SUMMER 2016

biosupply trends

QUARTERLY

SPECIAL FOCUS:
VACCINES

Centuries of Progress

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A UNIVERSAL GAME CHANGER?

NEW TECHNOLOGIES IN
Vaccine Administration

VACCINES FOR
International Travel

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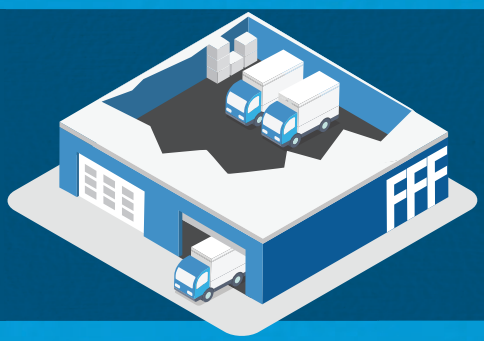
8 Critical Steps

Purchasing

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

Storage

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



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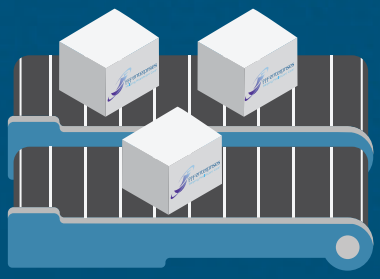

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Since 1988

To Guaranteed Channel Integrity™

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

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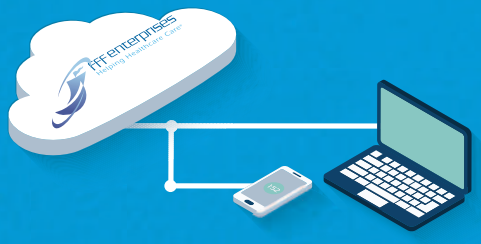

Verification

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

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Lot-Track™ electronically captures and permanently stores each product lot number, matched to customer information, for every vial of drug we supply.

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

FFF enterprises
Helping Healthcare Care®

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About BioSupply Trends Quarterly

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Despite Vaccine Benefits, Challenges Persist

Beginning with the development of the first vaccine in 1796 for the prevention of smallpox, vaccines now protect against a total of 26 diseases. While many vaccines are recommended for U.S. children and adults, some are recommended only in selected populations at high risk due to factors such as area of residence, age, medical condition or risk behaviors. Even so, though U.S. vaccination is at record high levels, many of the vaccine-preventable diseases persist in the U.S. and, especially, in developing countries.

First licensed in 1945 in the U.S., influenza vaccine continues to evolve. As discussed in our article "What's New with the Flu?," global, year-round surveillance efforts continue to better identify the mutating viruses to produce a vaccine well-matched to the circulating viruses of the upcoming flu season for increased protective effect. Additionally, new production methods such as the use of plants as growth media are being developed to more quickly and cheaply produce sufficient quantities of the vaccine to thwart pandemics. Yet, despite these advancements, influenza vaccination rates continue to flounder in the U.S. due to disbelief by the public that it will protect them and, more so, because of unwarranted fears.

With efficacy rates hovering just under 60 percent at best, many are unconvinced that the benefits of the influenza vaccine outweigh the perceived risks. But scientists say they are on the verge of developing a vaccine that may greatly improve its effectiveness. In our article "Influenza Vaccine: A Universal Game Changer?," we look at three of the many studies being conducted to develop a "universal" vaccine targeting the part of the influenza virus that doesn't mutate year to year, which could protect against virtually every type of flu virus. More importantly, it would be given less frequently.

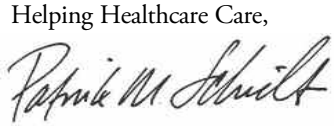
It seems logical that if influenza vaccinations were necessary only every decade, or perhaps only once in a lifetime, more people would comply. But, a jab is still a jab. And, that goes for all types of vaccines, not just influenza. The saving grace may be new technology that replaces the hypodermic needle. In our article "Evolving Technology in Vaccine Administration," we explore three different methods to make vaccination less painful, including needle-free injection, microneedle patches and nasal mists. These devices, some of which are currently available and others in development, will solve other problems, as well, such as reducing costs, improving pandemic management and providing for self-administration.

Despite all these scientific efforts and achievements, many vaccine-preventable diseases still exist, including poliomyelitus, or polio, for which a vaccine was first licensed in the U.S. in 1955. As we explain in our article "Update on Polio and Post-Polio Syndrome," most cases today occur in developing countries, most specifically Afghanistan and Pakistan. Yet, many Americans who contracted the disease prior to the vaccine availability continue to develop post-polio syndrome, suffering recurrence of symptoms.

While most individuals residing in the U.S. are immunized against polio, there are many other infectious diseases that are endemic to regions outside of North America for which we don't usually need protection. Until we travel. That's why, as our article "Vaccines for International Travel" outlines, it's crucial for individuals traveling abroad to be vaccinated against four diseases that are widely discussed in travel medicine: typhoid, hepatitis A, Japanese encephalitis and yellow fever.

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

Helping Healthcare Care,



Patrick M. Schmidt
Publisher

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

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CMS Issues Final Rule for DMEPOS

The Centers for Medicare and Medicaid Services (CMS) has issued a final rule that mandates prior authorization for some durable medical equipment prosthetics, orthotics and supplies (DMEPOS). Under the rule, documentation to meet authorization for DMEPOS is needed earlier in the process to furnish the items, 80 percent of which the cost will be covered if a physician deems the item necessary. The rule allows CMS to move away from a "pay and chase" model under which CMS makes payments on claims and then tries to recoup them after it identifies claims are improper. A 2011 report from the Health and Human Services Office of Inspector General found that 61 percent of power wheelchairs provided in the first six months of 2007 were medically unnecessary or lacked sufficient documentation to determine medical necessity.

The rule will include a master list of 135 products that are frequently deemed medically unnecessary that will be updated annually and for which a prior authorization process will be developed. Because the items on the master list don't automatically require prior authorization, CMS will publish a subset of that list in the Federal Register with 60 days notice for the products that do require prior authorization. ❖

CMS to Implement New Primary Care Payment Model

The Centers for Medicare and Medicaid Services (CMS) is planning to implement a new primary care payment model in up to 20 regions that will affect up to 5,000 practices, encompassing more than 20,000 doctors and clinicians. Under the Comprehensive Primary Care Plus initiative, providers will be able to participate in one of two ways. In Track 1, CMS will pay a monthly fee to practices for specific services in addition to the fee-for-service payments under the Medicare Physician Fee Schedule for care. In Track 2, practices will receive a monthly care management fee, as well as reduced Medicare fee-for-service payments and upfront comprehensive primary care payments. The goal of Track 2 is to allow greater flexibility in how practices deliver care outside of the traditional face-to-face encounter such as telemedicine visits or longer office visits for patients with complex needs. Currently, providers submit a claim to Medicare for payment after performing a service.

To be eligible for either track, providers must demonstrate that: 1) services are accessible and responsive to a person's preferences, and offer enhanced in-person hours and 24/7 telephone or electronic access; 2) patients at highest risk receive proactive, relationship-based care-management services to improve outcomes; 3) care is comprehensive, and practices can meet the majority of each individual's physical and mental healthcare needs, including prevention; care is also coordinated across the healthcare system, including specialty care and community services; and patients receive timely follow-up after emergency room or hospital visits; 4) the practice is patient-centered, recognizing that patients and family members are core members of the care team, and the practice actively engages patients to design care that best meets their needs; and 5) quality and utilization of services are measured, and data is analyzed to identify opportunities for improvements in care and to develop new capabilities.

CMS plans to identify regions to be affected after it assesses interest by providers. Once determined, practice applications will be accepted from July 15 through September 1. ❖

CMS Finalizes 2017 ACA Marketplace Plan Requirements


Final HHS Notice of Benefit and Payment Parameters for 2016

In March, the Centers for Medicare and Medicaid Services published its annual Notice of Benefit and Payment Parameters, a final rule that governs participation in the Affordable Care Act (ACA) health insurance marketplaces for 2017. Major provisions of the rule include:

- Qualified health plan (QHP) payment parameters were changed, including recalibrating the risk adjustment formula using most recent data and establishing separate growth rates for traditional and specialty drugs and medical/surgical expenditures; establishing a lower default risk adjustment charge for small insurers; increasing the default risk adjustment charge; updating the premium adjustment percentage; and setting the 2017 maximum annual limitation on cost sharing for $7,150 for individuals and $14,300 for families.
- "Surprise" bills that occur when out-of-network services are performed at an in-network facility are limited by requiring QHP insurers to count such out-of-pocket expenses toward an enrollee's out-of-pocket maximum unless notification requirements were met (beginning in 2018).
- Continuity of care protections were established to require QHP insurers to provide prior written notice to enrollees of discontinuation of a provider and, in cases in which a provider is terminated without cause, allow an affected enrollee to continue treatment at in-network cost-sharing rates, subject to certain parameters.
- Ratings will be included on HealthCare.gov related to each QHP's relative network coverage.
- QHP insurers will be allowed to offer plans with standardized cost-sharing options to facilitate consumer comparison of plans.
- QHP insurers will be required to verify that contracted hospitals with more than 50 beds either work with a patient safety organization, or implement an evidence-based initiative to improve healthcare quality through data collection and analysis of patient safety events to reduce all-cause preventable harm, prevent readmissions and improve care coordination.
- For 2017 and 2018, open enrollment will run from November 1 of the previous year through January 31 of the coverage year. In 2019 and beyond, open enrollment will run from November 1 through December 15 of the year preceding coverage.

The final rule also addresses Navigators' post-enrollment functions, Small Business Health Options Program plans, third-party cost-sharing payments, student health insurance coverage, the rate review program, the medical loss ratio program, eligibility and enrollment, exemptions and appeals, user fees for federally facilitated exchanges, and codification of a new "Stage-based Exchange on the Federal Platform" model.

In addition, CMS released the following guidance documents: the final Annual Letter to Insurers, which provides operational and technical guidance to insurers seeking to offer QHPs in the federally facilitated marketplaces or the federally facilitated Small Business Health Options programs; a bulletin on Timing of Submission and Posting of Rate Filing Justifications for the 2016 filing year for single risk pool coverage; frequently asked questions on the recently enacted moratorium on the ACA health insurance provider fee; and guidance on an additional extension of a transitional policy for certain nongrandfathered individual and small group health policies that are not compliant with specific ACA standards. ❖

Medicare Rights Launches New Medicare Interactive

The Medicare Rights Center has launched a new and improved Medicare Interactive (MI), a free online resource with hundreds of answers to Medicare questions. The new design allows users to find answers for themselves, family members or clients through smart links to relevant MI pages and case examples, a roll-over glossary and other resources. In addition, users can create a MI profile to bookmark favorite pages, manage newsletter subscriptions, access exclusive links/downloads and receive notices about key Medicare dates. A welcome e-packet and the New to Medicare Guide will be sent to new registrants.

Also on the site is a new MI Pro learning curriculum that provides users access to exclusive in-depth Medicare content, quizzes to test their progress and printable learning tools. A self-assessment can help users determine which courses are right for them. Users can complete coursework at their own pace with the ability to keep track of where they left off within each course. ❖

New Part B Drug Payment Models

THE PRICE OF drugs, immunologics and biologics and their complicated reimbursement structure have taken a toll on both patients and the healthcare environment. And now, new proposals, models and rules from the Centers for Medicare and Medicaid Services (CMS), the U.S. Food and Drug Administration and the Department of Health and Human Services (HHS) that will affect payments have emerged this spring, necessitating changes for healthcare practices. This column will concentrate on the proposed rule announced by CMS on March 8 that will test six different options for Medicare Part B reimbursement under the outpatient prospective payment system (OPPS).

Under the auspices of the Center for Medicare and Medicaid Innovation (CMMI) created by the Affordable Care Act, CMS has the authority to test innovative payment and service delivery models with the goal of reducing program expenditures under Medicare and Medicaid and at the same time preserving or enhancing the quality of care furnished to individuals under these programs. With this authorization, CMMI will test innovative payment and service delivery models that address a defined population for which there are deficits in care. Successful models will then be expanded to cover more geographic areas over a longer period of time.

Current Medicare Part B Drug Payments under OPPS

Drugs, biologics and radiopharmaceuticals currently are reimbursed by Medicare in one of several ways: as pass-through drugs, as separately payable drugs and as nonseparately payable products that are bundled or packaged into the reimbursement for the service or procedure. Bundling or packaging means there is no separate identified payment for the product, and disbursing the bundled payment is left to the discretion of the facility. Pass-through drugs and separately payable drugs currently are paid at a rate of average sales price (ASP) plus 6 percent (minus approximately 2 percent for as long as sequestration remains in place).

Medicare Part B Drug Payment Model Rule Proposed by HHS

If implemented, the new two-phase proposed rule by HHS would significantly impact how Medicare pays for separately payable Part B program drugs in about half of the states as early as August 1. In phase I, the new formula would change the incentives for prescribing certain drugs, strongly affecting reimbursement and revenues for a wide range of providers. Phase II would introduce "value-based drug pricing" that could further impact prescribing incentives, as well as hospital and physician revenues. (See Figure 1.)

In selecting participants, CMS considered five options for geographic areas in which clusters of providers would be assigned to one of four arms of the model. All providers and suppliers furnishing covered and separately paid Part B drugs would be required to participate if chosen. The proposal uses primary care service areas (PCSAs), which are clusters of ZIP codes that reflect primary care service delivery and are defined and updated under contract to the Health Resources and Services Administration by The Dartmouth Institute. Of the 7,144 PCSAs, 96 in Maryland where hospital outpatient departments operate under an all-payer model would be excluded. The remaining 7,048 PCSAs would be assigned to one arm of the model (the control and three test arms) using a stratified random approach.

The proposed rule would create a demonstration program to test ways to reimburse for separately payable prescription drugs that would largely impact Part B drug reimbursement in physician offices, hospital outpatient clinics and stand-alone clinics that specialize in areas such as oncology or immunology. It would include all Part B drugs and biologics (including biosimilars) with Healthcare Common Procedure Coding System codes.

The following products would be excluded from the model and would continue to be paid for in the current manner:

- Blood and blood products
- Contractor-priced drugs (unless the contractor opted to include them)
- Drugs infused with covered durable medical equipment (DME) (excluded from phase I)
- Drugs in short supply
- Drugs that fall under bundled or packaged payment
- End-stage renal disease drugs
- Influenza, pneumococcal, pneumonia and hepatitis B vaccines

CMS intends to test this program for five years, during which time the agency would monitor the progress and impact of the new payment scheme.

Phase I would recalculate the outpatient Part B payment formula from ASP plus 6 percent to ASP plus 2.5 percent plus a flat fee of $16.80 per drug per day. The start date for phase I would be 60 days following the final rule publication. The flat fee would be updated annually and would be based on the consumer price index for

medical care. Sequestration reductions of approximately 2 percent would apply to all payments, including the flat fee.

Phase II, implemented as early as January 2017, would use value-based tools for medication purchases. These tools would include concepts such as reference pricing (an average payment rate based on therapeutically equivalent drugs), indications-based pricing (based on comparative studies), discounting or eliminating patient cost sharing, and clinical decision support (evidence-based).

The rationale behind the design of the first phase of the model is that current payment methodology based on a percentage of cost markup may incentivize physicians to use more expensive drugs when equally effective but less costly ones are available. Whether or not this is the motivation, sites using expensive medications would be most impacted by the proposed model. The second phase would test a variety of value-based purchasing (VBP) strategies that could be beneficial to all sites regardless of specialty.

Using a range of analytical methods, researchers would separately evaluate the impact of each intervention assigned to each model test arm compared with those in areas assigned to the control arm. These key evaluation metrics would include, among others, whether the model resulted in:

- Reduction in Part B drug spending, as well as total Part B and total Medicare program expenditures
- Changes in overall utilization and prescribing patterns and for specific types of providers and suppliers
- Changes in the prices at which providers and suppliers are able to obtain Part B drugs
- Changes in the quality of care, access to care, timeliness of care and the patient care experience
- Observable, unintended consequences

Figure 1. Model Structure for Separately Payable Drugs

Phase I (two groups)	Phase II (four groups)
Implementation as early as Aug. 1, 2016	Implementation as early as Jan. 1, 2017
Goal: Test impact of new payment rate	Goal: Test impact of new payment rate and VBP tools
Group 1: ASP plus 6% for approximately 50% of Part B enrollees	Group 1. ASP plus 6% for approximately 25% of Part B enrollees (no VBP tools)
Group 2: ASP plus 2.5% plus $16.80 for approximately 50% of Part B	Group 2: ASP plus 6% for approximately 25% of Part B enrollees enrollees (VBP tools)
	Group 3: ASP plus 2.5% plus $16.80 for approximately 25% of Part B enrollees (no VBP tools)
	Group 4: ASP plus 2.5% plus $16.80 for approximately 25% of Part B enrollees (VBP tools)
Designed to be budget-neutral	Designed to generate savings
CMS expects some savings from behavioral responses	CMS doesn't have enough information on the VBP tools to generate a savings estimate
No estimate of potential savings provided by CMS	CMS solicits comments on the anticipated effects of its proposed changes on providers and suppliers

Source: Medicare Program: Part B Drug Payment Model: A Proposed Rule by the Centers for Medicare & Medicaid Services. Accessed at www.federalregister.gov/articles/2016/03/11/2016-05459/medicare-program-part-b-drug-payment-model.

Impact to Practice Sites

The proposed rule would have significant impact upon healthcare sites. Key points are the details of the proposed rule itself and its financial impact. It is likely that OPPS drug reimbursement will be less than the current model for drugs with ASP over $480, and more for drugs with ASP under $480. When performing an analysis for a healthcare site, the finance department must remember to exclude all specifically excluded products and all bundled payment products. This proposal would cover only separately payable Part B products. ❖

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ASK OUR EXPERTS

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

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

Medicines

FDA Approves First Coagulation Factor-Albumin Fusion Protein to Treat Hemophilia B

In March, the U.S. Food and Drug Administration (FDA) approved CSL Behring's Idelvion (coagulation factor IX [recombinant], albumin fusion protein) for on-demand control and prevention of bleeding episodes, management of bleeding following surgery and as a routine preventive measure to reduce the frequency of bleeding episodes in children and adults with hemophilia B. It is the first coagulation factor-albumin fusion protein product to be approved and the second factor IX fusion protein product approved in the U.S. that is modified to last longer in the blood.

Idelvion is used to replace factor IX, a naturally occurring clotting factor that is missing or defective in people with hemophilia B (also called congenital factor IX deficiency, or Christmas disease). It is produced by recombinant DNA technology linking factor IX to albumin, which accounts for the product lasting longer when given intravenously. Idelvion potentially requires less frequent injections than unmodified factor IX when used for prevention.

In two multicenter studies evaluating the safety and efficacy of Idelvion in 90 adult and pediatric patients with hemophilia B between age 1 year and 61 years, Idelvion was demonstrated to be effective in controlling bleeding episodes and in managing perioperative bleeding. In addition, Idelvion used as prophylaxis led to a significant reduction in the rate of spontaneous bleeding episodes per year despite less frequent infusions. No safety concerns were identified in the studies, and the most common side effect was headache. ❖

FDA Approves First Coagulation Factor-Albumin Fusion Protein to Treat Patients with Hemophilia B. U.S. Food and Drug Administration press release, March 4, 2016. Accessed at www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm489266.htm.

Medicines

FDA Expands Approval of Combination Therapy for Melanoma

Under accelerated approval based on progression-free survival (PFS), the U.S. Food and Drug Administration (FDA) has approved Opdivo (nivolumab) in combination with Yervoy (ipilimumab) for the treatment of patients with BRAFV600 wild-type and BRAFV600 mutation-positive unresectable or metastatic melanoma. This approval expands the original indication for the Opdivo plus Yervoy regimen for the treatment of patients with BRAFV600 wild-type unresectable or metastatic melanoma to include patients, regardless of BRAF mutational status, based on data from the Phase III CheckMate 067 trial in which PFS and overall survival were co-primary endpoints. FDA also expanded the use of Opdivo as a single agent to include previously untreated BRAF mutation-positive advanced melanoma patients. However, continued approval for this latter indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

CheckMate 067, a double-blind, randomized study that evaluated the Opdivo plus Yervoy regimen or Opdivo monotherapy versus Yervoy monotherapy in patients with previously untreated advanced melanoma, including both BRAFV600 mutant and wild-type advanced melanoma, enrolled 945 patients who were randomized to receive the Opdivo plus Yervoy regimen (Opdivo 1 mg/kg plus Yervoy 3 mg/kg every three weeks for four doses followed by Opdivo 3 mg/kg every two weeks thereafter), Opdivo monotherapy (Opdivo 3 mg/kg every two weeks) or Yervoy monotherapy (Yervoy 3 mg/kg every three weeks for four doses followed by placebo every two weeks). Patients were treated until progression or unacceptable toxic effects. The median duration of exposure was 2.8 months for patients in the Opdivo plus Yervoy regimen with a median of four doses, and 6.6 months duration for the Opdivo monotherapy with a median of 15 doses.

Results demonstrated a statistically significant improvement in PFS in patients with advanced melanoma treated with the Opdivo plus Yervoy regimen and with Opdivo as a single agent versus Yervoy monotherapy. Median PFS was 11.5 months for the Opdivo plus Yervoy regimen and 6.9 months for Opdivo monotherapy, vs. 2.9 months for Yervoy monotherapy. The Opdivo plus Yervoy regimen demonstrated a 58 percent reduction in the risk of disease progression versus Yervoy, while Opdivo monotherapy demonstrated a 43 percent risk reduction versus Yervoy monotherapy. In addition, the Opdivo plus Yervoy regimen and Opdivo monotherapy demonstrated higher confirmed objective response rates versus Yervoy monotherapy. ❖

Bristol-Myers Squibb's Opdivo (nivolumab) + Yervoy (ipilimumab) Regimen Receives Expanded FDA Approval in Unresectable or Metastatic Melanoma Across BRAF Status. BusinessWire, Jan. 23, 2016. Accessed at www.businesswire.com/news/home/20160123005053/en/Bristol-Myers-Squibb's-Opdivo-nivolumab-Yervoy-ipilimumab-Regimen.

Research

Study Provides Clues for Improving Effectiveness of Flu Vaccine

A study conducted by scientists at the National Institute for Allergy and Infectious Diseases (NIAID) has found that seasonal flu vaccines work better if they stimulate an immune response to the flu surface protein neuraminidase (NA), which enables newly formed flu viruses to exit the host cell and cause further viral replication in the body. Currently, seasonal flu vaccines are designed to induce high levels of protective antibodies against hemagglutinin (HA), which enables the virus to enter a human cell and initiate infection. Traditionally, HA antibodies levels have been used to guide vaccine strain selection and to infer how effective that vaccine might be against circulating viruses until field studies are available.

In the human challenge study (in which individuals are exposed to disease-causing pathogens under carefully controlled conditions), NIAID researchers enrolled 65 healthy volunteers aged 18 years to 50 years and measured the levels of existing anti-HA and anti-NA antibodies in participants' blood. Based on those results, participants were placed in two groups: those with high levels of anti-HA antibodies (25 participants) and those with low levels of anti-HA antibodies (40 participants). Each of the volunteers was then administered an intranasal dose (1 mL) of 2009 H1N1 influenza virus, after which they were required to stay in the study unit for nine days where they were monitored by medical staff 24 hours daily. After the nine-day testing period, participants were discharged after completing two days of negative flu tests. After that, they had four follow-up visits over an eight-week period.

