SUMMER 2021

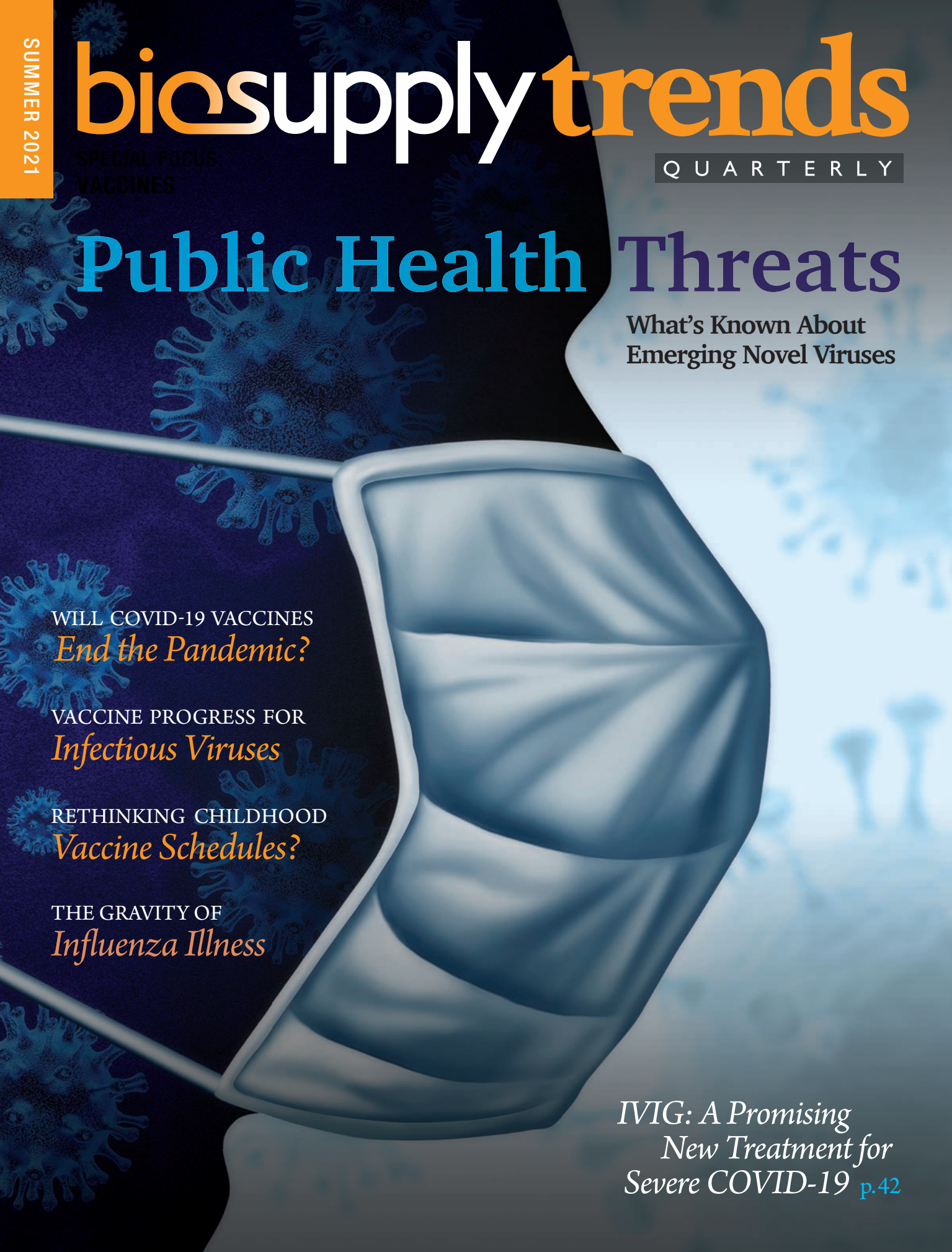
biosupply trends

QUARTERLY

SPECIAL FOCUS:
VACCINES

Public Health Threats

What's Known About Emerging Novel Viruses



WILL COVID-19 VACCINES
End the Pandemic?

VACCINE PROGRESS FOR
Infectious Viruses

RETHINKING CHILDHOOD
Vaccine Schedules?

THE GRAVITY OF
Influenza Illness

IVIG: A Promising New Treatment for Severe COVID-19 p.42

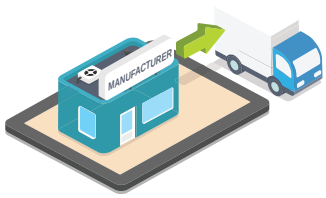
GuaranteedChannelIntegrity®

Guaranteed Channel Integrity®
8 Critical Steps

STEP 1

Purchasing

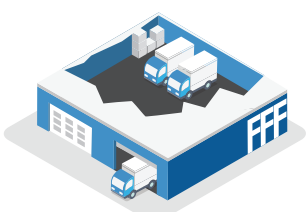
At FFF, we only purchase product from the manufacturer–never from another distributor or source–so the integrity of our products is never in question.



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

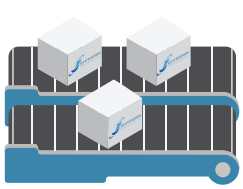
Specialty Packaging

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

STEP 4

Interactive Allocation

FFF's unique capability of interactive allocation allows us to do that through our field sales team's close relationship with our customers. Our team understands customers' ongoing requirements, responds to their immediate crises, and allocates product in real-time to meet patients' needs.



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.

800.843.7477 | Emergency Ordering 24/7

STEP 5

Delivery

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

Methods of Delivery

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

Verification

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.

biosupply trends QUARTERLY

Features

Up Front

BioTrends Watch

BioFocus

BioSources

About BioSupply Trends Quarterly

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

BioSupply Trends Quarterly (ISSN 1948-2620) is a national publication, with quarterly themed issues.

Publisher: FFF Enterprises, Inc., 44000 Winchester Road, Temecula, CA 92590

Subscriptions to *BioSupply Trends Quarterly* are complimentary. Readers may subscribe by calling (800) 843-7477 x1351.

BioSupply Trends Quarterly accepts manuscript submissions in MS Word between 600 and 2,500 words in length. Email manuscripts to or request submission guidelines at editor@BSTQuarterly.com. *BioSupply Trends Quarterly* retains the right to edit submissions. The contents of each submission and their accuracy are the responsibility of the author(s) and must be original work that has not been, nor will be, published elsewhere, without the written permission of *BioSupply Trends Quarterly*. A copyright agreement attesting to this and transferring copyright to FFF Enterprises will be required.

Advertising in BioSupply Trends Quarterly

BioSupply Trends Quarterly has a circulation of 40,000, with an approximate readership of more than 100,000 decision-makers who are comprised of general practice physicians, hospital and clinic chiefs of staff and buyers, pharmacy managers and buyers, specialist physicians and other healthcare professionals.

For information about advertising in *BioSupply Trends Quarterly*, you may request a media kit from Ronale Tucker Rhodes at (800) 843-7477 x1362, rrhodes@bstquarterly.com.

Protecting Against Existing and Emerging Infectious Diseases

EMERGING INFECTIOUS diseases — those that have either never before been recognized or are re-emerging — represent one of the greatest threats to humanity. The challenge in responding to these diseases is vaccines may not exist to prevent them, or if they do exist, people will resist them due to vaccine hesitancy, accessibility issues or lack of motivation to get vaccinated. While these issues have surfaced throughout history, during the last couple of decades and certainly during the current COVID-19 pandemic, the topic of vaccines has been at the forefront.

Until the COVID-19 pandemic struck, the worldwide population had not experienced such a deadly novel virus since the 1918 flu pandemic that killed 675,000 people in the U.S. alone. Instead, viruses people might remember today are polio that struck in 1952 and HIV that appeared in 1984. Yet, as we explain in our article "Emerging Novel Viruses" (p.14), while there are some 320,000 viruses thought to be able to infect mammals, most do not pose a high risk to humans. Indeed, only 200 of the current 7,000 cataloged viruses are known to infect humans. And, while much is still unknown about viruses and the threat they pose, as the field of virology rapidly expands, researchers are in pursuit of greater understanding.

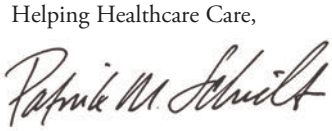
Thankfully, much has been discovered about the SARS-CoV-2 virus that causes COVID-19, which has been paramount in developing vaccines to prevent it. As we detail in our article "COVID-19 Vaccines: Where Are We Now?" (p.18), in just over a year, six vaccine candidates are most promising. Three of these have received emergency use authorization by the U.S. Food and Drug Administration, and three others are awaiting clinical trial results. Only time will tell how long they will provide protection and at what level.

While COVID-19 vaccines dominate the headlines, many more new vaccines are in development for other existing infectious diseases. In our article "New Vaccines in Development" (p.26), we review the encouraging research to develop vaccines for urinary tract infections, tick-borne encephalitis, HIV, malaria, cancer and other maladies.

Perhaps most troubling is the recurrence of some childhood diseases due to vaccine resistance from parents. For decades, many myths have circulated about childhood vaccines, which we dispel in our article "Myths and Facts: Childhood Vaccines" (p.36). Fostered by qualms ranging from vaccine necessity to ingredients, side effects and autism, the resistance against vaccines has been met time and again with evidence that vaccinations far outweigh the dangers of the diseases they prevent. And, vaccination adherence includes observing the current recommended childhood vaccine schedule. In our article "Rethinking Childhood Vaccination Schedules" (p.32), we provide explanations for parental adherence to the recommended shot schedule versus the a-la-carte approach many are proposing.

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

biosupply trends QUARTERLY

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

Publisher
Patrick M. Schmidt

Editor
Ronale Tucker Rhodes, MS

Assistant Editor
Cheryl Brooks

Art Director
Allan Bean

Contributing Writers
Keith Berman, MPH, MBA
Diane L.M. Cook
Bonnie Kirschenbaum, MS, FASHP, FCSHP
Trudie Mitschang
Jim Trageser
Meredith Whitmore

Please direct editorial, advertising and marketing communications to
44000 Winchester Road
Temecula, CA 92590
Ph: (800) 843-7477
Email: editor@BSTQuarterly.com

CMS Extends Marketplace Special Enrollment Period for COVID-19 Public Health Emergency

The Centers for Medicare and Medicaid Services (CMS) is extending access to the special enrollment period until Aug. 15, 2021, giving consumers additional time to take advantage of new savings through the American Rescue Plan. This action provides new and current enrollees an additional three months to enroll or re-evaluate their coverage needs with increased tax credits available to reduce premiums.

As a result of the American Rescue Plan, additional savings have been available for consumers through HealthCare.gov since April 1. These savings will decrease premiums for many, on average, by $50 per person per month and $85 per policy per month. On average, one out of four enrollees on HeathCare.gov will be able to upgrade to a higher plan category that offers better out-of-pocket costs at the same or lower premium compared to what they're paying today.

"Every American deserves access to quality, affordable healthcare — especially as we fight back against the COVID-19 pandemic," said Health and Human Services Secretary Xavier Becerra. "Through this special enrollment period, the Biden Administration is giving the American people the chance they need to find an affordable healthcare plan that works for them. The American Rescue Plan will bring costs down for millions of Americans, and I encourage consumers to visit HealthCare.gov and sign up for a plan before August 15."

Consumers can find local help at Localhelp.healthcare.gov or by calling the Marketplace Call Center at (800) 318-2596. TTY users should call (855) 889-4325. Assistance is available in 150 languages, and the call is free. ❖

2021 Special Enrollment Period Access Extended to August 15 on HealthCare.gov for Marketplace Coverage. Centers for Medicare and Medicaid Services press release, March 23, 2021. Accessed at www.cms.gov/newsroom/press-releases/2021-special-enrollment-period-access-extended-august-15-healthcaregov-marketplace-coverage.

2 Percent Medicare Sequester Cuts Eliminated Through 2021

The federal government has eliminated the 2 percent across-the-board cut to all Medicare payments, known as sequestration, until the end of 2021. To pay for the change, the bill increases the fiscal year 2030 sequester cuts. Last year, Congress paused the 2 percent Medicare cuts, but they were expected to resume April 1 without additional congressional action.

In addition to the 2 percent Medicare sequester cuts, the bill also makes several technical changes to the rural health clinic (RHC) provisions included in the Consolidated Appropriations Act (CAA) 2021. Specifically, the CAA required the payment rate for RHCs, including provider-based RHCs certified after Dec. 31, 2019, be capped at $100 per visit beginning April 1, 2021. This rate will increase over time based on the Medicare Economic Index, but will remain well below typical provider-based RHC rates. The bill corrects the Dec. 31, 2019, date to Dec. 31, 2020, and includes both Medicare-enrolled RHCs located in a hospital with less than 50 beds and RHCs that have submitted an application for Medicare enrollment as of this date.

"The AHA continues to work with Congress and the administration to ensure the hospital field has the support, resources and tools to serve their patients and communities. This includes continuing to advocate for more overall funding for the Provider Relief Fund, relief for hospitals and health systems with Medicare accelerated payments, hospital and health system priorities to be included in the upcoming infrastructure legislative package and Congressional action by the end of the year on Medicare cuts due to the effects of PAYGO," said Rick Pollack, president and CEO of the American Hospital Association (AHA). ❖

House Passes Bill That Extends Moratorium on 2% Medicare Sequester Cuts Through End of 2021, Makes Other Changes. American Hospital Association press release, April 13, 2021. Accessed at www.aha.org/special-bulletin/2021-04-14-house-passes-bill-extends-moratorium-2-medicare-sequester-cuts-through.

HHS Renews Contract with Teletracking to Provide COVID-19 Patient Data

The U.S. Department of Health and Human Services (HHS) has awarded a six-month contract to Pittsburgh-based analytics firm TeleTracking to continue collecting and reporting COVID-19 patient information. TeleTracking will continue working with the government to provide public health officials with COVID-19 data through HHS Protect. "Over a year ago, TeleTracking joined the fight against the COVID-19 pandemic through our partnership with HHS. Our work with federal, state and local

governments and hospitals across the country to collect patient data has played a critical role in the nation's response to this crisis," said Chris Johnson, TeleTracking co-CEO and president.

According to TeleTracking, the data it collects from hospitals provides visibility into response areas such as hospital capacity, hospitalization levels, personal protective equipment supplies, therapeutics usage, vaccinations and staffing, as well as insight into critical capacity and supply issues. ❖

Jercich K. HHS Renews TeleTracking Contract for Collecting COVID-19 Patient Data. Healthcare IT News, April 9, 2021. Accessed at www.healthcareitnews.com/news/hhs-renews-teletracking-contract-collecting-covid-19-patient-data.

CDC OKs the Purchase of Rapid Fentanyl Test Strips with Federal Funding

The Centers for Disease Control and Prevention (CDC) and the Substance Abuse and Mental Health Services Administration (SAMHSA) announced federal funding may now be used to purchase rapid fentanyl test strips (FTS) to help curb the dramatic spike in drug overdose deaths largely driven by the use of strong synthetic opioids, including illicitly manufactured fentanyl.

Approximately 88,000 drug overdose deaths occurred in the United States in the 12 months ending August 2020, the highest number of overdose deaths ever recorded in a 12-month period, according to provisional data from CDC, and overdose deaths have continued to accelerate during the COVID-19 pandemic. FTS can be used to determine if drugs have been mixed or cut with fentanyl, providing people who use drugs and communities with important information about fentanyl in the illicit drug supply so they can take steps to reduce their risk of overdose.

"This is a major step forward in the ongoing and critical work to prevent overdose and connect people who have substance use disorders to evidence-based treatment options," said Acting Assistant Secretary for Mental Health and Substance Use Tom Coderre, the interim leader at SAMHSA. "This will save lives by providing tools to identify the growing presence of fentanyl in the nation's illicit drug supply and — partnered with referrals to treatment — complement SAMHSA's daily work to direct help to more Americans."

This change applies to all federal grant programs as long as the purchase of FTS is consistent with the purpose of the program. Following are two examples of overdose response programs that can now use program funds to purchase FTS:

- CDC's multiyear Overdose Data to Action cooperative agreement began in September 2019 and funds health departments in 47 states; Washington, D.C.; two territories; and 16 cities and counties for drug overdose surveillance and prevention efforts. Funds awarded as part of this agreement support health departments in obtaining high-quality, more comprehensive and timelier data on overdose morbidity and mortality and

using those data to implement prevention and response efforts.

SAMHSA's State Opioid Response (SOR) grant aims to address the opioid crisis by increasing access to medication-assisted treatment, reducing unmet treatment need and reducing opioid overdose-related deaths through supporting prevention, treatment and recovery activities for opioid use disorder. SOR supplements current state and territory opioid-related activities and supports a comprehensive response to the opioid epidemic. ❖

Federal Grantees May Now Use Funds to Purchase Fentanyl Test Strips. Centers for Disease Control and Prevention press release, April 7, 2021. Accessed at www.cdc.gov/media/releases/2021/p0407-Fentanyl-Test-Strips.html.

Provider, Supply Chain and Payer Negotiations

By Bonnie Kirschenbaum, MS, FASHP, FCSHP

THERE WAS a time when healthcare providers could choose drugs and biologics, acquire them in a variety of ways depending on their practice site and submit claims to payers for reimbursement. In today's fast-paced healthcare industry, that's no longer the case, and naiveté about payers' requirements coupled with their supply chain stipulations can lead to reimbursement shock!

For many years, Medicare relied on local and national coverage determinations to provide facilities guidance about requirements for using designated products. But now, there's been a shift to the prior authorization mode of controlling costs for some products and procedures. And, with commercial payers also strengthening their prior authorization/medical necessity provisions, a heavy burden is placed on providers. Essentially, providers must identify patients' payers prior to prescribing drugs and biologicals, and they must fulfill their requirements before submitting claims for payment.

Payers have entered the supply chain space as well. Now, they no longer leave product acquisition to the discretion of the practice site, thereby strengthening their armamentarium of drug-spending control tools. Consequently, it is paramount providers know who is in their supply chain, what actions they need to take and the reimbursement potential.

Traditionally, almost all providers used the "buy and bill" model in which they purchased and/or stocked products though the normal supply chain such as a drug wholesaler or distributor, and then billed the payer/insurer for the products and injectable drug administration fees, which included preparation of the drugs.

