SUMMER 2020

biosupplytrends
QUARTERLY

SPECIAL FOCUS:
VACCINES

U.S. Vaccine Rates

Encouragement by Healthcare Workers Can Improve Compliance

HOW TO DISMANTLE THE
Anti-Vaccine Movement

CAN ADHERENCE BE INCREASED WITH
New Vaccine Delivery Methods?

COVID-19 MAY UNDERMINE
Other Infectious Disease Vaccines

GAINING CONTROL OVER THE
Ebola Epidemic

Are We Finally Closing In on a Universal Flu Vaccine? p.44

NOW AVAILABLE

HyperRAB®

rabies immune globulin (human)

3 mL (900 IU)

#1 PRESCRIBED HRIG[1] IN THE U.S.

OVER 1 MILLION PATIENTS TREATED.[2]

[1] Human rabies immune globulin
[2] References: Data on file, Grifols.

GRIFOLS

HyperRAB® 3 mL
Introducing Greater HRIG Dosing Convenience
NOW Available 3 mL (900 IU) Vial

The addition of a 3 mL vial may provide more convenience in up to 25% of cases.[2]

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HyperRAB 300 IU/mL - the first and only high-potency HRIG that offers:

1/2 The volume of medication administered in a total dose, potentially resulting in fewer injections.

2X The concentration of rabies antibodies per mL at the wound site.

Important Safety Information for HyperRAB® (rabies immune globulin [human])

Indication and Usage

HYPERRAB® (rabies immune globulin [human]) is indicated for postexposure prophylaxis, along with rabies vaccine, for all persons suspected of exposure to rabies.

Limitations of Use

Persons who have been previously immunized with rabies vaccine and have a confirmed adequate rabies antibody titer should receive only vaccine.

For unvaccinated persons, the combination of HYPERRAB and vaccine is recommended for both bite and nonbite exposures regardless of the time interval between exposure and initiation of postexposure prophylaxis.

Beyond 7 days (after the first vaccine dose), HYPERRAB is not indicated since an antibody response to vaccine is presumed to have occurred.

Important Safety Information

For infiltration and intramuscular use only.

Severe hypersensitivity reactions may occur with HYPERRAB. Patients with a history of prior systemic allergic reactions to human immunoglobulin preparations are at a greater risk of developing severe hypersensitivity and anaphylactic reactions. Have epinephrine available for treatment of acute allergic symptoms, should they occur.

HYPERRAB is made from human blood and may carry a risk of transmitting infectious agents, eg, viruses, the variant Creutzfeldt-Jakob disease (vCJD) agent, and, theoretically, the Creutzfeldt-Jakob disease (CJD) agent.

The most common adverse reactions in >5% of subjects during clinical trials were injection-site pain, headache, injection-site nodule, abdominal pain, diarrhea, flatulence, nasal congestion, and oropharyngeal pain.

Do not administer repeated doses of HYPERRAB once vaccine treatment has been initiated as this could prevent the full expression of active immunity expected from the rabies vaccine.

Other antibodies in the HYPERRAB preparation may interfere with the response to live vaccines such as measles, mumps, polio, or rubella. Defer immunization with live vaccines for 4 months after HYPERRAB administration.

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

HyperRAB®
Rabies Immune Globulin (Human)
300 IU/mL

For more information, contact **Grifols** customer service at 1-800-243-4153 or **customer.service@grifols.com**.

US-HB3-2000046

HyperRAB®

Rabies Immune Globulin (Human)

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use HYPERRAB® safely and effectively. See full prescribing information for HYPERRAB.
HYPERRAB [rabies immune globulin (human)] solution for infiltration and intramuscular injection.
Initial U.S. Approval: 1974

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

HYPERRAB is a human rabies immune globulin indicated for postexposure prophylaxis, along with rabies vaccine, for all persons suspected of exposure to rabies.

Limitations of Use

Persons previously immunized with rabies vaccine that have a confirmed adequate rabies antibody titer should receive only vaccine.

For unvaccinated persons, the combination of HYPERRAB and vaccine is recommended for both bite and nonbite exposures regardless of the time interval between exposure and initiation of postexposure prophylaxis.
Beyond 7 days (after the first vaccine dose), HYPERRAB is not indicated since an antibody response to vaccine is presumed to have occurred.

---------- DOSAGE AND ADMINISTRATION ----------

For infiltration and intramuscular use only. Administer HYPERRAB within 7 days after the first dose of rabies vaccine.

Postexposure prophylaxis, along with rabies vaccine, after suspected exposure to rabies.	HYPERRAB 20 IU/kg body weight OR 0.0665 mL/kg body weight. Single dose.	• Administer as soon as possible after exposure, preferably at the time of the first rabies vaccine dose. • Infiltrate the full dose of HYPERRAB thoroughly in the area around and into the wound(s), if anatomically feasible. • Inject the remainder, if any, intramuscularly.

---------- DOSAGE FORMS AND STRENGTHS ----------

300 IU/mL solution for injection supplied in 1 mL, 3 mL and 5 mL single-dose vials.

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

None.

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

- Severe hypersensitivity reactions may occur with HYPERRAB. Have epinephrine available immediately to treat any acute severe hypersensitivity reactions.
- HYPERRAB is made from human blood; it may carry a risk of transmitting infectious agents, e.g., viruses, the variant Creutzfeldt-Jakob disease (vCJD) agent, and, theoretically, the Creutzfeldt-Jakob disease (CJD) agent.

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

The most common adverse reactions in >5% of subjects in clinical trials were injection site pain, headache, injection site nodule, abdominal pain, diarrhea, flatulence, nasal congestion, and oropharyngeal pain.

To report SUSPECTED ADVERSE REACTIONS, contact Grifols Therapeutics LLC at 1-800-520-2807 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

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

- Repeated dosing after administration of rabies vaccine may suppress the immune response to the vaccine.
- Defer live vaccine (measles, mumps, rubella) administration for 4 months.

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biosupply trends QUARTERLY

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biosupplytrends QUARTERLY

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

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The Critical Need for Vaccines and Higher Vaccine-Compliance Rates

ONCE AGAIN, there is a critical and urgent need for a vaccine to protect people worldwide against an emerging infectious disease. The current COVID-19 pandemic, for which there is no known human immunity and no vaccine to protect against it, follows many others that have swept through human populations resulting in millions of deaths, including the bubonic plague (Black Death) in the 1300s, smallpox in the 1600s, cholera in the 1800s and several influenza (flu) pandemics, the deadliest of which was the Spanish flu in the 1900s. More recently, the world has been stricken by the SARS pandemic in 2003 and other serious illnesses of international concern such as Zika virus in 2015-16 and Ebola virus in 2014-16 (see "In the Shadow of COVID-19, Will Other Vaccine Development Programs Be Left Behind?" [p.32]). All these viruses, with the exception of Ebola, now have licensed vaccines to prevent infection, albeit influenza vaccines are not effective against all strains. But prior to vaccines, the biggest threat from these viruses was the death toll that ensued due to the lengthy time it takes to produce a vaccine — from months to years.

The triumph of vaccines is evidenced by their success rate in eradicating diseases such as diphtheria, tetanus, polio and measles, among others — due to vaccines given primarily during childhood to provide protection for a lifetime. But, herd immunity is dependent upon most people getting vaccinated. Unfortunately, while compliance with vaccination recommendations is rising in the U.S., it is still too low among all age groups. How, then, can Americans be persuaded to adhere to the recommended vaccine schedule? In our article "Trends in U.S. Vaccine Compliance" (p.20), we highlight the influential role medical providers can play in guiding parents' decisions to vaccinate their children, as well as convincing adults to get their flu shots. These illnesses, after all, can only be prevented by healthcare workers' participation in helping to raise vaccination rates.

Yet, despite rising rates of vaccination, the World Health Organization cites the anti-vaccination movement as "one of the 10 greatest risks to global health." As we explain in our article "Counteracting the Anti-Vaccine Movement" (p.24), anti-vaxxers are mainly parents and mostly mothers who have bought into misinformation spreading across social media, as well as by others who benefit financially from it. The good news is laws have been enacted in all 50 states that aim to overcome exemptions to vaccination. And, physicians have shown how they can be more effective in changing parents' attitudes about vaccination through open and honest communication and online tools that demonstrate vaccines' benefits over their potential risks. Looking ahead, their efforts will be especially important when a COVID-19 vaccine becomes available as there is already widespread resistance urged by members of the anti-vaxx movement.

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

Helping Healthcare Care,

Patrick M. Schmidt
Publisher

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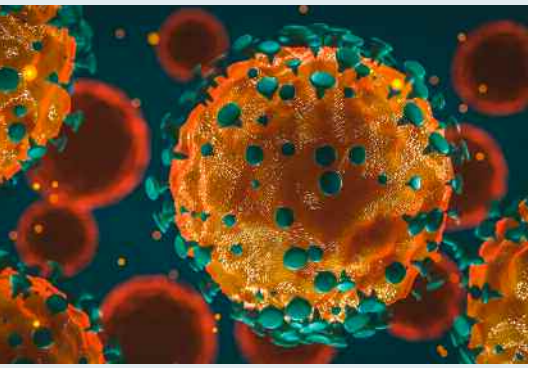

The U.S. Department of Health and Human Services (HHS) is using a $100 billion hospital and provider relief fund to pay hospitals at Medicare rates for uncompensated COVID-19 care for uninsured individuals. Funds will be distributed through the Public Health and Social Services Emergency Fund, which supports the National Disaster Medical System. According to HHS Secretary Alex Azar, hospitals that receive funds are banned from balance billing; however, he did not specify what cost-sharing obligations might be imposed for uninsured COVID-19 patients or whether ancillary providers will be included in the ban.

The White House administration has framed the relief fund as an alternative to reopening the Affordable Care Act exchanges for those who have lost employment and, thus, healthcare benefits. Health Management Associates, a leading independent national research and consulting firm in the healthcare industry, has predicted up to 40 million people in the U.S. could be uninsured if job losses from the coronavirus pandemic are severe. ❖

Cohrs R. HHS to Use Coronavirus Relief Funds to Pay for Care for Uninsured. Modern Healthcare, April 3, 2020. Accessed at www.modernhealthcare.com/politics-policy/hhs-use-coronavirus-relief-funds-pay-care-uninsured?utm_source=modern-healthcare-covid-19-coverage&utm_medium=email & utm_campaign=20200405&utm_content=article1-readmore.

Finalized Rule Gives Patients More Control Over Their Health Data

In March, the U.S. Department of Health and Human Services (HHS) finalized two rules that give patients unprecedented safe and secure access to their health data. The rules, issued by HHS Office of the National Coordination for Health Information and Technology (ONC) and Centers for Medicare and Medicaid Services (CMS), implement interoperability and patient access provisions of the 21st Century Cures Act and the MyHealthEData initiative.

The ONC final rule updates certification requirements for health information technology (IT) developers and establishes new provisions to ensure providers using certified health IT have the ability to communicate about health IT usability, user experience, interoperability and security, including (with limitations) screenshots and video that are critical forms of visual communication for such issues. It also requires electronic health records to provide the clinical data necessary, including core data classes and elements, to promote new business models of care. And, it advances common data through the U.S. Core Data for Interoperability (USCDI), a standardized set of health data classes and data elements essential for nationwide, interoperable health information exchange. The USCDI includes "clinical notes," allergies and medications among other important clinical data to help improve the flow of electronic health information and ensure the information can be effectively understood when it is received. It also includes essential demographic data to support patient matching across care settings.

Building on the foundation established by ONC's final rule, the CMS Interoperability and Patient Access final rule requires health plans in Medicare Advantage, Medicaid, Children's Health Insurance Program (CHIP) and federal exchanges to share claims data electronically with patients. Beginning Jan. 1, 2021, Medicare Advantage, Medicaid, CHIP and plan years beginning on or after that date, as well as plans on the exchanges will be required to share claims and other health information with patients in a safe, secure, understandable, user-friendly electronic format through the Patient Access application programming interface (API). The Patient Access API will allow patients to access their data through any third-party application they choose to connect to the API and could also be used to integrate a

health plan's information to a patient's electronic health record. To further advance the mission of fostering innovation, the CMS final rule establishes a new Condition of Participation for all Medicare and Medicaid participating hospitals, requiring them to send electronic notifications to another healthcare facility or community provider or practitioner when a patient is admitted, discharged or transferred to facilitate better care coordination and improve patient outcomes. Lastly, CMS is requiring states to send enrollee data daily beginning April 1, 2022, for beneficiaries enrolled in both Medicare and Medicaid to improve the coordination of care for this population. ❖

HHS Finalizes Historic Rules to Provide Patients More Control of Their Health Data. Centers for Medicare and Medicaid Services press release, March 9, 2020. Accessed at www.cms.gov/newsroom/press-releases/hhs-finalizes-historic-rules-provide-patients-more-control-their-health-data.

FDA Campaign Designed to Help Consumers Use New Food Label

The U.S. Food and Drug Administration (FDA) has launched a campaign to help consumers use the new Nutrition Facts label that appears on packaged foods to maintain healthy dietary practices. The label was finalized in May 2016, but most manufacturers with $10 million or more in annual food sales had until Jan. 1, 2020, to begin using it on their products. Manufacturers with less than $10 million in annual food sales have until Jan. 1, 2021, to start using the new label, although many already have.

The new campaign is part of FDA's comprehensive, multi-year Nutrition Innovation Strategy, which is designed to empower consumers with information about healthy food choices and to facilitate industry innovation toward healthier foods. The campaign's tagline "What's In It For You?" is designed to reach the general public and also focuses on consumers at increased risk of nutrition-related chronic diseases, including obesity. Included in the campaign are videos and educational materials of food products modeling their new looks, including on a fashion runway, after receiving a makeover.

The new label is the first redesign of the Nutrition Facts in more than 20 years, and its design is based on updated scientific information, including the link between diet and chronic diseases such as obesity and heart disease. It is most distinguishable by its bold listings for serving sizes and calorie counts. Additional changes include new required listing for added sugars, vitamin D and potassium, and a dual column version of the label for food packages that contain two to three servings that can be reasonably consumed at one time. On the dual label, one column lists the nutritional facts related to a single serving, and the other column lists nutritional facts for the contents of the entire package. Serving sizes have also been updated to reflect that the amount of food and beverages people eat and drink has changed.

The campaign is intended to educate consumers, as well as healthcare professionals, teachers, dietitians and community leaders. Information about the campaign can be accessed at www.fda.gov/food/nutrition-education-resources-materials/new-nutrition-facts-label. ❖

FDA Launches New Campaign to Help Consumers Use the New Nutrition Facts Label. U.S. Food and Drug Administration press release, March 11, 2020. Accessed at www.fda.gov/news-events/press-announcements/fda-launches-new-campaign-help-consumers-use-new-nutrition-facts-label.

Waiver Allows Medicare Patients to Receive Free Telehealth Services

The Centers for Medicare and Medicaid Services (CMS) has broadened access to Medicare telehealth services so beneficiaries can receive a wider range of services from their doctors without having to travel to a healthcare facility. CMS is expanding this benefit on a temporary and emergency basis under the 1135 waiver authority and Coronavirus Preparedness and Response Supplemental Appropriations Act. The benefits are part of the broader effort to ensure all Americans — particularly those at high risk of complications from the virus that causes the disease COVID-19 — are aware of easy-to-use, accessible benefits that can help keep them healthy while helping to contain the community spread of this virus.

Under this new waiver, Medicare will pay for office, hospital and other visits furnished via telehealth across the country and including in patients' places of residence as of March 6, 2020. A range of providers, including doctors, nurse practitioners, clinical psychologists and licensed clinical social workers, will be able to offer telehealth to their patients. Additionally, the U.S. Department of Health and Human Services Office of Inspector General is providing flexibility for healthcare providers to reduce or waive cost-sharing for telehealth visits paid by federal healthcare programs. Prior to this waiver, Medicare could only pay for telehealth on a limited basis: when the person receiving the service is in a designated rural area and when they leave their home and go to a clinic, hospital or certain other types of medical facilities for the service.

Medicare beneficiaries will be able to receive a specific set of services through telehealth, including evaluation and management visits (common office visits), mental health counseling and preventive health screenings, to help ensure Medicare beneficiaries who are at a higher risk for COVID-19 are able to visit with their doctor from their home, without having to go to a doctor's office or hospital, which puts themselves and others at risk. ❖

Medicare Telemedicine Health Care Provider Fact Sheet. Centers for Medicare and Medicaid Services press release, March 17, 2020. Accessed at www.cms.gov/newsroom/fact-sheets/medicare-telemedicine-health-care-provider-fact-sheet.

Guaranteed Channel Integrity®

8 Critical Steps

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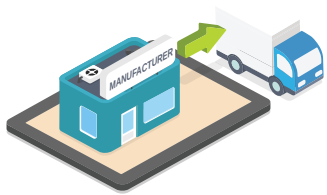
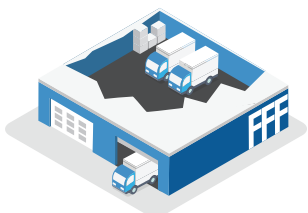
At FFF, we only purchase product from the manufacturer–never from another distributor or source–so the integrity of our products is never in question.



STEP 2

Storage

The healthcare products we store and transport are sensitive to temperature variations. Our state-of-the-art warehouse is temperature-controlled, monitored 24/7, and supported with backup generators in the event of power loss. In addition, we only stack products double-high to minimize pressure on fragile bottles and containers.



STEP 3

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

STEP 4

Interactive Allocation

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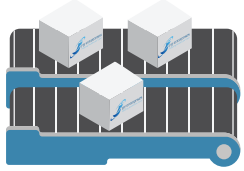

Our commitment to a secure pharmaceutical supply chain is demonstrated by our flawless safety record. The 8 Critical Steps to Guaranteed Channel Integrity have resulted in more than 11,600 counterfeit-free days of safe product distribution.

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STEP 5

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Our delivery guidelines are in compliance with the State Board of Pharmacy requirements. Products we deliver must only be transported to facilities with a state-issued license, and only to the address on the license. We make no exceptions. And we will not ship to customers known to have a distributor's license.

STEP 6

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We monitor for extreme weather conditions, and when the need arises, we ship overnight to maintain product efficacy. We also track patient need during life-threatening storms to make sure products are delivered when and where patients need them most.

STEP 7

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

STEP 8

Tracking

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

Data Integrity Vigilance: Telling Patient Pandemic Stories

By Bonnie Kirschenbaum, MS, FASHP, FCSHP

WHILE FOCUSING on being prepared, safe and innovative during the COVID-19 pandemic, healthcare providers mustn't overlook the critical importance of data integrity. That data, the subsequent pictures painted and the stories revealed from it, will be the industry's historical record. During this unprecedented time, the first instinct may be to triage activities, often weeding out the ones that seem least important. However, documentation must be comprehensive because COVID-19 patients' care must be coded thoughtfully to bring in desperately needed income, diminish financial toxicity for patients who are often eligible for expanded resources and avoid medical billing and payment issues in the months and years following this pandemic.

Although crucial, payment is only one outcome of submitted claims. Mining these claims that tell patient stories also generates vast amounts of epidemiological data, vital in an age of value-based care and bundled payment strategies where all payers require significant amounts of data on which to base their care pathways and payment strategies. Clearly, inaccurate or incomplete claims data skews epidemiological data. As a result, technology infrastructure and innovations are essential to support data analytics to track COVID-19 cases. And, even after the pandemic is over, integrity, telehealth and the necessity for accurate billing will be more important than ever.

How the CARES Act Benefits Providers

For years, telemedicine advocates have lobbied to make it easier for patients to access care remotely. The somewhat limited provisions for telehealth and virtual visits in the 2020 outpatient prospective payment system (OPPS) rules have now been greatly expanded with at least 80 additional payable services to allow clinicians to provide care remotely to mitigate the risk of the spread of the coronavirus. With the enactment of the Coronavirus Aid, Relief and Economic Security (CARES) Act, all Medicare beneficiaries can receive telehealth and other technology-based communications services wherever they are located whether they are new or established patients. Additionally, providers can waive Medicare (but not Medicare Advantage) co-payments for telehealth services, and commercial payers have also waived co-payments. There also are state-specific legal, policy and regulatory changes related to telehealth during the COVID-19 pandemic that further define state licensure flexibilities related to the pandemic, telehealth coverage and payment changes for commercial plans.