The researchers found that those with high levels of anti-HA antibodies experienced significantly lower incidence of mild-to-moderate influenza disease and some reduction in its duration compared with participants with low HA antibody levels. However, they also found that participants were just as likely to experience some flu symptoms as those with low levels of HA antibodies. Those results suggest that while high HA antibody levels may limit viral shedding and, thus, spread the virus from person to person, these levels may not prevent the development of flu symptoms, which may explain why some people who receive the flu vaccine might still get the flu. What surprised the researchers was that participants with high levels of NA antibodies experienced less severe disease, a shorter duration of viral shedding and symptoms, and fewer and less severe symptoms compared with those with high HA antibody levels.

The researchers concluded that HA and NA antibody levels together may be a better predictor of whether someone develops mild-to-moderate influenza disease and severity of symptoms than either factor alone; however, NA antibodies are the stronger factor for determining disease severity. And, they suggest that the role of NA immunity should be considered when studying influenza susceptibility, and NA antigens should be considered in the design of future flu vaccine platforms. ❖

National Institutes of Health. NIH Study Finds Factors That May Influence Influenza Vaccine Effectiveness. News release, April 19, 2016. Accessed at www.nih.gov/news-events/news-releases/nih-study-finds-factors-may-influence-influenza-vaccine-effectiveness.

Medicines

Second Biosimilar Drug in U.S. Is Approved by FDA

The U.S. Food and Drug Administration (FDA) has approved Celltrion's Inflectra (infliximab-dyyb), a biosimilar version of Johnson & Johnson's Remicade drug used to treat autoimmune diseases. Inflectra is approved to treat adult and pediatric patients (ages 6 years and older) with moderately to severely active Crohn's disease who have had an inadequate response to conventional therapy; adult patients with moderately to severely active ulcerative colitis who have had an inadequate response to conventional therapy; patients with moderately to severely active rheumatoid arthritis in combination with methotrexate; patients with active ankylosing spondylitis (arthritis of the spine); patients with active psoriatic arthritis; and adult patients with chronic severe plaque psoriasis. Respiratory infections, including sinus infections and sore throat, headache, coughing and stomach pain, are the most common expected side effects of the drug.

FDA approval was based on a demonstrated high degree of similarity between Inflectra and Remicade. Pfizer holds the exclusive commercialization rights to Inflectra in the U.S. It is the second biosimilar approved for sale in the U.S. ❖

FDA Approves Inflectra, a Biosimilar to Remicade. U.S. Food and Drug Administration press release, April 5, 2016. Accessed at www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm494227.htm.

Research

Flu Vaccine Given in the Morning Could Be More Effective

Researchers at the University of Birmingham in the United Kingdom have found that flu vaccines are more effective when given in the morning because patients' immune systems are capable of producing more antibodies in response to the vaccine in the first part of the day. In the study, the researchers monitored 276 adults age 65 and older being vaccinated against three strains of the flu virus. Some were given the vaccine in the morning between 9 a.m. and 11 a.m., and the others were given the vaccine in the afternoon between 3 p.m. and 5 p.m. One month after vaccination, those who received the morning vaccine showed a significantly larger concentration of antibodies to the virus compared with those who received the afternoon vaccine. The scientists plan to continue their research by testing their theory on a larger number of subjects aged 65 and older, including those with impaired immunity caused by illnesses such as diabetes or conditions affecting the liver and kidneys. They will also test the morning vaccination strategy with the pneumococcal vaccine in individuals age 65 and older. The study was published in the journal *Vaccine*. ❖

Flu Vaccine Found to Be More Effective When Given in the Morning. Yahoo News, April 26, 2016. Accessed at www.yahoo.com/news/flu-vaccine-found-more-effective-given-morning-145319740.html.

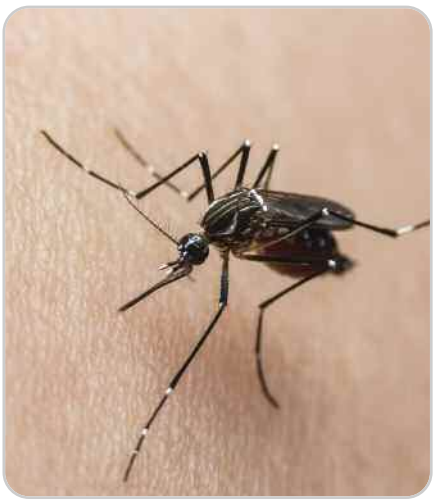
Policy

CDC Issues Guidelines for Prescribing Opioids for Chronic Pain

The Centers for Disease Control and Prevention (CDC) has released the *CDC Guideline for Prescribing Opioids for Chronic Pain — United States, 2016* that provides recommendations for prescribers of opioids for chronic pain outside of active cancer treatment, palliative care and end-of-life care. The goal is to improve the care and safety of patients, promote integrated pain management and collaborative working relationships with other providers such as pharmacists, and make reference to collaborative practice models for the dispensing of naloxone. In the guideline, CDC recommends non-opioid therapy as the preferred treatment of chronic pain; prescribing the lowest effective dosage when opioids are used; and working with patients to establish pain treatment goals, checking for improvements in pain and function regularly, assessing for risks and benefits and tapering or discontinuing opioids when risks outweigh benefits. The guideline can be accessed at www.cdc.gov/mmwr/volumes/65/rr/rr6501e1er.htm. ❖

Vaccines

Malaria Vaccine Candidate Generates Robust Immune Response



Findings from a first in-human study for a new malaria vaccine candidate have shown a robust immune response while significantly delaying parasitemia (a measurement of parasite load in the organism and an indication of the degree of an active parasitic infection) in 59 percent of vaccinated subjects. In the study, researchers at Walter Reed Army Institute of Research immunized 30 volunteers (who took part in a controlled human malaria infection [CHMI] model in which they were bitten by malaria-infected mosquitoes) with three doses of the vaccine. Efficacy of the vaccine was determined based on whether the volunteers developed malaria by looking at blood smears or if it took longer for malaria parasites to appear in the blood. Plasmodium vivax malaria can be dormant, causing no symptoms, and then become active causing symptomatic malaria weeks to months after initial infection.

"This study represents the first vaccine study to test the effectiveness of a P vivax vaccine candidate in humans using controlled human malaria infection," said Jason W. Bennett, the study's lead investigator. The CHMI model relies on blood donations from infected humans to initiate infections in mosquitoes.

Researchers were also able to demonstrate that individuals with low or absent levels of a specific liver enzyme were unable to convert primaquine, the only FDA-approved drug to treat the dormant stages of vivax malaria, to an active drug form to kill the dormant stage of the parasites. ❖

Research

Phase I Trial Launched for Extended Half-Life Factor VIII

Baxalta has begun a Phase I, first-in-human clinical trial of BAX 826, a recombinant factor VIII (rFVIII) treatment for hemophilia A that uses proprietary polysialic acid (PSA) technology to extend its circulating half-life. The open-label, dose-finding study will evaluate the safety and pharmacokinetics of BAX 826 in 30 patients in three dosing cohorts, and plans to complete enrollment by the end of 2016.

BAX 826 is being studied as the company's second extended half-life treatment based on Advate (antihemophilic factor [recombinant]). Baxalta has partnered with Xenetic Biosciences Inc. to develop novel forms of polysialyated blood coagulation factors, including FVIII, using Xenetic's PolyXen biopolymer PSA technology to extend the circulating half-life and potentially improve the pharmacokinetic profile. Preclinical studies indicated BAX 826 offered an extended circulating half-life compared to standard rFVIII. ❖

Baxalta Commences Phase I Clinical Trial of BAX 826, the Company's Second Extended Half-Life Factor VIII Treatment for Hemophilia A. Baxalta press release, April 4, 2016. Accessed at newsroom.baxalta.com/press-releases/press-release-details/2016/Baxalta-Commences-Phase-1-Clinical-Trial-of-BAX-826-the-Companys-Second-Extended-Half-Life-Factor-VIII-Treatment-for-Hemophilia-A/default.aspx.

Research

Genome Sequencing Uncovers New Autoimmune Syndrome

Using technology that allows scientists to read the script of a person's DNA, scientists have found a new autoimmune disease syndrome that combines severe lung disease and arthritis. The disorder appears early in childhood and is caused by mutations in a single gene that disrupt how proteins move around within cells. Patients with the disorder have a poor prognosis. While they can be treated with anti-inflammatory and immunosuppressant drugs, many have such severe lung disease that they require a lung transplant.

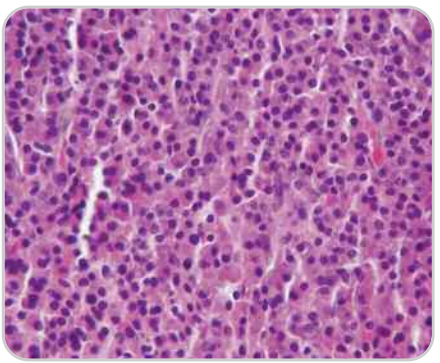
However, scientists remain hopeful that more effective treatments can be developed. "We believe there are small molecules in development that can help correctly traffic the proteins that are misdirected in this syndrome, so that's something we really want to go after," said Anthony K. Shum, MD, co-senior author of the report, which appeared in the journal *Nature Genetics*, and an assistant professor of medicine at the University of California, San Francisco.

The discovery was made after Dr. Shum treated a woman for a pulmonary hemorrhage and learned she had arthritis, too. He then learned that the patient had a sibling and an aunt both with the same lung disease and arthritis combination. ❖

Johnson M. New Autoimmune Syndrome Discovered Using Genome Sequencing. *Milwaukee-Wisconsin Journal Sentinel*, April 21, 2015. Accessed at www.jsonline.com/blogs/news/300808881.html.

Medicines

Empliciti Approved by FDA to Treat Multiple Myeloma



Empliciti (elotuzumab) in combination with Revlimid (lenalidomide) and dexamethasone (a type of corticosteroid) has been approved by the U.S. Food and Drug Administration (FDA) to treat individuals with multiple myeloma who have received one to three prior medications. Empliciti, marketed by Bristol-Myers Squibb, activates the body's immune system to attack and kill multiple myeloma cells.

Its safety and efficacy were tested in a randomized, open-label clinical study of 646 participants whose multiple myeloma came back after, or did not respond to, previous treatment. Those taking Empliciti plus the two other therapies experienced a delay in the amount of time before their disease worsened (19.4 months) compared with participants taking only Revlimid and dexamethasone (14.9 months). In addition, 78.5 percent of those taking Empliciti with the two other therapies saw a complete or partial shrinkage of their tumors compared with 60.1 percent in those taking only Revlimid and dexamethasone. The most common side effects were fatigue, diarrhea, fever, constipation, cough, nerve damage resulting in weakness or numbness in the hands and feet, infection of the nose and throat, upper-respiratory tract infection, decreased appetite and pneumonia. ❖

Research

Potential Tobacco-Based Vaccine Could Rival Egg-Based Vaccines

A new tobacco-based seasonal influenza vaccine being developed by Mitsubishi Tanabe Pharma and currently in Phase III studies could potentially rival traditional chicken egg-based vaccines. The new vaccine, which the company aims to launch in the U.S. for the 2018-19 flu season, uses technology that implants influenza genetic material into tobacco leaves, a method that can produce the vaccine in four weeks, which is six times faster than egg-based methods. ❖

New Tobacco-Based Flu Vaccine Offers Promising Alternative to Egg-Based Versions, Says GlobalData Analyst. *Manufacturing Chemist Pharma,* March 11, 2016. Accessed at www.manufacturingchemist.com/news/ article_page/New_tobaccobased_flu_vaccine_offers_promising_alternative_to_eggbased_versions_says_GlobalData_analyst/116474.

Research

Key Genetic Factor Behind Autoimmune Diseases and Cancer Is Identified

Scientists at Yale have uncovered a molecular mechanism that causes variants in a specific immune response gene known as MIF (macrophage migration inhibitory factor). Variants of MIF that cause overexpression of the gene contribute to a range of diseases, including rheumatoid arthritis, lupus, infectious diseases and cancer. Knowing the exact transcription factor, or protein, that regulates the gene could lead to more personalized treatment.

The Yale lab, led by Richard Bucala, MD, PhD, is already studying drugs that target MIF in clinical trials of cancer and autoimmunity. According to Dr. Bucala, having a deeper understanding of the gene's variants and expression will lead to precision drug targeting based on an individual's genetic profile. "Knowing what the transcription factor is presents the possibility of a real personalized medicine approach," he said. ❖

Kashef Z. Study Pinpoints Key Genetic Factor Behind Autoimmune Diseases, Cancer. *MedicalXpress,* Jan. 13, 2016. Accessed at medicalxpress.com/news/2016-01-key-genetic-factor-autoimmune-diseases.html.

Research

Scientists Find a Potential Cure for Cancer

Scientists from Harvard, MIT and University College London have made a discovery about the genetics of cancer tumors that could offer a new way to deliver customized immunotherapy drugs to kill all types of cancer, including the most complex such as melanoma and lung cancer. Currently, it is difficult to treat cancer effectively because as cancer tumors grow, they mutate into a mixture of many kinds of rogue cells that behave differently from one another. But, the researchers have found that even as the cells mutate, each still produces distinct "flags," or antigens, that appear on the surface of the tumor's cells. As one of the scientists explained: "A tumor's evolutionary tree is like a snowflake, unique for each patient. These tumors develop new branches with genetic mutations, and these mutations resist treatment. But the 'trunk' of this tree contains these flag proteins, and each branch that grows out of this trunk contains the same flag."

Finding these unique flags, deemed the "Achilles heel" of cancer, is the key for treatment to completely kill the cancer. Because an antigen has to be present on all tumor cells, identifying these unique flags will pave the way for treatments that would activate T cells to target and attack all tumor cells at once. "This opens up a way to look at individual patients' tumors and profile all the antigen variations to figure out the best ways for immunotherapy treatments to work, prioritizing antigens present in every tumor cell and identifying the body's immune T cells that recognize them," says the study's co-author Charles Swanton from the University College London Cancer Institute.

While the findings have not yet been used to treat live patients, the researchers say they hope to launch a study in lung cancer patients in the next two to three years. The study was published in the journal *Science.* ❖

McGranahan N, Furness AJS, Rosenthal R, et al. Clonal Neoantigens Elicit T Cell Immunoreactivity and Sensitivity to Immune Checkpoint Blockade. *Science,* March 3, 2016, doi: 10.1126/science.aaf1490. Accessed at science.sciencemag.org/content/early/2016/03/02/science.aaf1490.

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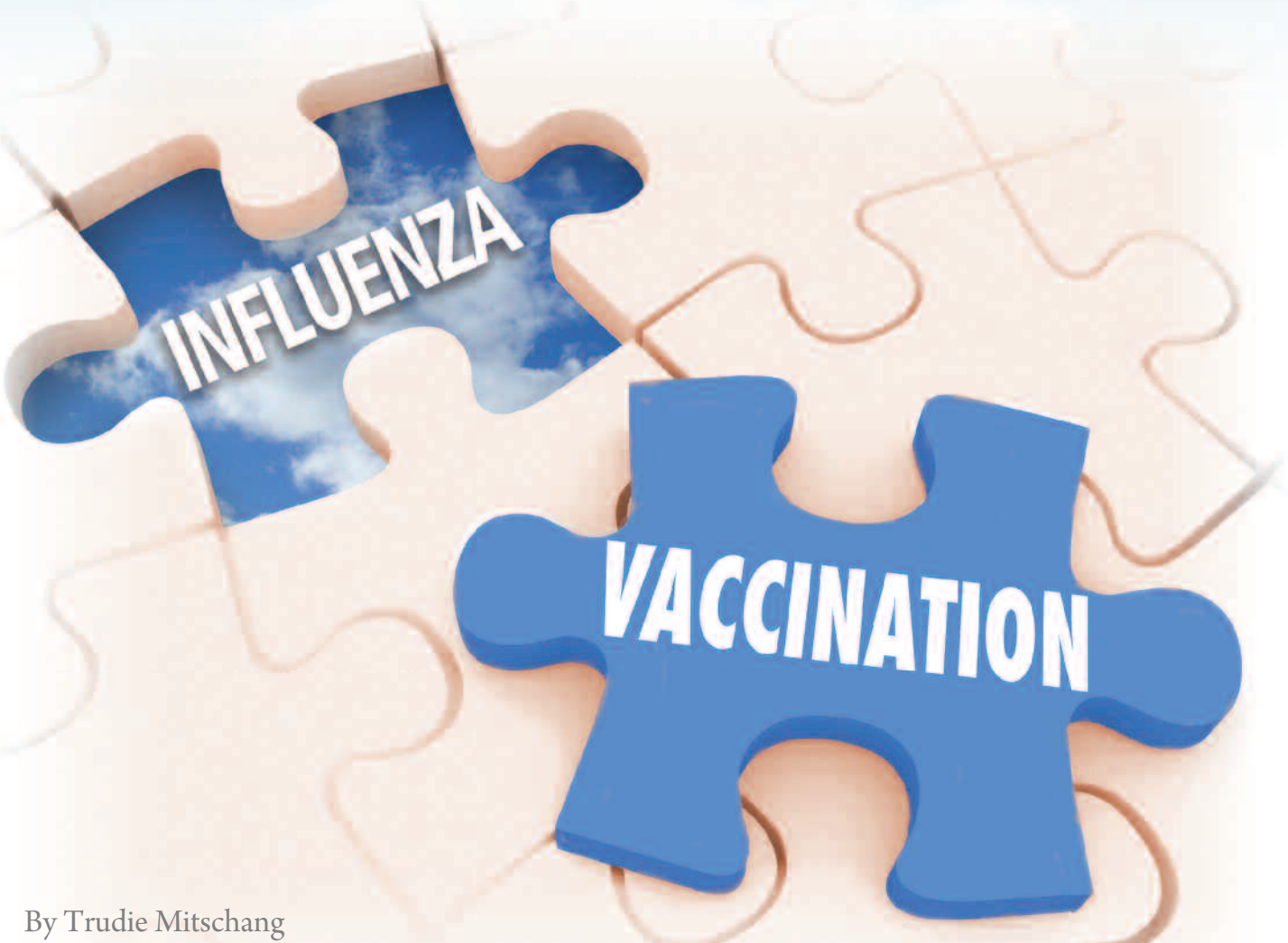
What's New with the Flu?



By Trudie Mitschang

Recent U.S. Food and Drug Administration advisory committee strain recommendations could make this season's influenza (flu) vaccine more effective than ever. But, will an epidemic of public apathy undermine immunization efforts?

THIS PAST YEAR, the U.S. Food and Drug Administration's Vaccines and Related Biological Products Advisory Committee unanimously voted to adopt the World Health Organization's (WHO) recommendations to make two changes to the 2016-2017 influenza vaccine based on global surveillance of circulating influenza strains, and on an evaluation of the effectiveness of the Northern Hemisphere vaccine for the 2015-2016 season.[1] Of the 146.4 million doses of flu vaccine distributed in the 2015-2016 season, there was an overall effectiveness rating of 59 percent, according to the Centers for Disease Control and Prevention (CDC). Strain-specific effectiveness ratings included a 51 percent rate for the A(H1N1) component and 76 percent effectiveness against B strains.[2]

Efforts to produce more effective vaccines to protect against influenza are ongoing, as are more effective methods of producing vaccines to make them available more quickly and in greater quantity. However, despite these changes, an unwillingness on the part of many to get immunized continues to put society at risk.

Understanding the Recommended Updates

Viral strains change and mutate each year, and as a result, vaccine formulations are customized for each flu season. Annually, more than 100 national influenza centers in over 100 countries conduct ongoing influenza surveillance to gather data for analysis. The surveillance involves receiving and testing thousands of influenza virus samples from patients with suspected flu illness. The laboratories then send representative viruses to five WHO Collaborating Centers for Reference and Research on Influenza, including locations in Atlanta, Ga., London, U.K., Melbourne, Australia, Tokyo, Japan, and Beijing, China.[3] WHO then consults with each center's experts to review the generated data and make recommendations for the composition of the influenza vaccine for the coming season. In March, it was announced that, based on its advisory group's in-depth analysis of the most recent circulating viruses, WHO recommends changing one strain for the Northern Hemisphere's 2016-17 flu season, and changing the order of the B strains. Based on the WHO recommendations, the vaccine formulation being distributed for the Northern Hemisphere's influenza season beginning in the fall of 2016 includes an A/California/7/2009 (H1N1)pdm09-like virus, an A/Hong Kong/4801/2014 (H3N2)-like virus and a B/Brisbane/60/2008-like virus for the trivalent influenza vaccine, as well as a B/Phuket/3073/2013-like virus for the quadrivalent influenza vaccine.

Growing the Next Great Vaccine

Each year, flu vaccine manufacturers make about 155 million doses of flu vaccine for the U.S. market alone, growing the virus in chicken eggs. Usually, the doses, which are designed to protect against strains that experts have predicted the previous February, are ready in time and in sufficient quantity.

However, it's widely known that the current system has its flaws. For instance, if the strain that appears during flu season varies from the one experts forecast, the vaccines might not be effective. The appearance of H1N1 swine flu in 2009-2010, for example, took experts by surprise, and the flu was already on its second wave before a new vaccine was ready. During that outbreak, an estimated 61 million people in the U.S. got swine flu and 12,500 died.[4] The search for new and faster methods of formulating the flu vaccine has been ongoing, and many manufacturers have begun looking at the viability of using plants in pharmaceutical production.

Each year, flu vaccine manufacturers make about 155 million doses of flu vaccine for the U.S. market alone, growing the virus in chicken eggs.

The use of plants to produce lifesaving pharmaceuticals captured global attention recently when it was revealed that the Ebola drug ZMapp is produced in the leaves of tobacco plants. Based on that success, it looks like the next big market for plant-based biopharmaceuticals will likely be influenza vaccines. Experts say making vaccines from plants is faster and cheaper than the established method of using chicken eggs; while one chicken egg can produce one or two doses of flu vaccine, one tobacco plant can produce 50 at a fraction of the cost.[5]

Timing is also a key advantage of the proposed plant-based vaccines. Leading producers currently need as much as six months to produce flu vaccine once scientists identify the dominant strains expected to circulate during flu season. Vaccine production from tobacco plants at manufacturers like Caliber Biotherapeutics in Bryan, Texas, could reportedly be available within a matter of weeks, and some are saying it could be a game changer. "Seven to 10 years from now, plants might be the dominant vaccine-production system," said Brett Giroir, MD, CEO of Texas A&M Health Science Center in Bryan. Texas A&M has one of three U.S. facilities tasked by the government to be ready to produce and deliver 50 million doses

of flu vaccine in a 12-week time span, and is working with Caliber toward that goal.

A tobacco-based virus-like particle (VLP) influenza vaccine is also being developed by Japan's Mitsubishi Tanabe Pharma. The technology used to create the vaccine, which involves implanting influenza genetic material into tobacco leaves, enables vaccine production in four weeks, six times faster than egg-based methods. Currently in Phase III studies, the vaccine is expected to be launched in the U.S. for the 2018–19 flu season.[6] Achilleas Livieratos, PhD, GlobalData's analyst covering infectious diseases, says "Mitsubishi Tanabe's pipeline tobacco product is one of a number of VLP influenza vaccines set to take over from the traditional kind, as they represent an exciting emerging vaccine class that can generate effective and longer-lasting protection, while also being amenable to a diverse array of production methods."[6]

If Mitsubishi Tanabe's product, or one like it, is approved, GlobalData expects a novel vaccine that boasts a rapid, plant-based manufacturing process to have a significant impact on the seasonal influenza vaccine landscape.