For years, financial assistance came in the form of zero-priced patient assistance drugs. Providers acquired zero- or nominally priced products for specific qualifying patients from the manufacturer or a foundation. And, while billing for these products was not an option, often a drug administration fee might have been available from payers.

Now, payer-mandated distributors are being used as a cost-containment measure. Providers must purchase products for specific patients from a payer-chosen distributor/supplier at their negotiated cost, which is outside any group purchasing organization (GPO) or other relationship providers use. As such, reimbursement is payer-dependent for products and IV drug administration fees.

Negotiating the "Bagging Trio"

The so-called bagging trio consists of white, brown and clear bagging models. White bagging refers to the distribution of patient-specific medications from a pharmacy, typically a specialty pharmacy, to the physician's office, hospital or clinic for administration. This often is used in specialty practices to obtain costly injectable or infusible medications distributed by specialty pharmacies and may not be available in all nonspecialty pharmacies. Brown bagging refers to the dispensing of medications from a pharmacy (typically a specialty pharmacy) directly to patients, who then transport the medications to the clinic or physician's office for preparation and administration. Clear bagging, the newest concept, refers to a health system's own specialty pharmacy delivering/shipping medication to its own clinics for preparation and administration.

In all three models, providers must acquire the designated patient-specific products from the designated specialty pharmacy at no cost since the payer reimburses the specialty pharmacy rather than providers. If negotiated, providers can bill payers/insurers for administrative drug handling fees and infusible drug administration fees. If the use of these bagging methods is widespread in an area, mandates may impact practices either positively or negatively. In any case, practices need to be aware of and track any white, brown or clear bagging mandates for patients, as well as any state acts or regulations that define these policies.

In addition, keeping up with the latest version of the self-administered drug exclusion list is vital to the accuracy of billing and reimbursement since these products are not reimbursable in a clinic or office setting effective April 1, 2021.[1]

Many hospital pharmacists are disgruntled about white/brown bagging and mandated restricted drug distribution models, causing them to prohibit white bagging at their facilities, while diligently trying to avoid restricted drug distribution, and perhaps even closing formularies to those affected products.

Inevitably, payer requirements will

continue to increase, and it will be financially worthwhile to negotiate with payers for anything that brings in revenue and recognizes pharmacies for their extra work. Negotiations could include anything from handling fees for white-bagged drugs to outpatient and ambulatory clinical services. This assumes there is a desire at the facility for a workable solution that provides some remuneration for their handling, administrating and administering the affected zero-priced drugs, albeit not the billed revenue from the markup on drugs that was lost. Negotiations are also dependent on hospital pharmacists' willingness to continue to advocate for patient assistance programs and work with their in-house financial navigators and other supporting agencies, as well as with negotiations with pharmaceutical companies. There is a possibility to negotiate handling fees for patient-specific zero-priced drugs since there is no billed revenue from them.

Many of the frustrations and concerns hospital pharmacists have about zero-priced drugs involve supply chain, storage, security and vetting of the products, functions that are very similar to those for zero-priced white/brown bagged drugs. In a March 8 white paper titled "Health Insurer Specialty Pharmacy Policies Threaten Patient Quality of Care," the American Hospital Association (AHA) urged regulators to prohibit certain health insurance pharmacy policies stating: "These policies limit the ability of hospital staff to have line of sight into the origin and handling of a drug prior to receipt by the hospital, raising significant concerns and creating substantial challenges. These actions pose significant risks to quality of care as providers have inadequate control in ensuring patient access to high-quality drugs, as well as the appropriate storage and handling of those drugs. These policies simply serve to drive more revenue to health insurers through their pharmacy benefit management and specialty pharmacy lines of business."[2]

Many hospital pharmacists are disgruntled about white/brown bagging and mandated restricted drug distribution models.

In March, the American Society of Health-System Pharmacists and AHA, joined by more than 60 health systems and GPOs, took extensive action to address payer-mandated white bagging, stating these same concerns. They then sent a joint letter to the U.S. Food and Drug Administration commissioner requesting a meeting to discuss concerns regarding payer-mandated distribution models and the Drug Supply Chain Security Act.

Consider the Patients

Before deciding on a course of action regarding the bagging trio, providers should examine their business contracting relationships with commercial payers, including Medicare Advantage. These annual contracts provide covered beneficiaries (patients) with services hospitals offer such as emergency room visits; inpatient and outpatient care, including infusion clinics; ambulatory, laboratory, radiology and occupational services; etc., depending on contract terms. These patients signed up with their carriers' plans for a substantial sum. So, they may be shocked to find a facility's pharmacy has denied the use of their expensive drugs their insurance carriers are willing to provide as zero-priced (white bagged) drugs. These patients may very well have chosen their plans because of drug coverage a facility now blocks.

Such a scenario illustrates the conundrum providers face when banning or refusing to work with white/brown bagging. It isn't a decision pharmacies should make unilaterally without the endorsement of the C-suite and disclosure to health insurance carriers. If that decision is made and facilities will provide all services with the exclusion of white/brown bagged drugs, that means the affected patients will need to seek services elsewhere or pay out of pocket for those products. Therefore, for the benefit of all, facilities need to work with payers to negotiate the trickle-down effects of decisions that have significant implications. ❖

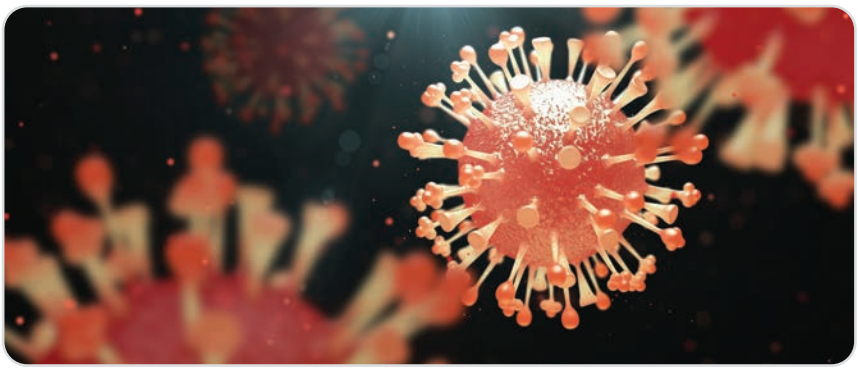
References

1. Centers for Medicare and Medicaid Services. Local Coverage Article: Self-Administered Drug Exclusion List (A53127). Accessed at www.cms.gov/medicare-coverage-database/details/article-details.aspx?articleId=53127&ver=95&name=368*1%7c370*1%7c369*1%7c371*1%7c372*1%7c331*1&UpdatePeriod=925&bc=AAAABAAAAAAA&.
2. American Hospital Association. Health Insurer Specialty Pharmacy Policies Threaten Patient Quality of Care. Accessed at www.aha.org/white-papers/2021-03-08-health-insurer-specialty-pharmacy-policies-threaten-patient-quality-care?utm_source=newsletter&utm_medium=email&utm_content=03082021%2Dat%2D-pub&utm_campaign=aha%2Dtoday.

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

Research

Study Provides Insight on Why Influenza Can Be Deadly



Researchers at the Karolinska Institutet have identified influenza (flu)-induced changes in the lower airways that affect the growth of pneumococci in the lungs, which is why the flu can be deadly.

Using an animal model, the researchers found different nutrients and antioxidants such as vitamin C and other normally cell-protective substances leak from the blood, creating an environment in the lungs that favors growth of the bacteria. The bacteria adapt to the inflammatory environment by increasing the production of the bacterial enzyme HtrA, which weakens the immune system and promotes bacterial growth in the influenza-infected airways. The lack of HtrA stops bacterial growth. "The ability of pneumococcus to grow in the lower airways during an influenza infection seems to depend on the nutrient-rich environment with its higher levels of antioxidants that occurs during a viral infection, as well as on the bacteria's ability to adapt to the environment and protect itself from being eradicated by the immune system" said principal investigator Birgitta Henriques Normark, professor in the Department of Microbiology, Tumor and Cell Biology at Karolinska Institutet.

The findings provide information on how bacteria integrate within their environment in the lungs, which could be used to find new therapies for double infections between the influenza virus and pneumococcal bacteria. It is unknown whether COVID-19 patients are also sensitive to such secondary bacterial infections, but the researchers believe similar mechanisms could potentially be found in severely ill COVID-19 patients. ❖

Sender V, Hentrich K, Pathak A, et al. Capillary Leakage Provides Nutrients and Antioxidants for Rapid Pneumococcal Proliferation in Influenza-Infected Lower Airways. *Proceedings of the National Academy of Sciences of the United States of America,* 2020 Nov 23;202012265. Accessed at pubmed.ncbi.nlm.nih.gov/33229573.

Research

KEDRAB Is Safe and Effective in Pediatric Patients Exposed to Rabies

A new study has found Kedrion Biopharma's KEDRAB 150 IU/mL (HRIG150, rabies immune globulin [human]) is a well-tolerated and effective post-exposure prophylaxis in patients 17 years and younger who have been exposed to rabies. In the study, 30 participants received 20 IU/kg HRIG150 infiltrated into the detectable wound site(s), with any remainder injected intramuscularly, concomitantly with the first of a four-dose series (days 0, 3, 7 and 14) of rabies vaccine. Rabies virus neutralizing antibody (RVNA) titers and tolerability were assessed on day 14 following administration. Participant safety was monitored for 84 days. No serious adverse events, rabies infections or deaths were recorded. Twenty-one participants (70.0 percent) experienced a total of 57 treatment-emergent adverse events (TEAEs) within 14 days following administration. Twelve participants (40.0 percent) experienced a total of 13 adverse events deemed treatment-related. All TEAEs were mild in severity. On day 14, 28 participants (93.3 percent) had RVNA levels of ≥0.5 IU/mL.

The study was the first trial of human rabies immune globulin in children. ❖

Hobart-Porter N, Stein M, Toh M, et al. Safety and Efficacy of Rabies Immunoglobulin in Pediatric Patients with Suspected Exposure. *Human Vaccines & Immunotherapeutics,* DOI: 10.1080/21645515.2020.1854000. Accessed at www.tandfonline.com/action/showCitFormats?doi=10.1080%2F21645515.2020.1854000&area=0000000000000001.

Research

COVID-19 Vaccine Responses to Be Studied in People with Immune Deficiencies

A study assessing how people with immune system deficiencies or dysregulations respond to COVID-19 vaccination has begun enrolling participants at the National Institutes of Health (NIH) Clinical Center in Bethesda, Md. The single-site study is led by researchers from the National Institute of Allergy and Infectious Diseases (NIAID) and aims to enroll 500 people, 400 with primary or secondary immune system disorders and 100 without such conditions.

"Through large Phase III trials, several experimental COVID-19 vaccines were shown to be safe and effective and three are now authorized by the U.S. Food and Drug Administration for emergency use in the United States," said NIAID Director Anthony S. Fauci, MD. "People with immune disorders are typically excluded from trials of experimental vaccines, and this was the case in the COVID-19 vaccine trials. This new study will characterize the features and adequacy of immune responses to COVID-19 vaccination in people with a range of immune deficiencies and dysregulation syndromes and will provide valuable information about benefits and potential risks in these individuals."

In addition to analyzing how they respond to vaccination, the study team will gather information about COVID-19 illness in people with immune deficiencies and dysregulation conditions. "Currently, there are few published studies on the incidence and clinical presentation of COVID-19 disease in people who have immune deficiencies, especially those who have inborn conditions involving deficits or dysregulations in antibody or cell-based immune responses to infections," said study principal investigator Emily Ricotta, PhD, MSc, of the NIAID Laboratory of Clinical Immunology and Microbiology. "Our study aims to fill this knowledge gap."

Potential volunteers may be identified and invited to join the new study through existing NIH study protocol pools of healthy volunteers or via existing protocols involving persons with immune system disorders. Healthcare providers also may refer their patients with immune deficiencies or dysregulation conditions for enrollment. Initially, the study will enroll participants 16 years of age and older. If COVID-19 vaccines are authorized for use in younger people in the future, the enrollment age criterion could expand to include them.

All study visits can be conducted either in person at the NIH Clinical Center or remotely. Participants may be enrolled if they are completely or partially vaccinated against COVID-19. If a volunteer has not yet been vaccinated, they will provide a blood sample to investigators seven days prior to receipt of a U.S. Food and Drug Administration-authorized COVID-19 vaccine. Study participants can receive any authorized COVID-19 vaccine in their local communities. Depending on which manufacturer's vaccine a participant receives, additional blood samples will be collected between 14 days and 28 days after the first dose. Participants who receive a vaccine that is administered as a two-dose regimen will provide an additional blood sample between 21 days and 28 days after the second vaccine dose. Participants who receive the one-dose Johnson & Johnson COVID-19 vaccine will provide a single blood sample between 21 days and 28 days after vaccination.

Blood sampled before and shortly after vaccination will be used to study short-term immunological effects of immunization. Participants have the option to provide additional samples approximately six, 12 and 24 months after the last dose. These samples will permit researchers to assess the persistence of vaccine-induced antibodies and T-cell responses and to compare responses made by people with and without immune system disorders. If vaccine "booster" injections are recommended in the future, volunteers may choose to provide additional blood samples following those booster vaccines.

At enrollment, participants will be asked if they have been diagnosed with COVID-19 in the past and about symptom severity, using standardized questionnaires. "This will allow us to characterize the different manifestations of COVID-19 illness in the study population and to determine what influence these may have on the immune response to COVID-19 vaccination," said Dr. Ricotta.

Participants also will have the option to be screened for SARS-CoV-2 infections following vaccination using at-home saliva collection kits they will return to NIH biweekly for six months. (SARS-CoV-2 is the virus that causes COVID-19.) During multiple follow-up timepoints in the trial, participants will be asked about any vaccine-related adverse events, which will allow the study team to better understand safety and tolerability of the vaccines in people with specific immune deficiency or dysregulation disorders.

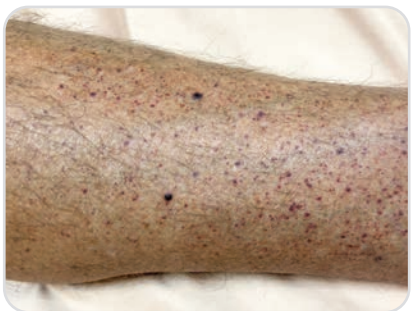
"The information we gather on how well COVID-19 vaccines protect these specific populations and about any adverse events experienced by those with immune dysregulation or other disorders will aid decision-making about vaccination," said Steven Holland, MD, director of the NIAID Division of Intramural Research, and the study's medically responsible principal investigator.

More information about the study is available at clinicaltrials.gov by searching on the identifier NCT04852276. Study staff may also be contacted by those interested in participating at NIAIDcovidvaccinestudy@niaid.nih.gov. ❖

National Institutes of Health. COVID-19 Vaccine Responses to Be Studied in People with Immune Deficits. Accessed at www.nih.gov/news-events/news-releases/covid-19-vaccine-responses-be-studied-people-immune-deficits.

Medicines

FDA Grants Fast Track Designation to Rilzabrutinib to Treat ITP



The U.S. Food and Drug Administration (FDA) has granted fast track designation (FTD) to Sanofi's rilzabrutinib, an oral investigational Bruton's tyrosine kinase (BTK) inhibitor, to treat patients with immune thrombocytopenia (ITP). In addition, following the observation of positive Phase I/II study results, Sanofi has initiated a Phase III study evaluating rilzabrutinib for ITP.

Rilzabrutinib is an oral, reversible covalent BTK inhibitor being investigated to treat immune-mediated diseases. BTK is involved in innate and adaptive immune responses and is a signaling molecule found in immune-mediated diseases.

"By awarding fast track designation to rilzabrutinib, an investigational candidate for the treatment of ITP, the FDA has recognized rilzabrutinib's potential to meaningfully improve outcomes for patients with this debilitating disease. This is an excellent acknowledgement as we initiate our Phase III study," said Dolca Thomas, chief medical officer of Principia, a Sanofi company. "FTD is designed to facilitate the development and expedite the review of investigational treatments that demonstrate the potential to address unmet medical needs in serious or life-threatening conditions."

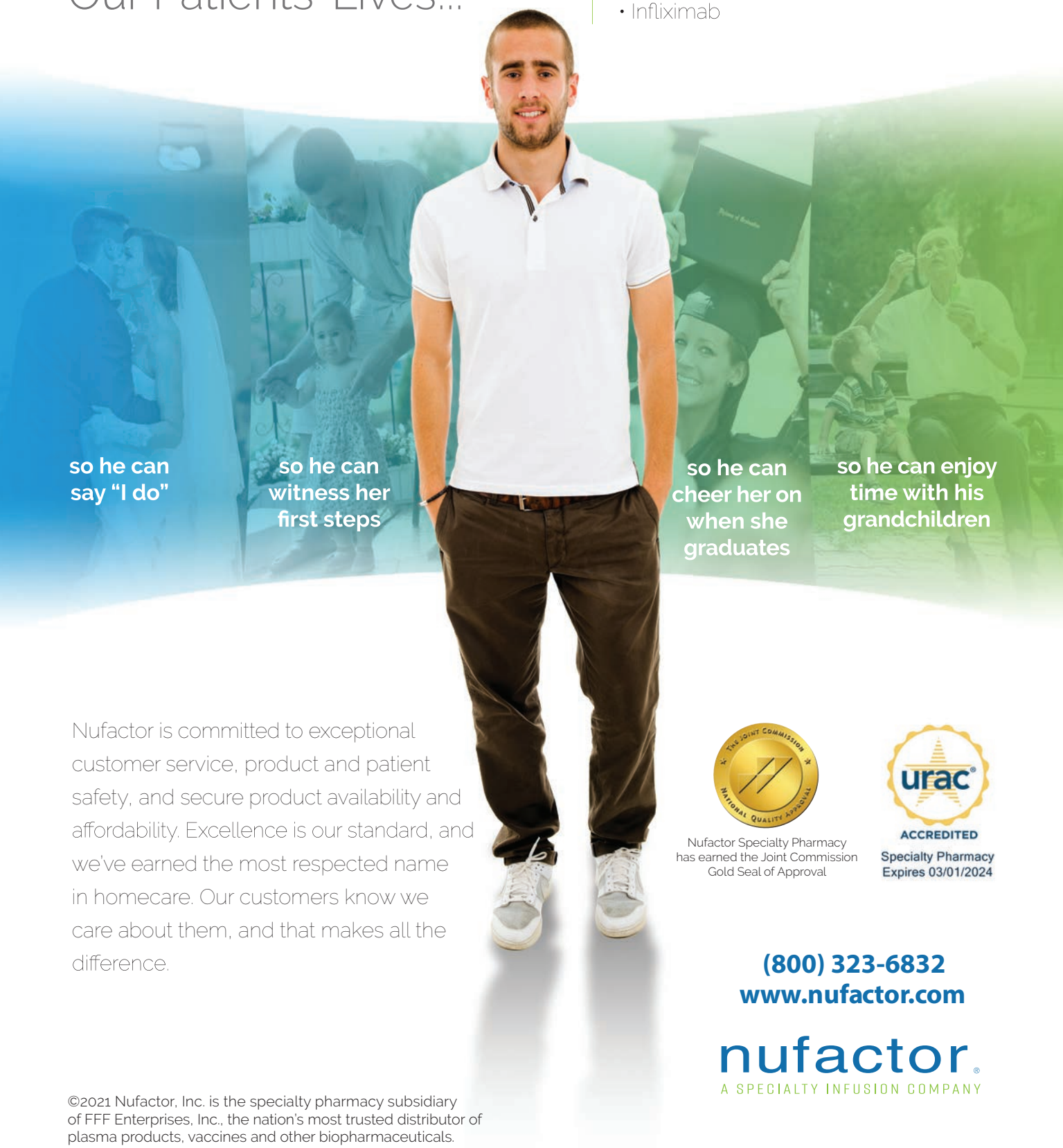
In October 2018, rilzabrutinib also received orphan drug designation from FDA to treat ITP.