Tucked into the recently invoked CARES Act is a provision that temporarily removes the Medicare sequester cutting funding from May 1, 2020, through Dec. 31, 2020, and suspends it an additional year through Dec. 31, 2021. This gives providers a guaranteed 2 percent increase on all Medicare payments in this temporary window. However, claims need to be complete and accurate to be processed quickly and paid completely. And, while funding is part of the stimulus package, it's up to each facility to request funds and use them wisely to help cover COVID-19-related expenses and lost revenue.

The Act also provides a 20 percent add-on payment to diagnosis-related group rates for COVID-19 patients treated at hospitals that are reimbursed through the inpatient prospective payment system using a new ICD-10-CM diagnosis code

(U07.1). An enhanced group assignment effective for discharges on or after April 1, 2020, corrected the underpayments possible from the original group assignment.

Reimbursement Post-Pandemic

Handling fees and drug administration charges. Some facilities struggle with capturing intravenous (IV) drug administration charges for zero/nominally priced drugs and possible handling fees. Under OPPS and the physician fee service (PFS), injectable drug administration fees cover some costs of products and supplies required for drug administration. Additionally, private insurers and Medicare Advantage plans also often offer these add-on payments. Drug administration for reimbursement purposes are bundled and include use of local anesthesia; starting the IV; access to IV, catheter or port; routine tubing, syringe and supplies; preparation of drug; flushing at completion; and hydration fluid. However, data capture with the requisite charting substantiating charges is essential. The 2020 injectable drug administration fee add-on codes remain "paid separately" for all five drug payment types covering status indicator G, K and N drugs.

Drug administration services. Two groups of current procedural terminology (CPT) codes cover a wide variety of injectable medication episodes for complicated drugs and simple common products. While there are differences in payment rates between OPPS and PFS, CPT codes and their definitions remain the same. The following are some of the more common CPT codes:

• CPT codes 96401-96459 (often referred to as chemotherapy, which is misleading) cover drugs requiring advanced practice training and competency for staff; special considerations for preparation, dosage or disposal; patient risk; and frequent monitoring. Examples of these include frequent changes in infusion rate, prolonged presence of nurses administering the solution to monitor patients and make infusion adjustments, and frequent conferring with physicians about these issues.

• CPT codes 96360-96379 for therapeutic, prophylactic, and diagnostic injections and infusions (often referred to as nonchemotherapy drugs).

• CPT codes 90461-90474 for intramuscular infusions and immunizations cover stop times.

Healthcare Common Procedure Coding System drug codes must be matched to correct drug administration CPT codes because any error represents either underbilling (e.g., immunotherapy drug matched with nonchemotherapy code) or overbilling (e.g., antibiotic matched with chemotherapy code).

Guidance regarding chemotherapy versus nonchemotherapy administration can be found in the *Medicare Claims Processing Manual*, Chapter 12, Section 30.5 (local Medicare administrative contractors may have further details/preferences).

Zero-priced drugs. To combat expensive drug costs, healthcare providers' focus should be on reducing the cost of drugs for patients. One way to accomplish this is by prescribing zero-priced drugs that come at no cost to providers. These include drugs for a specific patient supplied at no charge to a facility by a specialty pharmacy (white bagging), patient assistance program drugs and nominally/zero-priced drugs.

Such a process can also be accomplished through the supply chain. For instance, providers can obtain drugs from a traditional wholesaler, specialty pharmacy, specialty pharmacy for a specific patient at no cost to the facility, patient assistance drugs or even drugs brought by patients to allow continuance of a specific regimen of a biologic/immunologic/other specialty product, again at no cost to the facility.

New and innovative pathways can be developed to enable these methods of product acquisition. This includes building revenue cycle functions and IT systems to support these practices. In addition, drug pricing needs to be set at $0.01-$1.01 to prevent system charge rejection since the Centers for Medicare and Medicaid Services requires facilities charge less than $1.01 to get reimbursement for administration fees.

Handling fees for drugs acquired from specialty pharmacies, specialty distributors or mandated distributors that are white bagged depend on payer negotiation. If payers require providers to move outside of their traditional supply chain to accommodate patients with specific products from the sources they specify, providers negotiate a handling fee for this. The combination of these fees plus the IV drug administration charges may be that extra boost in revenue facilities need.

Medicare Telehealth Services and CPT Codes

- www.cms.gov/Medicare/Medicare-General-Information/Telehealth/Telehealth-Codes
- www.cms.gov/files/document/general-telemedicine-toolkit.pdf

Data Integrity Is Key

Data integrity ensures that what's documented and billed is accurate and complete, not only for reimbursement purposes but for providing a record of how every patient was treated. All providers need income to stay afloat during such uncertain times, and billing is a big part of that equation. Hopefully, much of the COVID-19 crisis will have passed by the time this column is published, but accurate billing is here to stay even in times of nonpandemics. ❖

Research

Study Suggests MMR Vaccine May Be Linked with Fewer Deaths from COVID-19

Epidemiological data suggests populations with the highest measles-mumps-rubella (MMR) vaccination rates often have the fewest deaths from COVID-19, which researchers believe could be why children, teenagers and other young adults often have few severe symptoms from COVID-19, and few deaths are attributed to COVID-19 in young age groups.

Larry P. Tilley, MD, co-investigator of the report "MMR Vaccine Link to COVID-19: Fewer Deaths and Milder Cases from SARS-CoV-2 in Measles-Rubella Vaccinated Populations," is working with the World Organization to begin MMR

titer testing of recovered novel coronavirus patients to determine if the link described between MMR vaccines and COVID-19 can be confirmed. Individuals who have recovered from COVID-19, regardless of how severe their case was, are encouraged to apply online to join World Organization's COVID-19 MMR Titer Study. As long as someone has tested positive, they can apply to join the study, even if they were asymptomatic. Tests will be administered at Quest Diagnostics laboratories across the United States. ❖

Measles-Rubella Vaccines May Reduce COVID-19 Danger According to World Organization. World Organization press release, May 2, 2020. Accessed at www.globenewswire.com/news-release/2020/05/02/2026412/0/en/Measles-Rubella-Vaccines-May-Reduce-COVID-19-Danger-According-to-World-Organization.html.
MMR Vaccine Link to COVID-19: Fewer Deaths and Milder Cases from SARS-CoV-2 in Measles-Rubella Vaccinated Populations. Accessed at world.org/COVID-19-MMR.pdf.

Research

Central Repository Created for SARS-CoV 2 Clinical Trials

Inato, a marketplace that helps biopharmaceutical companies increase the pool of available patients engaged in clinical trials, has unveiled its anticovid platform, a comprehensive, central repository for all existing clinical trials for SARS-CoV 2 (the virus that causes COVID-19). The anticovid platform is public, free to access and offers extensive search and filtering capabilities. The purpose of the platform is to provide the global healthcare community with easy and efficient access to any available COVID-19 trial information and research trends. In addition, the platform analyzes the latest COVID-19 clinical trial information, providing platform subscribers new analyses twice per week. In mid-April, the platform deduced:

- Nearly 1,000 COVID-19 trials were launched or anticipated in the previous four months, equating to an average of 210 trials per month.
- While China is responsible for most trials, other highly affected developed countries such as Italy, France and the U.S. have significantly increased their trials.
- Early signals suggest some antiviral agents could be ineffective for treating COVID-19 (at least in seriously ill patients); however, a significant focus of trials remains on those drugs.
- The most frequently tested therapeutic classes are antiviral agents chloroquine/hydroxychloroquine and traditional/Chinese medicine.

"We've been tracking COVID-19 clinical trials since January and noticed how difficult it was to consolidate, compare and take action on the hundreds upon hundreds of trials being developed," said Inato Co-Founder and CEO Kourosh Davarpanah. "Our company's objective is to bring new doctors and their patients into the clinical research ecosystem to unlock the potential of unengaged research sites so biopharma can bring innovative therapies to market faster. With our anticovid platform, we're taking things one step further by centralizing all COVID-19 clinical trial information and making it easy to navigate so that clinical researchers, physicians and biopharma companies can more efficiently participate

in the fight for a cure."

Individuals can access Inato's anticovid platform, register for weekly analysis updates and submit feedback at covid.inato.com/analysis. ❖

Research

Novartis Initiates Phase III Trial of Ilaris to Treat COVID-19 Patients with Pneumonia

Novartis has initiated a Phase III clinical trial to examine the efficacy of utilizing canakinumab (Ilaris), an interleukin (IL)-1β blocker, to treat a type of severe immune overreaction called cytokine release syndrome (CRS) in people with COVID-19 pneumonia. The primary objective of the study is to demonstrate the benefit of canakinumab in combination with standard of care (SoC) in increasing the chance of survival without the need for invasive mechanical ventilation among patients with COVID-19 pneumonia. Results are anticipated late summer 2020.

The study builds on early evidence from lab tests of COVID-19 patients who showed elevated IL-1β levels, among other cytokines. For the CAN-COVID trial, Novartis aims to rapidly enroll 450 patients at multiple medical centers across France, Germany, Italy, Spain, the United Kingdom and the United States, and randomize them to receive either canakinumab or placebo on top of SoC. ❖

Novartis to Begin Phase III Clinical Trial of Autoimmune Disease Drug in COVID-19 Patients with Pneumonia. Novartis press release, May 2, 2020. Accessed at www.hospimedica.com/covid-19/articles/294782125/novartis-to-begin-phase-iii-clinical-trial-of-autoimmune-disease-drug-in-covid-19-patients-with-pneumonia.html.

Research

Clinical Trial Will Assess IVIG for Treating COVID-19

Octapharma USA is supporting a new investigator-initiated clinical trial led by George Sakoulas, MD, of Sharp Memorial Hospital in San Diego, Calif., focused on treating the most critical coronavirus patients who are experiencing respiratory failure who become ventilator-dependent. The Randomized Open Label Study of Standard of Care Plus Intravenous Immunoglobulin (IVIG) Compared to Standard of Care Alone in the Treatment of COVID-19 Infection hopes to identify whether IVIG can halt coronavirus progression to respiratory failure requiring transfer into the intensive care unit (ICU) and mechanical ventilation in admitted COVID-19 patients, and whether adding IVIG to the standard of care will reduce days requiring oxygen therapy and total hospital days.

"It is currently believed that 80 percent of COVID-19 subjects will require no medical treatment, 15 percent will require non-ICU medical care and 5 percent may require ICU admission," said Dr. Sakoulas. "The goals of this study are to evaluate three parameters: the rate of subjects requiring mechanical ventilation; number of days patients require oxygen therapy; and length of hospital stay."

Secondary objectives of the study are to identify whether adding IVIG to the standard of care will reduce days requiring oxygen therapy, and to identify whether adding IVIG to the standard of care will reduce total hospital days.

"Although we are currently collecting convalescent plasma for future preparations, we need a treatment option for COVID-19 now for critical and soon-to-be critical patients," said Octapharma USA President Flemming Nielsen. "There is no known effective treatment for patients who are infected with COVID-19. IVIG is well-understood to treat immune-mediated diseases and for prophylaxis and treatment of severe infections, especially in immunocompromised patients."

In an earlier clinical trial in Wuhan, China, where the coronavirus outbreak began, it was noted that death from the disease is frequently the result of an abnormal pulmonary immune system response with multiple respiratory viral infections in which there is an elevation of cytokine and chemokine production referred to as a "cytokine storm" and associated with poor clinical outcomes.

"There have been few human cases analyzing the effects of utilizing IVIG for COVID-19 infection," said Dr. Sakoulas. "One small case series of three patients from China demonstrated clinical improvement allowing hospital discharge in clinically deteriorating COVID-19 patients. Motivated by this small study, our team employed a similar algorithm in a 62-year-old female with diabetes, hypertension and a history of prior chemotherapy due to breast cancer who was clinically deteriorating from COVID-19 infection, with oxygen requirement increasing from 2L to 6L in the first 48 hours of hospitalization. After receiving IVIG, the patient demonstrated a remarkable clinical improvement, becoming afebrile and breathing normally without external oxygen treatment in less than 72 hours, accompanied by improvement in inflammatory markers. She was discharged home uneventfully. We believe that at least some COVID-19 patients may benefit from IVIG treatment, especially when given at the right time before full-blown acute respiratory distress syndrome sets in."

Dr. Sakoulas hopes to enroll 20 adults hospitalized with COVID-19 requiring significant oxygen, but not on mechanical ventilation. Patients will be randomized to receive standard of care alone, or standard of care with IVIG treatment. For complete study information, contact Huub Kreuwel, vice president of scientific and medical affairs at Octapharma, at usmedicalaffairs@octapharma.com. ❖

New COVID-19 Clinical Trial Supported by Octapharma USA. Octapharma USA press release, April 16, 2020. Accessed at www.businesswire.com/news/home/20200416005144/en/New-COVID-19-Clinical-Trial-Supported-Octapharma-USA.

Research

Study of Kevzara Shifts from Severe to Critical COVID-19 Patients

Following a review by the Independent Data Monitoring Committee (IDMC) of preliminary results from the Phase II portion of an ongoing Phase II/III trial evaluating Kevzara (sarilumab), an interleukin-6 (IL-6) receptor antibody, in hospitalized patients with severe or critical respiratory illness caused by COVID-19, the trial was amended so only critical patients continue to be enrolled to receive Kevzara 400 mg or placebo.

The randomized Phase II portion of the trial assessed intravenously administered Kevzara higher dose (400 mg), Kevzara lower dose (200 mg) and placebo in 457 hospitalized patients who were categorized at baseline as having either severe illness (28 percent), critical illness (49 percent) or multi-system organ dysfunction (MSOD) (23 percent). Patients were classified as severe if they required oxygen supplementation without mechanical or high-flow oxygenation; or critical if they required mechanical ventilation or high-flow oxygenation or required treatment in an intensive care unit. Results demonstrated Kevzara rapidly lowered C-reactive protein (CRP), a key marker of inflammation, meeting the primary endpoint. Baseline levels of IL-6 were elevated across all treatment arms, with higher levels observed in critical patients compared to severe patients. Additionally, no new safety signals were observed with the use of Kevzara in COVID-19 patients.

Kevzara had no notable benefit on clinical outcomes when combining the severe and

critical groups versus placebo. However, there were negative trends for most outcomes in the severe group, while there were positive trends for all outcomes in the critical group. Subsequent to the IDMC review, Regeneron and Sanofi reviewed the discontinued severe group data, which revealed the negative trends in the Phase II trial (n=126) were not reproduced in the Phase III trial (n=276), and clinical outcomes were balanced across the Kevzara and placebo treatment arms. Outcomes for the severe group were better than expected based on prior reports, regardless of treatment assignment. For example, in the Phase II portion, approximately 80 percent of patients were discharged, 10 percent of patients died and 10 percent remain hospitalized.

"Even in a pandemic setting, it's both crucial and possible to obtain controlled data in adequately-sized trials to provide the evidence needed to inform optimal medical care," said George D. Yancopoulos, MD, PhD, Regeneron co-founder, president and chief scientific officer. "Emerging evidence with Kevzara and other repurposed drugs in the COVID-19 crisis highlight the challenges of making decisions about existing medicines for new viral threats using small, uncontrolled studies. We await results of the ongoing Phase III trial to learn more about COVID-19, and better understand whether some patients may benefit from Kevzara treatment. In addition, there is an acute need for tailored approaches that specifically target this virus." Regeneron has rapidly advanced its targeted anti-SARS-CoV-2 antibody cocktail, and it initiated clinical trials in June.

The Kevzara trial was designed after a small, single-arm study in China that found elevated IL-6 levels among mostly severe, febrile hospitalized COVID-19 patients, which suggested inhibiting this pathway with the IL-6 blocker tocilizumab rapidly reduced fever and improved oxygenation in severe patients, allowing for successful hospital discharge. These uncontrolled findings require confirmation in adequately-sized and well-controlled trials.

The ongoing portion of the Phase III trial, which is continuing to enroll, currently includes more than 600 patients in the critical group. Regeneron and Sanofi remain blinded to the ongoing portion of the Phase III trial. ❖

Regeneron and Sanofi Provide Update on U.S. Phase 2/3 Adaptive-Designed Trial of Kevzara® (sarilumab) in Hospitalized COVID-19 Patients. Regeneron Pharmaceuticals press release, April 27, 2020. Accessed at www.prnewswire.com/news-releases/regeneron-and-sanofi-provide-update-on-us-phase-23-adaptive-designed-trial-of-kevzara-sarilumab-in-hospitalized-covid-19-patients-301047326.html.

Medicines

FDA Approves Biosimilar to Rheumatoid Arthritis Drug

Amgen's biosimilar to Johnson & Johnson's rheumatoid arthritis drug, Remicade, has been approved by the U.S. Food and Drug Administration. The biosimilar, Avsola, has the same chemical components, dosage form and strength as Remicade and can treat a range of autoimmune disorders. It was approved for all eligible indications of Remicade, including the treatment of bowel disease, Crohn's disease and plaque psoriasis. The black box warning for the risks of serious infections and malignancy is similar to that of Remicade's. ❖

FDA Approves Amgen's Biosimilar to J&J's Rheumatoid Arthritis Drug. Healthword.com, Dec. 7, 2019. Accessed at health.economictimes.indiatimes.com/news/pharma/fda-approves-amgens-biosimilar-to-jjs-rheumatoid-arthritis-drug/72409782.

Research

Rituxan Superior to Mycophenolate Mofetil in Sustaining Complete Remission in Pemphigus Vulgaris Patients

Results from Genentech's Phase III PEMPHIX study evaluating the efficacy and safety of Rituxan (rituximab) compared to mycophenolate mofetil (MMF) in adults with moderate to severe pemphigus vulgaris (PV) showed the study met the primary endpoint at week 52 and demonstrated Rituxan is superior to MMF, with 40.3 percent of patients treated with Rituxan achieving sustained complete remission without the use of steroids for 16 consecutive weeks or more, compared to 9.5 percent in the MMF arm. All secondary endpoints were statistically significant in favor of Rituxan: lower cumulative oral corticosteroid dose, fewer flares, a greater likelihood of sustained complete remission, a lesser likelihood of flare and a greater improvement in the Dermatology Life Quality Index at week 52 (estimated mean change from baseline -8.87 vs. -6.00) compared to the MMF arm. Adverse events were generally consistent with those seen in previous Rituxan clinical studies in PV and other approved autoimmune indications.

"The approval of Rituxan for the treatment of pemphigus vulgaris was the first major advancement in the treatment of this rare, serious disease in more than 60 years," said Levi Garraway, MD, PhD, chief medical officer and head of global product development at Genentech. "The PEMPHIX study showed that 40 percent of people in the study could achieve complete remission from painful blistering without the need for corticosteroids for 16 weeks or more and that Rituxan may be a superior treatment option to mycophenolate mofetil."

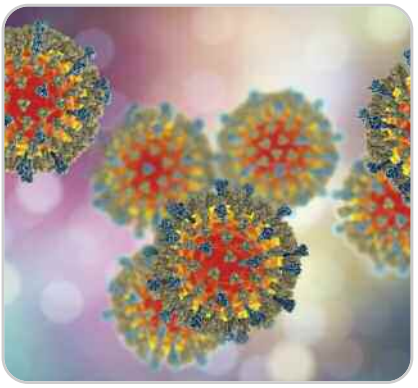
The study is ongoing, with patients participating in a 48-week safety follow-up period after treatment completion or discontinuation. ❖

Phase III PEMPHIX Study Shows Genentech's Rituxan (rituximab) Superior to Mycophenolate Mofetil in Patients with Pemphigus Vulgaris. Genentech press release, Oct. 14, 2019. Accessed at www.businesswire.com/news/home/20191013005048/en/Phase-III-PEMPHIX-Study-Shows-Genentech's-Rituxan.

