SUMMER 2019

biosupplytrends
QUARTERLY

SPECIAL FOCUS:
VACCINES

VACCINE UPDATE

Addressing Trends and Compliance

Improving Vaccination Rates in Seniors:
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Purchasing

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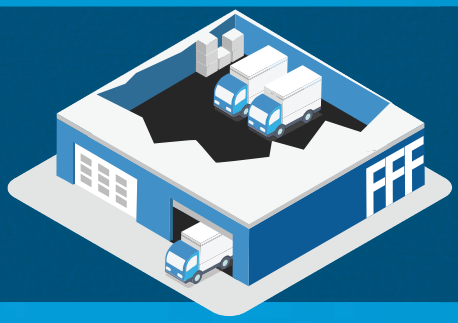

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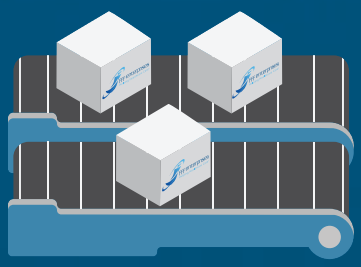

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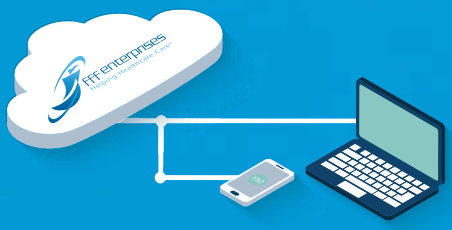

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BioSupply Trends Quarterly is the definitive source for industry trends, news and information for healthcare professionals in the biopharmaceuticals marketplace.

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Vaccination Remains Vital for Community Safety

ONCE CONSIDERED AN eliminated disease in the U.S., measles has surged in recent months in this country, with more than 1,000 people infected across 28 states as of this writing. Unfortunately, this uptick is caused by the low vaccination rates in some communities due to a lingering, misguided anti-vaccination movement. "The biggest misinformation has been this connection between measles vaccination and autism, which has completely been debunked as being absolutely false and based on no data," said Anthony Fauci, director of the National Institutes of Allergy and Infectious Diseases.[1] Thankfully, despite anti-vaccine rhetoric and a slight decline in vaccination rates in the U.S., the number of people immunized against vaccine-preventable diseases remains relatively high, providing herd immunity that is vital for community safety. In this annual vaccine-themed issue, we report trends and changes in vaccination among select populations, as well as a new promising vaccine technology.

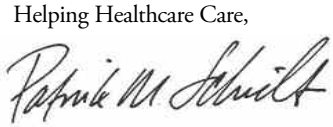
We begin our vaccines article series with a look at updates and improvements in vaccines for children and young adults. In our article "Following the Disease: Trends and Outbreaks Drive Subtle Changes to Vaccine Recommendations for Adolescents and Young Adults" (p.18), epidemiologist Hillary Johnson explores vaccine modifications for five diseases. A resurgence in mumps cases begun in 2015 has recently caused the Advisory Committee on Immunization Practices (ACIP) to revise its recommendation of two doses of the measles-mumps-rubella vaccine to three doses. Also revised are ACIP's expanded recommendation for the HPV vaccine for individuals age 27 years through 45 years in October 2018 and the American Academy of Pediatrics' discontinued preference for the flu shot over the nasal spray vaccine for the 2019-20 influenza season. In addition, new vaccines have been introduced for the adolescent population, including two brands of meningococcal serogroup B vaccine and a yeast-derived hepatitis B vaccine. With these updates, we hope more disease outbreaks can be thwarted.

While upwards of 90 percent of parents vaccinate their children, seniors represent one population with the lowest vaccine-schedule adherence. As we examine in our article "Vaccinations for Seniors: Addressing Compliance" (p.24), three primary challenges contribute to nonvaccine compliance: age-related immunity that reduces the effectiveness of some vaccines, nonunderstanding of what vaccines are recommended and when, and confusion about insurance coverage for vaccines. To reduce the health risks and the astronomical costs associated with vaccine-preventable illnesses, researchers are looking to develop optimally effective vaccines for older adults.

Considered highly promising, albeit technologically challenging, new DNA vaccines are more consistent in provoking immunity to disease, less expensive to produce, easier to speed to production and even helpful in fighting some cancers. Yet, as we explain in our article "Update on Conventional vs. DNA Vaccines" (p.30), the technology to produce DNA vaccines has been around for a quarter of a century, and still not one such vaccine has been created. The main problem stems from the delivery method of getting the bioengineered DNA into cells. If one promising method works, DNA vaccines may well be a new and better tool to fight infectious diseases.

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

1. Manchester J. Public Health Official Says Despite Being Debunked, Anti-Vaccine Rhetoric 'Still Lingers.' The Hill, April 17, 2019. Accessed at thehill.com/hilltv/rising/439269-public-health-official-says-link-between-autism-vaccines-is-biggest.

biosupply trends QUARTERLY

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

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HHS Grants Awarded to Help Americans Access HIV/AIDS Care and Medication

In 2018, the U.S. Department of Health and Human Services (HHS) awarded $2.34 billion in Ryan White HIV/AIDS Program grants to cities, counties, states and local community-based organizations. The funding supports a comprehensive system of HIV primary medical care, medication and essential support services to more than half a million people living with HIV in the U.S.

The Ryan White HIV/AIDS Program is a patient-centered system that provides care and treatment services to low-income people living with HIV to improve health outcomes and reduce HIV transmission among hard-to-reach populations. It serves approximately 50 percent of people living with diagnosed HIV infection in the U.S. "New medical advances and broader access to treatment have helped transform HIV/AIDS from a likely death sentence into a manageable chronic disease," said HHS Secretary Alex Azar. "The Ryan White HIV/AIDS Program is an important way to ensure that these lifesaving treatments reach the Americans who need them." ❖

HHS Awards $2.34 Billion in Grants to Help Americans Access HIV/AIDS Care and Medication. U.S. Department of Health and Human Services press release, Oct. 11, 2018. Accessed at www.hhs.gov/about/news/2018/10/11/hhs-awards-2-billion-grants-help-americans-access-hivaids-care-and-medication.html.

New Voluntary Medicare Part D Demo Aims to Reduce Spending on High-Cost Drugs

In January, the Centers for Medicare and Medicaid Services' (CMS) Center for Medicare and Medicaid Innovation announced a new model to allow Medicare Part D plans to share in savings generated by reducing costs in the program's catastrophic phase. The Part D Payment Modernization Model, part of President Trump's Blueprint to Lower Drug Prices and Reduce Out-of-Pocket Costs, aims to reduce government spending once patients have spent $5,100 in out-of-pocket drug costs. Once that level is reached, taxpayers become responsible for 80 percent of the costs, while the plans pay 15 percent. CMS believes the program will save taxpayers $2 billion per year.

Participants in the five-year model will take on a dual-sided risk. CMS will calculate a benchmark for what government spending would have been without plans taking on the additional risk, and Part D plans will share an unspecified percent of savings if they stay below the target. Plans that exceed the target will be accountable for 10 percent of the federal government's losses. In addition, the model will provide participants with additional tools to increase engagement between plans and beneficiaries and to promote better understanding of the Part D benefit, out-of-pocket costs and clinically equivalent therapeutic options. The model also includes a Part D Rewards and Incentives program that gives plans additional flexibility to strengthen the clinical relationship between the enrollee and his or her provider and chosen Part D plan. ❖

Sullivan T. Voluntary Part D Demo Incentivizes Plans to Reduce Spending on High-Cost Drugs. Policy & Medicine, Feb. 4, 2019. Accessed at www.policymed.com/2019/02/voluntary-part-d-demo-incentivizes-plans-to-reduce-spending-on-high-cost-drugs.html.

CMS Finalizes Rule on Medicare Advantage Pay Raise Based on Patient Encounter Data

The Centers for Medicare and Medicaid Services (CMS) has finalized its rule to give Medicare Advantage plans a 2.53 percent pay raise in 2020, up from its original plan to raise pay 1.59 percent. However, the raise is 3.4 percent lower than the one given to the plans in 2019, and it will be based on a higher percentage of patient encounter data. The finalized rule also allows the plans more flexibility to offer chronic illness patients supplemental benefits that won't necessarily cure their conditions but will address social and environmental factors that affect their health. Plans will also be able to tailor benefits or reduce cost-sharing to meet certain members' needs. For instance, according to CMS Administrator Seema Verma, the plans could pay for home air filters or carpet shampooing for patients with asthma or pay for heart-healthy meals for heart disease patients. This is a significant departure from the previous policy that allowed coverage only for services

that prevented, improved or cured patients' conditions, and that prohibited plans from offering different benefits to patients.

"These changes to the model better reflect costs and improve the financing for the care of beneficiaries with multiple conditions," said Verma. In addition to encounter data, CMS said it is moving ahead with plans to adjust payments to reflect patients' total number of medical conditions, a change required by the 21st Century Cures Act. ❖

Livingston S. CMS Finalizes Medicare Advantage Pay Raise, Ups Encounter Data Use. Modern Healthcare, April 1, 2019. Accessed at www.modernhealthcare.com/payment/cms-finalizes-medicare-advantage-pay-raise-ups-encounter-data-use?utm_source=modern-healthcare-am-tuesday&utm_medium=email&utm_campaign=20190402&utm_content=article1-headline.

FDA Implements Added Efforts to Tackle e-Cigarette Use and Addiction by Kids

With the rapid growth in the popularity of e-cigarettes among youth, the U.S. Food and Drug Administration (FDA) is making efforts as part of its Youth Tobacco Prevention Plan to ensure no tobacco products are marketed to, sold to or used by kids. In addition to launching public education campaigns to warn youth about the dangers of e-cigarette and other tobacco product use, FDA held a public hearing on the topic in January that provided a range of perspectives and new funding opportunities to support research on youth tobacco initiation, use and cessation. Another public scientific workshop was held May 15 to further discuss scientific understanding and treatment options for youth tobacco addiction and cessation, with a focus on e-cigarette cessation.

The May workshop, built on many of the scientific issues raised during the January public hearing, was intended to gather scientific information and stimulate discussion about the current science regarding youth tobacco use and addiction, as well as treatment strategies to support youth tobacco cessation. The workshop included presentations and panel discussions relating to the unique factors impacting youth tobacco use and addiction and the challenges associated with youth tobacco cessation. For example, discussion included the basic science of tobacco addiction in adolescents, the current state of behavioral and pharmacotherapy cessation strategies in adolescents, and the development of strategies to generate robust evidence to address youth tobacco cessation. According to FDA Commissioner Scott Gottlieb, MD, FDA wants to explore how it can support the development of such therapies.

The most recent data show more than 3.6 million middle and high school students across the country were current (within the past 30 days) e-cigarette users

in 2018 — a dramatic increase of 1.5 million students from the previous year. The data also showed youth who used e-cigarettes were using them more frequently, and they were using flavored e-cigarette products more often than in 2017. ❖

Statement from FDA Commissioner Scott Gottlieb, M.D., on New Efforts to Advance Treatment Strategies for Helping Youth Addicted to Nicotine as a Result of the Epidemic Rise in Teen Use of e-Cigarettes. U. S. Food and Drug Administration press release, April 1, 2019. Accessed at www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm634872.htm.

CMS Launches Artificial Intelligence Health Outcomes Challenge

The Centers for Medicare and Medicaid Services (CMS) has launched the Artificial Intelligence Health Outcomes Challenge, a three-stage competition to accelerate artificial intelligence solutions that will potentially be used by CMS's Innovation Center in testing innovative payment and service delivery models under the authority of section 1115A of the Social Security Act.

The challenge is an opportunity for innovators to demonstrate how artificial intelligence tools such as deep learning and neural networks can be used to predict unplanned hospital and skilled nursing facility admissions and adverse events. It also prioritizes explainable artificial intelligence solutions to help frontline clinicians understand and trust artificial intelligence-driven data feedback to target scarce resources and improve the quality of care. CMS is partnering with the American Academy of Family Physicians (AAFP) and the Laura and John Arnold Foundation to award up to $1.65 million to selected participants during the three stages of the challenge.

The three stages include the Launch Stage, during which participants will submit an application and provide information about their proposed solution. Up to 20 participants will be selected to advance to Stage 1. During Stage 1, participants will design and test their proposed solution using certain Medicare claims data sets. Up to five participants will be selected to advance to Stage 2, and each will be awarded up to $80,000. During Stage 2, finalists will be able to request additional Medicare claims data and refine their solutions. The grand prize winner in Stage 2 will be awarded up to $1 million, and the runner-up will be awarded up to $250,000.

The challenge will run for approximately one year. The Launch Stage ran from March 2019 through June 2019. Stage 1 will run from summer 2019 through fall 2019. And, Stage 2 will run from winter 2019 through spring 2020. The winner will be announced in April 2020. (Dates are subject to change.)

More information about the challenge can be found at ai.cms.gov. ❖

CMS Artificial Intelligence Health Outcomes Challenge. Centers for Medicare and Medicaid Services press release, March 27, 2019. Accessed at www.cms.gov/newsroom/fact-sheets/cms-artificial-intelligence-health-outcomes-challenge.

Impact of Payment Rules on Sites of Care

By Bonnie Kirschenbaum, MS, FASHP, FCSHP

THE U.S. HAS the most expensive healthcare in the world, well recognized for its unsustainable surging costs. Consequently, something must be done to curb this out-of-control growth. In answer, drug-pricing bills and proposals have flooded almost every government healthcare agency. Even the private payer sector is examining its insurance benefits and creating new payment models that lower prices for drugs and/or premiums. If these programs are implemented, patients will be able to obtain medicines at prices they can afford. However, for this to work, the healthcare sector must align the interests of all involved, including the patients, especially now when the focus is on high-investment medications and multiple complex drivers of change. To prepare for what's coming, providers must look ahead, collaborate across disciplines and stay informed to adapt and innovate in the clinical, operational and business spheres of care delivery.

Where the patient receives care, known as the site of service, represents an interesting opportunity for significant savings. Sites of service include hospital inpatient care, hospital outpatient care, nonhospital clinic care and homecare. Hospital inpatient care is the most expensive option, and for many years, it has remained an option only for the sickest patients or the most complicated surgeries or procedures with an emphasis on the shortest possible stays. However, one of the nation's biggest specialty care costs are provider-administered infused or injectable medical benefit drugs, and most often, these are administered in hospital inpatient centers. Therefore, to reduce costs, it is necessary to direct patients to the most cost-effective location to receive these medications while maintaining optimal clinical care. There are some concerns raised, though, about continuity of patient care, patients' access to certain medications and the ability to respond to emergent adverse drug events in nonhospital-based settings.

The 2019 outpatient prospective payment system final rule set launched a site-of-care normalization program for hospitals that are losing significant revenue from Medicare patient clinic visits. This program, phased in over three years, reduces to 70 percent the cost for Medicare and patients, eventually reducing costs to 40 percent in year three. The proposed goal is to promote patients' choice in site of service. If patients choose to remain with a hospital-based clinic, the cost both to Medicare and to patients (for their copay) is reduced. Since patients pay a 20 percent copay, staying with the hospital-based clinic prior to the launch of this program was a more expensive option than moving to a different site of care. But, with rate normalization, patient copays will be the same regardless of site-of-service choice. However, since Medicare currently does not negotiate Part B drug prices and sets its rates at average sale price plus 6 percent, patient copays for Part B drugs they receive during these clinic visits remain the same, and for many of the newer biologic, chemotherapy and immunotherapy drugs, these copays remain staggeringly high.

In 2018, there were 49 specialty drug approvals. Of these, 19 fell under Medicare Part D (the pharmacy benefit), 25 fell under Medicare Part B (the medical benefit) and five spanned the two benefit categories for various reasons. New Medicare Part B drugs included nine oncology/oncology support drugs, seven rare disease drugs, six autoimmune biosimilars, four in various other categories and two immune globulins (IGs). The private sector manages these with prior authorization, post-service claims edits, site-of-service shifts, dose optimization and implementation of biosimilar strategies.

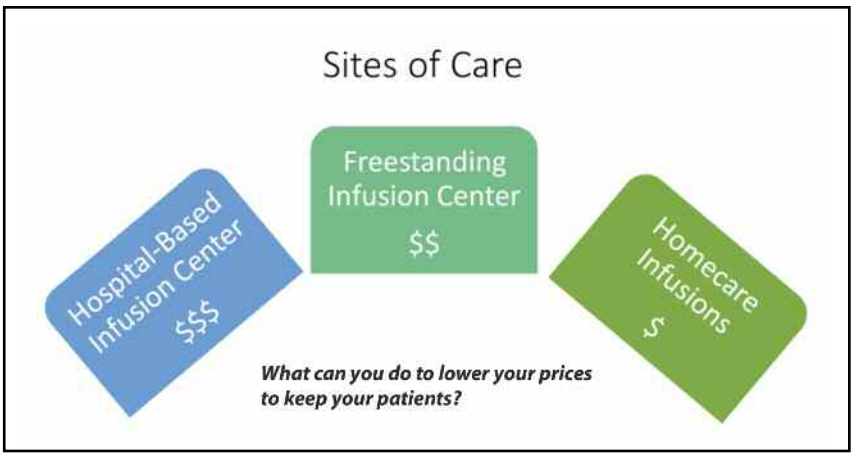
Private health insurance plans providing Medicare benefits to 20 million (one-third of all) beneficiaries will be able to negotiate Part B and Part D drug prices, as well as implement step therapy that can be applied only to new prescriptions for patients who are not actively receiving a given medication. Medicare Advantage plans are required to pass savings on to beneficiaries through rewards given as part of drug management care coordination that must be equivalent to more than half the amount saved on average per participant and can be in the form of lower premiums. Additionally, copays for Part B drugs received during clinic visits will fall accordingly.

To reduce unsustainable drug costs, private sector payers are providing insurance benefits to those purchasing plans through their employers, on their own or as Medicare supplemental or secondary plans. The goal is to reduce the cost of Part B drugs and drug administration, with priority given to high-investment and specialty drugs. This has resulted in a decline in the use of both hospital outpatient infusion centers and free-standing infusion centers, specifically for chemotherapy and infusions that are deemed simple. As a result, centers that had predicted a sustained growth pattern as seen in previous years are seeing flat or slow growth in infusions. Others are reporting limits on what they call "buy and bill" drugs or drugs that fall into the medical pharmacy management category. Contributing to this decline is an increase in oral drugs (both in types and number of patients).

The targets for this shift in site-of-service choice are high-investment medications across five classes: autoimmune, enzyme replacement, amyotrophic lateral sclerosis, immunodeficiency and human immunodeficiency virus. And, the shift in site of service may be from a hospital-based outpatient infusion clinic to a free-standing infusion clinic, or to homecare for products such as intravenous IG and other immunotherapy products.

> "Where the patient receives care, known as the site of service, represents an interesting opportunity for significant savings."

The goal of the site-of-care normalization program is to reduce unsustainable drug costs and lower patients' copays. Healthcare organizations need to ensure their pricing structures don't result in losing patients to another site of care. They must be proactively involved with payer relations and participate in payer contract amendments to avoid medication-related denials. And, they must identify the impact of site-of-care trends, understanding that any cost decreases also result in decreases in the organization's reimbursement and patients' copays. ❖



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.

Achieving HIPAA Compliance

By Ronale Tucker Rhodes, MS

COMPLIANCE WITH the Health Insurance Portability and Accountability Act of 1996 (HIPAA) is a vital component of any medical practice, especially as healthcare becomes more complex with the growing use of technology. Indeed, noncompliance with HIPAA can be extremely costly for covered entities and their business associates. In 2016, the Office for Civil Rights (OCR) in the Department of Health and Human Services (HHS) began conducting the second phase of its HIPAA audit program as part of its overall health information privacy, security and breach notification compliance activities. These random desk audits request documentation and evidence from small and large organizations across the U.S., and those not in compliance have faced fines from $215,000 on the low end up to millions of dollars.[1,2]

Because every covered entity and business associate is eligible to be audited by OCR, it's imperative they have a solid understanding of how to comply with HIPAA in their facilities. This includes the requirement for all covered entities to identify a HIPAA privacy and security officer responsible for developing and implementing policies and procedures that ensure the integrity of electronic protected health information (ePHI).[3]

HIPAA Security, Privacy and Breach Notification Rules

HIPAA is a series of national standards healthcare organizations must have in place to safeguard the privacy and security of PHI. PHI is defined as any demographic individually identifiable information that can be used to identify patients such as names, addresses, emails, telephone numbers, Social Security numbers and full facial photos.[4] With advancements in technology, in the last couple of decades, HIPAA has adopted national standards for electronic healthcare transactions and code sets, unique health identifiers and security, which have resulted in the privacy, security and breach notification rules.