Rilzabrutinib is also being investigated in a Phase III trial for pemphigus, an immune-mediated disease characterized by blisters in mucous membranes and skin. A Phase II study in the autoimmune condition IgG4 disease has also been initiated. ❖

Rilzabrutinib Granted FDA Fast Track Designation for Treatment of Immune Thrombocytopenia. Sanofi press release, Nov. 18, 2020. Accessed at www.sanofi.com/en/media-room/press-releases/2020/2020-11-18-07-15-00.

Making a Difference in Our Patients' Lives...

Specialty Solutions in Chronic Care
- Immune Globulin
- Factor
- Infliximab



Nufactor is committed to exceptional customer service, product and patient safety, and secure product availability and affordability. Excellence is our standard, and we've earned the most respected name in homecare. Our customers know we care about them, and that makes all the difference.

Nufactor Specialty Pharmacy has earned the Joint Commission Gold Seal of Approval

urac ACCREDITED Specialty Pharmacy Expires 03/01/2024

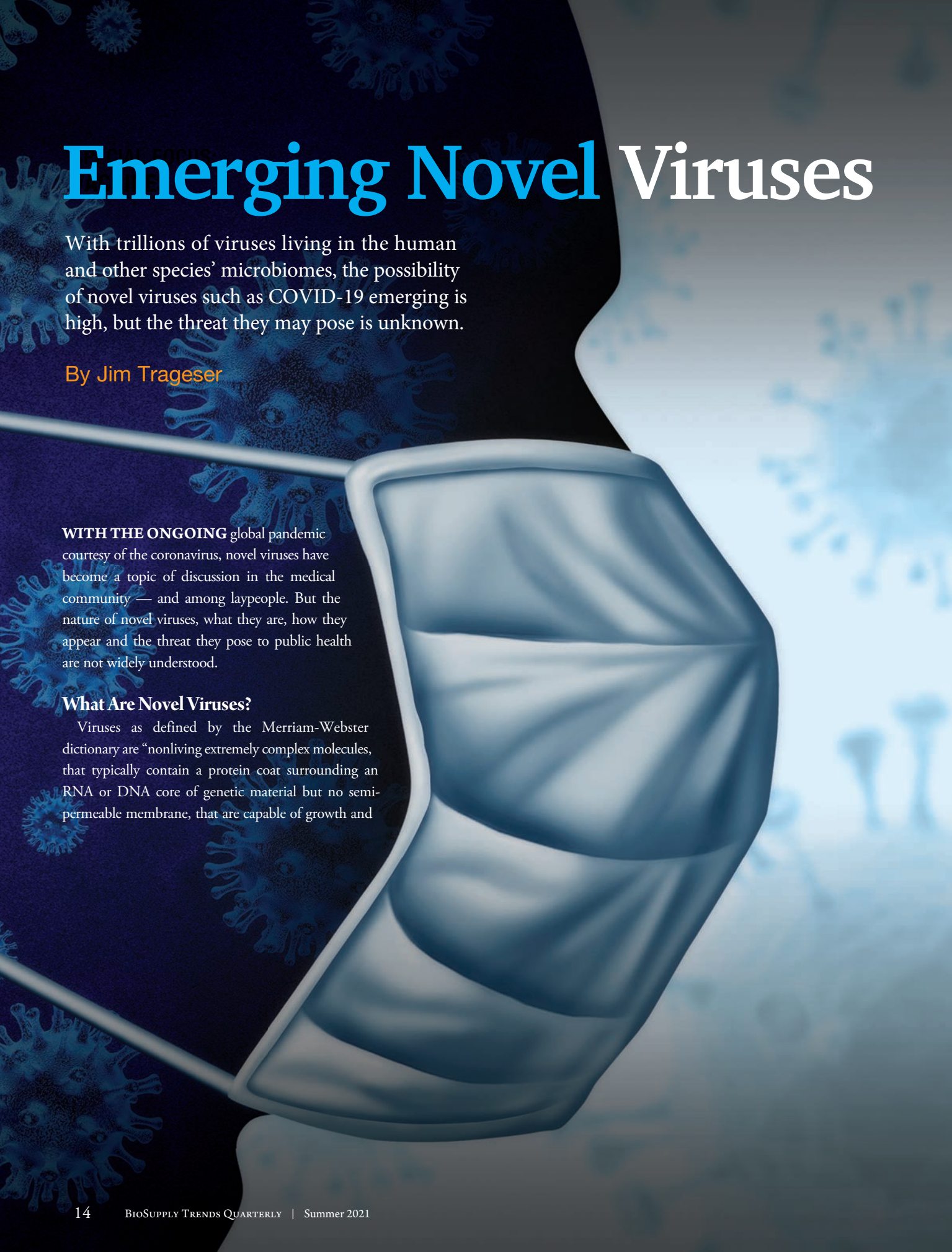
(800) 323-6832
www.nufactor.com

nufactor®
A SPECIALTY INFUSION COMPANY

Emerging Novel Viruses

With trillions of viruses living in the human and other species' microbiomes, the possibility of novel viruses such as COVID-19 emerging is high, but the threat they may pose is unknown.

By Jim Trageser



WITH THE ONGOING global pandemic courtesy of the coronavirus, novel viruses have become a topic of discussion in the medical community — and among laypeople. But the nature of novel viruses, what they are, how they appear and the threat they pose to public health are not widely understood.

What Are Novel Viruses?

Viruses as defined by the Merriam-Webster dictionary are "nonliving extremely complex molecules, that typically contain a protein coat surrounding an RNA or DNA core of genetic material but no semi-permeable membrane, that are capable of growth and

multiplication only in living cells."[1] Simply put, a novel virus is one that has not previously been identified by the scientific community and, thus, has not been named or categorized. In fact, novel viruses may have existed for years, but they were never encountered by human researchers. On the other hand, novel viruses may newly develop since genes in RNA and DNA are subject to mutation.

Almost 7,000 viruses have been described in detail, according to a March 24, 2020, article in *The New York Times*, and that number has undoubtedly grown. Still, it's estimated there may be hundreds of thousands, even millions, of viruses that have not yet been discovered. And, every one of them is a novel virus.

Viruses reproduce by latching onto a specific molecule on the membrane of a cell and then inserting themselves into the cell's interior where they hijack the cell's own replication processes to make copies of themselves. For instance, when a person has the influenza (flu) virus, that person's body may contain up to 100 trillion copies of that flu virus alone.[2]

And, because viruses penetrate a cell's exterior membrane by latching onto a specific molecule, they tend to specialize. This means a virus that can infect one life form is generally unable to infect another since different species' cells have different chemical makeups, including their membranes. A virus that will fit into one specific molecule will be unable to fit into all other molecules.

Yet, the same instability that allows new viruses to arise from old ones via genetic mutation also leads to viruses jumping from birds to humans (such as various forms of avian flu over the years) and, apparently, in the case of the novel coronavirus, from bats to humans: A mutation allows the virus to latch to a molecule unique to its new host.

In late April, the Centers for Disease Control and Prevention (CDC) reported the discovery of three novel influenza viruses — most recently, a child in Wisconsin infected with an (A(H1N1)v) virus, thought to have been acquired during contact with pigs.[3]

How Are Novel Viruses Discovered?

A virus's environment is cytoplasm. Viruses cannot survive outside a host cell, at least not for long.[2] Lacking a cellular membrane to protect their genetic coding, viruses are extremely vulnerable to environmental factors such as heat, cold, radiation, exposure to caustic materials and other factors that can cause them to quickly disintegrate when they are outside of a cell. Viruses also lack any means of locomotion, relying on their hosts for mobility.

Since viruses are only found, by and large, within the cells of organisms, searching for viruses is not like searching for new plants, animals or even microbes. Because viruses are so small that they live inside of cells, all but a handful (known as giant viruses) are too tiny to be seen with standard microscopes. Electron microscopes can capture images of viruses and are one tool used to discover viruses. Today, however, most recent and ongoing searches for novel viruses are conducted using chemical tests that look for specific genes known to be associated with viruses.[4]

Still, while technology such as electron microscopes and polymerase chain reactions allow us to search for viruses at their submicroscopic scale, most of those 7,000 viruses we currently know about were discovered the same way health officials became aware of the novel coronavirus: through the symptoms of infected hosts, human or otherwise.

Viruses reproduce by latching onto a specific molecule on the membrane of a cell and then inserting themselves into the cell's interior where they hijack the cell's own replication processes to make copies of themselves.

The symptoms of COVID-19 were just distinct enough to make researchers wonder if there was a new disease in late 2019 and early 2020. As researchers studied people exhibiting symptoms of this outbreak, they were able to determine there was a new, or novel, virus not previously known about: a coronavirus.

While the World Health Organization (WHO) continues to try to determine the exact origins of this novel coronavirus, the Wuhan Institute of Virology, a research laboratory in Wuhan province in China, is part of that investigation because it engages in the search for and identification of novel viruses, and the first cases of COVID-19 were diagnosed in that area. Whether this novel coronavirus infected a lab worker studying bat-borne viruses, and from there escaped into the general human population, is not yet known. WHO is conducting additional study after the original report dismissed that possibility but faced widespread criticism for its methodology.[5]

Still, laboratories such as the Wuhan Institute of Virology continue to search for new viruses in hopes of expanding our limited knowledge of viruses.

How Are Novel Viruses Named?

Unlike animals, plants, fungi and bacteria, viruses are not necessarily named for those who discover them. Instead, they are given a name by the International Committee on Taxonomy of Viruses (ICTV).[6]

Nor are viruses necessarily categorized by species, genus, family, order, class, phylum, etc. As viruses are not currently considered part of the kingdom of life, they are described and categorized by their molecular structure and any infections they are known to cause.[6] Hence, the novel coronavirus that causes COVID-19 is officially known as "severe acute respiratory syndrome coronavirus 2," which is shortened to SARS-CoV-2. (The term "coronavirus" refers to the globular shape of the virus.)

Since viruses reproduce and are self-described by their genetic code (RNA or DNA), there is ongoing reconsideration of whether viruses are indeed a life form. ICTV is formulating a new classification similar to that used for cellular life.[7] The organization has also been charged by WHO with creating a universal database of all known viruses.

The Threat of Novel Viruses

Although some 320,000 viruses are thought to be able to infect mammals,[8] most viruses do not pose a high risk to humans. Only approximately 200 of the 7,000 currently cataloged viruses are known to infect humans.[9] Other viruses that enter the body through airborne droplet transmission, by mosquito bites or by touching one's face after shaking hands are unable to penetrate the body's cells so they cannot cause infection. (Interestingly, the human body is naturally host to untold types of viruses that cannot penetrate human cells. These viruses live on the bacteria that inhabit the body, which is the so-called good bacteria in the digestive tract.[10])

However, some of those 200 viruses are very deadly. Hemorrhagic fevers such as ebola, dengue and yellow fever are among the most feared diseases known. Other viruses cause AIDS, encephalitis and polio. And, seasonal flu is also caused by viruses.

So, it is difficult to gauge what the health threat of a novel virus will be. It depends entirely on the type of virus, how infectious it is and how it affects its host. Ebola, for instance, has a mortality rate of up to 90 percent, but it does not seem able to spread much beyond its original source in equatorial Africa. The common cold, on the other hand, is highly contagious and endemic around the world, but it rarely causes serious health concerns.

Treating Novel Virus Infections

Since the specific nature of a novel virus is not known in advance, specifying treatment is also impossible. However, if a patient is exhibiting symptoms of an infection for which no obvious cause can be found, and blood work does not reveal any known bacterial or viral markers, the patient can be referred to a specialist.

For any unidentified infection, physicians carefully monitor a patient for any sudden deterioration in his or her condition. Any change in or appearance of a rash, a spike in fever, a persistent cough, difficulty breathing, severe headaches or body aches are all signs of a potential viral infection.

Relatively few viruses have an antiviral treatment on the market, and none will be approved for a novel virus, so the unfortunate reality is treatment for an infection caused by a novel virus will be rest and fluids unless the patient suffers such severe symptoms that hospitalization or other intervention becomes necessary.

It is important, when a new pathogen is suspected, doctors notify local and state public health agencies, as well as the CDC.

Ongoing Research

Even modern technology has some inherent limitations in aiding scientists' search for new viruses. For instance, polymerase chain reactions that can take a small sample of RNA or DNA and mass-produce copies of it so researchers can identify it via chemical tests only helps if there are common genetic strains already associated with known viruses.

When viruses are found that do not share RNA or DNA patterns with any known viruses (in one recent case, a virus residing in a South American amoeba), confirming a new virus has been found takes a lot more work.[11] In addition, the recent discovery that there are likely thousands of viral types living in the gut bacteria of human beings only hints at the scale of trying to identify and categorize as many viruses as possible. Just in homo sapiens, it is estimated there are more than 1,000 species of bacteria living in our digestive tracts.[12] Another recent study found there are likely 140,000 different virus types living in those 1,000 bacteria species in the human microbiome alone.[13]

Because most animals have gut bacteria involved in digesting food (among other functions), and since this microbiota varies from species to species, the number of separate bacteria to be studied — and the viruses that live within them — is astronomical. There are 6,000 different species of mammal alone, and a similar number of amphibians. Add to that 1,000 species of reptile and 9,000 or more bird species. This only hints at the number of potential undiscovered viruses.

In fact, invertebrates have microbiomes, too. Insects have bacteria in their digestive tracts,[14] as do spiders[15] and shellfish. There are some 925,000 species of insects currently identified. Even organisms without digestive tracts such as sponges, plants, fungi and nonbacterial single-celled organisms such as archaea[16] have viruses living within their cells.

In short, it seems there is almost no life form that does not have viruses associated with it. That's a lot of gut bacteria yet to be studied, and a lot of viruses living in those gut bacteria.

Looking Ahead

Given how little is known about viruses — how prevalent they are, their genetic diversity and their history — virology is likely to be a rapidly developing field over the coming decades. In fact, virology is at a point at which scientists are trying to determine how much still needs to be understood, according to Jônatas Abrahão, a virologist at the Federal University of Minas Gerais in Belo Horizonte, Brazil.[11]

While research into discovering previously unknown viruses in nature continues to accelerate, geneticists are also working on manipulating the RNA and DNA of viruses to better understand how they work and to find new ways of treating infections caused by viruses.

Although some 320,000 viruses are thought to be able to infect mammals, most viruses do not pose a high risk to humans.

Both prongs of research — discovering existing viruses and modifying the genes of viruses in the laboratory — carry the threat of spillover: Either a virus previously unexposed to homo sapiens makes the leap, or a bioengineered virus accidentally infects a researcher.