Research

Measles Virus Destroys Immune System's Memory of Past Infections

With the resurgence in measles epidemics worldwide, researchers conducted two studies to determine whether measles infection causes long-term damage to immune memory and found it can greatly diminish previously acquired immune memory, potentially leaving individuals at risk for infection by other pathogens. To identify and quantify long-term effects of measles on the immune system, the scientists used VirScan, an assay that tracks antibodies to thousands of pathogen epitopes in blood, to study 77 unvaccinated children before and two months after they became infected during a 2013 measles outbreak in the Netherlands. Results showed measles eliminated 11 percent to 73 percent of the antibody repertoire across individuals.

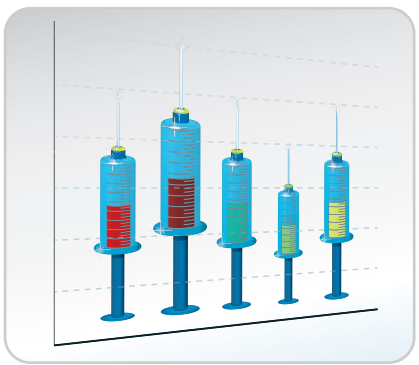


Before the children contracted measles, their blood contained antibodies to many common pathogens. "These were really healthy kids," said Michael Mina, a Harvard virologist and one of the researchers in the study. After the disease, the children lost, on average, about 20 percent of their antibody repertoire. Some fared much worse, losing more than 70 percent of their immunity to viral pathogens. They did not see the effect in their controls: five unimmunized children who never contracted measles over the course of the study, as well as more than 100 other children and adults. They also saw no loss of antibodies in children after they received a vaccination against measles. The reduction in humoral immune memory after measles infection generates potential vulnerability to future infections, underscoring the need for widespread vaccination. ❖

Mina MJ, Kula T, Leng Y, et al. Measles Virus Infection Diminishes Preexisting Antibodies That Offer Protection from Other Pathogens. *Science*, 01 Nov 2019: Vol. 366, Issue 6465, pp. 599-606. Accessed at science.sciencemag.org/content/366/6465/599.

Research

Competition Among Clinics Increased Influenza Vaccine Rates Among Patients, Study Showed



A recent experiment found offering healthcare providers financial incentives and creating competition by informing clinics how their performance ranked relative to others were effective in increasing influenza (flu) vaccine rates among patients. The experiment was conducted by two researchers at the University of North Carolina's Kenan-Flagler Business School who partnered with VaxCare, a technology company whose mission is to "transform the vaccine experience" by working with healthcare clinics to coordinate vaccination logistics.

In the experiment that was launched in August 2018, 145 healthcare clinics across nine different U.S. states were randomly assigned to one of three groups. The clinics in the first group received financial bonuses for year-over-year growth in the number of flu shots they administered, and they were paid additional money for all the shots they administered if they hit the growth target. Clinics in the second group were assessed on the same basis as the first but were just informed of their own ranking (the identities of the others in the ranking were not disclosed). The clinics in the third group, the control group, were neither offered a financial reward for increasing the number of vaccinated patients nor ranked relative to other clinics.

By December 2018, results of the experiment showed the total number of flu shots administered by the first two groups increased by about 6 percent more, on average, than the number administered by the control group. Interestingly, the number of flu shots administered by clinics that received performance rankings grew almost 10 percent, while the number of shots administered by clinics who received financial incentives increased by less than 1 percent.

According to the researchers, the experiment "provides more evidence of the potential of behavioral science to improve health outcomes and reduce costs." ❖

Niewoehner RJ and Staats B. How to Motivate Busy Physicians to Give More Flu Shots. *Harvard Business Review*, Nov. 5, 2019. Accessed at hbr.org/2019/11/how-to-motivate-busy-physicians-to-give-more-flu-shots.

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Trends in U.S. Vaccine Compliance

While vaccination rates in the U.S. are rising, they are still too low among all age groups.

By Meredith Whitmore

THE NEED FOR safe, effective and easily accessible vaccines has never been more evident than during the COVID-19 pandemic and the unprecedented global crisis it has caused. The first several months of this year alone served as a highly illustrative testament to how crucial protection is against pathogens and their effect on personal lives, cultures and economies. The world has now again faced an international pandemic requiring widespread social distancing and even isolation. Only time will tell how quickly and successfully governments and healthcare systems respond, and how soon a vaccine to prevent it is developed.

In the United States, the importance of vaccines is always at the forefront among healthcare professionals, researchers and others who have factual information about them. For example, since 1994, the Centers for Disease Control and Prevention (CDC) has collected data to estimate vaccination coverage among U.S. children. Because a number of vaccines are primarily distributed during childhood, vaccinated children are prepared for better health throughout the rest of their lives. Today, CDC and other health organizations such as the Blue Cross Blue Shield Association (BCBSA) remain diligent in their pursuit of herd immunity, safe vaccines and presenting scientifically accurate information to the public. Because of organizations like BCBSA, hundreds of millions of American children and adults are spared each year from contracting serious and potentially lethal illnesses as a result of their hard work to promote vaccine compliance.

Yet, each year, the perpetual question is: How are Americans — especially parents — responding to healthcare's call to vaccinate? And, depending on that answer, how can healthcare workers best respond to encourage more appropriate vaccine compliance? (See "Counteracting the Anti-Vaccine Movement" on p.24.) "Medical providers shouldn't underestimate their influence," encourages Hillary Johnson, MHS, an epidemiologist with the Massachusetts Department of Public Health's Immunization Program. "A strong provider recommendation for vaccination can go a long way in guiding a parent's decision to vaccinate."

Vaccine Compliance Among Young Children

In case there is any question regarding the importance of vaccination in young children, consider the following statistics: Since 2010, influenza-related hospital stays for children under age 5 years have ranged from 6,000 to 26,000 in the United States each year. And, remembering that vaccinated children mean vaccinated adults, an estimated 850,000 to 2.2 million people in the U.S. have chronic hepatitis B.[1]

Perhaps the best news, according to the BCBSA data from 2016 to 2017, is early childhood vaccination has risen to 77 percent for the CDC-recommended schedule of vaccinations, which includes diphtheria, tetanus, polio, hepatitis A and B, pneumococcal, rotavirus, measles, varicella and pertussis. "We believe that more and more people are realizing the information that had been put out on anti-vaccination was not based on science," says Brian Harvey, executive director of research and analytics at BCBSA. "And so they're starting to vaccinate their children at a higher rate. There are more children being vaccinated within that first 27 months."

The bad news is 23 percent of children ages birth to 27 months were not vaccinated. That is largely because "a child might actually be ill and may miss a well visit, causing them to be unable to complete their visits within the 27-month window. What we would stress to all the parents is that it is very important to complete those well vaccinations on time, particularly given viral diseases," adds Harvey. "If a child is not vaccinated, they're not protected. Parents want to get those completed as quickly as they can, which really is that 27-month window, or as quickly as they can do it for their child."

The bad news is 23 percent of children ages birth to 27 months were not vaccinated.

Harvey also cautions that documented parental/guardian refusals in BCBS Axis data increased nearly 70 percent for children born in 2013 compared to children born in 2010 (4.2 percent versus 2.5 percent, respectively), and most refusals were at the child's birth. This means if parents are going to refuse to vaccinate their children, most will refuse at the very beginning. "The important thing," explains Harvey, "is for agencies and healthcare workers to be educating parents how important it is to vaccinate their children and how important it is to get them protected against these diseases that can be fatal."

"There is still wide geographic variation in vaccine rates across the country," says Harvey. "For example, in 2016, the seven-vaccine series completion rates by state for children in the 2013 birth cohort ranged from a high of 86 percent in North Dakota to a low of 63 percent in Nevada." This variation might be because physicians could more effectively communicate the importance of vaccines, or because certain regions of the United States seem more prone to accept false anti-vaxxing information. For example, regarding the 2019 measles outbreak in this country, Harvey explains, "There's quite a bit of geographic variation that you can see in our data around that, too. When you look at the anti-vaccination trends, they track very closely with the news cycle from the last year. New York has the highest anti-vaccination rate of 8.4 percent. So, that's significantly above the national average of 6 percent. And then we've got Washington state at 7 percent. So, both of those places were a hotbed for the measles outbreak

because of the percentage of children who had not been vaccinated due to religious reasons and other cited exceptions. Those states also had the loosest physician exception policies. Since then, doctors have been tightening those up given the outbreak. And, we hope that when we look at 2019 data and 2018 data, we're able to see that trend going down and the number of people refusing vaccinations actually going down in the United States."

How can physicians and other healthcare providers improve vaccine compliance rates for children? According to Vincent Nelson, MD, chief medical officer (interim) and vice president of medical affairs at BCBSA: "Early childhood vaccination rates continue to improve among commercially insured children in the U.S." However, he says, "There is still wide geographic variation in vaccine rates across the country. Failure to attend routine well-child visits is the predominant reason identified for undervaccination among commercially insured children. There are reputable sources such as the Community Preventive Services Task Force, which makes a guide available that is supported by the CDC and has evidence-based interventions for increasing appropriate vaccination."[1]

Adolescent Vaccine Compliance

Among youth between 10 years and 18 years of age, the human papilloma virus (HPV) vaccine is of most concern since it is grossly underutilized. HPV vaccination coverage, as of 2016, shows 60 percent of adolescents 13 years to 17 years old have started the HPV series. And each year in the U.S., an estimated 31,500 newly diagnosed cancers in men and women are associated with HPV.[1] "Blue Cross Blue Shield of Alabama is encouraging physicians to boost HPV vaccination rates by including metrics in their value-based payment programs for physicians," says Dr. Nelson. And, such movements are occurring in other states as well.

According to Harvey, parents find the HPV vaccine the most confusing because it is a series of shots that is often poorly explained by physicians and medical literature. As a result, parents tend to avoid it. "Just the unmasked potential of what could have happened and what should have happened [with the HPV vaccine] if we actually had full herd immunity levels of 80 percent vaccination levels for boys and girls is worth mentioning," says Harvey. "If we had been able to get to [80 percent], there are a number of physicians who claim we would have eliminated cervical cancer by now. Cervical cancer would not be a concern because it's almost always translated from the HPV virus. If we can only educate parents that they do need to get this."

In some states, physicians present the HPV vaccine as elective. But, Harvey says, "This is not an optional vaccine. This is something that their children should receive. There's no downside risk to it. The biggest challenge that I think we have right now is the fact parents don't understand it. We did a survey and asked parents why they weren't vaccinating their children. The No. 1 reason is that they just don't understand it. And, they're getting conflicting information, and they think it's optional. They don't realize that it could really protect their children."

Stigma also plays a role in parents underutilizing the HPV vaccine. "Parents don't want to think of their child as an adult when they're only 12 or 13," Harvey says. "This vaccine requires a parent to think of the child as an adult, and what that adult might actually be doing later in just a few short years. In states

where the vaccine isn't presented as optional, North Dakota for example, there are very high vaccination rates. We talked to Blue Cross Blue Shield of North Dakota and asked them why this was. They told us that the vaccine is presented along with Tdap and meningococcal as nonoptional. They added that when a local doctor says, 'These are the three vaccines you need to get,' those are the three vaccines that patient gets.

"In other states where the HPV vaccine is presented as an option, people make the choice not to vaccinate. Then, they do a Google search and find all manner of anti-vaxxing information that gives them pause or scares them. So, parents need better information on that. And I think, around all vaccines, if there was better information available around the lack of risk for these vaccinations and the significant upside for all of them, there would be greater adherence and greater vaccination rates among our population."

Adult Vaccine Compliance

While there is not a required vaccine schedule for adults, the annual influenza (flu) vaccine is probably the most important. According to Harvey, "Some vaccines, like tetanus and the flu, do need to be refreshed on a regular basis. Again, it's important that people understand, just specifically looking at the flu and the flu shot, that even a partially effective flu vaccine has significant impact on what type of symptoms you're going to get and how severe your flu is going to be. If you're particularly in the at-risk population such as children or people who have underlying health conditions, or those over 60, those people should be vaccinated on an annual basis regardless for the flu. And, regardless of any news report as to whether or not that particular vaccine is a great match against the flu, the vaccine is going to help even if it isn't a complete match. People don't often hear that." Physicians, he said, must make that point clear to each patient.

Future Projections

What is likely to happen if vaccine compliance does not improve, or even worsens, among each group? Dr. Nelson addresses this possibility, explaining, "As vaccine rates fall, we put our population at risk of losing community immunity and protection from preventable diseases. Young children and persons with chronic conditions such as heart disease are especially vulnerable. Another group of people that everyone is concerned about are those who are receiving treatment for cancer conditions. Most vaccine-preventable diseases are viruses, which can spread quickly before an individual may realize that they are ill. Adequate vaccination is the best prevention." Once again, healthcare providers are the most influential sources of appropriate vaccination information.

With regard to COVID-19, Dr. Nelson explains that people respond to such dramatic illnesses with more receptivity to a vaccine, even though a vaccine may still be in development. But, people often ignore this fact when it comes to the flu. Flu is pandemic in North America, and although there is a vaccine, thousands die from it each year. News coverage likely plays a role since flu deaths are rarely reported with such vigor. "Novel diseases such as coronavirus may create fear and anxiety among people who may not understand their risks," says Nelson. "People look to various sources for information to help them decide what steps they should take to protect themselves. The best 'vaccine' against fear and anxiety is education. Blue Cross and Blue Shield companies provide timely and trusted information to their members through a variety of communication channels and maintain a state of readiness to respond to unusual outbreaks. BCBSA also supports clinical providers so that they have resources at hand to meet member needs."

While there is not a required vaccine schedule for adults, the annual influenza (flu) vaccine is probably the most important.

Indeed, such support is crucial, especially since flu vaccination rates reported by CDC speak to the misinformation surrounding the vaccine. In 2018, only 50.4 percent of children age 6 months to 17 years received an influenza vaccination, and only 34.2 percent of adults aged 18 years to 49 years received one. And, while 46.8 percent of adults aged 50 years to 64 years were vaccinated against the flu, and rates were even higher among adults aged 65 and older at 68.7 percent, that is still far too low.[2]

How vaccine compliance in general might affect COVID-19 will depend on time, among other factors, including news coverage and patients having appropriate literature on side effects and the importance of being protected. Right now, however, we can at least take some comfort in knowing vaccination rates, overall, have been on the rise. It is hoped that trend will continue and patients will come to understand many illnesses are preventable entirely. ❖

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Counteracting the Anti-Vaccine Movement

Social media platforms have given the anti-vaccine faction a significant voice that has undermined advances in public health. Now, in the wake of a global pandemic, healthcare stakeholders may have an opportunity to reclaim the narrative about vaccines with facts, not fiction.

By Trudie Mitschang

IN JANUARY 2019, the anti-vaccine movement was officially named one of the 10 greatest risks to global health by the World Health Organization (WHO). According to WHO, the thriving anti-vax movement is potentially as dangerous as the vaccine-preventable diseases themselves because it threatens to reverse decades of public health progress. In a report on the topic, WHO concedes the reasons why people choose to forgo vaccination are complex, but some of the main sources of pushback include mistrust of the pharmaceutical industry; skepticism regarding scientific facts; complacency among those who were born after many communicable diseases were eradicated by vaccines; and difficulty accessing and/or affording medical care. Then, there are those who avoid vaccination for personal reasons such as religious exemption. No matter the reason, vaccine avoidance is a trend that frustrates many in the healthcare community who recognize the important role vaccines play when it comes to global disease prevention, clearly a top-of-mind topic with the COVID-19 pandemic. "Vaccination is one of the most cost-effective ways to prevent diseases. It currently avoids two to three million deaths a year, and another 1.5 million could be avoided if vaccine coverage were improved in the world," reported WHO.[1]

Vaccine-Hesitation: A Parental Prerogative

When it comes to childhood vaccines, a strong majority of parents in the United States do comply with recommended vaccination schedules. Still, the anti-vax movement in both the U.S. and globally has steadily been on the rise. The question is: Who are the "anti-vaxxers," and what do they have in common? Understanding the psychological and demographic makeup of this highly vocal contingent may be the first step in formulating a plan to combat pervasive anti-vaccine agendas.

A 2018 study published in the *Journal of the Missouri State Medical Association* tackled this question and uncovered some interesting commonalities, while also dispelling a few stereotypes. For example, the study found no real correlation between vaccine attitudes and socioeconomic status or education level, stating better predictors include a high level of conspiratorial thinking; a low tolerance for infringement on perceived personal freedom; aversion to needles or blood; and religious-based concerns. But regardless of individual belief systems and mind-sets, the most significant consumers of vaccine misinformation are concerned parents, specifically mothers.[2]

When it comes to raising children and managing healthcare choices, mothers are without question critical decision-makers. As a group, they also tend to be very active and vocal in online forums. One study on the topic of mass communication and society found mothers who contributed frequently to online conversations about healthcare topics shared several common traits. Those who didn't strongly support childhood vaccinations were more likely to seek, pay attention to, forward information and speak out about the issue compared to those who do support childhood vaccinations. Also, those who believed vaccinations were an important issue (whether they were for or against them) were more likely to express an opinion, while those who opposed vaccinations were more likely to post their beliefs online.[2]

Addressing the Abundance of Misinformation

From social media posts to fully dedicated anti-vaccination websites, access to online misinformation about the safety and efficacy of vaccines abounds. One German study demonstrated individuals will perceive increased risk to vaccination after spending only five to 10 minutes scrolling through an anti-vaccination website.[3] Additionally, a Canadian study suggested the odds of parents perceiving vaccines as unsafe rose considerably for those who searched for vaccine safety information online.[4]

Few global events stand poised to confront anti-vaccine viewpoints as dramatically as the COVID-19 pandemic.

On the flip side, access to pro-vaccination messages online has not proven to be effective when it comes to combating pre-existing bias; researchers in the 2018 Missouri study concluded that a large part of the reason people buy into the anti-vaccination mind-set is due to what's known as "confirmation bias"; when presented with evidence opposing existing beliefs, individuals will forgo critical thinking and reject contradictory information outright. Given this bias, some direct pro-vaccination messages have actually backfired; a randomized trial on pro-vaccine communications found attempts to directly educate concerned parents with materials from the Centers for Disease Control and Prevention (CDC) served only to further reinforce their already exaggerated perception of risk.[5] According to the study's authors, "None of the interventions increased parental intent to vaccinate a future child. Refuting claims of an MMR/autism link successfully reduced misperceptions that vaccines cause autism but nonetheless decreased intent to vaccinate among parents who had the least favorable vaccine attitudes."

Understanding the Money Motivation

The anti-vaccination sentiments popularized in recent decades were in part fueled by the 1998 publication of a series of articles in *The Lancet* by former British doctor Andrew Wakefield. Dr. Wakefield suggested a connection between the measles, mumps

and rubella (MMR) vaccine and development of autism in young children. Despite his flawed research methodology and conflict of interest in funding of the study, MMR vaccine rates continued to drop dramatically, and panicked parents continued to share the articles' findings with one another. Even after Dr. Wakefield had his United Kingdom medical license revoked, he continued to oppose state bills against vaccine exemptions and personally profit from promoting anti-vax misinformation, including through his 2016 film titled "Vaxxed: From Cover-Up to Catastrophe." Not surprisingly, members of the anti-vaccine movement still cite Dr. Wakefield's discredited research as a talking point in refuting vaccinations.

But Dr. Wakefield is not the only one benefiting financially from the spread of anti-vax media. For example, conspiracy theory websites like InfoWars and Natural News regularly discredit medical science while benefiting from the sale of natural supplements and products that claim to offer alternative treatments for vaccine-preventable diseases.[6] The *Washington Post* reports that while one of the nation's oldest anti-vaccine advocacy groups has claimed it is supported primarily by small donations and concerned parents, over the past decade, a single donor has contributed more than $2.9 million to its cause, accounting for about 40 percent of the organization's funding. Court records show that donor, osteopathic physician Joseph Mercola, has amassed a fortune selling natural health products, including vitamin supplements he claims are alternatives to vaccines.[7] And, selling supplements and making films are not the only ways to profit from promoting an anti-vaccine agenda; anti-vaccine books, seminars, speaking engagements and online ads are all revenue-generators that can clearly muddy the waters when it comes to the movement's purported altruistic motives.

