preference in favor of payers (insurance companies), employers and patients. For instance, direct-to-consumer advertising of pharmaceuticals that costs in the billions of dollars is built into the price of the product, along with all other marketing expenses. In contrast with other countries, the U.S. is almost unique in allowing this marketing strategy.

The newest strategy is to set lower prices for new products, especially if there are no direct competitors or the new product meets an unmet need. However, this may not bode well for the many new drugs that don't target a unique niche or an unmet medical need. Two good examples of this occurred in late March, when pharmaceutical companies set lower-than-normal prices for two newly approved drugs, an eczema drug from Sanofi and Regeneron, and a multiple sclerosis drug from Roche. The eczema drug will cost $37,000 a year, compared to the $50,000-a-year price tags for similar, yet older treatments. The multiple sclerosis treatment is proposed to cost $65,000, which is a 25 percent decrease from the price of a competing treatment approved 15 years ago.

However, simply setting lower prices is not the end of this complex journey, and in the current environment, many other factors weigh into the ultimate price decision.

One factor is competition, which is needed to offer discounts to gain ground. But, there is a cost to discounting that is built into the price of the drug. The logic is if there is less competition and less need to offer discounts, the price can be lowered at no financial loss to the manufacturer.

Another factor is rebates that are paid for a variety of prenegotiated terms. These range from Medicaid rebates for outpatient prescription drugs, to pharmacy benefit manager (PBM) rebates for favoring product selection and group purchasing organization rebates for performance. On a smaller scale, a rebate may be for a therapeutic interchange program. The list is endless, but the concept is the same. The cost of a rebate is built into the price of the product. Where the dollars from the rebate go and who benefits from them is another issue.

Last issue, this column covered the 340B program and complexities of offering discounted prices on outpatient drugs to qualified entities that assume significant responsibilities for appropriate use of the program and appropriate use of the savings they receive. The cost of 340B discounts is built into the drug price formula as well. But it's not only the cost of the discounts, it's also the tremendous costs of administering the program that trickle into the pricing formula. Aside from military and VA price controls, the 340B program remains the only price-controlled program in the U.S. Those that qualify greatly benefit, but those that offer similar services but don't qualify are paying a nondiscounted price that has the cost of other discounts and administrative costs built in.

Patient assistance programs offered by the pharmaceutical industry are a welcome lifeline to those who qualify for the zero-priced or nominally priced products, but once again, the cost of the drugs and administration of the program both are built into the formula.

Cost Containment

When faced with growing expenses that loom larger than the budget to pay for them, cost containment and cost management quickly gain traction with both healthcare providers and payers. Once again, it's vital that the administrative costs don't overwhelm the savings.

Among others, some popular options include a closed formulary, prior authorizations from insurers, local and national coverage determinations from the Centers for Medicare and Medicaid Services, PBM management strategies, specialty pharmacies, closed distribution systems and one of the newer concepts, pay for performance. Although some may see these as odious, there is no question there is a vital need to choose and use expensive products wisely and judiciously. Administrative simplification would go a long way too. ❖

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

ASK OUR EXPERTS

Have a reimbursement question? Our experts are ready to answer them. Email us at editor@BSTQuarterly.com.

Editor's Note: The content of this column is intended to provide a general guide to the subject matter. Specialist advice should be sought about your specific circumstances.

Research

New Rotavirus Vaccine Is More Protective in Children

A new vaccine to protect against rotavirus, a deadly diarrheal disease that kills approximately 450,000 children younger than 5 years old each year, has been developed by Serum Institute of India. In a recently completed clinical trial conducted in Niger by Doctors Without Borders and the Harvard T.H. Chan School of Public Health and Epicentre in Paris, the vaccine was tested in 3,500 healthy infants who received three doses of either the vaccine or placebo at 6, 10 and 14 weeks of age and were monitored in local health centers for two years. It found that the vaccine, BRV-PV, was 66.7 percent effective in preventing severe gastroenteritis caused by the virus.

BRV-PV is a heat-stable vaccine that doesn't require refrigeration, is specifically adapted to the rotavirus strains found in

sub-Saharan Africa, the region of the world most disproportionately affected by the disease, and is less expensive than existing vaccines at a cost of $2.50. Currently, the two other rotavirus vaccines need to be refrigerated, making them difficult to distribute in resource-poor countries. The vaccine has been licensed in India but needs to be approved by the World Health Organization (WHO) before it can be purchased by the United Nations and government agencies. "The success of this trial shows that research and development into vaccines that are specifically adapted for use in low-income countries yield results," said Micaela Serafini, MD, Doctors Without Borders' medical director. "The quicker this vaccine is prequalified by the WHO, the sooner it can be used to prevent the deaths of thousands of children in the countries where it is needed most." ❖

Welch A. New Vaccine Could Prevent Thousands of Childhood Deaths. CBS News, March 23, 2017. Accessed at www.cbsnews.com/news/rotavirus-vaccine-could-prevent-thousands-of-childhood-deaths.

Research

Flu Vaccine May Cause Immune-Related Adverse Events with Checkpoint Inhibitors

Study results from the division of oncology at University Hospital Basel in Switzerland show that patients treated with PD-1/PD-L1 checkpoint inhibitors may be at an increased risk for adverse events after receiving the seasonal influenza vaccination. In the study, researchers evaluated immune responses after vaccination with a trivalent influenza vaccine in 23 patients (mean age 58.7 years) undergoing checkpoint blockade therapy compared with age-matched controls. Sixteen patients had non-small cell lung cancer, four had renal cell carcinoma and three had melanoma. More than half of patients received at least two prior lines of chemotherapy, and all were receiving PD-1/PD-L1 therapy at the time of vaccination.

All patients developed antibody titers against all three viral strains of influenza, and no patient developed influenza. However, immune-related adverse events occurred in 52.2 percent of patients, including six patients (26.1 percent) who experienced severe grade 3 or grade 4 immune-related adverse events. Historical rates at the researchers' center are 25.49 percent for all-grade adverse events and 9.8 percent for grade 3 and grade 4 adverse events. The most common immune-related adverse events included skin rashes (13 percent), arthritis (13 percent), colitis (8.7 percent), encephalitis (8.7 percent), hypothyroidism (4.3 percent), pneumonitis (4.3 percent) and neuropathy (4.3 percent). "Our hypothesis is that the vaccine results in an overwhelming activation of the immune system in this population," said Sacha Rothschild, MD, PhD, at the university.

However, according to Dr. Rothschild, "Although the observed rate of immune-related adverse events in our cohort is alarming, we believe that there is a particular concern for severe complications for an influenza infection — including pneumonia and respiratory failure — for patients with lung cancer under immunotherapy because of concomitant structural lung disorders." The researchers recommended testing these preliminary results in a larger study. "Some of these patients had prior resection of lung lobes or even a pneumonectomy and, therefore, had limited reserves due to small lung volume. When weighing benefit and potential risk of seasonal influenza vaccination for patients undergoing single-agent PD-1 or PD-L1 blocking — particularly those with lung cancer — we currently advise a case-by-case decision until we have results from larger cohorts." ❖

Flu Vaccine May Cause Immune-Related Adverse Events with Checkpoint Inhibitors. Immuno-Oncology Resource Center, April 26, 2017. Accessed at www.healio.com/hematology-oncology/lung-cancer/news/online/{b069ddd6-5fd2-4861-adfe-495bd4fd0da9}/flu-vaccine-may-cause-immune-related-adverse-events-with-checkpoint-inhibitors.

Medicines

FDA Approves Renflexis, Biosimilar to Remicade

The U.S. Food and Drug Administration has approved Renflexis (infliximab-abda, Samsung Bioepis), the second biosimilar to Remicade (infliximab, Janssen Biotech). Inflectra (infliximab-dyyb, Celltrion) was the first approved biosimilar. The tumor necrosis factor blocker is an intravenous infusion (100 mg) indicated for the same indications as Remicade: Crohn's disease, ulcerative colitis, rheumatoid arthritis (in combination with methotrexate), ankylosing spondylitis, psoriatic arthritis and plaque psoriasis. The most common adverse reactions that occurred in fewer than 10 percent of patients in clinical trials were infections (e.g., upper respiration infection, sinusitis and pharyngitis), infusion-related reactions, headache and abdominal pain, which are similar to those seen with Remicade. In addition, Renflexis also comes with the same boxed warning as Remicade concerning the increased risk of serious infections. ❖

Brooks M. FDA Clears Second Remicade Biosimilar (Renflexis). Medscape, April 21, 2017. Accessed at www.medscape.com/viewarticle/878963.

Research

Pertussis Vaccine in Pregnancy Protects Nine of 10 Newborns from Whooping Cough

A new study shows newborns of pregnant women who have gotten their pertussis booster vaccine are far less likely to get the disease than other babies. In the study, researchers tracked 148,981 full-term infants born at Kaiser Permanente Northern California between 2010 and 2015. All women were born prior to 1996, when the vaccine containing a whole pertussis bacteria cell was fully replaced by the current vaccine, which contains only a few proteins of the bacteria. Forty-six percent of mothers received the Tdap (tetanus, diphtheria, pertussis) vaccine during pregnancy at least eight days before giving birth. At 2 months old, infants of mothers who got the Tdap during pregnancy were 91.4 percent protected against pertussis. As the mothers' antibodies gradually declined by the time of each recommended DTaP vaccine for children, the researchers found the mothers' Tdap booster was still an average 88 percent effective just before the first dose of DTaP and 82 percent effective between the first and second doses. Maternal antibodies remained 69 percent effective against infection through the end of the child's first year.

The study also found high rates of prenatal vaccination. From 2014 to 2015, national rates of pertussis vaccination in pregnancy ranged from 27 percent to 42 percent. But at Kaiser Permanente Northern California, rates were at 12 percent in 2010 and rose to 87 percent in 2015.

"The bottom line is that receiving Tdap during pregnancy is extremely effective in protecting infants against pertussis across the first year of life," said senior author Nicola Klein, MD, PhD, co-director of the Kaiser Permanente Vaccine Study Center and a clinical instructor at Stanford University School of Medicine. ❖

Haelle T. Pertussis Vaccine in Pregnancy Protects 9 of 10 Newborns from Whooping Cough. Forbes, April 3, 2017. Accessed at www.forbes.com/sites/tarahaelle/2017/04/03/pertussis-vaccine-in-pregnancy-protects-9-of-10-newborns-from-whooping-cough/#129de9c27118.

Research

CDC Study Shows Flu Vaccine Reduces Risk of Death in Children

A new study conducted by the Centers for Disease Control and Prevention (CDC) shows that during the years 2010 through 2014, the influenza vaccine reduced the risk of flu-associated death by half among children with underlying high-risk medical conditions and by nearly two-thirds among healthy children. During those four flu seasons, 358 children died from laboratory-confirmed flu. Of the 291 deaths with known vaccination status, only one in four children (26 percent) had been vaccinated. Deaths were reported from 43 states, New York City, Chicago and Washington, D.C., and included children aged 6 months through 17 years.

Since the 2004-2005 season, flu-related deaths in children reported to CDC during regular flu seasons ranged from 37 (during 2011-2012) to 171 (during 2012-2013) depending on the severity of the season. In this current flu season, 61 children have reportedly died from the flu as of March 25, according to CDC. "Every year, CDC receives reports of children who died from the flu," said Brendan Flannery, PhD, lead author and epidemiologist in the CDC influenza division. "This study tells us that we can prevent more of these deaths by vaccinating more." ❖

Schmidt S. Vaccinations Significantly Reduce Risk of Death from the Flu, CDC Study Finds. *The Washington Post*, April 4, 2017. Accessed at www.washingtonpost.com/news/morning-mix/wp/2017/04/04/vaccinations-significantly-reduce-risk-of-death-from-the-flu-cdc-study-finds/?utm_term=.7214f4116aff.

Research

Study Shows Drug to Treat and Prevent Alzheimer's Is Safe and Well-Tolerated

A Phase I clinical trial to test the safety, pharmacokinetics and biomarker changes in amyloid peptides in the cerebrospinal fluid has shown that NGP 555, a drug developed to treat and prevent Alzheimer's disease, was safe and well-tolerated with dose-dependent plasma exposure. NGP 555 is believed to act by decreasing the levels of the plaque-forming amyloid, Abeta42, while increasing shorter, nontoxic forms such as Abeta37. The 14-day multiple ascending dose clinical trial was a randomized, placebo-controlled, double-blind study in healthy volunteers aged 40 to 65. Patients were dosed at 100 mg to 400 mg, after which analysis of Abetaalofoms in cerebrospinal fluid was measured using Mesoscale ELISA technology in a subset of subjects. Subjects showed a 51 percent favorable change in Abeta37/Abeta42 ratios at day 14 compared to baseline predrug levels for 400 mg (two subjects) and 36 percent for 200 mg (four subjects) versus 2 percent for placebo (one subject). In addition, a pharmacokinetic relationship was established with CSF biomarker changes.

The preclinical findings on NGP 555 were published in the *Alzheimer's & Dementia Journal: Translation Research and Clinical Intervention* online version published Oct. 14, 2016. ❖

NeuroGenetic Pharmaceuticals Complete Phase 1 Clinical Trials for NGP 555 to Treat and Prevent Alzheimer's Disease. Shown as Safe and Well-Tolerated in Healthy Volunteers. NeuroGenetic Pharmaceuticals press release, Jan. 9, 2017.

Did You Know?

In April, Octapharma USA sponsored the Hemophilia Federation of America's patient symposium titled "Hope Ignites: Stories to Inspire" to introduce attendees to the inspiring lives of patients with bleeding disorders, including Chris Bombardier, a mountain climber from Denver, Colo., who went on a mission to be the first person with severe hemophilia to summit Mount Everest; Andrew Basa of Easton, Mass., a 15-year-old diagnosed with von Willebrand disease at age 3; and Seth Rojhani, 26, of Denver, Colo., who is a paraplegic with hemophilia A. "We really believe it is important for families and patients to understand they can have a good quality of life while managing their bleeding disorder," said Flemming Nielsen, Octapharma USA's president. "We are determined to help patients maximize their quality of life. While not everyone can climb Mount Everest, with the right support, we hope that most patients can enjoy a healthy life, one without limits."

Policy

AMA Joins with Other Organizations to Reform Prior-Authorization Requirements

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

In 2016, the AMA House of Delegates adopted in-depth policy on standardization

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

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

Research

Type 2 Diabetes Patients Have Higher Prevalence of Chronic Hepatitis B

A study has found that patients with type 2 diabetes have a higher prevalence of chronic hepatitis B virus infection (CHB). Researchers at the University Affiliated Sixth People's Hospital in China investigated the prevalence of CHB in 381 patients with adult-onset diabetes, 1,365 patients with type 2 diabetes and 1,365 controls without diabetes. They found that patients with type 2 diabetes had a higher prevalence of CHB than the controls in the overall population (13.5 percent versus 10 percent) and among patients with normal hepatic function (13.3 percent versus 8.8 percent). However, CHB status was not different between patients with adult-onset autoimmune diabetes and the controls. The odds ratio of CHB increased 1.5-fold in patients with type 2 diabetes, compared to the control group, even after adjusting for age, gender and body mass index, regardless of hepatic function. According to the study's authors, further research is needed to determine whether CHB status increases the risk of developing type 2 diabetes, or whether type 2 diabetes, but not adult-onset autoimmune diabetes, increases the risk of CHB. ❖

Chronic Hepatitis B Prevalence Higher in Those With T2DM. Doctors Lounge, Dec. 23, 2016. Accessed at www.doctorslounge.com/index.php/news/pb/68815.

Vaccines

Vaccine in Development for Early-Stage Breast Cancer

Researchers at the Moffitt Cancer Center are developing a new vaccine that will help early-stage breast cancer patients who have HER2 positive disease. The HER2 protein is overexpressed in more than 25 percent of all breast cancer tumors. Previously, the researchers found that immune cells are less able to recognize and target cancer cells that express HER2 as breast cancer progresses into a more advanced and invasive stage, suggesting stimulating the immune system to recognize and target HER2 early may be a more effective treatment option. So, they created a vaccine from dendritic immune cells that are harvested from each individual patient to help the immune system recognize the HER2 protein on breast cancer cells.

In a clinical trial that included 54 women who have HER2-expressing early-stage breast cancer, patients were injected once a week for six weeks with a dose of their personal dendritic cell vaccine, which was prepared by isolating dendritic cells from the patients' blood and exposing them to fragments of the HER2 protein. The vaccine, which was injected into either a lymph node, the breast tumor or both sites, stimulated an immune response in the majority of patients, with approximately 80 percent experiencing a detectable immune response in their peripheral blood and/or in their sentinel lymph node where their cancer is most likely to spread first. Importantly, the immune responses among the patients were similar, regardless of the route of vaccine administration. To determine the effectiveness of the vaccine, the researchers looked at the percentage of patients who had detectable disease within surgical specimens after resection. Thirteen of the patients achieved a pathological complete response (absence of disease), and patients who had early noninvasive disease called ductal carcinoma in situ achieved a higher rate of pathological complete response than patients who had early-stage invasive disease. Additionally, patients who achieved a pathological complete response had a higher immune response within their sentinel lymph nodes. ❖

Wilkins J. Vaccine Shows Promising Results for Early-Stage Breast Cancer Patients. Moffitt Cancer Center, Jan. 3, 2017. Accessed at www.moffitt.org/newsroom/press-release-archive/2017/vaccine-shows-promising-results-for-early-stage-breast-cancer-patients.

Research

Study Finds New Subset of T Cells That Drive Inflammation in Peripheral Tissues

Researchers at Brigham and Women's Hospital have discovered a subset of T cells that collaborate with other immune cells to drive inflammation in peripheral tissues. The cells were found in cell samples taken from patients with rheumatoid arthritis (RA) during a study that aimed to answer which T-cell subtypes help orchestrate the damaging immune responses that underlie RA.

In the study, the researchers took a disease-deconstruction approach, relying on "sophisticated technologies, such as mass cytometry, which allowed them to rapidly sift through blood, joint tissue and fluid surrounding joints to isolate specific cells defined by the assortment of molecules on their surfaces." They also "harnessed RNA sequencing methods that can characterize even very small numbers of cells and reveal which genes are turned off." With the use of these tools, the researchers homed in on a unique population of T cells, a type of CD4+ or helper T cell, that are highly prevalent (accounting for roughly one-quarter) in the joints of RA patients. In addition to their abundance, they found that the T cells are programmed to infiltrate parts of the body that are inflamed, where they stimulate B cells to produce antibodies. However, as is known with autoimmune diseases like RA, so-called autoantibodies instead recognize normal components of the human body and contribute to tissue damage. This study was the first detailed description of a type of T cell with these features.

Now, the researchers will seek to understand the signals that coax these cells to develop, and whether they play other roles in autoimmune diseases such as lupus, multiple sclerosis and type 1 diabetes. They will also explore whether targeting these cells could provide a treatment for RA. ❖

New T-Cell Subtype Found. Harvard Medical School, Feb. 2, 2017. Accessed at hms.harvard.edu/news/new-t-cell-subtype-found.

Research

Study Finds Blood Plasma Can Restore Brain Function

Results from a new study show that brain function can be restored by human blood plasma. And, the younger the source of the blood plasma, the better the results. In the study, researchers injected elderly mice (specially bred with faulty immune systems to guard against rejection) with blood plasma from human umbilical cords every four days for two weeks. They then compared those mice with three groups of other mice: one that received blood plasma from young adults, another that received blood plasma from elderly people and a control group that received only saline. They found that those who received umbilical cord blood demonstrated the best improvement on memory and learning tests (they were able to learn faster and find their way through a maze better), while the mice that received elderly blood didn't show any improvement. The mice that received young adults' blood also showed some improvements in cognitive ability, but not as much.