The privacy rule, which was first published in December 2000 and later modified in August 2002,[5] established national standards for when PHI may be used and disclosed. PHI relates to "an individual's past, present or future physical or mental health or condition; the provision of healthcare to an individual; and past, present or future payment for the provision of healthcare to an individual."

The security rule, which was published in February 2003,[5] specifies safeguards that covered entities and their business associates must implement to protect ePHI confidentiality, integrity and availability. In essence, they must "implement reasonable and appropriate security measures through policies and procedures to protect the security of ePHI they create, receive, maintain or transmit." And, they must analyze the risks to ePHI in its environment and create appropriate solutions based on the nature of the business and its size, complexity and resources.

The breach notification rule requires covered entities to notify affected individuals, HHS and the local media (if affecting more than 500 patients) of a breach of unsecured PHI without reasonable delay and no later than 60 days following the breach discovery. A breach is considered an "impermissible use or disclosure under the privacy rule that compromises the security or privacy of PHI." And, the impermissible use or disclosure is presumed to be a breach unless the entity can demonstrate there is a low probability the PHI has been compromised based on the nature and extent of the PHI involved, including the types of identifiers and the likelihood of re-identification; the unauthorized person who used the PHI or to whom the disclosure was made; whether the PHI was acquired or viewed; and the extent to which the risk to the PHI has been mitigated.[6]

Covered Entities and Business Associates Defined

HHS defines covered entities as covered healthcare providers, health plans and healthcare clearinghouses. Covered healthcare providers are "providers of medical or other healthcare services or supplies that transmit any health information in electronic form in connection with a transaction for which HHS has adopted

a standard." Health plans are "individual or group plans that provide or pay the cost of healthcare" such as company health plans, government programs that pay for healthcare, health insurance companies and health maintenance organizations. Healthcare clearinghouses are "public or private entities that process another entity's healthcare transactions from a standard format to a nonstandard format or vice versa."

Business associates are persons or organizations that perform functions or provide services on behalf of a covered entity that involve access to PHI. They can also be subcontractors responsible for creating, receiving, maintaining or transmitting PHI on behalf of another business associate.[6]

Steps to Complying with HIPAA Rules

Basic compliance with HIPAA involves six steps:[4]

1) *Conducting audits.* Audits provide a baseline of where a practice stands against HIPAA law. Audits should be executed across all elements of the business using the HIPAA standards as their basis.

2) *Creating remediation plans.* These plans should be opened for each gap audits have uncovered, and they must be fully documented in one central repository, with limited role-based access depending on parties involved in the remediation process. Each remediation plan must assign responsibility to someone on the staff to fix the gap, along with action items and a timeline for completion.

3) *Developing policies and procedures and training employees.* Organizations are required to have policies and procedures in place that address each HIPAA standard, and which create uniform processes across all parts of the organization for handling PHI and other HIPAA-mandated implementation specifications. And, they must be tailored to the needs of the organization. Once in place, employees must be trained on their content, and all employees must sign an attestation they have read and understood the content of each policy.

4) *Executing business associate agreements with vendors.* These agreements, which must be executed before any PHI can be shared, describe the relationship between the covered entity and the business associate. They must also be reviewed annually, and amended if necessary to account for any changes in the relationship. In addition, covered entities are mandated to perform due diligence on their business associates before executing the agreements. Due diligence includes informally assessing the associate's current security/cyber-security infrastructure and their history of data breaches to determine whether it is a safe relationship to pursue.

5) *Managing incidents.* Because data breaches can still occur even when a HIPAA compliance program is in place, there should be processes for documenting, tracking and reporting breaches. These processes should set specific standards for both minor (fewer than 500 individuals) and meaningful (more than 500 individuals) breaches.

6) *Maintaining good documentation.* A compliance program relies upon documentation that demonstrates HIPAA compliance, both internally and to a federal investigator. And, that documentation must be kept in a centralized repository that can be accessed by necessary personnel and retained for six years.

The Role of the HIPAA Privacy/Security Officer

As mentioned previously, HIPAA mandates organizations to appoint a HIPAA security officer and a HIPAA privacy officer. However, depending on the size of the organization, it is possible for the two roles to be combined into one.

The specific responsibilities of the security officer include establishing, managing and enforcing the security rule safeguards and any subsequent rules issued by OCR; integrating IT security and HIPAA compliance with the organization's business strategies and requirements; addressing issues related to access controls, business continuity, disaster recovery and incident response; maintaining organizational security awareness, including staff training in collaboration with the HIPAA privacy office; conducting risk assessments and audits; and investigating data breaches and implementing measures for their future prevention and/or containment.

While the role of a HIPAA privacy officer is similar to a security officer since the individual also conducts risk assessments, trains staff and manages business associate agreements, the privacy officer is also responsible for establishing, managing and enforcing HIPAA-compliant policies and procedures to protect PHI in whatever format it is maintained.[3]

Customizing the Compliance Program

HIPAA compliance is not a voluntary undertaking, but rather a mandatory requirement governed by OCR. As such, a compliance program must be implemented by all covered entities and their business associates, and someone designated in the organization must oversee management of it. And, because entities vary in type and size, each will need to develop a program to meet their specific needs. ❖

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

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Vaccines

WHO Issues New Flu Vaccine Composition Recommendations for 2019-20 Season

The World Health Organization (WHO) advisory board issued its new recommendations on the composition of the influenza vaccines for use in the 2019-20 flu season in the Northern Hemisphere. According to the board, the egg-based quadrivalent vaccines should contain an A/Brisbane/02/2018 (H1N1)pdm09-like virus; an A/Kansas/14/2017 (H3N2)-like virus; a B/Colorado/06/2017-like virus (B/Victoria/2/87 lineage); and a B/Phuket/3073/2013-like virus (B/Yamagata/16/88 lineage). In addition, it recommended the influenza B virus component of trivalent vaccines be a B/Colorado/06/2017-like virus of the B/Victoria/2/87 lineage. ❖

World Health Organization. Recommended Composition of Influenza Virus Vaccines for Use in the 2019-2020 Northern Hemisphere Influenza Season, Feb. 21, 2019. Accessed at www.who.int/influenza/vaccines/virus/recommendations/2019_20_north/en.

Vaccines

Scientists Uncover Breakthrough in Development of Universal Flu Vaccine

Researchers at the University of Melbourne have discovered immune cells that can fight all different kinds of the influenza (flu) virus. Known as "killer cells," they can target influenza A, B and C strains, which shows promise for developing a one-time flu vaccine. The researchers started by analyzing parts of the flu virus that were all common in each flu strain, with a goal of finding out which section would be the best target for a universal vaccine. By doing this, they identified parts of the virus that haven't changed within the past century. According to one of the researchers, Katherine Kedzierska, PhD, a professor at the University of Melbourne,

"It was really like finding a needle in a haystack. We started with 67,000 viral sequences and narrowed it down to three sequences that the killer T cells can recognize."

Although this is a major breakthrough, Dr. Kedzierska says at this point, the universal vaccine would be effective only for half of the world's population because of the diversity of DNA, as in those who have the killer T cells and those who have a different set. Therefore, the researchers are now using similar cutting-edge technology to find similar killer T cells for the rest of the global population so everyone can be protected. ❖

Colagrossi M. Major Breakthrough May Lead to Universal Flu Vaccine. Big Think, Feb. 22, 2019. Accessed at bigthink.com/surprising-science/major-breakthrough-may-lead-to-universal-flu-vaccine.

Medicines

Novo Nordisk's Esperoct Approved to Treat Individuals with Hemophilia A

In February, the U.S. Food and Drug Administration approved Esperoct (antihemophilic factor [recombinant], glycopegylated-exei), an extended half-life factor VIII molecule for replacement therapy in people with hemophilia A, which provides a 1.6-fold half-life prolongation in adults and adolescents and a 1.9-fold half-life prolongation in children, compared to standard half-life factor VIII products. Esperoct is specifically indicated for use in adults and children with hemophilia A for on-demand treatment and control of bleeding episodes, perioperative management of bleeding and routine prophylaxis to reduce the frequency of bleeding episodes.

Approval was based on the PATHFINDER program, five prospective, multicenter clinical trials in 270 previously treated patients (202 adults/adolescents and 68 children) with severe hemophilia A (less than 1 percent endogenous FVIII activity) and no history of inhibitors. Total exposure to Esperoct was 80,425 exposure days corresponding to 889 patient years of treatment. Esperoct was shown to provide effective routine prophylaxis in people with severe hemophilia A through a fixed dosing regimen of one injection every four days in adults and adolescents or every three to four days (twice-weekly) in children. It provided effective prophylaxis and maintained a low median ABR of 1.18 when dosed at 50 IU/kg every four days in adults and adolescents. It was also found to be efficacious in treatment and control of bleeding episodes and perioperative management. ❖

CenterWatch. Esperoct [antihemophilic factor (recombinant), glycopegylated-exei]. Accessed at www.centerwatch.com/drug-information/fda-approved-drugs/drug/100354/esperoct-antihemophilic-factor-recombinant-glycopegylated-exei.

Testing

CMV Saliva Test Approved by FDA

Meridian Bioscience has received U.S. Food and Drug Administration (FDA) clearance for its new Alethia CMV Molecular Amplification Test (formerly, the Illumigene brand). The assay is designed to specifically detect congenital Cytomegalovirus (cCMV) infection in newborns from an easy-to-collect saliva sample. It is the first qualitative test in a molecular amplification format that is cleared by FDA for cCMV testing in newborns.

The most common congenital infection, cCMV is a leading cause of childhood hearing loss, cognitive deficits and visual impairment. According to the Centers for Disease Control and Prevention, approximately one in 200 babies are born with cCMV infection, and approximately 10 percent to 25 percent of all childhood sensorial hearing loss can be attributed to cCMV. Babies are at risk of infection during pregnancy if the virus in the mother's blood crosses through the placenta. Early detection is critical in establishing appropriate treatment. Diagnosis can be attained by detecting the virus in a baby's saliva or urine within two to three weeks from birth.

"Unfortunately cCMV infection is more common than other newborn-related illnesses, like group B strep for example, yet the level of awareness is considerably lower," said Jack Kenny, chief executive officer. "With Alethia CMV, we not only look to increase awareness, but also provide laboratories with an FDA-cleared test that they can use with confidence when diagnosing newborns with cCMV. Alethia CMV helps meet a critical need with a simple-to-collect saliva sample in combination with a procedurally simple, rapid and sensitive test." ❖

Meridian Gets FDA Clearance for New Neonatal Saliva CMV Test. Meridian Bioscience press release, Dec. 6, 2018. Accessed at globenewswire.com/news-release/2018/12/06/1662968/0/en/Meridian-Gets-FDA-Clearance-for-New-Neonatal-Saliva-CMV-Test.html.

Medicines

Takeda Receives FDA Approval to Manufacture Flexbumin at Georgia Facility

In March, the U.S. Food and Drug Administration (FDA) approved Takeda Pharmaceuticals' second submission for its new plasma manufacturing facility near Covington, Ga., for the production of Flexbumin 25% solution [albumin (human)], indicated for hypovolemia, hypoalbuminemia (burns, adult respiratory distress syndrome and nephrosis), cardiopulmonary bypass surgery and hemolytic disease of the newborn. The Georgia facility received its first FDA approval to manufacture Gammagard Liquid [immune globulin infusion (human)] 10% solution in June 2018.

"This latest approval is a significant milestone for the Georgia facility, Takeda and our patients," said Thomas Wozniewski, global manufacturing and supply officer. "This new state-of-the-art facility is providing much needed additional capacity for meeting increasing global demand for plasma-derived therapies, and our team there will continue to scale up production over the coming years." The Georgia facility currently employs more than 1,000 full-time and contract employees, and continues to hire to fill additional roles in manufacturing, quality, engineering, maintenance, utilities, warehouse and various support and facility roles. ❖

Takeda Receives U.S. FDA Approval to Manufacture FLEXBUMIN at New Plasma Manufacturing Facility near Covington, Georgia. BioSpace, March 18, 2019. Accessed at www.biospace.com/article/releases/takeda-receives-u-s-fda-approval-to-manufacture-flexbumin-at-new-plasma-manufacturing-facility-near-covington-georgia.

Medicines

IVIG Manufacturing Process for Bivigam Approved by FDA

ADMA Biologics has received approval from the U.S. Food and Drug Administration (FDA) for its prior approval supplement for Bivigam (immune globulin intravenous [human] 10% liquid), allowing the company to use its optimized intravenous immune globulin (IVIG) manufacturing process and market Bivigam to primary immunodeficiency patients in the U.S.

Bivigam was first approved by FDA in December 2012 and was then marketed by Biotest Pharmaceuticals Corp.; however, Biotest suspended commercial production of Bivigam due to manufacturing and compliance issues. Subsequent to ADMA's acquisition of the Biotest Therapy Business Unit in June 2017, ADMA resumed production of Bivigam during the fourth quarter of 2017, successfully manufacturing three conformance lots using the company's optimized IVIG manufacturing process. ADMA anticipates the relaunch of Bivigam for commercial sale during the second half of 2019.

"We are pleased to reintroduce Bivigam into the market, where demand for IVIG therapy continues to outpace supply," said Adam Grossman, president and chief executive officer of ADMA. "The $6 billion U.S. market for IVIG continues to grow, and the relaunch of Bivigam can help to alleviate a portion of the tight supply for this important patient population where dependable and consistent supply of IVIG is critical to patients' well-being." ❖

FDA Approves Prior Approval Supplement for Bivigam. ADMA Biologics press release, May 10, 2019. Accessed at www.apnews.com/Globe%20Newswire/14ab475b8dda73860e9c6695e902ae49.

Research

New Gene Therapy Treatment Offers Possible Cure for SCID-X1

Researchers at St. Jude Children's Research Hospital have cured infants with X-linked severe combined immunodeficiency (SCID-X1) using gene therapy involving a re-engineered virus. In the clinical trial, researchers used a modified version of HIV that can't cause AIDS to deliver the correct gene into the DNA of eight newly diagnosed SCID-X1 infants' blood stem cells, replacing those that do not function correctly. Two days prior to that, the infants received low-dose busulfan, an agent used in chemotherapy to help make space for donor stem cells to grow in the marrow. The majority of patients were able to leave the hospital within a month. And, all patients are developing normally so far, and none has incurred a life-threatening infection. In addition, none has developed leukemia, which was an outcome of previous gene therapy attempts for SCID-X1.

"While longer follow-up is needed to assess any late effects of treatment, these results suggest most patients treated with this gene therapy will develop a complete durable immune response without side effects," said co-author Mort Cowan, a University of California at San Francisco professor of pediatrics.

The only other viable treatment for SCID-X1 is a bone marrow transplant, but patients must have a matched sibling donor, and fewer than 20 percent of patients usually do. Instead, they have to rely on blood stem cells from donors who are not family, a situation that is better than no treatment, but often leads to marked side effects. ❖

IFL Science. Scientists "Cure" Patients with "Bubble Boy" Disease In Breakthrough Treatment. Accessed at hwww.iflscience.com/health-and-medicine/scientists-cure-patients-with-bubble-boy-disease-in-breakthrough-treatment.

Mamcarz E, Zhou S, Lockey T, et al. Lentiviral Gene Therapy Combined with Low-Dose Busulfan in Infants with SCID-X1. *New England Journal of Medicine,* 2019; 380:1525-1534. Accessed at www.nejm.org/doi/full/10.1056/NEJMoa1815408.

Medicines

First Cancer Drug for Specific Gene Mutation Gets FDA Approval

The U.S. Food and Drug Administration (FDA) has granted accelerated approval to Keytruda (pembrolizumab) for patients whose cancers have a specific genetic feature (biomarker). This is the first time the agency has approved a cancer treatment based on a common biomarker rather than the location in the body where the tumor originated. The indication covers patients with solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options and patients with colorectal cancer that has progressed following treatment with certain chemotherapy drugs.

Keytruda is indicated for the treatment of adult and pediatric patients with unresectable or metastatic solid tumors that have been identified as having a biomarker referred to as microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR). MSI-H and dMMR tumors contain abnormalities that affect the proper repair of DNA inside the cell. Tumors with these biomarkers are most commonly found in colorectal, endometrial and gastrointestinal cancers, but also less commonly appear in cancers arising in the breast, prostate, bladder, thyroid gland and

other places. Approximately 5 percent of patients with metastatic colorectal cancer have MSI-H or dMMR tumors.

The safety and efficacy of Keytruda for this indication were studied in patients with MSI-H or dMMR solid tumors enrolled in one of five uncontrolled, single-arm clinical trials. In some trials, patients were required to have MSI-H or dMMR cancers, while in others, a subgroup of patients were identified as having MSI-H or dMMR cancers by testing tumor samples after treatment began. A total of 15 cancer types were identified among 149 patients enrolled across the five clinical trials. The most common cancers were colorectal, endometrial and other gastrointestinal cancers. The review of Keytruda for this indication was based on the percentage of patients who experienced complete or partial shrinkage of their tumors (overall response rate) and for how long (durability of response). Of the 149 patients who received Keytruda in the trials, 39.6 percent had a complete or partial response. For 78 percent of those patients, the response lasted for six months or more.

"This is an important first for the cancer community," said Richard Pazdur, MD, acting director of the Office of Hematology and Oncology Products in FDA's Center for Drug Evaluation and Research and director of the FDA's Oncology Center of Excellence. "Until now, the FDA has approved cancer treatments based on where in the body the cancer started — for example, lung or breast cancers. We have now approved a drug based on a tumor's biomarker without regard to the tumor's original location." ❖

FDA Approves First Cancer Treatment for Any Solid Tumor with a Specific Gene Factor. U.S. Food and Drug Administration press release, Dec. 5, 2018. Accessed at www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm560167.htm.

Research

Flu Shot Does Not Cause Pregnant Women to Miscarry

A new study conducted by investigators at the Center for Clinical Epidemiology and Population Health at the Marshfield Clinic Research Institute in Wisconsin has found the influenza (flu) vaccine does not cause miscarriages in pregnant women. These results were discovered after the Centers for Disease Control and Prevention tasked the researchers with investigating the results of a smaller study conducted during the 2010-11 and 2011-12 flu seasons that found an increased risk for spontaneous abortion, or miscarriage, in the 28 days after a pregnant woman is vaccinated, but only in a small number of women who received the H1N1 vaccine two years in a row. There was no association between miscarriage and vaccination among women who had not been vaccinated in the previous year.

The new study, which examined the 2012-13, 2013-14 and 2014-15 flu seasons individually and together, matched 1,236 pairs of women, including 627 pairs who had been vaccinated in the previous season and 609 pairs who were not. For each flu season and even when all women and seasons were combined, there was no evidence of increased miscarriage risk after the flu vaccine during the first 28 days. In addition, there was no significant association between miscarriage and the flu vaccine in the 29- to 56-day risk window and beyond. "It didn't seem to matter which season of flu or whether they were vaccinated in the prior season or not," said lead investigator James Donahue, a senior epidemiologist at Marshfield. "The findings provide a high level of reassurance regarding the safety of influenza vaccine in early pregnancy and through pregnancy, and support the current recommendations of an influenza vaccination for all pregnant women." ❖

LaMotte S. Flu Shot Will Not Cause a Pregnant Woman to Miscarry, Study Says. CNN, Feb. 28, 2019. Accessed at www.cnn.com/2019/02/27/health/flu-vaccine-pregnancy-safety-miscarriage/index.html.