Addressing Complacent Public Perceptions

When asked about flu, any expert will tell you that the most predictable characteristic of the influenza virus is that it is unpredictable. This unpredictability — from the warnings of an upcoming severe flu season that never actually pan out, to the suddenly severe outbreak no one saw coming — has left an already skeptical public often willing to take their chances and forgo vaccination altogether. "Flu is pretty well-known, and people think they know what the symptoms are and when the flu season is, but overall, they don't regard it as a serious disease," said Brendan Flannery, PhD, a CDC epidemiologist. "They don't realize that there are people who are at especially high risk for severe disease, and everyone should be vaccinated to help that high-risk group."[7]

Kathleen M. Neuzil, MD, MPH, director of PATH's Vaccine Access and Delivery in Seattle, and clinical professor of allergy and infectious diseases and global health at the University of Washington, agrees, adding that public perception of flu is something that physicians have struggled with. One reason, she said, may be that the word "flu" is often used in a generic sense to describe any similar illness. "This definitely works against us, and it's something we have to explain to patients when we give them the flu vaccine," Dr. Neuzil said. "There are other viruses that can make you feel bad this winter. What makes flu different is its high attack rates and severity. Those make it absolutely worth preventing."[7]

WHO estimates between three million and five million cases of severe illness and between 250,000 and 500,000 deaths occur each year in the world due to influenza.[8] Still, even if the health dangers associated with the flu are insufficient to stimulate an uptick in flu vaccinations, the economic costs affecting America's pocketbook have the potential to sound the alarm. A total of 111 million lost workdays per year caused by the flu translates to a $7 billion loss in productivity. Direct medical costs associated with the flu average $10.4 billion annually, a significantly detrimental amount when you consider the current financial crises in healthcare systems. Additionally, the total yearly economic burden the influenza virus places on America is projected to exceed $87 billion.[9]

Given the potential personal and economic consequences, the question, then, is why do more than half of all Americans still fail to get an annual flu shot?[2] Studies suggest that if just 60 percent of America's population were vaccinated annually, the threat of another flu pandemic could be completely extinguished.[5] Although extensive time and energy have been funneled into flu education at the doctor-patient level, myths surrounding the efficacy and safety of the flu shot still play a significant role in deterring vaccination efforts. These misconceptions and excuses include:

- the widely circulated yet often refuted belief that the vaccine causes the flu (Influenza shots are made from either viruses that are inactivated and non-infectious, or from recombinant proteins that do not contain influenza viruses at all.);
- a phobia regarding needles (Other non-invasive methods of obtaining the vaccine such as a nasal spray or an intradermal needle injection are available for the needle-phobic); and
- the loudly asserted but officially debunked fear that the thimerosal preservative in some vaccines leads to autism (It is worth noting that thimerosal-free flu vaccines are also available for the unconvinced.).

Earlier this year, even Autism Speaks, a leading autism advocacy organization, came out in favor of vaccination.

"Over the last two decades, extensive research has asked whether there is any link between childhood vaccines and autism," the organization said in a statement. "Scientific research has not directly connected autism to vaccines. Efforts must be continually made to educate parents about vaccine safety. If parents decide not to vaccinate, they must be aware of the consequences in their community and their local schools."[10]

Boosting Immunity: Improving Vaccine Effectiveness

Current CDC statistics report the 2015-16 influenza vaccine's overall effectiveness at 59 percent.[11] While the percentage represents a good solid number, it may not be compelling enough to turn the tide of public apathy. As scientists search for ways to boost those numbers, a recent study suggests that timing rather than formulation may present an untapped opportunity to boost the efficacy of the flu shot.

British researchers have released the results of a study that claims getting vaccinated in the morning rather than the afternoon could increase the effectiveness of the flu vaccine. The randomized study, published in the journal *Vaccine*, included 276 men and women over age 65 who volunteered to be given the flu virus and were selected to get their flu shot either from 9 to 11 in the morning or 3 to 5 in the afternoon. The participants filled out questionnaires to assess health behaviors and socioeconomic status, gave a blood sample and were given the standard trivalent flu vaccine. A month later, they returned to give another blood sample. The researchers then compared anti-influenza antibodies in the two samples to measure the effect.[12] After controlling for differences in income, smoking, alcohol consumption, sleep duration and other health and behavioral characteristics, they found that for two of the three influenza strains contained in the vaccine, the response was significantly stronger in those vaccinated in the morning. For the third strain, morning or afternoon vaccination made no difference. "We know that there are fluctuations in immune responses throughout the day and wanted to examine whether this would extend to the antibody response to vaccination," said the study's author, Anna C. Phillips, PhD, a professor of behavioral medicine at the University of Birmingham.[13]

Chronobiology, the field of medical science that examines the way the body's biological systems respond differently throughout the course of a day, is currently being used to study a number of vaccine responses in animals and humans. "Being able to see that morning vaccinations yield a more efficient response will not only help in strategies for flu vaccination but might provide clues to improve vaccination strategies more generally," said Dr. Phillips.

The team plans to extend their research to investigate how the vaccination timing effect impacts individuals with existing conditions such as kidney disease and diabetes. If future results mirror those of the pilot study, the long-term impact on vaccination strategies could be significant, potentially boosting vaccination rates and ultimately saving lives.[13]

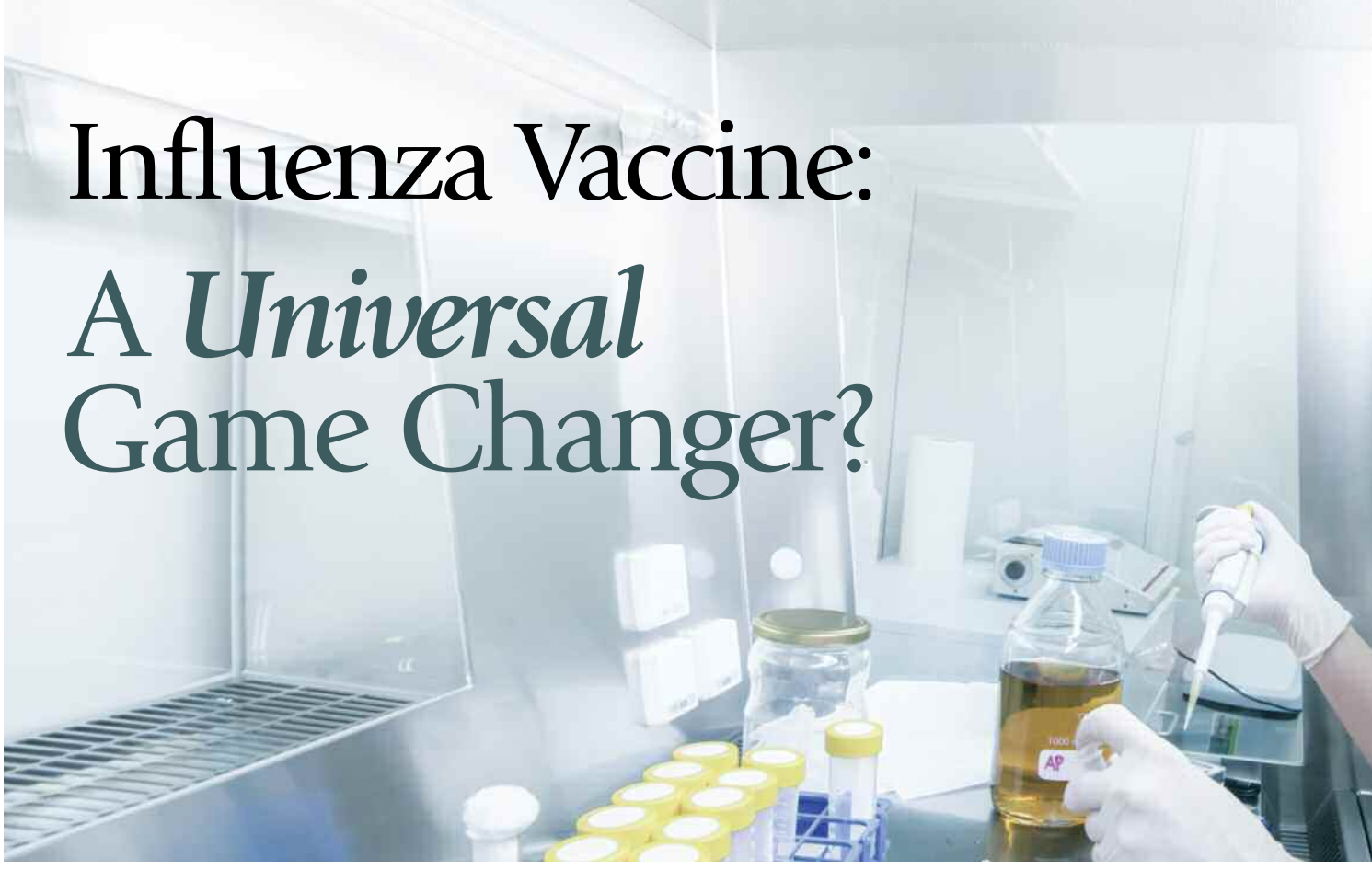
British researchers have released the results of a study that claims getting vaccinated in the morning rather than the afternoon could increase the effectiveness of the flu vaccine.

Speaking about the new research, Richard Pebody, MD, head of flu surveillance for Public Health England, said, "This is an interesting study and indicates more research is needed. Flu vaccine is the best protection we have against an unpredictable virus which can cause severe illness and deaths each year among at-risk groups, including older people, pregnant women and those with a health condition, even one that is well-managed."[12] ❖

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

References

1. Ault A. FDA Advisers Pick 2016-2017 Influenza Vaccine Strains. *Medscape Medical News*, March 4, 2016. Accessed at www.medscape.com/viewarticle/859922.
2. Centers for Disease Control and Prevention. 2015-2016 Flu Season. Accessed at www.cdc.gov/media/releases/2016/flu-vaccine-60-percent.html.
3. Centers for Disease Control and Prevention. Selecting Viruses for the Seasonal Influenza Vaccine. Accessed at www.cdc.gov/flu/about/season/vaccine-selection.htm.
4. Centers for Disease Control and Prevention. CDC: Update: Influenza Activity — United States, October 4, 2015–February 6, 2016. Accessed at www.cdc.gov/mmwr/volumes/65/wr/mm6506a3.htm.
5. Begley S. Plant-Based Vaccines Challenge Big Pharma for $3 Billion Flu Market. Reuters, Oct. 1, 2014. Accessed at www.reuters.com/article/us-flu-vaccine-analysis-idUSKCN0HQ2YO20141001.
6. New Tobacco-Based Flu Vaccine Offers Promising Alternative to Egg-Based Versions, says GlobalData Analyst. Manufacturing Chemist Pharma, March 11, 2016. Accessed at www.manufacturingchemist.com/news/article_page/New_tobaccobased_flu_vaccine_offers_promising_alternative_to_eggbased_versions_says_GlobalData_analyst/116474.
7. Healio Infectious Diseases in Children: Unpredictability Remains the One Constant with Seasonal Influenza. Infectious Diseases in Children, April 2015. Accessed at www.healio.com/pediatrics/influenza/news/print/infectious-diseases-in-children/%7Becb14d58-63ee-422a-85fb-1b7ae76e5b47%7D/unpredictability-remains-the-one-constant-with-seasonal-influenza.
8. Centers for Disease Control and Prevention. Estimating Seasonal Influenza-Associated Deaths in the United States: CDC Study Confirms Variability of Flu. Accessed at www.cdc.gov/flu/about/disease/us_flu-related_deaths.htm.
9. Woodrow C. Fear the Flu. *Stanford Journal of Public Health*, May 1, 2015. Accessed at web.stanford.edu/group/sjph/cgi-bin/sjphsite/flear-the-flu.
10. Barrett L. Why so Many Adults, Children Don't Get Flu Shots. Healthline News, Feb. 11, 2016. Accessed at www.healthline.com/health-news/why-so-many-adults-children-dont-get-flu-shots-021116#1.
11. Centers for Disease Control and Prevention. Flu Vaccine Nearly 60 Percent Effective. Accessed at www.cdc.gov/media/releases/2016/flu-vaccine-60-percent.html.
12. Knapton S. Flu Vaccine Four Times More Effective if Given in the Morning. *The Telegraph*, April 26, 2016. Accessed at www.telegraph.co.uk/science/2016/04/25/flu-vaccine-four-times-more-effective-if-given-in-morning.
13. Newman T. Morning flu shot might be more effective than afternoon. *Medical News Today*, April 27, 2016. Accessed at www.medicalnewstoday.com/articles/309514.php.



Influenza Vaccine: A *Universal* Game Changer?

The efficacy of influenza (flu) vaccines has been greatly improved over the past several decades, but the flu virus still severely sickens hundreds of thousands of individuals each year. Is it possible that scientists have discovered a way to change that?

By Ronale Tucker Rhodes, MS

IN THE 2014-2015 influenza season, approximately 151 million people (47.1 percent of the population) in the U.S. got a flu shot[1] in hopes of protecting themselves against the influenza virus that causes severe, and sometimes life-threatening, illness. A greater number of people, however, simply forwent the annual flu vaccine, many due to the fact that they questioned its efficacy either because they'd previously contracted the flu after receiving the vaccine or because of the sometimes dismal reported rates of effectiveness in a given year.

While no one wants to become ill with the flu, it's no secret that getting vaccinated against the flu provides the best possible protection. How much protection, however, varies each year and is sometimes modest at best, which is why scientists around the world are continuing to research methods to improve influenza vaccines. The hope is that, someday, a universal flu vaccine will be developed that will not only protect individuals from virtually every type of flu virus, but also will be given less frequently than the current annual influenza vaccine.

The Influenza Virus Challenge

The influenza virus is indeed a challenge. Although the first recorded influenza pandemic occurred in 1580, it wasn't until the devastation caused by the 1918-1919 "Spanish" influenza pandemic that it was discovered influenza virus types A, B and, in rare instances, C cause the flu.[2] (It was previously thought that a bacterium called Haemophilus influenzae caused the flu.)[3]

Since this discovery, much has been learned about flu viruses. They have eight genes, including two that are coded to produce the proteins hemagglutinin (H) and neuraminidase (N) that allow the virus to enter a host cell and spread from cell to cell. There are 16 H subtypes and nine N subtypes, making 144 possible HN combinations. But only three — H1N1, H2N2 and H3N2 — observed to date are fully adapted for infecting humans. Other combinations such as the H5N1 bird flu virus have only occasionally infected small numbers of humans.[4] Also, two antigenically distinct lineages of influenza B viruses have circlulated globally since 1985.[5]

Flu viruses change and mutate each year in one of two ways. The first is "antigenic drift," which is when small changes in the genes of influenza viruses happen continually over time as the virus replicates. The small changes usually produce viruses that are closely related to one another and usually share the same antigenic properties, which means an immune system exposed to a similar virus will usually recognize it and respond. Eventually, however, these small genetic changes accumulate over time and result in viruses that are antigenically different, which means the body's immune system may not recognize them. A second type of change is caused by "antigenic shift," an abrupt, major change in the influenza A viruses that result in a new influenza A subtype with an H and/or HN combination that has emerged from an animal population. This subtype is so different from the same subtype in humans that most people won't have immunity to it. (The 2009 H1N1 swine flu virus was a result of a shift.) Antigenic drift happens all the time, whereas antigenic shift happens only occasionally. And, importantly, while both changes can occur in influenza A viruses, only antigenic drift occurs in influenza B viruses.[6]

Interestingly enough, it is believed that the specific strain that wreaked havoc worldwide in 1918-1919,[4] which was estimated to have infected 50 percent of the world's population,[2] created the viral dynasty that continues to infect people today. "The 1918-1919 influenza pandemic was a defining event in the history of public health," said Anthony S. Fauci, MD, director of the National Institute of Allergy and Infectious Diseases. "The legacy of that pandemic lives on in many ways, including the fact that the descendants of the 1918 virus have continued to circulate for nine decades."[7]

Flu Vaccine Effectiveness

In 1938, the first inactivated influenza vaccine to protect against flu viruses was developed by Jonas Salk and Thomas Francis to protect U.S. military forces during World War II. Unfortunately, because the first vaccines developed weren't as purified as today's vaccines, they often caused side effects such as fever, aches and fatigue. And, since those are also the symptoms of flu, people mistakenly thought they were getting the virus from the vaccine,[3] a common misperception still believed by some today.

Much has been done to improve flu vaccines' effectiveness. For years, a troublesome issue surrounding influenza vaccines has been the strains' potential protective benefit. To address this issue, the U.S. Food and Drug Administration (FDA) and World Health Organization (WHO) have continued to struggle to predict the correct virus strains to include in the vaccines.

In some years, influenza vaccines protect only 50 percent to 70 percent of people who receive them. According to the Centers for Disease Control and Prevention's midseason vaccine effectiveness (VE) estimates, the 2015-2016 VE for protecting against having to go to the doctor because of flu illness is 59 percent. Specifically, it is 51 percent VE against the H1N1 viruses responsible for most flu illness this season, 76 percent VE against all influenza B viruses and 79 percent VE against the B/Yamagata lineage of B viruses.[8]

While no one wants to become ill with the flu, it's no secret that getting vaccinated against the flu provides the best possible protection.

Predicting which strains of the virus to include in the influenza vaccines is difficult at best, not only because the virus mutates from year to year, but the number of influenza subtypes A and B that can be selected for inclusion is limited. Prior to 2012 only trivalent influenza vaccines (TIVs) were manufactured. TIVs help protect against the two A virus strains most common in humans and the B strain expected to be predominant in a given

year. But, since the year 2000, two influenza B lineages (Victoria and Yamagata) have co-circulated to varying degrees each season. Various degrees of mismatch have occurred between the B lineage included in TIVs and the B lineage that actually circulated, causing an increased risk of influenza-related morbidity across all age groups. "Trivalent influenza vaccines have helped protect millions of people against flu, but in six of the last 11 flu seasons, the predominant circulating influenza B strain was not the strain that public health authorities selected," says Leonard Friedland, MD, vice president and head of GlaxoSmithKline North America Vaccines Clinical Development and Medical Affairs.[9]

Today, TIVs have been replaced with the IIV (inactivated influenza vaccine), comprised of two subclasses: IIV3 and ccIIV3, which stand for egg-based and cell-culture-based trivalent inactivated influenza vaccines, respectively. In addition, a second B strain has been added to some of the seasonal vaccines. These vaccines are known as IIV4s, which are the egg-based quadrivalent inactivated influenza vaccines. There are also RIV3 (recombinant trivalent hemagglutinin influenza vaccine) and LAIV4 (live attenuated quadrivalent influenza vaccine).[3]

In some years, influenza vaccines protect only 50 percent to 70 percent of people who receive them.

A final issue with current influenza vaccines is the widespread avoidance of them. On average, the number of people who get a flu shot each year hovers below the 50 percent range.[10] The reasons vary, but mainly it's due to misconceptions that the flu shot causes the flu, that the flu shot causes unwanted side effects, that it doesn't work and, for many, it's a fear of needles.[11]

As such, despite the strides made in improving influenza vaccines, WHO estimates between three million and five million cases of severe illness and between 250,000 and 500,000 deaths occur each year in the world due to influenza.[2]

A More Effective Vaccine on the Horizon

A universal influenza vaccine, which scientists say will soon be a reality, could be a game changer.

Many different groups of scientists are working to develop one. One key centers upon developing a vaccine that protects against the part of the virus that doesn't mutate as much: the stem. William Schaffner, MD, chairman of preventive medicine at Vanderbilt University Medical Center in Nashville, Tenn., describes the influenza virus as a sphere with "a bunch of lollipops on stems sticking out of it." The "sucker" part of the lollipop changes from year to year, but the stem parts do not, said Dr. Schaffner. Therefore, the universal vaccine would attack the stem portions of the virus, theoretically protecting against all strains. "A universal vaccine is the Holy Grail, and the prospects of what this could do for medicine is staggering," he added.[12] However, scientists have had trouble achieving an immune response with the stem rather than the ever-changing head.

Until now. Two U.S. teams of scientists have found success with formulating a vaccine that created antibodies from the stem. The vaccines were successful among mice, ferrets and monkeys and protected against flu strains like H5N1 avian flu and H1N1 swine flu. "The [experimental] designs were different, but the end results were very similar and highly complementary," said Ian Wilson, co-author of the paper reporting on one of the studies and a structural and computational biologist at the Scripps Research Institute in San Diego. "It's a promising first step, and it's very exciting to see this research come to fruition."

Both teams, which worked independently, tried to remove the variable head region and keep the stem as the base of their vaccines. Unfortunately, without the head, the stems fall apart so that antibodies aren't able to bind to it. So, to anchor the headless stem, they introduced a combination of mutations to stabilize the core of the hemagglutinin stem. One team bound a bacteria-derived nanoparticle to the stem, which pulled the subunits of the protein together to hold it in the right position. The other team applied a combination of mutations that realigned the subunits of the stem at the top. Both proved to make the stem a functional structure for the vaccine. They then vaccinated mice with the vaccine, and found that both vaccines provided full protection against H5N1, a lethal influenza strain distantly related to H1N1. The mice that didn't receive the vaccine died, but the vaccinated mice all survived. One vaccine also showed partial protection in ferrets, and the other vaccine showed partial protection in monkeys. The unvaccinated ferrets all died, but only two of the six vaccinated ferrets fell ill and died. None of the unvaccinated monkeys died, but the vaccinated monkeys had significantly lower fevers than the unvaccinated ones.[13]

The vaccines now need to be tested in clinical trials to see how well they work in humans. "We still need to perform human trials and also want to develop a vaccine that protects against all the types of influenza that cause human pandemics, so we don't have to worry about viruses like the bird flu that spread from animals to people," said Wilson. "The current flu vaccine only protects against two subtypes of influenza A (H1 and H3) and two lineages of influenza B. Although we are targeting the HA stem to stimulate production of broadly neutralizing antibodies,

there are still some differences between types of influenza. This makes it harder to develop a one-shot vaccine, but we're working on new mini-HA designs."[14]

Another group of researchers has discovered a new class of antibodies that they say may provide the basis for a universal flu vaccine. The researchers at McMaster University and the Icahn School of Medicine at Mount Sinai in New York compared an isolated strain-specific flu antibody (the type that current vaccines generate) with an isolated broadly neutralizing flu antibody (the type generated by universal vaccines). Initially, they found the universal vaccine type of antibody to be much less effective at neutralizing influenza than the strain-specific antibodies. However, when they isolated the universal-type antibodies in their natural setting from human blood, both types of antibodies were found to be comparable in effectiveness.

They also found that the subtype of antibodies located in the lungs and upper respiratory system are especially effective at neutralizing influenza. According to Matthew Miller, senior author of the study and assistant professor in McMaster's Department of Biochemistry and Biomedical Sciences at the Michael G. DeGroote School of Medicine, this finding provides guidance about whether an inactivated versus live-attenuated vaccine would be best for delivering a universal flu vaccine. Currently, the flu vaccine is an inactivated vaccine consisting of virus particles that are grown under controlled conditions and then killed, unlike an attenuated virus that is kept alive but has reduced virulence. With an attenuated vaccine, the virus is able to replicate in the upper-respiratory tract but isn't capable of infecting the lung, and when the live virus replicates harmlessly, an immune response is generated.