Combating Fear with Education and Legislation

In 2019, Peter Hotez, MD, PhD, FAAP, professor of pediatrics and dean of the National School of Tropical Medicine at Baylor College of Medicine, in Houston, Texas, addressed an audience at the American Academy of Pediatrics (AAP) Annual Conference and Exhibition in New Orleans, La. His session, "The Anti-Vaccine Movement in Post-Measles America: What's Next?" offered key insights into how to address the anti-vax movement, beginning with combating laws that allow parents to attain nonmedical exemptions to vaccination.[8]

Currently, all 50 states have legislation requiring specified vaccines for students. Although exemptions vary from state to state, all school immunization laws grant exemptions to children for medical reasons. Forty-five states and Washington, D.C., grant religious exemptions for people who have religious objections to immunizations, and currently, 15 states allow philosophical exemptions for those who object to immunizations because of personal, moral or other beliefs.[9] "The anti-vaccine movement has grown into its own political and media empire," Dr. Hotez said. "We have to work to close nonmedical exemptions, especially in the states allowing nonmedical vaccine exemptions for personal or philosophical beliefs."[8]

Dr. Hotez believes the first step to reversing the damage done by anti-vaccine propaganda is to dismantle the anti-vaccine media materials that are major contributors to the problem. Critics to this approach argue that stifling anti-vaccination commentary or limiting sales of anti-vaccine materials violates the First Amendment, but Dr. Hotez likens it to any retailer having the freedom to restrict the types of products they are willing to sell. Deliberate targeting of specific groups to lower vaccination rates by anti-vaccination promoters is also a widespread problem, he said, coupled with the absence of a robust pro-vaccination campaign. "Australians have done this. They put out a $12 million public service campaign," he explained. "We need to have a more visible national public health leadership. Right now, the default is the defense of vaccines falling to a handful of academic pediatricians."[8]

Anti-Vaxxers in the Age of COVID-19

Few global events stand poised to confront anti-vaccine viewpoints as dramatically as the COVID-19 pandemic. As the world's scientists and pharmaceutical companies actively race to bring a vaccine to market, anti-vaxxers are already actively bracing for plans of resistance. "Refuse, demonstrate," sums up attitudes on a British Facebook page in response to a post asking people how they would react if a COVID-19 vaccine became mandatory.[10]

Despite early resistance, polls show sentiments in parts of Europe may be gradually changing. In France, for example, a 2018 poll showed one in three people did not view vaccines as safe, but just 18 percent said they would refuse a coronavirus vaccine today, according to a March 2020 poll of approximately 1,000 people. The poll was taken just one day after France issued its COVID-19 lockdown. "If a vaccine were made available tomorrow, everyone would jump to get it," said Laurent-Henri Vignaud, who co-authored a history of France's anti-vax movement.[10]

Given the common mind-sets of anti-vaccine proponents, including a low tolerance for perceived risks to personal freedoms, it's not surprising the possibility of a mandatory vaccine would raise a collective cry of protest. At the time of this writing, it remains difficult to assess what overall public sentiment may be to a coronavirus vaccine once it finally becomes available. If history is any indicator, timing is everything when it comes to vaccine receptivity. For example, there was high demand for the polio vaccine in the 1950s because the risk level of the disease was very visible and present; images of children confined in iron lungs presented a compelling reason toward vaccine compliance. On the other hand, concerns about a vaccine being "rushed" to market during the 2009 H1N1 "swine flu" pandemic led to widespread vaccine resistance amid concerns about the vaccine's safety. Piggybacking on that line of thinking, some anti-vax groups are

already using references to COVID-19 vaccine trial participants as "guinea pigs," references that have the potential to create backlash long before an actual vaccine is made available to the public.[11]

Another hurdle presented by the COVID-19 pandemic is that access to routine immunization programs may have been interrupted as health resources have been directed elsewhere and annual well-visits for both children and adults take a back seat to pandemic intervention measures. "While it may be harder to routinely vaccinate people if health resources are directed elsewhere, and there is difficulty or reluctance to go to the doctor or other places where vaccination takes place (such as schools due to closure), making the best use of the vaccines already available is crucial to avoid other disease outbreaks on top of COVID-19," said Samantha Vanderslott, a postdoctoral researcher in social sciences at the University of Oxford.[11]

A Multipronged Approach May Hold Promise

At a time in America when public opinion is divided on many major fronts, perhaps one approach that might begin to bridge the conversational debate about vaccine safety is a simple one: open and honest communication. Doug Opel, MD, a pediatrician at Seattle Children's Hospital, is pioneering a study with collaborators at the University of Colorado, Denver, in which physicians are trained to use what's called the presumptive method when conversing with parents about vaccines. Dr. Opel explains the first step is simply asking parents what their vaccine concerns are. Physicians are then counseled to validate those concerns; they should tell parents that this is a hard decision, that it is confusing to hear so much conflicting information, and that, yes, unfortunately, vaccines are not 100 percent safe. Only then should pediatricians say their expert opinion — having looked at all the available data — is that vaccinating is unequivocally the right choice. "There is this tendency to dismiss these parents who have concerns as not being knowledgeable or being exposed to some really bad information on the Internet," says Jason Glanz, PhD, a senior research investigator with Kaiser Permanente's Institute for Health Research in Colorado. "That's partly true, but really they're concerned for their children. I think it's a small proportion who are adamantly against vaccination."[12]

Dr. Glanz's research on vaccine-hesitant parents uses online tools where participants can engage with information about shots with their healthcare providers, rather than just receiving a pamphlet or looking up information online. Dr. Glanz says it's crucial to acknowledge a parent's fears rather than dismiss his or her concerns about potential vaccine risks. Instead, physicians have to be honest with their patients; there are risks, they're just exceedingly small and are far outweighed by the benefits. Dr. Glanz notes it's also important for pediatricians to start vaccine conversations early during pregnancy, since his studies found parents begin forming their opinions on vaccines well before their child is born.

In addressing the recent anti-vax upsurge in measles cases and vaccine resistance in general, Dr. Glanz said, "I think there's not going to be one solution to this. A multipronged approach involving national public health messaging, physician communication strategies and better online resources is probably how we're going to accomplish a goal that all of us, even vaccine-hesitant parents, share: fewer measles cases.

"It took a while, but the smoking campaign worked. That used multiple modes, and it took many, many years, but it worked. We might be dealing with something similar here."[12] ❖

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Exploring New Vaccine Delivery Methods

Some promising new methods for delivering vaccinations could mean a pain-free alternative, the elimination of accidental needlesticks and reduced risk of infections.

By Jim Trageser

LET'S BE HONEST: Many if not most healthcare professionals secretly wish they had Dr. McCoy's hypospray device for delivering vaccinations on the TV show "Star Trek." Painless and risk-free, the make-believe hypospray is the perfect delivery method for vaccines: Just place the nozzle against the patient's arm, and it shoots the dose through clothing and skin with no puncture wound, pain or bleeding.

Unfortunately, today's real-world administration of vaccines is not as easy. With nearly all vaccines using a weakened or dead microbe (or part of one) to stimulate the patient's immune system, oral application is often not viable: Many microbes would simply be digested in the stomach and never promote the desired immune response. So most vaccines need to be placed directly into the bloodstream or muscle tissue to be effective. And while inhalers and patches are increasingly an option to administer vaccines, the fact remains that the hypodermic needle is still the dominant method of injection.

Interestingly, the writers of "Star Trek" based their make-believe hypospray device on a real-life (but ultimately flawed) device developed a few years before the series debuted in 1966: the jet injector, developed to replace the hypodermic syringe. The fact that we're still using hypodermic needles to administer the vast majority of vaccines a half-century after the jet injector was introduced to replace the needle shows just how difficult advancing the state of the art of vaccination can be.

The good news is new methods of administering vaccines continue to be introduced, and for good reason: Each year, more than 12 billion injections are given by medical professionals around the globe. Roughly 385,000 of those result with a healthcare professional experiencing an accidental needlestick with the risk of poisoning and/or infection.[1] Yet another risk is present: Fear of needles and the pain they cause can lead patients to avoid lifesaving vaccinations.[2]

Origins of the Needle

As pharmacology began its first stirrings in the late Middle Ages, efforts to deliver drugs directly to the tissue or bloodstream were also undertaken. While most early drugs were designed to be taken orally or rectally, or applied topically, there were some attempts to find a more efficient method of delivery.

Unfortunately, early needles — perhaps inspired by the fangs of snakes, which the ancients had known were able to deposit venom directly into muscle tissue or the circulatory system — were crude, large and more painful than our modern versions.

The first serious study of using a needle to deliver medicine into the body was not undertaken until 1656, when Christopher Wren improvised a hypodermic syringe and needle from an animal bladder and a goose quill. His experiments on dogs were noted, but the technique was not adopted.[3]

Some 200 years later, three developments occurred in short succession that made the modern needle a viable delivery method:

- Irish physician Francis Rynd, MD, administered morphine under the skin of a patient in May 1844 using a hollow needle, and he reported the patient's pain subsided more quickly and for longer than using other methods.[4]
- French veterinarian Charles Gabriel Pravaz connected a needle to a syringe at his Lyon laboratory in 1853, using it to inject iron chloride into an aneurysm.[5]
- A little later that same year, Scottish physician Alexander Wood, MD, independently developed his own syringe and needle and used it to administer morphine.[5]

At that time, however, the syringe was ahead of its time since fewer than 2 percent of drugs were available in an injectable form as recently as 1905.[6] However, the rapid development of vaccines in the 20th century quickly made the needle the best available delivery method since most vaccines could not be effectively administered orally. With new immunizations against typhoid fever, tuberculosis, whooping cough (pertussis), tetanus and diphtheria, the use of hypodermic needles exploded in the years before and after World War I.

Replacing the Needle

Despite its widespread use, there were so many disadvantages associated with the needle that it was viewed as an imperfect delivery method almost from its beginning. Shortcomings included risk of infection if a needle wasn't kept sterile, single-use delivery (the World Health Organization reports unsafe reuse of needles is a massive issue in developing nations[7]), the challenge of safe disposal and the fear of needles by many patients. Additionally, almost from its introduction, the needle was associated with narcotic addiction. Even Dr. Wood, who helped invent the syringe, was reported to have become addicted to the morphine he prescribed and administered to his patients.[6] Consequently, during the six decades following the needle's invention, the search to replace it was in motion.

An early attempt at replacement occurred when French factory workers experienced needle-less injections by accident when using high-powered grease guns as early as the late 1800s. Doctors who examined them after these accidents noticed there were grease deposits under the skin. Then, in 1935, an American mechanical engineer, Arnold K. Sutermeister, witnessed such an accident and worked with John Roberts, MD, to design a prototype jet injector for medical use.[8] Twelve years later, a working model designed by Marshall Lockhart was introduced for clinical testing, and he named the device the hypospray, which lived on in "Star Trek."

A slightly different design of a jet injector was adopted by the Army's Medical Corps in 1961 for vaccinations. That same year, the U.S. Centers for Disease Control and Prevention adopted similar technology for its mass civilian immunization program against polio.

Each year, more than 12 billion injections are given by medical professionals around the globe.

While the various jet injectors all avoided use of a needle, instead using high-pressure air to force a thin stream of liquid medication through the skin into the tissue beneath, these devices also had drawbacks. First, they weren't noticeably less painful than a needle, and because they breached the skin, occasional infections still occurred. Second, the blowback from the small wound created at the injection site could infect the applicator with fluids from one patient that could be inadvertently injected into subsequent patients.[9]

By the 1990s, the jet injector in its original form was no longer being used by the military since its drawbacks outweighed its efficiencies. However, the goal of a painless, safe and efficient method of administering vaccines was no less urgent.

Patches

The use of adhesive patches to deliver medication through the skin is now known to most laypeople due to the popularity of contraceptive patches to prevent pregnancy and nicotine patches for smokers trying to wean themselves off their addiction (a product popularly known as "the patch").

Originally introduced in 1979 to apply scopolamine for motion sickness,[10] transdermal patches offer several advantages over hypodermic syringes or jet injectors: less pain, lower fear threshold, no risk of cross-contamination or infection, less risk to medical staff and safer disposal. They can also reduce office visits since the patches can be delivered to patients who can then apply them themselves.

There is continued research studying whether delivering vac-

cines via skin patches can be as effective as pharmaceutical patches. Currently, anthrax[11] and influenza (flu)[12] are both being studied as candidates. But these studies have identified some challenges. Namely, dosage control is more difficult, and a longer period of time is required to administer the full dose to obtain full immunization.[11] Further, as with oral delivery, patches encounter the body's own first-line defenses — the skin's resistance to invasion — limiting the types of material that can be delivered via patch to those molecules small enough to pass through the skin.[13]

However, a new technology may offer a way around the skin's defenses: patches that utilize dissolving microneedles. This technology creates tiny hollow needles made of sugars and polymers that penetrate the skin with an encapsulated dose before breaking down and releasing the vaccine.[14] Early studies with seasonal flu vaccines show promise,[15] and patients report no pain with the microneedles.

Ongoing research at Rutgers University is utilizing 4-D printing (in which 3-D printed materials are designed to change shape after the printing process is complete) to create microneedles that mimic natural shapes known to penetrate the skin (basing the shape on microscopic parasites with backward-facing barbs).[16]

While jet injectors, skin patches, inhalers and oral vaccines are all currently approved for use (at least in some countries), additional new methods of delivery continue to be explored.

Inhalers

Just as smoking cessation programs have made "the patch" popular as an alternative form of delivery, the asthma inhaler introduced many laypeople to the concept of administering drugs via the lungs or nasal passages. While people have ingested drugs via their lungs by smoking for thousands of years, the modern application of therapeutic drugs via the lungs began in 1956 with the introduction of the metered dose inhaler.[17] Today, new inhalers are available to deliver a variety of drugs outside asthma relief, from insulin to loxapine.[18]

The use of inhalers to deliver vaccines has shown great promise. Inhalers bypass the issues in both oral and injection delivery methods. The lungs and nasal cavity offer a fast, efficient path to the blood supply without any of the body's more stringent defense mechanisms coming into play. Compared to injections, delivering a vaccine via the lungs may increase the body's mucosal immune response, resulting in higher overall immunological protection.[18] And, similar to patches, inhalers can reduce demand for office visits since patients can self-apply.

Currently, seasonal flu vaccines in the United Kingdom are primarily given to children via a nasal application.[19] This method is also licensed for use in individuals from 2 years up to 49 years old in the United States.

Yet, while delivery via the lungs or nasal cavity offers many advantages over other methods, there are challenges. First, different medications may require different inhaler designs to properly transport the substance through the mouth and airways into the lungs. Even with existing asthma and chronic obstructive pulmonary disease medications, there are a variety of different types of inhalers, from aerosols to nebulizers. Second, patients must be taught the proper technique for using these different types of inhalers since poor technique can negatively impact dosage and effectiveness.[17] Third, inhalers should not be shared between patients, which can drive up the total infrastructure cost of using them — a consideration in countries lacking financial resources. Lastly, an inhaled version of a drug will generally have a different composition than the injected formula, creating additional costs.

New Approaches to Oral Delivery

While oral delivery of most vaccines has been historically challenging due to the gastric acids' tendency to break down the proteins of the attenuated microbes, encapsulated edibles offer a delivery method that carries the vaccine past the toxic environment of the stomach before releasing the contents in the intestinal tract, where it can be absorbed into the bloodstream.[20]

Perhaps the most unusual of these new oral delivery methods is the RaniPill, which recently passed Phase I clinical testing.[21] The RaniPill contains a small balloon-powered syringe in a dissolvable capsule. Once delivered to the small intestines, the capsule dissolves, and the syringe injects the dose into the intestine wall, which lacks pain receptors that make an injection into the skin so painful. In clinical tests, subjects reported not noticing any pain from the process, outside of the discomfort of swallowing a larger-than-normal pill.

Another research direction is to use genetically engineered plant compounds to achieve the same effect by fine-tuning the formulation to withstand the stomach's environment and then dissolve in the intestines.[22]

As with inhaled vaccines, studies indicate orally delivered vaccines can increase mucosal immunities in comparison to injections.[22]

Revisiting the Jet Injector

While the original jet injector is no longer considered an acceptable form of delivery, engineers have continued to fine-tune the basic concept of using a high-pressure stream to inject without a needle. Like the hypodermic needle, the jet injector offers tremendous advantages over other methods in terms of dosage control, immediacy of application and control of rate of diffusion.

Today, the main change from the original design is the use of disposable components to prevent cross-contamination between patients. While the main compressor is reused, the tip is disposed of, much as needles have one-time use with a traditional syringe.[23] This means any blood or tissue splatter is safely removed from the equipment, and a fresh unused applicator is used for the next patient.

However, a 2015 study conducted in India that examined the use of disposable-syringe jet injectors for the delivery of the DTP-HB-Hib vaccine was halted early due to a high incidence of adverse reactions at the injection site. The study results, published last year, indicate the vaccine itself worked as well as the same formula delivered by hypodermic needle. However, the negative reaction (bleeding, discoloration, nodules) to the injection method needs further investigation.[24]

Another innovation under way is use of a combustible propellant to drive the liquid stream through the injector nozzle. It is believed this will provide greater control over the nozzle velocity, as well as add flexibility for different applications.[25]

Looking Ahead

While jet injectors, skin patches, inhalers and oral vaccines are all currently approved for use (at least in some countries), additional new methods of delivery continue to be explored.[25]

• Sonophoresis uses ultrasound to weaken the skin's structure to allow for a medication to penetrate the skin's defenses.[25] Several studies are proceeding on using this to deliver medications; however, vaccine delivery remains over the horizon for now.

• Iontophoresis or electroporation applies an electrical current to an area of the skin to make it permeable, similar to sonophoresis. It has been successfully tested in animals.[26]

• Elastic liposomes can be structured as a hollow carrier that can pass through cell membranes.[27]

Oral and inhaled delivery options for most existing vaccines are currently undergoing clinical study. In fact, vaccines that can currently only be administered via injection should have multiple application options in the near future. For instance, tuberculosis, typhoid fever, shigella and cholera all have alternative delivery methods currently under study.

Fortunately, with such promising new delivery methods for vaccinations, patients who avoid vaccines for fear of needles are unlikely to have to face that dilemma in years to come. ❖

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In the Shadow of COVID-19, Will Other Vaccine Development Programs Be Left Behind?

As governments around the world ramp up COVID-19 prevention activities, are other diseases of international importance and their prevention programs suddenly on pause?

By Hillary Johnson, MHS

ON FEB. 27, 2020, members of the White House Coronavirus Task Force held a press conference in the White House Press Briefing Room.[1] On that date, there were 15 confirmed cases of coronavirus disease 2019 (COVID-19) in the United States, all the result of recent travel, and there was not yet evidence of sustained community transmission. Yet, a question on everyone's mind was the status of a novel coronavirus vaccine. President Trump prefaced by stating the U.S. was rapidly developing a vaccine, and it was coming along well. Secretary of Health and Human Services Alex Azar listed vaccine and therapeutics development among the White House's top-five priorities in their request for funding from Congress. But, it was Anthony Fauci, MD, director of the National Institute of Allergy and Infectious Diseases at the National Institutes of Health, who spoke to the realities of developing a global vaccine.

Phase I and II clinical trials (determining safety and immunogenicity) would take about six months, he estimated. Then, he said, the vaccine would graduate "to a trial that involves hundreds if not low thousands of people to determine efficacy. At the earliest, an efficacy trial would take an additional six to eight months. So, although this is the fastest we have ever gone from a sequence of a virus to a trial, it still would not be any applicable to the epidemic unless we really wait about a year to a year and a half."

For the emerging global pandemic, it was clear, a vaccine would not be the answer over the next year. Dr. Fauci continued, "However, if this virus — which we have every reason to believe it is quite conceivable that it will happen — will go beyond just a season and come back and recycle next year — if that's the case, we hope to have a vaccine."