Considering what we know so far about viruses, COVID-19 is statistically unlikely to be the last novel virus to cause a major outbreak of disease. ❖

References

1. Merriam-Webster Dictionary. Virus. Accessed at www.merriam-webster.com/dictionary/virus.
2. Wei-Haas M. Viruses, Explained. *National Geographic*, Feb. 22, 2019. Accessed at www.nationalgeographic.com/science/article/viruses.
3. Centers for Disease Control and Prevention. FluView Summary Ending on April 10, 2021. Accessed at www.cdc.gov/flu/weekly/weeklyarchives2020-2021/week14.htm.
4. Racaniello V. How Many Viruses on Earth? Virology Blog, Sept. 6, 2013. Accessed at www.virology.ws/2013/09/06/how-many-viruses-on-earth.
5. Rauhala E. WHO Chief, U.S. and Other World Leaders Criticize China for Limiting Access of Team Researching Coronavirus Origins. *The Washington Post*, March 30, 2021. Accessed at www.washingtonpost.com/world/who-wuhan-tedros-lab/2021/03/30/896fe3f6-90d1-11eb-aadc-af78701a30ca_story.html.
6. World Health Organization. Naming the Coronavirus Disease (COVID-19) and the Virus that Causes It. Accessed at www.who.int/emergencies/diseases/novel-coronavirus-2019/technical-guidance/naming-the-coronavirus-disease-(covid-2019)-and-the-virus-that-causes-it.
7. Lefkowitz E, Dempsey D, Hendrickson R, et al. Virus Taxonomy: The Database of the International Committee on Taxonomy of Viruses (ICTV). *Nucleic Acids Research*, Jan. 4, 2018. Accessed at www.ncbi.nlm.nih.gov/pmc/articles/PMC5753373.
8. Anthony S, Epstein J, and Murray K. A Strategy to Estimate Unknown Viral Diversity in Mammals. *mBio*, July 30, 2013. Accessed at mbio.asm.org/content/4/5/e00598-13.
9. ViralZone. Human Viruses and Associated Pathologies. Accessed at viralzone.expasy.org/678.
10. Pride D and Ghose C. Meet the Trillions of Viruses that Make Up Your Virome. The Conversation, Oct. 9, 2018. Accessed at theconversation.com/meet-the-trillions-of-viruses-that-make-up-your-virome-104105.
11. Pennise E. Scientists Discover Virus with No Recognizable Genes. *Science*, Feb. 7, 2020. Accessed at www.sciencemag.org/news/2020/02/scientists-discover-virus-no-recognizable-genes.
12. Gilbert J, Blaser M, Caporaso J, et al. Current Understanding of the Human Microbiome. *Nature Medicine*, April 1, 2018. Accessed at www.nature.com/articles/nm.4517.
13. Wellcome Trust Sanger Institute. Scientists Identify More Than 140,000 Virus Species in the Human Gut. Science Daily, Feb. 18, 2021. Accessed at www.sciencedaily.com/releases/2021/02/210218142739.htm.
14. Engel P and Moran N. The Gut Microbiota of Insects — Diversity in Structure and Function. *FEMS Microbiology Reviews*, September 2013. Accessed at academic.oup.com/femsre/article/37/5/699/542120.
15. Busck M, Settepani V, Bechsgaard J, et al. Microbiomes and Specific Symbionts of Social Spiders: Compositional Patterns in Host Species, Populations, and Nests. *Frontiers in Microbiology*, July 31, 2020. Accessed at pubmed.ncbi.nlm.nih.gov/32849442.
16. Krupovic M, Iranzo J, Koonin E, et al. Viruses of Archaea: Structural, Functional, Environmental and Evolutionary Genomics. *Virus Research*, Jan. 15 2018. Accessed at pubmed.ncbi.nlm.nih.gov/29175107.

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

COVID-19 Vaccines: Where Are We Now?

With three vaccines in circulation and three more on the horizon, is the end of the COVID-19 pandemic in sight?

By Diane L.M. Cook

NOT SINCE THE Spanish flu of 1918 has the world experienced such a worldwide outbreak as COVID-19. Declared a pandemic by the World Health Organization (WHO) on March 11, 2020,[1] by April 1, 2021, more than 30 million Americans had contracted the SARS-CoV-2 virus and almost 550,000 Americans had died from it.[2] Scientists say the only way to halt further global spread of COVID-19 is with a vaccine.

Coronavirus disease of 2019 — or COVID-19 — is caused by infection with the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus strain. Because COVID-19 is a novel virus, it is more contagious than other currently circulating viruses because the global population does not have antibodies to fight it. Consequently, the COVID-19 virus has proven to be deadlier than the SARS-CoV-2 outbreak in 2003 and the Middle East respiratory syndrome (MERS-CoV) outbreak in 2012.

In addition to the original COVID-19 virus, there are three variants circulating around the world: B.117 (which originated in the United Kingdom); B.1.351 (which originated in South Africa) and P1 (which originated in Brazil). Therefore, not only do vaccine manufacturers have the daunting task of developing a novel vaccine in record time to prevent further COVID-19 infections, they must also adjust their vaccine formulae or develop new vaccines that will provide efficacy for the emerging variants.

To assist with this unprecedented endeavor, on May 15, 2020, the United States launched Operation Warp Speed (OWS) to accelerate the development, manufacturing and distribution of COVID-19 vaccines. Federally funded with $10 billion, OWS is a partnership among the Department of Health and Human Services, Centers for Disease Control and Prevention (CDC), National Institutes of Health (NIH), Biomedical Advanced Research and Development Authority and Department of Defense. OWS selected and provided funding to the vaccine manufacturers that had the most promising vaccine candidates.[3]

Three of the vaccine manufacturers have already received emergency use authorization (EUA) from the U.S. Food and Drug Administration (FDA). However, none of the vaccine candidates have yet received FDA approval or licensing. Even so, CDC, FDA and the vaccine manufacturers all believe the known and potential benefits of these vaccine candidates outweigh the known and potential risks of them.

Two types of COVID-19 vaccines are being developed. Messenger RNA (mRNA) vaccines, made from genetic material that tells a human body how to make proteins, wraps the mRNA in a coating to make delivery easy and keep the human body from damaging it. The mRNA in the vaccine teaches human cells how to make copies of the spike proteins found on the coronavirus so that if a human is exposed to the real virus, the body will recognize it and fight it.[4]

Viral vector vaccines use a harmless version of a different virus, called a "vector," to deliver information to the human body to help protect itself. These vaccines also teach the human body how to make copies of the spike proteins found on the coronavirus, thereby recognizing the real virus if exposed so it can fight it.[5]

At the time of this writing, six vaccine candidates are most promising.

Pfizer Inc.

On Dec. 11, 2020, FDA issued an EUA for Pfizer-BioNTech's BNT162b2 COVID-19 vaccine. This vaccine is based on BioNTech's proprietary mRNA technology, which is a lipid nanoparticle-formulated, nucleoside-modified messenger ribonucleic acid (mRNA) vaccine encoding the prefusion spike glycoprotein of SARS-CoV-2.

Pfizer's landmark Phase III clinical trial for BNT162b2 was designed as a 1:1 vaccine candidate to a placebo, randomized, observer-blinded study to obtain safety, immune response and efficacy data. The study enrolled 43,448 participants 16 years or older at 150 sites in the United States, Germany, Turkey, South Africa, Brazil and Argentina. Immunization consisted of two doses of the vaccine candidate administered three weeks apart.

The trial's primary endpoints were the prevention of infection by SARS-CoV-2 in participants who had and had not been previously infected by it prior to immunization. Secondary endpoints included the prevention of severe COVID-19 in both groups. Results showed the vaccine candidate was well-tolerated and demonstrated a vaccine efficacy of 95 percent against COVID-19 in participants without prior infection seven days or more after the second dose. Among participants with and without evidence of prior SARS CoV-2 infection, vaccine efficacy was found to be 94.6 percent.

At the time of this writing, six vaccine candidates are most promising.

Data from the study, including longer-term safety, comprehensive information on duration of protection, efficacy against asymptomatic SARS-CoV-2 infection, and safety and immunogenicity in adolescents 12 years to 15 years of age, will continue to be gathered. Pfizer-BioNTech have additional studies planned to evaluate BNT162b2 in pregnant women, children younger than 12 years and those in special risk groups such as the immunocompromised.[6]

Pfizer-BioNTech are also preparing for circulating variants by evaluating a booster dose of BNT162b2. This study will offer participants from the Phase I study in the United States the opportunity to receive a booster of the current vaccine six months to 12 months after receiving their initial two-dose regimen.

The companies are also in discussions with FDA and the European Medicines Agency (EMA) concerning a registration-enabling clinical study to evaluate a variant-specific vaccine that has a modified mRNA sequence. This study will use a new construct of Pfizer-BioNTech's vaccine based on the B.1.351 lineage that will allow the companies to quickly update their current vaccine from circulating strains.[7]

Real-world evidence of Pfizer-BioNTech's vaccine from the Israel Ministry of Health shows it dramatically lowers incidence rates of COVID-19 in individuals fully vaccinated. Specifically, evidence shows the vaccine prevents symptomatic infections, cases, hospitalizations, severe and critical hospitalizations and death. Evidence also shows that, two weeks after the second vaccine dose, protection is even stronger, at least 97 percent, in preventing symptomatic illness, severe and critical illness and death, and is at least 94 percent effective against asymptomatic infections.[8]

ModernaTX Inc.

On Dec. 18, 2020, FDA issued an EUA for ModernaTX's COVID-19 vaccine, formerly known as mRNA-1273. This vaccine, co-developed by Moderna and the National Institute of Allergy and Infectious Disease's Vaccine Research Center, also uses the mRNA vaccine technology.

Moderna's Phase III clinical trial, also known as the COVE study, was a randomized, 1:1 placebo-controlled study that enrolled more than 30,000 participants 18 years or older in the United States. The study included participants at high risk of severe complications from COVID-19, with more than 7,000 Americans over age 65 years. The study also included more than 5,000 Americans under age 65 years who had high-risk chronic diseases such as diabetes, severe obesity and cardiac disease that increased their risk of severe COVID-19. These medically high-risk participants represented 42 percent of the total participants. Most participants (82 percent) were considered to have had an occupational risk of exposure since 25.4 percent of them were healthcare workers. Immunization consisted of two doses of the vaccine candidate administered 28 days apart.[9]

The COVE study's primary endpoint was prevention of symptomatic COVID-19, and key secondary endpoints included prevention of severe COVID-19 and prevention of infection by SARS-CoV-2. Results showed the vaccine exhibited favorable tolerability and safety and a vaccine efficacy of 94.1 percent against COVID-19.[9]

Real-world evidence of Pfizer-BioNTech's vaccine from the Israel Ministry of Health shows it dramatically lowers incidence rates of COVID-19 in individuals fully vaccinated.

This study is ongoing, and additional data collection will include longer-term safety follow-up, duration of protection against COVID-19, and efficacy against asymptomatic SARS-CoV-2 infection. Moderna is also conducting a Phase II/III study of its vaccine in adolescents 12 years to 18 years, children younger than 12 years, pregnant women and people who are immunocompromised.[10]

Moderna recently enrolled 60 participants previously vaccinated with mRNA-1273 in Phase II to evaluate booster vaccine candidates against the B.1.351 variant first identified in South Africa. This booster vaccine, mRNA-1273.351, is a single vaccine designed to elicit a broad immune response as both a primary series and when administered as a boost to those who have previously received mRNA-1273.[11]

Moderna's Phase II/III two-part, open label, dose-escalation, age de-escalation (Part 1) and randomized, observer-blind, placebo-controlled expansion KidCOVE study (Part 2) will evaluate the safety, tolerability, reactogenicity and effectiveness of two doses of mNRA-1273 administered 28 days apart. It will enroll approximately 6,750 pediatric participants in the United States and Canada aged 6 months to less than 12 years.[12]

Janssen Pharmaceutical Companies of Johnson & Johnson

In February 2021, FDA issued an EUA for Janssen Pharmaceutical Companies of Johnson & Johnson's Ad26.COV2.S vaccine, also known as JNJ-78436735, which uses the company's AdVac viral vector vaccine platform.[13]

Janssen's Phase III ENSEMBLE study was a randomized, double-blind, placebo-controlled clinical trial that enrolled approximately 45,000 participants 18 years and older, and included a diverse and broad population, including 34 percent of participants older than 60 years. The study, conducted in eight countries on three continents, was designed to evaluate the efficacy and safety of the vaccine to protect moderate to severe COVID-19, with co-primary endpoints of 14 days and 28 days following vaccination. Among all participants from different geographies, including participants infected with an emerging viral variant, the vaccine was 66 percent effective overall in preventing moderate to severe COVID-19 28 days after vaccination, with the onset of protection observed as early as day 14. The level of protection against moderate to severe COVID-19 infection was 72 percent in the United States, 66 percent in Latin America and 57 percent in South Africa 28 days postvaccination.

In addition, the vaccine was 85 percent effective in preventing severe illness across all regions 28 days after vaccination in all adults 18 years and older. Efficacy against severe illness increased over time, with no cases in vaccinated participants reported after day 49. The vaccine also demonstrated complete protection against COVID-related hospitalization and death 28 days postvaccination. And, there was a clear effect of the vaccine on COVID-19 cases requiring medical intervention (hospitalization, ICU admission, mechanical ventilation, extracorporeal membrane oxygenation), with no reported cases among participants who had received the vaccine.

Finally, protection was generally consistent across race, age groups (including adults over 60 years) and all variants and regions, including South Africa where nearly all cases of COVID-19 (95 percent) were due to infection with a SARS-CoV-2 variant from the B.1.351 lineage.

The ENSEMBLE study results also included efficacy against newly emerging strains of coronavirus, including some highly infectious variants present in the United States, Latin America and South Africa. ENSEMBLE was conducted at the height of the COVID-19 pandemic, at a time when spread of the virus had accelerated throughout the world, resulting in people having increased exposure to the virus.

Janssen is also investigating immune responses for different doses and dosing regimens, as well as a two-dose regimen spaced two months apart, of its COVID-19 vaccine for efficacy in its ENSEMBLE 2 study. This second study will investigate if a second dose might provide greater or longer protection. Results are expected to be available in the second half of 2021.[14] Johnson & Johnson is planning to file a biologics license application with FDA later in 2021.

On April 9, 2021, EMA reported it was reviewing reports of rare blood clots in four people who received Johnson & Johnson's COVID-19 vaccine. Of the four serious cases of clotting and low platelets, three occurred in the United States during the rollout of the vaccine from its Janssen unit, and one person died during a clinical trial. The company said it was aware of the reports of blood clots possibly related to its vaccine and others, and it is working with regulators to assess the data and provide relevant information.[15] On April 13, 2021, FDA advised states to pause use of the Johnson & Johnson vaccine to investigate reports of potentially dangerous blood clots. However, the vaccine is once again being administered in the U.S.

Oxford-AstraZeneca

In collaboration with the University of Oxford, AstraZeneca is investigating its COVID-19 vaccine, formerly AZD1222, which uses the viral vector technology platform.

Results from AstraZeneca's Phase III study, called D8110C00001, showed its vaccine is 76 percent effective at preventing symptomatic COVID-19, 100 percent effective against severe or critical disease and hospitalization, and 85 percent effective against symptomatic COVID-19 in participants aged 65 years and older.[16]

This study was based on 32,449 participants at 88 trial centers in the United States, Peru and Chile. Participants were 18 years or older, with approximately 20 percent of them 65 years and older and approximately 60 percent who had comorbidities associated with an increased risk for progression of severe COVID-19. Participants were administered two doses of the vaccine at a four-week interval. Previous trials showed an extended interval of up to 12 weeks demonstrated greater efficacy, which was also supported by immunogenicity data, suggesting administration of the second dose with an interval longer than four weeks could further increase efficacy and accelerating the number of people who can receive their first dose. AstraZeneca will now prepare for its primary analysis to be submitted to FDA for EUA.[17]

On April 6, 2021, EMA said there is a "clear" link between AstraZeneca's vaccine and rare blood clots in the brain. However, the agency stressed that the benefits of the vaccine still outweigh any possible risks, a line EMA, WHO and a number of other regulators have held while many European countries suspended or restricted the use of the vaccine. Because the clotting seems to be of most concern in younger people, a number of countries,

including France and Germany, are restricting the vaccine to older populations. In late March, Canada paused vaccination for those under 55 years, citing a risk of blood clots. And, the United Kingdom's medicines regulator is reportedly considering offering those under 30 years different vaccines after 30 cases of rare blood clots were linked to the shot.[18]

AstraZeneca is also working on a COVID-19 treatment, a long-acting antibody (LAAB) combination called AZD7442, engineered with the company's proprietary half-life extension technology to increase the durability of the therapy for six months to 12 months following a single administration. The combination of two LAABs is also designed to reduce the risk of resistance developed by the SARS-CoV-2 virus.

LAABs mimic natural antibodies and have the potential to treat and prevent disease progression in patients already infected with the virus. They can also be given as a preventive intervention prior to exposure to the virus. Discovered by Vanderbilt University and licensed to AstraZeneca in June 2020, the antibodies were optimized by AstraZeneca with half-life extension and Fc receptor binding reduction. The LAAB has been shown preclinically to block the binding of the SARS-CoV-2 virus to host cells and protect against infection in cell and animal models of disease.[19]

Janssen is also investigating immune responses for different doses and dosing regimens, as well as a two-dose regimen spaced two months apart, of its COVID-19 vaccine for efficacy in its ENSEMBLE 2 study.

AZD7442 is currently being assessed in five late-stage prevention and treatment trials. The Phase III trial, STORM CHASER, started in December 2020 and is assessing the safety and efficacy of AZD7442 compared to placebo for the prevention of COVID-19 in approximately 1,125 participants after exposure to a specific identified individual with laboratory-confirmed SARS-CoV-2 infection (postexposure prophylaxis).

The Phase III PROVENT trial started in November 2020 and is assessing the safety and efficacy of AZD7442 compared to placebo for the prevention of COVID-19 in approximately 5,000 adults who are at increased risk for SARS-CoV-2 infection due to living or work situations, or who are at increased risk of responding inadequately to vaccines such as those who have compromised immune systems.

Both the STORM CHASER and PROVENT trials are being held at the Vaccine Research Centre at University College London Hospitals in the United Kingdom.

An AstraZeneca-sponsored Phase III TACKLE COVID-19 trial that started in January 2021 is evaluating the safety and efficacy of AZD7442 compared to placebo in treating nonhospitalized patients with mild to moderate COVID-19.

AZD7442 is also being studied as a potential treatment as part of NIH's Phase II/III ACTIV-2 (outpatient) and ACTIV-3 (hospitalized) trials, both of which started in February 2021.

Novavax Inc.

Novavax Inc. is investigating its COVID-19 vaccine candidate, NVX-CoV2373, which was developed using the company's recombinant nanoparticle technology to generate antigen derived from the genetic sequence of the coronavirus spike protein and is adjuvanted with Novavax's patented saponin-based Matrix-M.

The vaccine is in two Phase III clinical trials. The first is being conducted in the United Kingdom, which enrolled more than 15,000 participants between 18 years and 84 years old, including 27 percent over age 65. Results showed a vaccine efficacy of 96.4 percent against the original virus and 89.4 percent in more than 50 percent of cases attributable to the variant that is now predominant in the United Kingdom. In this trial and a Phase IIb trial, NVX-CoV2373 provided 100 percent protection against severe illness.[20]

The second study, the PRE-fusion protein subunit Vaccine Efficacy Novavax Trial, or PREVENT-19, is a randomized, placebo-controlled, observer-blinded study in the United States and Mexico that finished enrolling 30,000 participants aged 18 years and older in February 2021 to evaluate the efficacy, safety and immunogenicity of NVX-CoV2373. Two-thirds of participants have been assigned to randomly receive two intramuscular injections of NVX-CoV2373 21 days apart, while one-third of participants will receive a placebo.