"Unlike seasonal vaccines, which must be given annually, this type of vaccine would only be given once, and would have the ability to protect against all strains of flu, even when the virus mutates," said Miller. "This would prevent the occurrence of flu pandemics and poor vaccine efficacy in the case of mismatches." Miller and the other researchers are hopeful that their universal vaccine will be available in four to six years.[15]

FDA is also testing a potential vaccine. After studying related universal influenza vaccines, FDA scientists chose to study one developed by scientists at Okairos in Rome, Italy, because it is based on a virus to which humans have no prior exposure, thus avoiding any issue about prior immunity. Like some other universal vaccine candidates, this one triggered immune responses against conserved antigens (viral protein targets that mutate only slowly), which are similar among many strains of influenza viruses and, therefore, can generate immune responses that cross-react among virus strains.

The vaccine is made by genetically modifying a virus called PanAd3, which is isolated from a bonobo (a type of great ape). The modified virus, called a vector, carried two genes for proteins conserved among many different influenza viruses: M1 and NP. The vector can infect cells, causing them to express M1 and NP influenza antigens and, thus, immunize the recipient. However, it can't replicate itself and spread. FDA scientists tested the PanAd3 vaccine by administering a single dose in the noses of mice, which caused a strong immune response that protected the animals against infection a few weeks later by exposure to a high dose of a very virulent influenza virus called A/FM. The vaccine not only triggered antibody production, but also activated T cells. Importantly, strong T cell immunity was found in the lungs, the site of infection.[16]

A Universal Advantage

Undoubtedly, the public is better protected today from the flu than it was decades ago. But, it's still not as effective as needed, and too many people suffer from severe illness and, sometimes, die. Hopefully, with teams of scientists pursuing a breakthrough vaccine, the days of the yearly flu shot are numbered. It seems highly probable that a universal vaccine may soon arrive that could be given just once. It would protect against most types of flu, including seasonal varieties and the highly mutated kinds that cause pandemics. And, in contrast to the seasonal flu vaccine that takes six months to manufacture, a universal vaccine could be used immediately "off-the-shelf."[16] Now, that's a game changer. ❖

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References

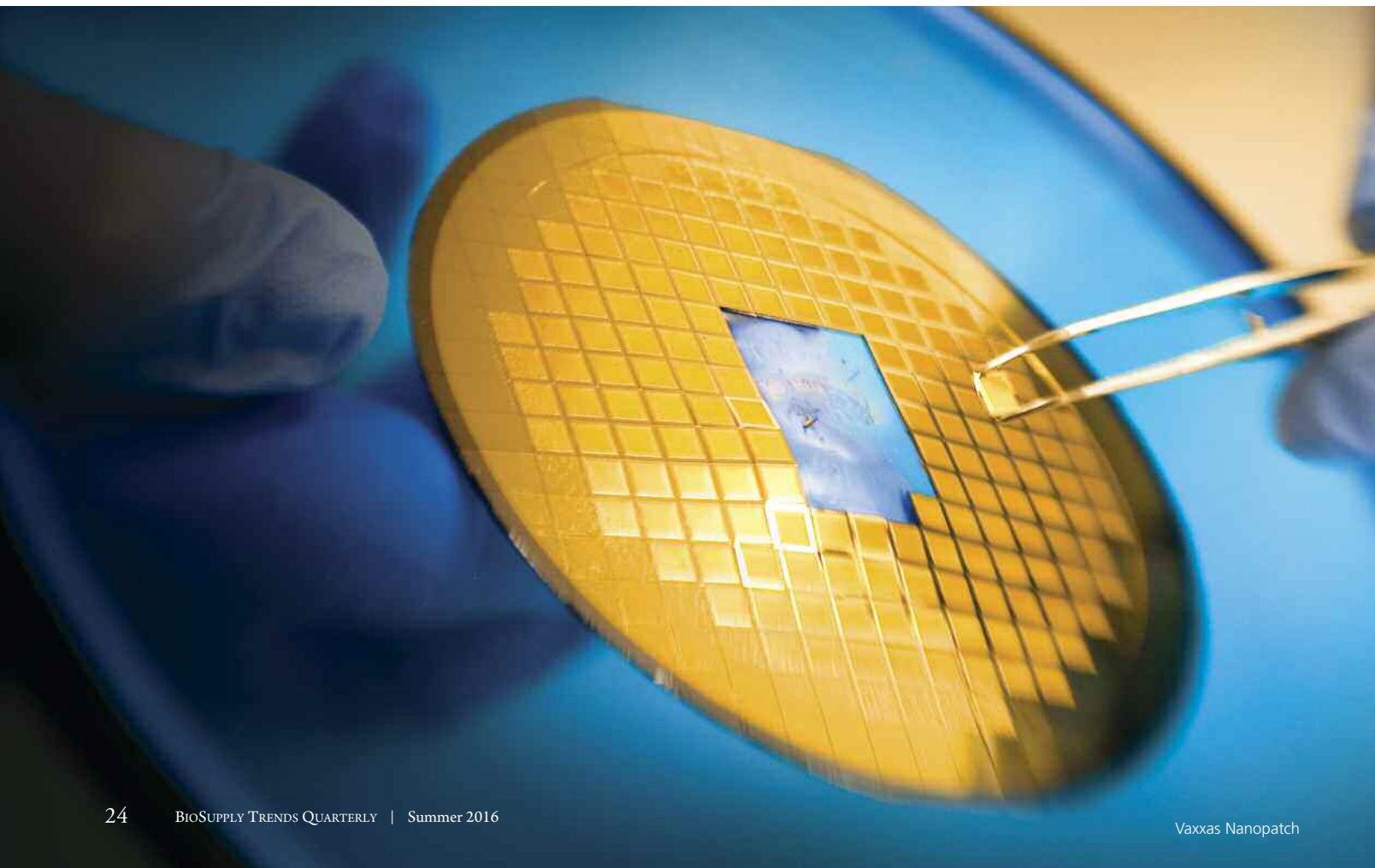
1. Wappes J. CDC: Flu Vaccine Coverage Up a Bit in 2014-15. CIDRAP News, Sept. 17, 2015. Accessed at www.cidrap.umn.edu/news-perspective/2015/09/cdc-flu-vaccine-coverage-bit-2014-15.
2. Medavera. The History of Influenza: From Devastation to Discovery. Accessed at www.historyofinfluenza.com.
3. eMedicineHealth. History and Development of Flu Vaccines. Accessed at www.emedicinehealth.com/flu_vaccine/page2_em.htm.
4. National Institutes of Health. Dynasty: Influenza Virus in 1918 and Today. NIH News, June 29, 2009. Accessed at www.nih.gov/news/health/jun2009/niaid-29.htm.
5. Ambrose CS and Levin MJ. The Rationale for Quadrivalent Influenza Vaccines. *Human Vaccines & Immunotherapeutics*, 2012 January 1; 8(1): 81–88. doi: 10.4161/hv.8.1.17623.
6. Centers for Disease Control and Prevention. How the Flu Virus Can Change: "Drift" and "Shift." Accessed at www.cdc.gov/flu/about/viruses/change.htm.
7. Spanish Flu Created a Viral Dynasty — Study. Keyt.com, May 3, 2012. Accessed at www.keyt.com/health/49504497.html.
8. Centers for Disease Control and Prevention. Flu Vaccine Nearly 60 Percent Effective. Press release, Feb. 24, 2016. Accessed at www.cdc.gov/media/releases/2016/flu-vaccine-60-percent.html.
9. GlaxoSmithKline. FDA Approves GlaxoSmithKline's Four-Strain Seasonal Influenza Vaccine for Use in the U.S. Press release, Dec. 17, 2012. Accessed at www.gsk.com/media/press-releases/2012/FDA-pproves-GlaxoSmithKline-four-strain-seasonal-influenza-vaccine-for-use-in-the-US.html.
10. Centers for Disease Control and Prevention. 2010-11 through 2014-15 State, Regional, and National Vaccination Trend Report. Accessed at www.cdc.gov/flu/fluvaxview/reportshtml/reporti1415/trends/index.html.
11. Steenhuysen J. Insight: U.S. Government Investment Gives Flu Vaccines a Shot in the Arm. Reuters, Jan. 19, 2013. Accessed at www.reuters.com/article/2013/01/19/us-flu-vaccines-idUSBRE90I0AI20130119.
12. Neporent L. Universal Flu Vaccine Soon a Reality, Scientists Say. ABC News, Jan. 13, 2015. Accessed at abcnews.go.com/Health/universal-flu-vaccine-reality-scientists/story?id=28167227.
13. Armitage H. Is a Universal Flu Vaccine on the Horizon? *Science*, Aug. 24, 2015. Accessed at www.sciencemag.org/news/2015/08/universal-flu-vaccine-horizon.
14. National Accelerator Laboratory. Q&A: Biologist Describes Milestone Toward a Universal Flu Vaccine, Jan. 4, 2016. Accessed at www6.slac.stanford.edu/news/2016-01-04-qa-biologist-describes-milestone-toward-universal-flu-vaccine.aspx.
15. McNamee D. One-Shot Flu Vaccine Will Be Ready 'Within 5 Years.' *Medical News Today*, Jan. 16, 2015. Accessed at www.medicalnewstoday.com/articles/288082.php.
16. Vitelli A, Quirion MR, and Lo CY. Potential "Universal" Influenza Vaccine Tested at FDA. U.S. Food and Drug Administration, March 16, 2015. Accessed at www.fda.gov/BiologicsBloodVaccines/ScienceResearch/ucm353397.htm.

Evolving Technology in Vaccine Administration

Some promising new methods for how vaccines are administered may soon eliminate many of the problems encountered by the healthcare industry.

By Diane L.M. Cook

FOR MORE THAN two decades, significant research and development progress has been made into evolving technologies in vaccine administration. The safety of hypodermic needle administration is evolving to help reduce injury and protect against virus contamination. And, it's feasible that in a few short years, the use of hypodermic needles to administer vaccines could be a thing of the past — replaced instead by new devices such as needle-free injectors, patches and nasal mists. The benefits of these devices in comparison with hypodermic needles include lower production costs, increased manufacturing in a shorter period of time, increased vaccination rates among people with needle phobia, elimination of costs associated with sharps disposal, elimination of cold chain storage, improved management of pandemics through mass-



Vaxxas Nanopatch

quantity shipping, and self-administration by nonhealthcare workers and even patients themselves.

While many devices are still in clinical trial stages, some of the world's biggest vaccine and device manufacturers are already offering new technologies in vaccine administration to the global market. Following is a small sample of what's now available and what's to come.

Needle-Free Injection

PharmaJet has developed two needle-free injectors for delivering vaccines. The Stratis Needle-Free Injector for intramuscular or subcutaneous injection received an indication for influenza delivery from the U.S. Food and Drug Administration (FDA) in August 2014 and was introduced to the marketplace during the 2014-2015 flu season. The spring-powered injector delivers vaccines through a narrow stream of fluid that penetrates the skin in about one-tenth of a second. It includes the injector, a 0.5 mL needle-free syringe, a 13 mm/20 mm vial-filling adapter and a reset station. It has a CE Mark and is PQS (performance, quality and safety)-certified by the World Health Organization (WHO).

"The PharmaJet injection technology is an especially important innovation for the millions of individuals who suffer from the fear of needles (20 percent of the population) and the many millions more who are needle-adverse, who consequently forgo their annual flu vaccination," says Ron Lowy, CEO of PharmaJet. "We believe this is a significant step forward in the effort to improve public health through broader immunization coverage, as well as improved safety of providers."

Because the device does not use needles, it eliminates the possibility of needlestick injuries and reuse, and reduces sharps management costs. "The injector addresses both provider safety concerns and patient issues with needles," says Lowy. "It has also been well-received by patients and healthcare providers alike. In post-market surveys, 93 percent of patients and 87 percent of providers reported that they would choose the PharmaJet needle-free option again."

The Stratis is currently available in 33 states and in approximately a dozen countries outside of the U.S. "The Stratis is available in India, and we are currently conducting several studies in that country, which will make the injector more widely available soon," adds Lowy. "The injector is also available in the larger countries in the Middle East. Additionally, in Europe, we are working on a prefilled format to administer vaccines."

And, the learning curve is relatively simple. "Educational materials are provided on the PharmaJet website," says Lowy. In addition, use of the Stratis "is part of the American Pharmacists Association training module used for new and current pharmacists. The average person can be trained in about 20 minutes and become proficient with the device after 10 to 15 injections."

PharmaJet is also producing another needle-free injector that has similar technology to the Stratis and is optimized for intradermal delivery. The Tropis is being used with nucleic acid vaccines in development, as well as others such as polio, and is expected to receive FDA approval in 2016.

Microneedle Patches

The benefits of microneedle patches are similar to needle-free injectors. However, Yasmine Gomaa, a research scientist at the School of Chemical and Biomolecular Engineering at the Georgia Institute of Technology, says the biggest benefit compared to hypodermic needles is that researchers "found immunization using dissolvable microneedle patches to increase vaccine immunogenicity and to allow dose sparing."

There are four types of microneedles that deliver vaccines through the skin. "Solid microneedles utilize the 'poke and patch' and the 'coat and poke' approaches," explains Gomaa. "The 'poke and patch' approach involves the application of a solid microneedle array to create micropores that is followed by removal of the array and application of the drug formulation in the form of a transdermal patch, gel or solution. The 'coat and

poke' approach relies on coating the vaccine formulation onto the solid microprojections and insertion of the microneedle patch into the skin. This coating can dissolve within a few minutes after insertion into the skin, after which the microneedles can be withdrawn and discarded, and the dissolved vaccine diffuses through the skin into the blood capillaries."

The third type, dissolvable microneedles, delivers vaccines through the "poke and release" approach. They release their encapsulated payload when inserted into the skin for bolus or sustained delivery. The fourth type, which uses mediated transdermal delivery, is through the "poke and flow" method. This consists of hollow microneedles that puncture the skin followed by infusion of liquid formulation through the needle lumens in a manner similar to hypodermic injection.

"With the rapid progress of this technology, microneedle patches should be readily available in pharmacies for patients to buy and self-administer within three to five years," says Gomaa.

Mark Prausnitz, PhD, a professor of biomolecular engineering at the Georgia Institute of Technology, has for the past decade been researching a number of vaccines that use microneedle patches to administer vaccines against influenza, poliomyelitis, hepatitis B, rubella, measles, tetanus and others. Currently, a Phase I clinical trial, sponsored by the National Institute of Biomedical Imaging and Bioengineering, is ongoing for inactivated influenza vaccine microneedle patches to assess safety, reactogenicity, acceptability and immunogenicity compared with hypodermic needles. The trial started in June 2015, and the last patient visit was in March. It has not yet been determined when Phase II of the trial will begin.

The microneedle patches used in the clinical trial are about a centimeter square and consist of arrays of 50 to 100 microscopic needles about as tall as the thickness of a few hairs that can be absorbed into the skin within minutes. When used to administer a vaccination, the patch is pressed onto a person's forearm to carry the vaccine into the outer layers of the skin, where they prompt an immune reaction from the body.

Another microneedle patch is under development by Vaxxas. Professor Mark Kendall, PhD, group leader, delivery of drugs and genes group with the Australian Institute for Bioengineering and Nanotechnology at the University of Queensland, invented the Nanopatch in 2004. Since then, he has been working on advancing the Nanopatch toward the first human applications, first at the University of Queensland and then through Vaxxas, a company he founded in 2011 in Cambridge, Mass. This has required scaling the technology from use in small animals to larger models, prototyping the human implementation of the device, and ensuring the manufactured product is economically compelling and industrially scalable. The company recently established the cGMP aseptic manufacturing infrastructure and operations that are required for clinical work in support of commercializing the technology. "Based on successful clinical demonstrations, the Nanopatch will be a game changer in the vaccine industry," said David Hoey, CEO of Vaxxas.

In 2012, Merck & Co., one of the world's largest vaccine manufacturers, entered into an agreement with Vaxxas to help fund research that will evaluate the Nanopatch technology. According to Kendall, the technology is based on the theory that vaccines can be more effective if they are delivered into the narrow layer just beneath the skin surface that contains a high density of antigen-presenting cells (APCs) required to generate an immune response, rather than into the muscle where such cells present at a much lower density.

The Nanopatch is a new method of controlled and targeted delivery of vaccine. The device is composed of an array of densely packed gold-coated silicon projections coated with vaccine antigen in dry form. Since the vaccine is dry, it offers thermostability and improved immune responses because it is targeted to a rich population of immune cells in the skin, which a needle misses when it delivers vaccines to muscles. When applied to the skin, the Nanopatch projections will penetrate the epidermis and upper dermis, depositing antigen directly to high populations of APCs residing within these skin layers. "The Nanopatch is distinct from existing microneedle devices by having very high packing density of projections tailored by a probability analysis to deposit antigen directly to thousands of epidermal and dermal APCs mapped within the skin, with the smaller diameter far less likely to damage cells near the projections," says Kendall.

During preclinical testing, the Nanopatch was applied to many different vaccines, including influenza (monovalent and trivalent), HPV, chikungunya, malaria, West Nile virus, HSV 2, pneumococcal, dengue and monovalent type 2 inactivated poliovirus vaccine. It is scheduled for vaccine clinical trials in 2016. "If the benefits seen in the animal model are translated to people, then the Nanopatch opens up more effective, cheaper vaccination to more people," says Kendall. "This can mean making existing vaccines work better by reducing the cost profiles (through lower doses), addresses needle phobia and eliminates the cold chain management process."

The benefits of the Nanopatch during a pandemic are three-fold, he adds: "Due to dose sparing, the need for a lower dose means that the vaccine could be rolled out more quickly to more people. As it relates to thermostability, the resource infrastructure for vaccine storage and transportation could be less. And, there is potential for self-administration. Taken together, these three benefits could potentially mean that the Nanopatch could be mailed out to people in a pandemic or even air-dropped into remote areas or a crisis zone."

Nasal Mists

FluMist Quadrivalent, a registered trademark of MedImmune, is licensed to AstraZeneca, a global biopharmaceutical company. AstraZeneca received approval for its FluMist Quadrivalent from FDA in February 2012 and approval from Health Canada in October 2015. The live attenuated influenza vaccine (LAIV) is administered through the nose, where the flu virus typically enters the body. Carlo Mastrangelo, director of corporate communications, says "this method closely mimics natural infection, which contributes to its superior efficacy when compared to the conventional flu vaccine." The vaccine does not contain any preservatives such as thimerosal (a mercury-based preservative). However, because it contains no preservatives of any kind, it needs to be refrigerated.

In the U.S., FluMist Quadrivalent is used to prevent the flu in people between 2 years and 49 years of age, and in Canada, in people between 2 years and 59 years of age. Compared to a conventional flu vaccine, the National Advisory Committee on Immunization recommends an LAIV vaccine like FluMist for children aged 2 years to 17 years because it has been shown to be 48 percent more effective across all strains. And, when compared with a placebo, the efficacy of two doses of an LAIV administered to children who have never been vaccinated was 83 percent against similar strains.

Increasing Safety and Reach

PATH, an international nonprofit health organization whose work in vaccine administration technologies, advanced in collaboration with numerous public and private sector partners, focuses on the development of devices, tools and methods that improve the safety, acceptability and effectiveness of vaccine delivery in developing countries. Darin Zehrung, program advisor for vaccine and pharmaceutical delivery technologies at PATH, says the organization has developed several evolving technologies and is currently working on other evolving technologies for administering vaccinations in low- to middle-income countries (LMICs) on a global scale.

For instance, PATH developed the SoloShot syringe, the first commercialized autodisable syringe. The syringe has a fixed needle that automatically disables after a single injection. After the vaccine has been administered, a barbed metal clip around the neck of the plunger locks into place prohibiting its reuse. SoloShot is used for the delivery of basic childhood vaccines and the introduction of new parenteral vaccines like MenAfriVac.

"PATH also developed the Uniject, the world's only compact, easy-to-use, prefilled, single-dose syringe with autodisable features," says Zehrung. The Uniject injection system contains a small plastic reservoir (bubble) prefilled with a single dose of vaccine. The bubble is attached to an injection-ready needle. Healthcare workers only need to depress the plastic reservoir to administer the vaccine, and the autodisable feature prevents its reuse. Uniject is currently used for the routine birth dose delivery of hepatitis B vaccine in Indonesia, and has helped to immunize millions of neonates since its introduction into the country's immunization program.

In addition, "PATH helped develop the West Intradermal Adapter that fits over needles like a sleeve, standardizing the injection depth and angle so healthcare workers can more easily and precisely administer vaccines intradermally using the Mantoux technique with a hypodermic needle and syringe," says Zehrung. PATH has also evaluated an autodisable version of the adapter to improve injection safety by preventing reuse.

> "Based on successful clinical demonstrations, the Nanopatch will be a game changer in the vaccine industry."

There are other evolving technologies, too, such as microarray patches (MAPs) that are placed over hypodermic needles. Although MAPs are still in development, "the technology platform has demonstrated the potential for greater thermostability, which could reduce cold storage and transportation burdens for immunization supply chains in LMICs," says Zehrung. "Research additionally shows less training may be required for their safe and effective administration, possibly allowing for self-administration. With these attributes, MAPs hold promise for increasing the number of people vaccinated in remote clinics or campaign settings that are common in LMICs, which could help public health programs to address coverage gaps."

Solutions Continue to Improve Vaccination Rates

Vaccine and device manufacturers, as well as academic and research institutions, are continuing their research and development of new and evolving technologies in vaccine administration to address the healthcare industry's concerns with hypodermic needles and to provide more people globally with vaccinations when and where they are needed. Clearly, the industry is just on the cusp of what promises to be revolutionary developments in the very near future. ❖

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VACCINES FOR INTERNATIONAL TRAVEL

Vaccination against these four specific diseases is recommended prior to travel to endemic areas.

By Bob Geng, MD

LNTERNATIONAL TRAVEL has made the world a far more interconnected place. But, it is crucial to keep in mind that much of the world is still in process of economic development, meaning that adequate standards of public health and sanitation are also in development. Furthermore, many regions of the world have conditions and climates that are conducive for the growth and spread of certain endemic bacteria, parasites and viruses not often found in North America.

Following are some of the important vaccines often discussed in travel medicine. It is not an exhaustive list of vaccines for all potential communicable diseases that could be encountered during international travel. Further, it does not address vaccinations that are routinely recommended for maintenance of health. It is always important to be up-to-date with routine recommended vaccinations while traveling abroad.

Typhoid

Typhoid fever is caused by a bacterium called Salmonella typhi, and affects around 21.5 million people in the world per year, according to the Centers for Disease Control and Prevention. It is acquired via the oral-fecal route, meaning that it is transmitted by food or beverage handled by infected individuals or contaminated with fecal material from infected individuals. Some infected individuals even following recovery can still continue to shed the bacteria as well. In the developing world where hand sanitation in food handling is not strictly enforced, the potential for infection increases.

Symptoms of typhoid fever include high fever, lethargy, abdominal pain, nausea, headache and, occasionally, a flat rash. The way to detect typhoid infection is by analyzing the stool or blood for presence of bacteria. Typhoid is endemic to many developing countries in Asia, Africa and Latin America.

Recommendations to prevent typhoid infection are to avoid eating food and drinking beverages from high-risk unsanitary places in developing countries. Instead, only foods that are thoroughly cooked and thoroughly cleaned should be consumed, and water should be boiled before drinking.

While typhoid infections can be treated with certain antibiotics, there is a rise in multidrug-resistant strains of the bacteria, so it is far better to practice good avoidance measures, as well as vaccination for prevention. There are currently two types of typhoid vaccines available in this country. Ty21a is a live oral vaccine, and Vi capsular polysaccharide vaccine (ViCPS) is a nonlive polysaccharide vaccine.