The researchers isolated a protein, TIMP2 (tissue inhibitor of metalloproteases 2) in the umbilical cord plasma that appeared to be responsible for the increase in cognitive abilities. As individuals age, they have lower levels of TIMP2. So, they performed an additional test by injecting the elderly mice with TIMP2 and found the effects were comparable with the results of the umbilical cord blood plasma injection. They also found that it restored a behavior that mice typically lose as they age: the instinct to use bits of cotton, paper and other material to create a bed to sleep on.

According to the researchers, the results suggest that as humans age, their blood gradually loses its potential to rejuvenate. They believe that both umbilical cord blood and TIMP2 work on the hippocampus, the part of the brain associated with learning, forming memories and recalling information. If proven right, it could lay the foundation for developing drugs to help fight against restoring its function. ❖

Study Finds First Evidence That Human Plasma Could Restore the Aging Brain. Wall Street Pit, April 23, 2017. Accessed at wallstreetpit.com/113319-human-plasma-restore-aging-brain.

Research

Study Shows Frog Slime Can Kill Flu Viruses

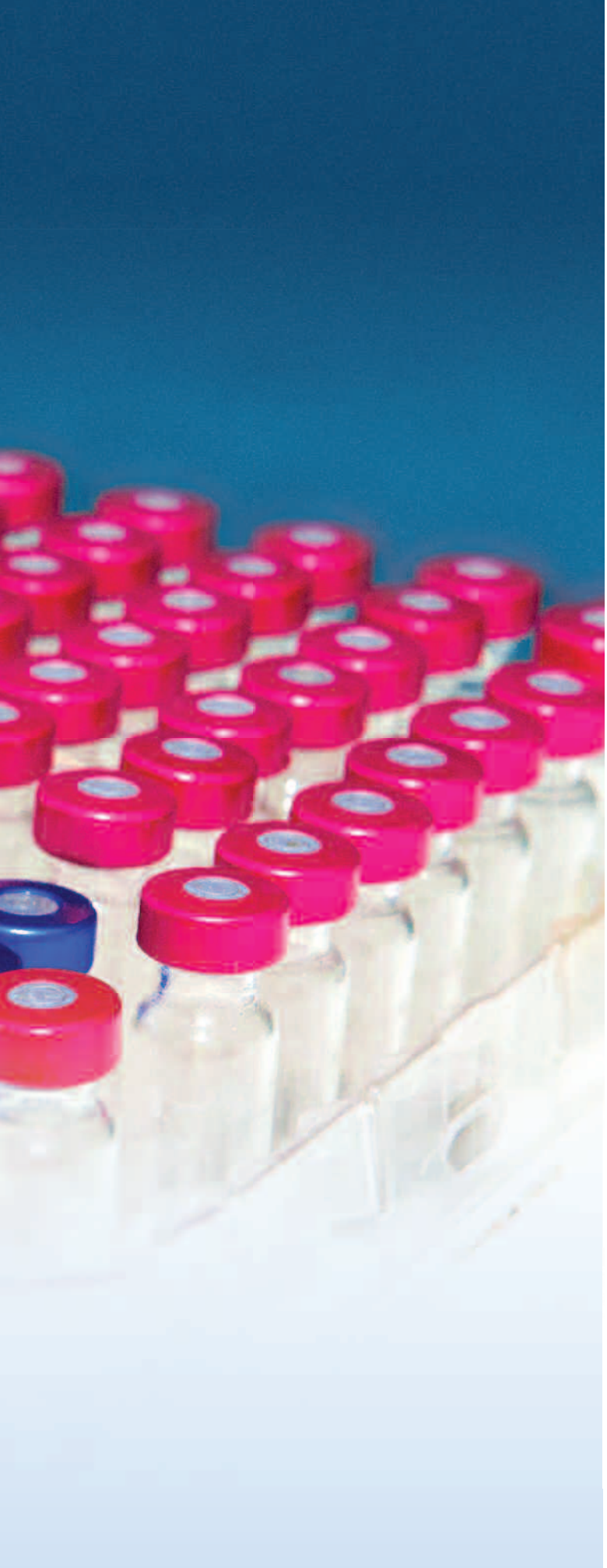
Researchers at Emory University and the Icahn School of Medicine at Mount Sinai in the U.S. and Rajiv Gandhi Center for Biotechnology in India have identified a peptide (a short chain of amino acids) in the mucus secreted by a South Indian frog that can kill certain types of flu viruses. In the study, the peptide (which they named "urumin" after a curved sword that comes from the same region of India as the frog) was injected into the nasal passages of one group of the Hydrophylax bahuvistara frogs, while another group received an inactive control liquid, five minutes before infecting them with the flu virus. They were then given urumin or control daily for the next three days to compare how the infection affected the mice's weight, how many mice died and how much flu virus was present in their lungs. They found urumin was effective at killing 60 percent of the eight types of H1N1 flu viruses tested, including the one that caused the 2009 swine flu pandemic. They also found it was effective at killing seven strains of H1N1 that were resistant to antiviral medicines such as Tamiflu.

According to the researchers, urumin is effective because it targets the part of the virus's structure that is shared across different H1 strains, called the stalk region. Seventy percent of mice treated with urumin survived compared with only 20 percent of those given the control. However, urumin was effective in killing only less than half of the H3N2 strain. ❖

Frog Slime Could Protect Us Against Future Flu Epidemic. NHS, April 19, 2017. Accessed at www.nhs.uk/news/2017/04April/Pages/Frog-slime-could-protect-us-against-future-flu-epidemic.aspx.

U.S. Vaccine Supply:
Understanding and Combating Shortages

While vaccine shortages do occur from time to time, there are plans in place to help mitigate those shortages to lessen their impact on both public and private sectors.



By Meredith Whitmore

VACCINES ARE ONE of the greatest success stories in medicine's history. Smallpox, once claiming countless lives worldwide, is eradicated from the planet.[1] Polio, much-feared in the United States during the 1950s, has been eliminated in this country.[2] Influenza, too, is held at bay by annual vaccines, with some 145 million Americans vaccinated during the 2015–2016 flu season.[3] And, hundreds of millions of Americans are spared each year from contracting serious illnesses such as measles, diphtheria, whooping cough and pneumonia, all thanks to vaccinations, many of which are given during childhood. Seventy-two percent of children 19 months to 36 months old receive the combined seven-vaccine series against nine infectious diseases, including chickenpox, mumps, hepatitis B and rubella. Ninety percent of American parents, in fact, vaccinate their children against various illnesses — most following the Centers for Disease Control and Prevention's (CDC) recommended schedule, which includes up to 28 immunizations before a child's second birthday.[4]

Suppose our country suffered a severe dearth of vaccine supplies to inoculate children and adults against multiple serious but preventable illnesses.

High vaccination rates, which boost "herd immunity," protect the general public from such crises as the 2013 New York City measles outbreak. Rather than infecting the entire city, the outbreak remained in the Brooklyn area because most New Yorkers who came into contact with the virus had been vaccinated. According to infectious disease specialist Jane Zucker, MD, "If we didn't have the high vaccination levels that we do in New York City … I can promise you we would have had hundreds, if not thousands, of [measles] cases."[5]

Suppose, however, that our country suffered a severe dearth of vaccine supplies to inoculate children and adults against multiple serious but preventable illnesses. What, then, stands between Americans and a pandemic such as the Spanish flu outbreak of 1918? In other words, how much does the average healthcare provider or researcher understand and appreciate the quantity and allocation of our nation's vaccine supply? Since vaccines are the best defense against infectious diseases, knowing more about their allocation could help providers purvey the importance of vaccines and advocate for adequate future supplies.

Since the year 2000, the country has endured many series of shortages of vaccines against various diseases.

Vaccine Distribution at a Glance

It is important to remember that there are both private and public sector vaccine distribution avenues, and the two occasionally overlap. The private sector (physician offices serving privately insured patients, for example) has several ways of obtaining vaccine, including directly through the manufacturer, ordering from a distributor who purchases from the manufacturer or even buying vaccine from a distributor that is more than one step removed from a manufacturer. However, private sector providers may be impacted by public supplies of vaccine, since many physicians serve both privately insured patients and those in federally funded, public sector CDC programs.

As Jeanne Santoli, MD, branch chief of vaccine supply and assurance at CDC, explains: "On the public side, which CDC manages, there are two large vaccine programs: Vaccines for Children [VFC], which has 44,000 enrolled providers, and the Section 317 program, which primarily serves targeted groups of adults. About 50 percent of the pediatric vaccine in the country goes through the VFC program. For adults, we purchase far less. Across the board, though, we play a very large role in the public sector supply chain for the distribution of vaccine."[6]

Vaccine Shortages

While Dr. Santoli says there are not specific vaccines necessarily more vulnerable to shortage from a biological standpoint (biologic substances can be repeatedly manufactured through specific processes), shortages do occur due to other reasons. A manufacturer, for example, might not be able to produce vaccine quickly enough to meet demand. Or a manufacturer's supplier may be unable to send vaccine out promptly. Each vaccine may have its own specific reasons for shortage, but there are often common factors, including economic, regulatory and legal issues. In the event of shortage, however, CDC works with vaccine manufacturers to lessen the impact on public and private sectors as much as possible. "There are times when the shortages are harder to mitigate," Dr. Santoli explains. "If only one manufacturer makes a vaccine, then I can go to the national vaccine stockpile, but I cannot talk to other manufacturers. It's harder to manage a shortage when there is a single manufacturer." Dr. Santoli, once again, assures physicians and the general public that no particular vaccine is more susceptible to shortage.[6]

Vaccine shortages have occurred since at least the 1960s, although since the year 2000, the country has endured many series of shortages of vaccines against various diseases.[7] Most shortages have been passing and relatively easy to minimize, lasting only a few days to a week. A few, however, have caused more disruption, including shortages of pediatric vaccines for tetanus, diphtheria, pneumococcal conjugate, trivalent inactivated influenza and meningococcal conjugate.[8] During such times, CDC informs healthcare providers how long the shortage will last and how to distribute current vaccine supply. In most cases, there is still vaccine available, but there are simply fewer doses than usual.

"During a shortage," Dr. Santoli adds, "doctors receive orders through the health department for VFC patients, whose vaccines are controlled. Doctors will receive an amount of vaccine that they are known to need, but they won't be able to get more because that is what keeps distribution equitable, which is the very best thing for minimizing the impact of a shortage." When doctors order from a manufacturer, that manufacturer will have a similar process in place. "If it's very much different from what a physician has been ordering previously, they will discuss that because, again, they don't want anyone to accumulate doses," explains Dr. Santoli. "A lot of providers who are impacted by a shortage are actually impacted by their public supply and their private supply, since in pediatrics, most of the doctors in our program are private providers who also serve insured patients."

To prevent shortages, CDC closely monitors vaccine supply across the country. Because they purchase large amounts of vaccine, their contracts with manufacturers are very detailed in terms of what is required. For one, manufacturers are mandated

to give as much advance notice as possible of any supply issues. When a manufacturer anticipates an order might be inadequate, CDC has various actions it can take to mitigate the impact. It will begin by estimating the extent and length of the vaccine supply gap expected, and then it will look at its own stockpile. "Through the Vaccines for Children program, the government owns and maintains stockpiles of routinely recommended pediatric vaccines," explains Dr. Santoli. "The program started in 1994, and over time, we have built up our stockpiles in order to be able to serve as a safety net. So if a manufacturer says they expect a certain amount of gap of this amount of doses over this period of time, the very first thing we'll do is look in our stockpile and see if that can be brought to bear."

Sometimes, the stockpile is sufficient to bridge the gap. If it is insufficient, though, CDC asks permission from the manufacturer to privately speak to other licensed manufacturers of alternative products that could be used. Then, CDC, and specifically Dr. Santoli, will approach an alternate manufacturer in confidence to see what they might be able to do to make additional doses available. "That takes a little bit of thinking," says Dr. Santoli. "They will respond back to me, and then, depending on what they say, we can put a plan into effect. Depending on what we anticipate, we might put a vaccine in controlled ordering. That is on CDC's side, with our states getting specific caps, and them working with providers to get vaccine equitably distributed. The manufacturers will often do something similar. We do it differently because we have the middleman, the state immunization programs, but controlled order usually happens across the board. That is the way we can fairly make sure that the public sector and the private sector and all the providers in it get the amount of vaccine that is their fair share so we can get through a time of what we think is going to be tight supply."

However, Dr. Santoli is quick to point out that "though not nearly as common, there's another strategy for more severe shortages. Say a manufacturer calls CDC to tell us about a shortage. We look at what's in the stockpile, and we see if we can do something there. We go to another manufacturer, and we see if we can do something there. But what happens if there is still a gap? In other words, suppose we need 100,000 doses a month to serve the nation, but it really looks like there will be only 50,000 a month. There's going to be an ongoing gap for a period of time. CDC will pull together its infectious disease experts and explain, for example, that a vaccine regularly given on a four-dose schedule could be decreased. So, maybe we don't have enough to give everyone the full four doses, but we could decide that we'll give people two doses. Then, when the shortage is over, we'll be recalling those children and giving them the doses that they missed."[6]

Balancing Supply with Price Points and Manufacturer Incentives

Perhaps the worst cause of shortage, other than missed production goals, is a manufacturer deciding to decrease production or stop producing a vaccine altogether because the company's financial gain is too minimal and drug production costs are too high. Development costs are often steep for pharmaceutical companies, too often leading to a decline in the number of manufacturers producing certain vaccines.[9] A recent Duke University study found that between 2004 and 2014, an average of almost three out of 22 vaccines suffered a supply gap in the United States. And, in 2007, a full one-third of vaccines were scarce. Duke University economics professor David Ridley, PhD, who headed the study, examined market tensions and price points required to draw vaccine manufacturers into increased production. "The government doesn't want to overpay," Dr. Ridley stated in a Fuqua School of Business news release, "but there's a tension between responsible use of government funds and giving manufacturers sufficient incentive to get into manufacturing — and stay in."[10]

A recent Duke University study found that between 2004 and 2014, an average of almost three out of 22 vaccines suffered a supply gap in the United States.

Dr. Ridley and his colleagues also discovered that during the past decade or more, there has been a correlation between vaccine price and shortage probability. More specifically, for every 10 percent increase in price, there was a 1 percent lower probability of a shortage. They looked at the supply and price of 22 vaccines between 2004 and 2013, and found 24 cases of shortage during that time. The shortages were due to a diminishing supply and low demand. Among vaccines priced at $75 or higher per dose, however, there had been no shortages since 2004.[10,11]

While the government has been willing to pay higher fees for new vaccines, the price of older vaccines is much lower, making manufacturers unlikely to invest in expansion or new developments for them. These deflated prices might be too low to

sustain certain vaccines because, without that investment, vaccine shortages are increasingly more likely. "You'll be reluctant to invest in expensive new technology if you're not going to make any money," Dr. Ridley added. "It's expensive to get into manufacturing, so if someone exits, it's hard for someone to step in and take their place. If you're not making money anyway, you're not going to have excess capacity sitting around."[10]

Several studies have found that at even 10 times their cost, vaccines would still save the country money.

Vaccine prices are often purposely reduced by government programs provided for low-income families that would not otherwise have coverage. In fact, federal and state programs purchase more than 50 percent of childhood vaccine doses at a discount. VFC, the largest federal vaccine program, may adjust prices within a year, but only downward. This constrains changes in what the program pays for, with some vaccines falling below the overall inflation rate. And, although the program keeps a six-month backup supply of vaccines on hand, the average shortage lasts three times that long, according to the Duke study.[10]

Commercial market vaccine prices are higher than government ones, but not often by enough to inspire manufacturer investment and prevent shortages of older, less-expensive vaccines.[12] In a 2011 study on the effects of regulation and competition on vaccine supply, researchers discovered the government's role in purchasing a large portion of vaccines could be to blame, in part, for the small number of vaccine suppliers.[13]

Finding the Best Chance for Adequate Supply

Vaccines are perhaps the most cost-effective treatment available, unlike other medical treatments, since they save money by preventing disease and promoting a country's healthy productivity. Despite this, the U.S. government seems determined to undervalue vaccines' prices, though studies have shown that vaccines would still be worth their cost if they were 10 times more expensive. Several studies have found that at even 10 times their cost, vaccines would still save the country money.[14,15]

"I think the public has a sense that higher prices encourage investment in research," said Dr. Ridley. "I think what's overlooked is that higher prices also encourage manufacturers to invest in capacity and quality. Without those investments, shortages become more likely."[10]

Dr. Santoli's perspective on vaccine supply is somewhat more encouraging: "Vaccine supply, we understand, is a critical priority. It's a very effective tool. It's a cost-effective tool, of course, but it's also an effective tool for preventing disease. We place a very, very high priority on the planning that we do about how to manage shortages, and to the extent that we can manage them. Then, we can make future shortages least burdensome on providers and on families. There can be a potential shortage beginning, for example, but we can have it all managed so that it won't even be an issue or a concern that either sector will have to deal with. That's what we're always trying to do by having these strategies and using them. Strategies are the cornerstone of being able to prevent vaccine-preventable diseases. Still, we must anticipate that a shortage could happen for any vaccine at any time."[6]

Perhaps one day scientific research and development on more expensive vaccines can advance vaccine production across the board, improving storability or lessening the drugs' production time, mitigating the likelihood of future shortages. Today, though, the country's best chance to supply adequate, equitable vaccine appears to be finding a balance between pharmaceutical company incentives and governmental devaluing of vaccine cost. ❖

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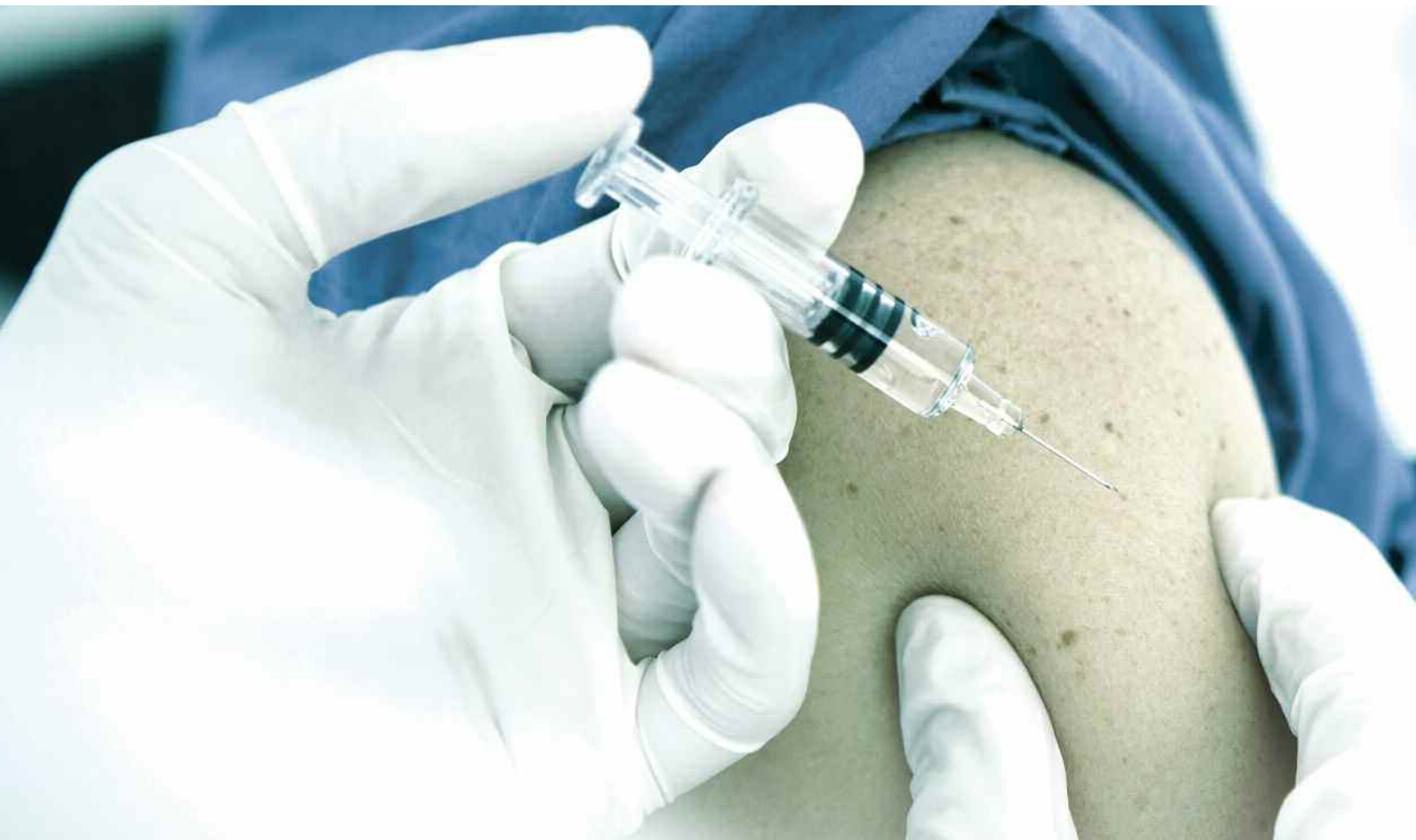
Adult Vaccines: *A Needed Boost*

With suboptimal vaccination rates among adults to protect against preventable diseases, steps are being taken to heighten awareness and increase access to adult vaccines.