After efficacy is determined, participants will remain eligible for a crossover arm of the trial, during which they will be given the opposite (active vaccine or placebo) of what they originally received. Depending on the results, Novavax was expecting to file an EUA with FDA in the second quarter of 2021.[21]

The Phase IIb trial, conducted in South Africa, enrolled more than 4,400 patients. Results showed an efficacy of 55 percent for

the prevention of mild, moderate and severe COVID-19 that was observed in 94 percent of the study population that was HIV-negative. This study took place in a region where the vast majority of strains are B1.351 escape variants that contain three critical mutations in the receptor binding domain (RBD) and multiple mutations outside the RBD.[20]

Novavax initiated development of constructs against the various strains of SARS-CoV-2 in January 2021 and expects to select ideal candidates for a booster and/or combination bivalent vaccine against the B1.351 strain soon. The company is conducting preclinical testing and was expected to be in human testing in the second quarter of 2021.[22]

Sanofi-GSK and Sanofi-Translate Bio

In collaboration with GlaxoSmithKline (GSK), Sanofi Pasteur is investigating two vaccine candidates for COVID-19, a recombinant protein-based vaccine that uses its recombinant antigen and GSK's pandemic adjuvant, both of which are established vaccine platforms proven successful against influenza. The combined platforms provide the advantages of stability at temperatures used for routine vaccines, the ability to generate high and sustained immune responses, and the potential to prevent virus transmission.

In February 2021, Sanofi-GSK announced a new Phase II clinical trial, a randomized, double-blind, multi-center dose-finding study to evaluate the safety, reactogenicity and immunogenicity of two injections given 21 days apart. Three different antigen doses with a fixed dose of adjuvant will be tested in a total of 720 participants aged 18 years and older, with equal numbers of participants aged 18 years to 59 years and participants 60 years and older in the United States and Honduras.

If data from this study are positive, a global Phase III study is planned for the second quarter of 2021. Positive results from the Phase III study would lead to regulatory submissions in the second half of 2021, with the vaccine expected to be available in the fourth quarter of 2021, if approved.

With the emergence of new SARS-CoV-2 variants and their potential impact on vaccine efficacy, in parallel to this new Phase II study, Sanofi has commenced work against new variants that will be used to inform next stages of the Sanofi-GSK development program.[23]

Sanofi is also working in partnership with Translate Bio to develop an mRNA-based vaccine candidate called MRT5500. Encouraging preclinical data showed two immunizations of the mRNA vaccine induced high neutralizing antibody levels that are comparable to the upper range of those observed in infected humans.

In March 2021, Sanofi announced the start of its Phase I/II randomized, double-blind and placebo-controlled study of MRT5500 to evaluate its safety, reactogenicity and immunogenicity. A total of 415 healthy participants aged 18 years and older will be enrolled in the trial at 13 sites. Participants will receive one dose of MRT5500, or two doses 21 days apart, with three different doses given. Interim results are expected in the third quarter of 2021.[24]

On April 6, 2021, EMA said there is a "clear" link between AstraZeneca's vaccine and rare blood clots in the brain.

Looking Ahead

Despite these extraordinary vaccine developments, even as vaccine manufacturers receive EUAs from FDA for their vaccine candidates, and hundreds of millions of individuals are ultimately vaccinated, these vaccines will not completely eradicate the COVID-19 virus. The reasons are many, including the inability of everyone to receive a vaccine and vaccine-hesitancy. It's possible herd immunity might not be achieved, and the COVID-19 virus will continue to circulate around the globe, albeit not necessarily at a pandemic level. Scientists believe the CVOID-19 virus might eventually become part of our annual cold and flu season.

Furthermore, when a vaccine receives EUA from FDA, it does not mean the vaccine is approved or licensed. Vaccine manufacturers still need to file for a biologics license application with FDA for their vaccines to receive official approval and licensing.

Another caveat: After vaccine manufacturers have received EUA from FDA for their vaccines, they are required to monitor Phase III participants for at least two years after they have received their first and/or second dose of the vaccine. Data from this two-year period are submitted to FDA for review and approval as part of the vaccine licensing process.

In addition, vaccine manufacturers state their vaccines do not have 100 percent efficacy. Their vaccines may not provide protection for all vaccinated individuals, they do not know the length of their vaccines' efficacy, and they do not know if their vaccines will provide protection for all the variants currently circulating or new ones that have yet to emerge.

Vaccine manufacturers also state individuals should not receive their vaccines if they are under 12 years, have received another COVID-19 vaccine (since it is currently unknown if vaccines are interchangeable), have severe allergies (specifically to ingredients in the mRNA vaccine's formula) and/or are immunocompromised.

Despite the extraordinary vaccine developments, even as vaccine manufacturers receive EUAs from FDA for their vaccine candidates, and hundreds of millions of individuals are ultimately vaccinated, these vaccines will not completely eradicate the COVID-19 virus.

A recent cohort study published in the *American Journal of Obstetrics & Gynecology* showed the Pfizer and Moderna vaccines are safe for pregnant and lactating women. According to the study's authors, "Pregnant and lactating women elicited comparable vaccine-induced humoral immune responses to nonpregnant controls, and generated higher antibody titers than those observed following SARS-CoV-2 infection in pregnancy. Vaccine-generated antibodies were present in umbilical cord blood and breastmilk after maternal vaccination." Additional studies will be needed for the Johnson & Johnson (Janssen) and AstraZeneca vaccines to determine if they are also safe for pregnant and lactating women.[25]

It should be noted the Spanish flu pandemic lasted for two years with four waves. To date, the COVID-19 pandemic has lasted approximately one-and-a-half years with three waves. If history repeats itself, the global population can expect the COVID-19 pandemic to continue at least another six months with at least one more wave. Ultimately, only time will tell if these COVID-19 vaccines, after they are approved and licensed, will become part of the world's regular vaccination programs. ❖

References

1. World Health Organization. WHO Director-General's Opening Remarks at the Media Briefing on COVID-19, March 11, 2020. Accessed at www.who.int/director-general/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19---11-march-2020.
2. Centers for Disease Control and Prevention. COVID-19, April 1, 2021. Accessed at www.cdc.gov/coronavirus/2019-ncov.
3. U.S. Department of Health and Human Services. Coronavirus Fact Sheet: Explaining Operation Warp Speed, Jan. 21, 2021.
4. Centers for Disease Control and Prevention. How mRNA COVID-19 Vaccines Work. Accessed at www.cdc.gov/coronavirus/2019-ncov/vaccines/different-vaccines/mrna.html#:~:text=Future%20mRNA%20vaccine%20technology%20may,to%20target%20specific%20cancer%20cells.
5. Centers for Disease Control and Prevention. How Viral Vector COVID-19 Vaccines Work. Accessed at www.cdc.gov/coronavirus/2019-ncov/vaccines/different-vaccines/viralvector.html#:~:text=Viral%20vector%20vaccines%20use%20a,important%20instructions%20to%20our%20cells.
6. Pfizer and BioNTech Announce Publication of Results from Landmark Phase 3 Trial of BNT162b2 COVID-19 Vaccine Candidate in *The New England Journal of Medicine*. Pfizer press release, Dec. 10, 2020. Accessed at www.pfizer.com/news/press-release/press-release-detail/pfizer-and-biontech-announce-publication-results-landmark.
7. Pfizer and BioNTech Initiate a Study as Part of Broad Development Plan to Evaluate COVID-19 Booster and New Vaccine Variants. Pfizer press release, Feb. 25, 2021. Accessed at www.pfizer.com/news/press-release/press-release-detail/pfizer-and-biontech-initiate-study-part-broad-development.
8. Real-World Evidence Confirms High Effectiveness of Pfizer-BioNTech COVID-19 Vaccine and Profound Public Health Impact of Vaccination One Year After Pandemic Declared. Pfizer press release, March 11, 2021. Accessed at www.pfizer.com/news/press-release/press-release-detail/real-world-evidence-confirms-high-effectiveness-pfizer.
9. Moderna Announces FDA Authorization of Moderna COVID-19 Vaccine in U.S. ModernaTX press release, Dec.19, 2020. Accessed at investors.modernatx.com/news-releases/news-release-details/moderna-announces-fda-authorization-moderna-covid-19-vaccine-us.
10. Moderna Announces Publication of Results from the Pivotal Phase 3 Trial of the Modern COVID-19 Vaccine in *The New England Journal of Medicine*. ModernaTX press release, Dec. 31, 2020. Accessed at investors.modernatx.com/news-releases/news-release-details/moderna-announces-publication-results-pivotal-phase-3-trial.
11. Moderna Announces First Participants Dosed in Study Evaluating COVID-19 Booster Vaccine Candidates. ModernaTX press release, March 10, 2021. Accessed at investors.modernatx.com/news-releases/news-release-details/moderna-announces-first-participants-dosed-study-evaluating.
12. Moderna Announces First Participants Dosed in Phase 2/3 Study of COVID-19 Vaccine Candidate in Pediatric Population. ModernaTX press release, March 16, 2021. Accessed at investors.modernatx.com/news-releases/news-release-details/moderna-announces-first-participants-dosed-phase-23-study-0.
13. Johnson & Johnson COVID-19 Vaccine Authorized by U.S. FDA for Emergency Use — First Single-Shot Vaccine in Fight Against Global Pandemic. Johnson & Johnson press release, Feb. 27, 2021. Accessed at www.jnj.com/johnson-johnson-covid-19-vaccine-authorized-by-u-s-fda-for-emergency-usefirst-single-shot-vaccine-in-fight-against-global-pandemic.
14. Johnson & Johnson Announces Single-Shot Janssen COVID-19 Vaccine Candidate Met Primary Endpoints in Interim Analysis of its Phase 3 ENSEMBLE Trial. Johnson & Johnson press release, Jan. 29, 2021. Accessed at www.jnj.com/johnson-and-johnson-announces-single-shot-janssen-covid-19-vaccine-candidate-met-primary-endpoints-in-interim-analysis-of-its-phase-3-ensemble-trial.
15. Aripaka P and Mishra M. J&J COVID-19 Vaccine Under EU Review Over Blood Clots, AstraZeneca Probe Grows. Yahoo!News, April 9, 2021. Accessed at news.yahoo.com/eu-reviews-j-j-covid-123052507.html.
16. AZD1222 US Phase III Primary Analysis Confirms Safety and Efficacy. AstraZeneca press release, March 25, 2021. Accessed at www.astrazeneca.com/content/astraz/media-centre/press-releases/2021/azd1222-us-phase-iii-primary-analysis-confirms-safety-and-efficacy.html.
17. AZD1222 US Phase III Trial Met Primary Efficacy Endpoint in Preventing COVID-19 at Interim Analysis. AstraZeneca press release, March 22, 2021. Accessed at www.astrazeneca.com/content/astraz/media-centre/press-releases/2021/astrazeneca-us-vaccine-trial-met-primary-endpoint.html.
18. Hart R. AstraZeneca Covid-19 Vaccine Has 'Clear' Link to Rare Blood Clots, European Public Health Official Says. *Forbes*, April 6, 2021. Accessed at www.forbes.com/sites/roberthart/2021/04/06/astrazeneca-covid-19-vaccine-has-clear-link-to-rare-blood-clots-european-public-health-official-says/?sh=2d3edef858a9.
19. COVID-19 Long-Acting AntiBody (LAAB) Combination AZD7442 Rapidly Advances Into Phase III Clinical Trials. AstraZeneca press release, Oct. 9, 2020. Accessed at www.astrazeneca.com/media-centre/press-releases/2020/covid-19-long-acting-antibody-laab-combination-azd7442-rapidly-advances-into-phase-iii-clinical-trials.html.
20. Novavax Confirms High Levels of Efficacy Against Original and Variant COVID-19 Strains in United Kingdom and South Africa Trials. Novavax press release, March 11, 2021. Accessed at novavax.reportablenews.com/pr/novavax-confirms-high-levels-of-efficacy-against-original-and-variant-covid-19-strains-in-united-kingdom-and-south-africa-trials.
21. Novavax Completes Enrollment of PREVENT-19, COVID-19 Vaccine Pivotal Phase 3 Trial in the United States and Mexico. Novavax press release, Feb. 22, 2021. Accessed at ir.novavax.com/news-releases/news-release-details/novavax-completes-enrollment-prevent-19-covid-19-vaccine-pivotal.
22. Novavax COVID-19 Vaccine Demonstrates 89.3% Efficacy in UK Phase 3 Trial. Novavax press release, Jan. 28, 2021. Accessed at ir.novavax.com/news-releases/news-release-details/novavax-covid-19-vaccine-demonstrates-893-efficacy-uk-phase-3.
23. Sanofi and GSK Initiate New Phase 2 Study of Their Adjuvanted Recombinant Protein-based CVOID-19 Vaccine Candidate. Sanofi press release, Feb. 22, 2021. Accessed at www.sanofi.com/en/media-room/press-releases/2021/2021-02-22-11-40-00.
24. Sanofi and Translate Bio Initiate Phase 1/2 Clinical Trial of mRNA COVID-19 Vaccine Candidate. Sanofi press release, March 12, 2021. Accessed at www.sanofi.com/en/media-room/press-releases/2021/2021-03-12-07-00-00-2191846#.
25. Gray, KJ, Bordt, EA, Atyeo, C, et al. COVID-19 Vaccine Response in Pregnant and Lactating Women: A Cohort Study. *American Journal of Obstetrics & Gynecology*, Volume 224, Issue 3, March 25, 2021. Accessed at www.ajog.org/article/S0002-9378(21)00187-3/fulltext.

DIANE L.M. COOK, B. Comm., is a Canadian freelance magazine writer with more than 330 articles published in several trade journals, including *Oilweek*, *Oilsands Review*, *Alberta Construction Magazine* and *Canadian Lawyer*.


securite
products™
Your source for
safe and effective
infection control
products
(888) 371-7551 | info@securiteproducts.com

Beyond COVID-19 vaccines, research is showing potential for new vaccines to treat several other diseases.

FOR MORE THAN 200 years, vaccines have protected people from serious and often lethal diseases that have historically hindered their freedom and productivity. And, each year, researchers further develop new, life-changing and often lifesaving vaccines that make our quality of life more sustainable. Although not a magic bullet, vaccines offer a solid protective buffer from disease that everyone can celebrate.

While COVID-19 vaccine research and production have dominated headlines and kept scientists working overtime for more than a year, other exciting and crucial vaccines in the pipeline warrant attention. Possibilities in the making for the near future include urinary tract infections, super gonorrhea, staphylococcus aureus, tick-borne encephalitis, HIV, malaria and cancer vaccines. And, while only time will tell whether the current research and trials will result in effective products, endeavors look positive.

Urinary Tract Infections (UTIs)

Scientists at Duke University Medical Center have developed a vaccine strategy to prevent UTIs. In mouse models, the strategy clears the bacteria responsible for causing UTIs and reprograms the immune system to fight off the bacteria that could cause future infections. The researchers found bladder-immunized mice fought off E. coli and eliminated all residual bladder bacteria. And, while this is significant for all, it is especially so for women who experience recurring UTIs that require repeated rounds of antibiotics. According to lead author of the study Jianxuan Wu, PhD, "The new vaccine strategy attempts to 'teach' the bladder to more effectively fight off the attacking bacteria. By administering the vaccine directly into the bladder where the residual bacteria harbor, the highly effective vaccine antigen, in combination with an adjuvant known to boost the recruitment of bacterial-clearing cells, performed better than traditional intramuscular vaccination."

Soman Abraham, PhD, senior author of the paper, states, "Although several vaccines against UTIs have been investigated in clinical trials, they have so far had limited success.… Our study describes the potential for a highly effective bladder vaccine that can not only eradicate residual bladder bacteria, but also prevent future infections. We are encouraged by these findings, and since the individual components of the vaccine have previously been shown to be safe for human use, undertaking clinical studies to validate these findings could be done relatively quickly."[1]

Super Gonorrhea

For roughly 14 years, gonorrhea has shown signs of becoming "supercharged," or resistant to antibiotics.[2] Considering how prevalent gonorrhea has become in recent years, this is dire news. The Centers for Disease Control and Prevention (CDC) estimates approximately 1.6 million new gonococcal infections

NEW VACCINES IN DEVELOPMENT

By Meredith Whitmore

occurred in the United States in 2018, and more than half occur among young people age 15 years to 24 years.[3] The World Health Organization (WHO) estimates roughly 78 million people per year are infected with gonorrhea globally. Of U.S. cases, an estimated 550,000 involve drug-resistant bacteria. Drug-resistant Neisseria gonorrhea is identified by WHO as a "priority" pathogen, and it is said to be an "urgent" public health threat that requires aggressive action by CDC.[4]

CARB-X (Combating Antibiotic-Resistant Bacteria), a Boston University-based nonprofit dedicated to accelerating antibacterial research to tackle the global rising threat of drug-resistant bacteria, has awarded Oxford University's Jenner Institute $2 million to develop a vaccine to combat the sexually transmitted gonorrhea infection. The vaccine, labeled dmGC_0817560 NOMV, consists of fluid-filled blisters from the outer surface of gonococcus. The goal is for the vaccine to induce protective immunity against gonorrhea that will prevent individuals from developing the disease and also interrupt the spread of antibiotic resistance found in gonococcal bacteria. The project is currently in lead optimization, a crucial early development phase in which the most promising preclinical vaccine candidate is identified. It is hoped a clinical trial phase will be reached by 2024. Working alongside the Oxford Vaccine Group, researchers also aim to produce an affordable vaccine for global use.[4]

Staphylococcus

CARB-X is also funding Affinivax to develop a vaccine to prevent Staphylococcus aureus (S. aureus), the most common form of staph infection, which is a serious threat to hospital patients and the immunocompromised, among others. In 2017, an estimated 119,247 S. aureus bloodstream infections, with 19,832 associated deaths, occurred in the United States.[5]

Affinivax's S. aureus vaccine candidate will be funded through Phase I testing and will use the company's multiple antigen-presenting system (MAPS) vaccine technology platform. The vaccine is designed to "induce a B-cell protective immune response to multiple highly conserved staphylococcal protein antigens."[6] It will also induce Th17 and Th1 responses against each of the protein antigens the vaccine introduces. This offers the possibility for protection not only against invasive staphylococcal infections, but also from a reduction in mucosal colonization by the bacteria, which is often the first step in pathogenesis.