Ty21a is given by mouth to individuals 6 years and older. It requires four doses on days one, three, five and seven. It must be given at least one week prior to potential exposure (travel to endemic area). Another booster needs to be given five years following initial vaccination. Since it is a live vaccine, it should not be given to individuals who have compromised or weakened immune systems. In addition, because it is a live vaccine and requires the body's natural immune response to take effect, it cannot be given within 72 hours of any antibiotic therapy. Lastly, since it is a live vaccine, individuals who actively have a fever or gastrointestinal illness should not receive the vaccine.

ViCPS is a nonlive polysaccharide vaccine given as a single intramuscular injection. It has to be given at least two weeks prior to potential exposure or travel, which is a week longer than the live vaccine. The age limit minimum is 2 years, which is far lower than the limit for the live vaccine. However, it does require a booster every two years as compared to five years for the live vaccine.

Once a person is infected, the treatment of typhoid fever is antibiotics. Fluoroquinolone antibiotics have traditionally been the backbone of therapy, but due to drug-resistant strains, other antibiotics may need to be used; therefore, susceptibility testing is often necessary to decide on the best treatment regimen.

Hepatitis A

Hepatitis A is a virus that causes acute liver disease in infected individuals. The incidence is around three to 11 per 100,000 in areas of the world with intermediate to high risk. Like typhoid, it is not common in industrialized developed countries, but highly prevalent in underdeveloped or developing countries. It is found in higher incidence in Latin America, Africa, Eastern Europe and parts of Asia.

Unlike hepatitis B or C, hepatitis A is transmitted via the fecal-oral route, meaning that infection occurs when individuals consume substances that are contaminated by fecal materials from infected individuals. Therefore, good hygiene practices are crucial in reducing hepatitis A transmission. The presentation of hepatitis A can vary, and the length of acute illness can vary between a few weeks to several months. Unlike hepatitis B or C, hepatitis A does not lead to chronic liver disease. However, unlike typhoid, hepatitis A is a virus and not a bacterium, which means that antibiotics are not effective in its treatment. The vast majority of people completely recover from hepatitis A without treatment, but the course of disease can be severe. Rarely, hepatitis A can lead to severe liver failure and, potentially, death, mostly in patients who have concurrent chronic liver disease.

Patients who are infected with hepatitis A may experience fever, nausea/vomiting, fatigue, abdominal pain, jaundice, light-colored stools and dark urine. However, some patients may have only a few of those symptoms. Diagnostic tests include blood testing to determine whether there are antibodies made against hepatitis A.

Hepatitis A vaccine is an inactive hepatitis A virus. It is given as two injections six months apart. The first injection can be given anytime prior to travel to an endemic region. The vaccine is licensed for anyone 1 year and older. It can often be given together with the hepatitis B vaccine in the Twinrix combination formulation. For healthy patients younger than 40 years old, one dose is sufficient prior to travel. However, for older patients and patients who have weakened immune systems, intramuscular immune globulin (IG) injection should be given concomitantly to provide additional protection.

IG therapy is a collection of antibodies derived from pooled human plasma to provide protection against infections. It can be used for prevention of hepatitis A or for post-exposure prophylaxis within two weeks following exposure before signs of infection occur. It is given intramuscularly at 0.02 mL/kg, and provides up to three months of protection. For travel that lasts longer than three months, additional doses can be given. IG therapy can be given also to patients who choose not to receive hepatitis A vaccine, as well as individuals who cannot receive the vaccine such as patients with known serious allergic reactions to hepatitis A vaccine or those who are younger than 1 year of age.

Japanese Encephalitis

Japanese encephalitis (JE) is a viral infection endemic to Asia and the Western Pacific regions, particularly in rural agricultural areas. It is a mosquito-borne illness that can lead to significant inflammation in the brain, leading to neurologic dysfunction. Symptoms generally develop five to 15 days following transmission from mosquito bite. There is a large variation in clinical presentation. Some patients develop very mild symptoms of fever, headache, nausea/vomiting or fatigue. Others can develop significant inflammation of the central nervous system, leading to seizures, paralysis

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  - –The rate of adverse reactions per infusion has been calculated at 0.091% with a rate of serious adverse reactions at 0.076%[1]
  - –The most common adverse reactions (≥5%) were headache, fatigue, infusion site reaction, nausea, sinusitis, increased blood pressure, diarrhea, dizziness, and lethargy[2]

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BIVIGAM® [Immune Globulin Intravenous (Human), 10% Liquid] is indicated for the treatment of primary humoral immunodeficiency (PI). This includes, but is not limited to, the humoral immune defect in common variable immunodeficiency (CVID), X-linked agammaglobulinemia, congenital agammaglobulinemia, Wiskott-Aldrich syndrome, and severe combined immunodeficiencies.

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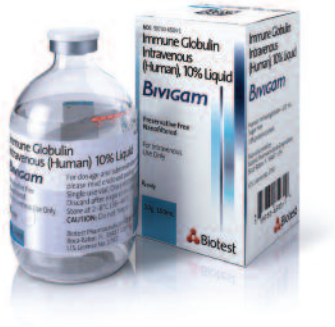

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Warning: **Thrombosis may occur with immune globulin intravenous (IGIV) products, including BIVIGAM. Risk factors may include advanced age, prolonged immobilization, hypercoagulable conditions, a history of venous or arterial thrombosis, the use of estrogens, indwelling vascular catheters, hyperviscosity and cardiovascular risk factors. Renal dysfunction, acute renal failure, osmotic nephrosis, and death may occur with the administration of Immune Globulin Intravenous (Human) (IGIV) products in predisposed patients. Renal dysfunction and acute renal failure occur more commonly in patients receiving IGIV products containing sucrose. BIVIGAM does not contain sucrose. For patients at risk of thrombosis, renal dysfunction, or renal failure, administer BIVIGAM at the minimum dose recommended and infusion rate practicable. Ensure adequate hydration in patients before administrations. Monitor for signs and symptoms of thrombosis and assess blood viscosity in patients at risk for viscosity.** ***See full Prescribing Information for complete boxed warning.***

Please see BIVIGAM Important Safety Information and Prescribing Information on next page, including black box safety warnings, contraindications, and dosing.

*IVIG is also known as IGIV, Immune Globulin Intravenous (Human).

References: 1. Wasserman RL. A new intravenous immunoglobulin (BIVIGAM®) for primary humoral immunodeficiency. *Expert Rev Clin Immunol.* 2014;10(3): 325–337.
2. BIVIGAM [package insert]. Boca Raton, FL: Biotest Pharmaceuticals Corporation; 2013.

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BIVIGAM® [Immune Globulin Intravenous (Human), 10% Liquid] Rx only

Brief summary: Consult the full Prescribing Information for complete product information

WARNING: THROMBOSIS, RENAL DYSFUNCTION , AND ACUTE RENAL FAILURE

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

Indication and Usage: BIVIGAM is an Immune Globulin Intravenous (Human), 10% Liquid, indicated for the treatment of primary humoral immunodeficiency (PI).

Contraindications: BIVIGAM is contraindicated in patients who have had an anaphylactic or severe systemic reaction to the administration of human immune globulin. BIVIGAM is contraindicated in IgA deficiency patients with antibodies to IgA and a history of hypersensitivity.

Warnings and Precautions: Thrombosis: Thrombosis may occur following treatment with IGIV products, including BIVIGAM. Risk factors may include: advanced age, prolonged immobilization, hypercoagulable conditions, history of venous or arterial thrombosis, use of estrogens, indwelling central vascular catheters, hyperviscosity and cardiovascular risk factors. Thrombosis may occur in the absence of known risk factors. Consider baseline assessment of blood viscosity in patients at risk for hyperviscosity, including those with cryoglobulins, fasting chylomicronemia/markedly high triacylglycerols (triglycerides), or monoclonal gammopathies. For patients at risk of thrombosis, administer BIVIGAM at the minimum dose and infusion rate practicable. Ensure adequate hydration in patients before administration. Monitor for signs and symptoms of thrombosis and assess blood viscosity in patients at risk for hyperviscosity**. Hypersensitivity:** Severe hypersensitivity reactions may occur with IGIV products, including BIVIGAM. In case of hypersensitivity, discontinue BIVIGAM infusion immediately and institute appropriate treatment. Medications such as epinephrine should be available for immediate treatment of acute hypersensitivity reactions. BIVIGAM contains trace amounts of IgA (≤ 200 micrograms per milliliter). Patients with known antibodies to IgA may have a greater risk of developing potentially severe hypersensitivity and anaphylactic reactions. BIVIGAM is contraindicated in IgA deficient patients with antibodies against IgA and a history of hypersensitivity reaction. **Acute Renal Dysfunction and Acute Renal Failure**: Acute renal dysfunction/failure, osmotic nephrosis, and death may occur upon use of human IGIV products. Ensure that patients are not volume depleted before administering BIVIGAM. Periodic monitoring of renal function and urine output is particularly important in patients judged to be at increased risk of developing acute renal failure. Assess renal function, including measurement of blood urea nitrogen (BUN) and serum creatinine, before the initial infusion of BIVIGAM and at appropriate intervals thereafter. If renal function deteriorates, consider discontinuing BIVIGAM. In patients who are at risk of developing renal dysfunction, because of pre-existing renal insufficiency or predisposition to acute renal failure (such as diabetes mellitus, hypovolemia, overweight, use of concomitant nephrotoxic medicinal products or age of >65 years), administer BIVIGAM at the minimum infusion rate practicable. **Hyperproteinemia, Increased Serum Viscosity, and Hyponatremia**: Hyperproteinemia, increased serum viscosity, and hyponatremia may occur in patients receiving IGIV therapy, including BIVIGAM. It is critical to clinically distinguish true hyponatremia from a pseudohyponatremia that is associated with or causally related to hyperproteinemia with concomitant decreased calculated serum osmolality or elevated osmolar gap, because treatment aimed at decreasing serum free water in patients with pseudohyponatremia may lead to volume depletion, a further increase in serum viscosity, and a possible predisposition to thrombotic events. **Aseptic Meningitis Syndrome (AMS):** AMS may occur infrequently with IGIV treatments including BIVIGAM. AMS usually begins within several hours to 2 days following IGIV treatment. Discontinuation of IGIV treatment has resulted in remission of AMS within several days without sequelae. AMS is characterized by the following signs and symptoms: severe headache, nuchal rigidity, drowsiness, fever, photophobia, painful eye movements, nausea, and vomiting . Cerebrospinal fluid (CSF) studies frequently reveal pleocytosis up to several thousand cells per cubic millimeter, predominantly from the granulocytic series, and elevated protein levels up to several hundred mg/dL, but negative culture results. Conduct a thorough neurological examination on patients exhibiting such signs and symptoms, including CSF studies, to rule out other causes of meningitis. AMS may occur more frequently in association with high doses (2 g/kg) and/or rapid infusion of IGIV. **Hemolysis:** IGIV products, including BIVIGAM, may contain blood group antibodies that can act as hemolysins and induce in vivo coating of red blood cells (RBCs) with immunoglobulin, causing a positive direct antiglobulin reaction and, rarely, hemolysis. Delayed hemolytic anemia can develop subsequent to IGIV therapy due to enhanced RBC sequestration, [13] and acute hemolysis, consistent with intravascular hemolysis, has been reported. Monitor patients for clinical signs and symptoms of hemolysis. If these are present after BIVIGAM infusion, perform appropriate confirmatory laboratory testing. If transfusion is indicated for patients who develop hemolysis with clinically compromising anemia after receiving IGIV, perform adequate cross-matching to avoid exacerbating on-going hemolysis. **Transfusion-Related Acute Lung Injury (TRALI):** Noncardiogenic pulmonary edema may occur in patients following IGIV treatment including BIVIGAM. TRALI is characterized by severe respiratory distress, pulmonary edema, hypoxemia, normal left ventricular function, and fever. Symptoms typically appear within 1 to 6 hours following treatment. Monitor patients for pulmonary adverse reactions. If TRALI is suspected, perform appropriate tests for the presence of anti- neutrophil antibodies in both the product and the patient's serum. TRALI may be managed using oxygen therapy with adequate ventilatory support. **Transmissible Infectious Agents**: Because BIVIGAM is made from human blood, it may carry a risk of transmitting infectious agents, e.g., viruses, and theoretically, the Creutzfeldt-Jakob disease (CJD) agent. No cases of transmission of viral diseases or CJD have been associated with the use of BIVIGAM. All infections suspected by a physician possibly to have been transmitted by this product should be reported by the physician or other healthcare provider to Biotest Pharmaceuticals Corporation at 1-800-458-4244. Before prescribing BIVIGAM, the physician should discuss the risks and benefits of its use with the patient . **Monitoring Laboratory Tests:** Periodic monitoring of renal function and urine output is particularly important in patients judged to be at increased risk of developing acute renal failure. Assess renal function, including measurement of blood urea nitrogen (BUN) and serum creatinine, before the initial infusion of BIVIGAM and at appropriate intervals thereafter. Because of the potentially increased risk of thrombosis with IGIV treatment, consider baseline assessment of blood viscosity in patients at risk for hyperviscosity, including those with cryoglobulins, fasting chylomicronemia/markedly high triacylglycerols (triglycerides), or monoclonal gammopathies. If signs and/or symptoms of hemolysis are present after an infusion of BIVIGAM, perform appropriate laboratory testing for confirmation. If TRALI is suspected, perform appropriate tests for the presence of anti-neutrophil antibodies in both the product and patient's serum. **Interference with Laboratory Tests** : After infusion of immunoglobulin, the transitory rise of the various passively transferred antibodies in the patient's blood may yield positive serological testing results, with the potential for misleading interpretation. Passive transmission of antibodies to erythrocyte antigens (e.g., A, B, and D) may cause a positive direct or indirect antiglobulin (Coombs') test.

ADVERSE REACTIONS: Serious adverse reactions observed in clinical trial subjects receiving BIVIGAM were vomiting and dehydration in one subject. The most common adverse reactions to BIVIGAM (reported in ≥5% of clinical study subjects) were headache, fatigue, infusion site reaction, nausea, sinusitis, blood pressure increased, diarrhea, dizziness, and lethargy. **Clinical Trials Experience**: *Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in clinical trials cannot be directly compared to rates in the clinical trials of another product and may not reflect the rates observed in clinical practice.* In a multicenter, open-label, non-randomized clinical trial, 63 subjects with PI, on regular IGIV replacement therapy, received doses of BIVIGAM ranging from 254 to 1029 mg/kg (median dose 462.8 mg/kg) every 3 weeks or 4 weeks for up to 12 months (mean 317.3 days; range 66 – 386 days). The use of pre-medication was discouraged; however, if subjects required pre-medication (antipyretic, antihistamine, or antiemetic agent) for recurrent reactions to immune globulins, they were allowed to continue those medications for this trial. Of the 746 infusions administered, 41 (65%) subjects received premedication prior to 415 (56%) infusions. Fifty-nine subjects (94%) had an adverse reaction at some time during the study. The proportion of subjects who had at least one adverse reaction was the same for both the 3- and 4-week cycles. The most common adverse reactions observed in this clinical trial were headache (32 subjects, 51%), sinusitis (24 subjects, 38%), fatigue (18 subjects, 29%), upper respiratory tract infection (16 subjects, 25%), diarrhea (13 subjects, 21%), cough (14 subjects, 22%), bronchitis (12 subjects, 19%), pyrexia (12 subjects, 19%), and nausea (9 subjects, 14%). Adverse reactions (ARs) are those occurring during or within 72 hours after the end of an infusion . In this study, the upper bound of the 1-sided 95% confidence interval for the proportion of BIVIGAM infusions with one or more temporally associated adverse reactions was 31%. The total number of adverse reactions was 431 (a rate of 0.58 ARs per infusion).

Seven subjects (11.1%) experienced 11 serious ARs. Two of these were related serious ARs (vomiting and dehydration) that occurred in one subject. One subject withdrew from the study due to ARs related to BIVIGAM (lethargy, headache, tachycardia and pruritus). All 63 subjects enrolled in this study had a negative direct antiglobulin (Coombs') test at baseline. During the study, no subjects showed clinical evid ence of hemolytic anemia. No cases of transmission of viral diseases or CJD have been associated with the use of BIVIGAM. During the clinical trial no subjects tested positive for infection due to human immunodeficiency virus (HIV), hepatitis B virus (HBV) , or hepatitis C virus (HCV). There was a single positive finding for parvovirus (B19 virus) during the study. This subject came in contact with acute B19 virus from working at a school greeting children where a child was reported to have symptomatic Fifth's disease. There was no cluster (no other cases in other subjects) of B19 virus transmission with the IGIV batch concerned.

Table: Adverse Reactions (ARs) (within 72 hours after the end of a BIVIGAM infusion) in ≥5% of Subjects

ARs	**No. Subjects Reporting ARs (% of Subjects) [n=63]**	**No. Infusions With ARs (% of Infusions) [n=746]**
Headache	27 (43%)	115 (15.4%)
Fatigue	15 (24%)	59 (7.9%)
Infusion Site Reaction	5 (8%)	5 (0.7%)
Nausea	5 (8%)	8 (1.1%)
Sinusitis	5 (8%)	5 (0.7%)
Blood Pressure Increased	4 (6%)	5 (0.7%)
Diarrhea	4 (6%)	4 (0.5%)
Dizziness	4 (6%)	4 (0.5%)
Lethargy	4 (6%)	4 (0.5%)
Back Pain	3 (5%)	3 (0.4%)
Blood Pressure Diastolic Decreased	3 (5%)	5 (0.7%)
Fibromyalgia[a]	3 (5%)	17 (2.3%)
Migraine	3 (5%)	8 (1.1%)
Myalgia	3 (5%)	4 (0.5%)
Pharyngolaryngeal Pain	3 (5%)	3 (0.4%)

[a]**Symptoms occurring under pre-existing fibromyalgia**

DRUG INTERACTIONS Live Virus Vaccines : Immunoglobulin administration may transiently impair the efficacy of live attenuated virus vaccines such as measles, mumps, rubella, and varicella because the continued presence of high levels of passively acquired antibody may interfere with an active antibody response. The immunizing physician should be informed of recent therapy with BIVIGAM so that appropriate measures may be taken.

and loss of consciousness. Diagnosis is made by both signs and symptoms, as well as confirmatory testing in the blood or spinal fluid for antibodies made to fight off the virus.

The treatment for JE is currently only supportive, and there is no specific antiviral therapy for the condition. Therefore, prevention by vaccination is very important. The vaccine that is currently available in the U.S. is JE-IXIARO, which is an inactivated vaccine derived from cell cultures. The previously used JE-MB vaccine that was derived from inactivated mouse brain is no longer available in the U.S. JE-IXIARO vaccine is administered in two doses spaced 28 days apart. For patients 3 years and older, the dose is 0.5 mL, and for those younger than 3 years, the dose is 0.25 mL. For individuals who have ongoing risk for developing JE, another booster can be given a year following the second dose.

Patients who have had severe hypersensitivity reactions to JE vaccines should avoid getting repeated doses.

Yellow Fever

The yellow fever virus is related to the West Nile, St. Louis and Japanese encephalitis viruses. It is endemic to the tropical regions of South America and Sub-Saharan Africa, and is transmitted by infected mosquitoes. The clinical presentation of infection varies among individuals. Some patients may exhibit little or no symptoms, whereas others may develop fever, body aches, nausea/vomiting, weakness and severe headaches. The time from infection to illness varies between three and six days. In the most severe cases, patients can develop bleeding, jaundice and multi-organ system failure. The mortality rate among patients who develop these severe symptoms is between 20 percent and 50 percent.

Since there is no specific treatment following infection, and management is supportive and symptom-driven, it is important to receive vaccination prior to potential exposure in endemic regions. Some countries even have yellow fever vaccination requirements prior to entry if the traveler is coming from an endemic region. The yellow fever vaccine is a live attenuated virus. A single dose of the vaccine is considered sufficient for lifelong protection, and is indicated for people older than 9 months of age traveling to endemic regions of yellow fever. However, some countries require booster vaccines every 10 years.

Since the yellow fever vaccine is a live virus vaccine, patients with weakened or compromised immune systems should not receive it. Administration of the vaccine needs to be at least 30 days apart from administration of any other live attenuated vaccines, but can be given concomitantly with other inactivated vaccines. Patients younger than 6 months of age should also not receive the vaccine, and it must be given with caution to those between 6 months and 9 months. Individuals older than age 60 should also receive the vaccine with caution, given potentially weakened baseline health and weakened immune systems with age.

Japanese encephalitis is a viral infection endemic to Asia and the Western Pacific regions, particularly in rural agricultural areas.

Adverse effects following yellow fever vaccination can be divided into several categories. First, like all vaccines, there are individuals who may develop immediate hypersensitivity or allergic reaction to the vaccine. This is a rare phenomenon. Second, patients may develop neurologic disease that is either secondary to direct viral infection of the central nervous system or the induction of an autoimmune reaction targeting against the nervous system. The incidence of neurologic adverse events rises with older age (older than 60 years). Lastly, in rare cases, vaccination may actually lead to disseminated viral infection similar to the severe type of naturally acquired yellow fever disease. Again, individuals with weakened immune systems and older age tend to be risk factors.

Avoiding the Potential Spread of Communicable Diseases

As global travel becomes ever more prevalent, the potential spread of communicable diseases rises. Highlighted here are some of the important specific international travel-related vaccines that are available for administration in the U.S. However, in addition to these specific vaccines, individuals should be up-to-date with all their routine recommended vaccinations as well in order to be as best protected as possible whether at home or abroad. Lastly, prior to international travel, it is always important to check both the Centers for Disease Control and Prevention and the World Health Organization websites for precautions, as well as consult with a physician for additional more detailed recommendations. ❖

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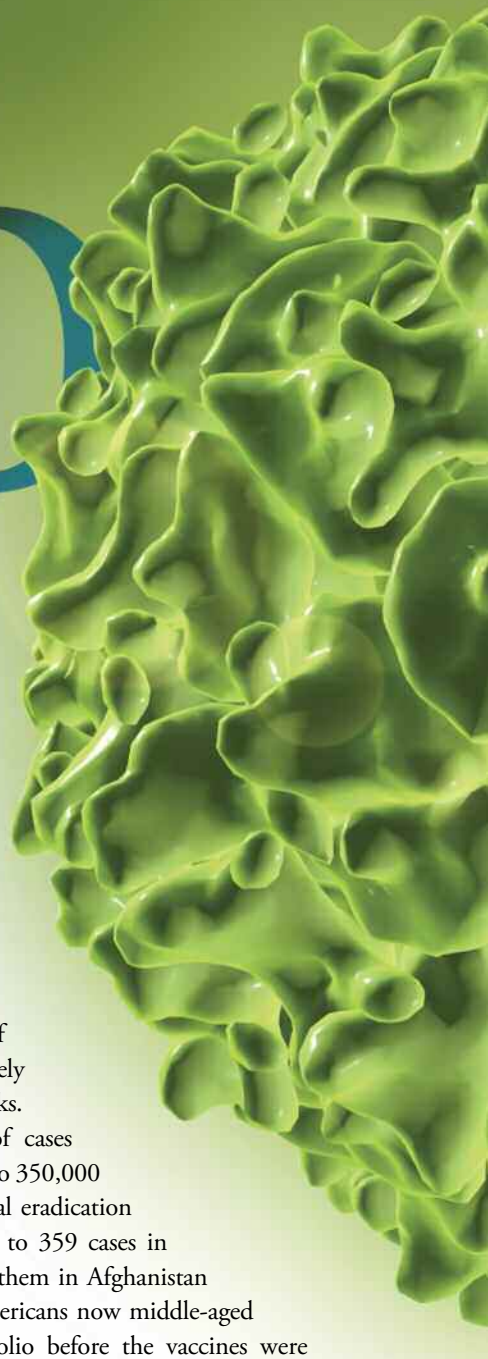
UPDATE on Polio and Post-Polio Syndrome



This soon-to-be-eradicated disease still plagues a few parts of the world, and some of its past victims are vulnerable to a recurrence but in a less serious form.