By Ronale Tucker Rhodes, MS

EACH YEAR, THERE are countless media reports surrounding the debate about childhood vaccination rates. Yet, little attention is paid to the exceedingly low adult vaccination rates. This should be alarming since only 300 U.S. children die each year from vaccine-preventable diseases, compared with approximately 42,000 U.S. adults.[1] Indeed, more adults die from vaccine-preventable diseases than from breast cancer, HIV/AIDS or traffic accidents.[2]

The reasons behind these low vaccination rates vary from lack of patient education and/or perceived value to inadequate recommendations from healthcare providers and insurance reimbursement. But, there do exist very clear recommended vaccine guidelines by the Centers for Disease Control and Prevention (CDC) for adults young and old, as well as those who are pregnant and have health conditions. As such, to increase vaccination rates, programs and campaigns are being implemented to promote the importance of vaccination throughout the lifespan.



Assessing the Numbers

In 2016, CDC published a report that looked at the lifetime use of seven common vaccines — influenza, pneumococcal, tetanus toxoid-containing (tetanus and diphtheria [Td] or tetanus and diphtheria with acellular pertussis [Tdap]), hepatitis A, hepatitis B, herpes zoster [shingles] and human papillomavirus [HPV]) — among adults in 2014, three of which — pneumococcal disease, shingles and hepatitis B — have goals in its Healthy People 2020 documents. According to the report, compared with 2013, only modest increases occurred in Tdap vaccination among adults older than 19 years and herpes zoster vaccination among adults older than 60 years. Coverage among adults for all other vaccines didn't improve at all.

Specifically, the report showed that influenza vaccination coverage among adults older than 19 years was 43.2 percent; pneumococcal vaccination among high-risk persons aged 19 through 64 years was 20.3 percent and among adults older than 65 years was 61.3 percent; Td, hepatitis A and hepatitis B vaccination coverage among adults older than 19 years was 62.2 percent, 9 percent and 24.5 percent, respectively; HPV vaccination coverage among adults 19 through 26 years was 40.2 percent for females and 8.2 percent for males; and herpes zoster vaccination coverage among adults older than 60 was 27.9 percent. CDC's goal is to have 90 percent of adults immunized with the pneumococcal and hepatitis vaccines and 30 percent of adults over age 60 immunized with the herpes zoster vaccine by 2020.

Why are the numbers so low? Interestingly, CDC's report showed that having health insurance coverage and a usual place for healthcare (regardless if they have health insurance) are associated with higher vaccination coverage, but those factors don't ensure optimal coverage. For instance, even among adults who had health insurance and more than 10 physician contacts within 2014, between 23.8 percent and 88.8 percent (depending on the vaccine and age) reported not having received vaccinations that were recommended.[3]

Robert Wergin, MD, president of the American Academy of Family Physicians, says lack of patient education is one cause of low vaccination rates among adults. "Many adults don't know what vaccines they should have," said Dr. Wergin. This is because unlike children, adults don't have regular well-child visits where they get vaccinated. And, while public health officials say doctors need to recommend vaccines more often when they see patients, Carolyn Bridges, MD, associate director for adult immunization at CDC, says, "Primary care doctors think vaccines are important, but it's difficult for them to incorporate vaccination into giving routine care."[4]

According to a policy researcher at RAND Corp., adults may not see the consequences of not getting a vaccine.[5] In a RAND survey of adults who went unvaccinated for the flu in the 2009-2010 season, more than half cited factors relating to a perceived lack of value as their main reason. Reasons included a lack of perceived need (28 percent), lack of belief in flu vaccines (14 percent) and a perceived risk of illness or side effects (14 percent). In another RAND study, an analysis of data from 2008 calculated missed opportunities based on vaccination and care use data, and found that more than 53 million U.S. adults had at least one healthcare provider contact between October and December but remained unvaccinated. According to the study, if all of those patients had been vaccinated, it would have increased overall vaccination by about 23 percent. Yet, the analysis also found that if only those unvaccinated adults who were willing to be vaccinated were counted, the gains would be an increase of only about 14 percent, suggesting that resistance to vaccination plays a significant role.[6]

A survey conducted by researchers from the University of Colorado School of Medicine in collaboration with CDC in 2014 identified the following barriers to the delivery of adult vaccines: failure of healthcare providers to assess vaccination needs of patients, insufficient stock of vaccines, inadequate insurance reimbursement, record-keeping challenges and high costs. The survey was answered by 79 percent of general internists and 62 percent of family physicians surveyed from March 2012 through June 2012 in the U.S. Almost all physicians reported assessing patients' vaccination status at annual visits or first visits, but only 29 percent of general internists and 32 percent

of family physicians reported doing so at every visit. The survey also found that most physicians aren't stocking all recommended vaccines, with money cited as the top reason.[7] For instance, physicians often don't store the shingles vaccine in their office because it has a limited shelf life, and billing private Medicare prescription drug insurers is complex. So, doctors often issue a prescription for the shot for the patient to fill it at a pharmacy or health clinic, which is an extra step that deters some people.[4] In addition, the most commonly reported reasons for referring patients elsewhere such as pharmacies, retail stores and public health departments for vaccines were insurance coverage for the vaccine (36 percent) or inadequate reimbursement (41 percent).[7] While the Affordable Care Act requires private insurers to pay 100 percent for all preventive services, including vaccines, that is not so for Medicare. Flu and pneumonia vaccines are free Under Medicare Part B, but vaccinations for shingles and tetanus are covered under Medicare Part D and often require co-payments of $100 or more.[4]

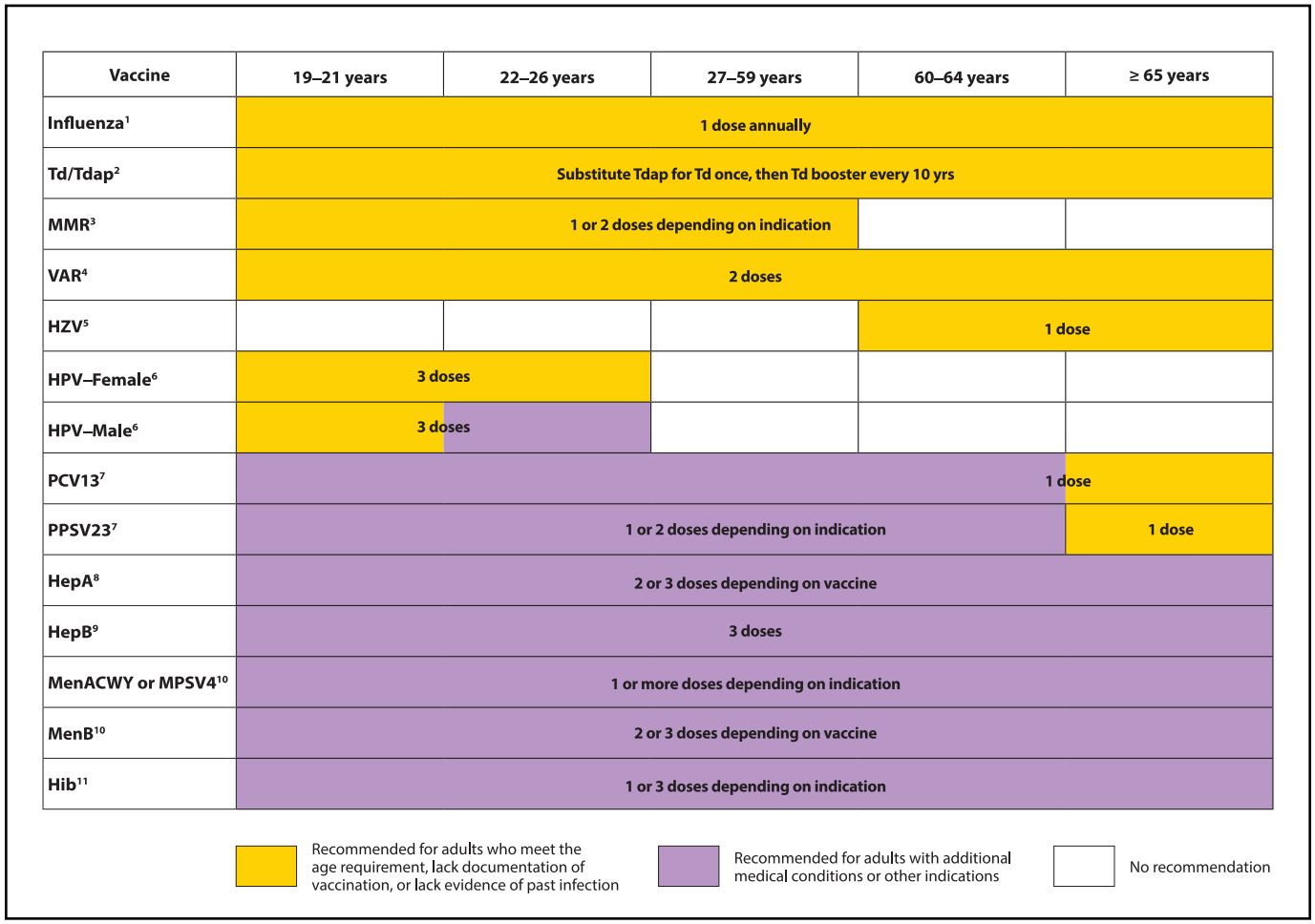
The Recommendations

Each year, CDC's Advisory Committee on Immunization Practices (ACIP) releases its recommended schedule of vaccinations for all adults. Vaccinations are recommended for specific populations based on a person's age, health conditions, behavioral risk factors, occupation, travel and other indications (Figures 1 and 2).[8]

All adults. ACIP recommends all adults get the annual flu shot every year. It also recommends that all adults get the Tdap vaccine if they did not receive it as a child, and then a Td booster shot every 10 years.

Adults 19 through 26 years old. Young adults should receive the HPV vaccine to protect against the human papillomaviruses that cause most cervical and anal cancers and anal warts. The HPV

Figure 1. Recommended Immunization Schedule for Adults Aged 19 Years or Older by Age Group, United States, 2017



Note: Figure 1 is intended to be read with the footnotes found at www.cdc.gov/vaccines/schedules/downloads/adult/adult-combined-schedule.pdf that contain important general information and considerations for special populations. Source: Centers for Disease Control and Prevention

vaccine is recommended for women up to age 26 years, men up to age 21 years and men ages 22 to 26 years who have sex with other men.

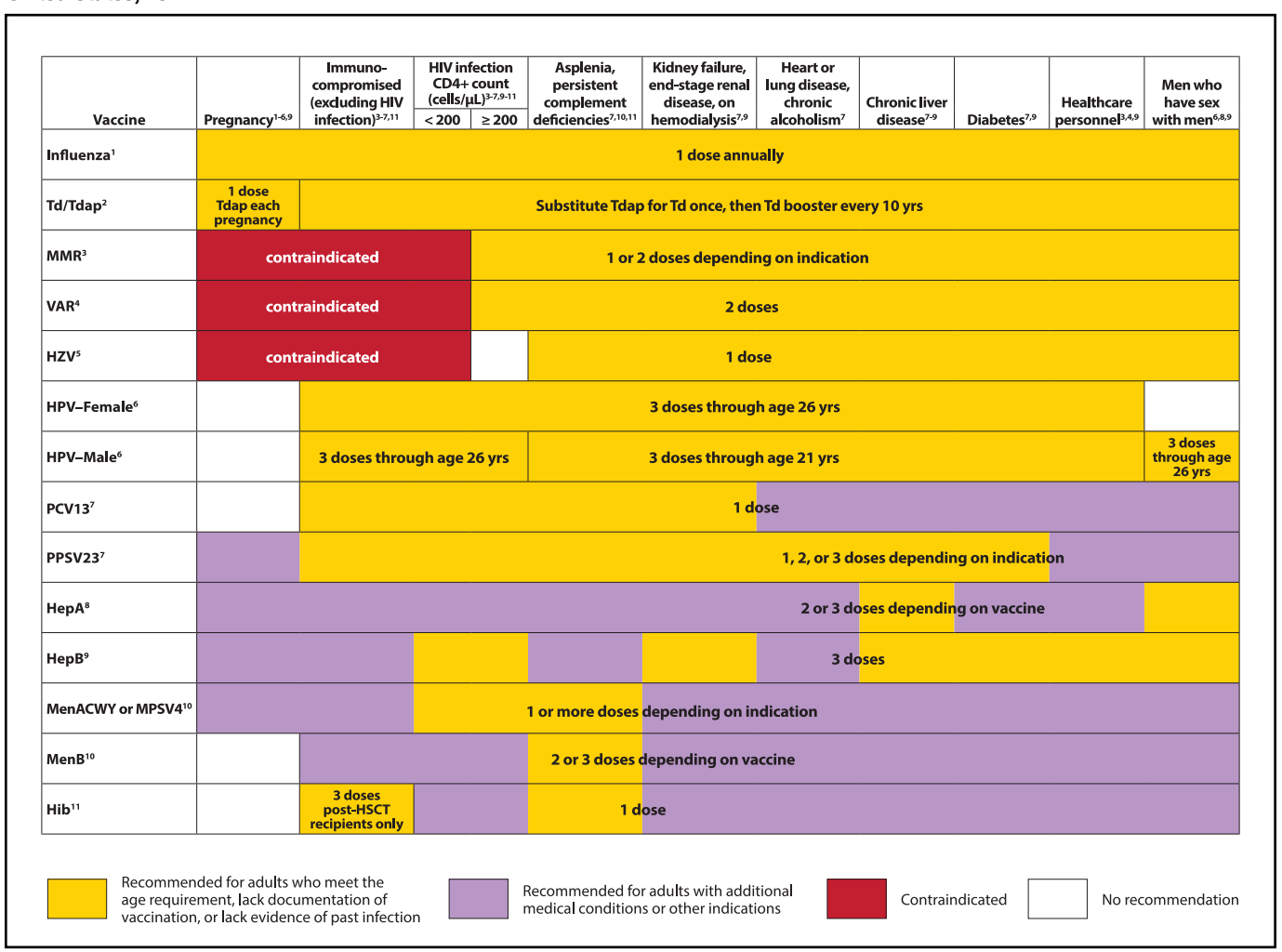
Adults 60 years and older. The zoster vaccine that protects against shingles is recommended for adults 60 and older. ACIP recommends the pneumococcal vaccine that protects against pneumococcal disease, including infections in the lungs and bloodstream, for all adults over 65, and for adults younger than 65 who have chronic health conditions.

Adults with health conditions. While no specific vaccines are recommended for adults with health conditions other than the seasonal flu vaccine and the Tdap or Td vaccine, ACIP does recommend individuals speak with their doctor if they have asplenia; diabetes types 1 or 2; heart disease, stroke or other cardiovascular disease; HIV infection; liver disease; renal disease; or a weakened immune system.

Pregnant women. Women who are pregnant should receive a Tdap vaccine between 27 and 36 weeks of pregnancy (preferably during the earlier part) to help protect against whooping cough. They are also recommended to receive a flu shot during flu season, which is October through May.

Healthcare workers. Because of the risk of exposure to serious diseases, healthcare workers should receive the hepatitis B vaccine, the measles, mumps and rubella (MMR) vaccine if they were born in 1957 or later and have not had the MMR vaccine, and the varicella (chickenpox) vaccine if they have not had chickenpox. If they don't have documented evidence of a complete hepB vaccine series or an up-to-date blood test that shows them immune to hepatitis, MMR or varicella, they should receive the full-dose series of the vaccines. In addition, those who are routinely

Figure 2. Recommended Immunization Schedule for Adults Aged 19 Years or Older by Medical Condition and Other Indications, United States, 2017



Note: Figure 2 is intended to be read with the footnotes found at www.cdc.gov/vaccines/schedules/downloads/adult/adult-combined-schedule.pdf that contain important general information and considerations for special populations. Source: Centers for Disease Control and Prevention

exposed to isolates of N. meningitidis should get one dose of the meningococcal vaccine.

ACIP also makes recommendations for international travelers and immigrants/refugees, as well as recommendations for those who should not be vaccinated against certain diseases, which can be found at www.cdc.gov/vaccines/adults/rec-vac/index.html.

Taking Steps to Turn the Tide

In response to survey results, RAND Corp. researchers suggest many strategies for boosting vaccination rates. One way is to step up conventional strategies, including mail/telephone reminders and physician recommendations and offering vaccines at more convenient locations. Another is to make special efforts to reach out to healthy young adults who do not visit providers often and are difficult to reach. These efforts could include using new media to deliver public service announcements and making vaccines available at work. And, for those who are skeptical about vaccines, they suggest one-on-one counseling with healthcare providers to help them understand that vaccination poses little risk compared to the risk of going unvaccinated both for themselves and those around them.[6]

Efforts are being made at a grassroots level to improve vaccination rates. Some examples include clinics and hospitals offering drive-through flu shots that are given to people in their cars; the Uber ride-sharing service letting customers use their cell phone app to get free flu shots in Washington, Boston and New York; some health systems using their electronic medical records to identify seniors who need vaccines and then advising physicians to call them; and health systems giving bigger roles to nurses and medical assistants by allowing them to review patients' records and offer vaccines without interrupting physicians.[4]

A good example of a grassroots initiative was launched by Duke University in Durham, N.C., in 2016. Titled the Adult Immunization Project, it focuses on working with providers throughout the Duke Health System. According to Tracy Y. Wang, MD, MHS, MSc, associate professor at Duke University, researchers analyze educational interventions used in primary care practices throughout the Duke system to try to understand which are successful and why. The data are then fed into an analytics platform where healthcare providers are able to view a patient's vaccination status, identify high-risk patients and connect patients with targeted interventions.[9]

In addition, many state and federal organizations have come up with programs and campaigns to address the issue. At the state level, for example, the New Hampshire Department of Health and Human Services launched the Start the Conversation campaign designed to promote a two-way conversation between healthcare providers and patients, stressing the importance of vaccination through the lifespan. Included in the campaign is a toolkit with resources for the entire healthcare team, including nurses, nurse practitioners, physicians, physician assistants, practice managers, clinical managers and administrative staff.[10]

At the federal level, the National Vaccine Advisory Committee launched the National Adult Immunization Plan (NAIP) in 2015 that "is intended to facilitate coordinated action by federal and nonfederal partners to protect public health and achieve optimal prevention of infectious diseases and their consequences through vaccination of adults." The NAIP establishes four key goals, each of which is supported by objectives and strategies to guide implementation through 2020:[11]

- Strengthen the adult immunization infrastructure;
- Improve access to adult vaccines;
- Increase community demand for adult immunizations; and
- Foster innovation in adult vaccine development and vaccination-related technologies.