And with that, COIVD-19 joined the long list of global infectious diseases with ambitious targets for mitigation through vaccination. But as a world in quarantine shifts focus and resources to COVID-19 response, where are we with other emerging infectious diseases that very recently also dominated the global newsreel, namely the Zika and Ebola viruses?

The Zika Virus

In March, the International Olympic Committee postponed the 2020 Tokyo Olympic Games due to the spread of COVID-19. While this will be the first time in Olympic history that the Games are postponed,[2] it is not the first time concerns over a spreading virus have cast a shadow over the global event.

The previous Summer Games in Rio de Janeiro sparked a heated debate over safety and the possibility of Zika virus transmission, as outbreaks in Brazil beginning the year before resulted in an estimated 200,000 cases.[3]

Spread mostly by the bite of an infected Aedes species mosquito, Zika virus typically causes mild clinical symptoms, and many infected have no symptoms at all. However, in 2016, the World Health Organization (WHO) declared a Public Health Emergency of International Concern[4] based upon accumulating data showing the link between Zika virus in pregnancy and fetal birth defects, as well as the potential for Guillain-Barré syndrome in infected adults.

Multiple scientists and organizations called for the Games to be canceled, but WHO ultimately determined there was no public health justification for postponing or canceling the games[5] based upon an assessment at the time that Zika virus was already circulating in almost 60 countries globally and 39 countries in the Americas. However, WHO did advise pregnant women not to travel to Rio de Janeiro.

The Summer Olympics came and went with minimal Zika fanfare (WHO reported no new cases associated with the event[6]), but the threat of Zika virus did not immediately abate. That year, the U.S. reported more than 5,000 cases within the United States and more than 36,000 cases in the U.S. territories.[7] A 2016 *Lancet* study[8] estimated more than two billion people were potentially at risk for Zika virus infection across Asia and Africa. With data on the association between Zika virus and microcephaly in infants continuing to mount, interest in development of an acceptable vaccine candidate was also growing. WHO announced a Zika virus vaccine target product profile (TPP) for emergency use that same year.[9]

TPPs describe the desired characteristics of a product that will address a certain disease, and the TPP for Zika virus vaccine was no small feat. This "wish list" for a Zika vaccine included preventing clinical illness in subjects 9 years and older, and providing at least a year of protection in a single dose, a long shelf life when frozen and acceptable use in pregnant and lactating women.

As with many vaccines proposed for the global stage, logistics can be a primary barrier. Complex cold chain storage requirements make many vaccines suboptimal in warmer climates with questionable power consistency. The ideal Zika vaccine will need to be easily stored and administered, particularly in warm rural climates.

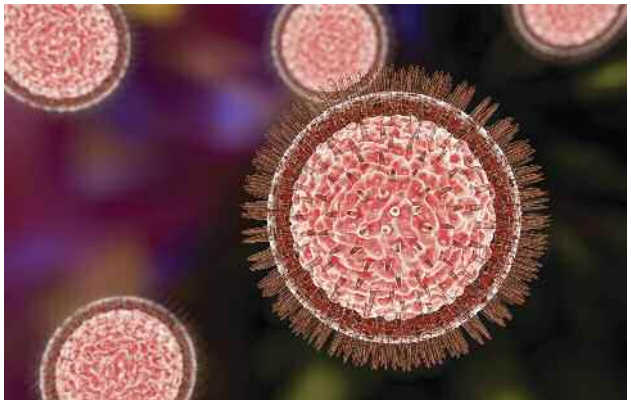
But beyond common logistical concerns, a potential vaccine faces significant challenges. Early research stumbled due to initial deficiencies in animal modeling (many preliminary efforts to generate different Zika virus strains in mice were unsuccessful).[10] Additionally, Zika virus sequelae of greatest concern pertain to pregnant women, a challenging priority population for vaccine development; it is not yet known if correlates of immunity for fetal protection differ from those that will be identified for prevention of disease in the mother.[11] Also at issue is live vaccines are contraindicated in pregnancy, potentially limiting vaccine design options.

Zika virus is a flavivirus and shares a similar genome to other Flaviviridae RNA viruses known for causing widespread morbidity and mortality around the world (examples include Japanese encephalitis, yellow fever and West Nile).[12] But it is its resemblance to the dengue flavivirus that is most notable and creates multiple challenges in geographic areas where both viruses can be found. To begin, many diagnostic tests have difficulty distinguishing between dengue virus and Zika virus due to cross-reacting antibodies. At the patient level, this can make an explicit diagnosis challenging. But

in a clinical trial, where researchers would be looking to measure baseline antibodies pre- and post-infection, as well as pre- and post-vaccination, the ability to distinguish between Zika virus and pre-existing immunity to dengue virus in a population is paramount.

Then, there is the theoretical phenomenon of antibody-dependent enhancement (ADE), a suboptimal antibody response to the dengue virus, and due to their flavivirus similarities, it is not yet known if the same phenomenon could apply to Zika as well.[11] With ADE, infection with one dengue serotype may produce mild illness and leave behind heterotypic antibodies. But if a patient is reinfected at a later date with a different serotype, their leftover cross-reactive but non-neutralizing antibodies can actually help the invading virus by binding with it but not neutralizing it. The theory behind ADE is that the binding antibodies from the previous infection serve as a Trojan horse for the virus entering a cell, allowing significant viral replication and, ultimately, much more severe disease.

Due to the similarities across flaviviruses, the question remains: Is the body's immune response to Zika affected by natural immunity to other flaviviruses and potentially by other flavivirus vaccines?



Yet, progress has been made. The Mayo Clinic published a state of the science review of Zika vaccine development in late 2019[13] in which it mentioned more than 30 Zika vaccines in various stages of development, from early stage research to Phase II clinical trials. The proposed formulations run the gamut: live virus, inactivated virus, whole-virus, subunit, mRNA, protein and vector-based formulations. But the most advanced vaccine candidates reported in the paper are two DNA-based plasmid vaccines (encoding for prM and E proteins of a French Polynesian strain of Zika) showing success in mouse and rhesus macaques animal studies and now undergoing Phase II clinical trials in healthy adults. The Mayo Clinic additionally highlights a purified, inactivated, whole-virus, alum-adsorbed vaccine developed using the same platform as the IXIARO Japanese encephalitis vaccine in which early studies show success in eliciting neutralizing antibodies. All promising, considering this emerging pathogen only really came to the global forefront in 2016.

Unfortunately, global attention has waned due to epidemiological uncertainties. Incidence of Zika virus infection peaked in the Americas in 2016, but substantially declined in 2017 and 2018. In 2019, there were no confirmed cases of Zika virus in the U.S. territories.[7] On the surface, decreases in incidence are desired. Yet not knowing when and where the next outbreaks will occur makes clinical trial site selection difficult, and progression to more Phase II and Phase III clinical trials may be problematic. Single injections of supplemental funding in outbreaks can jump-start progress (as in 2016), but if not sustained, progress can stymie. For Zika virus vaccines, the next stage for vaccine development may be a long time in coming.

The Ebola Virus

The quest for Ebola vaccine development may share some similarities with Zika (both emerging pathogens of global concern); however, one key difference is clear. The Ebola vaccine candidates benefited from already being in development when relevant outbreaks struck.

The 2014-2016 Ebola outbreak in Western Africa dominated international headlines. Travelers leaving West Africa were screened at airports, and the United States even implemented enhanced entry screening by diverting travelers to designated airports and requiring traveler health monitoring for a period of time following entry to the U.S.[14] (similar to international travel restrictions for COVID-19 in early 2020). WHO declared the outbreak a Public Health Emergency of International Concern, and over the two-and-a-half-year epidemic, the world would see more than 28,600 cases and 11,325 deaths across 10 different countries,[15] in what would become the largest Ebola outbreak in history.

Ebola virus disease (EVD) is a rare but deadly disease first discovered near the Ebola River of the Democratic Republic of Congo (DRC) in the 1970s. Spread through direct contact with the bodily fluids of an infected person, EVD can cause hemorrhagic fevers, diarrhea, vomiting and, in up to half of cases, death.[16] Healthcare workers are particularly at risk; a WHO study from the West Africa Ebola outbreak found health workers were between 21 and 32 times more likely to be infected with Ebola than the general population, and two-thirds of those infected died.[17]

Multiple response activities are credited with ending the Western Africa outbreak, including strong government partnerships, establishing laboratories and improved surveillance methods, community mobilization and hygiene education campaigns, and building local trust. The well-timed introduction of a powerful vaccine and implementation of a ring vaccination strategy also made it possible to limit the spread of the epidemic. The prodigal vaccine, Ervebo, is manufactured by Merck, and consists of a recombinant vesicular stomatitis virus as a vector that is genetically engineered to contain a glycoprotein from the Zaire strain of the Ebola virus. Phase I and II trials were well underway (confirming safety and immunogenicity), allowing Phase III trials (looking at

efficacy) and the tail end of the outbreak to align in 2015.

In a trial, following laboratory confirmation of a case, researchers identified contacts and contacts of contacts for targeted vaccination efforts, known as a ring vaccination strategy and modeled after smallpox vaccination efforts. Through ring vaccination, everyone who has been, or could have been exposed to a diseased patient receives the vaccine. The trial was a success, showing a vaccine efficacy of 100 percent.[18] The same strategy was applied again in 2018 when DRC began its current Ebola outbreak. Preliminary study data from DRC show a 97.5 percent efficacy rate, and also suggest that vaccinating people after infection can reduce their chance of dying.[19]

Through compassionate-use protocols and the clinical trials in the DRC, more than 290,000 people[20] have been vaccinated so far with Ervebo. DRC, Burundi, Ghana and Zambia all announced they were licensing Ervebo in February, meaning they will be able to stockpile and administer the vaccine going forward outside of clinical trials.

In September 2019, Congolese health authorities began administering a second Ebola vaccine under a compassionate-use protocol. This second Ebola vaccine employs a different strategy to expand protection, bypassing the identified close contacts and social networks of ring vaccination targeted with Ervebo, and instead is being administered in the surrounding geographic areas without confirmed Ebola transmission, but still potentially at risk. The two-dose regimen leverages two different vaccines (Ad26.ZEBOV and MVA-BN-Filo) administered eight weeks apart. The vaccines utilize a viral vector strategy (genetically modifying adenovirus serotype 26 [Ad26] and modified vaccinia virus Ankara [MVA]) to safely induce the production of Ebola virus proteins and trigger an immune response. Together they are referred to as the Janssen vaccine regimen and are manufactured by Johnson & Johnson.[21]

Looking Forward

When compared with Zika, Ebola virus prevention programs seem better situated for potential challenges ahead due to the new availability of an internationally licensed vaccine (and additional vaccines in the Phase III pipeline). But a drain on international resources caused by novel coronavirus could threaten the upkeep of surveillance and response operations for both diseases worldwide. The Ebola outbreak in DRC was just two days shy of reaching the milestone of two incubation periods (42 days) with no new cases when an additional case was identified in the town of Beni in April. Reaching that milestone would have declared an end to the world's second largest Ebola outbreak. Instead, confirmed cases rose to 3,476 (with 2,276 deaths), and the clock reset for tracking another two incubation periods.[22]

Both the Zika virus and the Ebola virus have had their moments as emerging pathogens of global concern. But sustained progress in prevention will require a continued seat at the international table. Under current circumstances, maintaining a high global profile in the era of the COVID-19 pandemic (essential to ensuring continued resource allocation and capacity development) will be difficult. ❖

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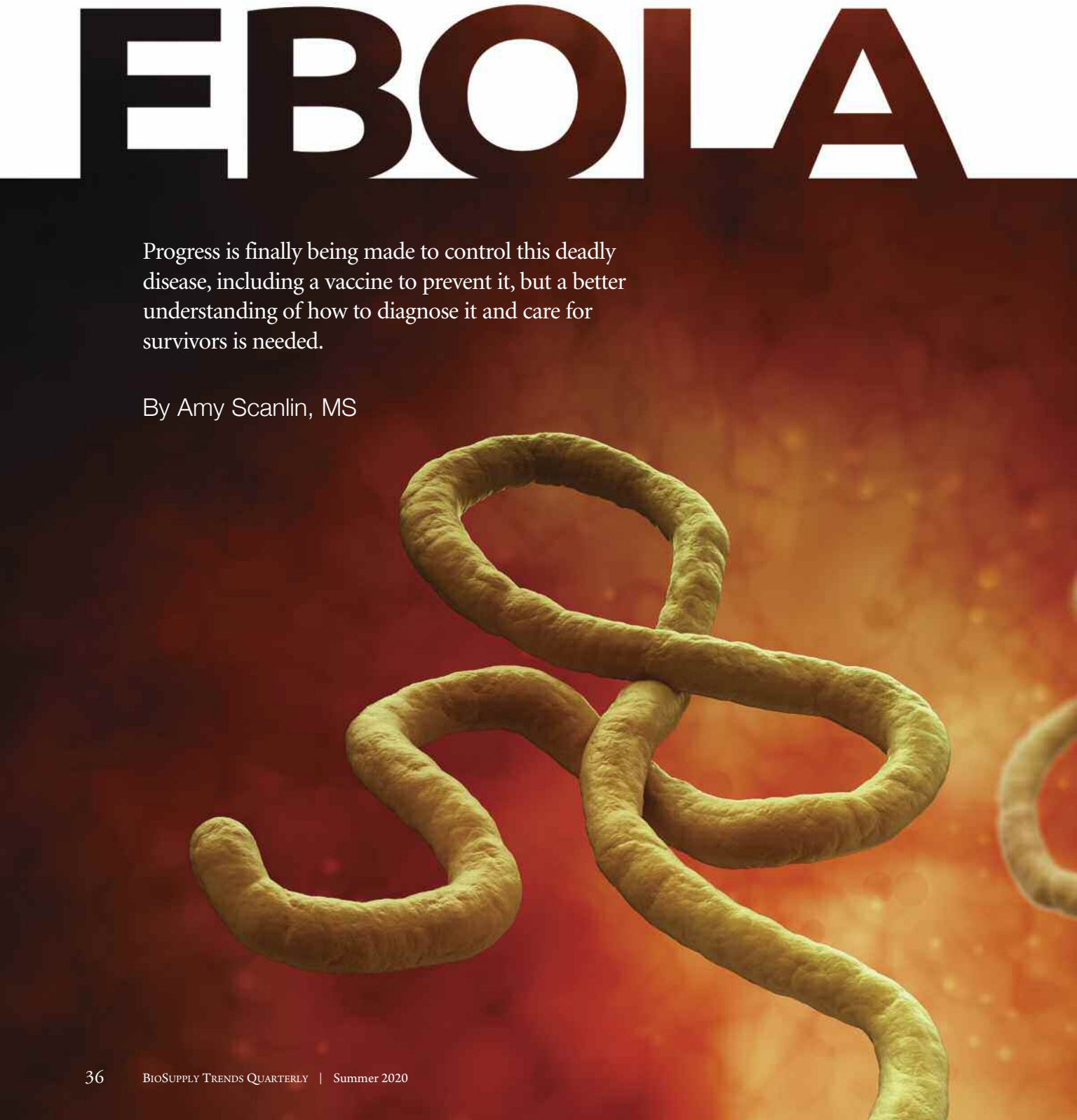
An Update on Ebola



Progress is finally being made to control this deadly disease, including a vaccine to prevent it, but a better understanding of how to diagnose it and care for survivors is needed.

By Amy Scanlin, MS

THE INTERNATIONAL community breathed a sigh of relief in the last quarter of 2019 when, more than 40 years since Ebola virus disease (EVD) was first identified, the World Health Organization (WHO) supported the use of and the European Commission and the U.S. Food and Drug Administration (FDA) approved the first vaccine for the prevention of EVD, which is caused by Zaire Ebola virus in humans. Called a "critical milestone in public preparedness and response," approval of Merck & Co.'s Ervebo for individuals 18 years and older was no easy task, complete with fits, starts and near misses. However, with efficacy determined to be 100 percent, Ervebo is expected to offer untold benefits, particularly to those in Africa where outbreaks have caused the destruction of lives, families and communities. Yet, existing challenges remain, including the need for better EVD diagnostics and how to care for Ebola survivors.

Emergence of the VSV Vaccine

While EVD was originally documented in the 1970s, notoriety about the outbreak didn't grow until 2014 with its spread in Guinea. Prior to that, scientists had been working on an EVD vaccine. But with only sporadic outbreaks, no testing beyond animal models and little opportunity to do so, there was little interest in the pharmaceutical community to develop such a costly endeavor.

In the 1990s, researchers in Marburg, Germany, began experimenting with a livestock virus called vesicular stomatitis virus, or VSV, for use as a vaccine delivery system. It was thought VSV could be an effective vehicle for a vaccine since it produces a rapid immune system response with high levels of antibodies. Already studied as a backbone to experimental vaccines for pathogens such as bird flu, measles, SARS and Zika, VSV was combined with Ebola genes, replacing the glycoprotein on the VSV with Ebola glycoprotein, allowing it to be studied at lower biocontainment levels.

The VSV construct was eventually brought to a Canadian national microbiology laboratory, a biosafety level four (BSL-4) facility, where work on a vaccine began. Mice were infected with the VSV virus containing the Ebola glycoprotein followed by the Ebola virus itself, and all survived. The method was then replicated in monkeys with good results. Therefore, the VSV vector loaded with the Ebola glycoprotein was determined safe and could be used to develop an EVD vaccine.

While EVD was originally documented in the 1970s, notoriety didn't grow until 2014 with its spread in Guinea.

But vaccine development is expensive, estimated to cost around $1 billion, and although EVD outbreaks are deadly, they were sporadic. With little market incentive, it can be difficult for pharmaceutical companies to take on such a monumental task. So, the Canadian government granted $2 million for the creation of human-grade lots of the VSV vaccine for Ebola Zaire to be used in testing, which were then manufactured and tested by a German contract partner to ensure no inadvertent contamination.[1]

In March 2014, WHO declared an EVD outbreak in Guinea. However, at that point, no testing on humans had been conducted.

Five months later, the outbreak became a global health emergency that would eventually infect 28,000, killing more than 11,000 across West Africa. According to WHO, 90 percent of those who become infected with EVD can die from it. It was then that Doctors Without Borders began urging the use of the VSV vaccine, and the Canadian government donated its version (other companies were also in vaccine development) to WHO. While NewLink Genetics held the license to develop the VSV vaccine, the company did not have the expertise to take on the clinical testing required, so Merck was identified as a new pharmaceutical partner for its capabilities, and it purchased NewLink's license.[2]

However, since the VSV vaccine for EVD had never been tested in humans, the ethics of doing so in the midst of an outbreak were questioned. In response, an "ethical imperative" prevailed allowing Phase I trials, planned in part by the U.S. National Institutes of Health (NIH) and Walter Reed Army Institute for Research, to be conducted in 10 countries. Differing from traditional random study design with control and placebo groups, the EVD trials conducted during the outbreak included those with known exposure who were randomly assigned to an immediate or delayed vaccination. "Ebola virus disease is a rare but severe and often deadly disease that knows no borders. Vaccination is essential to help prevent outbreaks and to stop the Ebola virus from spreading when outbreaks do occur," said Peter Marks, MD, PhD, director of the FDA's Center for Biologics Evaluation and Research.[3]

Early symptoms of EVD can mirror diseases and infections from organisms to which it is closely related, which is why accurate and rapid diagnosis is key.