By Jim Trageser

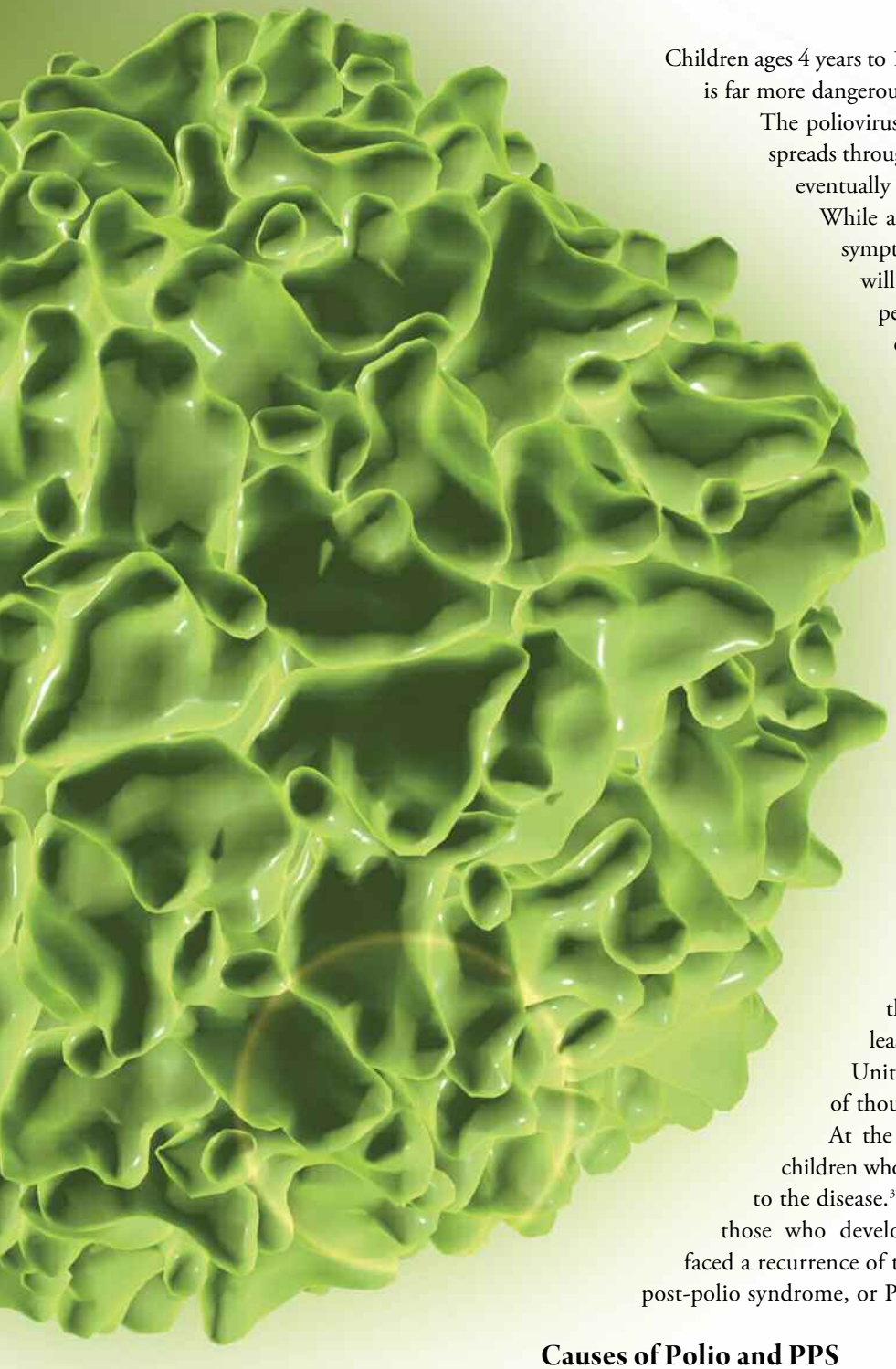
BY ALL RIGHTS, polio should be extinct, alongside smallpox. And yet, not only is polio still with us — although eradication comes closer year by year — more than 100,000 Americans still suffer from or will yet develop post-polio syndrome.

After several decades as one of humanity's true nightmare diseases (the kind of illness that kept parents awake at night worrying for their children, the sort of malady that caused families to flee to the countryside during outbreaks in order to avoid infection), polio became one of medical science's greatest triumphs: the twin victories of Jonas Salk and Albert Sabin in 1955. Polio, and the resultant paralysis that afflicts approximately one-half of 1 percent of its victims, inspired such dread in the 20th century that even at the height of the Cold War, the Soviet Union awarded Sabin, an American, with the Order of Friendship Among Peoples for his work in helping eradicate polio in Russia.[1] Sabin's and Salk's efforts against polio in the West were so successful that few people born after the 1950s have any recollection of how utterly terrifying polio was — the specter of iron lungs and leg braces largely consigned to the history books.

From tens of millions of cases each year in the early 1950s to 350,000 cases globally in 1988, global eradication efforts reduced the number to 359 cases in 2014[2] — with nearly all of them in Afghanistan or Pakistan. Only those Americans now middle-aged or older who contracted polio before the vaccines were developed, or immigrants who contracted polio before moving here, are still coping with post-polio syndrome or are at risk of developing it.

What Are Polio and Post-Polio Syndrome?

Poliomyelitis, generally shortened to polio, is an incurable but easily prevented infectious disease caused by the poliovirus.



Children ages 4 years to 14 years are most susceptible, although the disease is far more dangerous and severe in adults.[3]

The poliovirus enters its host orally. Once in the intestines, it spreads throughout the body, and in a small number of people, eventually attacks the nervous system (acute poliomyelitis).[4] While about 70 percent of those infected will suffer no symptoms, and most who do get sick from the infection will have minor flu-like symptoms, about one in 200 people who get the disease will develop what is called acute poliomyelitis and will suffer temporary or permanent paralysis due to damaged nerves in the spinal cord. Of those who develop the acute form of the disease, up to 10 percent will die when the muscles associated with breathing stop working.[4]

Not only was polio one of the most dreaded diseases of the 20th century, it was only in that century that polio epidemics occurred. Prior to the 1900s, polio was a dangerous infection that could cause death or paralysis, but outbreaks were small in number of victims, as well as geographically contained.[5] It was only with the rapid urbanization that followed the Industrial Revolution in the United States and Western Europe that polio epidemics began to occur in large cities. Some 2,700 cases were reported in New York City alone in a 1907 outbreak. In 1916, more than 6,000 deaths were attributed to polio in the United States.[3] Each following year saw at least one major polio outbreak somewhere in the United States, with thousands dying and many tens of thousands paralyzed.

At the time, it was already noted by researchers that children who had been infected and survived gained immunity to the disease.[3] It would become apparent that a percentage of those who developed and recovered from acute poliomyelitis faced a recurrence of the symptoms decades later, a condition termed post-polio syndrome, or PPS.[6]

Causes of Polio and PPS

There are three strains of the wild poliovirus, types 1, 2 and 3, differentiated by the proteins in their capsid, or shell. Type 2 is now extinct in the wild, with no new cases reported since 1999.[7] Types 1 and 3 have now been eradicated from Nigeria in the last few years, leaving Afghanistan and Pakistan as the last nations where wild polio remains extant.

A small number of infections result from the use of the attenuated live-virus Sabin vaccine due to natural mutations that occur when the virus in the vaccine reproduces in the human digestive tract, resulting in a more lethal variety shed through the feces. There were 580

cases identified from 2000 to 2011, during which time more than 15,000 children were paralyzed by wild poliovirus worldwide.[8]

There is no difference in symptoms or mortality between the strains, however. Poliovirus is spread through a feces-oral cycle; its spread is the result of a lack of hygienic practices. Infected food or water or dirty fingers are the primary sources of poliovirus.[9] The virus reproduces in the intestines, and new viruses are expelled from the host body in the feces during the infection, usually in a matter of a few weeks.

The causes of PPS are presently unknown.[6] Researchers have determined that 25 percent to 40 percent of those who develop acute poliomyelitis will later develop PPS, generally 25 years to 40 years after the original infection.

Symptoms and Progression

On average, some 70 percent of patients who contract polio will be asymptomatic and, in fact, wholly unaware they ever were infected.[10] For those who do exhibit symptoms, most will be similar to the flu: fever, nausea, fatigue and general achiness.

The vast majority of patients who develop symptoms will never progress to acute poliomyelitis, but will instead experience a milder version referred to as nonparalytic polio. Those very few cases that progress to acute status, also known as paralytic polio, will see a worsening severity of symptoms within a week: loss of reflexes, severe muscle pain or weakness and loose limbs.[10]

The poliovirus attacks motor-control nerve cells in the spinal cord or brain stem; as the muscles are cut off from the brain, they begin to atrophy. In some cases, the paralysis is permanent. But other patients see some eventual improvement. Researchers believe that the body generates new receptors on surviving neurons after a polio infection to make up for the loss of the attacked cells. Over time, these cells may become overworked and begin to give out.[6]

However, some 40 percent of these recovered patients will eventually develop PPS. Symptoms of PPS are a recurrence of muscle weakness, muscle atrophy, general fatigue, difficulty swallowing and increased sensitivity to cold temperatures.[11]

Diagnosis

A diagnosis of poliomyelitis would be extremely rare for an American or European physician today. However, it is possible if a patient is returning from Afghanistan or Pakistan. Polio is confirmed by examination of stool, throat secretions or spinal fluid for the presence of the poliovirus.

PPS remains a common occurrence in the West, as there are hundreds of thousands who survived a bout with polio as a youngster.

There is no single test to confirm PPS; instead, a physician will consider a battery of different tools to narrow down a diagnosis. These may include:[12]

- A previous diagnosis of acute poliomyelitis. Only those who were infected by the poliovirus will contract PPS.
- Electromyography (EMG). An EMG can help eliminate other possible causes for the symptoms the patient is experiencing.
- Magnetic resonance imaging (MRI) or computerized tomography (CT). An MRI and/or CT can help determine if a spinal disorder is causing the symptoms.
- Biopsy. A small sample of muscle tissue may be removed and examined to eliminate other causes.
- Blood test. A patient with PPS will have a normal blood test, so this test will help eliminate other possible causes.

Treatment

There is no cure for polio or PPS. Treatment for polio is supportive, including bed rest, pain relievers, nutrition and mild physical therapy to try to minimize loss of function.[13] Treatment for PPS focuses on preserving as much function and quality of life as possible. Physical therapy and pain relievers may be called for to help ease symptoms. The Mayo Clinic suggests working with patients to help them learn energy conservation techniques to cope with their condition.[14]

One area showing some promise is the use of intravenous immune globulin (IVIG), which the National Institutes of Health (NIH) indicates shows improvements in pain management and quality of life.[6] However, the Mayo Clinic[14] and the Post-Polio Health International both argue that the benefits of IVIG are still unproven.[15]

Other treatment approaches have proven either ineffective or harmful. NIH currently advises against the use of prednisone due to the severity of the side effects. Another study on the anticonvulsant lamotrigine showed promise, but the study was limited.[6]

Prevention

Polio is wholly preventable through vaccination, and it may be that 2016 is the year that the last pockets of wild poliovirus are eradicated in Pakistan and Afghanistan, relegating this fearsome disease to the history books. As with smallpox samples stored by U.S. and Russian health authorities in case a new vaccine is ever needed, small samples of poliovirus may exist in secure laboratory facilities for some years as a source of future immunizations.

There is not yet an effective prevention for PPS, although those who have not had acute poliomyelitis are not at risk.

Research

With so few polio patients in the world today, and with multiple vaccines readily available, there is little research into

polio treatment. It is likely that within a year or so, polio will be exterminated.

However, we will still have PPS around for some time, and research is ongoing to try to find a way to prevent onset of PPS, as well as effective treatments.

Some areas of study include immunology to see if an autoimmune response is a trigger. Other researchers are looking into the possible roles of fatigue and nutrition as possible triggers for PPS onset.[6] However, the NIH clinical trials page listed no ongoing or upcoming trials regarding polio or PPS as of this writing.

Looking Ahead

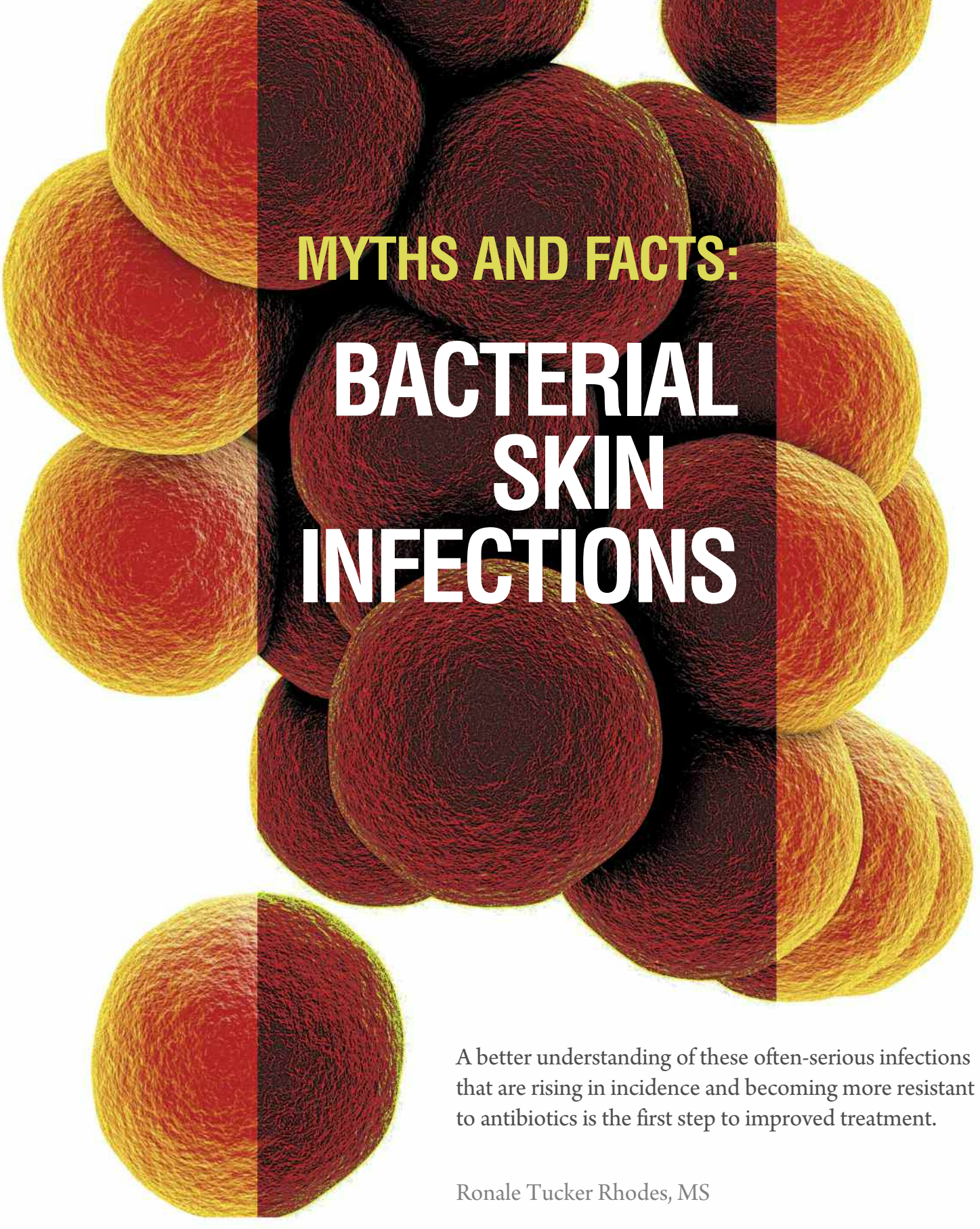
The technology and infrastructure to eliminate polio from the world exist; what allows polio to continue has been a lack of political will. But with Nigeria now being polio-free, we are very close to the day that polio becomes extinct.

That said, once the last case of polio is reported, we will still have another 80 years or so of a population pool susceptible to developing PPS. And with people moving around the world as never before, physicians everywhere need the proper protocols to diagnose and treat PPS for the foreseeable future. ❖

JIM TRAGESER is a freelance journalist in the San Diego area.

References

1. Smithsonian National Museum of American History. Two Vaccines. Accessed at amhistory.si.edu/polio/virus vaccine/vacraces2.htm.
2. World Health Organization. Does Polio Still Exist? Is It Curable? Accessed at www.who.int/features/qa/07/en.
3. Wikipedia. History of Poliomyelitis. Accessed at en.wikipedia.org/wiki/History_of_poliomyelitis.
4. World Health Organization. Poliomyelitis. Accessed at www.who.int/mediacentre/factsheets/fs114/en.
5. Trevelyan B, Smallman-Raynor M, and Cliff AD. The Spatial Dynamics of Poliomyelitis in the United States: From Epidemic Emergence to Vaccine-Induced Retreat, 1910–1971. *Annals of the Association of American Geographers,* Volume 95, Issue 2, 2005. Accessed at www.tandfonline.com/doi/abs/10.1111/j.1467-8306.2005.00460.x
6. National Institutes of Health. Post-Polio Syndrome Fact Sheet. Accessed at www.ninds.nih.gov/disorders/post_polio/detail_post_polio.htm.
7. Polio Global Eradication Initiative. The Virus. Accessed at www.polioeradication.org/Polioandprevention/ Thevirus.aspx.
8. Polio Global Eradication Initiative. Vaccine-Derived Polioviruses (VDPV). Accessed at www.polioeradication.org/Polioandprevention/Thevirus/Vaccinederivedpolioviruses.aspx.
9. Cedar Crest College. The Life-Cycle of Polio. Accessed at www2.cedarcrest.edu/academic/bio/hale/bioT_EID/lectures/poliolifecycle.html.
10. Mayo Clinic. Polio: Symptoms. Accessed at www.mayoclinic.org/diseases-conditions/polio/basics/symptoms/con-20030957.
11. Mayo Clinic. Post-Polio Syndrome: Symptoms. Accessed at www.mayoclinic.org/diseases-conditions/post-polio-syndrome/basics/symptoms/con-20021725.
12. Mayo Clinic. Post-Polio Syndrome: Tests and Diagnosis. Accessed at www.mayoclinic.org/diseases-conditions/post-polio-syndrome/basics/tests-diagnosis/con-20021725.
13. Mayo Clinic. Polio: Treatment and Drugs. Accessed at www.mayoclinic.org/diseases-conditions/polio/basics/treatment/con-20030957.
14. Mayo Clinic. Post-Polio Syndrome: Treatment and Drugs. Accessed at www.mayoclinic.org/diseases-conditions/post-polio-syndrome/basics/treatment/con-20021725.
15. Headley JL. IVIG Update. Post-Polio Health International. Accessed at www.post-polio.org/edu/pphnews/PPH28-2spr12p9.pdf.



MYTHS AND FACTS:

BACTERIAL SKIN INFECTIONS

A better understanding of these often-serious infections that are rising in incidence and becoming more resistant to antibiotics is the first step to improved treatment.

Ronale Tucker Rhodes, MS

DURING THE PAST several years, disturbing headlines about flesh-eating bacteria have raised fear among the public, but few think they'll actually be the next victim. That was certainly true of Cindy Martinez, who, in May 2015, somehow contracted one strain of the dangerous bacteria known to cause necrotizing fasciitis. A former Marine and mother of two small children, Cindy survived but only after her feet and right hand were amputated to halt the bacteria's effects.[1] Necrotizing fasciitis is rare. According to the Centers for Disease Control and Prevention (CDC), which tracks specific infections in the U.S. through a special system called Active Bacterial Core surveillance (ABCs), there are about 650 to 850 cases of necrotizing fasciitis caused, predominantly, by group A Streptococcal bacteria each year in the U.S. (although this is likely an underestimate because some cases are probably not reported). And, thankfully, the number of annual infections does not appear to be rising.[2]

That's not true of all bacterial skin infections. Necrotizing fasciitis is but one of a host of these infections and also one of the rarer ones. Other types of bacterial skin infections include cellulitis, erysipelas, erythrasma, folliculitis and skin abscesses, hidradenitis suppurativa, impetigo and ecthyma, lymphadenitis, lymphangitis and Staphylococcal scalded skin syndrome.[3,4] All of these infections may be uncomplicated or complicated. Indeed, since all uncomplicated infections have the potential to become complicated,[4] it's important to understand the facts about them to ensure appropriate diagnosis and treatment.

Separating Myth from Fact

Myth: Bacterial skin infections are not common.

Fact: Despite the fact that skin forms an effective barrier to protect against infection when coming into contact with bacteria, bacterial skin infections are still common. This is because any break in the skin such as a cut or scrape gives opportunity for bacterial disease to establish itself.[5] A study published in the *Annals of Internal Medicine* states that in 2005, there were approximately 14 million outpatient visits to doctors' offices and emergency clinics for suspected skin and soft tissue infections (also known as skin and skin structure infections, or SSSIs) in the U.S.[6] And, according to the Healthcare Cost and Utilization Project Statistical Briefs, there were 656,000 hospitalizations due to SSSIs in 2010, which was an increase of 75 percent from 1997.[7]

Staphylococcus and Streptococcus are the most common types of bacteria involved in bacterial skin infections. Staphylococcal infection can result in many types of infections, but typically, it causes abscesses or boils, which are sometimes referred to as furuncles. These uncomfortable and frequently painful red lumps associated with a hair follicle may cluster together to form carbuncles.[5] More seriously, Staphylococcus can result in methicillin-resistant Staphylococcus aureas (MRSA), which can be a life-threatening infection because certain antibiotics in the penicillin family cannot treat it.[8] Streptococcal infection also can cause many types of infections, but it more regularly causes impetigo, which results in a rash several days after infection with small blisters that burst and leave crusty, golden patches on the skin — occurring most commonly on the face.[5] Both Staphylococcus and Streptococcus also commonly cause cellulitis, which can occur anywhere on the body; however, the most common location is the lower leg.[9] Cellulitis is a painful infection of the deeper layers of the skin that appears as an area of redness, warmth and swelling that gradually spreads.[5]

According to the Healthcare Cost and Utilization Project Statistical Briefs, there were 656,000 hospitalizations due to SSSIs in 2010, which was an increase of 75 percent from 1997.

Myth: Bacteria that cause skin infections are always disease-causing.

Fact: Most bacteria are not harmful. In fact, many of the different types help in the digestion of food, destroy disease-causing cells and give the body needed vitamins; less than 1 percent of bacteria make people sick. However, infectious bacteria quickly reproduce in the body, giving off toxins that can damage tissue and make people ill.[10]

Myth: Bacterial skin infections are equally opportunistic in people.