Preclinical data from a lead MAPS S. aureus vaccine candidate developed at Boston Children's Hospital have shown that impacting multiple immune pathways with a single vaccine offers the potential for both robust and broad protection from S. aureus infection. In preclinical studies, the protein antigens induced B-cell responses that led to a reduction in mortality following invasive disease challenge, Th1 or Th17 responses that led to

prevention of skin abscesses and the clearance of bacteria from the gastrointestinal tract, and both B-cell and T-cell responses that contributed to the prevention of dermonecrosis.[7]

In addition to Affinivax's efforts, Cologne University Hospital and the German Center for Infection Research are partnering to develop another possible S. aureus vaccine after decades of research. Initially, they characterized several S. aureus antigens as potential vaccine candidates. With the help of monoclonal antibodies that had exhibited a protective effect in the infection model, Alexander Klimka, PhD, first author of the German study, was able to locate their binding sites, known as epitopes, in the vaccination antigens.[6] As Dr. Klimka explains, "For the S. aureus protein coproporphyinogen III oxidase (CgoX), we were able to narrow the epitope to a section comprising 12 amino acids. What makes this work special is that it has been possible with this extremely small section of CgoX to trigger a protective immune response against the S. aureus infection. Narrowing the vaccine to a small epitope of 12 amino acids constitutes an unprecedented precision of a vaccine candidate against S. aureus."

It is especially hopeful that more than 97 percent of the more than 35,000 researched clinical strains of S. aureus feature this epitope unchanged and that this vaccine candidate will therefore have a wide-ranging effect. According to Martin Krönke, PhD, director of the Institute for Medical Microbiology, Immunology and Hygiene at Cologne University Hospital, "Epitope-focused immunization represents a new quality in vaccine development because far fewer adverse immune reactions can be anticipated than those observed occasionally for the use of total proteins or even inactivated pathogens."[8]

Tick-Borne Encephalitis (TBE)

While not common in the United States, between 5,000 and 12,000 cases of TBE are reported in Europe each year alone, primarily in the Baltic states.[9] Other cases of TBE are found throughout Asia, including China and Siberia. TBE often requires hospitalization since the disease attacks the central nervous system with the potential to cause long-term neurological symptoms and death.[11]

To prevent TBE, Pfizer's vaccine, TicoVac, has been used for more than 40 years outside the U.S., and more than 160 million doses of it have been distributed since 1976. Yet, the vaccine has only very recently received U.S. Food and Drug Administration (FDA) approval for priority review, thus promoting its potential to save many American travelers thousands of dollars in medical expenses and sick time while easing fears of severe illness. The vaccine is effective in individuals 1 year of age and older. "For many years, our TBE vaccine has helped protect millions of people in Europe from this potentially serious disease," says Nanette Cocero, PhD, global president of vaccines at Pfizer Inc. "We are proud that today's U.S. FDA priority review acceptance acknowledges the potential value that our vaccine candidate can bring. If approved in the U.S., we hope this vaccine will help protect those traveling to or residing temporarily in at-risk locations, potentially including military personnel who are serving overseas."[11]

HIV

Approximately 1.2 million people in the U.S. are living with HIV today, some 14 percent of whom (one in seven) don't know it and need testing. According to the latest estimates from CDC, approximately 36,400 new HIV infections occurred in the United States in 2018. And while annual infections in the U.S. have been reduced by more than two-thirds since the height of the epidemic in the mid-1980s, CDC data indicate progress has stalled in recent years, with about 38,000 new HIV infections each year occurring between 2014 and 2018. The latest estimates indicate effective HIV prevention and treatment are not adequately reaching those who could most benefit from them, and certain groups such as men who have sex with men, transgender persons, African Americans and Hispanics/Latinos continue to be disproportionately affected.[12]

In April, a Phase I clinical trial showed a new HIV vaccine resulted in a 97 percent response rate. In the trial involving

48 adult volunteers, the vaccine successfully stimulated the production of rare immune cells needed to generate antibodies against HIV, which causes AIDS and interferes with the body's ability to fight infections. While a 97 percent response rate is exceptional, it is important to note this Phase I study represented only a small group of subjects.

According to *The European Pharmaceutical Review*, the vaccine is meant to act as an immune primer that triggers the activation of cells via a process called "germline-targeting." Its purpose is to act as the first step in a vaccine regimen that would elicit the production of a variety of broadly neutralizing antibodies. Stimulating this type of response has been pursued in HIV research for decades because it could target a wide range of HIV variants. Much like the coronavirus, the surface of HIV has proteins called spikes. Antibodies generated by a future version of this vaccine would disable them from entering human cells.

The next phase of clinical trials will begin to incorporate technology developed by Moderna, which was also used in Moderna's COVID-19 vaccine. If this vaccine is approved, it could become the first stage of a multistep strategy to combat HIV and other viral diseases.[13]

Malaria

Each year, approximately 210 million people are infected with malaria, a mosquito-borne infectious disease, and about 440,000 people die from it, the majority of whom are young children in Africa. In fact, malaria has caused four times as many deaths as COVID-19 over the past year. Each year, billions of dollars are spent on bed nets, insecticide spray and antimalarial drugs to prevent this fatal disease. But now, research shows effective vaccines against malaria could be closer than ever. In one recent clinical trial, a vaccine has prevented the disease 77 percent of the time. And, while WHO's target efficacy for malaria vaccine is greater than 75 percent, this level has never been reached until now.

A multinational group of researchers led by professor Halidou Tinto who is based in Ouagadougou, Burkina Faso, studied the new R21 malaria vaccine in 450 children and found it to be safe and effective in those aged 5 months to 17 months. In the trial, 105 of the 147 children who received a placebo contracted malaria. But, of the 292 who received a dose of the vaccine, only 81 contracted the disease. A new Phase III trial that will test the safety and efficacy of the vaccine in a much larger number of people was due to start in four African countries in late April, aiming for accelerated approvals if successful. Manufacturing of the vaccine is ongoing at the Serum Institute of India, the world's largest vaccine supplier. The vaccine uses a chimpanzee adenovirus called ChAdOx1 for delivery, a technology previously tested for use against malaria.[14]

In other malaria vaccine research, Yale scientists recently filed a patent for a malaria vaccine using a RNA platform. This new vaccine, generated by Richard Bucala and Andrew Geall is an saRNA (similar to mRNA, but more efficient) vaccine that encodes the PMIF that plasmodium normally uses to disarm our immune system. Plasmodium MIF stands for cytokine macrophage migration inhibitory factor, whose job is to regulate the movement of immune cells to the site of an infection. As Bucala and Geall discovered, immunizing patients with saRNA that encodes PMIF uses the parasite's own gene against it and confers protection. These results were also seen in a study from 2018, in which MIF was tested successfully as a treatment for malaria infection in a mouse model.[15]

Cancer

A personalized cancer vaccine, PGV-001, developed through a Mount Sinai computational vaccine pipeline platform, called OpenVax, is showing benefit, is well-tolerated and has raised no safety concerns. An investigator-initiated Phase I trial showed the vaccine could benefit patients who have various cancers that have a high recurrence rate, including lung and bladder cancer.

In the trial, the team of researchers sequenced each patient's tumor and germline DNA and tumor RNA. They then identified the tumor-specific target to help them predict whether the patient's immune system would recognize vaccine targets. OpenVax helped researchers identify and sort immunogenic targets to synthesize and use in the vaccine.

To prevent TBE, Pfizer's vaccine, TicoVac, has been used for more than 40 years outside the U.S., and more than 160 million doses of it have been distributed since 1976.

The trial participants statistically had a high chance of disease recurrence before the vaccine. Thirteen patients received the Mount Sinai vaccine: 10 had solid tumor diagnoses and three had multiple myeloma. All patients received at least seven doses of

the vaccine, and 11 patients received all doses of the vaccine. After a mean follow-up of 925 days, four patients still had no evidence of cancer, four were receiving subsequent lines of therapy, four had died, and one chose not to continue the trial. The median progression-free survival from time of surgery or transplant was 618 days. The vaccine was well-tolerated, with roughly one-third of patients developing grade 1 injection-site reactions. Among the patients without evidence of disease, diagnoses include myeloma, lung, breast and urothelial cancer.

The mRNA technology used to develop the Moderna and Pfizer vaccines also shows potential for developing a vaccine to kill cancerous tumors.

Thomas Marron, MD, PhD, assistant director for early phase and immunotherapy trials at the Tisch Cancer Institute (TCI) and assistant professor of medicine, explains, "While immunotherapy has revolutionized the treatment of cancer, the vast majority of patients do not experience a significant clinical response with such treatments." However, he says, "Cancer vaccines, which typically combine tumor-specific neoantigens with an adjuvant that primes the immune system, may be a viable treatment strategy for patients without a pre-existing antitumor response."

The vaccine was given with the immunostimulant poly-ICLC, which is "a synthetic, stabilized, double-stranded RNA capable of activating multiple innate immune receptors, making it the optimal adjuvant for inducing immune responses against tumor neoantigens," said study author Nina Bhardwaj, MD, PhD, director of the immunotherapy program and the Ward-Coleman Chair in Cancer Research at Mount Sinai's TCI.

"Our results demonstrate that the OpenVax pipeline is a viable approach to generate a safe, personalized cancer vaccine, which could potentially be used to treat a range of tumor types," said Dr. Marron.[16]

The mRNA technology used to develop the Moderna and Pfizer vaccines also shows potential for developing a vaccine to kill cancerous tumors. While there are already vaccines that prevent infection with viruses that cause cancer such as the hepatitis B vaccine that prevents some types of liver cancer and the human papillomavirus vaccine that prevents cervical cancer, the flexibility of mRNA vaccines has researchers thinking more broadly about tackling cancers not caused by viruses.

BioNTech is developing an mRNA vaccine that shows promise for people with advanced melanoma. CureVac has developed a vaccine for a specific type of lung cancer, with results from early clinical trials. And, there's promise of personalized anticancer mRNA vaccines specific to each patient's tumor that could train the immune system to fight its own individual cancer. Several research groups and companies are working on this.[17]

Coming Results

While no one can guarantee success or failure in vaccine development, advances so far are encouraging. Hopefully, 2021 and beyond will bring more peace, productive research and breakthrough developments to much-needed vaccines that will change the world. ❖

MEREDITH WHITMORE is an English professor and freelance journalist in the Northwest.

References

1. Duke University Medical Center. Goodbye UTIs: Scientists Develop Vaccine Strategy for Urinary Tract Infections: In Tests in Mice, the Vaccine Administered Directly to the Bladder Cleared Bacteria. ScienceDaily, March 1, 2021. Accessed at www.sciencedaily.com/releases/2021/03/210301151532.htm.
2. Pandi K. A 'Super Gonorrhea' Vaccine in Pipeline. Times Now New, March 31, 2021. Accessed at www.timesnownews.com/health/article/a-super-gonorrhea-vaccine-in-pipeline-team-astrazeneca-that-developed-covid-19-shots-at-work/739437.
3. Centers for Disease Control and Prevention. Gonorrhea Fact Sheet (Detailed Version). Accessed at www.cdc.gov/std/gonorrhea/stdfact-gonorrhea-detailed.htm.
4. CARB-X. CARB-X Is Funding University of Oxford's Jenner Institute to Develop a New Vaccine to Prevent Gonorrhea. Accessed at carb-x.org/carb-x-news/carb-x-is-funding-university-of-oxfords-jenner-institute-to-develop-a-new-vaccine-to-prevent-gonorrhea.
5. Centers for Disease Control and Prevention. Vital Signs: Epidemiology and Recent Trends in Methicillin-Resistant and in Methicillin-Susceptible Staphylococcus aureus Bloodstream Infections — United States, March 8, 2019. Accessed at www.cdc.gov/mmwr/volumes/68/wr/mm6809e1.htm
6. Affinivax Announces Award from CARB-X for up to $22 Million to Advance its Staphylococcus aureus MAPS Vaccine Candidate into Clinical Trials. Affinivax press release, March 9, 2021. Accessed at affinivax.com/affinivax-announces-award-from-carb-x-for-up-to-22-million-to-advance-its-staphylococcus-aureus-maps-vaccine-candidate-into-clinical-trials.
7. Zipkin M. CARB-X Places $22 Million Bet on Affinivax Staph Vaccine. BioSpace, March 9, 2021. Accessed at www.biospace.com/article/carb-x-places-22-million-bet-on-affinivax-staph-vaccine.
8. German Center for Infection Research. Hope for a Vaccination Against Staphylococcus Aureus Infections? ScienceDaily, Jan. 21, 2021. Accessed at www.sciencedaily.com/releases/2021/01/210121132118.htm.
9. World Health Organization. Tick-Borne Encephalitis in Europe. Accessed at www.euro.who.int/__data/assets/pdf_file/0010/246169/Fact-sheet-Tick-borne-encephalitis-Eng.pdf.
10. European Centre for Disease Prevention and Control. Factsheet About Tick-Borne Encephalitis. Accessed at www.ecdc.europa.eu/en/tick-borne-encephalitis/facts/factsheet.
11. U.S. FDA Accepts for Priority Review Pfizer's Application for Ticovac (Tick-Borne Encephalitis Vaccine). Pfizer press release, Feb. 23, 2021. Accessed at www.pfizer.com/news/press-release/press-release-detail/us-fda-accepts-priority-review-pfizers-application#:~:text=About%20TicoVac%E2%84%A2%20(TBE%20vaccine%2C%20whole%20virus%20inactivated)&text=The%20vaccine%20helps%20provide%20protection,Siberian%20and%20Far%20Eastern%20subtypes.
12. HIV.gov. U.S. Statistics. Accessed at www.hiv.gov/hiv-basics/overview/data-and-trends/statistics#:~:text=Fast%20Facts%201%20Approximately%201.2%20million%20people%20in,diagnosis%20in%20the%20U.S.%20...%20More%20items...%20.
13. Midkiff S. An HIV Vaccine Is Getting Promising Results. Yahoo!Life, April 12, 2021. Accessed at www.yahoo.com/lifestyle/hiv-vaccine-based-moderna-covid-220148354.html.
14. Hill A. A Global Team of Researchers Has Developed a Malaria Vaccine with "Unprecedented" Effectiveness. Quartz Africa, April 25, 2021. Accessed at qz.com/africa/2001084/new-malaria-vaccine-has-landmark-results-in-burkina-faso-trial.
15. Willman M. Researchers Create an Effective RNA Vaccine for Malaria. Massive Science, April 29, 2021. Accessed at massivesci.com/articles/malaria-mrna-vaccine-covid-biotech-patents.
16. American Association for Cancer Research. Personalized Cancer Vaccine Given After Adjuvant Therapy Safe, Shows Early Efficacy in Multiple Tumor Types, April 10, 2021. Accessed at www.aacr.org/about-the-aacr/newsroom/news-releases/personalized-cancer-vaccine-given-after-adjuvant-therapy-safe-shows-early-efficacy-in-multiple-tumor-types.
17. 3 mRNA Vaccines Researchers Are Working On (That Aren't COVID). The Conversation, April 14, 2021. Accessed at theconversation.com/3-mrna-vaccines-researchers-are-working-on-that-arent-covid-157858.

FFF enterprises
Helping Healthcare Care®

Going BEYOND DISTRIBUTION

by reinforcing the security and efficiency of the pharmaceutical supply chain.

FFF Enterprises is dedicated to improving and safeguarding specialty pharmaceuticals through Guaranteed Channel Integrity® — our commitment to purchase only from manufacturers and ship only to licensed clinicians. And with the addition of our RightNow Inventory™ product management solutions, now the critical-care products your patients need, are already there.

Products You Need, When You Need Them.

- Adult Vaccines
- Albumin/Plasma Protein Fraction
- Ancillaries
- Antithrombin
- BioSurgical
- Coagulation Factor
- Controlled Substances
- Essential Medicines
- Hyperimmune Globulin
- Immune Globulin
- Influenza Vaccines
- Oncology
- Ophthalmology
- Orthopedic
- Pediatric Vaccines
- Pharmaceuticals

RESPONSIBLE DISTRIBUTION

Controlled Volume Measures™

Ensuring healthcare systems are prepared with adequate supplies of essential medications, especially during times of crisis or shortage.

FAIR PRICING

Costparency™

Our pledge to reject deceptive pricing tactics and only provide the best available lowest cost for products and services.

WORRY-FREE PRODUCT TECHNOLOGY

RightNow Inventory™

Inventory management system continuously monitors critical-care pharmaceuticals to minimize product waste and maximize patient safety.