In addition, the National Foundation for Infectious Diseases has created a national Campaign for Adult Immunization. In partnership with leading experts and organizations on adult vaccination, the campaign's goals are to close the funding gap, support an Immunization Congressional Caucus and ensure all adults are fully aware of and have access to appropriate immunizations.[12]

Protection Is Needed Now

Vaccines are just as important for adults as they are for children to prevent getting and spreading diseases. With a disproportionate number of adults dying from vaccine-preventable diseases when compared to the experience of children, there is a pressing need to address the causes behind the abysmally low adult vaccination rates. It is hoped that some of the strategies put into place at both the grassroots and government levels will help to convince individuals of the need for these lifesaving vaccinations and doctors of the importance of doing their part to ensure adult patients are protected too. ❖

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Influenza: The Quest for a Universal Vaccine

Promising research is targeting the hemagglutinin protein to develop vaccines that could protect against all strains of the flu.

By Diane L.M. Cook

ACCORDING TO THE World Health Organization (WHO), worldwide annual influenza (flu) epidemics are estimated to result in three million to five million cases of severe illness and 250,000 to 500,000 deaths. WHO continuously monitors the flu viruses circulating in humans and twice a year updates the composition of flu vaccines that targets the three most representative virus types in circulation — two subtypes of influenza A virus and one influenza B virus — for the development of trivalent vaccines, as well as a second influenza B virus to support quadrivalent vaccine development.[1] However, because of antigenic drift, current flu vaccines only contain antibodies for circulating viruses and can only prevent some illnesses and deaths, not all.

But researchers believe they have found the key to eradicating seasonal and pandemic flu. That key is a new vaccine design that can protect against all flu viruses, both circulating viruses and mutated viruses that have not yet occurred. This next generation of flu vaccines is being touted as the precursor to a universal flu vaccine and is expected to dramatically reduce the number of cases of illness and the high morbidity rates that result from the flu.

More than 40 universal influenza vaccine designs are currently in development.[2] Some of the more promising research is focusing on how to elicit an immune response that targets the whole hemagglutinin (HA) protein (found on the surface of influenza viruses), just the hemagglutinin head (where flu viruses mutate constantly) or just the hemagglutinin stalk (where viruses do not mutate as often).

An academic research lab and a vaccine manufacturer are working together to design a synthetic flu vaccine that targets the whole hemagglutinin protein, both the head and stalk, by looking at the entire sequence holistically.

The COBRA Vaccine

An academic research lab and a vaccine manufacturer are working together to design a synthetic flu vaccine that targets the whole hemagglutinin protein, both the head and stalk, by looking at the entire sequence holistically.

It all started in 2012, when Ted Ross, PhD, director of the Center for Vaccines and Immunology at the University of Georgia, began collaborating with Sanofi Pasteur on a new type of broadly protective influenza vaccine (BPIV) called computationally optimized broadly reactive antigen, or COBRA. The COBRA method focuses on neutralizing epitopes (the part of an antigen that is recognized by the immune system) of the hemagglutinin, building off of the current standard of care.

Between 2011 and 2013, two studies demonstrated that a novel hemagglutinin for H5N1 influenza, derived using the COBRA method, elicited a broad antibody response against H5N1 isolates from different clades in mice and nonhuman primates.[3] The researchers then conducted a joint study in which they designed nine independent COBRA hemagglutinin genes to elicit antihemagglutinin antibodies directed at the head domain of the H1N1 hemagglutinin protein.[2] The antibodies were assessed as vaccines used alone, in cocktails or in prime-boost combinations. The most effective regimens elicited the broadest hemagglutinin-inhibition response against a panel of H1N1 viruses isolated over the past 100 years, even against viruses whose sequences were not included in the design strategy. The study represents the first demonstration of a COBRA-based hemagglutinin vaccine strategy that elicits a broadly reactive response against both seasonal and pandemic H1N1 isolates.[3]

According to study results, the monoclonal antibody binds to conformational epitopes in the conserved stem domain of H1N1 hemagglutinin proteins. In contrast, the two hemagglutinin head-specific monoclonal antibodies bound to some, but not all, COBRA hemagglutinin proteins. Overall, the pattern of monoclonal antibody binding indicates that each of the COBRA hemagglutinin proteins has differently exposed epitopes and, therefore, may have different antigenic properties. Even so, a COBRA hemagglutinin vaccine has the potential to recall a broader repertoire of memory responses to protect against more antigenic H1N1 variants.[2]

According to Harold Kleanthous, PhD, head of research (North America) and associate vice president at Sanofi Pasteur, the differences between the yearly flu shot and the COBRA vaccine is that the "annual seasonal influenza vaccines are preselected and matched to circulating viruses. Sometimes, though, viruses drift prior to rollout of these vaccines, and they are not as well-matched, leading to reduced vaccine effectiveness." When an antigenic shift occurs, making it even less possible to predict the circulation of a new virus in humans, explains Dr. Kleanthous, today's vaccine strategies are not able to reliably protect against the strains that emerge, as was the case with the introduction of the A/California H1N1 strain in 2009. This, he says, is "the advantage of a synthetic approach that is designed to represent many more circulating viruses. The COBRA vaccine … is able to represent several influenza viruses within a subtype — influenza A H1, H3 and both influenza B viruses — isolated over several years, preferentially displaying to the immune system only the most important domains of influenza viruses, that have the potential to protect against strains yet to emerge into circulation. [It offers] greater breadth of protection, and when coupled with suitable immune stimulants, may eliminate the need for an annual flu shot."

Another benefit of the COBRA vaccine, says Dr. Ross, is that it can be tested using the U.S. Food and Drug Administration's approved hemagglutinin-inhibition assay, which detects vaccine-elicited antibodies that block the receptor binding sites on the hemagglutinin head to bind to the hemagglutinin receptor on human and animal cells (sialic acid). These epitopes are found on the globular head. "Other universal vaccine designs, of which

there are many and some that do not focus on the hemagglutinin at all, do not have this benefit," he says. "An assay with correlation to human protection may have to be established."

The Chimeric Vaccine

Researchers at two North American labs are working together to develop a new vaccine design that targets only the stalk of the hemagglutinin protein, which is highly conserved and is not prone to mutation. The vaccine focuses only on influenza A viruses because they are the ones that cause pandemics.

Normally, upon exposure to an influenza A virus, humans generate high quantities of strain-specific antibodies that bind to the head domain of hemagglutinin — the viral protein that mediates attachment to human cells, which is extremely variable among different strains of flu and is prone to mutation. Thus, the immunity these antibodies provide is very short-lived. Because yearly flu vaccines seek to elicit antibodies that bind to the head domain of hemagglutinin, they must be reformulated annually to keep pace with the rapidly mutating virus, and they do not provide protection against the emergence of new pandemics.

However, during the 2009 H1N1 swine flu pandemic, the Palese Laboratory at the Icahn School of Medicine at Mount Sinai in New York, along with several other labs around the world, discovered infected humans generate unusually high amounts of antibodies that target the highly conserved stalk domain of the hemagglutinin protein. Unlike the strain-specific antibodies that humans normally generate, these stalk-binding antibodies have the ability to neutralize diverse strains and subtypes of influenza A virus. According to Matthew Miller, PhD, assistant professor in the department of biochemistry and biomedical sciences at McMaster University, "It was quickly recognized that a vaccine capable of generating similarly high levels of hemagglutinin stalk-binding antibodies might then be capable of providing universal protection against influenza A viruses."

Researchers at Dr. Miller's lab, as well as at other institutions, demonstrated that these broadly neutralizing antibodies were boosted most efficiently anytime the immune system thought it was being exposed to a pandemic-like strain of flu. So, they developed chimeric hemagglutinin proteins that are capable of tricking the immune system into thinking it has been exposed to a pandemic virus and thereby efficiently boosts levels of broadly neutralizing antibodies in animal models.

"In the context of this chimeric vaccine, we refer to the hemagglutinin proteins as 'chimeric' because they are, in fact, a 'chimera' of two proteins," explains Dr. Miller. "Basically, we take the stalk domain from one influenza virus subtype (an H1, for instance) and then fuse it to the head domain of a different influenza virus subtype (an H5, for example). The nomenclature we then use to describe this chimeric hemagglutinin protein would be 'cH5/1' where 'c' equals chimeric, 'H' equals hemagglutinin, '5' equals head domain of H5 virus and '1' equals stalk domain of H1 virus."

Extensive preclinical work from the Palese Laboratory demonstrated that vaccines containing these chimeric hemagglutinin molecules are able to provide broad, or universal, protection against influenza A virus infection in animals and are now being developed clinically. However, work is also being conducted to target influenza B viruses using chimeric hemagglutinin, so they are working to define the optimal types and specificities of antibodies capable of generating "universal immunity" to optimize their chimeric vaccine design.

"An important benefit of this chimeric vaccine platform relative to other vaccines that are being developed, such as the headless hemagglutinin vaccine or viral-vectored vaccines that target M2e [influenza matrix protein 2], is that these chimeric hemagglutinin molecules retain functionality," says Dr. Miller. "As a result, they can be incorporated into the existing influenza virus vaccine platforms, either inactivated vaccine or live-attenuated vaccine. This is not true of many other platforms which are subunit-based or rely on viral-vectored delivery of synthetic genes. Such platforms will need to undergo much more rigorous preclinical testing in animals, and Phase I clinical trials must be completed to test safety and immunogenicity of the vaccine in humans."

Next Steps

Dr. Kleanthous says the University of Georgia's and Sanofi Pasteur's intent is to move the most promising approaches for a BPIV into the clinic as expeditiously as possible after all preclinical proof-of-concept criteria have been met: "We expect to take an iterative approach to early clinical studies because of the complex history of influenza exposure and pre-existing immune response all humans have."

According to Dr. Miller, the next steps for the chimeric vaccine in the next couple of years is the completion of the preclinical and clinical trials: "We also need to establish a correlate of protection for the broadly neutralizing antibodies elicited by this universal vaccine, since we still do not know what levels of these antibodies will be required to protect humans from infection." ❖

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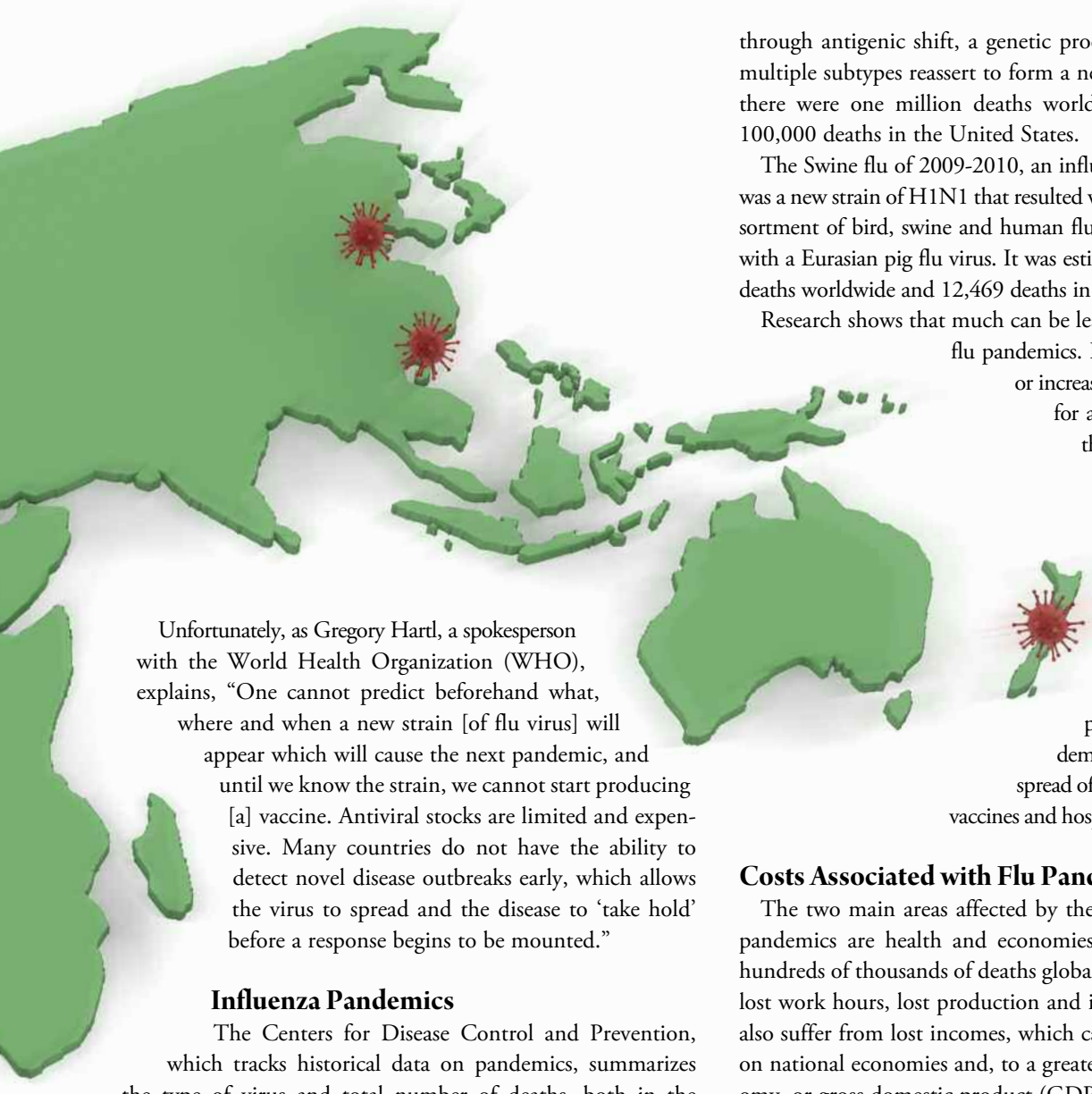
The Rising Costs of Influenza Pandemics

It's not a matter of if, but rather when, the next flu pandemic will occur, so preparations are being made now to save lives and reduce costs.

By Diane L.M. Cook

THE NEXT SEVERE influenza (flu) pandemic could cause an estimated tens of millions of deaths in the world, with the World Bank Group predicting an economic impact of 4.8 percent of gross domestic product, or $5 trillion.[1]

In the last 99 years, there have been four flu pandemics. The types and costs associated with them can be financially devastating to developing countries. As such, government agencies and private organizations around the world are trying to prevent the next severe flu pandemic with better surveillance techniques, transmission reduction and preparedness plans. And, they are developing new financing and insurance plans to help developing countries with the costs of dealing with it.



Unfortunately, as Gregory Hartl, a spokesperson with the World Health Organization (WHO), explains, "One cannot predict beforehand what, where and when a new strain [of flu virus] will appear which will cause the next pandemic, and until we know the strain, we cannot start producing [a] vaccine. Antiviral stocks are limited and expensive. Many countries do not have the ability to detect novel disease outbreaks early, which allows the virus to spread and the disease to 'take hold' before a response begins to be mounted."

Influenza Pandemics

The Centers for Disease Control and Prevention, which tracks historical data on pandemics, summarizes the type of virus and total number of deaths, both in the United States and globally, for the last four flu pandemics:[2]

The Spanish flu of 1918-1919, an influenza A H1N1 virus, was an especially virulent new strain of influenza in which there were three waves over a two-year period that infected an estimated 500 million people. There were an estimated 50 million to 100 million deaths worldwide, with an estimated 675,000 deaths in the United States.

The Asian flu of 1957-1958, an influenza A H2N2 virus, caused an estimated 1.1 million deaths worldwide and 116,000 deaths in the United States.

The Hong Kong flu of 1968-1969, an influenza A H3N2 virus, was a category 2 influenza pandemic that was caused by an H3N2 strain of the influenza A virus, descended from H2N2 through antigenic shift, a genetic process in which genes from multiple subtypes reassert to form a new virus. It was estimated there were one million deaths worldwide and approximately 100,000 deaths in the United States.

The Swine flu of 2009-2010, an influenza A H1N1 pandemic, was a new strain of H1N1 that resulted when a previous triple reassortment of bird, swine and human flu viruses further combined with a Eurasian pig flu virus. It was estimated there were 284,500 deaths worldwide and 12,469 deaths in the United States.

Research shows that much can be learned from these last four flu pandemics. For one, by implementing or increasing surveillance techniques for avian and swine influenzas, the ability to contain and eradicate the virus in animals is great. Second, by eliminating or reducing the transmission of zoonotic diseases, the risk of a flu pandemic can be greatly reduced or eliminated. And, last, preparation for flu pandemics can greatly lessen the spread of the virus, thereby reducing vaccines and hospital costs to fight the virus.

Costs Associated with Flu Pandemics

The two main areas affected by the costs associated with flu pandemics are health and economies. Flu pandemics average hundreds of thousands of deaths globally and cost money due to lost work hours, lost production and insurance claims. Farmers also suffer from lost incomes, which can have a profound effect on national economies and, to a greater extent, the global economy, or gross domestic product (GDP).

While the costs of the last four flu pandemics are unknown, they varied based on the type of influenza virus, when the virus occurred, where the virus broke out, how fast the virus spread and how many people were infected.

With the passage of time, and as the world's population increases (the United Nations reports the world population was 7.3 billion in July 2015 and is expected to reach 8.5 billion by 2030),[3] it is not a matter of "if" another flu pandemic will happen but "when" it will happen. And when the next pandemic does happen, especially if it is a severe strain, the costs will increase exponentially.

In a paper titled "The Inclusive Cost of Pandemic Influenza Risk," the National Bureau of Economic Research found that:[4]

• Expected pandemic deaths exceed 700,000 per year worldwide with an associated annual mortality cost of approximately $490 billion. The authors used published figures to estimate expected lost income at $80 billion per year and, hence, the inclusive cost would be $570 billion per year, or 0.7 percent of global income (range 0.4 percent to 1.0 percent).

• For moderately severe pandemics, about 40 percent of inclusive costs result from lost income. For severe pandemics, this fraction declines to 12 percent. The intrinsic cost of elevated mortality becomes completely dominant.

• The estimates of mortality cost as a percent of gross national income range from approximately 1.6 percent in lower-middle-income countries down to 0.3 percent in high-income countries, mostly as a result of much higher pandemic death rates in lower-income environments.

• About 95 percent of the expected costs result from pandemics that would be expected to kill more than seven million people worldwide.

Combating Pandemics and Their Costs

One Health Initiative (OHI). Due to the complexity of the development and transmission of animal viruses to humans, an ever-increasing global population, as well as global traveling and trading, an approach was created to reduce or eradicate novel A influenza viruses. Founded in 2006, OHI globally promotes the concept that human, animal and environmental health are linked. OHI's mandate is to educate international scientific and medical communities, governments and the public about this concept to encourage interdisciplinary collaboration to advance global health and save millions of lives.

The types and costs associated with flu pandemics can be financially devastating to developing countries.

In 2008, OHI created a website that serves as a repository of information pertaining to human, animal and environmental health. Through its website, OHI helps developed and developing countries learn about disease surveillance in animals, mitigate or control zoonotic diseases, understand drivers of antimicrobial resistance and develop pandemic influenza plans. In its approach to surveillance, management and preparedness for influenza pandemics, Laura Kahn, MD, MPH, MPP, FACP, a cofounder of OHI, says, "A One Health approach would conduct surveillance of wild waterfowl to determine what antigenic shifts and drifts are occurring in the virus. This information would give scientists advanced warning as to what might be jumping to domestic birds and humans."