Medicines

Nivestym, a Biosimilar to Neupogen, Approved by FDA

Pfizer's Nivestym (filgrastim-aafi), a biosimilar to Neupogen, has been approved by the U.S. Food and Drug Administration (FDA) for all eligible indications of the reference product. Approval was based on a review of a comprehensive data package and totality of evidence demonstrating a high degree of similarity of Nivestym compared to Neupogen.

Nivestym is indicated:

• To decrease the incidence of infection, as manifested by febrile neutropenia, in patients with nonmyeloid malignancies receiving myelosuppressive anticancer drugs associated with a significant incidence of severe neutropenia with fever;

• For reducing the time to neutrophil recovery and the duration of fever, following induction or consolidation chemotherapy treatment of patients with acute myeloid leukemia;

• To reduce the duration of neutropenia and neutropenia-related clinical sequelae (e.g., febrile neutropenia) in patients with nonmyeloid malignancies undergoing myeloablative chemotherapy followed by bone marrow transplantation;

• For the mobilization of autologous hematopoietic progenitor cells into the peripheral blood for collection by leukapheresis; and

• For chronic administration to reduce the incidence and duration of sequelae of severe neutropenia (e.g., fever, infections, oropharyngeal ulcers) in symptomatic patients with congenital neutropenia, cyclic neutropenia or idiopathic neutropenia.

Nivestym is expected to be available in the U.S. at a significant discount to the current wholesale acquisition cost of Neupogen. It is Pfizer's fourth biosimilar approved by FDA. ❖

FDA Approves Nivestym (filgrastim-aafi), a Biosimilar to Neupogen. Drugs.com, July 20, 2018. Accessed at www.drugs.com/newdrugs/fda-approves-nivestym-filgrastim-aafi-biosimilar-neupogen-4785.html.

Medicines

Accelerated Dosing Regimen Approved for Japanese Encephalitis Vaccine

Valneva USA, the U.S. subsidiary of global vaccine biotech company Valneva SE, has received U.S. Food and Drug Administration (FDA) approval of an accelerated dosing regimen for IXIARO (Japanese encephalitis vaccine, inactivated, adsorbed). IXIARO is the only vaccine approved in the U.S. indicated for protection against disease caused by Japanese encephalitis (JE) virus, a rare but serious disease and the most common form of vaccine-preventable encephalitis and viral-induced neurologic disability in Asia. For effective protection from JE virus, adults aged 18 years to 65 years may now receive two separate doses of IXIARO seven days apart. Previously, the time between doses for this age group was 28 days. The standard 28-day schedule still applies to children 2 months to 17 years and adults 66 years and older; adults aged 18 years to 65 years may also follow this schedule. The accelerated and the standard dosing schedules must be completed at least seven days before travel to endemic areas.

"The FDA approval of this accelerated seven-day dosing schedule is a positive step toward protecting more people from JE," said Charles Daily, Valneva's general manager in the U.S. "For travelers who do seek protection with a vaccine prior to travel, oftentimes they are not aware of the dosing schedule and, therefore, have not visited their doctor soon enough to allow for two doses. Eliminating this time barrier will make it easier for patients to plan for their travel health needs and to better protect themselves."

A recent survey found 72 percent of U.S. adults who traveled to Asia for 10 or more days reported visiting at least one area, or participating in an activity, that put them at increased risk for exposure to JE virus and, based on guidelines, should consider a vaccine along with other protective measures. However, the same survey found more than one-third began preparing for travel less than a month before departure. "I encourage anyone planning international travel to visit a travel health practitioner well in advance of their anticipated departure date to learn about preventative measures for travel-related diseases," said Scott Morcott, MD, family physician and medical director of Passport Health Chicago. "For those whose travel plans change unexpectedly, this shorter vaccine dosing regimen may help to protect them in less time." ❖

VALNEVA Announces FDA Approval of Accelerated IXIARO Vaccination Schedule. Global Newswire, Oct. 5, 2018. Accessed at www.benzinga.com/pressreleases/18/10/g12462593/valneva-announces-fda-approval-of-accelerated-ixiaro-vaccination-sched.

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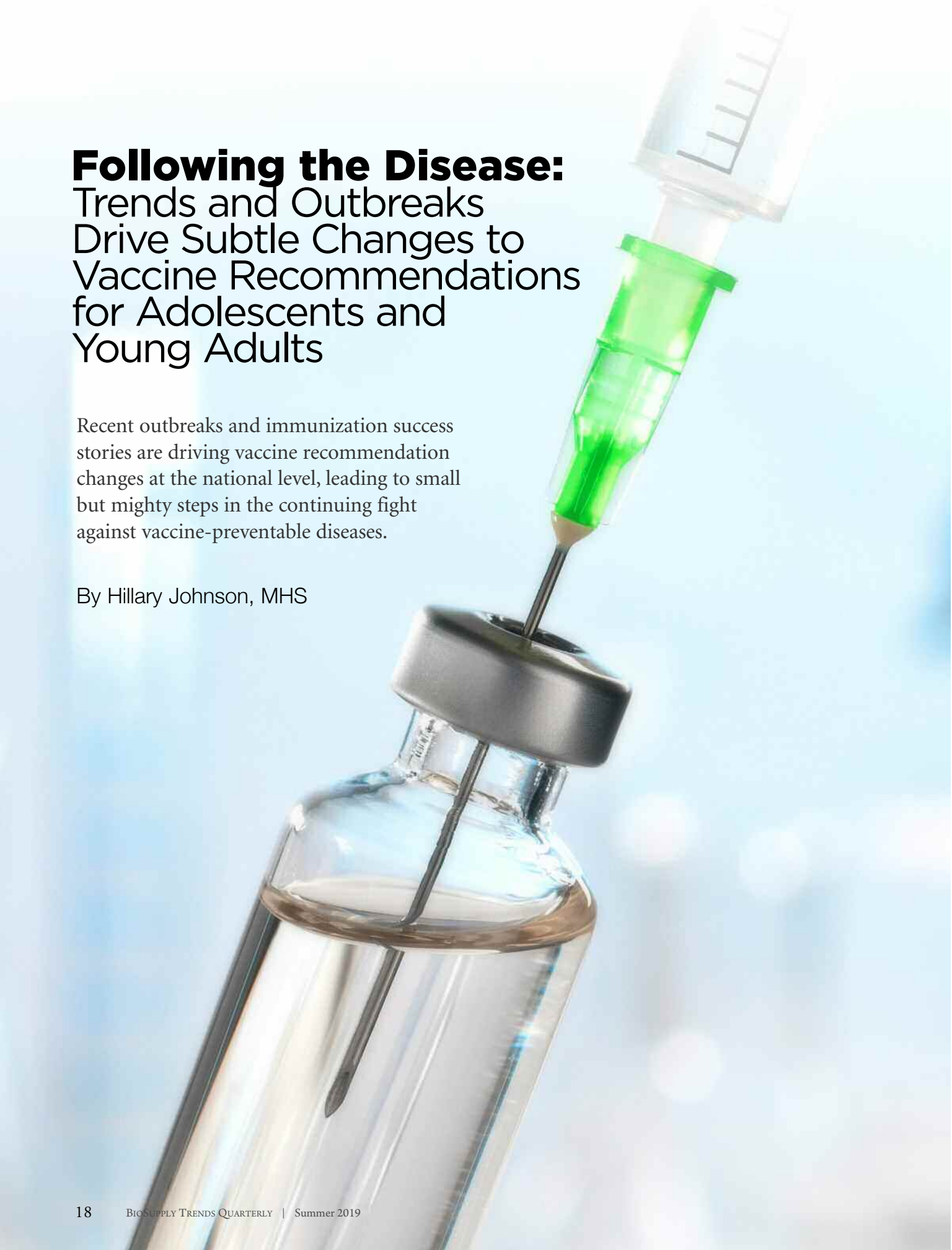
Following the Disease: Trends and Outbreaks Drive Subtle Changes to Vaccine Recommendations for Adolescents and Young Adults

Recent outbreaks and immunization success stories are driving vaccine recommendation changes at the national level, leading to small but mighty steps in the continuing fight against vaccine-preventable diseases.

By Hillary Johnson, MHS



EACH YEAR, THE Advisory Committee on Immunization Practices (ACIP) develops and updates recommendations on the use of vaccines in U.S. civilians, ultimately informing and providing the Centers for Disease Control and Prevention's (CDC) public health guidance for the safe use of vaccines. ACIP is composed of medical and public health experts, and its work sets the official routine vaccination schedule for children and adults. Some years, the updates are dramatic (such as adding an entirely new vaccine for a previously unaddressed disease), and sometimes the updates are more targeted (such as adjusting a recommended age range or the wording of a vaccine recommendation's footnote). In all cases, the committee relies on medical research and surveillance data to inform its decisions.

Recent trends in diseases among adolescents and young adults have fueled some subtle yet significant updates to the vaccine schedule. Many updates have been outbreak-driven, particularly among college campuses (such as the cases of mumps and meningococcal disease). Others reflect vaccine improvements and innovations (HPV and influenza prevention). All are critical in the fight to improve the health of U.S. citizens.

Universities and Mumps: A Major Interruption

Measles has dominated the national headlines due to various outbreaks in 2019. Most prolific has been the outbreak in Washington state, but an additional 11 states have also contributed to the 228 measles cases reported to CDC by the first week of March. And, while these trends are alarming, particularly as measles was declared eliminated in the U.S. in 2000, spikes in measles cases have not spurred much change or updates to standard vaccination recommendations; the best protection against measles remains two doses of the measles-mumps-rubella (MMR, Merck) vaccine. Not surprisingly, for the measles outbreaks mentioned above, most cases have occurred in largely unvaccinated populations.

It is the resurgence in mumps cases and outbreaks beginning in 2015 and 2016 that has caused ACIP to review available vaccine and morbidity data and to determine a third dose of the MMR vaccine is safe and effective and may be applicable for preventing additional disease.

From January 2016 to June 2017, U.S. health departments reported 150 outbreaks and more than 9,200 cases of mumps.[1] Fifty percent of the outbreaks (defined as three or more cases linked by place and time) occurred in university settings.[2] Two large outbreaks from the University of Iowa and University of Illinois at Urbana-Champaign (UIUC) each involved several hundred university students, and even elite settings like Harvard University did not go unscathed, with officials reporting 66 confirmed cases in the spring of 2016, with additional cases continuing the following school year.[3]

What makes these mumps outbreaks notable is, contrary to what we are seeing in most measles outbreaks in which cases largely occur in unvaccinated pockets, these outbreaks are occurring despite high two-dose coverage. (UIUC vaccination records showed two-dose MMR vaccination coverage at greater than 97 percent of its student body.[4] University of Iowa reported 98.1 percent.[5])

What makes these mumps outbreaks notable is, contrary to what we are seeing in most measles outbreaks in which cases largely occur in unvaccinated pockets, these outbreaks are occurring despite high two-dose coverage.

How is this possible? There is no single answer. Mumps is spread through close contact like kissing and sharing drinks, utensils, water bottles or lip balm, and spreads particularly easily in close congregate settings such as dormitories or among members

Mumps Control Is Challenging for College Students

Mumps can be quite isolating for college students since symptomatic individuals must be segregated for an additional five days after the onset of their parotid swelling. This means no classes, activities or cafeteria meals — a particular challenge in settings with close contact such as college dormitories. While the current two-dose measles-mumps-rubella (MMR) recommendation seems adequate for general populations, it is insufficient for mumps control in prolonged, close-contact settings, even where two doses of MMR vaccine is high.[2]

of the same sports team, making universities ripe for mumps transmission. Cases can be infectious up to two days before classic symptoms (swelling of the parotid glands) begin, and the incubation period is quite long — up to 25 days — enabling considerable viral transmission among individuals in close quarters before actual cases are identified and confirmed.

From January 2013 to May 2018, seven states reported a combined total of 10 university-based meningococcal disease outbreaks, all caused by serogroup B, resulting in 39 cases and two deaths.

Additionally, all things are not equal within the MMR vaccine, and while the measles vaccine component boasts a high efficacy at 97 percent for two doses,[6] the mumps component is estimated at 78 percent effective with one dose and 88 percent effective after two doses for preventing mumps.[7] Studies also show possible waning immunity to mumps as more time passes postvaccination.[8]

Throughout 2017, ACIP reviewed summaries of evidence regarding mumps epidemiology, MMR vaccine effectiveness, duration of protection, immunogenicity and safety for two and three doses, and in October 2017, following a period of public comment, ACIP members unanimously approved a proposed recommendation for a third dose of vaccine during mumps outbreaks. It concluded a third dose provided at least short-term benefit in outbreak settings, with no serious adverse events and benefits outweighing the small risk of vaccine-associated adverse events. Its January 2018 guidance states: "Persons previously vaccinated with two doses of a mumps virus-containing vaccine who are identified by public health authorities as being part of a group or population at increased risk for acquiring mumps because of an outbreak should receive a third dose of a mumps virus-containing vaccine to improve protection against mumps disease and related complications."[2]

Several universities have responded to outbreaks with MMR vaccination campaigns — providing evidence for at least three epidemiological studies on the use of a third dose of MMR vaccine in preventing mumps.[2] And, while data is insufficient at this time to fully characterize the impact of a third dose on reducing the size and duration of mumps outbreaks overall (all finding lower attack rates among third-dose recipients, but only one study showing a statistically significant risk ratio), studies are ongoing to address this question.

A 'Plan B' for Preventing Meningococcal Disease

While meningococcal disease is still relatively rare (372 cases reported in the U.S. in 2016), it can be quite devastating, with 10 percent to 15 percent of patients dying, and up to 20 percent of survivors sustaining lifelong disabilities such as arm or leg amputation, hearing loss or neurological damage.[9] Since 2005, ACIP has recommended adolescents receive routine quadrivalent meningococcal conjugate vaccine covering serogroups A, C, W and Y (MenACWY) for preventing meningococcal disease (adding a booster dose at age 16 in 2010). However, noticeably absent from the quadrivalent vaccine is serogroup B, the current predominant serogroup overall and now accounting for more than half of meningococcal disease cases among persons 16 years to 20 years of age.[10]

From January 2013 to May 2018, seven states reported a combined total of 10 university-based meningococcal disease outbreaks, all caused by serogroup B, resulting in 39 cases and two deaths.[10] Previously, CDC had maintained college students in general were not at a higher risk for serogroup B disease than non-college students of the same age.[11] That changed in 2014, when CDC implemented an enhanced meningococcal disease surveillance program, collecting more in-depth data (such as college status) and more routinely typing meningococcal isolates from patients.[12] CDC's enhanced findings now suggest that while the incidence of serogroup B meningococcal disease in college students remains low, college students age 18 years to 21 years are at increased risk compared to noncollege students.[11] (Enhanced findings continued to show no difference in incidence of serogroups C, W and Y among college and noncollege students, likely due to all adolescents routinely receiving MenACWY.[11])

Thankfully, the adolescent vaccine platform just got a little wider with the introduction of two brands of meningococcal serogroup B vaccine (MenB): Bexsero (GSK) and Trumenba (Pfizer).[13] These vaccines differ in formulation from the MenACWY vaccines since they are made of capsular proteins rather than MenACWY's capsular polysaccharides.

MenB vaccination may be the key to stopping college outbreaks, and it was used in response to all 10 of the serogroup B college outbreaks mentioned above. How much MenB vaccination helped in ending each outbreak has not yet been established. (Five of the 10 outbreaks ended following implementation of MenB vaccination with no new cases, but additional cases did occur at the other five universities. All cases occurred in unvaccinated

individuals except in one case, which occurred six days after MenB vaccination,[10] likely too early postvaccination to elicit a fully developed immune response in the individual.[14])

While there is clearly a specific need for MenB vaccination, larger questions remain. Such rare diseases make true vaccine effectiveness trials difficult, and instead licensure is based upon documented serum antibody response — the best measure available at estimating protection. There are also uncertainties regarding how long immunity lasts and when and how booster doses should be administered.[15] MenB vaccine does not appear to affect nasopharyngeal colonization, which is crucial for effective herd immunity.[16] Protection also comes at a financial cost. CDC estimates 15 to 29 cases and two to five deaths could be annually prevented with a routine adolescent MenB vaccine program, but those numbers price MenB at over 20 times greater than the cost for other routinely recommended vaccines (in terms of cost per quality-adjusted life years saved).[17]

Still, schools are recommending and in some cases even starting to require MenB. (Fourteen schools are noted to have documented MenB requirements via the Meningitis B Mandate Tracker.[18] Among them is Smith College, which was involved in a serogroup B outbreak in a Five College Consortium in 2017.) So, while at this time MenB vaccine has not been added to the routinely recommended vaccines for all adolescents, ACIP has made MenB a Category B recommendation, allowing for individuals 16 years to 23 years of age to be vaccinated with the MenB series based on individual clinical decision-making.

Luckily, another tool has emerged for helping to combat the spread of hepatitis B in young adults.

A New Vaccine for Hepatitis B

The U.S. Department of Health and Human Services (HHS) is reporting low rates of vaccination coverage among adults and increasing rates of injection drug use to be fueling a rise in hepatitis B virus (HBV) infections.[19]

And, while HBV transmission among people who inject drugs has always been a concern, the current national opioid epidemic has health officials worried. Massachusetts recently reported an outbreak of hepatitis B associated with injection drug use (noting 2017 acute hepatitis B cases were up 78 percent from 2016 in the state).[20] Similarly, Kentucky, Tennessee and West Virginia reported a 114 percent increase in acute HBV infection from 2006 to 2013, with a significant increase in the proportion of cases in which injection drug use was reported between 2010 and 2013.[21]

Despite a routine recommendation for hepatitis B vaccination at birth since the early 1990s,[22] data from the 2013 National Health Interview Survey found only 32.6 percent of adults between 19 years and 49 years were fully covered by a complete hepatitis B three-dose vaccine series.[23] CDC surveillance also indicated that in 2015, the acute hepatitis B infection rate in the U.S. increased by 20.7 percent.[24]

Luckily, another tool has emerged for helping to combat the spread of hepatitis B in young adults. In 2018, ACIP recommended

Hepatitis B Transmission

Hepatitis B can lead to chronic infection and liver cancer. It is particularly dangerous when passed perinatally from mother to child, where one-fourth of infected infants will eventually die from chronic liver disease.[32] While the U.S. has a strong perinatal hepatitis B prevention program, newly infected young women may not be aware of their status and may pass the virus on to their children, which is a growing concern for vulnerable adults with connections to the opioid epidemic.

What Is a Category B Recommendation?

Category B recommendations allow for individual clinical decision-making and were formerly referred to as "permissive" recommendations. In reference to the MenB (meningococcal B) vaccine, the Category B recommendation could be summarized by concluding there is not enough evidence to recommend "all" 16- to 18-year-olds receive a vaccine, but there is enough evidence to recommend the age group be given the choice to receive the vaccine, based upon individuals' own risk and their conversations with their doctors.

Heplisav-B (Dynavax), a yeast-derived vaccine prepared with a novel immunostimulatory sequence adjuvant, for use in persons 18 years and older. The vaccine joins the other two single antigen hepatitis B vaccines on the market available to adults, Engerix-B (GlaxoSmithKline) and Recombivax HB (Merck). Heplisav-B is notable for requiring only a two-dose series (Engerix-B and Recombivax HB each require three doses), making it an appealing option among young adults with connections to the opioid crisis; fewer required doses mean a greater likelihood of series completion, particularly among a population that might be less likely to engage in routine and preventive care.

Approval of Heplisav-B was based on clinical trials that compared seroprotection rates following two doses of Heplisav-B to rates following three doses of Engerix-B. Seroprotection rates were 90 percent to 95 percent following two doses of Heplisav-B and 65 percent to 81 percent following three doses of Engerix-B among people 18 years to 70 years old. Local reactions (injection site pain, redness and swelling) were similar in frequency to those following Engerix-B.[15]

HHS reports new cases of hepatitis B linked to injection drug use are particularly prevalent among adults age 30 years to 49 years who were not vaccinated as children.[19] Heplisav-B comes at a critical juncture as the nation examines the varied sequelae of the opioid epidemic, and it will hopefully serve as a useful tool in reducing outbreaks and spread of this harmful disease.