(800) 843-7477 | FFFenterprises.com
Biosupply.FFFenterprises.com | MyFluVaccine.com

Rethinking Childhood Vaccine Schedules

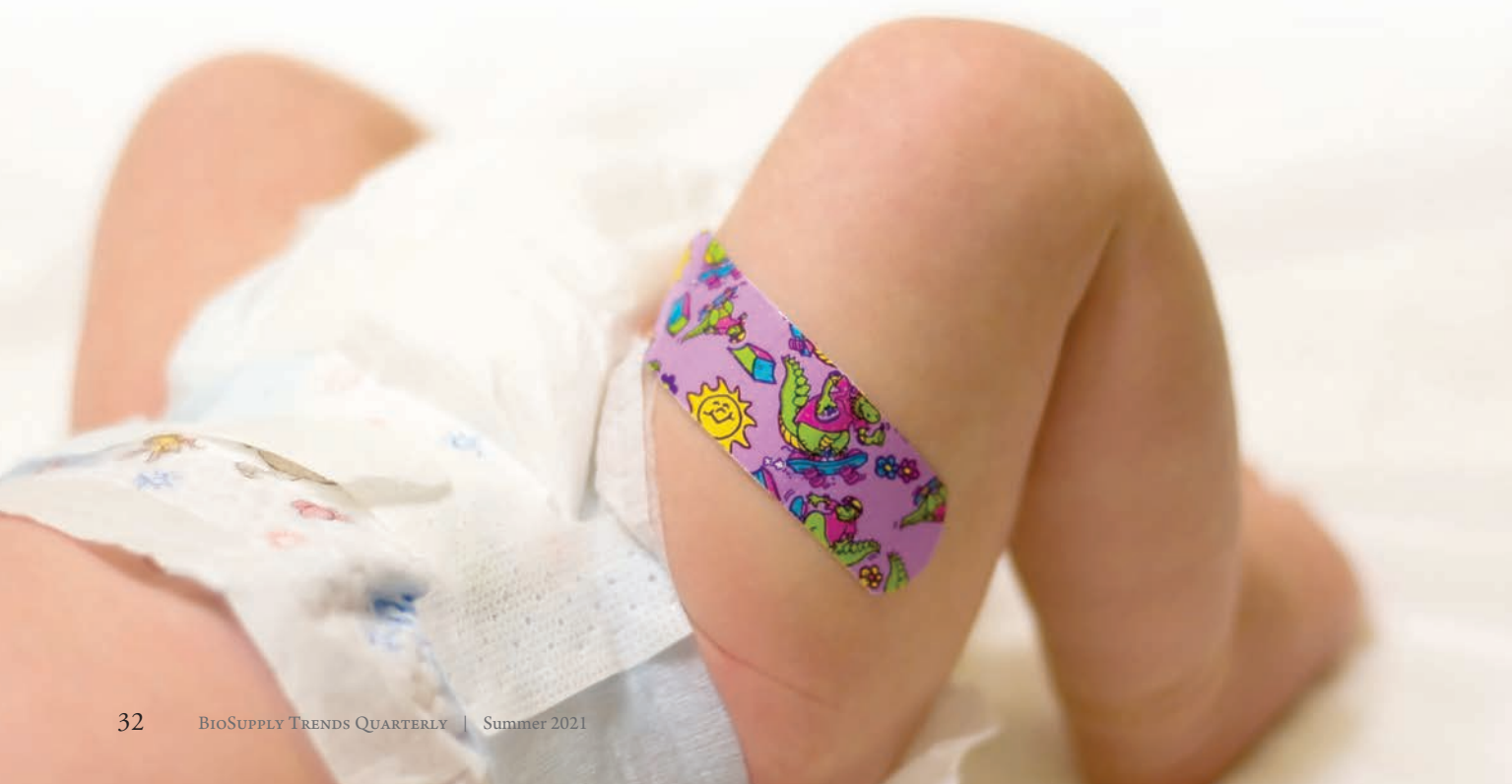
A growing demographic of "vaccine-hesitant" parents is driving demand for an alternative vaccine schedule that differs from CDC guidelines. But is it safe?

By Trudie Mitschang

CHILDHOOD IMMUNIZATIONS have had an enormous impact when it comes to protecting infants and school-age children from vaccine-preventable diseases. However, a shift in public opinion linked to the anti-vaccine movement has raised questions about vaccine efficacy and safety, particularly among parents of young children. Despite the well-documented health benefits of routine childhood immunization, the past few decades have seen a notable increase in the numbers of parents who request an alternative vaccination schedule that differs from the childhood vaccination schedule recommended by the Centers for Disease Control and Prevention (CDC).[1]

In a national telephone survey of 1,500 parents of children ages 6 months to 23 months, approximately three percent of respondents had refused all vaccines and 19.4 percent had refused or delayed at least one of the recommended childhood vaccines. Another study conducted in a metropolitan area of Oregon reported rates of alternative immunization schedule usage have increased nearly fourfold in recent years, and in some parts of the country the use of "personal belief exemptions" from vaccinations has grown to rates in excess of five percent of the school-aged population.[2]

This changing tide of opinions on childhood vaccines often puts pediatricians on the frontlines of educating wary, vaccine-hesitant parents. The American Academy of Pediatrics (AAP) revealed 75 percent of pediatricians it surveyed have encountered vaccine hesitancy. Physicians state the most common parental concerns were the belief that vaccines are unnecessary and the fear that they cause autism.[2] Clearly, the increasing frequency of vaccine resistance or even refusal indicates there are significant barriers to overcome to ensure the next generation of children are immunized and protected from vaccine-preventable diseases.



Understanding Vaccine Hesitancy

The term vaccine hesitancy has emerged in recent years to help depolarize the "pro" versus "anti" vaccination rhetoric that has made a once benign topic so contentious. Vaccine hesitancy is characterized by the World Health Organization (WHO) as "a behavior influenced by a number of factors, including issues of confidence (do not trust a vaccine or a provider), complacency (do not perceive a need for a vaccine or do not value the vaccine) and convenience (access)."[3]

According to WHO, those who are vaccine-hesitant may display varying degrees of indecision about specific vaccines or about vaccinations in general. In some cases, vaccine-hesitant individuals may accept vaccines overall, but remain concerned about them, or they may refuse or delay some vaccines but accept others.

WHO acknowledges the reasons people choose to delay or refuse vaccinations are complex. For example, in the United States, vaccine-preventable diseases have been significantly reduced through the use of antibiotics, improved medical technology, better access to healthcare and routine vaccinations, which has resulted in an entire generation who do not perceive vaccine-preventable diseases as a threat.[2]

One of the biggest drivers of vaccine hesitancy among parents of young children revolves around perceptions of risk. Fears of detrimental side effects are a prime reason parents refuse traditional vaccine schedules. And, although it is more widely publicized now, the misinformation surrounding vaccine risk is not new. In the 1970s, for example, the diphtheria, tetanus and pertussis (DTaP) vaccine was alleged to cause high fevers, seizures and even permanent brain damage, causing some parents to reject the vaccine for their children. Although large epidemiological studies eventually proved the safety of the vaccine, many parents remained fearful and skeptical. Similarly, concerns about the measles, mumps and rubella (MMR) vaccine leading to autism is a narrative that surfaced in the 1990s. Although widely debunked in multiple scientific studies, suspicions and fears linger.[3]

There are also parents who do not question the safety of a specific vaccine, but rather are wary of multiple vaccines administered simultaneously, either as several shots or as combined vaccines given with one shot. To alleviate concerns, these parents may opt to delay some vaccines in a manner that conflicts with CDC guidelines. "Some parents feel that giving so many antigens in the same visit is not healthy for the child," says Duke Global Health Institute faculty member Lavanya Vasudevan. "The perception is that we're overburdening the child's immune system, but we're actually constantly exposed to pathogens and antigens that stimulate our immune system in our daily lives."[4]

In explaining the shift in perspectives on an alternative vaccine schedule, Jeffrey Paul Baker, MD, PhD, a professor of pediatrics at Duke University School of Medicine, notes that spacing out vaccines feels like a compromise to parents who struggle to navigate the complex web of vaccine information they access online. "You're trying to decide what's right for your child. You go onto the Internet. You read different things. You try to decide whom to trust, but the sides of the argument can get pretty complicated," he says. "One response is to pick what seems like an in-between, middle-of-the-road approach."[4]

But, Dr. Baker notes, this approach can be problematic, not just because it puts children at risk of getting vaccine-preventable diseases during the delay, but also because it's difficult for physicians and parents to keep track of alternate vaccine schedules. And, when it comes to vaccine protection, timing is everything.

This changing tide of opinions on childhood vaccines often puts pediatricians on the frontlines when it comes to educating wary, vaccine-hesitant parents.

Does One Size Fit All?

To make sure children receive their vaccines on time, CDC, AAP and the Academy of Family Physicians have established a recommended schedule of shots, with specific vaccines administered in a regular cadence from birth through 15 months. In a nutshell, the schedule recommends a total of 26 shots in the first 15 months of life,[5] with a schedule of additional doses spaced out through age 12 years. The recommended vaccine schedule immunizes children from:

- Whooping cough (pertussis)
- Diphtheria
- Tetanus
- Mumps
- Measles
- Rubella
- Rotavirus
- Polio
- Hepatitis B

For parents who perceive that the recommended vaccine schedule seems excessive, AAP offers guidance on when a more flexible approach is acceptable in its FAQ response sheet: "The schedule is considered the ideal schedule for healthy children, but there may be exceptions. For example, your child might not receive certain vaccines if he or she has allergies to an ingredient in the vaccine, or if they have a weakened immune system due to illness, a chronic condition or another medical treatment. Sometimes a shot needs to be delayed for a short time, and sometimes not given at all."[6]

But what about an approach that simply spreads the vaccines out over a longer period of time? Is there really any downside to taking things more slowly? AAP covers this question as well: "The recommended schedule is designed to work best with a child's immune system at certain ages and at specific times. There is no research to show that a child would be equally protected against diseases with a very different schedule. Also, there is no scientific reason why spreading out the shots would be safer. But we do know that any length of time without immunizations is a time without protection."[6]

With so many varying opinions, both sides of the argument agree that parents hoping to make the right decision for their child should pursue due diligence by educating themselves on the topic.

Of course, not all pediatricians agree with AAP. In 2007, California-based pediatrician Robert Sears published *The Vaccine Book: Making the Right Decision for Your Child*, which seeks to address the biggest concerns of parents who are looking for a middle ground between the official CDC vaccine schedule and not getting any vaccines at all. Dr. Sears' book includes an alternative vaccine schedule, which allows for fewer shots at each visit and sometimes pushes back specific vaccines for months or even years after the official schedule's recommendations. "My main worry about [CDC's] schedule is that there really hasn't been enough research on the various chemicals and ingredients in many vaccines to prove that they are 100 percent safe," he says. "It has also been my experience that giving five or six vaccines at a time can increase the likelihood of a severe reaction."

Dr. Sears recommends an alternative vaccine schedule that spreads the shots out over a longer period of time, up to age 6 years. He also recommends not giving kids more than two vaccines at a time, and his schedule changes the order of vaccines, prioritizing what Dr. Sears believes are the most crucial vaccines, based on how common and severe the diseases are. The advantage, he says, is that his alternative schedule won't overwhelm young immune systems, but it still provides complete vaccine protection. "If some of the theoretical problems with vaccines are real, this schedule circumvents most of them," he explains. "If the problems aren't real, then the only drawback is the extra time, effort and cost for the additional doctor's office visits."[7]

Arguments Against the "Al-la-Carte" Approach

A 2009 article in *Pediatrics*, the official journal of AAP, takes issue with Dr. Sears' vaccine advice, stating that he misrepresents data about vaccine science and essentially misinforms parents. "He believes that parents' fears should be indulged by offering alternative schedules, not countered by scientific studies, and he fails to explain that good science is the only way to determine whether a vaccine causes a particular adverse event," the article reads. "A vaccine either causes a problem or it does not."[8]

AAP also says the required extra visits to the pediatrician (five for the CDC's schedule versus a dozen for Dr. Sears' schedule) will discourage compliance and leave children potentially vulnerable to vaccine-preventable diseases.

With so many varying opinions, both sides of the argument agree that parents hoping to make the right decision for their child should pursue due diligence by educating themselves on the topic. Dr. Sears' website states: "Before proceeding with the full regular vaccine schedule, I encourage parents to become fully informed about each disease and vaccine so they can understand the safest way to vaccinate their children."[7]

Likewise, Children's Hospital of Philadelphia encourages parents to think through their vaccine decisions thoroughly before committing to a schedule that contradicts CDC guidelines. An article on their website states: "Vaccines are added to the schedule based on when an infant is likely to be most susceptible to the disease. During the first few months of life, babies are somewhat protected from infectious diseases by maternal antibodies present in their bloodstream at birth or in their mother's milk. However, protection afforded by maternal antibodies wanes during the first year of life and is somewhat variable."[9]

The article goes on to say that since the length of protection

and robustness of the maternal response cannot be predicted, eliciting the infant's own immune response before the maternal response wanes is the most conservative approach when it comes to vaccinations.

According to nurse practitioner Erin Gennocro, APRN, of Weiss Pediatric Care, one of the biggest concerns she hears from vaccine-hesitant parents is that there are too many vaccines given at a time, which may overload their child's immune system. Those fears, she says, are unfounded. "If a parent has concerns about the safety of vaccines, instead of focusing on vaccinations themselves, parents need to focus on learning about the disease."[9]

To Delay or Not to Delay: Comparing the Numbers

On the delayed vaccine schedule, children are immunized against eight diseases by 15 months of age. They will not be immunized against measles, rubella, chickenpox, Hepatitis A or B. Children on this delayed schedule receive a total of 17 shots and visit the doctor's office nine times, nearly twice as many visits as compared to the CDC schedule.

By comparison, when a child is vaccinated by the CDC's recommended schedule, they are immunized against 14 diseases by age 2 years. With this schedule, babies see their doctor five times in the first 15 months of life and receive as many as 18 shots (when using combination vaccines), or as many as 26 shots when using individual antigens.[10]

So where does that leave us? A study published in March 2020 in *Pediatrics* found one-third of parents in the United States are now choosing to delay vaccinations for their young children. The findings, it says, are consistent with several trends reported by American doctors in recent years, including parental requests to limit the number of vaccinations given at each visit, increased need for a strong and consistent physician recommendation for vaccination, and potentially wavering vaccine confidence. "The findings in this study reaffirm that deviations from the recommended immunization schedule, whether as the result of parents following an alternate schedule or other factors, result in many children remaining out-of-date for an extended period of time," say the study's authors.

The study's authors concluded that although a majority of U.S. children adhere to a recommended vaccination schedule for early childhood immunizations, adherence differs by key sociodemographic characteristics, and future research should focus on identifying the parent actions and circumstances that increase the likelihood of deviating from the recommended schedule. Interventions, they say, should target both providers (to ensure all eligible vaccines are offered) and parents (to ensure all eligible vaccines are received), ultimately contributing to greater numbers of U.S. children who are protected and up-to-date on all recommended childhood immunizations.[11] ❖

References

1. Dempsey AF, Schaffer S, Singer D, et al. Alternative Vaccination Schedule Preferences Among Parents of Young Children. *Pediatrics*, November 2011, 128 (5) 848-856. Accessed at pediatrics.aappublications.org/content/128/5/848?ijkey=1d23c32105722cf686a30c152e4fcddf17f3b865&keytype2=tf_ipsecsha.
2. Edwards K, Hackell JM, and the Committee on Infectious Diseases, the Committee on Practice and Ambulatory Medicine. Countering Vaccine Hesitancy. *Pediatrics,* September 2016, 138 (3) e20162146. Accessed at pediatrics.aappublications.org/content/138/3/e20162146.
3. World Health Organization. SAGE Working Group Dealing with Vaccine Hesitancy (March 2012 to November 2014). Accessed at www.who.int/immunization/sage/sage_wg_vaccine_hesitancy_apr12/en.
4. Gallagher S. The Many Faces of Vaccine Hesitancy. Duke Global Health Institute, April 21, 2019. Accessed at globalhealth.duke.edu/news/many-faces-vaccine-hesitancy .
5. Centers for Disease Control and Prevention. 2021 Recommended Vaccinations for Infants and Children (Birth Through 6 Years) Parent-Friendly Version. Accessed at www.cdc.gov/vaccines/schedules/easy-to-read/child-easyread.html.
6. American Academy of Pediatrics. The Childhood Immunization Schedule: Why Is It Like That? Accessed at www.aap.org/en-us/advocacy-and-policy/Documents/Vaccineschedule.pdf.
7. Lenneman F. Understanding Childhood Vaccine Options. Accessed at www.oprah.com/health/dr-sears-alternative-and-cdcs-childhood-vaccine-schedules/all#ixzz6sdmDQgvb.
8. Offit PA and Moser CA. The Problem with Dr. Bob's Alternative Vaccine Schedule. *Pediatrics*, January 2009, 123 (1) e164-e169. Accessed at pediatrics.aappublications.org/content/123/1/e164.
9. Children's Hospital of Philadelphia. Vaccine Schedule: Altering the Schedule. Accessed at www.chop.edu/centers-programs/vaccine-education-center/vaccine-schedule/altering-the-schedule .
10. Immunize for Good. Fact or Fiction: Delayed Schedule. Accessed at www.immunizeforgood.com/fact-or-fiction/delayed-schedule.
11. Hargreaves AL, Nowak G, Frew PM, et al. Adherence to Timely Vaccinations in the United States. *Pediatrics,* March 2020, 145 (3) e20190783. Accessed at pediatrics.aappublications.org/content/145/3/e20190783.

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

Myths and Facts: Childhood Vaccines

Despite proof of lifesaving benefits of vaccines, parental hesitancy to immunizing their children is often fueled by the plethora of myths surrounding vaccine safety.

By Ronale Tucker Rhodes, MS

IMMUNIZATIONS ARE one of the success stories of modern medicine, having eradicated smallpox, slashed child mortality rates and prevented lifelong disabilities. And as new viruses continue to threaten the public, protecting against these and long-standing illnesses will continue to be important in the decades and centuries ahead.

Since the first vaccine was developed to prevent smallpox in the late 1700s, scientific advances have led to many more vaccine discoveries, especially during the first half of the 20th century when vaccines that protected against whooping cough (1914), diphtheria (1926), tetanus (1938), influenza (1945) and mumps (1948) came about. Thereafter, new manufacturing techniques allowed for vaccine production to be scaled up, setting global vaccination and disease eradication efforts in motion. In the second half of the 20th century, other vaccines were added to the list of those that could protect against viruses such as polio in 1955, measles in 1963 and rubella in 1969.[1]

While both children and adults need vaccinations, the childhood vaccination schedule is vitally important. As vaccination rates rise, the entire population benefits from "herd immunity," which occurs when a large part (typically between 83 percent and 94 percent) of the population is immune to a specific disease. Also, when children are vaccinated, they help prevent the spread of serious illnesses and protect vulnerable groups such as older adults and people with compromised immune systems.