Since its inception, OHI has learned that many emerging zoonotic diseases result either directly or indirectly from meat production and consumption. "In my course, Hogs, Bats, and Ebola: An Introduction to One Health Policy, we discuss the intersection between global health, agriculture, food safety and security, and emerging diseases. They are all tied together. Ultimately, we need to figure out how to sustainably feed ourselves without unleashing deadly diseases," explains Dr. Kahn.

The International Monetary Fund's (IMF) Catastrophe Containment and Relief (CCR) Trust. A severe flu pandemic that could cost billions or trillions of dollars in high-income countries would be financially devastating in low-income countries (LICs). To assist LICs with pandemic costs, organizations around the world have established funds to assist them. In February 2015, IMF established the CCR Trust to enhance support for eligible LICs hit by public health disasters, including flu pandemics. According to IMF, "These grants can ease pressures on the members' balance of payments and create fiscal space to tackle relief and recovery challenges."[5]

Although flu pandemics are infrequent, IMF's paper titled "Proposal to Enhance Fund Support for Low-Income Countries Hit by Public Health Disasters," says, "The rough estimates of the probability of an influenza pandemic event in any given year is between 3 and 4 percent based on the historical observation that there have been 10 to 13 influenza pandemics since 1700 (including three occurrences in the 20th century). However, the probability of a severe pandemic event is more difficult to estimate and is assessed by staff to be very small, around the order of 1 [to] 2 percent.[6]

"A severe pandemic could have substantial economic implications and pose risks to the global financial system. Economic disruptions would arise through high rates of absenteeism, as well as dysfunctions or standstill in transportation, trade, payment systems and major utilities. Sharp declines in consumption and investment, along with financial repercussions, could further exacerbate the crisis.[6]

"Model-based simulations for advanced economies show that a severe pandemic event can plausibly have an economic impact ranging from between 4 percent and 10 percent of GDP. The Congressional Budget Office (CBO, 2006) estimates the impact of a severe and a mild pandemic event in the United States. In a severe scenario, about 90 million people fall sick and two million people die, resulting in a decline in real GDP by about 4 [to] 4½

percentage points. In the mild-pandemic scenario, GDP would decline by about 1 percentage point. A study by Cooper and others (2006) incorporates the effect of trade disruptions and finds that a severe pandemic would reduce annual GDP growth by 6 percentage points, and a mild pandemic would reduce GDP growth by 2 percentage points in the U.S."[6]

The World Bank Group's Pandemic Emergency Financing (PEF) Facility. An old instrument applied in a new way could also assist LICs with the cost of flu pandemics: a financing facility that acts like an insurance policy.

The World Bank Group, in collaboration with WHO and other public and private sector partners, launched the PEF Facility in May 2016 with an expectation of being operational by spring 2017. According to the World Bank Group, it has worked closely with WHO to design PEF, which will complement WHO's Contingency Fund for Emergencies (CFE) and fill a critical gap in the current global financing architecture: "PEF financing is activated once an outbreak reaches a significant level of severity, well after the CFE has disbursed to support early response efforts. The PEF was designed specifically to respond to outbreaks from a defined set of viruses with pandemic potential."

PEF will offer coverage to all countries eligible for financing from the International Development Association, the World Bank Group's fund for the poorest countries, in the event an outbreak meets the activation criteria. PEF will also provide funding to qualified international agencies involved in the response to a major outbreak in affected countries.[7]

PEF will also provide much-needed surge funding for response efforts to help prevent rare, high-severity disease outbreaks from becoming deadlier and costlier pandemics. It covers outbreaks of infectious diseases most likely to cause major epidemics, including new orthomyxoviruses (new influenza pandemic virus A, B and C).

PEF provides a maximum of $500 million in insurance and $50 million to $100 million in cash for uninsured risks such as pandemics, including new orthomyxoviruses, to LICs. According to the World Bank Group, this insurance will fill the critical financing gap between the limited funds available at the early stages of an influenza pandemic and the assistance that is mobilized once the outbreak has reached crisis proportions. Maximum coverage under the PEF's insurance window is $500 million for three years. In addition, PEF includes a replenishable cash window targeted at $50 million to $100 million.

PEF is expected to accelerate and improve outbreak response, save lives and reduce the costs of response. "By providing resources swiftly to countries and international responders to stem an outbreak before it reaches pandemic proportions, the PEF will help save thousands of lives. It will also keep the cost of response in the millions rather than the billions that donors now spend on response and recovery efforts, and the billions, or potentially trillions, lost in GDP from a pandemic," says the World Bank Group.

Over time, PEF is also expected to create a new market for pandemic insurance that will bring greater discipline and rigor to pandemic preparedness and incentivize better pandemic response planning. PEF will also stimulate efforts by countries and development partners to build better core public health capabilities for disease surveillance and health systems strengthening toward universal health coverage.[7]

An old instrument applied in a new way could assist low-income countries with the cost of flu pandemics: a financing facility that acts like an insurance policy.

Combating Expenses Upfront

The costs of the oldest three flu pandemics were borne several decades ago. When the next flu pandemic does occur, it is going to be much more expensive on all fronts. However, if developed and, specifically, developing countries work on surveillance, transmission reduction and preparedness for the next flu pandemic, with the addition of IMF's CCR and the World Bank Group's PEF, developed countries can keep their costs down, and developing countries will not go bankrupt trying to pay for yet another pandemic. ❖

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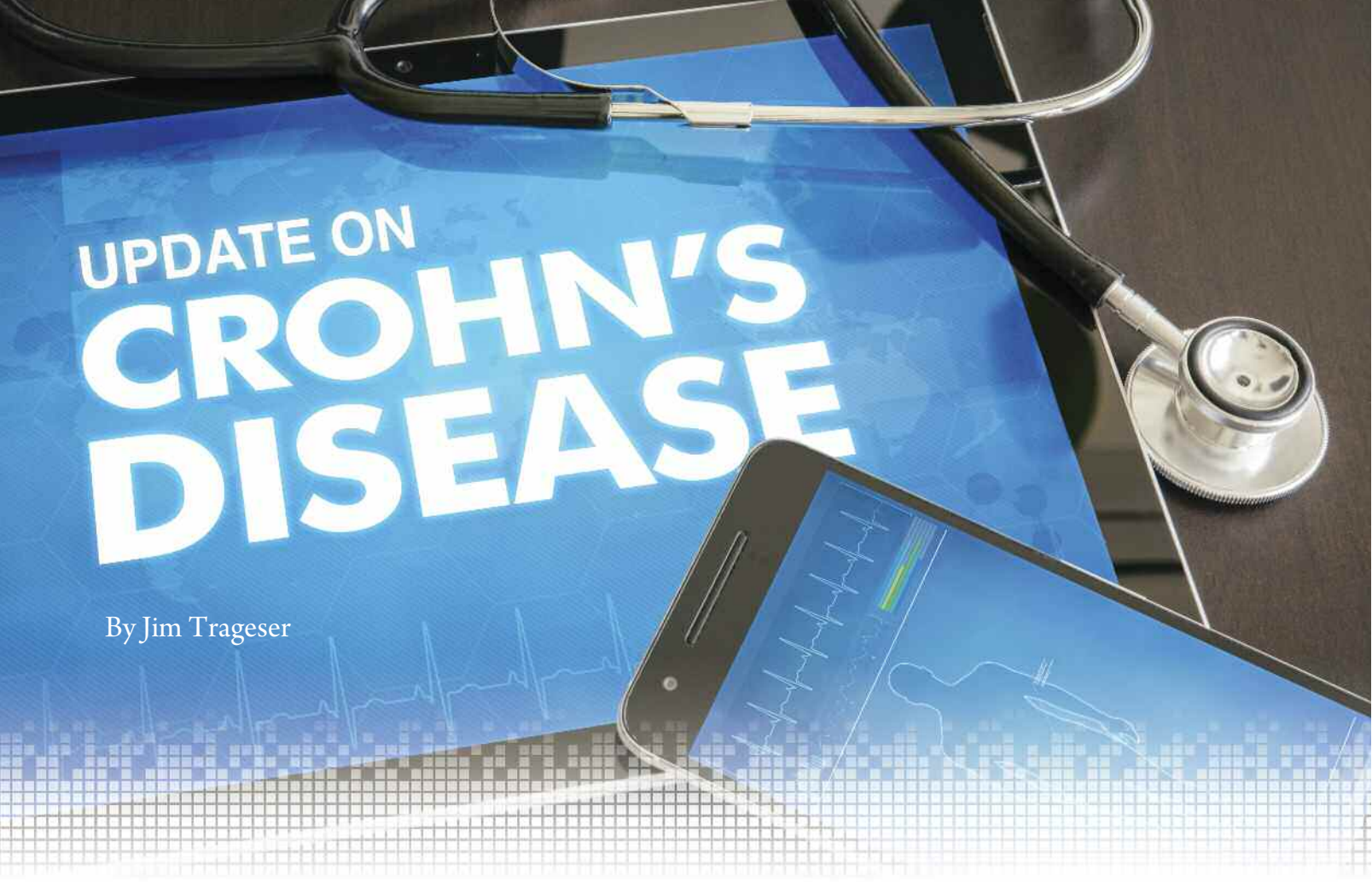

UPDATE ON CROHN'S DISEASE

By Jim Trageser

A considerable amount of research is being conducted to determine the causes, as well as more effective treatments, for this sometimes life-threatening chronic illness.

WITHOUT A CLEAR understanding of its underlying causes, a cure or even a single test to make a diagnosis, Crohn's disease remains a baffling chronic illness that presents patients and their physicians with an ongoing set of challenges for addressing its significant health risks. This inflammatory bowel disease (IBD) initially manifests as gastrointestinal (GI) distress, but it can progress to life-threatening blockages and ulcers, requiring emergency surgical intervention. Even in the majority of cases, when patients enjoy long periods of remission, Crohn's requires constant monitoring and persistent dietary and lifestyle changes that demand close cooperation between patients and their physicians.

What Is Crohn's Disease?

Crohn's was first described as a specific subset of IBD in a 1932 article written by Burrill Bernard Crohn, MD, of New York City's Mount Sinai Hospital. A follow-up paper was cowritten with fellow physicians Leon Ginzburg and Gordon Oppenheimer, but Crohn's name was listed first due to alphabetical precedent, and the condition became known as Crohn's disease.

Crohn's is a chronic IBD that affects the lining of the digestive tract.[1] Any part of the GI system can be affected, from the mouth to the anus,[2] although the most common areas affected are the lower large intestine near the anus (the sigmoid colon), and the area of the small intestine nearest the large intestine (the ileum).[3] Crohn's is differentiated from other IBDs by the specific type of lesions found in the digestive tract, as well as the types of ulcers and fistulas that develop in severe cases.

Mild cases affect only the innermost layer of the GI tract, the mucosa, which becomes inflamed. However, the disease can also affect deeper layers, and in severe cases becomes life-threatening due to the development of blockages, ulcers or fistulas[3] that can require surgery to repair. Healthy segments of the intestines can exist alongside diseased segments, with abrupt transitions between affected and healthy tissue.[4] Children with the disease often exhibit stunted growth and delayed puberty due to the lack of nutrients processed by the diseased GI tract.[5]

Crohn's is categorized into five subtypes, based on the location of the inflammation:[6]

• Ileocolitis: This is the most common type, which affects the ileum, occurring in approximately 45 percent of Crohn's patients.

• Ileitis: This type, occurring in approximately 30 percent of Crohn's patients, also affects the ileum, but it is more severe and can lead to the formation of abscesses or fistulas, or abnormal tubes between the intestines and the abdomen or skin.

• Granulomatous: One-fifth of all Crohn's patients have this type, affecting the main part of the large intestine, including the sigmoid.

• Gastroduodenal: This relatively rare type affects the area between the stomach and the small intestine, affecting only about 5 percent of patients.

• Jejunoileitis: The remaining 5 percent of patients develop this type, which affects the main part of the small intestine.

Crohn's generally manifests in the late teens or 20s, although it can appear at any age.[7] People of European ancestry are at slightly higher risk, particularly Ashkenazi Jews.[2] It is also more prevalent in developed nations and urban areas.[8]

Roughly 780,000 Americans have Crohn's at any time,[9] according to the Crohn's and Colitis Foundation of America. However, a Crohn's disease information website hosted by AbbVie Inc., a U.S. pharmaceutical firm, puts the number at 700,000,[10] while a 2016 *USA Today* report cites 570,000.[11] The Centers for Disease Control and Prevention cautions that due to inconsistent definitions and diagnoses, a precise number cannot be known.[12]

Of those with the disease, nearly half are in remission, 30 percent have a mild case, 20 percent have a moderately severe case and 2 percent have a severe case.[9] This will change in each patient, however, and roughly 75 percent of patients with Crohn's will require surgery at some point in their lives.

Causes of Crohn's Disease

The cause of Crohn's is not presently understood. Researchers are looking at a variety of possible causes, ranging from immune system disorders to genetics. It is not currently believed that stress or diet play a role in triggering Crohn's,[13] although smoking tobacco is associated with both increased risk and severity of disease.[8]

While most people with Crohn's do not have a family history of it, it is still more prevalent in some families than others, meaning there may be a hereditary predisposition.[8]

Numerous studies are ongoing to try to determine the cause — or, more likely, causes — of Crohn's. One recent study suggests it may be the result of a specific combination of bacteria and fungi in the digestive tract.[11] Another recent study, built upon earlier studies that looked into genetic links to Crohn's, found a series of mutations of genes that regulate the body's ability to react to the presence of bacteria in the digestive tract. It is thought that the inability to recognize these bacteria as normal and necessary may cause the body to react in a way that damages the body itself.[14]

Symptoms and Progression of Crohn's Disease

The first symptoms of Crohn's are similar to those of other IBDs and numerous other unrelated GI afflictions.

Diarrhea, cramping, bloating, gas, fever and fatigue are all common symptoms of Crohn's in its early stages. Those with a more severe case may also exhibit oral ulcers, bloody stool and anal drainage.[15] Depending on the location of the inflammation, patients may experience unexplained and unplanned weight loss due to intestines' inability to extract nutrients from food.

As the disease progresses, it can lead to GI strictures (which can produce obstructive symptoms such as vomiting, bloating, severe abdominal distress and distension), ulcers or fistulas. In rare cases, the disease's severity will spread to the skin, blood and even endocrine system (known as extra-intestinal manifestations, or EIMs).[16] Pyoderma gangrenosum, which is associated with Crohn's (and ulcerative colitis), is a deep skin ulcer often found on the legs. Other EIMs include episcleritis (inflammation of the eye), some types of arthritis and erythema nodosum (red nodules on the skin, usually near the ankles).[16]

If the disease affects the small intestine in those diagnosed before adulthood, the resulting malnutrition will lead to growth retardation or delayed onset of puberty.[17]

In most patients, Crohn's is marked by long periods of remission, punctuated by periodic flare-ups of varying severity.

> Crohn's is categorized into five subtypes, based on the location of the inflammation.

Diagnosing Crohn's Disease

Because of the similarity of Crohn's symptoms to other GI maladies, and because Crohn's is a definition based on symptoms, making a specific diagnosis can be challenging. For instance, differentiating between Crohn's affecting the large intestine and ulcerative colitis can sometimes prove impossible, leading to a diagnosis of indeterminate colitis.[18]

A diagnosis of Crohn's will most often result from eliminating other possible causes for symptoms experienced by patients. While GI symptoms are similar to those of many other diseases, ranging from indigestion to cancer, the presence of any EIMs alongside diarrhea, cramping, etc., can strongly indicate the possibility of Crohn's or other IBD.

As other explanations are ruled out and Crohn's becomes a possible diagnosis, there are a variety of tools available. An

endoscopy can be ordered to visually look at the internal damage to the GI tract and take biopsies. Depending on the specific symptoms and results of prior tests, the physician may order a colonoscopy to check the large intestine, an upper GI endoscopy to inspect the stomach and duodenum, or an enteroscopy to look at the small intestine. Biopsies will be examined for the presence of granulomas, which can indicate Crohn's. If a physician isn't sure which part of the digestive tract is symptomatic, or if there is a need for a fuller picture of the patient's GI system, then a capsule endoscopy may be used.[19] A computed tomography scan or magnetic resonance image may also be ordered to look for damage consistent with Crohn's.[20]

Treatment generally begins with an anti-inflammatory drug to try to control symptoms and, hopefully, promote remission.

Treating Crohn's Disease

There is presently no way to prevent Crohn's, and there is no cure. Treatments vary widely depending on where in the patient's GI tract it manifests, how severe the case is and the patient's age and overall health.

While surgery is often necessary to remove strictures or other heavily damaged segments of the intestinal tract, or to repair or remove ulcers, most physicians will begin with a medication regimen and diet and lifestyle changes. The goal of Crohn's treatment is to induce remission and sustain it as long as possible to reduce the number and severity of flare-ups.[21]

Treatment generally begins with an anti-inflammatory drug to try to control symptoms and, hopefully, promote remission. Anti-inflammatory drugs used to treat Crohn's fall into two broad categories: aminosalicylates (which have been used to treat Crohn's disease for more than 30 years) and corticosteroids. Both classes of drugs cause significant side effects, and neither is 100 percent effective at bringing about improvement in all patients. The patient's history, specifics of the disease and overall health will help the physician devise the best approach.

Aminosalicylates, according to the National Institutes of Health's National Institute of Diabetes and Digestive and Kidney Diseases, are used by many physicians to treat new, mild cases of Crohn's. This class of drugs, which is administered orally, includes balsalazide, mesalamine, olsalazine and sulfasalazine.[22] Unfortunately, the side effects are often the same as the symptoms from Crohn's: diarrhea, vomiting, nausea and abdominal pain. However, some studies indicate that mesalamine can induce remission in about half of patients who receive it.[23]

According to Britain's National Health Service, corticosteroids are also used first by many doctors.[21] Prednisolone can be taken orally, or hydrocortisone can be given via injection. However, due to the numerous side effects (facial swelling, weight gain, reduced immune response, weakening of the bones), corticosteroids are generally only prescribed for short durations. And, some patients will not respond to corticosteroids.

If anti-inflammatory drugs are not successful, then other, more powerful — and potentially dangerous — drugs may be tried. These include immunosuppressant drugs, TNF inhibitors, ustekinumab, cyclosporine and high-dose immune globulin (IG).

The most widely used immunosuppressant drugs include azathioprine (Imuran) and mercaptopurine (Purinethol).[24] Potential side effects include higher risk of infection and some cancers, as well as inflammation of the liver and pancreas, so they require regular monitoring.

Tumor necrosis factor (TNF) inhibitors are used for moderate to severe cases of Crohn's. These powerful drugs work by neutralizing the TNF protein in the body's immune system, and include infliximab (Remicade), adalimumab (Humira) and certolizumab pegol (Cimzia). These drugs cannot be used in any patient with tuberculosis or other serious infections. They have proven effective in helping patients who have developed fistulas as a result of Crohn's, and they may also help induce remission.[24] Use of these drugs is also tied to an increased risk of certain cancers.

Ustekinumab (Stelara), which inhibits production of interleukin 12 and interleukin 23, has also shown some promise in controlling symptoms of Crohn's, specifically in patients who show no or only temporary improvement as a result of TNF inhibitors.[25] (Interleukins are a class of cytokines secreted by white blood cells as part of the body's regulation of its immune system.)