HPV Vaccine — An Immunization Success Story

HPV vaccine has very quickly evolved since ACIP's initial routine recommendation for HPV vaccination in girls age 11 years to 12 years in 2007. Since then, vaccine recommendations have also been made for boys (2011), and bivalent Cervarix (2vHPV, GlaxoSmithKline) and quadrivalent Gardasil (4vHPV, Merck) have ceased distribution in the United States, replaced by the more comprehensive Gardasil 9 (9vHPV, Merck). The inactivated 9-valent vaccine contains seven oncogenic (cancer-causing) HPV types (16, 18, 31, 33, 45, 52 and 58) and the two HPV types that cause most genital warts (6 and 11).

ACIP immunization recommendations represent the state of the science, and are constantly under review.

The U.S. Food and Drug Administration (FDA) origiinally licensed Gardasil 9 in 2014 for use in males and females age 9 years through 26 years, and notably approved expanded use of Gardasil 9 to include individuals 27 years through 45 years in October 2018.[25] This change has initiated discussions at ACIP for potentially updating age recommendation language, as well as harmonizing the recommendations that still differ for males and females (currently, females are recommended vaccine through age 26, males through age 21 unless at higher risk).[26] While harmonization for males and females may be an ACIP priority, many studies are showing HPV vaccination of adults becomes less cost-effective as the age of vaccination increases, due to the fact that older adults are likely already infected with HPV.[27] By age 31, 75 percent of women with cervical cancer have already acquired their "causal" HPV.[26]

Regardless of any imminent changes in response to the updated FDA approval, HPV vaccines continue to show excellent modeling for efficacy and safety, and are proving a potent preventive tool for reducing HPV infections and HPV-associated cancers in adolescents. So much so, data now shows early administration of HPV vaccine reduces the need for all three originally recommended doses.[28] Available immunogenicity evidence has shown a two-dose schedule (0, 6-12 months) will have efficacy equivalent to a three-dose schedule (0, 1-2 months, 6 months), assuming the HPV vaccination series is initiated before a child's 15th birthday.[29] In other words, the younger a child starts the vaccine series, the better his or her body responds and the more immunity developed (higher geometric mean titers measured). This data led ACIP in October 2016 to recommend a two-dose series for everyone who initiates the series at 9 years to 14 years.[28] (A three-dose series is still recommended for those initiating the series at 15 years through 26 years of age.)

Influenza Nasal Spray Makes a Comeback

Many are excited about next year's influenza (flu) vaccine options following a determination by the American Academy of Pediatrics (AAP) to discontinue its preference for the flu shot over nasal spray vaccine for the 2019-20 influenza season. This change comes after a rough couple of years for the nasal spray. Data from several individual U.S. studies had shown live attenuated influenza vaccine (LAIV) nasal spray had demonstrated poor effectiveness and offered less protection against A/H1N1 when compared to injected inactivated influenza vaccine (IIV) since the 2013-2014 season, causing ACIP and AAP to not recommend the nasal spray for the 2016-17 and 2017-18 seasons consecutively.[30] In response, LAIV manufacturer, AstraZeneca, reformulated the nasal spray to include a new strain (A/Slovenia) with the goal of producing a better antibody response to circulating A/H1N1 than with the previously utilized (A/Bolivia) strain.

LAIV was brought back to the market for the 2018-2019 season, although not without discord between AAP and ACIP, as

AAP stated a preference for use of the flu shot, indicating nasal spray should really be used only for children who would otherwise not receive a vaccine at all. ACIP did not express a preference between the two.

HPV vaccines continue to show excellent modeling for efficacy and safety, and are proving a potent preventive tool for reducing HPV infections and HPV-associated cancers in adolescents.

LAIV's reformulation seems to have worked in its favor, and following review of data from Europe showing LAIV has been effective against influenza A/H1N1 for children this season, AAP will not express a preference for either nasal spray or injectable vaccine for 2019-20.[31] ACIP will not make the final call on its flu recommendations until after this article is published, but it has stated it does not anticipate any major changes, meaning AAP and ACIP will likely have similar influenza vaccine recommendations this fall.

Somewhere, needle-adverse patients are cheering.

Small and Large, ACIP Recommendations Provide the Evidence-Based Tools to Help Guide Our Nation's Health

ACIP immunization recommendations represent the state of the science, and are constantly under review. Immunization successes can shift other diseases into focus, or help to highlight pockets of people at elevated risk and in need of additional considerations. Medical providers questioning appropriate vaccination in an outbreak setting should consult their local health department directly for the most up-to-date data in their area and official guidance on applicable vaccination recommendations. Together, medical providers and public health officials may be able to stop the next outbreak in its tracks. ❖

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Vaccinations for Seniors: Addressing Compliance

Several challenges promote a disconnect between preventive vaccines and compliance in older adults.

By Amy Scanlin, MS

IMMUNIZATION SCHEDULES for children are well-communicated, well-understood and, except for a small anti-vaccine contingent, largely adopted with more than 90 percent[1] of parents seeking to protect their children from vaccine-preventable diseases. On the opposite end of the age spectrum, however, adherence rates for seniors to their recommended vaccine schedule are significantly lower, causing concern not just due to the increased health risks for this older population, but for the potential health risks silent carriers pass on to others in their communities.

While some vaccines wear off over time, requiring boosters throughout life (tetanus, diphtheria and pertussis are three examples), others such as the shingles and pneumococcal vaccines are unique to the senior community with first administration given later in life. And, while with increasing age, immunosenescence causes vaccines to be less effective, they remain vital for reducing risk and severity of vaccine-preventable diseases. In fact, vaccinations are second only to clean water at improving health and quality of life, making compliance key. More than an individual responsibility, vaccines' positive herd immunity makes them a civic responsibility.

Vaccine Noncompliance in an Aging Population

As the population ages, the number of people over 60 years of age is expected to double, reaching 2.1 billion by 2050. Additionally, the population of those age 80 and older is expected to increase by 309 million between the years 2015 and 2050.[2] Advances in healthcare and self-care have improved mortality and morbidity; however, without improved preventive strategies that vaccinations provide, the implications for older adults is staggering.

Cases in point: Approximately 36,000 people in the U.S. die of influenza (flu) annually, and 100,000 are hospitalized. Most of these are seniors. Over half of the viral reactivation of varicella zoster virus occurs in adults over 85 years old.[2] And, while invasive pneumococcal disease affects the young and old, community-acquired pneumonia mainly affects older adults. According to the National Foundation of Infectious Diseases, about one million U.S. adults get pneumococcal pneumonia every year, and tens of thousands die. About 18,000 of those deaths are adults age 65 and older.[3] Lastly, tetanus and diphtheria antibody levels are lower than that considered to be protective for most adults, and this is particularly true for seniors.[2]

These numbers equate to exorbitant healthcare costs, according to the Alliance for Aging Research's *Silver Book* statistics. Shingles, for example, costs patients $1 billion in direct and indirect medical expenses. More than half of hospitalizations and 65 percent of the economic burden of flu complications is attributed to those 65 years and older. And, Medicare patients who contract pneumonia can expect medical expenses nearly $16,000 higher during their illness and the year after than Medicare patients who do not contract the disease.[4]

Vaccines have proven to be effective and safe for the senior population. Even considering years when the flu vaccine is a mismatch to the predominate strain, the vaccine is considered largely safe, and even when it is not as efficacious, it is still beneficial. A flu vaccine can reduce the risk of illness by as much as 60 percent. The shingles vaccine, Shingrix, protects as many as 97 percent of people in their 50s and 60s, and as many as 91 percent of those in their 70s and 80s. A Tdap vaccine is effective in seven out of 10 patients in its first year. And, the pneumococcal conjugate vaccine is estimated to have prevented more than 30,000 cases of invasive pneumococcal disease and 3,000 deaths in its first three years of use.[5]

So, why the disconnect between these very effective and simple interventions and compliance in this vulnerable age group? While vaccination rates for infants and children have risen, the same cannot be said for seniors. By some estimates, one-third of older adults skip getting a flu vaccine, three quarters of seniors choose not to receive a shingles vaccination, and just under half do not get vaccinated for pneumonia or tetanus. This is in stark contrast to goals set by the Centers for Disease Control and Prevention, which is aiming for a 90 percent compliance rate for the flu vaccine by 2020.[1]

Three challenges in particular plague progress of increasing vaccination compliance rates in the elderly:

- Varying degrees of vaccine effectiveness, particularly due to changes in immunity as one ages
- Noncommunication about which vaccines are recommended and when they are due
- Insurance coverage confusion, particularly for vaccines that fall under Medicare Part D

Challenge 1: Age-Related Immunity

With aging comes the inevitable changes to the immune system, making seniors more susceptible to a host of medical conditions, including vaccine-preventable communicable diseases. While this immune system decline can be observed in a laboratory, scientists are actively trying to understand how to apply that information so patients better understand their health index. "It is the next frontier of immunology research," shares E. John Wherry, PhD, chair of the department of systems pharmacology and translational therapeutics at the Perelman School of Medicine at the University of Pennsylvania.

Why the disconnect between these very effective and simple interventions and compliance in this vulnerable age group?

Unfortunately, this decreased immunity also means reduced impact of vaccines since studies show antibodies after vaccinations are lower in seniors. "There is a lot of attention being paid to different formulations which enhance a vaccine's strength and potency," says Dr. Wherry. By altering a vaccine's formulation, it is hoped to better stimulate the immune system. One such example is the theory of original antigenic sin now being studied in flu vaccines. Original antigenic sin hypothesizes past exposure to flu strains throughout life impacts response to flu vaccines in the future. Studies are now looking at how information of past exposure can be captured and used for the benefit of future vaccinations.

While most vaccines are nearly 100 percent effective, some are not, including the flu and pneumococcal vaccines. However, there are some options showing promise for seniors, including a high-dose flu vaccine, which has been approved for use in the U.S. since 2009 for those over 65 years old. The high-dose vaccine contains four times the amount of antigen as a regular flu shot, and results from a clinical trial of more than 30,000 participants showed adults 65 years and older who received the high-dose vaccine had 24 percent fewer flu infections compared to those who received the standard-dose flu vaccine.[6]

In addition, the use of adjuvants, alternate routes of administration such as nasal sprays, and live versus inactivated vaccines are being considered. At least one study has demonstrated an adjuvanted vaccine can lower the risk of hospitalizations for flu or pneumonia symptoms by 25 percent in seniors. And, inactivated vaccines are not only potentially safer and more effective for older adults, they are also safer for immunocompromised patients for whom a live attenuated vaccine is contraindicated.[2]

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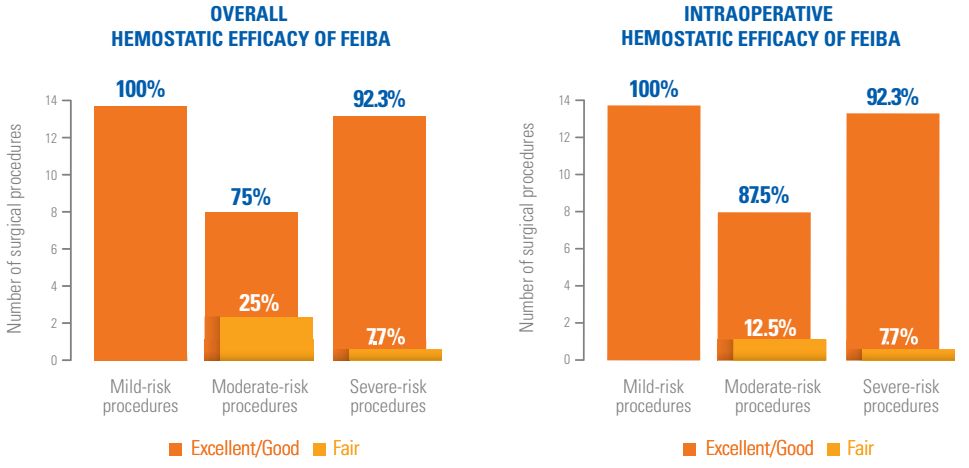
FEIBA effectively maintained bleed control perioperatively[2]



91% Overall efficacy was rated as excellent or good for 91% of surgical procedures (n=34)[2]

94% Intraoperative efficacy was rated as excellent or good for 94% of surgical procedures (n=34)[2]

ADVERSE EVENTS IN THE STUDY

Treatment-Related: 1 serious AE, a case of a clot in an arteriovenous fistula, occurred during a moderate-risk surgery; 1 nonserious AE, a case of postoperative anemia, occurred after a severe-risk surgery[2]
Not Treatment-Related: 2 serious AEs; 1 case of anemia and 1 case of hemarthrosis; each occurred during severe-risk surgeries[2]

STUDY DESIGN

The SURgical Interventions with FEIBA (SURF) study was an open-label, prospective, non-interventional, observational, post-authorization study, specifically designed to clinically evaluate the perioperative use of FEIBA and accumulate a database of experience with perioperative FEIBA treatment that can be used to identify best practices in the surgical hemostatic management of hemophilia patients with inhibitors. This study evaluated outcomes for 35 surgical procedures in 24 patients. Of the surgeries performed, the risk level was considered severe for 13 procedures, moderate for 9 procedures, and mild for 13 procedures. The SURgical interventions with FEIBA (SURF) study, hemostatic efficacy was defined as follows: **Excellent** = hemostatic expectations were met or exceeded in light of previous experience with bypassing agents **Good** = efficacy was "somewhat less than expected" but still adequate compared with previous bypassing therapy **Fair** = hemostasis was significantly less than expected compared with previous bypassing therapy.[2]

FEIBA
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FEIBA [Anti-Inhibitor Coagulant Complex] Indications and Detailed Important Risk Information

FEIBA is an Anti-Inhibitor Coagulant Complex indicated for use in hemophilia A and B patients with inhibitors for:

- Control and prevention of bleeding episodes
- Perioperative management
- Routine prophylaxis to prevent or reduce the frequency of bleeding episodes.

FEIBA is not indicated for the treatment of bleeding episodes resulting from coagulation factor deficiencies in the absence of inhibitors to coagulation factor VIII or coagulation factor IX.

Detailed Important Risk Information for FEIBA

WARNING: EMBOLIC AND THROMBOTIC EVENTS

- **Thromboembolic events have been reported during post-marketing surveillance following infusion of FEIBA, particularly following the administration of high doses (above 200 units per kg per day) and/or in patients with thrombotic risk factors.**
- **Monitor patients receiving FEIBA for signs and symptoms of thromboembolic events.**

CONTRAINDICATIONS

FEIBA is contraindicated in patients with:

- History of anaphylactic or severe hypersensitivity reactions to FEIBA or any of its components, including factors of the kinin generating system
- Disseminated intravascular coagulation (DIC)
- Acute thrombosis or embolism (including myocardial infarction)

WARNINGS AND PRECAUTIONS

Thromboembolic events (including venous thrombosis, pulmonary embolism, myocardial infarction, and stroke) can occur, particularly following the administration of high doses (>200 units/kg/day) and/or in patients with thrombotic risk factors.

Patients with DIC, advanced atherosclerotic disease, crush injury, septicemia, or concomitant treatment with recombinant factor VIIa have an increased risk of developing thrombotic events due to circulating tissue factor or predisposing coagulopathy. Potential benefit of treatment should be weighed against potential risk of these thromboembolic events.

Infusion should not exceed a single dose of 100 units/kg and daily doses of 200 units/kg. Maximum injection or infusion rate must not exceed 2 units/kg/minute. Monitor patients receiving >100 units/kg for the development of DIC, acute coronary ischemia and signs and symptoms of other thromboembolic events. If clinical signs or symptoms occur, such as chest pain or pressure, shortness of breath, altered consciousness, vision, or speech, limb or abdomen swelling and/or pain, discontinue FEIBA and initiate appropriate diagnostic and therapeutic measures.

WARNINGS AND PRECAUTIONS (continued)

Safety and efficacy of FEIBA for breakthrough bleeding in patients receiving emicizumab has not been established. Cases of thrombotic microangiopathy (TMA) were reported in a clinical trial where subjects received FEIBA as part of a treatment regimen for breakthrough bleeding following emicizumab treatment. Consider the benefits and risks with FEIBA if considered required for patients receiving emicizumab prophylaxis. If treatment with FEIBA is required for patients receiving emicizumab, the hemophilia treating physician should closely monitor for signs and symptoms of TMA. In FEIBA clinical studies TMA has not been reported.

Hypersensitivity and allergic reactions, including severe anaphylactoid reactions, can occur. Symptoms include urticaria, angioedema, gastrointestinal manifestations, bronchospasm, and hypotension. Reactions can be severe and systemic (e.g., anaphylaxis with urticaria and angioedema, bronchospasm, and circulatory shock). Other infusion reactions, such as chills, pyrexia, and hypertension have also been reported. If signs and symptoms of severe allergic reactions occur, immediately discontinue FEIBA and provide appropriate supportive care.

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

FEIBA contains blood group isohemagglutinins (anti-A and anti-B). Passive transmission of antibodies to erythrocyte antigens, e.g., A, B, D, may interfere with some serological tests for red cell antibodies, such as antiglobulin test (Coombs test).

ADVERSE REACTIONS

Most frequently reported adverse reactions observed in >5% of subjects in the prophylaxis trial were anemia, diarrhea, hemarthrosis, hepatitis B surface antibody positive, nausea, and vomiting.

Serious adverse reactions seen are hypersensitivity reactions and thromboembolic events, including stroke, pulmonary embolism and deep vein thrombosis.

DRUG INTERACTIONS

Consider possibility of thrombotic events when systemic antifibrinolytics such as tranexamic acid and aminocaproic acid are used with FEIBA. No adequate and well-controlled studies of combined or sequential use of FEIBA and recombinant factor VIIa, antifibrinolytics, or emicizumab, have been conducted. Use of antifibrinolytics within approximately 6 to 12 hours after FEIBA is not recommended.

Clinical experience from an emicizumab clinical trial suggests that a potential drug interaction may exist with emicizumab.

Please see FEIBA Brief Summary of full Prescribing Information on following page.

References: 1. FEIBA Prescribing Information. **2.** Négrier C, Lienhart A, Numerof R, et al. SURgical interventions with FEIBA (SURF): international registry of surgery in haemophilia patients with inhibitory antibodies. *Haemophilia.* 2013;19:e143-e150. **3.** Rota M, Cortesi PA, Crea R, Gringeri A, Mantovani LG. Thromboembolic event rate in patients exposed to anti-inhibitor coagulant complex: a meta-analysis of 40-year published data. *Blood Adv.* 2017;1(26):2637-2642.

Takeda

FEIBA (anti-inhibitor coagulant complex)

for intravenous use, lyophilized powder for solution

Brief Summary of Prescribing Information: Please see package insert for Full Prescribing Information

WARNING: EMBOLIC AND THROMBOTIC EVENTS

- **Thromboembolic events have been reported during post-marketing surveillance following infusion of FEIBA, particularly following the administration of high doses and/or in patients with thrombotic risk factors.**
- **Monitor patients receiving FEIBA for signs and symptoms of thromboembolic events.**

INDICATIONS AND USAGE

FEIBA is an Anti-Inhibitor Coagulant Complex indicated for use in hemophilia A and B patients with inhibitors for:

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- Perioperative management
- Routine prophylaxis to prevent or reduce the frequency of bleeding episodes.

FEIBA is not indicated for the treatment of bleeding episodes resulting from coagulation factor deficiencies in the absence of inhibitors to coagulation factor VIII or coagulation factor IX.

CONTRAINDICATIONS

- Known anaphylactic or severe hypersensitivity reactions to FEIBA or any if its components, including factors of the kinin generating system.
- Disseminated intravascular coagulation (DIC).
- Acute thrombosis or embolism (including myocardial infarction).

WARNINGS AND PRECAUTIONS

Embolic and Thrombotic Events

Thromboembolic events (including venous thrombosis, pulmonary embolism, myocardial infarction, and stroke) can occur with FEIBA, particularly following the administration of high doses (above 200 units per kg per day) and/or in patients with thrombotic risk factors [see *Adverse Reactions*].