By the time Phase III trials were ready in 2015 (with agreements in place in Liberia and Sierra Leone), WHO with the help of Doctors Without Borders initiated a cluster ring vaccination study of Ervebo in Guinea. In the study, people who had direct contact with anyone infected with EVD were vaccinated, as were their contacts, either immediately or with a 21-day delay. Results were promising, with the immediate cluster group showing no cases of EVD with symptom onset 10 days or more after receiving the vaccine, compared with 10 cases of EVD in the 21-day delayed cluster group. Similar antibody results were also seen in studies conducted in Sierra Leone, Liberia, Canada, Spain and the U.S. It was determined the vaccine had worked, so Merck moved forward in developing the rVSV-ZEBOV vaccine with the support of the Biomedical Advanced Research and Development Authority.[1]

When a new outbreak of Ebola flared in August 2018 in Equateur, a province in the Democratic Republic of the Congo, compassionate use of Ervebo was approved, and vaccinations began eight days later. Since then, more than 3,300 in the Democratic Republic of the Congo have contracted EVD, making it the second worst outbreak on record. What makes the spread of EVD so challenging is the ability of the disease to relapse and subsequently spread in patients thought to be cured. This was the case in December 2019 when the outbreak in the Democratic Republic of the Congo, thought to be contained, resurfaced. Today, with thousands of EVD survivors, the risk of resurgence, though rare, is significant.[4]

In December 2019, FDA approved Ervebo supported by the Guinea study during the 2014-2016 outbreak, as well as additional studies mentioned above.[3]

The Need for EVD Diagnostics

Early symptoms of EVD can mirror diseases and infections from organisms to which it is closely related, which is why accurate and rapid diagnosis is key. But, until recently, clinical labs used specific tests to identify pathogens (e.g., PCR assays that identify certain genes such as those containing antimicrobial resistance markers), which often require specialized equipment and can take hours or days depending on the tests' and the labs' capabilities.[5] In 2017, FDA cleared a diagnostic test for EVD, and in 2019 allowed marketing of a de novo test kit for rapid detection and presumptive diagnosis (that must be confirmed) of EVD antigens in human blood from both living and deceased persons who are suspected to have died from EVD. This rapid diagnostic test was previously authorized for emergency use under the FDA's emergency use authorization (EUA). Additionally, there are 10 diagnostic tests available for emergency use also under EUA (one rapid antigen and nine molecular).[6]

Today, the development of new diagnostic techniques using nucleic acids from Ebola and Ebola-like computer-simulated organisms housed in FDA's ARGOS database are filling gaps in a fundamental limitation of next-generation diagnostic testing by developing reference databases that analyze diagnostic test performance. Next-generation sequencing allows study of dangerous organisms without the high biosafety containment level requirements since they look at nucleic acids or organisms, which may be obtained from samples that have been rendered noninfectious.[5] As part of this line of study, regulatory-grade reference sequence standards are urgently needed to help diagnose and rule out Ebola infection.

How to Care for Ebola Survivors

To date, there are no FDA-approved drugs to treat Ebola, although several experimental treatments are under development. EVD is not a high risk for the U.S. population because transmission is through direct contact with an infected animal (bat or primate) or person (live or dead), and this transmission has historically occurred primarily in Sub-Saharan Africa.

Current treatment recommended by the Centers for Disease Control and Prevention (CDC) is supportive therapy, balancing patients' fluids and electrolytes, maintaining their oxygen status and blood pressure, and treating any complicating infections. Healthcare providers are trained to use standard precautions, and when they suspect a patient could meet the criteria for EVD exposure and symptoms, they immediately separate the patient from others, notify authorities and begin following CDC guidelines for protective personal equipment, testing and isolation. Numerous resources for handling a suspected EVD case can be found on the CDC website, the scope of which is well beyond this article.[7]

FDA and government partners are conducting studies in West Africa to better understand how EVD affects patients who have survived, as well as to learn how to more effectively treat survivors' chronic health problems. Many survivors of EVD suffer headaches, joint pain and eye problems, although the causes of these aftereffects are not understood. These studies will explore human immunopathology for chronic post-EVD signs and symptoms and provide further understanding of the natural course of the disease and lasting health problems.

Since 2016, Stanford University has been studying EVD in support of new treatment efforts. In 2019, FDA in collaboration with the National Institute of Allergy and Infectious Diseases (NIAID) and NIH began working with Stanford laboratories to apply new methods to the study of EVD and Zika tissue samples, which includes multiplexed ion beam imaging to identify viral cells or anatomical sites where viruses accumulate and persist. Stanford is also beginning to look at Quantum Barcoding (QBC), an experimental diagnostic single-cell technology that can rapidly measure multiple targets, including RNA, DNA and proteins, as a primary means to analyze single cells in a laboratory and field stations. At the conclusion of this collaboration in May 2021, Stanford will deploy QBC to a federal laboratory facility at NIH for onsite testing and use in high-containment laboratories, including BSL-4 labs.[8]

Back to the Future

As of this writing, the global COVID-19 pandemic has sickened more than three million worldwide and killed nearly 250,000. Science is again seeking answers. Phase III clinical trials of remdesivir, a drug developed by Gilead Sciences and unsuccessful against the 2014 Ebola outbreak, has shown promise in shortening recovery times in hospitalized patients with severe manifestations of this novel coronavirus. Double-blind clinical trials sponsored by the NIAID in the U.S. are still ongoing.[9] Though not a cure, it may be a start, and as one door closes another opens as science continues to unravel the many questions surrounding what works and why. Discoveries found to be ineffective for one disease can become the lead candidate for another. ❖

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Myths and Facts: **Fibromyalgia**

Dispelling the many popular myths surrounding this chronic painful disorder that afflicts millions of people will ensure patients can get the treatment they need.

By Ronale Tucker Rhodes, MS

AS A DISORDER considered by many to be fictitious, fibromyalgia (FM) affects a surprising number of people worldwide. In fact, it is one of the most common chronic pain conditions, affecting an estimated 10 million people in the U.S. and an estimated 3 percent to 6 percent of the world population. Of the one in 50 Americans who suffer from FM, 75 percent to 90 percent are women; however, the disease also occurs in men and children of all ethnic groups.[1] And, it is believed there is a genetic component since a study conducted by the American College of Rheumatology showed women who have FM often have a family member diagnosed as well.[2]

FM dates back to the 1600s when it was coined "muscular rheumatism";[3] however, the condition wasn't actually studied until the 1800s. William Balfour, MD, a surgeon at the University of Edinburgh, was the first person to medically describe FM in 1816, and in 1824, he described its tender points and what they are. In 1904, the name to describe symptoms of FM was changed to fibrositis by Sir William Gowers, a British neurologist, to recognize the tender points those with the condition experienced.[2] Hugh Smythe, MD, laid the foundation for the modern definition of FM by describing widespread pain and tender points. During that same time, no evidence of inflammation could be found, so the name of the disorder was changed from fibrositis to FM (meaning pain in muscles and tissues).[3]

Unfortunately for those afflicted by the disorder, it wasn't until 1987 when FM was recognized as a "real" physical condition by the American Medical Association, and it took until 1990 for the American College of Rheumatology (ACR) to develop diagnostic criteria to be used for research purposes.[3] The reasons for the delayed recognition were differing theories about what FM is and what causes the disease. Further, since FM mostly affects women, most doctors considered it a psychological disorder whose victims were "hypochondriacs, malingering or simply trying to get attention." Indeed, many people still view the condition skeptically, with some physicians believing it is a "fad" disease.[3,4] Therefore, it is crucial to separate myths from facts about FM to ensure patients receive the care they require.

Separating Myth from Fact

Myth: FM is not a real disorder.

Fact: FM is a real, neurologic chronic condition. It is the second most common condition affecting the bones and muscles (the first is osteoarthritis). Classic symptoms are widespread pain in muscles, joints and tendons throughout the body and fatigue.[5] Yet, FM is often misdiagnosed and misunderstood. Some doctors don't believe the condition is real since pain is subjective and can be difficult to measure. "The most common and pervasive myth about fibromyalgia (amongst the medical community and at large) is that 'it's all in your head,'" said Donnica Moore, MD, president of Sapphire Women's Health Group. "While we don't know the exact mechanism of fibromyalgia, we do know that it is a diffuse, common pain syndrome characterized by patterns of muscular tenderness on both sides of the body called trigger points."[6]

"Most doctors think that if your elbow hurts, or your knee hurts or your shoulder hurts, the pathology is directly in those areas," said Don L. Goldenberg, MD, a rheumatologist and professor emeritus of medicine and nursing at Oregon Health and Science University in Portland. "In fibromyalgia, that doesn't work. The pain is actually coming from the brain." Misunderstanding of the origins of the pain, said Dr. Goldenberg, is "one of the reasons it's very controversial, and was for a long time kind of pooh-poohed as 'it's all in your head.'"[7]

Myth: The only symptom of FM is pain.

Fact: While widespread pain is the most common symptom of FM, there are many other symptoms that often accompany it, including irritable bowel syndrome, daytime fatigue, thinking and memory problems, insomnia, depression, headaches, numbness and tingling, pelvic pain and temporomandibular disorder (TMJD).[5,8] In 1999, the Fibromyalgia Network discovered that up to 90 percent of FM patients have the sensitivity that mimics TMJD, and half of FM patients display sensitivity to odors, bright lights, noise, various foods and medications.[2]

The pain caused by FM can be so severe that people can often be unable to do things they otherwise love to do. And, these additional symptoms can seriously impact everyday life and the ability to live a normal life.[6]

Myth: FM and arthritis are the same condition.

Fact: Arthritis and FM have little in common other than sensations of pain and fatigue. Whereas arthritis affects the joints, FM does not; it affects muscle and soft tissue. In addition, FM isn't a disease characterized by inflammation, and in those afflicted, inflammation markers tend to be normal.[7]

Myth: It is known what causes FM.

Fact: The causes of FM are unclear and may differ for different people. What is known is FM is not from an autoimmune, inflammation, joint or muscle disorder. Instead, the central nervous system (brain and spinal cord) is thought to be involved. Researchers believe FM amplifies painful sensations by affecting the way the brain processes pain signals. Specifically, repeated nerve stimulation causes an abnormal increase in levels of certain chemicals in the brain that signal pain (neurotransmitters). In addition, the brain's pain receptors seem to develop a memory of the pain and become more sensitive, meaning they can overreact to pain signals.[9]

Researchers also believe certain genes can make people more prone to FM and other health problems that can occur with it (but genes alone do not cause FM).[9] A study conducted in 2009 by the Centers for Disease Control and Prevention (CDC) found as many as 28 percent of children born to a parent with FM eventually develop the disease.[2]

According to the National Institute of Arthritis and Musculoskeletal and Skin Disorders, there are likely numerous factors that increase the risk of triggering FM, including a physically or emotionally traumatic event such as a car accident (50 percent, according to the CDC study[2]), repetitive injuries, genetics, problems with the central nervous system contributing to how the brain processes pain and a connection with other illness[6] (FM often occurs in individuals who have other rheumatic diseases such as lupus and rheumatoid arthritis[2]). However, the CDC study also found 40 percent of FM cases occur spontaneously without any apparent cause or trigger.[2]

Many people still view the condition skeptically, with some physicians believing it is a "fad" disease.

Myth: FM is a "catchall" diagnosis.

Fact: Because there isn't any single test or obvious symptom for FM, which makes it difficult to diagnose, many believe it to be a "catchall" or "fallback" diagnosis. However, there are specific diagnostic criteria developed by ACR.[7]

Since 1990, FM was diagnosed primarily by the presence of tender points (small areas of the body located near but not on a joint that causes pain when pressed). Yet, while tender points are characteristic of FM, studies have long questioned their ability to correctly diagnose the disease. In response, ACR revised its guidelines for diagnosis in 2010 and again in 2016, replacing the tender points exam with two separate tests that characterize the overall symptomatic experience: the widespread pain index (WPI) and the symptom severity scale (SS).

WPI is a questionnaire that asks patients if they have experienced pain in any one of 19 parts of the body in the past week. Each "yes" response is given a score of one for a possible maximum

score of 19. SS is a questionnaire that ranks the severity of four different symptoms (fatigue, unrefreshed sleep, cognitive symptoms and physical symptoms) on a scale of zero to three for a possible maximum score of 12. To definitively diagnose FM, a doctor needs to confirm either a WPI of seven or more with an SS of five or more *or* a WPI of three to six with an SS of nine or more, persistent symptoms at a similar level for at least three months and no other explanation for symptoms.

According to ACR, these new criteria shifted the focus from a specific pain at a point in time to an overall characterization of the disease state. Research published in the journal *Arthritis Care & Research* showed these new criteria were able to capture 88.1 percent of people with FM without the need for a tender point exam — a significant improvement over the previous criteria for which early studies had suggested tender points, when used in isolation, could render a correct diagnosis in only 50 percent of cases.[10]

However, it is important to note that a positive WPI and SS can only render a presumptive diagnosis. First, other conditions that can present with similar symptoms based on age, sex, medical history and co-occurring illnesses must be ruled out. These include:[10]

- Ankylosing spondylitis
- Hepatitis C
- Hypothyroidism
- Lupus
- Multiple sclerosis
- Myasthenia gravis
- Polymyalgia rheumatica
- Rheumatoid arthritis
- Scleroderma
- Sjögren's syndrome

Myth: There are no medicines to treat FM.

Fact: There are three U.S. Food and Drug Administration (FDA)-approved medicines to treat FM, as well as other non-FDA-approved medicines. Lyrica (pregabalin) was the first medicine approved to treat FM in 2007. Lyrica and another non-approved drug, gabapentin (Neurontin), work by blocking the overactivity of nerve cells involved in pain transmission. The downside to these medicines is they can cause dizziness, sleepiness, swelling and weight gain. Since then, two other medicines have been approved to treat FM that change some of the brain chemicals (serotonin and norepinephrine) that help control pain levels. These include duloxetine (Cymbalta) approved in 2008 and milnacipran (Savella) approved in 2009. In addition, two older medicines that affect these same brain chemicals (amitriptyline [Elavil] and cyclobenzaprine [Flexeril]) can also be used to treat FM. And, antidepressant drugs can be helpful in some patients.[8]

Opioid narcotics are discouraged for use in treating FM since they can cause greater pain sensitivity or make pain persist. However, tramadol (Ultram) may be used short-term if an opioid narcotic is needed. And, while over-the-counter medicines such as acetaminophen (Tylenol) or nonsteroidal anti-inflammatory drugs such as ibuprofen (Advil, Motrin) or naproxen (Aleve, Anaprox) are not effective for FM pain, they can treat the pain triggers of FM.[8]

Myth: Only prescription medicines can relieve FM symptoms.

Fact: Robert Bolash, MD, a pain management specialist at Cleveland Clinic, said medications account for only 20 percent to 30 percent of treatment.[5] In fact, Mark J. Pellegrino, MD, of Ohio Pain and Rehabilitation Specialists and author of 13 books on FM, says the "three pillars of treatment" for FM are medicine, supplements and physical therapy.

Dietary supplements commonly used to treat FM symptoms include:[11]

- 5-HTP (5-Hydroxytryptophan), a building block for the brain chemical serotonin. Since low levels of serotonin are associated with depression, it's believed that raising serotonin levels can lead to a better mood. One study found 5-HTP supplements may also help ease anxiety, insomnia, FM pain and morning stiffness.
- SAMe (S-Adenosyl-L-Methionine), an amino acid derivative that may boost levels of serotonin and dopamine, another brain chemical. Limited research suggests SAMe may improve mood and sleep.
- Magnesium, an element that may be linked to FM. However, research has not found that taking magnesium supplements improves symptoms.
- Melatonin, a hormone often used in supplements to improve sleep, which may ease FM pain.
- St. John's wort, an herb sometimes used to treat certain FM symptoms. But, there's no evidence it works. And, while a few studies suggest it may help with mild depression, it can also limit the effectiveness of some medications.

In addition to physical therapy, patients are encouraged to incorporate other forms of nondrug therapies such as cognitive

behavioral therapy, acupuncture, chiropractic care and massage.[8] Recently, a study published in the *Journal of Sleep Research* found cognitive behavioral therapy for pain can lead to an immediate decrease in the use of sleep medications among people with insomnia due to FM. However, such behavioral therapy is not effective in the long-term or as a stand-alone treatment, with medication use returning to pretreatment levels after about six months.[12] A study in 2017 found a connective tissue massage helped with pain, fatigue and sleep disruption in women with FM.[7]

It is also recommended to address risk factors and triggers for FM, including sleep disorders such as sleep apnea and mood problems such as stress, anxiety, panic disorder and depression, which may require involvement of other specialists such as a sleep medicine doctor, psychiatrist and therapist.[8]

Finally, another recent study published in *Clinical and Experimental Rheumatology* shows adding medical cannabis to standard pain relief therapy leads to clinical improvements in a significant proportion of patients with FM, particularly among those with sleep problems and a lower body mass index. Medical cannabis treatment is a recently introduced therapeutic option for patients who are dissatisfied with their current pain relief treatment.[13]

Myth: People with FM shouldn't exercise.

Fact: According to ACR, exercise is the single most effective treatment for FM. Aerobic exercises that include walking, biking, swimming and water aerobics have been found to be most useful. But, stretching and strengthening exercises using weights, machines, bands or one's own body weight are also helpful.[7]

Yoga and tai chi are also highly recommended to ease symptoms of FM. In fact, a 2018 study suggests tai chi may be as good or better than aerobic exercise. In the study, 226 participants, of which 92 percent were women who had suffered from FM for an average of nine years and had not been treated with alternative medical therapies in the six months preceding, compared the effectiveness of sessions of tai chi with aerobic exercise. Changes in their symptoms were assessed at 12, 24 and 52 weeks, and participants continued their standard medical treatment throughout this time. Findings showed better outcomes for patients who took part in twice-weekly tai chi classes than for those who took part in supervised aerobic exercise. What's more, long-term practice of the discipline was found to be more effective than more frequent sessions, with little difference among patients who did tai chi once or twice a week, but increased benefits after 24 weeks of practice as opposed to 12 weeks.[14]

Myth: FM is a life-threatening disease.

Fact: FM isn't life-threatening, and it doesn't directly cause physiological damage to the body. However, FM can affect a person's life in different ways. "If you become hopeless in your attitude and focus only on your pain, there is a more likely chance that you will develop other physiological and emotional illnesses," says Lynne Matallana, founder and president of the National Fibromyalgia Association. For example, she says, if a person doesn't stay socially active, he or she could become depressed. If someone doesn't exercise because of his or her pain, symptoms can become worse and can lead to illnesses such as osteoporosis and diabetes.

Yoga and tai chi are also highly recommended to ease symptoms of FM.

There are also other potential complications of FM, including lower quality of life, more frequent hospitalizations, higher rates of depression, increased rates of other rheumatologic conditions and higher rates of death from suicide or injury.[15]

Dispelling the Myths Now

FM is a disorder that affects millions of people in the U.S. The pain and other accompanying symptoms of FM can severely disrupt a person's quality of life. Yet, like many other disorders, people with FM have good days and bad. And, with proper treatment, regular exercise and avoidance of triggers, most people attain good symptom relief. But the only way FM patients can get the treatment they need is by dispelling the myths surrounding this disorder, especially the myth that it is a psychological disorder. ❖

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Are We Finally Closing In On a Universal Influenza Vaccine?

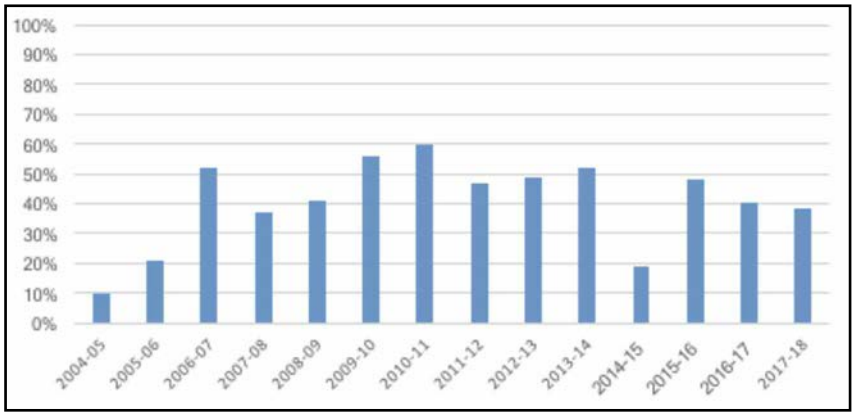
By Keith Berman, MPH, MBA

THANKS TO A remarkable ability to keep a step ahead of human immunity, seasonal influenza (flu) returns every year with a vengeance to afflict more than 28 million U.S. residents, resulting in 460,000 hospitalizations and more than 40,000 deaths.[1] While vaccination is the primary intervention for influenza prevention, the effectiveness of flu vaccines is limited, as well as time-limited to a single flu season. Less than two-thirds of U.S. children and just 45 percent of adults bother to get the annual flu shot,[2] facilitating transmission of circulating viral strains and further boosting the flu caseload. "Among the two dozen vaccine-preventable diseases, including measles, mumps, polio, smallpox and hepatitis, seasonal influenza is the only one for which a new vaccine is recommended every year. A more efficient approach is long overdue," noted Anthony Fauci, MD, director of the National Institute of Allergy and Infectious Diseases (NIAID).