Cyclosporine (Gengraf, Neoral, Sandimmune) and tacrolimus (Astagraf XL, Hecoria) can also be used to treat those with fistulas when other drugs have proved ineffective. Again, the potential side effects are serious: kidney and liver damage, seizures and even potentially lethal infections.[24]

High-dose IG has shown promise in inducing remission. While the data pool is currently small, a 2014 study showed that both intravenous and subcutaneous IG had been used with patients who subsequently entered remission. However, the study's authors argued that these results warrant further study.[26]

In many cases, other medications — most often, antibiotics and over-the-counter painkillers — are used in combination

with one of the above drugs to ameliorate side effects.[27]

There are also other treatment approaches. One is to introduce parasites into the GI tract. A 2015 study that showed the presence of hookworms was associated with a higher incidence of remission suggests the ability of parasites to regulate the body's immune system to promote their own survival.[28] Another is bowel rest in which patients are put on a liquid diet, intravenous solution or feeding tube to give the GI tract a few days or longer off to allow inflammation to subside.[22]

When none of these strategies proves effective, surgery can become unavoidable, with some 75 percent of patients requiring it at some point.[29] The introduction of laparoscopic surgical techniques has reduced the risks, as well as recovery times and the length of hospitalization, but it is not an option for all procedures. Common surgical interventions will deal with strictures, abscesses or ulcers. In some cases, sections of the intestines or colon are removed if they are too damaged. The most serious cases of Crohn's can lead to ileostomy, in which the colon and anus are removed, which has serious quality-of-life implications for patients.[29]

Treating most EIMs involves effectively addressing the underlying Crohn's that is causing them. For example, because of the seriousness of pyoderma gangrenosum, it may need to be treated apart from Crohn's. Immunosuppression is the most commonly used treatment for pyoderma gangrenosum, although corticosteroids are also sometimes used.[30]

Due to the heightened risk of developing cancer with Crohn's, most physicians will schedule more frequent endoscopic examinations as part of patients' ongoing treatment.

In addition to all of the above, another important part of treatment is working with patients to help them control the severity of symptoms and reduce the likelihood of flare-ups. Patients can do this by watching their diet and, if they smoke, by stopping. Studies indicate that limiting the amount of dairy and fried foods, eating smaller portions more frequently and keeping on eye on fiber can all help moderate symptoms.[31] Juvenile patients whose Crohn's is affecting their growth rate or sexual development can reverse those particular effects with nutritional support.[17]

Finally, having a serious chronic condition like Crohn's is a frightening and emotionally draining experience for patients. Therefore, they should be encouraged to join a support group to help them deal with the emotional turmoil. The Crohn's and Colitis Foundation of America maintains a database of local support groups.[32] For patients exhibiting higher than expected stress in dealing with their condition, a referral to a therapist may be useful.[33]

Ongoing Research

There are currently more than 1,000 ongoing clinical studies for Crohn's disease. The British National Health Service lists 1,356 clinical studies just in the United Kingdom and U.S. as of this writing.[34] The U.S. federal government's ClinicalTrials.gov lists 307 (with duplicates between the two lists).

Research into Crohn's is proceeding on multiple fronts: learning what causes it, finding more effective treatments and searching for a cure. Discovering what causes Crohn's is most critical because it will obviously allow for more effective and efficient treatments, as well as a clearer path toward an eventual cure.

The Crohn's and Colitis Foundation of America underwrites the Broad Medical Research Program, which has invested $50 million over the past 15 years into basic research regarding Crohn's. The foundation aims to raise $2 million per year to put back into primary research. In addition, it is underwriting two other interrelated research programs titled the Genetics Initiative and the Microbiome Initiative. These two programs fund and encourage studies to identify those genes specifically tied to a likelihood of developing Crohn's, as well as identifying specific bacteria and fungi in the digestive tract. Other initiatives are funding research into pediatric IBD and IBD and pregnancy.

There are currently more than 1,000 ongoing clinical studies for Crohn's disease.

Among the more than 1,300 studies underway in the U.S. and United Kingdom are those to determine the long-term effects and efficacy of dozens of existing medications. Other studies are looking at genetic markers, vitamin supplements to assist juveniles with Crohn's, using patients' own fat to grow stem cells to repair fistulas, new surgical techniques to reduce the impact on patients' quality of life, and new electronic imaging processes to minimize invasive diagnostic testing.

And, there are new medications well into the study pipeline showing real promise:

• Mongersen is an antisense oligonucleotide that targets SMAD7, a protein involved in the body's regulatory system. Early results of an ongoing study at the University of California,

San Diego, found that some 60 percent of patients who received Mongersen entered remission.[35]

• A Finnish study looking at the molecular level of the immune regulatory system suggests that use of the anti-rejection medication daclizumab (Zinbryta) may be useful in treating Crohn's, as well as multiple sclerosis.[36]

There are also some other interesting studies:

• Looking into the interplay between human genes and the naturally occurring microbes that assist with digestion in the GI tract, a 2016 study involving U.S., French and Belgian researchers looked at the population composition of the microbiome (the community of microorganisms naturally occurring in the human digestive tract) of patients with Crohn's and their family members without Crohn's. They found a marked difference in the makeup of microbes in those who had Crohn's versus those who did not. It is not yet known whether this is a result of the changed environment of a GI tract with Crohn's, or a contributing cause, but it does offer insight into possible treatment options.[37]

• An article in *Nature Immunology* argues that introducing certain beneficial bacteria into the GI tract can help reduce inflammation. Examinations of the microbiome showed that in patients with Crohn's, the ratio of different species was different than in healthy patients, and by artificially restoring the healthy ratio, inflammation was reduced.[38]

• A study at Arizona State University has identified unique biomarkers that only appear in blood samples of those with Crohn's, suggesting a one-step blood test for diagnosing is possible.[39]

• An analysis of previous studies suggests that while anti-inflammatory drugs can be effective at relieving symptoms, they do not promote healing of the mucosa layer of the GI tract. On the other hand, several TNF inhibitors — infliximab and adalimumab — have shown promise in promoting healing of the tissue scarred by Crohn's.[40]

Looking Ahead

As physicians work with their patients to help them maintain as high a quality of life as possible, and to avoid the kinds of life-altering surgical procedures that Crohn's can require, it is likely that new techniques, drugs and treatments will continue to arrive yearly, if not more often.

Inoculation and/or a cure may be beyond the current horizon, but treatment options that maximize patient quality of life are in the pipeline and on the way. ❖

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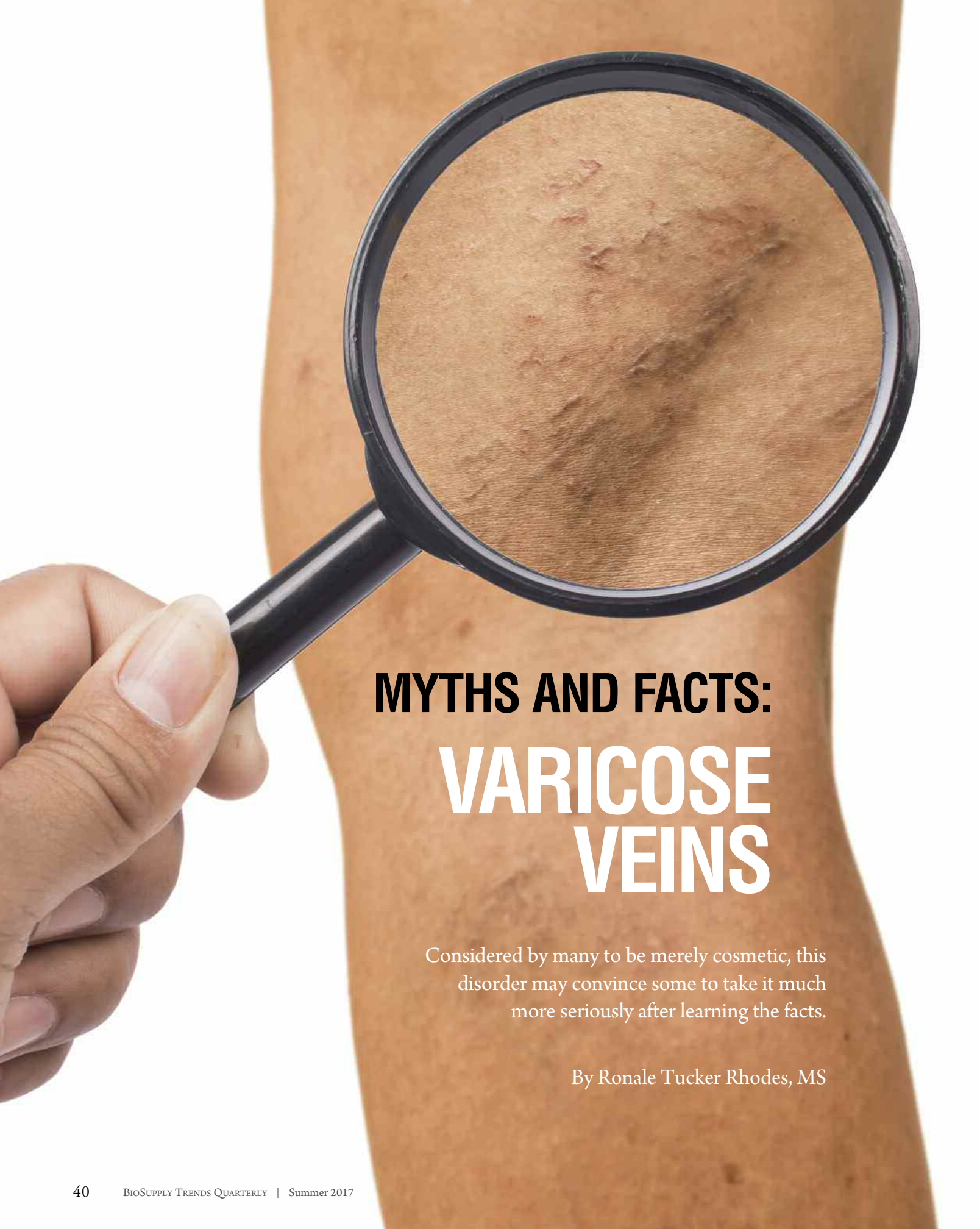

MYTHS AND FACTS: VARICOSE VEINS

Considered by many to be merely cosmetic, this disorder may convince some to take it much more seriously after learning the facts.

By Ronale Tucker Rhodes, MS

DEPENDING ON THE source, between 20 million and 40 million people in the U.S. suffer from varicose veins.[1,2] But, it's likely this number is highly underestimated by both patients and healthcare professionals because it is not a lethal condition and the consequences of the disorder are often overlooked.[3]

Varicose veins are one of the most common conditions of chronic venous disease (CVD) in the lower extremities,[2] with recent estimates placing the cost of all CVD treatment at $3 billion per year in the United States (or up to 2 percent of the total healthcare budget of all Western countries).[3] In addition to healthcare budgets, the condition has a significant impact on patients' quality of life and leads to more people unable to work than does arterial disease.[2]

Yet, despite the fact that varicose veins affect a significant proportion of the population, causing considerable morbidity and adversely affecting quality of life, it is often ignored as an important public health issue. This is why the facts surrounding the condition need to be told to help spread awareness among the public and healthcare authorities and professionals so patients are diagnosed early and effectively treated.

Separating Myth from Fact

Myth: There is only one type of varicose veins.

Fact: There are actually two types: primary and secondary. Primary varicose veins are frequently associated with heredity, female gender, pregnancy and older age. Secondary varicosities are a direct result of deep vein occlusion (the formation of a blood clot within a deep vein).[2] Both of these visible and bulging veins are more common in the legs and thighs, but they can develop anywhere in the body, and they can be visible, bulging, palpable (felt by touching), long and dilated (greater than 4 millimeters in diameter). In addition, small spider veins, or telangiectasis (a common, mild variation of varicose veins), can appear on the skin's surface that look like short, fine lines, starburst clusters or a web-like maze, but they are not palpable.[4]

Myth: Only women get varicose veins.

Fact: While the prevalence of varicose veins is greater in women (55 percent), the percentage of men who also suffer from them is not much lower (45 percent). An estimated 50 percent of the U.S. population and 41 percent of women over age 50 have varicose veins. In addition, women who are moderately overweight (body mass index [BMI] 25-29.9) have a 50 percent increased risk of developing varicose veins compared to women who are not overweight, and women with a BMI greater than 30 percent are three times more likely to develop them.[1]

Myth: Varicose veins are an inevitable sign of aging.

Fact: Age is a risk factor for varicose veins, but not all older individuals will get them. As mentioned previously, only 50 percent of individuals over age 50 develop varicose veins.[1] According to Kathleen D. Gibson, MD, a vascular surgeon practicing in Bellevue, Wash., "It's a degenerative process that gets worse and more prominent as we age." At her practice, the average age of patients treated for varicose veins is 52, but she has treated patients as young as 13 years.

"The cause of varicose veins is primarily genetic," says Dr. Gibson. So, if someone has a parent or grandparent with varicose veins, it's likely he or she will, too.[5] Other causes of varicose veins include older age, pregnancy, female sex, overweight or obesity, lack of movement and leg trauma. As a person ages, veins can lose elasticity, causing them to stretch. In addition, veins may become weak and allow blood that should be moving toward the heart to flow backward. Weakness and a lack of elasticity may cause poor venous circulation, or pooling of the blood, leading to varicose veins.[6,4]

Despite the fact that varicose veins affect a significant proportion of the population, causing considerable morbidity and adversely affecting quality of life, it is often ignored as an important public health issue.

During pregnancy, the volume of blood in a woman's body increases, but the flow of blood from the legs to the growing fetus decreases, which causes a circulatory change that enlarges veins in the legs. Varicose veins may occur for the first time or may worsen during pregnancy when the uterus exerts greater pressure on the legs. And, hormones during pregnancy can play a role. In addition to pregnancy, females are more likely to develop varicose veins because of premenstruation or menopause that can relax vein walls, as well as due to taking hormone replacement therapy or birth control pills that increase the risk.[6]

Being overweight puts added pressure on veins. And, people who stand or sit for long periods of time can have a problem with blood flow that can cause varicose veins.[6]

Less-common causes of varicose veins include phlebitis (inflammation of the veins), blood clots or any obstruction to blood flow in the veins, or congenital abnormalities of the veins.[4]

Myth: Varicose veins are noticeably visible.

Fact: Of the approximately 50 percent of the U.S. population that has varicose veins, 20 percent to 25 percent of women and 10 percent to 15 percent of men will have visible varicose veins[7] that are bulging, visible ropes on the legs. But, in others, they are not visible because they are too deep, even though they may still cause symptoms such as swelling, tired and achy legs, leg cramps, itchy rashes and darkening.[8] "It really depends on the makeup of the leg," says Dr. Gibson. "If you've got a lot of fatty tissue between the muscle and the skin, you may not see them. Sometimes, surface veins are the tip of the iceberg, and there's a lot going on underneath."[5]

In many cases, lifestyle and home remedies can both prevent and slow the development of varicose veins.

Myth: Varicose veins aren't painful.

Fact: For many, varicose veins don't cause any pain. Instead, their only symptoms are veins that are dark purple or blue and those that appear twisted and bulging, often like cords. However, a significant portion of patients will eventually develop painful symptoms that may include an achy or heavy feeling in the legs; burning, throbbing, muscle cramping and swelling in the lower legs; worsened pain after sitting or standing for a long time; itching around one or more of the veins; bleeding from the veins; a painful cord in the vein with red discoloration of the skin; color changes; hardening of the vein; inflammation of the skin;[6] and more serious complications such as wounds, ulcers and blood clots.[7]

Varicose veins usually become painful with time when pooling of blood and pressure in the veins increase. When there is high pressure in the veins, blood can leak out of the vessels and into the tissues and become trapped in the skin and turn brown (typically occurring around and above the ankles). If left untreated, blood leakage can cause skin damage and ulcers of the skin. However, only 1 percent of adults over age 60 have chronic ulceration.[7]

Myth: Lifestyle changes won't help to prevent or improve varicose veins and its symptoms.

Fact: In many cases, lifestyle and home remedies can both prevent and slow the development of varicose veins. While some people believe running can cause varicose veins, exercise, including running, is actually a good thing.[9] Pablo Sung Yup Kim, MD, assistant professor of surgery at Mount Sinai's Icahn School of Medicine in New York City, says, "Exercise is always good for the circulation. Walking or running can lead to more calf-muscle pumping and more blood returning to the heart." Dr. Gibson adds that while running doesn't cause varicose veins, there is some controversy over whether it makes them worse. Therefore, she recommends wearing compression stockings afterward to help prevent blood from pooling in the lower legs, as well as elevating the legs.[5] In fact, taking several short breaks daily to elevate the legs is another self-help measure that should be taken even by those who don't run because it helps improve circulation.[9]

Patients should also watch their weight. Excess weight puts unnecessary pressure on the veins, which is added work that can cause the veins and the valves inside them to weaken and break, thus leading to varicose veins. In addition, being overweight or obese can hide varicose veins because they are not as close to the surface of the skin as they are for thinner people. This can be problematic because varicose veins and their underlying causes go unseen and untreated, which can lead to serious vascular and other health issues, including leg ulcers.[10]

Lastly, patients should avoid sitting or standing for long periods of time. And, they should watch what they wear. High heels should be avoided in favor of low-heeled shoes that work calf muscles more. And, tight clothes around their waist, legs or groin should be avoided because they can reduce blood flow.[9]

Myth: Surgery is the only treatment option for varicose veins.

Fact: Treatment is not always necessary such as when varicose and spider veins are primarily a cosmetic issue and don't affect quality of life. However, there are many treatment options for those who want and need it. Treatments are based on the size and location of the varicose veins, presence of symptoms and skin changes. These include compression dressings/stockings, sclerotherapy, ablation and surgery.

Compression stockings, which come in various brands and styles, squeeze the leg to reduce the amount of blood and pressure in the veins. A healthcare professional fits the stocking to the leg as determined by the amount of pressure to apply. Cases that don't respond to compression therapy require further treatment.

Sclerotherapy has been used since the 1920s to treat spider veins and varicose veins up to 15 millimeters in diameter. It involves using a fine needle to inject a solution (most commonly, hypertonic saline and sodium tetradecyl sulfate [Sotradecol] and polidocanol [Aethoxysklerol, Asclera]) directly into the vein that irritates its lining, causing the vein to swell and the blood to clot.

The vein's surrounding tissue is then wrapped in compression bandages for several days, and patients are put on walking regimens to force the blood to flow into other veins and prevent blood clots. The vein then turns to scar tissue and may eventually fade from view. Typically, more than one treatment is required.

For smaller varicose veins, laser therapy can be applied as an intense energy to destroy the small blood vessels in the surface of the skin. Larger varicose veins can be destroyed with endovenous (inside the vein) catheter ablation, or laser surgery. This involves inserting a probe (or catheter) into a large vein in the lower leg and closing it by applying heat generated through laser.

In use since the 1950s, vein stripping surgery strips out the problematic veins by passing a flexible device through them and removing them through an incision near the groin. Smaller tributaries of the veins are also removed through a series of small incisions. Those veins that connect to the deeper veins are then tied off.[4] It should be noted that vein stripping is an older surgical procedure that has been largely replaced by sclerotherapy and laser treatments, which are less invasive. Studies show that vein stripping surgery is only 71 percent effective, compared with a 98 percent success rate of minimally invasive laser therapies.[11]

Recently, researchers at the Center for Advanced Studies of Peter the Great St. Petersburg Polytechnic University (SPbPU) in collaboration with industrial partner Company Neo developed new technology to eliminate varicose veins by using focused high-intensity ultrasound. With this method, the patient's lower limb is placed into a container with liquid conducting ultrasound. The physician marks areas that must be subjected to irradiation on the screen of the device. The program then determines the required number of areas, presses the irradiated portion of the vessel to stop the blood flow (applying mechanical press with compression cuffs), and the device starts the irradiation procedure under a physician's supervision. The advantage of this technique is that it is carried out without damaging the skin and, therefore, is not performed in the operating room. Moreover, this is the first method combining both diagnostics and treatment: Ultrasound diagnoses the disease and also affects blood vessels for their obliteration. The researchers are now planning to create an automated diagnostic ultrasound that will consist of two or more diagnostic modules operating simultaneously to create a unified picture of the lower limb's venous network, thus significantly increasing the speed of the procedure.[12]

Myth: Insurance doesn't pay for varicose vein treatment.