Patients with DIC, advanced atherosclerotic disease, crush injury, septicemia, or concomitant treatment with recombinant factor VIIa have an increased risk of developing thrombotic events due to circulating tissue factor or predisposing coagulopathy. Potential benefit of treatment with FEIBA should be weighed against the potential risk of these thromboembolic events.

Monitor patients receiving more than 100 units per kg of body weight of FEIBA for the development of DIC, acute coronary ischemia and signs and symptoms of other thromboembolic events. If clinical signs or symptoms occur, such as chest pain or pressure, shortness of breath, altered consciousness, vision, or speech, limb or abdomen swelling and/or pain, discontinue the infusion and initiate appropriate diagnostic and therapeutic measures.

The safety and efficacy of FEIBA for breakthrough bleeding in patients receiving emicizumab has not been established. Cases of thrombotic microangiopathy (TMA) were reported in a clinical trial where subjects received FEIBA as part of a treatment regimen for breakthrough bleeding following treatment with emicizumab. Consider the benefits and risks with FEIBA if considered required for patients receiving emicizumab prophylaxis. If treatment with FEIBA is required for patients receiving emicizumab, the hemophilia treating physician should closely monitor for signs and symptoms of TMA. In FEIBA clinical studies thrombotic microangiopathy (TMA) has not been reported.

Hypersensitivity Reactions

Hypersensitivity and allergic reactions, including severe anaphylactoid reactions, can occur following the infusion of FEIBA. The symptoms include urticaria, angioedema, gastrointestinal manifestations, bronchospasm, and hypotension. These reactions can be severe and systemic (e.g., anaphylaxis with urticaria and angioedema, bronchospasm, and circulatory shock). Other infusion reactions, such as chills, pyrexia, and hypertension have also been reported. If signs and symptoms of severe allergic reactions occur, immediately discontinue administration of FEIBA and provide appropriate supportive care.

Transmission of Infectious Agents

Because FEIBA is made from human plasma it may carry a risk of transmitting infectious agents, e.g., viruses, and the variant Creutzfeldt-Jakob disease (vCJD) agent, and theoretically, the Creutzfeldt-Jakob disease (CJD) agent. The risk has been minimized by screening plasma donors for prior exposure to certain viruses, by testing for the presence of certain current virus infections and by inactivating and removing certain viruses during the manufacturing process [see *Description* in full prescribing information]. Despite these measures, the product may still potentially transmit human pathogenic agents. There is also the possibility that unknown infectious agents may still be present.

All infections thought by a physician to have been possibly transmitted by this product should be reported by the physician or other healthcare providers to Baxalta US Inc., at 1-800-423-2090 (in the U.S.) and /or to FDA Med Watch (1-800-FDA-1088 or www.fda.gov/medwatch).

Presence of Isohemagglutinins and Interference with Laboratory Tests

FEIBA contains blood group isohemagglutinins (anti-A and anti-B). Passive transmission of antibodies to erythrocyte antigens, e.g., A, B, D, may interfere with some serological tests for red cell antibodies, such as antiglobulin test (Coombs test).

ADVERSE REACTIONS

The most frequently reported adverse reactions observed in >5% of subjects in the prophylaxis trial were anemia, diarrhea, hemarthrosis, hepatitis B surface antibody positive, nausea, and vomiting.

The serious adverse reactions seen with FEIBA are hypersensitivity reactions and thromboembolic events, including stroke, pulmonary embolism and deep vein thrombosis.

Clinical Trials Experience

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

The safety assessment of FEIBA is based on the review of the data from two prospective clinical trials in which FEIBA was used for the treatment of acute bleeding episodes and a prospective trial that compared the use of FEIBA prophylactically versus on-demand treatment.

The adverse reactions reported from two prospective clinical trials in which FEIBA was used for the treatment of acute bleeding episodes were chills, chest pain, chest discomfort, dizziness, dysgeusia, dyspnea, hypoesthesia, increase of inhibitor titer (anamnestic response), nausea, pyrexia, and somnolence. Specifically, the first trial was a multicenter randomized, double-blind trial in 15 hemophilia A subjects with inhibitors to factors VIII. The second trial was a multicenter FEIBA study conducted in 44 hemophilia A subjects with inhibitors, 3 hemophilia B subjects with inhibitors and 2 acquired factor VIII inhibitor subjects. Of the 489 infusions used to treat acute bleeds during the second trial, 18 (3.7%) caused minor transient reactions of chills, fever, nausea, dizziness and dysgeusia. Out of 49 subjects, 10 (20%) had a rise in their inhibitor titers after treatment with FEIBA. Five of these subjects (50%) had increases that were, tenfold or more, and 3 (30%) of these subjects received factor VIII or IX concentrates within 2 weeks prior to treatment with FEIBA. These anamnestic rises were not associated with decreased efficacy of FEIBA.

Table 1 lists the adverse reactions in >5% of subject reported in the randomized, prospective prophylaxis trial comparing FEIBA prophylaxis with on-demand treatment in 36 hemophilia A and B subjects with inhibitors to factors VIII or IX. The trial population included 33 (92%) subjects with hemophilia A and 3 (8.3%) subjects with hemophilia B. Four (11%) subjects were ≥7 to <12 years of age, 5 (14%) were ≥12 to <16 years of age, and 27 (75%) were ≥16 years of age. A total of 29 (80.6%) subjects were Caucasian, 3 (8.3%) Asian, 2 (5.6%) Black/African American, and 2 (5.6%) other. The subjects received a total of 4,513 infusions (3,131 for prophylaxis and 1,382 for on-demand).

Table 1 Prophylaxis Study Adverse Reactions (ARs) in >5% of Subjects

MedDRA System Organ Class	Adverse Reaction	Number of ARs	Number of Subjects	Percent of Subjects (N=36)
Blood And Lymphatic System Disorders	Anemia	2	2	5.6
Gastrointestinal Disorders	Diarrhea	2	2	5.6
	Nausea	2	2	5.6
	Vomiting	2	2	5.6
Investigations	Hepatitis B Surface Antibody Positive	4	4	11.1
Musculoskeletal And Connective Tissue Disorders	Hemarthrosis	5	3	8.3

Postmarketing Experience

The following adverse reactions have been identified during post-approval use of FEIBA. Because post-marketing reporting of adverse reactions is voluntarily and from a population of uncertain size, it is not always possible to reliably estimate the frequency of these reactions or establish a causal relationship to product exposure.

Blood and Lymphatic System Disorders: disseminated intravascular coagulation

Cardiac Disorders: tachycardia, flushing

Respiratory, Thoracic, and Mediastinal Disorders: bronchospasm, wheezing

Gastrointestinal Disorders: abdominal discomfort

Skin and Subcutaneous Tissue Disorders: pruritus

General Disorders and Administration Site Conditions: malaise, feeling hot, injection site pain

DRUG INTERACTIONS

Concomitant Medications

Consider the possibility of thrombotic events when systemic antifibrinolytics such as tranexamic acid and aminocaproic acid are used during treatment with FEIBA. No adequate and well-controlled studies of the combined or sequential use of FEIBA and recombinant factor VIIa antifibrinolytics, or emicizumab have been conducted. Use of antifibrinolytics within approximately 6 to 12 hours after the administration of FEIBA is not recommended.

Clinical experience from an emicizumab clinical trial suggests that a potential drug interaction may exist with emicizumab when FEIBA was used as part of a treatment regimen for breakthrough bleeding (see *Warnings and Precautions* above; see also Oldenburg et al. Emicizumab Prophylaxis in Hemophilia A with Inhibitors. *N Engl J Med* 2017:377:809-818).

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Challenge 2: What and When?

The second challenge to senior vaccine compliance is simply understanding which vaccines are needed and when, particularly when a booster is required. Healthcare settings experience good results with increasing frontline communications via nurses and medical assistants. One example is a University of Pittsburgh practice that saw a 40 percent improvement in vaccination rates by placing more emphasis on vaccines with this group. Another example, Mercy Care Alliance in Massachusetts, is having good results with identifying those for whom vaccinations are due using scans of electronic health records. It was able to identify 1,000 seniors who were due for the pneumococcal vaccine and facilitated outreach to those in need.[1]

"Interestingly, the anti-vax movement does not seem to have influenced older adult attitudes," says Susan Peschin, MHS, president and CEO of the Alliance for Aging Research. "In fact, a 2016 Pew Research Center survey showed 90 percent of adults ages 65 and older support a requirement that children be vaccinated against measles, mumps and rubella before they could be enrolled in school, compared to just 8 percent who said that parents should be able to decide whether or not to vaccinate their child — the lowest percentage of any age group."

The Alliance for Aging Research believes older adults can play an influential role in increasing the immunity of their family members and social circles, particularly those who are vulnerable to infectious disease or who are too young to receive vaccinations themselves, by making sure their own vaccinations are up-to-date. They can also inject a dose of reality into the myth-driven debates around vaccines and lead their families by example.

It may also be effective to help seniors understand the very low cost of a vaccination compared to the potentially high costs of illness. For instance, it is estimated every dollar spent on vaccinations saves at least $18.40 in direct and indirect healthcare costs. The flu vaccine alone could save anywhere from $50 to $4,000 in prevention, and immunocompetent adults age 60 and older could save as much as $82 million to $103 million in healthcare costs by receiving a vaccine.[4]

Challenge 3: Insurance Confusion

Thankfully, private insurers are required by the Affordable Care Act to cover 100 percent of the cost for preventive vaccines. However, Medicare beneficiaries encounter cost-sharing for certain vaccines due to the lack of consistent coverage under Medicare Part D drug plans. Of the recommended vaccines for older populations, only flu and pneumococcal are included at no cost to patients under Medicare Part B. And, while Medicare Part D covers the cost of additional vaccines, including shingles and Tdap, there are generally co-pays. "Under Part D, nearly 24 million beneficiaries in stand-alone prescription drug plans are subject to cost-sharing requirements ranging from $14 to $103 per vaccine," said Peschin. "Consequently, the higher the cost-sharing, the more likely it is that the beneficiary will not elect to receive the vaccine. As more vaccines reach the market, Part D cost-sharing will pose an increasing burden on Medicare beneficiaries seeking this important preventive medical care."

With aging comes the inevitable changes to the immune system, making seniors more susceptible to a host of medical conditions, including vaccine-preventable communicable diseases.

More Work Is Needed

Clearly there is work to be done, from improving outcomes for older populations through new vaccine interventions and delivery, to helping seniors understand the benefits and timing of these potentially lifesaving interventions. Currently, 137 vaccines are being studied, according to the Alliance for Aging Research, with some of these studies focusing on improving outcomes for seniors. Researchers are also investigating how aging and chronic disease impacts the immune system so better vaccines that work optimally in older adults can be developed. Above all, says Dr. Wherry, as progress continues, the ability to quantify and define a person's immune health will be of immeasurable benefit in the future.

August is National Immunization Awareness Month, offering an open opportunity to plan for and execute new initiatives that enhance communication with senior patients, helping them to increase their understanding and ownership of this crucial line of defense. ❖

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Update on **Conventional vs. DNA Vaccines**

New vaccine technology may one day help to prevent diseases, as well as treat cancer, once challenges are overcome.

By Jim Trageser

WIDESPREAD IMMUNIZATION is perhaps the greatest technological achievement of the 20th century. More than powered flight, telecommunications, the adoption of electrical power grids or the computer revolution, the use of vaccines to largely eradicate dozens of diseases that formerly ravaged cities and nations improved more human lives than any other single innovation — perhaps even more than all the above developments combined.

Smallpox, yellow fever, pertussis, measles, polio, cholera, typhoid fever, encephalitis and meningitis are diseases that once caused epidemics that today are nearly unknown in developed nations due to the introduction of vaccines (although measles has shown a resurgence in outbreaks largely due to the antivaccine movement). Individuals are also now routinely inoculated against less deadly but still costly diseases such as chickenpox and mumps.

Somewhat amazingly, the basic medical underpinnings of vaccines haven't changed since the first vaccine was discovered in 1796, when Edward Jenner exposed a young boy to deadly cowpox, and then demonstrated the boy had developed an immunity to the far more deadlier smallpox. Since then, every developed vaccine has stimulated the body to produce protective antibodies by introducing a dead virus or bacteria, a weakened (attenuated) virus or bacteria, or a closely related but less dangerous virus or bacteria (e.g., cowpox to provide protection against smallpox).

New technology, though, promises a more fine-tuned approach — one that is more consistent in provoking immunity while also potentially less expensive to produce and easier to speed production in case of a future outbreak.[1] This new "DNA vaccine" technology has also shown some early promise in helping the body fight some cancers. To date, however, the only DNA vaccine approved is a veterinary vaccine for West Nile virus in horses.[2] No human vaccines are yet approved for use.

The Development of Vaccines

It was known even in antiquity that survivors of smallpox gained immunity to further infections of the disease. The first inoculations involved swabbing the tip of a lancet on a pustule of an infected patient and then piercing the skin of an uninfected person. It was highly unsanitary, and it often resulted in secondary infections such as tuberculosis or syphilis. But it also worked, with a much lower fatality rate than a regular case of smallpox, and those who survived the inoculation didn't have to fear contracting it again.

When the wife of the British ambassador to Turkey saw how the Turks inoculated their children by this method in 1718, she had her own children treated, and she demanded the British government adopt a similar program. This practice, known as variolation, remained the standard preventive for smallpox until Edward Jenner's use of cowpox six decades later.

While Jenner was far from the first to realize exposure to cowpox granted immunity to smallpox (it was common knowledge in dairy-producing regions of Europe), he was the first to devote himself to promoting the use of cowpox as a widespread vaccine to prevent smallpox. His efforts resulted not only in formal vaccination programs in Britain and Europe, but in the United States as well, where President Thomas Jefferson was persuaded by one of Jenner's associates to start the National Vaccine Institute after his own family and neighbors were successfully vaccinated.[3]

How Traditional Vaccines Work

While doctors knew an initial infection generally granted immunity to further infections of the same disease (not just for smallpox, but also chickenpox, mumps and other common diseases), they didn't understand why. It was only in the 20th century when physicians and researchers discovered how vaccines stimulated immunity in the body, and those discoveries led to new ways of inoculating against infectious diseases.

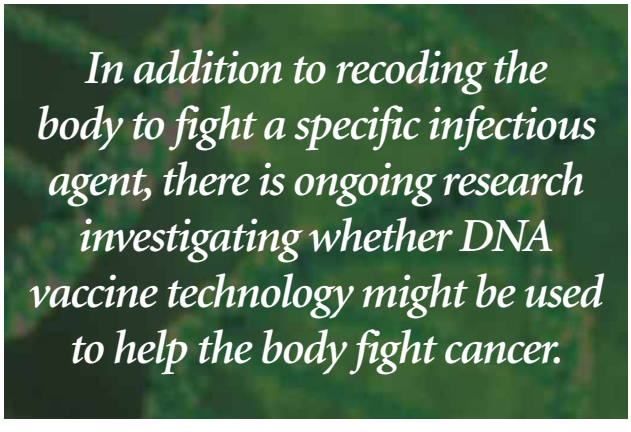
When a hostile microbe (virus, bacteria or fungus) invades the body, it is met by specialized white blood cells called macrophages that will attack any cell that doesn't have the same surface markers as all the other cells produced by the body. But, after destroying the invading microbe, the macrophage preserves a portion of its membrane and takes it to the lymph nodes, where the body begins churning out millions of immune cells to go look for that specific pattern of marker (also known as an antigen).[4] These antibodies have an interlocking molecular pattern on their surface, so when they find another microbe with the antigen that matches, they can latch on to it and prevent it from reproducing.

Somewhat amazingly, the basic medical underpinnings of vaccines haven't changed since the first vaccine was discovered in 1796.

During an initial infection for a specific disease, it can take the body a few days to ramp up its defenses and kill off the invaders. But, it keeps a supply of those specific antibodies on hand, and if a patient again comes into contact with that same bacteria or virus (or one with very similar antigens), it will overwhelm the invader before it has a chance to multiply.

Vaccines harness the body's own self-defense mechanisms to mimic that initial invasion and ramp up production of the antibodies to fight off that species of infection so when the patient is exposed, the body is ready to fight.[4] Most vaccines do this by introducing a weakened strain of the microbe in question, or by using dead microbes. Others such as the early smallpox vaccine use a closely related microbe that fools the body. Some vaccines use live-attenuated viruses such as those for chickenpox, yellow fever and rotavirus.[5] With live-attenuated vaccines, a patient often gets a mild case of the disease, but acquires the ability to fight off future infections. Other vaccines such as those for influenza (flu), hepatitis A and polio use a dead version of the virus. With these, there is no risk the patient will acquire an active infection, yet the body still produces the antibodies that will identify these microbes if they enter the body.

More recently, researchers have discovered they can stimulate the body's immune system with only a portion of the microbe — a specific protein or its capsid. These are safer for patients who have a compromised immune system, but often need periodic boosters to maintain immunity. Examples of these subunit, polysaccharide and conjugate vaccines are those for Haemophilus influenza type b (Hib), hepatitis B, meningitis, pertussis and human papillomavirus (HPV).[5]



How DNA Vaccines Work

The promising new approach of DNA vaccine involves injecting a small strand of bioengineered DNA that has been crafted into a circle, known as a plasmid, into a patient by one of several means. The cells that absorb this plasmid then follow the instructions of the DNA it contains and begin manufacturing that antigen and incorporating it into their cellular membrane, stimulating the body to produce antibodies to fight it. Researchers emphasize the plasmid does not enter the cell's nucleus or mingle with the cell's own DNA; instead, the DNA plasmid remains in the cell's cytoplasm.[6]

DNA vaccine technology helps to accelerate the immune system's ability to identify a hostile antigen and respond to it. However, early tests in the 1990s of this technology found too few cells absorbed the plasmids to sufficiently stimulate an immune response. Therefore, subsequent research has focused on new methods of getting the plasmids into cells in the body.[6] Some possible delivery systems being studied include encasing the plasmid in a live harmless bacterium and introducing it into the body, or using nanoparticles of a specific chemical makeup to increase the odds of them being absorbed into a cell.[7]

Researchers point out that once a plasmid has been created for one disease, repurposing it for another simply requires swapping out the genes that code the antigens.[8] In theory, for instance, this would allow effective vaccines to be produced for each seasonal strain of the flu. Rather than the current practice of trying to guess which flu strains will be most predominant and creating a vaccine months ahead of time, pharmaceutical companies could wait for the first outbreaks and then quickly manufacture a vaccine in a matter of weeks.

While DNA vaccine technology has not yet been approved for use in humans, clinical trials are under way. Studies on mice have found DNA vaccines are highly effective, but that success has not translated to larger mammals — mainly because of the failure of enough cells to absorb the DNA plasmids and construct the antigens.

DNA vs. Recombinant Vaccines

What can get a bit confusing is that vaccines using recombinant DNA have been on the market. But, recombinant DNA vaccines are a similar but distinct process. They are manufactured by introducing the DNA strand for creating an antigen into a bacterial or other nonhuman cell, allowing it to create the antigens, and then harvesting the antigens to use in the vaccine.[9] In other cases, the genetically altered bacteria with the antigen on its outer membrane can serve as the vaccine, thus mimicking the infectious microbe and provoking the body's immune system to produce antibodies.[10]

Other Uses for the Technology

In addition to recoding the body to fight a specific infectious agent, there is ongoing research investigating whether DNA vaccine technology might be used to help the body fight cancer. Since cancer cells mutate quickly, and often feature an antigen different from the body's own cellular membrane markers, it may be possible to use DNA vaccine technology to stimulate the body's immune system to more efficiently target and destroy malignant cells.[11]

Other researchers are investigating whether DNA vaccines can help desensitize the body to allergens. These use a dendritic cell-based approach to enhance immunogenicity.[12]

Risk Factors with DNA Vaccines

There are some concerns associated with DNA vaccines. Because little is known about the long-term implications of introducing altered genetic material into human cells, scientists are warning there may be unanticipated risks. These include 1) insertional mutagenesis, in which the DNA of a treated cell in a patient is permanently altered by the vaccine, 2) accidentally altering the DNA of a cell that could conceivably make it malignant and 3) whether the presence of these antigens in the body might introduce tolerance instead of immunity over a long time period.