Fact: Individuals using medications to treat certain disorders are more susceptible to bacterial skin infections. These include individuals who have diabetes and use insulin, HIV/AIDS, kidney failure requiring dialysis, weakened immune systems (either from a disease or medications that suppress the immune system), cancer (especially those who are undergoing chemotherapy or radiation), skin damage (from conditions such as eczema, insect bites or minor trauma that opens the skin) and respiratory illness such as cystic fibrosis or emphysema.[11] Some other common risk factors for bacterial skin infections are recent antibiotic use, recent hospitalization, frequent needlesticks and

playing contact sports like wrestling and football. People who have had previous bacterial skin infections due to Staphylococcus are also more likely to develop them again.[6] In addition, it's possible for skin infections caused by less-common bacteria to develop in people while hospitalized or living in a nursing home, while gardening or while swimming in a pond, lake or ocean.[12]

Age can be a determinant of the type of skin infection. From adolescence to age 45 or 50, the most common type of infection is a boil, or a furuncle. Children are more susceptible to impetigo. Newborns sometimes contract Staphylococcal scalded skin syndrome caused by toxins from a staph infection in the mother during pregnancy, which causes a fever and scalp rash. And older adults typically develop cellulitis.[6]

Only 10 percent of infections caused by Staphylococcal bacteria respond to common antibiotics such as penicillin.

Myth: Uncomplicated bacterial skin infections are not dangerous.

Fact: Uncomplicated infections, also called uncomplicated SSSIs (uSSSIs), are usually not dangerous because they typically respond well to systemic antibiotics and local wound care. However, all bacterial skin infections can be dangerous because uncomplicated ones have the potential to become complicated.[4]

Unfortunately, physicians can't easily identify the cause of SSSIs, so they typically must all be treated empirically. And, timely treatment matters to ensure that the bacterial cause is not a drug-resistant strain. If left untreated, uSSSIs may progress to cell death in deep tissue such as necrotizing fasciitis discussed earlier.[13]

Myth: Recognizing when a bacterial skin infection has become complicated is simple.

Fact: Complicated infections, also known as complicated SSSIs (cSSSIs), are not always identifiable simply by appearance. Instead, according to the U.S. Food and Drug Administration, a skin infection is considered complicated when it meets two of the following five criteria: 1) involves a preexisting wound or ulceration of the skin, 2) involves the deeper soft tissues, 3) requires surgical intervention, 4) is caused or exacerbated by underlying comorbid disease states (e.g., diabetes, system immunosuppression) and 5) is unresponsive to conventional antibiotic therapy or is recurrent. As such, initial treatment may not recognize that an infection is complicated.

For example, a 55-year-old male who had a prior history of insulin-dependent diabetes presented to the emergency department with erythema and cellulitis in the right axilla. He was administered oral cephalexin and returned three days later with a large abscess in the right axilla. A surgical evaluation confirmed a large abscess and a large surrounding area of cellulitis, and he was taken to the operating room for incision and drainage. His abscess culture grew MRSA, at which time it was determined that he had a cSSSI due to MRSA, the leading cause of skin infections in patients presenting to the emergency department.[14]

Myth: There are no easy ways to prevent bacterial skin infections.

Fact: Most bacterial skin infections are spread through direct person-to-person contact with someone who has the infection. They can also be spread indirectly through contact with items such as athletic gear, towels, razors, cell phones, etc., that are contaminated with the bacteria.[8]

However, it is possible in many instances to prevent these infections. Key to prevention is keeping skin undamaged and clean. Any cuts or scrapes should be washed with soap and water and covered. Petrolatum applied to open areas can help prevent bacterial invasion. Antibiotic ointments are not recommended because of the risk of developing an allergy to the antibiotic. Abscesses need to be cut open by a physician and allowed to drain, and any dead tissue should be surgically removed.[12]

CDC has issued standard precautions to prevent the spread of MRSA in healthcare settings in its *Guideline for Isolation Precautions: Preventing Transmission of Infectious Agents in Health Settings 2007*. Specifically, the agency recommends performing hand hygiene after touching blood, body fluids, secretions, excretions and contaminated items, whether or not gloves are worn; wearing gloves when it can be reasonably anticipated that contact with blood or other potentially infectious materials, mucous membranes, nonintact skin or potentially contaminated intact skin could occur; using personal protective equipment to protect the mucous membranes of the eyes, nose and mouth during procedures and patient-care activities that are likely to generate splashes or sprays of blood, body fluids, secretions and excretions; wearing a gown to protect skin and prevent soiling or contamination of clothing during procedures when contact with blood, body fluids, secretions or excretions is anticipated; handling used patient-care equipment soiled with blood, body fluids, secretions and excretions in a manner that prevents skin and mucous membrane exposures, contamination of clothing and transfer of microorganisms to other patients and environments; and handling, transporting and processing used

linen to avoid contamination of air, surfaces and persons.[15]

Myth: Bacterial skin infections are easily treated.

Fact: Most infections can be treated with oral antibiotics, antibiotic ointments and drainage of the infected area. However, only 10 percent of infections caused by Staphylococcal bacteria respond to common antibiotics such as penicillin. As such, the emergence of antibiotic-resistant strains of staph bacteria such as MRSA has led to the use of alternative antibiotics such as vancomycin with the potential for more side effects.[16]

All types of microbes (bacteria, viruses, fungi and parasites) have the ability to develop resistance to the drugs created to destroy them, becoming drug-resistant organisms. A major factor in the growth of antibiotic resistance is spread of the resistant strains of bacteria. According to CDC, aggressive action is needed now to keep new resistance from developing and to prevent the resistance that already exists from spreading.[17]

Myth: Bacterial skin infections are not life-threatening.

Fact: Most skin infections caused by Streptococcal bacteria such as impetigo are relatively mild. However, occasionally, these bacteria can cause much more severe and even life-threatening diseases such as necrotizing fasciitis. In fact, approximately 9,000 to 11,500 cases of invasive Streptococcal disease occur in the U.S. each year resulting in 1,000 to 1,800 deaths. But CDC estimates less than 10 percent of these are cases of necrotizing fasciitis and Streptococcal toxic shock syndrome (a bacterial infection unrelated to the skin).[18]

Staphylococcal bacteria also typically result in only minor skin infections. But, if the bacteria invade deeper into the body, entering the bloodstream, joints, bones, lungs or heart, a number of serious infections can occur. When staph bacteria are present in the blood, a condition known as Staphylococcal sepsis (widespread infection of the bloodstream), or Staphylococcal bacteremia, exists. When untreated, Staphylococcal sepsis has a mortality rate of over 80 percent.[19]

Dispelling the Myths Now

The human body is a natural host for many bacterial species that colonize the skin as normal flora. Unfortunately, Staphylococcus and Streptococcus account for a wide variety of bacterial skin infections. These infections are a significant public health condition in the U.S., and research is ongoing to address it.

Researchers at the National Institute of Allergy and Infectious Diseases (NIAID) have discovered the genetic sequence for five strains of the group A Streptococcus bacterium. NIAID is using this information to develop a group A Streptococcus vaccine, and several candidate vaccines are in various phases of development. While some scientists are conducting animal model studies to obtain data to pursue clinical trials in humans, other scientists are evaluating group A Streptococcus vaccine candidates in Phase I clinical trials. The first group A Streptococcus vaccine clinical trial found that the vaccine was well-tolerated by patients and has led to further clinical evaluation of a similar vaccine candidate. According to NIAID, an effective vaccine will prevent not only strep throat and impetigo but also more serious invasive disease and post-infectious complications.[20]

Similar vaccines are in development to protect against the Staphylococcal bacteria. One study is being conducted on NASA's International Space Station (authorized by the 2005 NASA Authorization Act). The study is taking advantage of knowledge gained in previous space flight studies to identify the target genes for MRSA virulence. Each flight opportunity provides additional insight about the bacteria and the changes that are occurring as they grow in space. The knowledge is being applied to streamline and accelerate the development of vaccines and therapeutics on Earth.[21]

Until researchers develop improved ways to prevent bacterial skin infections, perhaps in the form of vaccines, better understanding of these conditions will help to treat patients most effectively. ❖

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References

1. Mom's Feet, Hand Amputated to Stop Flesh-Eating Bacteria. *USA Today*, June 26, 2015. Accessed at www.usatoday.com/story/news/nation/2015/06/25/marine-flesh-eating-bacteria/29298075.
2. Centers for Disease Control and Prevention. Necrotizing Fasciitis: A Rare Disease, Especially for the Healthy. Accessed at www.cdc.gov/features/NecrotizingFasciitis.
3. WebMD. Skin Infections. Accessed at www.webmd.com/skin-problems-and-treatments/guide/skin-problems-treatments-treatment-care.
4. Dhar AD. Overview of Bacterial Skin Infections: Professional Version. Merck Manual. Accessed at www.merckmanuals.com/professional/dermatologic-disorders/bacterial-skin-infections/overview-of-bacterial-skin-infections.
5. WiseGeek. What Are Bacterial Skin Infections? Accessed at www.wisegeek.com/what-are-bacterial-skin-infections.htm.
6. Rice SC. Are Staph Infections on the Rise? *Healthline News*, July 26, 2013. Accessed at www.healthline.com/health-news/aging-are-staph-skin-infections-becoming-more-common-072613#3.
7. Pfuntner A, Wier LM, and Stocks C. Most Frequent Conditions in U.S. Hospitals, 2010, Statistical Brief #148. *Healthcare Cost and Utilization Project (HCUP) Statistical Briefs*, January 2013. Accessed at www.ncbi.nlm.nih.gov/books/NBK127490.
8. New York State Department of Health. Bacterial Skin Infections: Impetigo and MRSA. Accessed at www.health.ny.gov/diseases/communicable/athletic_skin_infections/bacterial.htm.
9. Mayo Clinic. Cellulitis: Causes. Accessed at www.mayoclinic.org/diseases-conditions/cellulitis/basics/causes/CON-20023471.
10. MedlinePlus. Bacterial Infections. Accessed at www.nlm.nih.gov/medlineplus/ecoliinfections.html.
11. Mayo Clinic. Staph Infections: Risk Factors. Accessed at www.mayoclinic.org/diseases-conditions/staph-infections/basics/risk-factors/CON-20031418.
12. Dhar AD. Overview of Bacterial Skin Infections: Consumer Version. Merck Manual. Accessed at www.merckmanuals.com/home/skin-disorders/bacterial-skin-infections/overview-of-bacterial-skin-infections.
13. Keating KN, Friedman H, and Perfetto EM. Fluoroquinolone Therapy for Uncomplicated Skin and Skin Structure Infections. *Clinical Drug Investigation*, 2005;25(1): 621-631. Accessed at www.medscape.com/viewarticle/513825_1.
14. Napolitano L. Managing the Complicated Skin and Soft Tissue Infection. Medscape Multispecialty. Accessed at www.medscape.org/viewarticle/571378.
15. Centers for Disease Control and Prevention. Precautions to Prevent the Spread of MRSA in Healthcare Settings. Accessed at www.cdc.gov/mrsa/healthcare/clinicians/precautions.html.
16. Mayo Clinic. Staph Infections: Treatment and Drugs. Accessed at www.mayoclinic.org/diseases-conditions/staph-infections/basics/treatment/con-20031418.
17. Centers for Disease Control and Prevention. About Antimicrobial Resistance. Accessed at www.cdc.gov/drugresistance/about.html.
18. New York State Department of Health. Streptococcal Infections (Invasive Group A Strep, GAS). Accessed at www.health.ny.gov/diseases/communicable/streptococcal/group_a/fact_sheet.htm.
19. MedicineNet.com. What Types of Diseases Are Caused by Staph? Accessed at www.medicinenet.com/staph_infection/page6.htm.
20. National Institute of Allergy and Infectious Diseases. Group A Streptococcal Infections. Accessed at www.niaid.nih.gov/topics/streptococcal/Pages/Default.aspx.
21. NASA. National Laboratory Pathfinder — Vaccine — Methicillin-Resistant Staphylococcus Aureus (NLP-Vaccine-MRSA) — 05.13.15. Accessed at www.nasa.gov/mission_pages/station/research/experiments/789.html.

Childhood Vaccine Refusal: *The Bad Outcomes of Good Intentions*

It isn't what we know that gives us trouble, it's what we know that just ain't so.
— Will Rogers

By Keith Berman, MPH, MBA

VACCINES INCLUDED IN the routine childhood immunization schedule are extremely safe. Serious side effects are quite rare. Yet, today, a small but growing minority of parents — swayed by misinformation about vaccine-related health dangers or motivated by political, philosophical or religious beliefs — are choosing not have their children immunized, leaving them unprotected against a host of vaccine-preventable infectious childhood diseases.

This phenomenon is not new. A century ago, when smallpox vaccine was first deployed by health departments throughout the country to battle common outbreaks of the deadly disease, ardent anti-vaccination activists distributed bogus accounts of victims allegedly disfigured or killed by smallpox vaccine, invoked religious objections to vaccination and railed against government intervention in private life. Some successfully lobbied state legislatures to block or repeal compulsory vaccination laws.[1] Meanwhile, in just the first four years, public vaccination programs drove down the average annual number of reported U.S. smallpox cases and deaths more than 12- and 24-fold, respectively.[2] By 1930, smallpox was eradicated in this country.

But the anti-vaccination zealots of that era did manage to have a short-term impact. By the 1920s, prior to the eradication of smallpox, their efforts left just 10 states with compulsory vaccination

laws, while 32 others either did not or even prohibited such laws. A lookback study later determined that the disease case rate in the 32 states where people could secure exemptions from receiving a smallpox vaccine was 10-fold higher than in the 10 states with laws making vaccination compulsory during smallpox outbreaks.[2] While obviously unintended, the actions and fallacies spread by anti-vaccination advocates of that era accounted for many preventable smallpox deaths.

The Modern-Day "Anti-Vaxxer" Movement

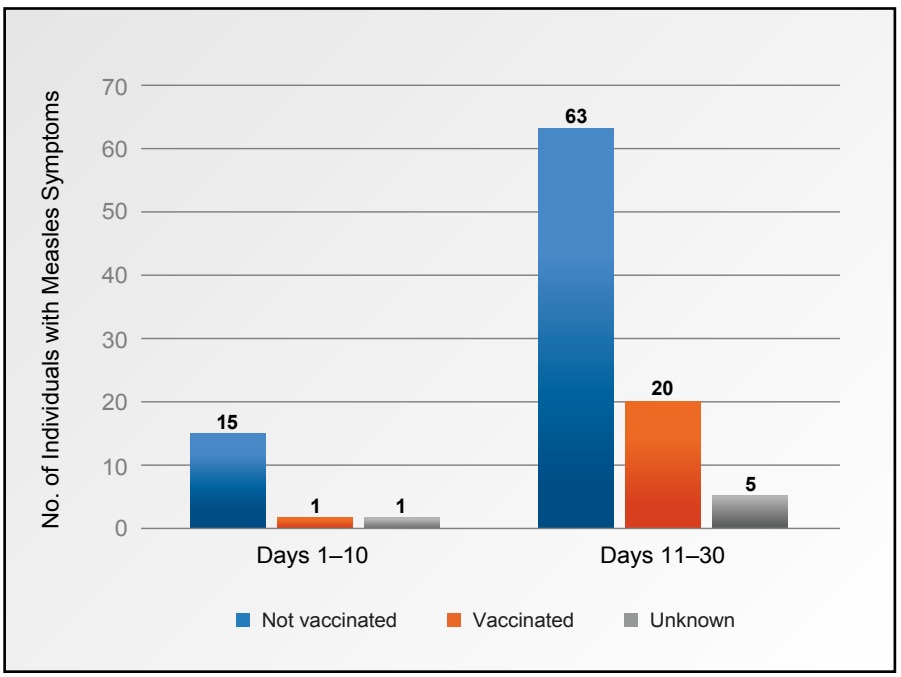
If history does not exactly repeat itself, it certainly rhymes. Motivated by beliefs echoing those that drove the opponents of smallpox vaccination a century ago, the emergence of today's generation of "anti-vaxxers" has coincided with significant declines in childhood vaccination rates in some communities. Anti-vaxxers disseminate and share misinformation about vaccine safety across the Internet, often taking form in heart-rending stories and personal testimonials posted on parenting blogs and discussion forums.[3]

> "Children who had a vaccine exemption were 35 times more likely to contract measles than vaccinated children."

All of this, of course, plays on the emotions of parents. Findings from a 2010 national survey of 376 households with children aged 6 years and younger revealed a surprising undercurrent of worry: 30 percent of parents reported concern that vaccines may cause learning disabilities such as autism, and about 35 percent said they believed their child was receiving too many vaccines in a single visit or in the first two years of life. Just 23 percent of parents reported no concerns about vaccine safety.[4]

But a comprehensive new literature review published in the *Journal of the American Medical Association (JAMA)* offers some powerful new insights into the unique vulnerability of unvaccinated children, and how these unprotected children, in turn, act as the fuel that feeds disease outbreaks and epidemics.[5] These insights may be helpful in bridging the understanding gap, both for parents and for state legislators considering bills to restrict or eliminate nonmedical vaccine opt-out exemptions.

Figure 1. Vaccination Status of Reported Cases in 18 Measles Outbreaks Over First 30 Days



Measles: Connecting Vaccine Exemption and Disease Risk

The *JAMA* authors identified 18 small measles outbreaks between 2000 and 2015, consisting of 145 cases, with sufficient information about vaccination status and symptom onset to construct a cumulative epidemic curve (Figure 1). Over outbreak days one through 10, 15 of the 17 earliest-generation measles cases were unvaccinated (one had received at least one dose of measles vaccine, and one had unknown vaccination status). From day 11 through day 30, 63 of 83 measles

Table 1. Unvaccinated and Undervaccinated Children Among Cases with Vaccination History in Three Statewide Pertussis Epidemics, 2010 to 2014[5]

State/Year	Study cases (Total cases)	Findings in children with vaccination history
California/2010[18]	4,415 (9,154)	2,001 (45%) of 4,415 children aged 6 months to 18 years were not vaccinated (380) or undervaccinated (1,621)
Oregon/2012[19]	289 (719)	89 (31%) of 289 pertussis cases with vaccination histories were unvaccinated and 71 (24%) were undervaccinated
California/2014[20]	222 (9,935)	Of 222 cases among neonates and infants under age 12 months with detailed vaccine histories, only 53 (24%) had received any doses of DTaP, despite more than half (51%) being age-eligible (older than 2 months) for pertussis vaccination

cases with known vaccination status — more than 75 percent — were also unvaccinated.

In a society where the vast majority of children and adults are immunized with measles-mumps-rubella vaccine, unvaccinated individuals are clearly critical to sustain measles transmission; without them, it is unclear how an outbreak could start or sustain itself.

Just how much higher is the risk that an unvaccinated child will contract measles during an outbreak? The *JAMA* authors cited national measles surveillance data reported to the CDC from 1985 through 1992, a period that included a 1989-1992 measles resurgence.[6] What they found should be shared with every parent seriously considering opting out: Children who had a vaccine exemption were 35 times more likely to contract measles than vaccinated children. Unsurprisingly, additional data analysis revealed two important patterns:

1) High local aggregation — clustering — of individuals with exemptions is associated with greater measles incidence; and

2) Increased prevalence of vaccine exemptions in a geographic region is associated with higher disease risk in the nonexempt vaccinated population in that region.

Pertussis: Interplay of Vaccine Refusal and Waning Post-DTaP Immunity

Unlike measles, pertussis has remained endemic in the U.S. The introduction of whole-cell vaccine in the 1940s eventually reduced the incidence of this highly contagious bacterial disease, also known as whooping cough, to a nadir of just more than 1,000 cases in 1976. There has been a major resurgence of the disease over that last decade, which can cause serious and even life-threatening illness, particularly in infants. The largest recent epidemics included 9,154 cases in 2010 and 9,935 cases in 2014. An average of more than 31,000 cases were reported over the five-year period from 2010 through 2014, including an astonishing 48,277 cases of pertussis in the peak year of 2012.[7]

One factor contributing to this resurgence of pertussis is a problem of waning immunity to acellular pertussis vaccines introduced in the mid-1990s, which are less reactogenic than the whole-cell vaccine but also less durably protective. A recent meta-analysis of long-term immunity to pertussis after three or five doses of diphtheria-tetanus-pertussis (DTaP) vaccine determined that the odds of contracting pertussis increases by 1.33 times for each additional year after the last dose of vaccine.[8] But atop this, the *JAMA* review documented the interplay of vaccine refusal in pertussis susceptibility: Across multiple reported statewide pertussis epidemics, unvaccinated or undervaccinated children comprised a very substantial share of reported cases (Table 1).

Much like the measles risk data for unvaccinated children, a large case-control study analyzing pertussis cases from 1996 through 2007 found a nearly 20-fold increased risk of contracting the disease among individuals with vaccine refusal exemptions.[9] A separate large case-control study affirmed that the risk of contracting pertussis is proportional to the number of missed doses of DTaP.[10]

These and other studies provide irrefutable evidence that childhood vaccine refusal for nonmedical reasons can cause harm in multiple ways:

- As the percentage of unvaccinated or undervaccinated children increases, so do the size and spread of disease outbreaks when an infected child arrives in the community;
- Unvaccinated and undervaccinated children place everyone else, and in particular medically exempt unvaccinated individuals, at increased risk of becoming infected during disease outbreaks; and

• The unvaccinated or undervaccinated child has a substantially greater risk of contracting the disease in the event of an outbreak compared to vaccinated children in the community.

States Move to Restrict Vaccination Exemptions

Sobering information of this nature can help providers educate resistant parents about the serious health risks that vaccine refusal creates for their child and the larger community. However, evidence from recent clinical trials suggests that even alarming messages about vaccine-preventable diseases and reassurance about the safety and societal benefits of vaccines may not be sufficient to convince many hesitant parents to vaccinate their children.[11,12]

Noting the proportion of parents claiming nonmedical exemptions from school immunization requirements and the association of vaccine refusal with disease outbreaks, public health experts are calling for restriction or elimination of nonmedical vaccine exemptions.[13,14] Following a much-publicized measles outbreak in December 2014 that started at the Disneyland theme park in Anaheim, Calif., the state's legislature passed a bill last year that eliminates personal and religious belief exemptions, and requires all children attending public and private schools to be vaccinated.[15]

> Studies provide irrefutable evidence that childhood vaccine refusal for nonmedical reasons can cause harm in multiple ways.

Since the new California law went into effect on July 1 of this year, just three vaccine exemptions remain in California: medical, special education and home schooling or independent study. Now, private or public childcare centers, preschools, elementary schools and secondary schools cannot admit children unless they are immunized against 10 diseases: diphtheria, Haemophilis influenza type b (bacterial meningitis), measles, mumps, pertussis, polio, rubella, tetanus, hepatitis B and varicella (chickenpox).

"There is persuasive evidence that stringent vaccination mandates reduce the risk of vaccine-preventable illness," Stanford health law experts wrote in a *New England Journal of Medicine* commentary after the law's passage. "Less clear is the effect California's move will have on the politics of vaccination."[16] In fact, nearly all states (except California, Minnesota, Mississippi and West Virginia) continue to allow religious exemptions, and 17 states allow both religious and personal exemptions.[17] Of the 11 states in which legislation was introduced in 2015 to remove personal belief, philosophical or religious exemptions, only California passed a bill that solely retains the medical exemption. Vermont removed only the philosophical exemption. The other nine states rejected the removal of any nonmedical exemption.