Influenza A and B viruses owe their special ability to evade human immunity to the constant generation of minor RNA mutations that alter the antigenic appearance of the large mushroom-like head region of the hundreds of hemagglutinin proteins that coat the membrane surface and enable the virus to attach to our cells. Collectively, these mutations confound the ability of antibodies produced against earlier influenza strains to bind and inhibit viral entry into cells; our immune system fails to recognize the new "drifted" influenza virus strain. The result is the annual necessity of an elaborate and costly global effort to isolate strains projected to circulate in the upcoming season, and produce customized flu vaccines against those strains in time to try to provide protective immunity.

But the extraordinary pace of mutation of flu viruses creates a second problem. Once influenza hunters identify the strains believed likeliest to become epidemic, ongoing genetic drift can significantly alter their antigenic appearance over the six months or more that elapse between identification of the presumptive epidemic strain and shipment of egg- or cell culture-based vaccine to pharmacies and clinics.

Figure 1. Adjusted Influenza Vaccine Effectiveness Estimates for 2004-2018 Seasons[3]



As a result, influenza vaccine effectiveness varies from one season to the next. Over the 15 flu seasons between 2004-2005 and 2018-2019, vaccine effectiveness ranged from as high as 60 percent to as low as 10 percent, averaging just 35 percent over the five most recent flu seasons (Figure 1).[3] This rather dismal record tends to erode public confidence in the value of flu vaccines and accounts in part for the low annual immunization rates.

As if antigenic drift doesn't present enough of a challenge, sporadic influenza A pandemics can also occur — as has happened four times over the past century — when one particular viral subtype acquires the HA-encoding gene segment of a different subtype to create a reassortant virus for which we have no preexisting immunity. There is an ever-present worry about the potential for a future pandemic that could rival the catastrophic 1918 Spanish flu pandemic, which claimed more than 650,000 U.S. lives. And because production of a vaccine reasonably well-matched to a newly emergent pandemic influenza strain requires months, there is currently no way to prevent spread of a highly virulent pandemic influenza virus through the population.

For decades, scientists have discussed the concept of a "universal" flu vaccine that, with one or perhaps two doses, could provide broad protection against seasonal and pandemic influenza viruses. This universal vaccine would eliminate the need for annual vaccination, confer some degree of herd immunity to reduce risk of infection for those who fail to get immunized, and protect against the ever-looming threat of a

lethal pandemic influenza strain. The NIAID recently defined four criteria for any universal influenza vaccine. It should:[4]

- Be at least 75 percent effective;
- Protect against both group I and II influenza A viruses;
- Have durable protection that lasts at least one year; and
- Be suitable for all age groups.

While the optimal universal vaccine would provide protection against all influenza A viruses and potentially influenza B viruses, it is fully acknowledged that a particular "universal" vaccine's breadth of coverage may end up falling somewhere along a continuum — such as subtype-specific or multi-subtype — that is short of true universality (Figure 2).[5]

Recent advances in influenza virology, immunology and vaccinology have convinced many experts that development of an effective universal or near-universal influenza vaccine is attainable. Particularly encouraging has been the discovery of a number of antibodies with broadly neutralizing activity against different influenza strains.[6] A number of promising universal influenza vaccine candidates have emerged from academic, private sector and government research laboratories, several of which are now in early or mid-stage clinical testing.

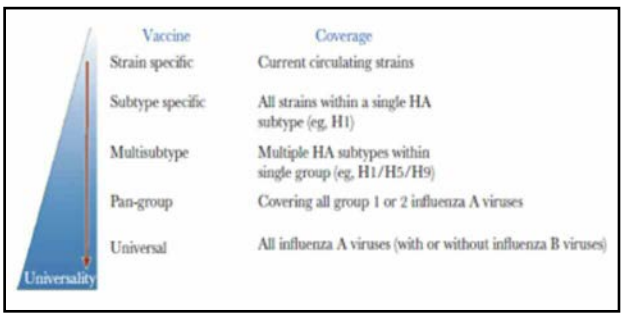
Universal Influenza Vaccine Strategies

To clear invading influenza viruses, the human immune system mostly targets epitopes on the exposed — but perpetually mutating — hemagglutinin globular head. Most universal vaccine candidates are designed to induce antibody or cellular immunity to viral proteinaceous structures conserved across different strains and subtypes. There are currently three leading vaccine strategies:[7]

- *Recombinant stalk-specific hemagglutinin.* The stalk domain anchors the globular head of HA to the viral membrane and is highly similar across viral strains and types. A concern is that investigational head-deleted hemagglutinin stalk vaccines can induce anti-stalk antibodies, but against epitopes that are inaccessible in a natural influenza virus infection.
- *Chimeric recombinant hemagglutinin.* This universal vaccine is a construct that fuses the stalk of a widely circulating influenza strain (e.g., the H1 subtype of influenza A) to the globular head of a nonhuman influenza A strain. Again, the objective is to generate widely cross-reactive antibodies against the conserved stalk domain. A potential downside of this strategy is a tendency for chimeric hemagglutinin vaccine candidates to enrich for hemagglutinin head antibodies but not the desired stalk-specific antibodies.
- *Recombinant M2 ion channel protein.* Until recently, the highly conserved M2 protein has not been a major focus of vaccine development on account of its poor accessibility by antibodies. But recent vaccine candidates have been specifically designed to generate broadly neutralizing antibodies against its exposed surface domain.

Several vaccines are also targeting neuraminidase, a second surface protein that, together with hemagglutinin, decorates the influenza virus membrane (Figure 3).

Figure 2.
Protective Levels Leading to a Universal Influenza Vaccine



Targeting Conserved Regions of Hemagglutinin

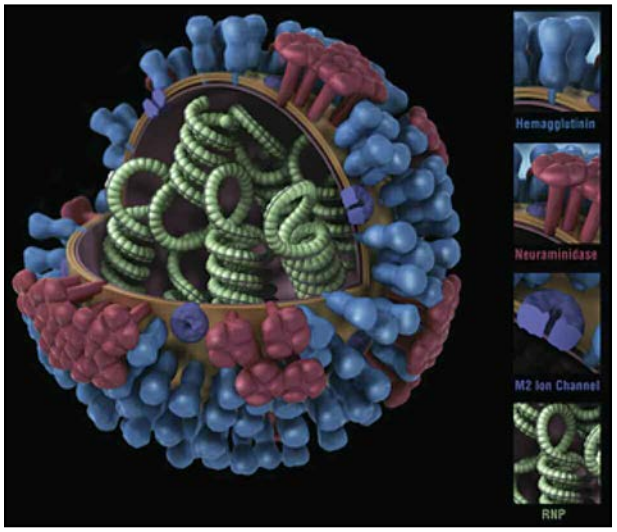
Current seasonal flu vaccines induce production of antibodies that recognize and bind to the hemagglutinin head, inhibiting its ability to mediate viral entry into cells. By the following flu season, rapid mutation in the head region has created new influenza A and B strains that escape the antibodies generated by these vaccines. The hemagglutinin stalk is far more resistant to mutations, making it particularly appealing for universal flu vaccine development.

In a very productive collaboration, researchers at the University of Michigan tracked household flu transmission in a cohort of Nicaraguan families, focusing on the 2013 and 2015 flu seasons. Blood samples drawn from 300 household members who lived with 88 individuals with confirmed influenza were sent to the laboratory of Florian Krammer, PhD, at the Icahn School of Medicine at Mount Sinai in New York. Using a novel assay to specifically measure hemagglutinin stalk antibodies, tests run by Dr. Krammer's team showed a rise of four times in the stalk antibody levels correlated with a 42 percent reduction in symptomatic influenza.

Chimeric hemagglutinin. Over the last several years, Dr. Krammer and colleagues have developed and tested intact hemagglutinin vaccines with the intention of inducing an immune response to conserved epitopes on the stalk domain. But antibodies generated in animals immunized with vaccines containing the entire hemagglutinin protein tended, as in humans, to target only the head domain. In an attempt to redirect the immune response, the Mount Sinai team designed hemagglutinin chimeras comprising the head domain from a nonhuman, typically exotic virus such as a bird flu, and the stalk domain from a human influenza A subtype, such as H1, H2 or H9.

When animals were vaccinated twice over a few weeks with chimeric hemagglutinin vaccines that included identical stalks but

Figure 3. Protein Structural Elements of Influenza Viruses



Source: www.cdc.gov/flu/images/h1n1/3D_Influenza_black_key_pieslice_lrg.jpg

different heads, their immune systems generated many more antibodies against the stalk region common to both flu strains than to the head regions. Somehow these chimeric hemagglutinins "redirect the immune response to the stalk domain, which is more conserved, so at least in animal models, they work much better than the regular vaccines that we used," Dr. Krammer noted.[8]

Early this year, Dr. Krammer's team reported that a single vaccination with an adjuvanted inactivated chimeric influenza vaccine construct induced high anti-hemagglutinin stalk antibody titers. Further, these anti-stalk antibodies against the H1 subtype were cross-reactive with the H2, H9 and H18 hemagglutinin subtypes. A single dose of this chimeric, hemagglutinin-based adjuvanted vaccine thus "might induce protective titers against all group 1 hemagglutinin-expressing viruses, making it an excellent candidate for development as a group 1 pandemic vaccine," the investigators concluded.[9]

Hemagglutinin stalk nanoparticles. A team of NIAID scientists has developed an entirely different experimental universal flu vaccine candidate that genetically fuses the conserved HA stalk portion from an H1N1 influenza virus to the surface of a microscopic nanoparticle made of nonhuman ferritin. This construct, called "H1ssF_3298," protected animals from infection with an entirely different influenza subtype (H5N1), indicating the antibodies induced by the vaccine can protect against other influenza subtypes within the same group.[10]

One or two intramuscular doses of H1ssF_3298 are currently being evaluated in a Phase 1 safety, tolerability and immunogenicity study in 70 healthy adults, whose health status and antibody response to the vaccine will be monitored over 12 months to 15 months.[11]

Conserved hemagglutinin head region epitopes. Perhaps furthest along in the clinical pipeline is a peptide-based vaccine developed by the Israeli biotechnology firm BiondVax Pharmaceuticals, dubbed M-001, which contains nine highly conserved HA head domain epitopes that are common to some 40,000 influenza viruses isolated over the years and listed in a National Institutes of Health database. BiondVax early trials found M-001 and a standard killed virus flu vaccine appear to have a synergistic effect: While M-001 by itself does not stimulate antibodies against HA, it does when followed by an inactivated flu vaccine.

In mid-2018 NIAID launched a Phase 2 randomized, double-blind, placebo-controlled clinical trial to assess the reactogenicity, immunogenicity and safety of two priming doses of M-001, followed by a seasonal quadrivalent inactivated influenza vaccine in healthy adults aged 18 years to 49 years.

Just ahead of the 2018-2019 Northern Hemisphere flu season, BiondVax initiated a Phase 3 clinical trial of M-001 — the first-ever pivotal trial of any universal influenza vaccine candidate. The study will enroll and randomize 12,460 eastern European participants aged 50 years and older to be immunized twice with M-001 or saline placebo and followed for up to two seasons.[12] Clinical endpoints include the frequency of confirmed influenza cases and severity of illness in each group. Initial results are expected late this year.

FLU-v: Peptides That Induce Cellular Immunity

Most universal influenza vaccine candidates are designed to induce a protective antibody response to infecting virus. But small animal challenge studies dating back to the early 1990s have shown it is also possible, in the absence of neutralizing antibodies, to induce cytotoxic CD8+ T lymphocytes that target conserved viral antigens to provide broadly cross-reactive cellular immune protection.[13,14]

More than a decade ago, UK-based SEEK Group and its collaborators showed FLU-v, a mixture of four polypeptides encoding conserved T cell-immunoreactive regions common to all influenza A and B viruses, protected mice against a lethal challenge with influenza virus; this protection occurred entirely in the absence of neutralizing antibodies.[15]

Earlier this year, results from a randomized, placebo-controlled Phase 2 study in 175 healthy adult volunteers found adjuvanted FLU-v mediated a protective vaccine-specific cellular response compared to adjuvanted placebo.[16] Participants who received a single dose of FLU-v were significantly less likely than control subjects to develop mild-to-moderate influenza disease following intranasal challenge with a single H1N1

influenza A strain (32.5 percent versus 54.8 percent).[17] "Larger studies are now needed to evaluate how the vaccine interacts with influenza strains in different cohorts in a real-world setting," said lead study investigator Olga Pleguezuelos, PhD.

Targeting Matrix Proteins and Nucleoprotein

As opposed to the high degree of variability in surface proteins across influenza virus strains and subtypes, there is far greater similarity between the essential proteins — nucleoprotein and matrix proteins 1 and 2 — found internally within these viruses. These proteins are beyond the reach of antibodies that deliver the first line of immune defense, but memory T cells that have seen these deeper-placed proteins during prior flu infections can recall their unique antigenic "signature" and be reawakened to contain the infection once it is underway.

M1-nucleoprotein vaccinia virus vector. In late 2017, United Kingdom-based Vaccitech successfully completed a small Phase 1 study of VTP-100, an investigational universal flu vaccine that exploits a nonreplicating vaccinia virus to infect human cells and direct production of nucleoprotein and matrix protein 1 (M1). "With a single dose, we saw a boost in pre-existing T-cell responses of between eight- and ten-fold in humans," said Vaccitech co-founder and lead investigator Sarah Gilbert, PhD.[6]

But in January of this year, the company reported disappointing topline findings from a pair of clinical studies. A randomized field-based Phase 2b trial for seasonal influenza with 2,149 participants, VTP-100 failed to achieve the targeted reduction in the incidence of laboratory-confirmed influenza when used as an add-on to a licensed quadrivalent influenza vaccine (QIV), compared to QIV alone. A placebo-controlled influenza challenge Phase 2 trial in 118 healthy adults similarly did not reach its primary endpoint of a 30 percent reduction in overall viral shedding. Like many candidate universal flu vaccines that have preceded it, the VTP-100 program has been discontinued.

M2-deleted influenza virus. A very different kind of replication-defective flu vaccine is being developed by Madison, Wis.-based FluGen: an M2-deleted, single replication (M2SR) influenza virus. The deletion of the M2 gene restricts the virus to a single replication cycle in the host. The body recognizes M2SR as an influenza infection and activates a robust immune response, but because the virus can only replicate once, it cannot spread to other cells and cause symptoms of a real-world infection. The hope is that by convincing the host's immune system that it has been infected with influenza, M2SR will activate a broad and durable wild-type immune response. FluGen's vaccine development effort has backing from both NIAID and the U.S. Department of Defense.

Topline results of a Phase 2 clinical trial in 99 healthy adults were announced by the company early last year.[18] Subjects were intranasally vaccinated with placebo or FluGen's M2SR vaccine matching a flu virus from 2007, then challenged with a mismatched live H3N2 influenza virus from the 2014-2015 flu season. Despite the significant mismatch, more than half of the participants receiving M2SR showed a serum antibody response to the vaccine and a 34 percent reduction of viral load during the challenge phase of the study, compared to placebo. Subjects who developed antibody to both M2SR and the challenge virus showed a 62 percent reduction in viral load, compared to placebo. These same groups showed 51 percent and 56 percent reductions, respectively, in symptom scores, indicating M2SR reduced both viral load and symptoms when the subject was challenged with a high dose of a highly mismatched H3N2 flu virus. "The remarkable results from this trial of FluGen's M2SR vaccine mark an important step forward in the development of a more universal flu vaccine," said FluGen clinical advisory board chair Robert Belshe, MD. Further clinical studies are planned.

Looking Forward to Real-World Studies

Epidemiologists estimate that, at current vaccination rates, a universal vaccine that can meet NIAID's 75 percent efficacy goal could potentially avert 17 million influenza cases, 251,000 hospitalizations and 19,500 deaths each year; $3.5 billion could be saved annually in direct medical costs,[1] and even more in lost productivity costs.[19] And as the ongoing COVID-19 pandemic reminds us, the value of a universal influenza vaccine capable of protecting against a future pandemic influenza strain is incalculable.

By far the most challenging hurdle for any universal influenza vaccine candidate still lies ahead: real-world testing in thousands of participants spanning multiple flu seasons to demonstrate efficacy against multiple strains or subtypes. A number of reported successful live virus challenge studies to date in healthy adult volunteers have been encouraging, but will the putative vaccine protect elderly individuals and very young children at high risk for hospitalization or death due to serious complications? We are still years away from an answer, but for the first time, we now have a number of promising vaccine candidates with a realistic chance to fulfill the dream. ❖

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

Editor's note: References are available upon request.

In 2004, Jeanna Giese-Frassetto became the first person to survive the rabies virus after it was too late to receive a preventive vaccine. While not a distinction anyone would relish, she has embraced the notoriety and helps raise awareness about this typically fatal disease.

Rabies: *A Patient's Perspective*

By Trudie Mitschang

JEANNA GIESE-FRASSETTO was only 15 years old when her life permanently changed following a chance encounter with a bat. The Fond du Lac, Wis., resident was attending Sunday mass with her family when the winged creature began circling the church. An usher hit the bat with a prayer book, sending it crashing to the floor, stunned. A passionate animal lover, Giese-Frassetto rushed to pick it up by its wings and take it outside where she could set it free. "It began screeching, and as I went to throw it into a bush, it sank its fangs into my left finger," she recalled.

Once home, her parents cleaned the superficial wound and did not consider additional medical treatment. Three weeks later, Giese-Frassetto began displaying signs that something was seriously wrong, including fatigue, double vision, vomiting and tingling in her left arm. By the time she was rushed to the hospital where she was officially diagnosed with rabies, it was too late to administer an anti-rabies vaccine. Her parents were told the devastating news that she had only hours to live.

Rabies is a vaccine-preventable viral disease that spreads from animals to humans. In both animals and people, the rabies virus travels to the brain, where it reproduces and then travels back through the nerves into other parts of the body. Eventually, the virus reaches the salivary glands, where it produces the telltale symptom referred to as "foaming at the mouth." Rabies eventually kills by compromising the brain's ability to regulate breathing, salivation and heartbeat. According to the World Health Organization (WHO):[1]

- Dogs are the main source of human rabies deaths, contributing up to 99 percent of all rabies transmissions to humans.
- Infection causes tens of thousands of deaths every year, mainly in Asia and Africa.
- Forty percent of people bitten by suspect rabid animals are children under 15 years of age.

The WHO fact sheet emphasizes that timing is critical when it comes to rabies postexposure prophylaxis (PEP) treatment. In the United States, PEP consists of a regimen of one dose of immune globulin and four doses of rabies vaccine over a 14-day period. Rabies immune globulin and the first dose of rabies vaccine should be given as soon as possible after exposure.

Giese-Frassetto was fortunate, to say the least. Rodney Willoughby, MD, a pediatrician and infectious disease specialist at the Children's Hospital of Wisconsin in Milwaukee, made a bold decision not to give up on her, despite the odds. After consulting with various books and drawing on his own expertise, he devised an impromptu plan of action credited with saving her life. It would later be dubbed the "Milwaukee Protocol."