Yet, researchers are optimistic these side effects will not manifest. "DNA has an extraordinary safety profile so far in the clinic," said David Weiner, PhD, executive vice president and director of the University of Pennsylvania Wistar Institute's Vaccine and Immunotherapy Center. "I think we are well over 35,000 people without a single major adverse event related to product." According to him, there has been no evidence DNA plasmids are accidentally merging with the cells' own genome in the nucleus, an obvious concern.[8]

Ongoing Research

As of this writing, there are more than 500 DNA vaccines studies listed on clinicaltrials.gov. Among them are studies investigating the effectiveness and safety of DNA vaccines targeting hepatitis B, melanoma, genital herpes, dengue fever, several strains of flu, pancreatic cancer, prostate cancer, hantavirus, metastatic breast cancer, HIV, malaria, HPV and dozens more. And, most of these diseases have several ongoing studies that take different approaches to deliver DNA into the cells.

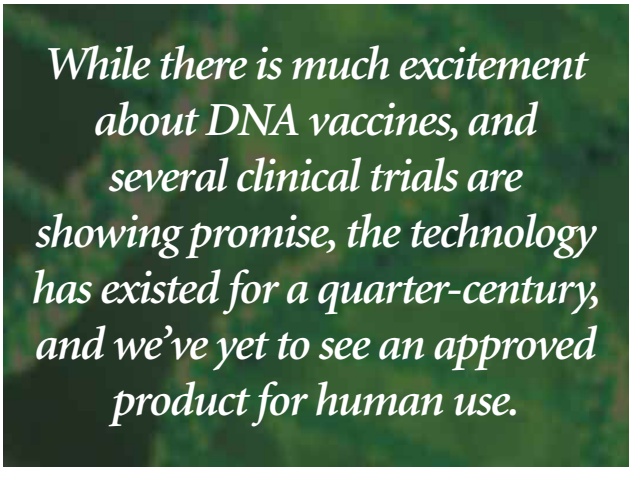
One such approach is the use of electroporation, which introduces a pulse of electricity to momentarily open the pores of cellular membranes to allow the DNA plasmid to be absorbed. According to researchers, this process looks promising for an efficient delivery mechanism to induce the DNA plasmids to be absorbed into the body's cells to begin producing the antigens that will stimulate the body's immune response.[13] Indeed, this delivery method is part of nearly every disease study looking at vaccination with DNA technology.

Political Considerations

Given the small but well-organized and passionate opposition to mandatory inoculations with existing technology, it is difficult to imagine DNA vaccines won't be met with resistance. Lingering suspicions arising from a long-discredited (and withdrawn) 1998 article that purported to link vaccines with a rise in the number of children diagnosed with autism continues to fuel much of the opposition. Whether an entirely new technology of vaccines will help to alleviate that political pushback remains to be seen, but it is something policymakers and public health officials will have to factor into their long-term plans.

The Future

While there is much excitement about DNA vaccines, and several clinical trials are showing promise, the technology has existed for a quarter century, and we've yet to see an approved product for human use. So, while the promise is very real, there are considerable technical challenges facing researchers and clinicians. It is possible electroporation will prove to be the magic bullet for an effective delivery system, unlocking a technological logjam in the very near future.



For now, the promise of DNA vaccines is balanced by a tremendous amount that remains unknown. Physicians should continue to stay current on developments, as it seems likely DNA vaccines will at some point be another tool available to help prevent both infectious diseases and possibly treat cancer as well. ❖

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Disaster Preparedness: Are Physicians Prepared?

When disasters strike, physicians are relied upon to provide care to those in need, but their ability to perform is dependent on a well-defined advance plan.

By Meredith Whitmore

EVEN A CASUAL glance at the news illustrates why disaster preparedness is a crucial field in which healthcare professionals need to understand and participate. Public health emergencies of many kinds happen regularly, and they can occur at any time and in any place. And, while the public often views physicians as all-knowing and extremely prepared professionals, doctors are sometimes the least equipped when it comes to disaster readiness. A 2015 study published in *Disaster Medicine and Public Health Preparedness* indicates fewer than half of the 1,603 practicing physicians interviewed felt ready to handle a natural disaster. Beyond this, less than a third of those interviewed had signed up to receive mobile alerts of emergencies and disasters from local and federal agencies.[1]

Healthcare professionals need to ask themselves: Is our practice prepared to face a situation such as a wildfire, hazardous chemical spill, terrorism attack, mass shooting or an epidemic? Could we effectively organize resources and staff should infrastructure be damaged and inoperative indefinitely — including clinics, roads and vehicles? Could we seamlessly work with other healthcare professionals and professionals from other fields to secure an area, transport patients, garner supplies or perform unusual yet crucial tasks necessary to ensure people's well-being? And, could we do all of these things under potentially stressful conditions?

Whether healthcare workers serve in rural or major metropolitan areas, they are wise to prepare in advance to respond efficiently and effectively in the face of worst-case scenarios. They must have a specific plan of response for virtually any dangerous situation that is in place prior to a hazardous event. Only then will they best protect their patients, the general public and themselves, depending on the nature and scope of the emergency. They should also train together as a team and with teams of other professionals, including those from law enforcement and other local, state and federal

agencies that could be involved should an entire region be affected by a crisis situation.

Taking the necessary steps to successfully anticipate and navigate large-scale emergencies can seem daunting — especially since disaster preparedness is an emergent and developing field. But, today, there are clear steps physicians can take to become better equipped.

What Is Preparedness?

Disaster medical science is a comprehensive new field involving many practices and types of workers, and understanding a few of its fundamental principles is crucial.

Disaster. Kristi L. Koenig, MD, FACEP, FIFEM, FAEMS, emergency medical services medical director of San Diego County and professor emeritus of emergency medicine and public health at the University of California, Irvine, says, "A common question surrounding disaster preparedness is, 'Are we ready?' The tempting retort is: 'Ready for what?'" This is a valid question considering descriptions of a disaster can be contradictory or even vague. "On a conceptual level, a 'disaster event' can be defined as a condition or situation (with or without casualties) for which the available resources are inadequate at a given point in time," explains Dr. Koenig.[2] She uses the fitting acronym "PICE" for any type of potential injury/illness creating event, since it is a concise, all-encompassing term that eliminates the descriptors of "manmade" or "natural."

Incident command/management system (ICS). Another principle is ICS, which is functionally based and depends on positions rather than people. The Federal Emergency Management Agency (FEMA) defines ICS as "a management system designed to enable effective and efficient domestic incident management by integrating a combination of facilities, equipment, personnel, procedures and communications operating within a common organizational structure." Such a command center typically oversees and organizes five major areas: command, operations, planning, logistics, intelligence and investigations, and finance and administration.[3]

Surge capacity. Surge capacity is any medical system's ability to manage a sudden influx of patients when patient care needs exceed available resources. To have adequate surge capacity requires a well-functioning ICS, enough space to accommodate extra patients, adequate supplies and the flexibility to manage special situations, including the presence of contaminated or contagious patients.[4]

Dr. Koenig defines surge capacity as "the components necessary to care for a sudden, unexpected increase in patient volume that exceeds current capacity."[5] She further explains surge capacity with the "3S concept": staff (personnel), stuff (supplies and medications) and structure (physical location for patient care and management structure).[2] Without an understanding of the concept of surge capacity, and the resultant preparation needed, even the most well-meaning clinic or hospital will be severely challenged when faced with an influx of patients during a large-scale disaster.

Comprehensive emergency management (CEM). CEM involves four phases of disaster management that address all aspects of disaster management:[6,7]

Mitigation: Efforts to limit loss of life by decreasing the impact of disasters

Preparedness: Garnering and developing resources to limit the impacts of disasters

Response: Efforts/activities to prevent or manage the disaster and its effects

Recovery: Short- and long-term restoration of the resources and capabilities affected by disasters

Dr. Koenig believes all four phases should be more thoroughly embraced rather than merely "focusing only on the highly visible 'response' phase,"[2] which tends to get the most media coverage and resources. Understanding and anticipating all four phases ensures management of a disaster throughout its life cycle. Understanding CEM ensures resources will remain available and patient care and safety will continue after a disaster occurs.

Whether healthcare workers serve in rural or major metropolitan areas, they are wise to prepare in advance to respond efficiently and effectively in the face of worst-case scenarios.

Community resilience. When considering how best to prepare for a disaster, the community in which the healthcare practice is located must also be considered. Community resilience involves how well people adapt to and recover from trauma. It involves both emotional and physical resources, including socioeconomic status, education, mental health and behavioral factors, and previous traumas, among other factors. Physicians must assess their community's resources in these areas to determine how a disaster plan needs to be adapted to meet their particular needs.[7]

Preparedness Is Fluid, Not Static

Contrary to popular misconception, disaster preparedness is not an unchanging, one-time event for which a single plan of

response is needed. Preparedness must be ever-changing with teams of medical professionals and first responders training together regularly since resources, current events and even weather change often. And, because a disaster could affect an entire community or region, medical teams must work in conjunction with law enforcement, public health and other local, state and federal agencies.

Preparedness should also be strategic and flexible enough to cover all types of disasters. This is why all-hazard preparedness is crucial. Rather than preparing for a specific event such as an earthquake or flood, being prepared for all hazards means developing an emergency management system that is flexible and ready to manage any event, even if it is unusual. For example, in California, where physicians very likely expect a wildfire and are prepared for it, they would not necessarily expect a hurricane even though one could occur.

Questions to Ask

As physicians navigate disaster medicine for their practices, the following questions should be asked:

1) Is our plan adequate? To answer this seemingly simple yet complicated question, the Joint Commission, FEMA and other organizations have guidelines in place to guide physicians. Although these plans are not necessarily comprehensive or tailor-made for specific circumstances, they can be helpful.

2) How will the disaster be managed? Who has authority to activate the ICS? Are personnel trained in their roles? Which personalities and skills on the team best fit these roles?

3) What are the practice's resources, and how will they be managed? How will additional necessary resources be identified and obtained?

4) Is the disaster plan well-documented and adequately shared for all involved to understand it and have access to it?

5) Is there a list of all hazardous materials within the facility, as well as health information about each?

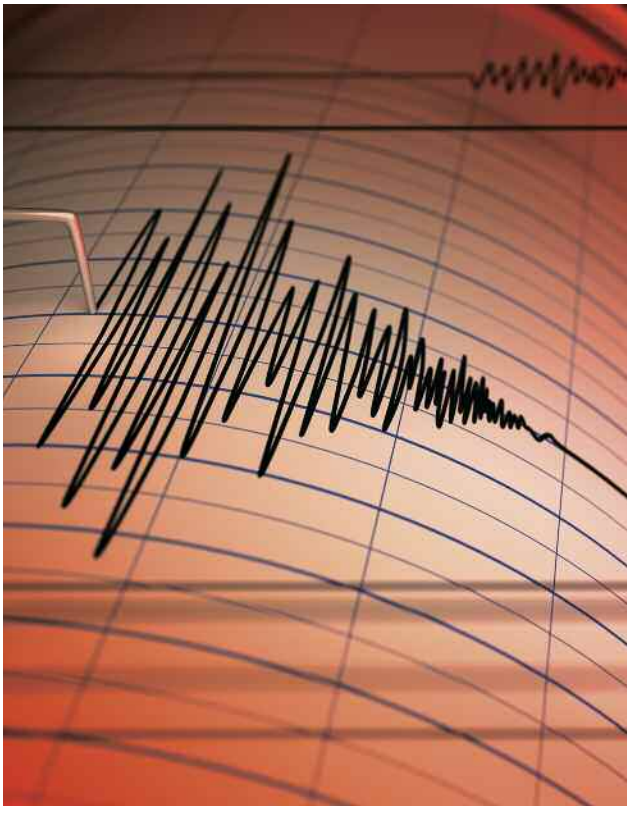
6) How would the practice withstand a disaster? There are six critical elements to maintain a practice's operations: physical plant, personnel, supervision, supplies and equipment, communication and transportation.[8] How are these elements best protected?

7) Is every team member in agreement regarding the disaster preparedness effort? If not, how can they be encouraged to be onboard?

8) If regular communications systems are disrupted, what backup options are available? For example, will handheld radios or ham radios be needed? Would a bullhorn be helpful?

9) Is there a plan for document recovery should records get lost? For instance, is the cloud available for storage? Does the practice have a subscription service that maintains documents online?

While these are merely a few possible questions, they are a good place to begin the discussion and thought processes necessary to prepare a team physically, mentally and emotionally to respond well in the face of a large-scale disaster.



Helpful Resources

When a disaster strikes, physicians will be relied upon to provide medical care to those in need. To prepare them, a number of helpful texts on disaster preparedness are available, including *Koenig and Schultz's Disaster Medicine: Comprehensive Principles and Practices* in which well-researched and exhaustive information is presented on a variety of disaster management topics. Dr. Koenig is an expert in the field of disaster preparedness, and she encourages physicians to do their part to help protect public safety. ❖

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Myths and Facts: **Women and Cardiovascular Disease**

Cardiovascular disease poses a significant risk for women, even more so than for men, yet most women and their caregivers remain unaware mainly due to myths and misconceptions.

By Jim Trageser

IN WESTERN SOCIETY, heart disease is still largely viewed as a male health problem. Even many women's health advocacy organizations focus more on cancers than on cardiovascular disease (CVD). For instance, pink ribbon campaigns to help raise awareness about the importance of breast cancer detection, treatment and research are hugely popular, and have no trouble gaining celebrity supporters to raise their public profiles. Meanwhile, the "Go Red for Women" campaign to raise awareness of women's heart disease largely flies under the popular radar. Yet, the facts are plain: CVD kills seven times more women than breast cancer every year. In fact, it kills more women than all cancers combined.[1]

CVD isn't just about heart attacks. Atherosclerosis can lead to strokes and heart attacks, and women are more prone to strokes than men. Hypertension can cause kidney disease if left untreated, and more than half of American adults with high blood pressure are women.[2] Finally, women are subject to some risk factors for CVD that simply don't affect men, including eclampsia or pre-eclampsia during pregnancy, use of birth control pills (which are shown to increase the risk of hypertension) and early onset menopause.[3] Of course, women are also vulnerable to all the modern risk factors for CVD that have been shown to afflict men: an unbalanced diet, weight gain, lack of exercise, workplace stress, smoking and too much alcohol.

Despite all of this, polls show many women and their caregivers remain uninformed about the true risk CVD poses to their long-term health, as well as the comparative risk CVD poses versus other diseases and conditions. And, while the information is available, it is often overwhelmed by myths and misconceptions.

Separating Myth from Fact

Myth: Women aren't as prone to CVD as men.

Fact: CVD is the leading cause of death for women in the United States, and more women than men died of heart disease each year between 1984 and 2012.[4] And, even though more men than women have died each year from a heart attack since then, the rates are very close, with some 290,000 women dying each year.[5]

And, while men are twice as likely to suffer a heart attack, women are more likely to die from one — and even more likely to die within a few years after suffering their first heart attack.[6] Women are also more likely than men to suffer a stroke. Every year in the U.S., roughly 425,000 women experience a stroke, compared with only 370,000 men.[3] And, about 80,000 of those women will die from the stroke,[7] which is about twice as many as those who die from breast cancer.[8] Studies also show female stroke survivors face a tougher rehabilitation than do men, with more mobility challenges and greater pain reported.[3]

Myth: Women and men display the same symptoms during a heart attack.

Fact: There is conflicting evidence about this issue, likely due to the fact most research about CVD has focused on men, until recently. A 2013 report in *JAMA Internal Medicine* found earlier research that suggested differing symptoms of a heart attack between the sexes failed to account for age differences (women are on average older when they experience a first heart attack) and overall health differences (diabetes, which is more prevalent in women, can mask some symptoms of a heart attack).[9] However, this study is still fairly new and not unanimously accepted. There is still much literature based on earlier research that indicates women are statistically less likely to exhibit some of the more typical symptoms associated with a heart attack: pain in the left arm, pain or pressure in the chest, sweating, dizziness and shortness of breath. In fact, both the 2013 study and another with different conclusions agree the original study of chronic heart disease in the mid-20th century was flawed since it was based primarily on middle-aged Caucasian males (typical of most medical research at that time).

The full picture of heart attack symptoms experienced by men and women likely won't be understood until further research about CVD in women complements the existing body of research on men.

The full picture of heart attack symptoms experienced by men and women likely won't be understood until further research about CVD in women complements the existing body of research on men. Regardless, women and men should both be aware of all the different possible signs of a heart attack and be ready to seek medical assistance if any of them are observed:[10]

- Chest pain or pressure
- Increased shortness of breath
- Unusual sweating
- Lightheadedness or dizziness

Other symptoms reported as more common in women include:[11]

- Nausea
- Extreme fatigue
- Pain in the lower chest or upper abdomen

Myth: Medical research about CVD represents women and men equally.

Fact: As indicated above, most research conducted about heart disease and strokes in the mid- to late-20th century underrepresented women. Indeed, until 2006, studies that were supposed to include both sexes included only 34 percent women — not even close to half.[12] In 1991, cardiologist Bernadine Healy, MD, who was the first woman to head the National Institutes of Health, warned this gender bias in research had "reinforced the myth that coronary heart disease is a uniquely male affliction and generated data sets in which men are the normative standard."[13] This has only slowly been rectified by researchers in the decades since.

Myth: Women receive the same quality of CVD care as male patients.

Fact: Female patients who are treated by women physicians in hospital emergency rooms are more likely to survive a heart attack. In fact, numerous studies over the last few decades have shown a consistent statistical difference in women heart attack patients treated by female doctors versus those treated by male doctors. (Among male patients, there is no statistical variance between those treated by male versus female physicians.)[13]

Preventive care also is not equal. An American Heart Association study in 2005 indicated only 8 percent of general practitioners and 17 percent of cardiologists knew CVD killed more women than men.[4] Other studies have shown public information campaigns about health shape patient perceptions about their risk factors. Men are far more likely to broach the subject of heart disease with their physicians, while most female patients are far more concerned about developing breast cancer than CVD, even though they are at far higher risk of heart disease and stroke.[14] And, many women patients report when they do discuss CVD with their primary physicians, their concerns are not taken seriously, and symptoms are often attributed to other causes with no follow-up.[14] Women patients are also less likely than males to be prescribed beta blockers, statins or ACE inhibitors to treat symptoms of CVD before or even after a heart attack.[15]

Myth: Young women do not have to worry about cardiovascular disease.

Fact: Smoking and birth control pills each raise the risk of heart disease or stroke, and the number of heart attacks in women in their 30s and 40s has been increasing in recent years, with sudden cardiac deaths rising 30 percent among women under age 50 over the past decade.[15] In addition, women under age 45 who suffer their first heart attack are more likely than men to die within 12 months.[11] Young women are also more likely to develop hypertension, chronic kidney disease or diabetes — all risk factors for a subsequent heart attack or stroke — than men their same age.[15]

Myth: Women who are athletic or physically active don't develop CVD.

Fact: High cholesterol and hypertension can still manifest even in the most physically fit individuals. A poor diet or unlucky genes (such as hereditary high cholesterol) will not be eliminated by even the most disciplined fitness regimen.[11] Therefore, women who are physically active should exercise the same discipline in tracking their CVD risk factors as women who are not.

Myth: If parents and grandparents did not have CVD, an individual is not at risk.

Fact: Lifestyle can trump good genes. According to A. Marc Gillinov, MD, chairman of the Department of Thoracic and Cardiovascular Surgery in the Sydell and Arnold Miller Family Heart and Vascular Institute at Cleveland Clinic, 90 percent of CVD risk comes from a patient's individual choices, including diet, smoking and exercise.[16] While a family history of CVD is one risk factor, it is not a determinant factor, and a lack of family history should not induce a false sense of complacency.