It is anybody's guess whether or when the political climate will ultimately evolve to prompt other states to do away with nonmedical vaccine exemptions. Likelier than not, it will take even more disease outbreaks — accompanied by their toll in hospitalizations and childhood deaths — to overcome the passionate opposition of well-meaning people in the anti-vaxxer movement. ❖

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References

1. Colgrove J. Science in a democracy: the contested status of vaccination in the progressive era and the 1920s. *Isis* 2005;96:167-191.
2. World Health Organization. *Smallpox and Its Eradication.* Chapter 8: The Incidence and Control of Smallpox Between 1900 and 1958. Accessed at ww.zeropox.info/bigredbook/BigRed_Ch08.pdf.
3. Kata A. Anti-vaccine activist, Web 2.0, and the postmodern paradigm — An overview of tactics and tropes used online by the anti-vaccination movement. *Vaccine* 2012 May 28;30(25):3778-89.
4. Kennedy A, LaVail K, Nowak G, et al. Confidence about vaccines in the United States: Understanding Parents' Perceptions. *Health Affairs* 2011;30(6):1151-9.
5. Phadke VK, Bednarczyk RA, Salmon DA, et al. Association between vaccine refusal and vaccine-preventable diseases in the United States: A review of measles and pertussis. *JAMA* 2016 Mar 15;315(11)1149-58.
6. Salmon DA, Haer M, Gangarosa EJ, et al. Health consequences of religious and philosophical exemptions from immunization laws. *JAMA* 1999;282(1):47-53.
7. Centers for Disease Control and Prevention. Pertussis Cases by Year (1922-2014). Accessed at www.cdc.gov/pertussis/surv-reporting/cases-by-year.html.
8. McGirr A and Fisman DN. Duration of pertussis immunity after DTaP immunization: a meta-analysis. *Pediatrics* 2015 Feb;135(2):331-43.
9. Glanz JM, McClure DL, Magid DJ, et al. Parental refusal of pertussis vaccination is associated with an increased risk of pertussis infection in children. *Pediatrics* 2009;123(6):1446-51.
10. Glanz JM, Narwaney KJ, Newcomer SR, et al. Association between undervaccination with diphtheria, tetanus toxoids, and acellular pertussis (DTaP) vaccine and risk of pertussis infection in children 3 to 36 months of age. *JAMA Pediatr* 2013;1611(11):1060-4.
11. Hendrix KS, Finnell SM, Zimet GD, et al. Vaccine message framing and parents' intent to immunize their infants for MMR. *Pediatrics* 2014;134(3):e675-83.
12. Nyhan B, Reifler J, Richey S, et al. Effective messages in vaccine promotion: a randomized trial. *Pediatrics* 2014;133(4):e835-42.
13. Salmon DA, Dudley MZ, Glanz JM, et al. Vaccine hesitancy: Causes, consequences, and a call to action. *Vaccine* 2015 Nov 27;33 Suppl 4:D66-71.
14. Davis MM. Toward high-reliability vaccination efforts in the United States. *JAMA* 2016 Mar 15;315(11):1115-7.
15. California Legislative Information. SB-277 Public health: vaccinations. (2015-2016). Accessed at leginfo.legislature.ca.gov/faces/billNavClient.xhtml?bill_id=201520160SB277.
16. Mello MM, Studdert DM, and Parmet WE. Shifting vaccination politics — The end of personal-belief exemptions in California. *New Engl J Med* 2015 Aug 27;373:785-7.
17. Sandstrom A. Nearly all states allow religious exemptions for vaccination. Pew Research Center, July 16, 2015. Accessed at www.pewresearch.org/fact-tank/2015/07/16/nearly-all-states-allow-religious-exemptions-for-vaccinations.
18. Winter K, Harriman K, Zipprich J, et al. California pertussis epidemic, 2010. *J Pediatr* 2012 Dec;161(6):1091-6.
19. Liko J, Robison SG, and Cieslak PR. Pertussis vaccine performance in an epidemic year — Oregon, 2012. *Clin Infect Dis* 2014;459(2):261-3.
20. Winter K, Glaser C, Watt J, et al. Centers for Disease Control and Prevention (CDC): Pertussis epidemic — California, 2014. *MMWR* 2014;63(48):1129-32.

An incorrect diagnosis of a rare form of cancer led to a new career as a patient advocate for Trisha Torrey.

Patient Advocacy: *A Patient's Perspective*

By Trudie Mitschang

Following a dire misdiagnosis, Trisha Torrey harnessed her anger and frustration and parlayed that life-altering experience into a new career as Every Patient's Advocate.

IT WAS LATE June 2004 when Trisha Torrey discovered a golf-ball-sized lump on her torso. Little did she know her life was about to change in more significant ways than she could ever imagine. "I contacted my family doctor the next day, and he immediately sent me to a surgeon to remove it that afternoon," she says. "He told me they'd let me know as soon as they heard back from the lab."

A week passed with no word, so she contacted the surgeon's office and was told they didn't have the results back yet. After yet another week, the surgeon finally called with grim news: Torrey had a very rare cancer — a lymphoma — called subcutaneous panniculitis-like T-cell lymphoma. A second devastating blow came when Torrey was told that the reason the lab results took so long was because the outcome was so rare, and that a second lab had been called for a second opinion. "Two labs have independently confirmed these results," she was told. "We'll make an oncology appointment for you as soon as possible."

While waiting two weeks for the oncology appointment, Torrey scoured the Internet for information about her rare diagnosis, and the dismal prognosis and high death rate only fueled her fears. When she finally met with the oncologist, she was surprised when additional blood work and a CT scan showed no signs of lymphoma. Even more surprising was the fact that despite doubts being raised, her physician insisted she begin chemotherapy immediately. "I asked about the possibility that the lab results were wrong," she explains. "I was told there was not a chance since two labs had independently confirmed the results."

Unconvinced, Torrey sought a second opinion. Offended when he learned she was postponing chemo, one of her doctors confronted her, snapping: "What you have is so rare, no one will know any more about it than I do!" Torrey says the anger she felt in that moment caused a shift in her perspective that not only propelled her to get a referral to an oncologist with expertise in her diagnosis, it also prompted her to take a closer look at her own lab results, where she uncovered numerous inconsistencies. "If I had to pinpoint an exact moment when my patient advocacy mission began, that moment would be it," says Torrey.

At her insistence, Torrey's biopsy was sent for review to a specialist at the National Institutes of Health, and three weeks later came the shocking news: Torrey did not have cancer. Her second diagnosis was panniculitis (an inflammation of fat cells), although that proved to be inaccurate as well. To date, Torrey has never been correctly diagnosed.

After working through the shock, anger and relief, Torrey was left with something else: purpose. "I believe everything happens for a reason," she says. "I am here today advocating for others — an outcome from a horrible experience that can result in good for others. Today I write, speak, and look for ways patients, their caregivers, advocates and providers can collaborate to make the healthcare system work."

Widely recognized as Every Patient's Advocate, Torrey says her mission is helping patients get what they need from the healthcare system, whether that comes from advice, improved communications between patients and their providers, or by matching them with an advocate who can help them. The author of six books, Torrey was named CNN's Hero of Patient Empowerment in 2008. "One of the biggest blessings in my life has been my ability to use my personal experiences to propel my work, and that the very worst thing that had ever happened to me (a terminal cancer diagnosis) has turned out to be the very best thing that ever happened to me (a career that I love)," she says. "The lesson is that one can take anger, fear and frustration and disable its death grip by using it to create good in the world." ❖

Patient Advocacy:
A Professional's Perspective

CONNIE SUNDERHAUS, RN-BC, CCM, is a former patient advocate who is currently on staff at the Professional Patient Advocate Institute (PPAI). PPAI is a resource and training institute for practitioners who want to enhance, elevate and improve their skills in the burgeoning field of patient advocacy. According to its mission statement, PPAI exists to help professional advocates (PAs) navigate the increasingly complex world of healthcare by offering training to improve skills and, ultimately, patient outcomes.

BSTQ: For those unfamiliar with the profession, what is a PA?

Sunderhaus: There are a variety of definitions, but in general, a PA is a professional who can objectively assist individuals in understanding and making sense of their healthcare needs. The Society of Healthcare Consumer Advocacy further defines a PA as "professionals who represent and advocate for consumers across the healthcare continuum."

BSTQ: Tell us about your experience in patient advocacy.

Sunderhaus: I am not currently practicing as a designated PA; however, I am a registered nurse and a certified case manager. On occasion, I do have direct patient interaction with injured workers and am involved with coordination of recovery and return-to-work activities and treatments. With the PPAI, I serve as current chair of the advisory board, monitor any customer service inquiries and serve as an instructor for the Hospital Patient Advocate certificate course.

BSTQ: To what do you attribute the increased demand for PAs?

Sunderhaus: Many factors have impacted the growing need for PAs, including a growing number of senior populations, increasing numbers of individuals with multiple chronic conditions, the need for healthcare systems to prevent readmissions and improve patient satisfaction, and increased recognition of the importance of smooth transitions of care.

BSTQ: What type of training or certification is available?

Sunderhaus: Currently, there is no national certification for PAs. However, there is a board that has developed the types of requirements needed, and it is looking to move toward a national accreditation/certification process. There are also online certificate programs and several colleges that offer certificate programs.

BSTQ: How do PAs support/assist the healthcare provider?

Sunderhaus: The PA is primarily available to work with the individual healthcare user and is focused on supporting the individual within the healthcare system. As a support to the provider, the PA could assist in clarifying instructions given by the provider, help with appointment management and transportation arrangements, and assist with transitions of care between care settings.

BSTQ: How are PAs compensated?

Sunderhaus: PAs most often have a contractual arrangement directly with the patient or family. This type of direct arrangement could also be made through a trust officer or attorney. Hospitals and healthcare systems also are employers of PAs, where they are used in a variety of coordinating roles. ❖

Types of Patient Advocacy

Hospital-Based Advocates: PAs at hospitals are employed by the institution to assist patients receiving care. In general, they handle patient complaints regarding treatment or healthcare providers. They are employed by the hospital at no cost to the patient.

Nonprofit Advocates: Nonprofit PAs typically offer free advice by phone and are employed by any number of nonprofit organizations. Organizations that focus on specific diseases or conditions typically offer access to specialized advocates. For example, the American Cancer Society can connect patients with advocates who are familiar with cancer-related resources.

For-Profit (Employer-Based) Advocates: For-profit PAs are part of a healthcare company that usually contracts with employers, usually at no cost to patients. These advocates may fall under an employee assistance program, and the services vary and are often provided over the phone.

Independent Advocates: Independent PAs work closely with patients on a variety of issues concerning healthcare. Their fees vary, and sometimes they offer a sliding fee based on ability to pay. Most patients find these advocates through referrals from friends, coworkers and healthcare providers.

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

Wearable Biosensor

HealthPatch MD is a new wearable biosensor to make it easier for clinical trial participants to engage in normal daily activities while ensuring improved safety and data collection. The disposable biosensor worn on the chest monitors vital signs in real time and communicates them to trial administrators. The HealthPatch MD biosensor has two components: the reusable sensor module and the disposable patch. It detects the following vital signs and biometric measurements: single-lead ECG, heart rate, heart rate variability, respiratory rate, skin temperature, body posture, including fall detection/severity, and steps. When deployed with the Medidata Clinical Cloud, HealthPatch MD comprehensively collects large volumes of objective data that is reliable, secure and analysis-ready. By providing continuous insight into patient health metrics in near-real time, the combined tchnologies can enable faster, more patient-centric clinical research while ensuring compliance and data quality.

Vital Connect,
www.vitalconnect.com/healthpatch-md

Electronic Prescription for Controlled Substances Portal

In anticipation of Drug Enforcement Administration (DEA) mandates taking effect, Meditab has augmented its Intelligent Medical Software (IMS) solution with electronic prescriptions for controlled substances (EPCS) functionality. IMS EPCS is a DEA- and Surescripts-certified solution for EPCS. Its IMS ClientConnect portal allows providers to initiate a remote identity proofing event, conducted in partnership with Exostar via Experian or from a live web cam video. Each provider receives a unique one-time password hardware token, reducing the risk for unauthorized access while ensuring compliance and accountability. The e-Prescribing workflow of IMS automatically applies a digital signature when the provider is ready to submit the prescription.

Meditab, (510) 201-0130,
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Chronos Express is a new single-use shipper utilitizing phase-change materials and high-performance foam insulation to give consistent temperature stability in excess of 72 hours. It is available in 6-, 12-, 28-, 56- and 96-liter volumes covering temperature ranges +2 Celcius to +8 Celcius and +15 Celcius to +25 Celcius. Other features of Chronos Express are payload to external volume ratios to reduce storage and distribution costs; an error-free packing process through single temperature, one-size CoolPhase PCM coolants; and high-performance foam and PCM technology to reduce excursions and increase compliance.

Pelican BioThermal,
(763) 412-4800,
www.pelicanbiothermal.com

Workplace Safety App

The WorkplaceAware mobile app is designed to help companies improve safety by eliminating barriers to reporting. The app includes the MessageQube, a mini cellular desktop printer that receives text and photo messages from any cellular phone. Using the app, employees can photograph near misses, type a description of the incident and quickly send it to their company or supervisor's MessageQube. Once a report prints on the MessageQube, it is also posted to the employer's online Enterprise Dashboard, where management can view and manage reports, including documenting corrective action taken and escalating reports to higher authorities. A green light flashes each time a new report prints, making managers aware that a report has been submitted. The app is compatible with Apple and Android operating systems.

Mobile Innovations, www.workplaceaware.com

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APhA Pharmacists' Patient Care Services Digest

Author: American Pharmacists Association (APhA)

APhA has released its 2016 edition of the *APhA Pharmacists' Patient Care Services Digest*, which shows the continued growth of pharmacists' patient care services and highlights the expanded roles pharmacists have in the healthcare system. The digest also identifies emerging and distinct pathways for providing patient care services, including a community-based pathway and an integrated health organization pathway, and explores opportunities, needed infrastructures and challenges associated with implementation. Formerly known as the *APhA Medication Therapy Management Digest*, the scope of the publication was expanded in 2014 to better reflect the enhanced roles pharmacists are playing in providing patient care services. According to a 2015 survey, pharmacists are increasingly providing medication management, disease state management and education, health and wellness services and care transition services. The digest is available for download free of charge.

media.pharmacist.com/documents/APhA_Digest.pdf

Intravenous Immunoglobulin (IVIG) Market — Global Industry Analysis, Size, Share, Growth, Trends and Forecast, 2013-2019

Author: Transparency Market Research

Transparency Market Research Pvt. Ltd.
In-depth Analysis, Accurate Results

This new report provides an extensive evaluation of the factors fueling and impeding the growth of the market for IVIG. The projections in the study are collated by evaluating the present market trends, as well as the market's potential in the forecast horizon from 2013 to 2019 on the basis of both value and volume. The study also comprises a comprehensive evaluation of each geographical segment, helping to determine the prevalent opportunities within these regions. The key government regulations related to the use of IVIG purification and production are also discussed in-depth. In addition, a strengths, weaknesses, opportunities and threats evaluation of the prime market players is provided to illustrate the business strategies adopted by these key players. The report segments the market into Asia Pacific, North America, Europe and the rest of the world.

www.transparencymarketresearch.com/sample/sample.php?flag=B&rep_id=1930

A CDC Update for Clinicians on Zika Virus Disease

Author: Centers for Disease Control and Prevention

This is an on-demand PowerPoint session by Joanne Cono, MD, ScM, director of Office of Science Quality, Office of the Director, Centers for Disease Control and Prevention (CDC). In her session, Dr. Cono addresses questions to help clinicians prepare for Zika in the U.S. Topics include health effects related to Zika; the latest CDC Zika virus guidelines and recommendations for pregnant women, women of reproductive age, infants and children; clinical evaluation, diagnostic testing and treatment for Zika; and opportunities for clinicians to support prevention and control of Zika. Participants can interact with other session participants on the #ZikaChat hashtag.

event.webcasts.com/viewer/event.jsp?ei=1098250

Strategies for Biosimilars Approval: A Map to 351(k) Success

Author: U.S. Food and Drug Administration

This new management report provides candid advice, including the evolution of FDA's thinking on the clinical requirements for showing biosimilarity, right up to and including the 2015 guidance; how participating in FDA's Biological Product Development Program can benefit companies; the supporting clinical data companies must include in filings to gain approval quickly; the correct way to apply FDA's latest recommendations for demonstrating that a proposed product is "highly similar" to a reference; how to effectively use key evaluations and modeling and simulation tools; and how to anticipate legal and regulatory hurdles such as patent and litigation issues, interchangeability and state substitution laws. Also included is a detailed review of four critical topics from the recent FDA guidance: 1) How to establish a step-wise approach to product development — the way FDA prefers; 2) The agency's "totality of evidence" methodology for assessing 351(k) applications; 3) Using foreign reference products and the need for bridge studies; and 4) How analytics should be designed for pharmacokinetics and pharmacodynamics.

www.fdanews.com/products/category/101/product/50902-strategies-for-biosimilars-approval-a-map-to-351k-success

Gene Therapy Results in Sustained Factor VIII Expression and Reduced Bleeding Episodes in Dogs with Severe Hemophilia A

Two young adult male dogs with severe hemophilia A treated with liver-targeted gene therapy experienced significant improvement in disease phenotype over follow-up periods of 31 months and 24 months, according to investigators at The Children's Hospital of Philadelphia and the University of Pennsylvania. The dogs received separate injections of two adeno-associated viral (AAV) vectors containing the light and heavy chains of recombinant B domain-deleted (BDD) canine factor VIII (cFVIII). Vector administration was well-tolerated. Liver enzymes remained within reference range for both dogs following gene therapy.

For "Dog 1" and "Dog 2," circulating levels of AAV-cFVIII-BDD remained stable at 1.6 percent to 2 percent and 1 percent of normal, with no evidence of inhibitors to cFVIII. Both dogs, which were privately owned and returned to their families following gene therapy, experienced a 90 percent reduction in spontaneous bleeding episodes over 55 total months of follow-up (a total of three episodes, compared to 22 episodes documented over a total of 41 months preceding AAV injection). The modest relative increase in FVIII activity following AAV gene therapy was sufficient to prevent most spontaneous bleeding in these two severely hemophilic dogs, consistent with conversion to a moderate disease phenotype.

"This is the first report of gene therapy in privately owned dogs with hemophilia A resulting in a significant improvement in the disease phenotype after a single vector injection, resembling the success of early phase clinical trials for humans with hemophilia B," the investigators concluded.

Callan MB, Haskins ME, Wang P, et al. Successful phenotype improvement following gene therapy for severe hemophilia A in privately owned dogs. PLoS ONE *2016 Mar 24;11(3):e0151800.*

Meta-Analysis Reveals No Evidence that IVIG Administration Increases Risk of Thromboembolic Events

Analysis of 31 randomized controlled trials (RCTs) published between 1995 and 2015 found no evidence of increased thromboembolic event (TEE) risk among patients treated with intravenous immune globulin (IVIG) compared to control patients, according to a report by a team of investigators that included epidemiologists at the U.S. Food and Drug Administration (FDA).

Of a total of 4,129 participants (2,318 IVIG-treated, 1,811 control) who were eligible for quantitative synthesis, no significant difference was found in TEE risk (odds ratio = 1.10, 95% confidence interval [CI]: 0.44, 2.88; risk difference = 0.0%, 95% CI: -0.7%, 0.7%, I2 = 0%). No significant increase in risk was found when arterial and venous TEEs were analyzed as separate endpoints.

These findings are at odds with prior case reports and observational studies indicating that IVIG may cause TEEs, leading the FDA to require a boxed warning in 2013. The

investigators acknowledged, however, that "trial publications provided little specific information concerning the methods used to ascertain potential adverse events." They added that "care should be taken in extrapolating our results to patients with higher baseline risks of TEE."

Ammann EM, Haskins CB, Fillman KM, et al. Intravenous immune globulin and thromboembolic adverse events: A systematic review and meta-analysis of RCTs. Am J Hematol *2016 Mar 11 [Epub ahead of print].*

Medicare IVIG/SCIG Reimbursement Rates

Rates are effective July 1, 2016, through Sept. 30, 2016.

Product	Manufacturer	HCPCS	ASP + 6% (before sequestration)	ASP + 4.3%* (after sequestration)
BIVIGAM IVIG	Kedrion Biopharma	J1556	$74.81	$73.61
CARIMUNE IVIG	CSL Behring	J1566	$68.07	$66.97
FLEBOGAMMA IVIG	Grifols	J1572	$75.78	$74.56
GAMMAGARD SD IVIG	Baxalta	J1566	$68.07	$66.97
GAMMAPLEX IVIG	Bio Products Laboratory	J1557	$73.86	$72.67
OCTAGAM IVIG	Octapharma	J1568	$79.55	$78.28
PRIVIGEN IVIG	CSL Behring	J1459	$76.47	$75.24
HIZENTRA SCIG	CSL Behring	J1559	$98.35	$96.77
HYQVIA SCIG	Baxalta	J1575	$129.98	$127.90
GAMMAGARD LIQUID IVIG/SCIG	Baxalta	J1569	$80.00	$78.72
GAMMAKED IVIG/SCIG	Kedrion	J1561	$81.80	$80.49
GAMUNEX-C IVIG/SCIG	Grifols	J1561	$81.80	$80.49

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

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IVIG/SCIG Reference Table

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

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

2016-2017 Influenza Vaccine

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

Manufacturer	Product	Presentation	Age Group	Code
TRIVALENT				
SEQIRUS	AFLURIA (IIV3)	5 ML multi-dose vial	5 YEARS AND OLDER*	90658/Q2035
		0.5 ML prefilled syringe, 10-BX		90656
SEQIRUS	FLUVIRIN (IIV3)	5 ML multi-dose vial	4 YEARS AND OLDER	90658/Q2037
		0.5 ML prefilled syringe, 10-BX		90656
SEQIRUS	FLUAD (IIV3)	0.5 ML prefilled syringe, 10-BX	65 YEARS AND OLDER	90653
PROTEIN SCIENCES	FLUBLOK (RIV3)	0.5 ML single-dose vial, 10-BX	18 YEARS AND OLDER	90673
SANOFI PASTEUR	FLUZONE HIGH-DOSE (IIV3)	0.5 ML prefilled syringe, 10-BX	65 YEARS AND OLDER	90662
QUADRIVALENT				
SEQIRUS	FLUCELVAX (ccIIV4)	0.5 ML prefilled syringe, 10-BX	4 YEARS AND OLDER	TBD
GSK	FLUARIX (IIV4)	0.5 ML prefilled syringe, 10-BX	3 YEARS AND OLDER	90686
GSK	FLULAVAL (IIV4)	5 ML multi-dose vial	3 YEARS AND OLDER	90688
MEDIMMUNE	FLUMIST (LAIV4)	0.2 ML live virus intranasal spray	2-49 YEARS	90672
SANOFI PASTEUR	FLUZONE (IIV4)	5 ML multi-dose vial	6-35 MONTHS	90687
			3 YEARS AND OLDER	90688
		0.5 ML prefilled syringe, 10-BX	3 YEARS AND OLDER	90686
		0.5 ML single-dose vial, 10-BX		90686
SANOFI PASTEUR	FLUZONE PEDIATRIC (IIV4)	0.25 ML prefilled syringe, 10-BX	6-35 MONTHS	90685
SANOFI PASTEUR	FLUZONE INTRADERMAL (IIV4)	0.1 ML prefilled microinjection, 10-BX	18-64 YEARS	90630

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

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

Afluria may be used in persons aged ≥9 years.

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