Fact: Many people falsely believe that insurance doesn't cover treatment for varicose veins because they view it as a cosmetic issue. In fact, 90 percent of cases are covered by insurance because they are not just an aesthetic concern.[11]

Myth: Varicose veins can be cured.

Fact: While treatments are effective, they aren't a cure because they can come back after treatment. "What I tell my patients is it's kind of like weeding a garden," says Dr. Gibson. "We clear them all out, but that doesn't mean there's never going to be another dandelion popping out."[5]

Myth: Varicose veins aren't dangerous.

Fact: Varicose veins can result in serious complications that require medical attention. Ulcers may form on the skin near varicose veins, particularly near the ankles, caused by long-term fluid buildup in the tissues due to increased pressure of blood within affected veins. In some instances, veins deep within the legs can swell considerably, which may indicate a blood clot (thrombophlebitis). And, veins very close to the skin may burst, resulting in minor bleeding.[6]

In the U.S., approximately two million people per year develop deep vein thrombosis, and up to 600,000 are hospitalized. Deep vein thrombosis can lead to blood clots in the lung (pulmonary embolism), a more serious complication that results in at least 650,000 deaths each year, making it the third most common cause of death in the U.S.[13]

Dispelling the Myths Now

Varicose veins are a long-term problem, but their symptoms can be controlled. In many cases, the condition isn't serious. But, if lifestyle measures aren't taken to deter the worsening of varicose veins, serious consequences can occur. That's why it's necessary for patients to understand the facts surrounding varicose veins and for physicians to educate patients about the potential seriousness of the condition so proper treatment, if needed, can be provided. ❖

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

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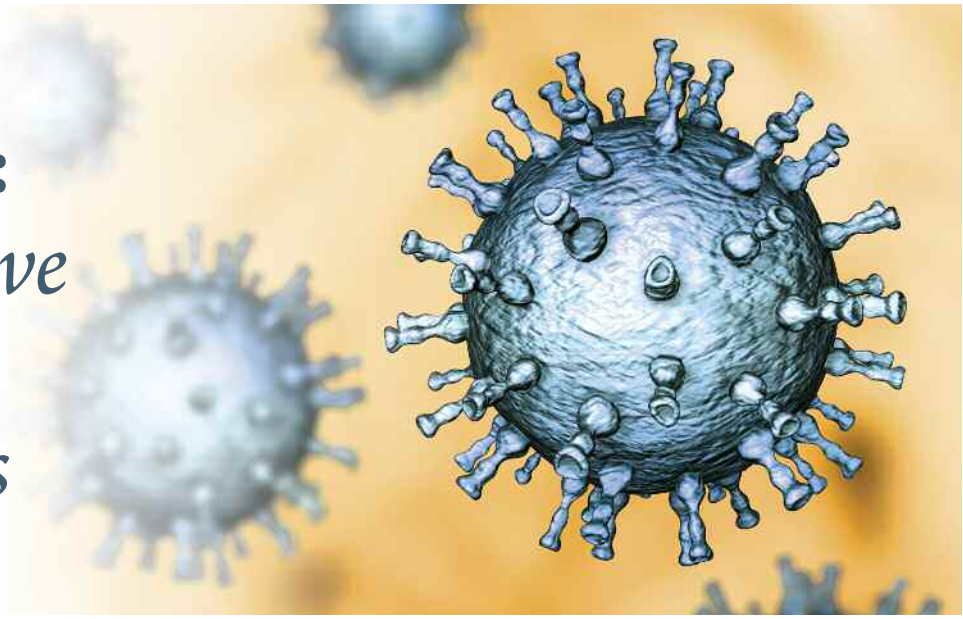
Coming Soon: *A Highly Effective New Vaccine to Prevent Shingles*



By Keith Berman, MPH, MBA, and Luke Noll

IN ITS BEST-known clinical manifestation as chickenpox, primary infection with the varicella zoster virus (VZV) has left generations of children with lasting memories of itchy, uncomfortable misery. But this common virus does something quite extraordinary: In everyone it infects, it manages to evade complete immune clearance by remaining latent in the dorsal root or cranial nerve ganglia. There, VZV waits — for decades — until weakened or suppressed host immunity allows it to reactivate.

The second incarnation of VZV as herpes zoster, or shingles, starts with localized unilateral burning or tingling skin pain limited to a small area, followed by a rash that turns into fluid-filled blisters. For some individuals, the course is relatively mild, while others suffer intense pain with the gentlest touch or breeze on the skin.

The risk of shingles rises steeply after age 50 years, as innate immunity that has kept VZV in its latent state begins to decline. Due to natural immunosenescence, an 80-year-old faces roughly 10 times the risk of developing shingles than a 50-year-old. Immunosuppressive drug therapy or immunodeficiency disorders also predispose individuals to higher risk of shingles.

Most cases of shingles resolve within three to five weeks. But it can lead to an array of neurological, ocular, auditory, infectious and other complications.[1] By far, the most frequent of these is postherpetic neuralgia (PHN), defined as pain lasting at least 90 days following resolution of the rash. As people get older, they are more likely to develop PHN. This ongoing severe pain, which often lasts for many months or years, may interfere with daily activities like dressing, cooking and eating, and can lead to insomnia, chronic anxiety, depression and weight loss.

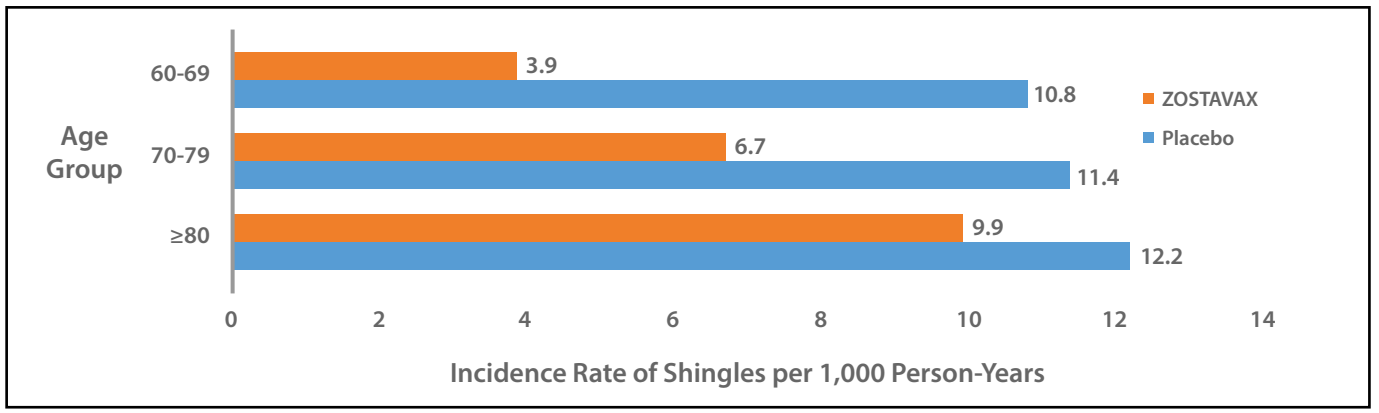
Approximately one million cases of shingles are reported annually in the U.S., and we all have about a one-in-three lifetime risk, according to Centers for Disease Control and Prevention estimates. Half of individuals over age 85 years are likely to develop shingles.[2] The need for a vaccine that can provide protective immunity against shingles and PHN in older at-risk adults is clear.

ZOSTAVAX: The First Preventive Vaccine for Shingles

Merck responded to this need by developing ZOSTAVAX, a live-attenuated zoster vaccine licensed by the U.S. Food and Drug Administration (FDA) in 2006. It was approved following review of the company's Shingles Prevention Study (SDS) trial, which randomized more than 38,000 subjects aged 60 years and older to receive a single dose of ZOSTAVAX or placebo. They were followed for a median of just over three years, and confirmed shingles cases were evaluated for three age strata: 60 to 69 years, 70 to 79 years and 80 years and older. A separate trial randomized more than 22,000 subjects between ages 50 and 59 years, and followed them for a median of 1.3 years.

The overall effectiveness of ZOSTAVAX to prevent shingles disease was 51 percent in subjects 60 years of age and older. But the vaccine's efficacy differed widely by

Figure 1. Efficacy of ZOSTAVAX vs. Placebo to Prevent Herpes Zoster (Shingles) in Persons Age 60 Years and Older by Age Group



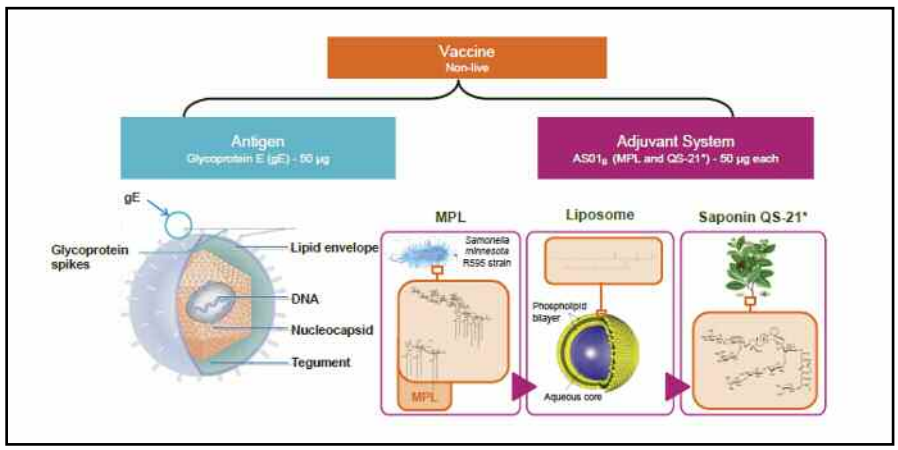
age group (Figure 1). The SDS study documented 70 percent and 64 percent nominal reductions in the incidence rate of shingles in subjects aged 50 to 59 years and 60 to 69 years, respectively. But in subjects aged 70 to 79 years, the vaccine reduced risk of shingles by only 41 percent, and in those aged 80 years and older, it offered minimal or no protection (18 percent; statistically nonsignificant).

The 51 percent overall reduction in incidence of shingles was actually exceeded by a nearly 67 percent lower risk of PHN.[3] This reflects the finding that vaccinated subjects diagnosed with shingles were nearly 40 percent less likely to progress to PHN than were placebo control subjects who developed shingles (8.6 percent versus 12.5 percent; 95 percent confidence interval [CI], 7 percent to 59 percent). But, clearly, the primary benefit of ZOSTAVAX was its ability to prevent many cases of herpes zoster.

While ZOSTAVAX importantly reduces the risk of shingles in adults older than 50 years, its efficacy is clearly more limited for people in their 70s, then precipitously declines for those in their 80s — the two age groups with the highest disease risk and disease burden. And because it is a live vaccine, ZOSTAVAX is contraindicated for immunosuppressed or immunodeficient individuals.

Two recent observational studies additionally found the vaccine's effectiveness markedly declines over time; by the ninth postvaccination year, it has no significant protective effect against shingles.[4,5] Thus vaccination in one's 50s, for example, provides peak protection at a time when shingles is much less likely to occur. This limitation may be addressable, however: A recent Merck-sponsored study found that administration of a booster dose of ZOSTAVAX 10 or more years after initial vaccination was well-tolerated and elicited a humoral and cellular immune response of similar magnitude to individuals receiving their first dose.[6]

Figure 2. Composition of Investigational SHINGRIX Vaccine (HZ/su)



Source: Colindres R. Safety Summary of Investigational Vaccine: SHINGRIX (HZ/su). Presentation to Advisory Committee on Immunization Practices (ACIP). Feb. 22, 2017

SHINGRIX: Evidence of Superior Efficacy

More than 15 years ago, GlaxoSmithKline (GSK) initiated development of its own herpes zoster vaccine with a number of aspirations in mind:

- High vaccine efficacy in persons 50 years and older, and in particular more elderly persons (70 years and older) at highest risk for shingles and PHN
- Safety and efficacy in all persons at increased risk for shingles, including immunocompromised persons
- Prolonged duration of protection
- Ease of manufacture and reliability of supply

To try to fulfill this ambitious set of aspirations, GSK designed a nonlive VZV subunit vaccine dubbed HZ/su, with the proposed brand name SHINGRIX.* It combines a viral antigen (recombinant glycoprotein E) with a novel adjuvant called $AS01_B$ (Figure 2). Glycoprotein E is the most abundant protein found on

** Subject to approval by relevant regulatory review bodies.*

the envelope of VZV. $AS01_B$ is a liposome-based adjuvant system that contains two immunostimulants: 3-O-desacyl-4'-monophosphoryl lipid A (MPL), which enhances cellular and humoral immunity, and the saponin QS-21, which is known to induce Th1 cell-mediated immunity and cytotoxic T-lymphocyte activity. MPL and QS-21 act synergistically to generate an enhanced proinflammatory response to copresented antigen; this recruitment of innate immunity results in a more rapid, stronger and longer-lasting immune response.[7]

> The risk of shingles rises steeply after age 50 years, as innate immunity that has kept VZV in its latent state begins to decline.

Early safety and immunogenicity studies guided both the most optimal combination of adjuvant and antigen (50 µg each of glycoprotein E, MPL and QS-21) and a regimen of two intramuscular doses administered two months apart.

Two randomized, placebo-controlled Phase III clinical trials were conducted to assess the efficacy and safety of SHINGRIX. The first, ZOE-50, evaluated the two-dose regimen in 15,411 participants 50 years and older, stratified according to age group (50 to 59, 60 to 69 and 70 and older). After a mean follow-up of 3.2 years, just six participants in the vaccine group had confirmed shingles, compared with 210 in the placebo group. This translated into an overall vaccine efficacy of 97.2 percent (95 percent CI, 93.7 percent to 99.0 percent; P<0.001). Even more remarkable was the finding that vaccine efficacy was similarly high across the three successively older age groups: 96.6 percent, 97.4 percent and 97.9 percent.[8]

A second trial conducted in an identical manner (ZOE-70) narrowed the focus to 13,900 adults 70 years of age and older, who are at the highest risk of shingles and severe PHN. During a somewhat longer mean follow-up period of 3.7 years following completion of two doses of SHINGRIX or saline placebo injections, shingles occurred in 23 vaccine recipients and in 223 placebo recipients (0.9 versus 9.2 per 1,000 person-years), translating into a vaccine efficacy of 89.8 percent (95 percent CI, 84.2 percent to 93.7 percent; P<0.001). There was no significant difference in shingles risk between the 70-to-79-years and 80-years-and-older cohorts, affirming the ZOE-50 findings.[9] No important vaccine safety concerns were identified in either the ZOE-50 or ZOE-70 trial.

A pooled analysis of nearly 16,700 participants in the ZOE-50 and ZOE-70 trials documented approximately 90 percent vaccine efficacy for both the 70-to-79-years and 80-years-and-older cohorts (Figure 3). For the overall 70-years-and-older cohort, the incidence rate of PHN was 0.1 case per 1,000 person-years for the SHINGRIX group and 1.2 cases per 1,000 person-years for the placebo group — a similar 89 percent risk reduction (P<0.001).

The pooled analysis also revealed that SHINGRIX' very high protective efficacy persisted over the entire four-year follow-up

Figure 3. Efficacy of SHINGRIX vs. Placebo to Prevent Herpes Zoster (Shingles) in Persons Age 70 Years and Older by Age Group (Pooled ZOE-50 and ZOE-70 Studies)

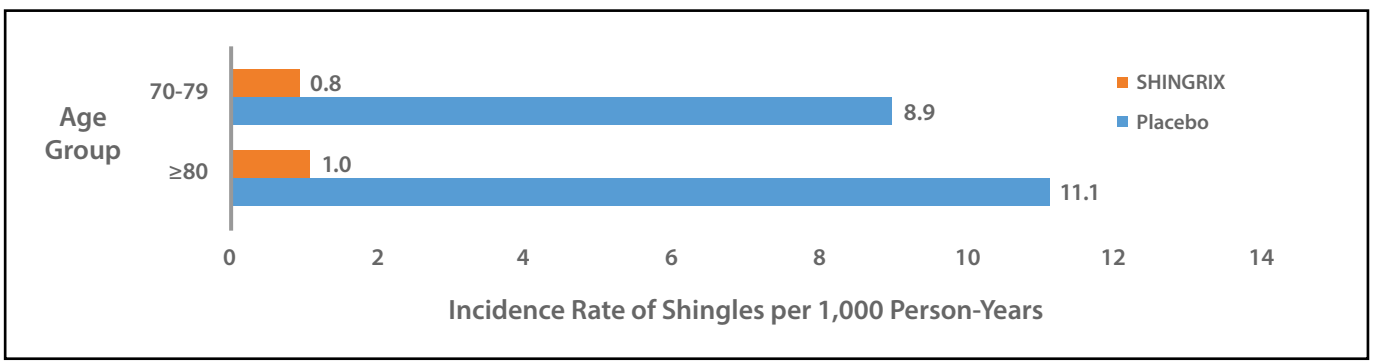
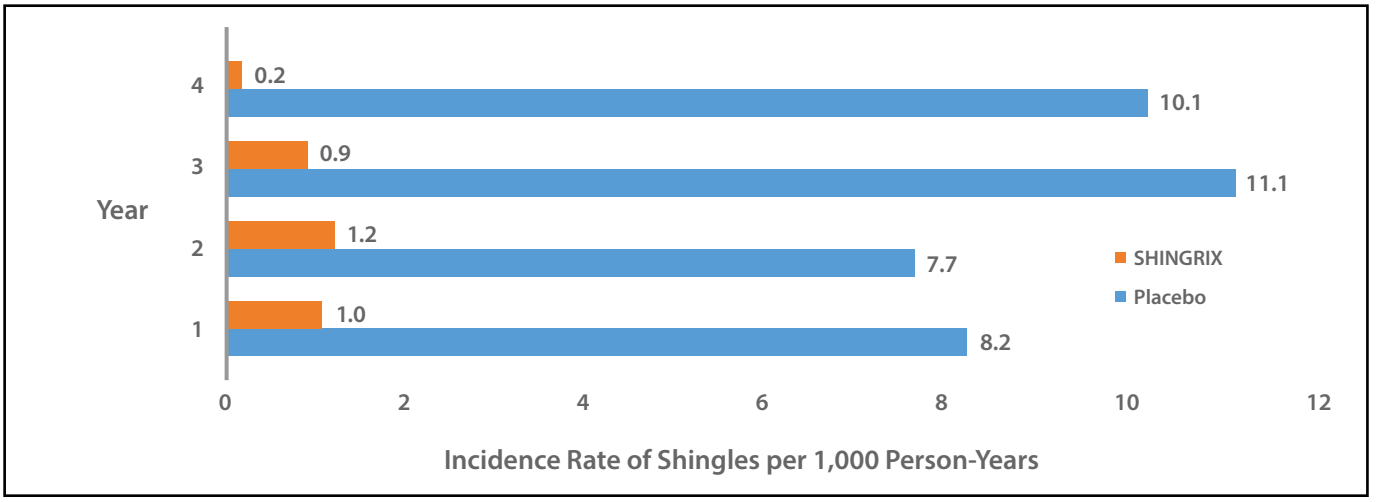


Figure 4. Efficacy of SHINGRIX vs. Placebo to Prevent Herpes Zoster (Shingles) in Persons Age 70 Years and Older By Study Year (Pooled ZOE-50 and ZOE-70 Studies)



period (Figure 4). GSK is conducting a ZOE-50 and ZOE-70 extension study to characterize the efficacy, safety and immunogenicity persistence of SHINGRIX up to 10 years postvaccination.