Myth: If parents and grandparents had CVD, there is nothing a person can do.

Fact: While lifestyle can't trump bad genes, it can certainly help ameliorate the risk of developing CVD. Researchers and physicians estimate 80 percent of the risk factors for heart disease are preventable through lifestyle choices: Getting regular exercise, avoiding weight gain or losing weight, maintaining a healthy diet, avoiding tobacco usage, moderating alcohol consumption and maintaining a healthy blood pressure.[4]

Dispelling the Myths Now

Many health advocacy organizations are actively educating women and their physicians about the realities of heart disease in women. But, one bit of advice is the same for women and men, and it's the advice men have been bombarded with for the last half-century: Take control of your health, and if you have any concerns, bring them up with your doctor.

Since many women's primary healthcare provider is their OB/GYN, they may have to take a more active role in requesting tests and keeping an eye on their cardiovascular system. Or, better yet, they should schedule an annual visit with a general practitioner who is likely to be more familiar with CVD risk factors.[17] Women with multiple risk factors should consider requesting a referral to a cardiologist. In addition, the American Heart Association recommends an annual cholesterol check beginning at age 20. And, blood pressure should be watched in all patients.[11]

While lifestyle can't trump bad genes, it can certainly help ameliorate the risk of developing CVD.

While there is a popular stereotype that women are better communicators than men, one study found only 35 percent told their physician about CVD symptoms they had experienced. And, fewer than one-quarter of women diagnosed with CVD followed up with more questions for their physician.[4] Therefore, physicians and other healthcare professionals need to be proactive in discussing heart health with their female patients. They should encourage them to share any concerns, and direct them to accurate, up-to-date information that bypasses the myths that can prevent women from effectively preventing and being treated for CVD. ❖

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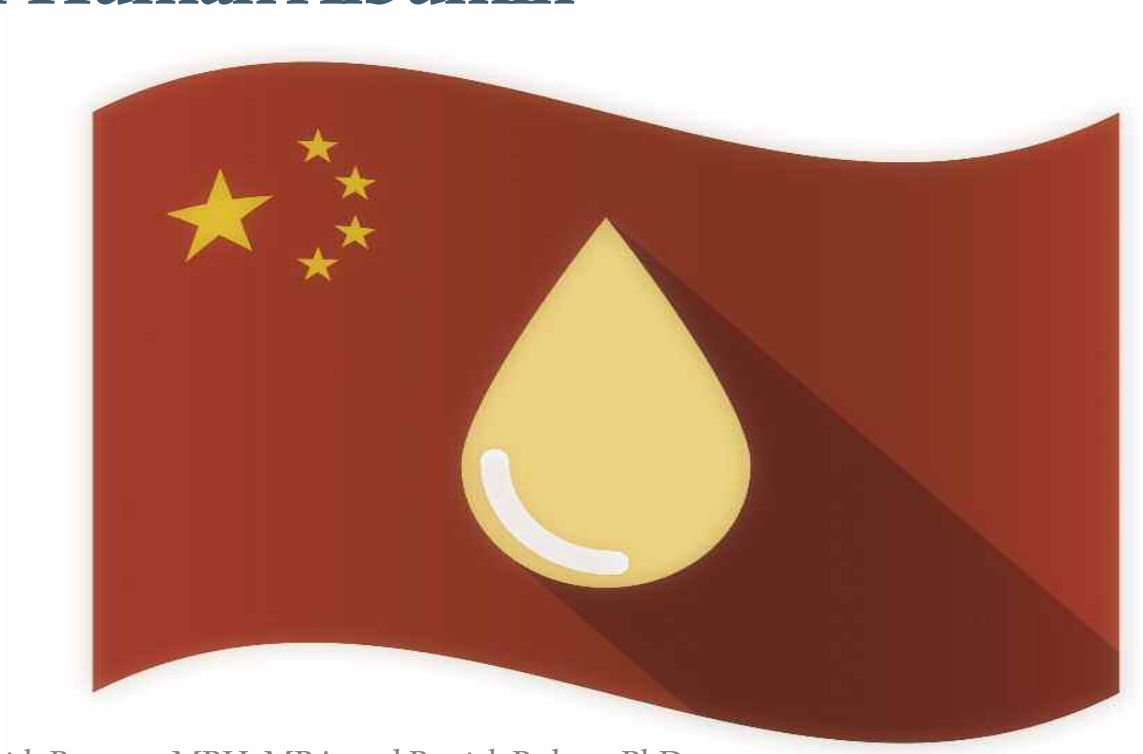
Feeding China's Growing Appetite for Human Albumin



By Keith Berman, MPH, MBA, and Patrick Robert, PhD

MORE THAN 40 years since embracing free market reforms, trade and investment, China has transformed itself from one of the world's poorest countries to an industrial behemoth that has lifted as many as 800 million residents out of poverty.[1] Well over 300 million people have migrated from rural villages to fast-growing cities offering manufacturing jobs.[2] Projected 8 percent growth in retail spending this year by a burgeoning middle class is expected to propel China past the United States to become the world's largest consumer goods market.[3] Chinese demand for everything from cars to cell phones to imported foods is now a critical component of the global economy.

But this new consumer spending power is just one aspect of how China's economic ascendency has raised living standards for its people. For most in a country whose per capita gross domestic product (GDP) as recently as 2007 was just $2,700 (compared to $46,400 in the U.S.), comprehensive medical care had historically been out of reach.[4,5] But by 2017 — just 10 years later — healthcare expenditures as a percentage of China's GDP increased by 50 percent,[6] and per capita healthcare spending jumped nearly five-fold.

To appreciate how the "Chinese economic miracle" has helped improve access in particular to advanced medical care, one need look no further than its utilization of a single product that is widely used in hospitals to treat severely ill intensive-care unit and other patients. That product, now China's highest dollar-value prescribed therapeutic, is human albumin.

Blood, Albumin and Healthcare Access

As is done here in the U.S., Chinese physicians order albumin for acute blood volume loss situations and for hypotension or hypotensive shock, most commonly in the context of underlying severe liver or kidney disease. Advanced liver disease is a leading indication for albumin in China, which not coincidentally has the world's highest chronic hepatitis B virus (HBV) infection burden.

Of an estimated 240 million people globally living with chronic HBV, some 90 million live in China, of whom an estimated 28 million require treatment and seven million require urgent, intensive treatment for advanced liver disease. Ten million others live with chronic hepatitis C virus (HCV) infection, 2.5 million of

whom with cirrhosis or liver cancer also require urgent treatment that sometimes includes administration of albumin.[7] Atop this is a growing prevalence of cirrhosis and end-stage liver disease traceable to dramatic increases in alcoholic and nonalcoholic fatty liver disease (NAFLD), which in turn are related to recent lifestyle changes throughout the industrialized world.[8]

In China, it is also not unusual for albumin to be given to other very ill and commonly hypoproteinemic patients with cancers, lower respiratory disorders, including COPD and other severely debilitating diseases. This practice originates with the principle in traditional Chinese medicine (TCM) that blood is closely identified with the individual's "*qi*," which translates as "life force" or "vital energy."[9] In TCM, *qi* and blood are two of the vital substances that are crucial to health. Blood is the liquid life force that nourishes and restores the body and organs that, in turn, produce more *qi*. Conversely, according to TCM, the loss of blood weakens the individual; thus, many Chinese, including older adults in particular, are unwilling to donate blood.

While the influence of TCM on Chinese medical practice has diminished over the past several decades, this association between blood and *qi* still appears to account for some albumin prescribing for cancer and other patients experiencing weakness, malaise or exhaustion.

But in a country where, as recently as 2010, annual spending on healthcare per resident was just $200, most Chinese still had limited access to advanced hospital care where albumin treatment is provided. That picture has changed dramatically over the ensuing eight years as healthcare spending — and demand for albumin in particular — has outpaced even the torrid pace of economic growth that doubled China's GDP to more than $13 trillion.

China's Albumin Demand Far Outpaces Plasma Supply

From a 108 million-gram market in 2006, utilization of albumin in China grew nearly four-fold to 412 million grams by 2017, or nearly 300 grams per 1,000 residents (Figure 1).[10,11] As a result of this extraordinary demand growth, which approximately equaled that of all other countries combined (Figure 2), China today accounts for fully one-third of the global albumin market.

A series of purification or "fractionation" steps yields about 25 grams of albumin from each liter of collected donor plasma. More than 90 percent of the global supply of plasma for fractionation comes from "source plasma," which is typically collected from remunerated donors in dedicated licensed centers that use automated apheresis equipment to perform plasmapheresis to separate and retain only the plasma portion of donor blood. The balance of the plasma supply comes from "recovered plasma" separated from whole blood donations that is not needed for direct transfusion into hospital patients. In 2017, approximately two-thirds of the fractionation industry's global plasma supply needs were met by 35 million liters

Figure 1. The Chinese Market for Human Albumin: 2006-2017

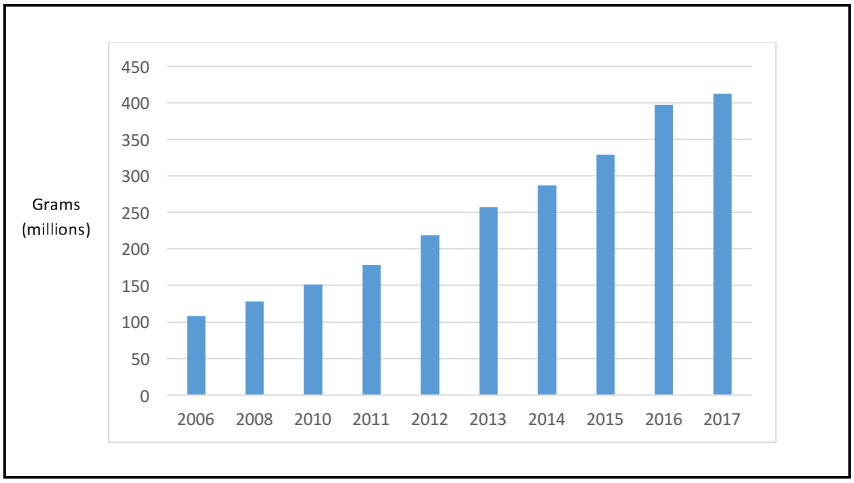
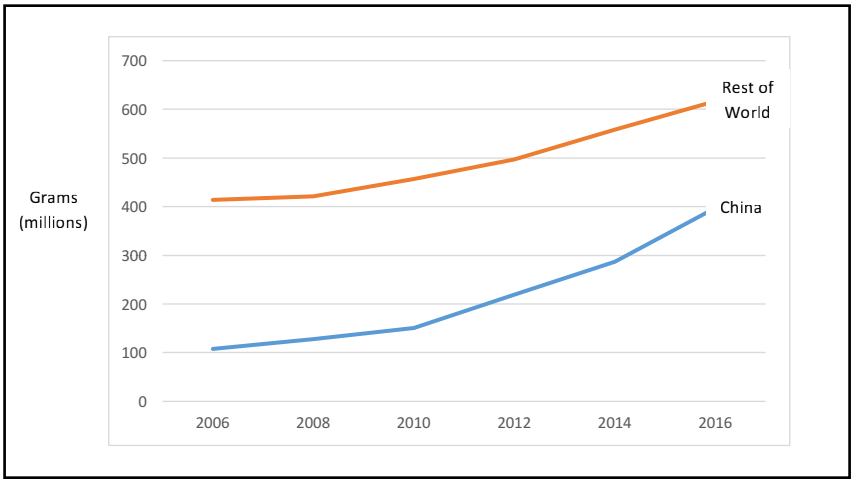


Figure 2. China vs. Rest of World: Growth in Albumin Demand: 2006-2016



of source plasma collected at more than 700 U.S. plasma donor centers, together with about two million liters of recovered plasma from U.S. whole blood donations.

China's current legislation permits only source plasma to be used for domestic fractionation into albumin and other plasma-based therapeutics. To meet the country's current albumin needs would require collection of well over 16 million liters of source plasma. With a population four times that of the U.S., one might reasonably expect that China is — or soon could become — self-sufficient in meeting its own plasma requirements.

But, in fact, China remains heavily reliant on imported albumin manufactured mainly from U.S. source plasma. In 2017, domestically sourced plasma from about 250 collection centers accounted for just 40 percent of the country's 412 million-gram albumin requirement (Figure 3).[11] The other 60 percent was met by importing albumin products manufactured by the world's four leading commercial suppliers: CSL Behring, Grifols, Takeda (formerly Shire/Baxalta) and Octapharma.

Several factors combine to constrain China's ability to expand domestic plasma collection activity:

- As a result of a government policy mandating a large geographic separation from blood donor centers, plasmapheresis facilities generally must be situated in outlying rural areas, making the donation experience more time-consuming and inconvenient. And, more than one billion people, including many in China's most populous cities, live entirely outside the designated regions where source plasma can be collected.[11]
- Chinese plasmapheresis donors can contribute no more frequently than once every two weeks — four times less frequently than the U.S. twice-weekly donation limit.
- Otherwise available unused plasma from whole blood donations is not permitted for manufacture into albumin and other plasma products; however, this policy is being reconsidered by Chinese health authorities.[12]
- A still widely-held belief that loss of blood weakens one's *qi* dissuades many Chinese from considering donating blood or blood plasma.

Despite all these limitations, new plasma collection centers continue to be opened in some Chinese provinces, and total domestic plasma collections have increased an average of about 15 percent annually over the last three years for which data are available (Figure 4).[11]

Figure 3. Domestically Produced and Imported Albumin in China: 2012-2017

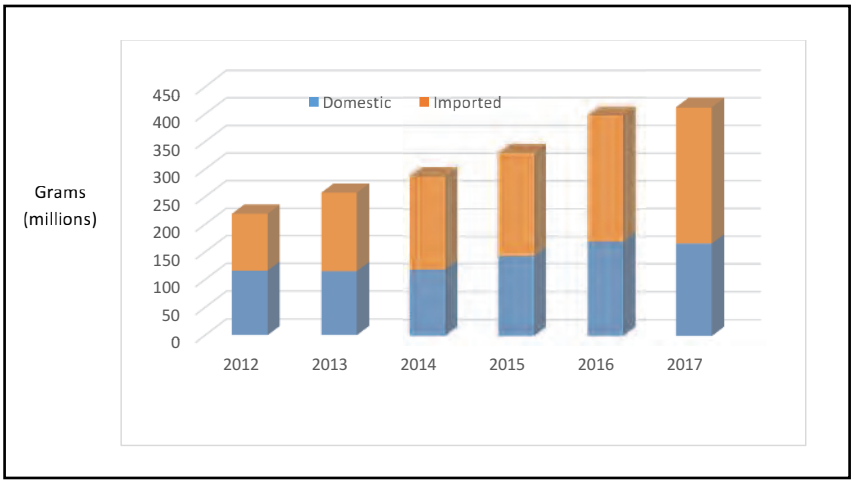
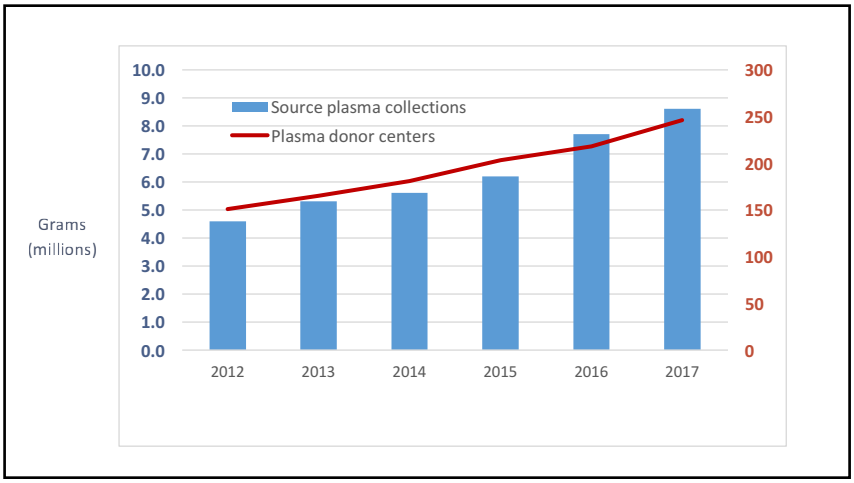


Figure 4. Source Plasma Collections and Donor Centers in China: 2012-2017

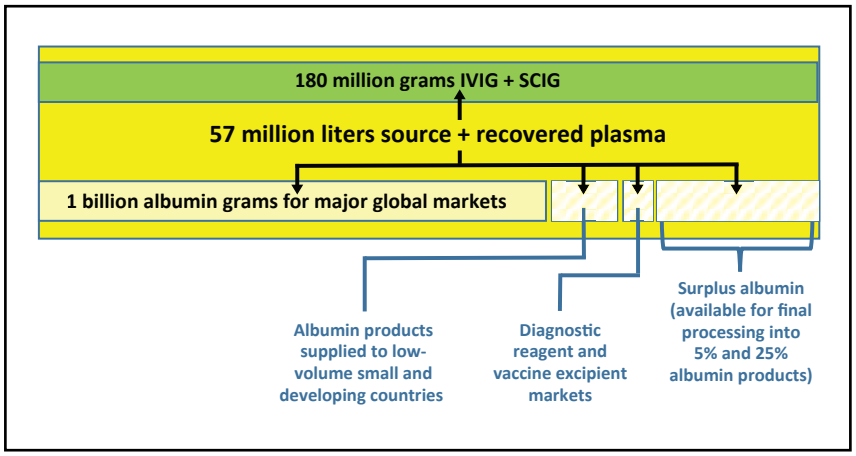


Excess Production Capacity Equals Market Stability

It now appears that the remarkable run-up in demand that established China as by far the world's largest albumin market may be winding down. After a decade of double-digit growth, China's albumin consumption grew just 4 percent in 2017. Preliminary data indicate a similarly low growth rate in 2018. This slowdown in albumin demand growth coincides with several government-mandated distribution and other healthcare policy reforms introduced in early 2017.

But, even if we assume that China's current 15 percent plasma collections growth pace is sustainable and domestic albumin demand growth will indefinitely remain in

Figure 5. Liters of Plasma Fractionated Worldwide Into IG and Albumin Products: 2017



the low single digits, the country will likely not become plasma self-sufficient until midway through the next decade.

Fortunately, China's ongoing reliance on imported albumin products does not in any way impact the availability of albumin for the U.S. or other countries; commercial fractionators can readily continue to fill China's albumin supply gap. The reason lies in the fact that global requirements for the plasma raw material are not dictated by albumin demand, but instead by the global demand for intravenous immune globulin (IVIG) and subcutaneous immune globulin (SCIG) products.

In 2017, an estimated 57 million liters of donor plasma were processed to produce more than 180 million grams of polyvalent IG products to supply the global market demand (Figure 5).[13] Not surprisingly, IG product supplies here in the U.S. and internationally were — and continue to be — tight, as plasma raw material supply and IG products manufactured from it just manage to keep pace with worldwide demand growth.

To meet albumin demand in the U.S. and about 70 other countries with well-documented albumin consumption data, just over one billion grams were purified from that same plasma in 2017. But since each liter of plasma yields an average of 25 grams of albumin, only about 40 million (one billion grams divided by 25 grams/liter) of the 57 million processed liters of plasma were needed to meet that one billion-gram albumin requirement.

What happens to the roughly 425 million grams of albumin purified from those 17 million additional liters of plasma that were processed to keep up with global IG demand? Some is supplied as finished product to small and developing countries mainly on the Asian and African continents, for which reliable albumin and other plasma protein utilization data are not available. An estimated 5 percent is sold to manufacturers of diagnostics and vaccines for use as a reagent or product excipient. But most of the rest is simply surplus albumin with no immediate end-user market. Some of that surplus albumin may be stored in a bulk form called Fraction V, which is not final-purified or bottled.

So, because the global plasma requirement dictated by global IG demand substantially exceeds the plasma requirement to meet global albumin, there is in essence a global "safety stock" of plasma albumin protein that can absorb a surge in albumin demand. That is why, in the midst of China's "economic miracle" that boosted its albumin imports by nearly 200 million grams between 2007 and 2017, here in the U.S., albumin remained in good supply, and its price remained stable.