The treatment plan began with putting the teen into a medically induced coma to isolate her brain and give her immune system an opportunity to kick in and fight the virus. In addition to inducing the coma, doctors gave her the antivirals ribavirin and amantadine, tapering them off when tests showed her immune system was, in fact, kicking in. A week after beginning the experimental treatment, doctors slowly brought Giese-Frassetto out of the coma; she had survived, but the road to recovery would be a difficult one. She spent 11 weeks in the hospital, taking as many as 17 pills a day and embarking on a rigorous rehabilitation program. For approximately six months after her release, physicians also gave her a compound called tetrahydrobiopterin that is chemically similar to the B-complex vitamin folic acid and known to boost production of serotonin and dopamine, the neurotransmitters needed to perform motor, speech and other routine bodily functions. "I felt lucky to be alive, but I was frustrated, isolated and desperate to go home. The whole left side of my body was affected, I had balance issues, and my speech was badly impaired. It was so slow to begin with that I despaired that I'd never recover."

Giese-Frassetto's rehabilitation initially included physical, occupational and speech therapy, as well as tutoring to help her keep up with schoolwork. Years later, she also incorporated equine therapy to assist with balance issues. Although difficult, her recovery has been remarkable.

It's been well more than a decade later since that fateful morning mass, and Giese-Frassetto's life has since been marked by more celebratory milestones, including college graduation, marriage and motherhood. But, rather than distance herself from the most difficult yet defining experience of her life, she's used it as a platform to educate others, sharing her experience as a public speaker, volunteering for animal rights groups and even serving as an ambassador for the Global Alliance for Rabies Control. "I feel so grateful for my survival and the life I've had since the bite. I don't take anything for granted." ❖

Reference

1.World Health Organization. Fact Sheet on Rabies. Accessed at www.who.int/news-room/fact-sheets/detail/rabies.

Rabies: *A Physician's Perspective*

Dr. John J. Ross, who specializes in infectious diseases such as rabies, which has a 100 percent fatality rate, emphasizes that all patients with undiagnosed neurological disease should be suspected of having rabies.

JOHN J. ROSS, MD, is an associate physician and hospitalist at Brigham and Women's Hospital, Boston, an assistant professor of medicine at Harvard Medical School and a fellow of the Infectious Diseases Society of America.

BSTQ: What should medical professionals know about rabies?

Dr. Ross: While rabies is rare in the United States, it retains a disproportionate importance because of its historic 100 percent fatality rate. Hospitalists should know this about rabies: Suspect rabies in all patients with undiagnosed neurological disease. Making the diagnosis of rabies as early as possible is more critical than ever, now that a potential treatment exists. Unfortunately, in the U.S., rabies is rarely considered when patients first present for medical attention.

BSTQ: What are the symptoms?

Dr. Ross: During the prodromal phase of rabies, which lasts about four days, patients have nonspecific symptoms of fever, malaise and nausea. This is quickly followed by paresthesia at the bite or wound site, personality change and hallucinations, and the classic manifestations of "furious rabies": agitation, delirium, hydrophobia, aerophobia, aggression and spasms affecting swallowing and respiration. In up to 20 percent of patients, the disease may present in atypical form as "dumb rabies," an ascending paralysis that may mimic Guillain-Barré syndrome.

BSTQ: How is rabies diagnosed?

Dr. Ross: Tests for rabies include polymerase chain reaction of cerebrospinal fluid or saliva, antibody testing of serum and cerebrospinal fluid, and direct fluorescent antibody of biopsy from the nape of the neck, where the virus congregates in hair follicles.

BSTQ: What questions should physicians ask if they suspect rabies exposure?

Dr. Ross: Ask all patients about bat and animal exposure when rabies is in the differential. Worldwide, there are 55,000 cases of human rabies a year, the vast majority of which occur in developing countries as a result of dog bites. In the U.S., there are only a handful of human cases of rabies each year, almost always associated with bat exposure. It is not necessary to get a bat bite or scratch to be at risk for rabies. Some U.S. patients seem to have contracted rabies after exposure to bat saliva or vapors, sometimes having been bitten while asleep. Any patient who wakes up in a room or cabin and finds a bat should be considered at risk for rabies. Other animals commonly infected with rabies in the U.S. include raccoons, skunks and foxes. Unvaccinated dogs and cats also are at risk of transmitting rabies.

BSTQ: What is the prescribed treatment plan for rabies exposure?

Dr. Ross: Post-exposure prophylaxis with rabies vaccine is still the mainstay of prevention. Sometimes antibodies to rabies are given as well. There are no other proven therapies to prevent or treat rabies.

BSTQ: What are the best ways to avoid rabies infection?

Dr. Ross: Consider prevention the best treatment. If a patient is bitten by an animal, wash bite wounds with 20 percent soap and irrigate with povidone-iodine to reduce the risk of rabies by up to 90 percent. If the biting animal is available for observation, the rabies vaccine may be deferred or not administered at all if the animal is well after 10 days. Many state laboratories will also perform rabies testing on euthanized animals. If the biting animal is unavailable for observation, promptly give the rabies vaccine and immune globulin.

BSTQ: Are rabies vaccines safe?

Dr. Ross: Current rabies vaccines are safe and highly effective in preventing infection after exposure, provided they are given in a timely fashion. Vaccine and immune globulin have no role in treatment once rabies symptoms have developed.

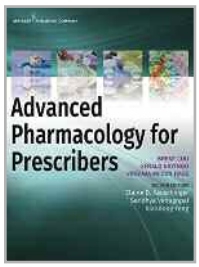
BSTQ: What is the biggest misconception about post-exposure treatment?

Dr. Ross: Many people are still leery about getting rabies vaccine, as the older version of the vaccine consisted of several large and painful shots in the belly with significant side effects. No shots in the stomach are required! The current version of the vaccine consists of four shots in the shoulder muscle over four weeks. Side effects are usually limited to soreness at the injection site, which is much better than dying of an untreatable brain infection.

BSTQ: Jeanna Giese-Frassetto is the first known survivor of rabies without a vaccine. Is her treatment method (now known as the Milwaukee Protocol) still being used? And, if so, have other patients survived without a vaccine?

Dr. Ross: Jeanna Giese-Frassetto is still the only person to have survived rabies without vaccination. Further experience with the Milwaukee Protocol has been profoundly disappointing. There have been at least more than 40 other patients reported in the research literature who died despite receiving the Milwaukee Protocol. Some specialists believe some of the components of the Milwaukee Protocol such as therapeutic coma are actually harmful and should be avoided. ❖

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



Advanced Pharmacology for Prescribers

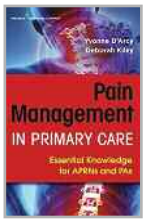
Author: Gerald Kayingo, PhD, PA-C

This evidence-based pharmacology text and reference for advanced practice students and clinicians guides users in analyzing the pharmacological foundations of drug therapy and fosters the development of sound clinical judgment in determining the appropriate medication for every patient across the lifespan. Featuring an applied therapeutic approach to major disorders and their pharmacologic treatment, the book examines how medications act on the body and vice versa, while teaching the rationale for using specific therapeutic agents or drug classes. Each chapter includes case studies that apply the concepts discussed, diagnostic studies, applicable guidelines, genomics and important lifespan considerations. A chapter on pharmacogenetics explains the basic principles underlying current understanding of genetic variations in response to pharmacotherapy and adverse drug reactions.

www.amazon.com/Advanced-Pharmacology-Prescribers-Brent-PharmD-ebook/dp/B081J3MX1X

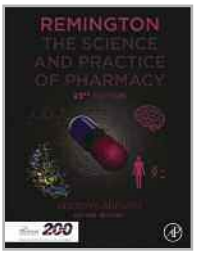
Pain Management in Primary Care: Essential Knowledge for APRNs and PAs

Authors: Yvonne D'Arcy, FAANP, MS, APN-C, CNS, and Deborah Kiley, FAANP, DNP, ANP, NP-C, FNP-BC



Written specifically for advanced practice registered nurses and physician assistants, this evidence-based text delivers practical guidance on how to assess, treat and manage patients with pain in the primary care and family practice setting. Written by pain management experts versed in both pharmacologic and nonpharmacologic therapies, the text provides an overview of the sources and physiology of pain and delineates a multidimensional assessment approach to guide readers in developing a patient care plan. With an emphasis on strategies for safe prescribing, an extensive portion of the book addresses regulatory considerations, special populations and coverage of how to safely prescribe opioids, including risk screening, proper management and identification and treatment of withdrawal. The text also provides concise, easy-to-reference information about medications, supplements and nonopioid therapeutics.

www.amazon.com/Pain-Management-Primary-Care-Essential-ebook/dp/B07TFSMLLT/ref=sr_1_36

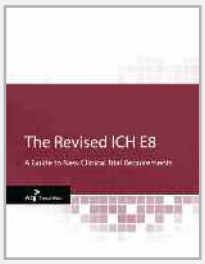


Remington: The Science and Practice of Pharmacy, 23rd Edition

Author: Adeboye Adejare, PhD

This book offers a completely updated source of information for education, training and development of pharmacists. Published for the first time with Elsevier, this edition includes coverage of biologics and biosimilars since uses of those therapeutics have increased substantially since the previous edition. Also discussed are formulations and drug delivery, including prodrugs, salts and polymorphism. The book also features color illustrations, fundamental information on a range of pharmaceutical science areas and information on new developments in industry.

www.amazon.com/Remington-Science-Practice-Pharmacy-Practiice/dp/0128200073



The Revised ICH E8: A Guide to New Clinical Trial Requirements

Author: U.S. Food and Drug Administration

This management report explains the International Council for Harmonisation (ICH) E8 updates and guides readers through assessing the impact of key concepts on current and future clinical development practices, including the framework and approaches for identifying quality-by-design and critical-to-quality factors. The report reviews the scope and general principles of the ICH E8(R1) guideline; the impact on current research practices and influences on standard operating procedures, processes and documentation; the framework and approaches for identifying critical-to-quality factors; clinical development areas that may be impacted by the adoption of the ICH E8(R1) guideline and approaches for compliance; as well as other expectations.

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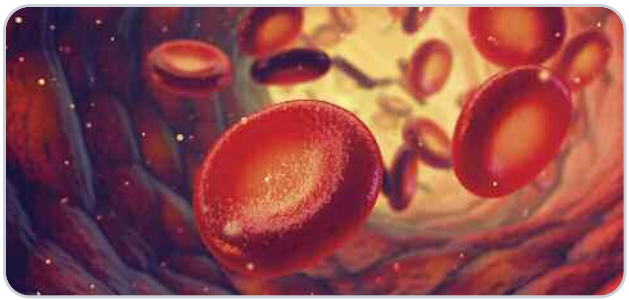
Bleed Protection with up to 14-Day Dosing of Long-Acting Recombinant Factor IX Product in Selected Children with Hemophilia B

In pharmacokinetic studies, a recombinant fusion protein genetically linking human coagulation factor IX with human albumin (rIX-FP) (IDELVION, CSL Behring) has been shown to have an approximately five-fold longer half-life compared with standard recombinant factor IX products. Following a pivotal Phase III study in which children with moderate to severe hemophilia B received weekly prophylaxis, a Phase 3b prospective, multicenter extension study assigned 24 participants to a seven-day (25-50 IU/kg), 10-day or 14-day (50-75 IU/kg) regimen for approximately 30 months. Investigator and subject preference dictated the dosing frequency for the first six months of the study. At six-month intervals thereafter, the investigator could change the regimen based on an assessment of efficacy, safety, treatment compliance and/or preference. Among various endpoints evaluated across the three dosing regimens were spontaneous annualized bleeding rate (AsBR) and monthly consumption of rIX-FP.

Compared with their initial six-month starting regimen, by the end of the study, dosing intervals were the same, extended and shortened in 16, four and four subjects, respectively. Seventeen, three and four subjects, respectively, ended the study on the seven-, 10- and 14-day prophylaxis regimens. The respective median AsBRs were 0.0, 0.0 and 1.1. Subjects on a 14-day regimen maintained a mean steady-state trough factor IX level of >7.2 IU/dL.



Mean overall monthly consumption of rIX-FP, including both for prophylaxis and control of bleeding events, was 231.2, 224.2 and 185.4 IU/kg for the seven-, 10- and 14-day dosing regimens, respectively, with 4.6, 3.4 and 2.6 mean monthly infusions.

Noting that "reduced infusion frequency provides dosing flexibility," the investigators concluded extended dosing intervals of 10 days or 14 days are feasible with rIX-FP in selected pediatric patients who are well controlled on a seven-day regimen, while still maintaining adequate efficacy.

Kenet G, Chambost H, Male C, et al. Long-term safety and efficacy of recombinant coagulation factor IX albumin fusion protein (rIX-FP) in previously treated pediatric patients with hemophilia B: results from a phase 3b extension study. Thromb Haemost *2020 Mar 17 [epub ahead of print]*

Large-Dose Albumin Supplementation Does Not Reduce Mortality or Need for Critical Care Interventions: Retrospective Review

Serious burns affecting ≥20% of the total body surface area (TBSA) trigger capillary leakage and loss of serum proteins, including albumin, commonly resulting in persistent hypoalbuminemia. Investigators conducted a retrospective review of 38 cases treated at Taipei Veterans General Hospital between January 2007 and December 2018 to determine whether more aggressive albumin supplementation can benefit major burn patients with persistent hypoalbuminemia.

No significant differences were identified in baseline characteristics of patients who received <25 mg/kg/%TBSA/day of human albumin solutions and those who received more than this quantity. Renal replacement therapy, duration of mechanical ventilation, length of stay in the burn unit and in-hospital mortality were not statistically different between the two groups. The serum C-reactive protein/albumin ratio was associated with in-hospital mortality (P = 0.036).

The investigators concluded no significant mortality benefit was associated with administration of large quantities of supplemental albumin to correct prolonged hypoalbuminemia in major burn patients.

Chen YF, Ma H, Perng CK, et al. Albumin supplementation may have limited effects on prolonged hypoalbuminemia in major burn patients: An outcome and prognostic factor analysis. J Chin Med Assoc *2020 Feb;83(2):206-10.*

Medicare Immune Globulin Reimbursement Rates

Rates are effective July 1, 2020, through Sept. 30, 2020

	Product	Manufacturer	HCPCS	ASP + 6% (before sequestration)	ASP + 4.3%* (after sequestration)
IVIG	FLEBOGAMMA	Grifols	J1572	$74.86	$73.66
	GAMMAGARD SD	Takeda	J1566	$133.87	$131.72
	GAMMAPLEX	BPL	J1557	$107.07	$105.35
	OCTAGAM	Octapharma	J1568	$77.92	$76.67
	PANZYGA	Pfizer	90283/J1599	**	**
	PRIVIGEN	CSL Behring	J1459	$82.55	$81.23
IVIG/SCIG	GAMMAGARD LIQUID	Takeda	J1569	$84.06	$82.72
	GAMMAKED	Kedrion	J1561	$83.38	$82.04
	GAMUNEX-C	Grifols	J1561	$83.38	$82.04
SCIG	CUTAQUIG	Octapharma	90284/J3590	**	**
	CUVITRU	Takeda	J1555	$139.17	$136.94
	HIZENTRA	CSL Behring	J1559	$107.93	$106.20
	HYQVIA	Takeda	J1575	$140.67	$138.41
	XEMBIFY	Grifols	J1558	$168.42	$165.72

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

Calculate your reimbursement online at www.FFEnterprises.com.

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

Immune Globulin Reference Table

	Product	Manufacturer	Indication	Size
IVIG	FLEBOGAMMA 5% DIF Liquid	Grifols	PI	2.5 g, 5 g, 10 g, 20 g
	FLEBOGAMMA 10% DIF Liquid	Grifols	PI, ITP	5 g, 10 g, 20 g
	GAMMAGARD S/D Lyophilized, 5% (Low IgA)	Takeda	PI, ITP, B-cell CLL, KD	5 g, 10 g
	GAMMAPLEX Liquid, 5%	BPL	PI, ITP	5 g, 10 g, 20 g
	GAMMAPLEX Liquid, 10%	BPL	PI, ITP	5 g, 10 g, 20 g
	OCTAGAM Liquid, 5%	Octapharma	PI	1 g, 2.5 g, 5 g, 10 g
	OCTAGAM Liquid, 10%	Octapharma	ITP	2 g, 5 g, 10 g, 20 g, 30 g
	PANZYGA Liquid, 10%	Pfizer	PI, ITP	2.5 g, 5 g, 10 g, 20 g, 30 g
	PRIVIGEN Liquid, 10%	CSL Behring	PI, ITP, CIDP	5 g, 10 g, 20 g, 40 g
IVIG/SCIG	GAMMAGARD Liquid, 10%	Takeda	IVIG: PI, MMN SCIG: PI	1 g, 2.5 g, 5 g, 10 g, 20 g, 30 g
	GAMMAKED Liquid, 10%	Kedrion	IVIG: PI, ITP, CIDP SCIG: PI	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
SCIG	CUTAQUIG Liquid, 16.5%	Octapharma	PI	1 g, 2 g, 4 g, 8 g
	CUVITRU Liquid, 20%	Takeda	PI	1 g, 2 g, 4 g, 8 g
	HIZENTRA Liquid, 20%	CSL Behring	PI, CIDP	1 g, 2 g, 4 g, 10 g
	HYQVIA Liquid, 10%	Takeda	PI	2.5 g, 5 g, 10 g, 20 g, 30 g
	XEMBIFY Liquid, 20%	Grifols	PI	1 g, 2 g, 4 g, 10 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

2020-2021 Influenza Vaccine

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

Product	Manufacturer	Presentation	Age Group	Code
Trivalent				
FLUAD (aIIV3)	SEQIRUS	0.5 mL PFS 10-BX	65 years and older	90653
Quadrivalent				
AFLURIA (IIV4)	SEQIRUS	0.5 mL PFS 10-BX	3 years and older	90686
AFLURIA (IIV4)	SEQIRUS	5 mL MDV	6 months and older	90688
AFLURIA PEDIATRIC (IIV4)	SEQIRUS	0.25 mL PFS 10-BX	6-35 months	90685
FLUAD (IIV4)	SEQIRUS	0.5 mL PFS 10-BX	65 years and older	90694
FLUARIX (IIV4)	GSK	0.5 mL PFS 10-BX	6 months and older	90686
FLUBLOK (ccIIV4)	SANOFI PASTEUR	0.5 mL PFS 10-BX	18 years and older	90682
FLUCELVAX (ccIIV4)	SEQIRUS	0.5 mL PFS 10-BX	4 years and older	90674
FLUCELVAX (ccIIV4)	SEQIRUS	5 mL MDV	4 years and older	90756*
FLULAVAL (IIV4)	GSK	0.5 mL PFS 10-BX	6 months and older	90686
FLUMIST (LAIV4)	ASTRAZENECA	0.2 mL nasal spray 10-BX	2-49 years	90672
FLUZONE (IIV4)	SANOFI PASTEUR	0.5 mL PFS 10-BX	6 months and older	90686
FLUZONE (IIV4)	SANOFI PASTEUR	0.5 mL SDV 10-BX	6 months and older	90686
FLUZONE (IIV4)	SANOFI PASTEUR	5 mL MDV	6 months and older	90688
FLUZONE HIGH-DOSE (IIV4)	SANOFI PASTEUR	0.7 mL PFS 10-BX	65 years and older	90662

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

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

FFF enterprises

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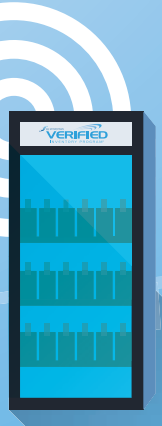
WHEN MINUTES MATTER



VIPc CABINET INSTALLATION

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PRODUCT SAFETY

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Emergency Ordering 24/7

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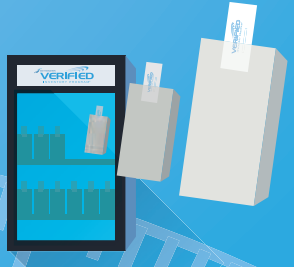
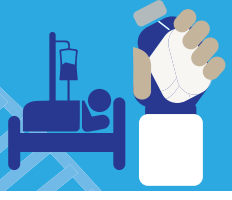
- High-touch service
- Integrated split-billing

CONVENIENT WEB PORTAL & AUTOMATED ALERTS



CUSTOMIZED INVENTORY

NATIONWIDE COVERAGE



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