Although the immunological basis for this strong and lasting protective effect is not known, the investigators postulate that it is partly attributable to the demonstrated ability of SHINGRIX to induce strong glycoprotein E-specific CD4+ T-cell responses that are preserved with age.[10] "The robustness of the immune responses to glycoprotein E are attributable to the action of the $AS01_B$ adjuvant system," they conclude, "which has also been shown to enhance CD4+ T-cell and humoral immune responses to subunit antigens from other pathogens."[7] These include antigens isolated from HIV, mycobacterium tuberculosis, hepatitis B virus and human papillomavirus.[11]

More SHINGRIX Studies in the Pipeline

Last October, GSK submitted a biologics license application with FDA seeking approval to market SHINGRIX for the prevention of herpes zoster/shingles in people 50 years and older. A decision by FDA is anticipated by late October. Meanwhile, GSK has clinical trials underway to evaluate SHINGRIX in immunosuppressed and certain immunodeficient persons at increased risk of shingles, including:

- Solid and hematological cancer patients
- Hematopoietic stem cell and renal transplant recipients
- Persons infected with HIV

A clinical study is also underway to evaluate revaccination in subjects who have previously been vaccinated against shingles with the currently available live-attenuated vaccine.

As effective as the two-dose SHINGRIX vaccination regimen appears, some individuals still experience breakthrough shingles and PHN. Not content with this, GSK initiated a multinational clinical study last year to evaluate the safety, immunogenicity and efficacy of one or two additional doses in persons 50 years and older. This study will enroll more than 7,700 subjects and is projected to be completed in 2023.

In a study of the costs of medically managing shingles and PHN published earlier this year, Canadian investigators concluded that "the likely future of herpes zoster burden is one of rising costs, primarily driven by the demographic shifts of an increasing and aging population." The new subunit vaccine from GSK promises an entirely different future, one largely absent of the profound suffering or the economic burden of this human scourge. ❖

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William Stiles was a young attorney and newlywed, on top of the world with a new baby on the way. His life changed in an instant when a sudden seizure left him hospitalized, unemployed and unable to even recognize his new bride.

Multiple Sclerosis: *A Patient's Perspective*

By Trudie Mitschang

SEPTEMBER 2014 WAS a happy month for William Stiles. The 37-year-old married his wife, Amber, and by October, the couple were expecting their first child. William's good fortune continued, and in February 2015, the young attorney won the first court case he tried at his new law firm. In March, his good fortune came to a screeching halt, and all he remembers is waking up in a hospital room. "I was very confused because I have been healthy my entire life," he says. "I was hospitalized for half of March, and when I woke up, I didn't recognize Amber or my family members who came to check on me. The doctors advised Amber that I was not likely to regain my memory and gave her the name of several nursing homes. We'd been married six months."

An infusion of Rituxan eight days later helped stabilize his condition and restore his memory, but his health did not improve. MRIs revealed countless lesions on the left side of William's brain. As it turned out, the nagging vision troubles and leg pain he'd been experiencing were symptoms of multiple sclerosis (MS).

At a friend's recommendation, William was referred to Shepherd Center in Atlanta, a private not-for-profit hospital specializing in medical treatment, research and rehabilitation for people with spinal cord injury, brain injury, MS and other neuromuscular conditions. It was there that William embarked on a treatment plan that helped him get his life back.

Learning to Live with Loss

As devastating as a diagnosis of MS was for a young husband and father, the initial loss of health, memory and mobility was only the beginning of a series of setbacks for William and his growing family. "While I was hospitalized, I received a termination letter from my company. Apparently, my termination was communicated to me and my wife via telephone, but I have no recollection of the conversation. I wrongly believed I was still employed when released from the hospital."

For William, the only thing more painful than the job loss was the way close friends suddenly disappeared when they learned of his diagnosis: "The most difficult aspect of this journey has been the loss of individuals I once regarded as true friends and family. It is an unfortunate reality that in your hour of greatest need, your true friends are revealed."

Getting Back in the Game

William considers himself fortunate to have been referred to a center that specializes in MS treatment. His treatment plan is very focused and includes a Rituxan infusion once every six months, coupled with vitamin B, vitamin D and fish oil every day. The regimen has helped keep his memory intact and has removed the lesions that had developed on his brain. He also has no vision issues and no physical pain. "The lifestyle changes that have been the most significant for me have been dietary," he adds. "I have a mostly vegetarian diet with chicken and fish at times. No soda or products with preservatives or high fructose corn syrup. I lost over 50 pounds while in the hospital (dropping to 187 pounds). Despite the change in diet, I am now up to a healthy 241 pounds, with no real physical limitations other than I can't run as far as I used to, and my basketball game has gotten very bad!"

Today, William is the active father of a 22-month-old and 2-month-old and is optimistic about the future. Within a year of his diagnosis and release from the hospital, he received a lucrative job offer, and this past year, he was sworn into the U.S. Supreme Court's bar association, making him eligible to argue cases before the highest court in the land. "The diagnosis of MS should not be considered a disability. It's an opportunity to overcome a difficult challenge and to provide an example to others to overcome any challenges they face," he says. "Without question, there are moments of uncertainty and fear. But I have kept a keen focus on recovering and returning to the world in a manner in which I would not be a burden on others. For me, it was getting the right treatment plan and the power of love and faith in God. He provides a way, he heals and helps us overcome all obstacles." ❖

Multiple Sclerosis:
A Physician's Perspective

BEN THROWER, MD, is a clinical instructor of neurology at Emory University and participates actively in clinical research. He serves on the board of directors of the Georgia Chapter of the National MS Society and has served on the board for the Consortium of Multiple Sclerosis Institutes. Combining his professional interests with his love of motorcycles, he founded the nonprofit organization HAMS, Hogs Against Multiple Sclerosis (MS).

BSTQ: What drew you to the specialty of neurology and then to the treatment of MS?

Dr. Thrower: I found the brain and spinal cord interesting, and I focused on neurology. My wife and I met in medical school. She'd taken an Air Force scholarship, so we were at the mercy of the Air Force as to where we'd live. They sent her to San Antonio, and I got a training slot in neurology and completed four years of residency there. The Air Force then sent us to Spokane, Wash. I was in private practice, and that part of the country has a high rate of MS. And, I found I really enjoyed working with MS patients. I also realized it took more than just a neurologist to manage them. I started envisioning a comprehensive center for MS in Spokane. The Providence Health System there gave us space and some therapists to start this comprehensive approach. Later, I got a call about a position at Shepherd Center. I wanted to get closer to family, so I joined the medical staff at Shepherd in June 2001.

BSTQ: What are some of the most common medical misperceptions surrounding MS?

Dr. Thrower: In spite of an explosion in our knowledge about MS and treatment options, misperceptions still exist. Some of the common ones are:

1) Everyone with MS will end up in a wheelchair. With early and appropriate treatment, this is frequently not the case.

2) People with MS are fragile and should not exert themselves. Not true. Exercise is not only tolerated, but has numerous benefits specific to MS.

3) Women with MS should not have children. False. Pregnancy is typically associated with a quieting of MS symptoms and a low risk of relapse. There is a slightly higher risk of relapse after delivery, but overall, the effects of pregnancy and delivery are not a significant risk to women with MS.

BSTQ: How has treatment evolved since you started working with MS patients?

Dr. Thrower: In 1993, we saw the first U.S. Food and Drug Administration (FDA) approval of a medication that could alter the course of MS. In March 2017, with the approval of Ocrevus (ocrelizumab), we now have 16 FDA-approved treatment options.

BSTQ: What have you found most challenging when it comes to treating MS patients?

Dr. Thrower: MS is a complex disease, and sometimes it feels like there is just not enough time to deal with all of the issues that a person is struggling with. In addition, it is frustrating to see some people with MS fail to progress even when they are on the appropriate treatment. As much as we have learned about MS, we still don't have a cure.

BSTQ: Where are we in terms of finding a cure?

Dr. Thrower: Cure means different things to different people with MS. For some, it may mean preventing MS in the first place. For others, it means having a treatment that halts progression in 100 percent of those affected. For those with MS-related disability, it may mean neural repair and a reversal of that disability. For many with MS, we are able to achieve the second option, stopping all MS progression. I do think we are closer to neural repair and a reversal of disability via numerous research avenues. Preventing MS in the first place may be the most difficult given the complex genetic and environmental factors at play.

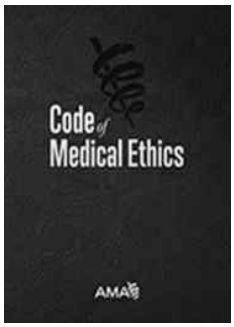
BSTQ: Are there any promising therapies in the pipeline?

Dr. Thrower: I expect we will see more and more disease-modifying therapies. Some may be improvements on existing ideas. The approval of Ocrevus represented a milestone in that it is the first therapy approved for primary progressive MS. Research on mesenchymal stem cells for neural repair appears promising, as does the search for biomarkers. The latter would be tests to help predict the course of an individual's MS, select the perfect therapy or help determine the effectiveness of his or her therapy. ❖

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

Code of Medical Ethics

Author: American Medical Association (AMA)



Completely updated after an eight-year modernization project, the revised edition of the *Code of Medical Ethics* is available from the AMA in hardcover or e-book. The revised edition contains ethical guidance improved for relevance, clarity and consistency to help physicians keep pace with emerging demands they face with new technologies, changing patient expectations and shifting healthcare priorities. The book has played a central role as medicine's authoritative guide to professional values and responsibilities since it was created by the AMA in 1847. Packed with clear, concise direction for the ethical practice of medicine, the book is regularly cited as the medical profession's authoritative voice in legal opinions, medical journals and news outlets.

commerce.ama-assn.org/store/search/searchResults.jsp?search=code%20of%20medical%20ethics

STEADI: The Pharmacist's Role in Older Adult Fall Prevention

Authors: Centers for Disease Control and Prevention (CDC) and American Pharmacists Association

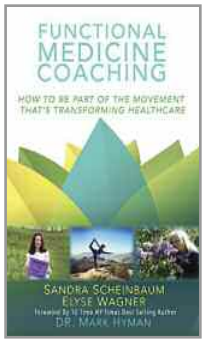
STEADI
Stopping Elderly Accidents, Deaths & Injuries

This free, online, application-based activity is based on CDC's Stopping Elderly Accidents, Deaths and Injuries (STEADI) initiative. After completing the training, pharmacists will be able to describe the burden of falls among older adults; identify health conditions and types of medications that increase fall risk; implement fall screening, assess risk factors and offer prevention strategies; and discuss strategies to improve patient care coordination for fall prevention. The program's goal is for pharmacists to integrate screening into their routine practice. The training is accredited by the Accreditation Council for Pharmacy Education.

www.cdc.gov/steadi/training.html

Functional Medicine Coaching: How to Be Part of the Movement That's Transforming Healthcare

Authors: Sandra Scheinbaum and Elyse Wagner



Functional Medicine Coaching contains inspirational stories that describe the personal transformations and journeys toward physical health and well-being as a result of working with a health coach. Both aspiring coaches and those already working in the field will learn the power of combining the principles of functional medicine with positive psychology coaching. The powerful blending of these two approaches addresses what individuals need to thrive. This book is intended for anyone with a passion for helping others and desiring to enter the rapidly exploding fields of health and functional medicine coaching.

www.amazon.com/Functional-Medicine-Coaching-Transforming-Healthcare-ebook/dp/B01NAVHJPG/ref=sr_1_21?s=books&ie=UTF8&qid=1491333313&sr=1-21&keywords=medicine

Drugmaker's Guide to the 21st Century Cures Act

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

This newly published e-book tells drugmakers what to expect from the 21st Century Cures Act, which new provisions are likely to cause trouble and how to get out in front of the changes. Readers will learn about how FDA will be forced to accept "consistent, parallel scientific advice" from clinical trials outside their jurisdiction (i.e., non-U.S. research); how FDA will no longer conduct quality inspections of manufacturers of excipients; how sponsors of investigational drugs will have to create a policy for evaluating and responding to requests for expanded access to the drugs; how universities' and hospitals' local institutional review boards will be locked out of most trials; and how vague terms like "in the best interest of patients" and "probable benefit" leave holes.

www.fdanews.com/products/category/101-books/product/54041-drugmakers-guide-to-the-21st-century-cures-act-changing-the-face-of-pharmaceutical-and-biologics-regulation

Plasma-Derived Apolipoprotein A-I Infusions Are Well-Tolerated, Acutely Increase Cholesterol Efflux Capacity

Human and recombinant apolipoprotein A-I (apoA-I) is the primary functional component of high-density lipoprotein, and has been shown to increase cholesterol efflux capacity and to regress atherosclerotic disease in animal and clinical studies. In a Phase IIb, multicenter dose-ranging study, a total of 1,258 patients with myocardial infarction (MI) were randomized to receive, within seven days of their MI event, four consecutive weekly infusions of low or high doses of reconstituted human plasma-derived apoA-I (CSL112; CSL Behring) or placebo. This study was primarily intended to assess the safety and tolerability of CSL112, focusing on markers of hepatic and renal function, but also examined cholesterol efflux.

Four weekly infusions of CSL112 at both low (2 g) and high (6 g) doses were not associated with alterations in either liver or kidney function. Major adverse coronary event rates were generally comparable between groups, although cardiovascular mortality was higher in the 6 g group compared with the placebo group (4 versus 0 deaths; P= 0.0477). The 2 g dose elevated apoA-I 1.29-fold and total cholesterol efflux capacity 1.87-fold, while the 6 g dose elevated them 2.06-fold and 2.45-fold, respectively. The elevation of cholesterol efflux capacity mediated by CSL112 is transient, receding to baseline with clearance of the apoA-I. The investigators concluded that "further assessment of the clinical efficacy of CSL112 for the reduction of early recurrent cardiovascular events after acute MI is warranted in an adequately controlled, multicenter, randomized Phase III trial."

Gibson CM, Korjian S, Tricoci P, et al. Safety and tolerability of CSL112, a reconstituted, infusible, plasma-derived apolipoprotein A-I, after acute myocardial infarction. Circulation *2016 Dec 13;134:1918-30.*

Intravenous Immune Globulin Improves Systemic Sclerosis Symptoms

Administration of high-dose intravenous immune globulin (IVIG) significantly improved muscle and joint pain, muscle weakness and markers of systemic inflammation, according to a retrospective evaluation of 46 systemic sclerosis patients at 19 French centers. At baseline, the large majority of patients had muscle involvement (78 percent) and digestive tract involvement (89 percent), and about one-half had joint involvement (50 percent) and digital ulcers (52 percent). Before IVIG initiation, most patients (84 percent) had received at least one anti-inflammatory, immunosuppressive or immunomodulatory drug for a mean duration of 2.67 ± 3.65 years; regimens usually included corticosteroids (80 percent), either alone (20 percent) or combined with immunosuppressants (54 percent).

Patients received a mean 14.5 ± 18.2 IVIG cycles administered over a mean 14.8 ± 19.4 months; just over 90 percent received the usual dosage of 2.0 g/kg/cycle. In 35 percent of patients, IVIG was used as an add-on treatment without modification of other drug therapy; in the rest, background therapy was modified at IVIG initiation and/or during the IVIG course.

Improvements from start to cessation of IVIG treatment were documented in pain associated with muscle involvement (74 percent vs. 20 percent, $p < 0.0001$), weakness (45 percent vs. 21 percent, $p = 0.01$), joint pain (44 percent vs. 19 percent, $p = 0.02$), creatinine kinase levels (1069 ± 1552 UI vs. 288 ± 449 UI, $p < 0.0001$) and C-reactive protein levels (13.1 ± 17.6 mg/L vs. 9.2 ± 16.6 mg/L, $p = 0.001$). There were also trends for improvement of gastroesophageal reflux disease (GERD) (68 percent vs. 53 percent, $p = 0.06$) and bowel symptoms (42 percent vs. 27 percent, $p = 0.06$). Skin and cardiorespiratory involvements remained stable. The daily corticosteroid dose was also significantly lower by the end of treatment (13.0 ± 11.6 mg/day vs. 8.9 ± 10.4 mg/day, $p = 0.01$). The study authors also reviewed previous studies suggesting the efficacy of IVIG for various organ involvements.

Sanges S, Rivière S, Mekinian A, et al. Intravenous immunoglobulins in systemic sclerosis: Data from a French nationwide cohort of 46 patients and review of the literature. Autoimm Rev *2017 Apr;16(4):377-84.*

Medicare Immune Globulin Reimbursement Rates

Rates are effective July 1, 2017, through Sept. 30, 2017

	Product	Manufacturer	HCPCS	ASP + 6% (before sequestration)	ASP + 4.3%* (after sequestration)
IVIG	CARIMUNE NF	CSL Behring	J1566	$65.88	$64.83
	FLEBOGAMMA	Grifols	J1572	$55.86	$54.96
	GAMMAGARD SD	Shire	J1566	$65.88	$64.83
	GAMMAPLEX	BPL	J1557	$93.38	$91.88
	OCTAGAM	Octapharma	J1568	$68.25	$67.16
	PRIVIGEN	CSL Behring	J1459	$77.21	$75.97
IVIG/SCIG	GAMMAGARD LIQUID	Shire	J1569	$80.39	$79.10
	GAMMAKED	Kedrion	J1561	$76.82	$75.59
	GAMUNEX-C	Grifols	J1561	$76.82	$75.59
SCIG	CUVITRU	Shire	J3490 / J3590 / J7799	**	**
	HIZENTRA	CSL Behring	J1559	$98.29	$96.71
	HYQVIA	Shire	J1575	$130.36	$128.27

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

** CUVITRU does not yet have Medicare rates.

Calculate your reimbursement online at www.FFFenterprises.com.

Immune Globulin Reference Table

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

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

2017–2018 Influenza Vaccine

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

Product	Manufacturer	Presentation	Age Group	Code
Trivalent				
AFLURIA (IIV3)	SEQIRUS	0.5 mL PFS 10-BX	5 years and older*	90656
AFLURIA (IIV3)	SEQIRUS	5 mL MDV	5 years and older*	90658/ Q2035
FLUAD (aIIV3)	SEQIRUS	0.5 mL PFS 10-BX	65 years and older	90653
FLUVIRIN (IIV3)	SEQIRUS	0.5 mL PFS 10-BX	4 years and older	90656
FLUVIRIN (IIV3)	SEQIRUS	5 mL MDV	4 years and older	90658/ Q2037
FLUZONE HIGH-DOSE (IIV3)	SANOFI PASTEUR	0.5 mL PFS 10-BX	65 years and older	90662
Quadrivalent				
AFLURIA (IIV4)	SEQIRUS	0.5 mL PFS 10-BX	18 years and older	90686
AFLURIA (IIV4)	SEQIRUS	5 mL MDV	18 years and older	90688
FLUARIX (IIV4)	GSK	0.5 mL PFS 10-BX	3 years and older	90686
FLUBLOK (ccIIV4)	PROTEIN SCIENCES	0.5 mL PFS 10-BX	18 years and older	90682
FLUCELVAX (ccIIV4)	SEQIRUS	0.5 mL PFS 10-BX	4 years and older	90674
FLUCELVAX (ccIIV4)	SEQIRUS	5 mL MDV	4 years and older	TBD
FLULAVAL (IIV4)	GSK	5 mL MDV	6 months and older	90688
FLUMIST** (LAIV4)	MEDIMMUNE	0.2 mL nasal spray 10-BX	2-49 years	90672
FLUZONE (IIV4)	SANOFI PASTEUR	5 mL MDV	6 months and older	90688
FLUZONE (IIV4)	SANOFI PASTEUR	0.5 mL PFS 10-BX	3 years and older	90686
FLUZONE (IIV4)	SANOFI PASTEUR	0.5 mL SDV 10-BX	3 years and older	90686
FLUZONE INTRADERMAL (IIV4)	SANOFI PASTEUR	0.1 mL prefilled microinjection 10-BX	18-64 years	90630
FLUZONE PEDIATRIC (IIV4)	SANOFI PASTEUR	0.25 mL PFS 10-BX	6-35 months	90685

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

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

Afluria may be used in persons aged ≥9 years.

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