Could rising economic fortunes in other developing countries in Asia or elsewhere generate a major new surge in demand for albumin? In the event we see a near-term spike in demand for albumin imports, it is reassuring to know the industry is fully prepared to address it — without missing a single delivery to any albumin customer anywhere in the world. ❖

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Jannae Yslas-Roach and husband, Aaron, received public backlash over their decision not to vaccinate their family against measles — a decision Jannae says she now regrets and has reversed.

Measles: *A Patient's Perspective*

By Trudie Mitschang

IN 2015, Jannae Yslas-Roach's private decision to forgo vaccinations for her four children exploded into a public debate after she and her husband, Aaron, took their family to Disneyland for five days in mid-December. "It was to be the big Christmas present for the kids," she recalls. But what the Kearny, Ariz., family didn't realize was Disneyland had just become the staging ground for a measles outbreak that would eventually sweep the country.

Shortly following the trip, four members of the Yslas-Roach household got sick with cough, high fever and rash. During the next two weeks, Jannae says, family members visited medical professionals on multiple occasions without getting a firm diagnosis. Their son Gabriel was the first to get sick on January 2, with a fever and rash on his forehead. Medical tests were inconclusive, although scarlet fever was suspected. Gabriel was prescribed an antibiotic, and after three doses of the medication, his condition improved. But by January 7, Jannae and sons Christian and Isaiah had all come down with 103-degree fevers, cough, rash and nausea. Her daughter, Serenity, had a high fever but no rash.

Jannae immediately quarantined the family, staying home from her job and keeping the sick kids out of school. By January 11, Christian's condition had significantly worsened, and he was taken to urgent care. By then, the family knew of the measles outbreak and alerted the center their son had been to Disneyland and possibly exposed. Unfortunately, the attending physician decided against testing for measles and instead diagnosed Christian with a viral infection. It was a decision with dire consequences. Pinal County Public Health officials later determined Christian did have measles, and his urgent care visit exposed 18 other people, one of whom became infected. That patient later returned to the urgent care center and exposed at least 195 others.

Jannae was the next family member to seek medical help when she awakened on January 14 around midnight, unable to breathe. "Something's wrong," she whispered to her husband. "I've got to get to the hospital."

After arriving at the hospital, Jannae received chest X-rays and blood work, but test results were still inconclusive for measles. It was nearly a week later on January 22, after testing by a team from the Pinal County Public Health Services District, that all sick family members were definitively diagnosed with measles. While the news came as a bit of a relief, the ensuing backlash from the media threw the family into an unwelcome spotlight. After a public health announcement about a local family of four children contracting measles at Disneyland, it was not long before Jannae and her family were identified, and the outcry was intense, with many chastising them for what they perceived as gross negligence and irresponsibility.

Jannae says she felt horrible about exposing others to measles: "Our family went through hell, dealing with the commentary on social media. It was difficult to listen to people's opinions on your parenting, and people can be cruel. I had to remember that everyone has a right to voice their opinion. I am a firm believer in free speech even when it's not easy to hear. There were days we just shut off the television, closed Facebook and stayed off the Internet."

Jannae recognizes many medical professionals today have never seen a case of measles, and she does not blame the doctors who inaccurately diagnosed her family, inadvertently putting others at risk. She explains she was not immunized in childhood because her uncle had a severe reaction to a vaccine and her mother decided against them. Later, when Jannae had her first child at 19, she also chose not to immunize because she worried about what she dubbed "a one-size-fits-all vaccine."

Without question, the experience she and her family had with measles gave her pause, and she used the opportunity to do her own research on the efficacy of vaccines. In the end, she made the decision to vaccinate. "I found an amazing pediatrician who listened," Jannae explained. "She answered any questions and helped me ease into vaccinations."

The experience also sparked some positive, ongoing dialogue about healthcare decisions between Jannae and her kids, who are now 17, 13, 11 and 9. "It led to a lot of different talks for us, some about not bullying, some about understanding others' opinions, some about my decision not to vaccinate and the responsibility that comes with making that choice (not intentionally infecting others)," says Jannae. "Then, explaining how the world is changing and 'bugs' are becoming stronger and not wanting them to experience something like this again. I want my kids to always make informed decisions about everything, but especially about their health." ❖

Dr. Sandra C. Quinn, who studies public attitudes toward vaccination, believes social media is to blame for the proliferation of vaccine misinformation. But, with the renewed measles outbreak, she believes people are beginning to understand the dangers of this and other diseases.

Measles: *An Expert's Perspective*

MEASLES, A DISEASE that was once considered eradicated in the U.S., has once again been making headlines. Due to declining measles vaccine coverage, the U.S. and other countries are experiencing increased widespread outbreaks. In a report published in the *New England Journal of Medicine*, experts noted how quickly the disease can spread, citing one case in which a single child with measles infected 23 other children at a pediatric oncology clinic, which had a fatality rate of 21 percent.[1]

As professor and chair of family science at the University of Maryland School of Public Health, Sandra C. Quinn, PhD, recently weighed in on this rising public health concern. Dr. Quinn is also a researcher funded by the National Institutes of Health and the U.S. Centers for Disease Control and Prevention to examine public attitudes toward vaccines.[2]

BSTQ: Is something changing in the national conversation about vaccination and resistance to vaccination?

Dr. Quinn: The proliferation of social media has enabled a spread of misinformation in ways that are frankly hard for us not only to keep up with, but hard for us to understand who's doing the talking, who's doing the communicating and what their motives are. We also see bad actors like bots and trolls that are not just promoting misinformation, but also seeking to sow discord or to sell you something.

BSTQ: How does social media help incite resistance to vaccines?

Dr. Quinn: People questioning vaccines has been around a long time, but social media has amplified voices that may not represent the larger public. When you look at the Pew survey data, we still see very high support for vaccination. If you look at social media data, you might not see that. With social media and the Internet, many people don't know how to identify credible, legitimate information. That's not a criticism of individuals; it's more a criticism of organizations and providers that don't necessarily help foster the kind of health literacy that's needed.

BSTQ: What about the move to push companies or websites like Amazon and YouTube to make anti-vaccine content less available?

Dr. Quinn: That's the $64,000 question. There's a part of me that's relieved in some ways it is happening. There's another part of me that says, just because people can't get it here doesn't mean they won't get it somewhere else. It's also a little bit of a challenge for me because of the concept of freedom of speech, and I feel torn between that and reducing disinformation and fostering high vaccination rates as a collective good for our society. But I also know from our research how many of those anti-vaccine messages are paid ads. This isn't all about private citizens expressing themselves.

BSTQ: What action is needed (to address philosophical exemptions to vaccines)?

Dr. Quinn: There still are 17 states that allow for philosophical exemptions to vaccination requirements. That can just be, "I don't believe in vaccination." That is increasingly becoming a focus of policymakers. After the Disneyland outbreak in 2014 and 2015, California changed its state laws and did away with exceptions except for medical exemptions. Policymakers in Washington state are literally battling that out as we speak. I think policymakers and the public are beginning to recognize we have tipped so far that we are at a danger point for these diseases. I would argue it is time to look at our policies and reconsider the implications for the health of our children and communities that result from lax laws that allow many possible exemptions for nonmedical reasons.

BSTQ: Is anything changing for the better?

Dr. Quinn: With the number of outbreaks and cases that just keep increasing — it's measles now, but we've had pertussis outbreaks, we've had mumps outbreaks — I think there's beginning to be a renewed appreciation that these diseases are dangerous, but they also are preventable. I think it is also being understood that the decision to vaccinate one's own children is not just about one's own children, it's about the broader community, and particularly about protecting people who are vulnerable because they cannot be vaccinated for real health reasons. As we've seen in places where there are outbreaks, when you go below a certain percentage vaccinated, you lose herd immunity that protects everyone. With the U.S. this year already surpassing the 2018 case number, I am hopeful more legislators will take action and more parents will step forward to protect their own and others' children from unnecessary suffering. ❖

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

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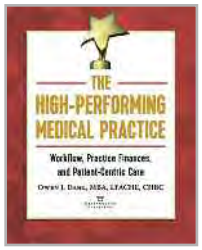
Editor's note: Portions of this article are reprinted with permission from an article written by Chris Carroll and published in Maryland Today*, a publication of the University of Maryland: today.umd.edu/articles/faltering-shield-against-disease-5f19f347-f16d-4986-8bed-95ebde0fd1cb.*

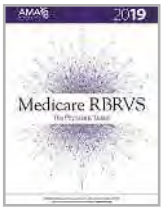
The High-Performing Medical Practice: Workflow, Practice Finances, and Patient-Centric Care

Author: Owen J. Dahl, MBA, LFACHE, CHBC



In this new resource, Owen Dahl provides physicians and administrators with examples showing exactly how their team can re-engineer a healthcare practice. It starts with an assessment and audit of the practice, and then covers the essential needs of the healthcare practice, along with a road map of how to apply sound business wisdom effectively to get the results needed. Samples of topics include how to increase workflow by identifying the bottlenecks; how to provide the optimum patient experience; how to effectively use the SWOT (strengths, weaknesses, opportunities, threats) analysis to gauge practice health; how to use patient surveys to increase efficiency and quality; how Lean Six Sigma can significantly improve workflow; and how the move toward value-based reimbursement will impact the practice. Chapters include a collection of worksheets and forms that can be put to work in the practice.

www.amazon.com/High-Performing-Medical-Practice-Workflow-Patient-Centric-ebook/dp/B07NQH1LWB/ref=sr_1_34?keywords=Physicians&qid=1554132640&refinements=p_n_publication_date%3A1250227011&rnid=1250225011&s=books&sr=1-34



Medicare RBRVS 2019: The Physicians' Guide

Author: American Medical Association

The 28th edition of *Medicare RBRVS: The Physicians' Guide* provides the much-needed updated information on the new 2019 Medicare Physician Payment Schedule, payment rules, conversion factor, current procedural terminology (CPT) and healthcare common procedure coding system (HCPCS) relative value units (RVUs), and geographic practice cost indices (GPCI) that affect the physician practice. Included are the complete RVU table in an electronic file, detailed background information on the RBRVS system, updated information on new payment rules that take effect in 2019, updated RVUs for 2019 CPT codes, a list of RVUs for CPT and HCPCS-coded procedures and services, a list of RVUs for anesthesiology services and a list of GPCIs for each Medicare payment locality.

www.amazon.com/Medicare-RBRVS-2019-Physicians-Guide-ebook/dp/B07CZ7KFVD/ref=sr_1_5?keywords=Physicians&qid=1554131700&refinements=p_n_publication_date%3A1250227011&rnid=1250225011&s=books&sr=1-5

Physician's Guide to Better Medical Decision Making: Critical Thinking in Medicine

Author: Thomas Falasca, MD

This book is a valuable tool for physicians, medical students and health professionals to identify and remedy factors leading to hazardous and costly medical decision errors. It includes experimental evidence showing how specific influences lead to bad medical decisions, effective identification tools for flawed medical decisions derived from an unexpectedly varied range of disciplines, practical and specific countermeasures to the influences facilitating poor medical decisions and numerous medical examples that are familiar and relatable. The book synthesizes experimental research and methods from diverse fields, including perceptual psychology, cognitive psychology, illusion management, experimental design, medication testing and approval, formal logic, mathematical statistics and civil law. It then applies these results specifically to the making of sound medical decisions.

www.amazon.com/Physicians-Better-Medical-Decision-Making-ebook/dp/B07M73R14J/ref=sr_1_25?keywords=Physicians&qid=1554132324&refinements=p_n_publication_date%3A1250227011&rnid=1250225011&s=books&sr=1-25

The 21st Century Take on Observational Studies

Author: U.S. Food and Drug Administration

This guide discusses the opportunities and pitfalls observational studies can offer, as well as looks at the growing trend toward observational research and how provisions in the 21st Century Cures Act create more incentives to rely on real-world evidence in the development of medical products. The report covers the evolution of patient-focused research; how observational studies can be used in the preapproval and postmarket stages; the potential for saving time and money; new data sources that make observational studies a viable alternative to clinical trials; and how drug- and devicemakers view observational research and how they are using it. New in this edition are results of a groundbreaking study from Tufts University's Center for the Study of Drug Development.

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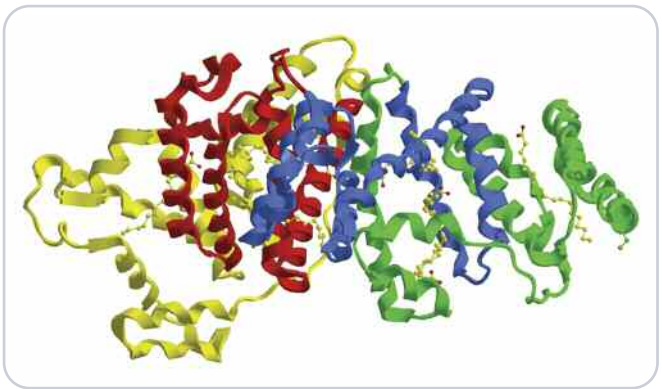
Serum Albumin a Strong Predictor of Mortality in Sepsis: Two New Studies



A retrospective, correlational study of all patients admitted to a U.S. regional hospital's intensive care unit (ICU) with a primary diagnosis of sepsis showed admission serum albumin level, serum albumin trend over time and lowest serum albumin level were all significant unique predictors of mortality. The probability of survival decreases by 70.6 percent when there is a strong negative trend in serum albumin level, by 63.4 percent when admission serum albumin is ≤2.45 g/dL, and by 76.4 percent when the lowest serum albumin level is ≤1.45 g/dL.

The investigators encouraged clinicians to measure serum albumin levels in patients with sepsis. "Low serum albumin levels and a strong negative trend in serial measurements should instigate aggressive monitoring and treatment in this population," they concluded.

In a separate study published the same week, Japanese investigators at Osaka University found daily negative changes in serum albumin level was especially strongly associated with mortality in a retrospective study of 136 septic patients treated in the ICU for more than seven days ($p<0.05$). Decreases in the values of total protein, total cholesterol and cholinesterase were also significantly associated with mortality during prolonged ICU stays.

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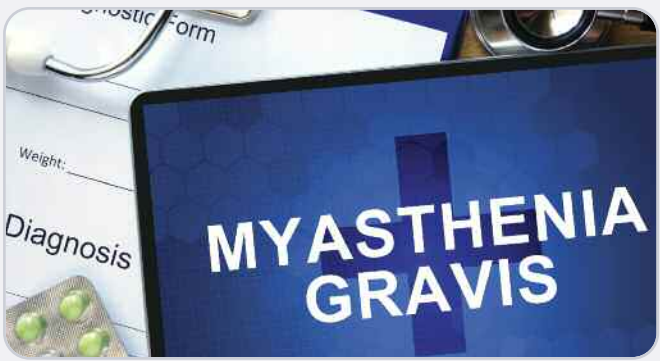
Excellent Response to Therapeutic Plasma Exchange in Myasthenia Gravis Patients with or Without Autoantibodies

A 96 percent response rate to treatment with therapeutic plasma exchange (PLEX) was seen in a series of 58 consecutive myasthenia gravis (MG) patients, with no significant difference in response between those with or without autoantibodies, according to a study by investigators at the University of Texas Southwestern Medical Center. Eighty-eight percent (51 of 58) of patients were autoantibody-positive, 44 had antibodies to acetylcholine receptor (AChR) and seven had antibodies against muscle-specific kinase (MuSK).

A complete response with resolution of symptoms was seen in 26 patients, 24 of whom were antibody-positive. Eighteen of these 24 complete responders (16 antibody-positive) required only an acute course of PLEX. Twenty-four other patients remain on maintenance PLEX, and two patients had no or minimal response (both of whom were AChR antibody-positive). All seronegative patients, who comprised 12 percent of patients in this study, responded to PLEX, although the majority of them required maintenance therapy.

While AChR antibodies, MuSK antibodies, early-onset MG, thymoma and thymectomy were not significantly associated with outcome, patient sex did show significant association with outcome, with males more likely to experience complete response and females more likely to require maintenance PLEX therapy. Late-onset MG was also significantly associated with higher likelihood of complete response to PLEX therapy ($P = 0.03$).



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Medicare Immune Globulin Reimbursement Rates

Rates are effective July 1, 2019, through Sept. 30, 2019

	Product	Manufacturer	HCPCS	ASP + 6% (before sequestration)	ASP + 4.3%* (after sequestration)
IVIG	FLEBOGAMMA	Grifols	J1572	$71.71	$70.56
	GAMMAGARD SD	Takeda	J1566	$124.44	$122.44
	GAMMAPLEX	BPL	J1557	$92.06	$90.59
	OCTAGAM	Octapharma	J1568	$77.35	$76.11
	PANZYGA	Octapharma	J1599	**	**
	PRIVIGEN	CSL Behring	J1459	$81.21	$79.90
IVIG/SCIG	GAMMAGARD LIQUID	Takeda	J1569	$81.93	$80.62
	GAMMAKED	Kedrion	J1561	$77.29	$76.05
	GAMUNEX-C	Grifols	J1561	$77.29	$76.05
SCIG	CUVITRU	Takeda	J1555	$138.56	$136.34
	HIZENTRA	CSL Behring	J1559	$101.89	$100.26
	HYQVIA	Takeda	J1575	$140.24	$137.99

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

** ASP-based Medicare payment rate not yet available; payment rate assigned by your Medicare Administrative Contractor.

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Immune Globulin Reference Table

	Product	Manufacturer	Indication	Size
IVIG	FLEBOGAMMA 5% DIF Liquid	Grifols	PI	2.5 g, 5 g, 10 g, 20 g
	FLEBOGAMMA 10% DIF Liquid	Grifols	PI, ITP	5 g, 10 g, 20 g
	GAMMAGARD S/D Lyophilized, 5% (Low IgA)	Takeda	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
	PANZYGA Liquid, 10%	Octapharma	PI, ITP	2.5 g, 5 g, 10 g, 20 g, 30 g
	PRIVIGEN Liquid, 10%	CSL Behring	PI, ITP, CIDP	5 g, 10 g, 20 g, 40 g
IVIG/SCIG	GAMMAGARD Liquid, 10%	Takeda	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%	Takeda	PI	1 g, 2 g, 4 g, 8 g
	HIZENTRA Liquid, 20%	CSL Behring	PI, CIDP	1 g, 2 g, 4 g, 10 g
	HYQVIA Liquid, 10%	Takeda	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

2019–2020 Influenza Vaccine

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

Product	Manufacturer	Presentation	Age Group	Code
Trivalent				
FLUAD (aIIV3)	SEQIRUS	0.5 mL PFS 10-BX	65 years and older	90653
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	3 years and older	90686
AFLURIA (IIV4)	SEQIRUS	5 mL MDV	6 months and older	90688
AFLURIAPEDIATRIC (IIV4)	SEQIRUS	0.25 mL PFS 10-BX	6-35 months	90685
FLUARIX (IIV4)	GSK	0.5 mL PFS 10-BX	6 months and older	90686
FLUBLOK (ccIIV4)	SANOFI PASTEUR	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	90756*
FLULAVAL (IIV4)	GSK	0.5 mL PFS 10-BX	6 months and older	90686
FLULAVAL (IIV4)	GSK	5 mL MDV	6 months and older	90688
FLUMIST (LAIV4)	ASTRAZENECA	0.2 mL nasal spray 10-BX	2-49 years	90672
FLUZONE (IIV4)	SANOFI PASTEUR	0.5 mL PFS 10-BX	6 months and older	90686
FLUZONE (IIV4)	SANOFI PASTEUR	0.5 mL SDV 10-BX	6 months and older	90686
FLUZONE (IIV4)	SANOFI PASTEUR	5 mL MDV	6 months and older	90688
FLUZONE PEDIATRIC (IIV4)	SANOFI PASTEUR	0.25 mL PFS 10-BX	6-35 months	90685/90687

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

* Providers should check with their respective payers to verify which code they are recognizing for Flucelvax Quadrivalent 5 mL MDV product reimbursement for this season.

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