Today, the Centers for Disease Control and Prevention's (CDC) Advisory Committee on Immunization Practices (ACIP) recommends children receive 10 vaccines in various doses from birth to 15 months old and another nine vaccines (some of which are the same) in various doses between 18 months and 18 years of age (Tables 1 and 2).[2] For children aged birth to 24 months, ACIP recommends vaccination against 14 potentially serious illnesses (Table 3).[3] Fortunately, vaccination rates among children in the U.S. have remained relatively high. According to CDC, national coverage by age 24 months was greater than 90 percent for three or more doses of poliovirus vaccine, three or more doses of hepatitis B vaccine, more than one dose of varicella vaccine and more than one dose of measles, mumps and rubella vaccine (MMR), although MMR coverage was less than 90 percent in 14 states. Coverage with two or more doses of influenza vaccine was higher for children born during 2016-2017 (58.1 percent) than for those born during 2014-2015 (53.8 percent), but it was lowest among all vaccines studied. Only 1.2 percent of children had received no vaccinations by age 24 months.[4]

However, researchers from Kaiser Permanente who evaluated the uptake and coverage for recommended vaccines among nearly one million children aged birth through 18 years since the outbreak of COVID-19 found vaccine coverage continued to decline even after uptake recovered among certain age cohorts, causing the number of unvaccinated children to grow. "When vaccination rates decline, we worry about an increase in vaccine-preventable diseases that can be harmful to children," said Bradley Ackerson, MD, a Kaiser Permanente South Bay Medical Center pediatric infectious disease specialist and an investigator with the Kaiser Permanente Southern California Department of Research & Evaluation's vaccine team. "Also, we know there has been a reduction in childhood vaccinations worldwide, and as COVID-19 restrictions are relaxed, there will be an increased risk of outbreaks due to vaccine-preventable diseases among children returning from outside the United States, unless children here are vaccinated."[5]

Table 1. CDC Recommended Vaccinations Birth to 15 Months

Vaccine	Birth	1 mo	2 mos	4 mos	6 mos	9 mos	12 mos	15 mos
Hepatitis B (HepB)	1st dose	←2nd dose→			←3rd dose→			
Rotavirus (RV) RV1 (2-dose series); RV5 (3-dose series)			1st dose	2nd dose	See notes			
Diphtheria, tetanus, & acellular pertussis (DTaP: <7 yrs)			1st dose	2nd dose	3rd dose			←4th dose→
Haemophilus influenzae type b (Hib)			1st dose	2nd dose	See notes		←3rd or 4th dose, See notes→	
Pneumococcal conjugate (PCV13)			1st dose	2nd dose	3rd dose		←4th dose→	
Inactivated poliovirus (IPV: <18 yrs)			1st dose	2nd dose	←3rd dose→			
Influenza (IIV)					Annual vaccination 1 or 2 doses			
or Influenza (LAIV4)								
Measles, mumps, rubella (MMR)					See notes		←1st dose→	
Varicella (VAR)							←1st dose→	
Hepatitis A (HepA)					See notes		←2-dose series, See notes→	
Tetanus, diphtheria, & acellular pertussis (Tdap: ≥7 yrs)								
Human papillomavirus (HPV)								
Meningococcal (MenACWY-D ≥9 mos, MenACWY-CRM ≥2 mos, MenACWY-TT ≥2years)			See notes					
Meningococcal B (MenB)								
Pneumococcal polysaccharide (PPSV23)								

Source: Centers for Disease Control and Prevention. To see notes, go to www.cdc.gov/vaccines/schedules/hcp/imz/child-adolescent.html#birth-15

Regrettably, COVID-19 is only one reason many parents are reluctant to vaccinate their children. Rather, a growing number of parents are refusing to vaccinate due to persistent myths that have circulated for decades.

Separating Myth from Fact

Myth: Vaccine-preventable diseases are just part of childhood.

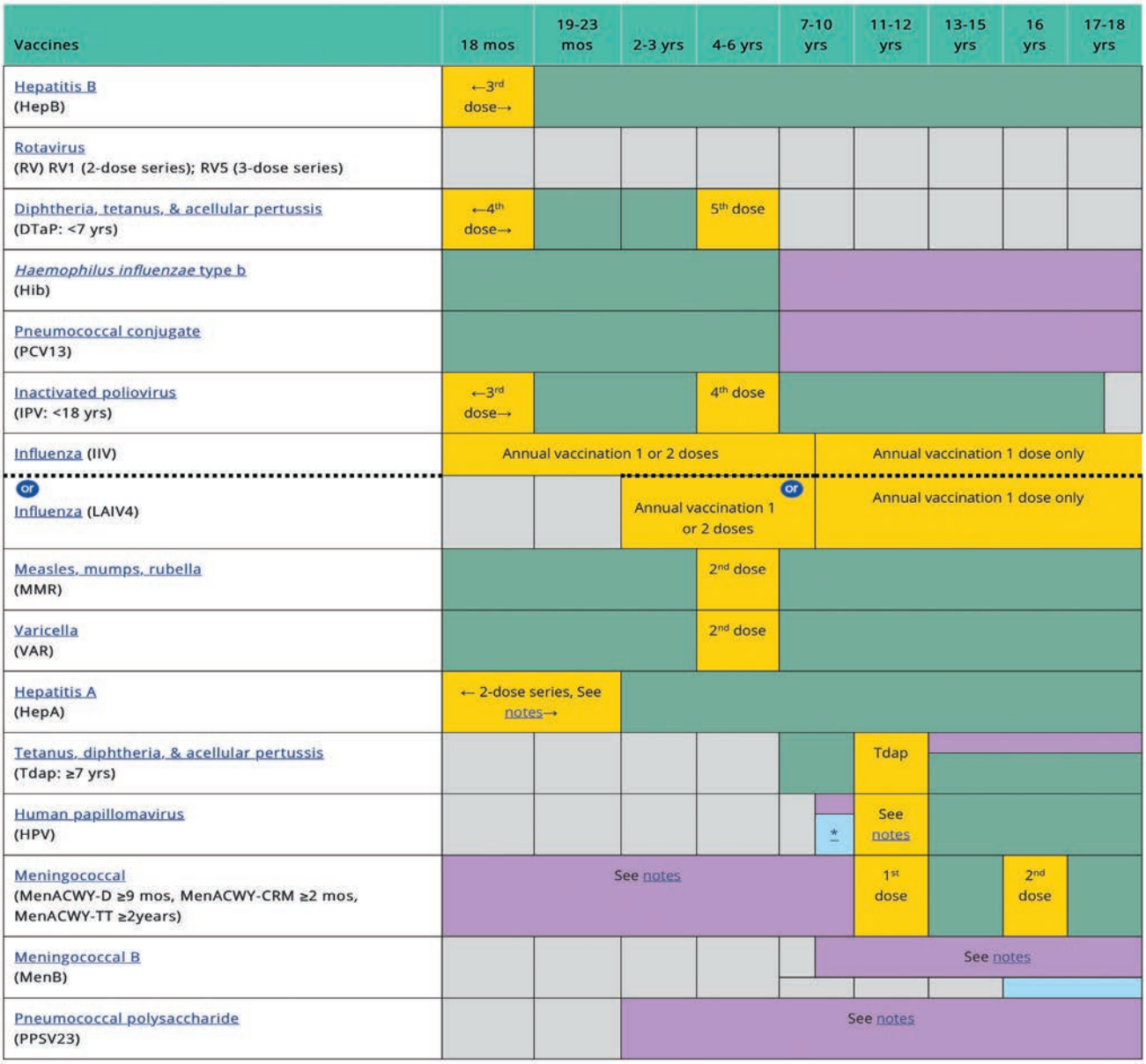
Fact: Vaccine-preventable diseases can be serious and lethal. While natural immunity — catching a disease and getting sick — results in a stronger immunity to a disease than a vaccination, the dangers far outweigh the benefits. In contrast, serious complications can be avoided through immunization. For example, if a child contracts measles, he or she would face a one in 500 chance of death from symptoms, whereas the number of people who have had severe allergic reactions from an MMR vaccine is less than one in a million.[6]

Consider these other statistics: About one person in 10 infected with diphtheria dies; approximately 100 people die each year from liver failure caused by hepatitis A; prior to the Haemophilus influenzae type b (Hib) vaccine, one child in four suffered permanent brain damage, and one in 20 died; prior to the MMR vaccine, about 48,000 children were hospitalized each year, 7,000 had seizures, about 1,000 suffered permanent brain damage and about 450 died; and prior to the rotavirus vaccine, the disease caused more than 400,000 doctor visits, 200,000 emergency room visits, up to 70,000 hospitalizations and 20 to 60 deaths each year.[7]

Myth: Since vaccine-preventable diseases have been virtually eliminated, children really don't need to be vaccinated.

Fact: It's true vaccines have reduced most vaccine-preventable

Table 2. CDC Recommended Vaccinations 18 Months to 18 Years



Source: Centers for Disease Control and Prevention. To see notes, go to www.cdc.gov/vaccines/schedules/hcp/imz/child-adolescent.html#birth-15

diseases to very low levels in many countries. However, some of them are still prevalent and even epidemic in other parts of the world, and travelers can unknowingly bring these diseases into any country. So, without vaccinations, these diseases can quickly spread throughout the population. In fact, relatively few cases of a disease could quickly become tens or hundreds of thousands of cases without protection from vaccines.

And, importantly, there are people who cannot be vaccinated, including infants, pregnant women and immunocompromised people, and their only hope of protection is for people around them to be protected so they don't spread the disease. This is known as herd immunity; for each infectious disease, a certain percentage of people in an area must be vaccinated to keep outbreaks at bay. This means children who can be vaccinated but aren't are more likely to get sick if an outbreak occurs.[9]

Myth: Vaccines contain harmful ingredients.

Fact: Vaccines contain ingredients that allow the products to be safely administered. These ingredients include thimerosal (a mercury-containing compound), formaldehyde and aluminum. And, while these chemicals are toxic to the human body in certain levels, only trace amounts of them are used in U.S. Food and Drug Administration (FDA)-approved vaccines. On the other hand, people are naturally exposed to mercury in milk, seafood and contact lens solutions; formaldehyde is produced at higher rates by people's own metabolic systems, and they are exposed to it through automobile exhaust, household

products and furnishings, paint and felt-tip markers, and some health products; and the amount of aluminum in vaccines (approximately 0.125 mg to 0.625 mg per dose) is much less than what the average person consumes in a day (30 mg to 50 mg) in foods, drinking water and medicines.

In fact, the type of mercury used in vaccines, ethylmercury, is quite different from methylmercury, which is highly toxic and found in some seafood. In addition, ethylmercury leaves the body within a few days and poses no danger to children. In addition, many vaccines now produce single-dose vials, which has greatly decreased the use of thimerosal in vaccines. It's also important to note that not all vaccines contain aluminum.[6,9,10]

Myth: Vaccines can cause harmful side effects and even death.

Fact: All vaccines can cause side effects, but rarely are they serious, and so few deaths are attributed to vaccines that it's hard to assess the risk. Most adverse effects are mild such as pain, swelling or redness where the shot was given, mild fever, chills, feeling tired, headache, muscle and joint aches and fainting. Most of these side effects are a sign the body is starting to build immunity (protection) against a disease. Serious side effects occur in only one per thousands to one per millions of doses. Signs of a severe allergic reaction can include difficulty breathing, swelling of the face and throat, a fast heartbeat, a bad rash all over the body, and dizziness and weakness. See Table 4 for the possible side effects of the routinely recommended vaccines.[11,12]

Myth: Vaccines cause autism and sudden infant death syndrome (SIDS).

Fact: Science hasn't yet determined the cause of autism and SIDS. The association between vaccines and these diseases is due to diagnoses made during the same age range that children are receiving their routine immunizations. And, while that may point to a causal connection, the logic is faulty. For instance, bread could be associated with car crashes since most drivers who crash cars could probably be shown to have eaten bread within the past 24 hours.[8,10] However, bread played no part in causing the crashes.

Fear was generated about the association between vaccines and autism after a study was published in *The Lancet* in 1998 that purported to link autism to the MMR vaccine, which children typically receive at 12 months and 4 years of age. But that study was ultimately debunked and retracted, and an overwhelming majority of experts agree vaccines don't cause autism. In fact, Andrew Wakefield, the lead author of the discredited study, was forbidden to practice medicine in the United Kingdom in part because he falsified the study's findings. Since that study was published, numerous other studies have found no connection between autism and vaccines.[9]

The DTaP vaccine is often linked to the cause of SIDS. But, similar to autism, most SIDS deaths occur during the age range when three shots of DTaP are given. And, when a number of well-controlled studies were conducted during the 1980s, investigators nearly unanimously found the numbers of SIDS deaths temporarily associated with DTaP vaccination was within the range expected to occur by chance, which means the SIDS deaths would have occurred even if no vaccinations had been given. And, in several of the studies, children who had recently received the DTaP vaccine were less likely to die from SIDS.[8]

Table 3. Vaccine-Preventable Diseases and the Vaccines That Prevent Them

Disease	Vaccine
Chickenpox	Varicella
Diphtheria	DTaP*
Haemophilus influenzae type b (Hib)	Hib
Hepatitis A	HepA
Hepatitis B	HepB
Influenza (flu)	Flu
Measles	MMR**
Mumps	MMR**
Pertussis	DTaP*
Polio	IPV
Pneumococcal	PCV13
Rotavirus	RV
Rubella	MMR**
Tetanus	DTaP*

** DTaP combines protection against diphtheria, tetanus and pertussis*
*** MMR combines protection against measles, mumps and rubella*

Myth: Children can get the disease from the vaccine.

Fact: Yes and no, depending on the type of vaccine. Only vaccines made from live viruses or bacteria carry any risk of transmitting a disease, and even then, the risk is very small and symptoms are generally very mild. Most vaccines are inactivated (killed) vaccines, so it isn't possible to contract the diseases from them.

There are several types of vaccines:[13]

- Attenuated vaccines are made from live viruses and live bacteria that have been weakened, usually by repeated replication in a lab. And, because these organisms are alive, it's possible for them to cause a very mild form of the disease, but this happens very rarely. Doctors are cautious about giving live vaccines to

Table 4. Possible Side Effects to Routinely Recommended Vaccines[10]

Vaccine	Common	More Serious	Very Rare
DTaP	Soreness or swelling where the shot is given, fever, fussiness, feeling tired, loss of appetite and vomiting	Seizures, nonstop crying for 3 hours or more or high fever (over 105°F)	Long-term seizures, coma, lowered consciousness or permanent brain damage
Hepatitis A	Soreness or swelling where the shot is given, fever, fussiness, feeling tired and loss of appetite	Allergic reaction	
Hepatitis B	Soreness where the shot is given or fever	Allergic reaction	
Hib	Redness, warmth and swelling where the shot is given, and fever	Allergic reaction	
Influenza	Soreness, redness and swelling where the shot is given, fever, muscle aches and headache	Small increased risk of Guillain-Barré syndrome, seizure caused by fever (when given along with pneumococcal vaccine [PCV13] and/or DTaP vaccine)	
MMR	Soreness, redness or rash where the shot is given, rash all over the body, and fever or swelling of the glands in the cheeks or neck	Seizures (often associated with fever), temporary pain and stiffness in the joints (mostly in teenage or adult women), pneumonia, swelling of the brain and/or spinal cord covering, or temporary low platelet count that can cause unusual bleeding or bruising	In people with serious immune system problems, an infection that may be life-threatening
MMRV	Soreness, redness or rash where the shot is given, fever or swelling of the glands in the cheeks or neck, seizures (often associated with fever)	Pneumonia, swelling of the brain and/or spinal cord covering, or temporary low platelet count that can cause unusual bleeding or bruising	In people with serious immune system problems, an infection that may be life-threatening
Pneumococcal	Redness, swelling, pain or tenderness where the shot is given, and fever, loss of appetite, fussiness (irritability), feeling tired, headache and chills		
Polio	A sore spot with redness, swelling or pain where the shot is given		
Rotavirus	Irritability or mild, temporary diarrhea or vomiting	Intussusception (a type of bowel blockage)	
Varicella	Sore arm from the injection, fever, or redness or rash where the shot is given	Pneumonia, infection of the brain and/or spinal cord covering, or seizures (often associated with fever)	In people with serious immune system problems, an infection that may be life-threatening

anyone with a weakened immune system such as someone being treated for cancer. Four vaccines are made from live viruses: chickenpox (varicella), MMR, rotavirus and influenza (only nasal spray). None of the other vaccines on the immunization schedule, including the polio shot, are made from live viruses or bacteria. The oral polio vaccine is made from live viruses, but it is no longer administered in the United States.

• Inactivated or killed vaccines are made from bacteria or viruses that have been killed by heat or chemicals. These vaccines can't cause the disease because the infectious agent can't reproduce. However, the dead virus or bacteria is still enough to stimulate the body's immune system. The flu shot and injected polio vaccine are inactivated vaccines.

• Component, or fractional or subunit, vaccines are inactivated vaccines made from just a part of the virus or bacteria. For the Hib vaccine, for example, part of the coating of the bacteria is introduced, which stimulates immunity against the bacteria. The hepatitis A and B vaccines and the pneumococcal vaccine are also component vaccines. Partial viruses and bacteria are unable to reproduce or cause disease.

• Toxoid vaccines contain a toxin or chemical made by the virus or bacteria, so they protect against the harmful effects of infection rather than the actual infection. These vaccines include the DTaP vaccine. Toxoid vaccines do not contain the virus or bacteria and cannot cause disease.

Most illnesses reported after receiving vaccines are due to the vaccines' triggering an immune response to the disease, helping the body fight off and remember the germ so it can attack it if the germ invades again.

Myth: "Hot lots" of vaccines are associated with more adverse events and deaths.

Fact: Hot lots of vaccines are based on the presumption that the more reports of adverse events a vaccine lot is associated with, the more dangerous the vaccine is in that lot. But this is misleading because, for one, an adverse event report following vaccination doesn't mean the vaccine caused the event. Statistically, a certain number of serious illnesses and deaths are expected to occur by chance among children recently vaccinated. Secondly, vaccine lots are not the same. Vaccine lot sizes may vary from several hundred thousand doses to several million, and some are in distribution much longer than others. A larger lot or one in distribution for longer will be associated with more adverse events. And, more coincidental deaths are associated with vaccines given in infancy because the background death rates for children are highest during the first year of life. Therefore, reviewing published lists of hot lots won't help parents identify the best or worst vaccines.[8]

Myth: The proximity of multiple childhood vaccines increases the risk of harmful side effects and overloads children's immune systems.

Fact: Recommendations for the age at which vaccines are administered are influenced by age-specific risks for disease, complications and responses to vaccination, and potential interference with the immune response by passively transferred maternal antibodies. Vaccines are generally recommended for members of the youngest age group at risk for experiencing the disease for which vaccine efficacy and safety have been demonstrated.[1,4]

CDC recommends vaccination providers adhere to recommended vaccination schedules to provide optimal protection. While some parents worry having so many vaccines in a short period early in life (children can get as many as 29 shots by age 6 years) can overwhelm their children's immune systems, most experts agree it is unwise to space out vaccines since CDC bases the schedule on disease risks and vaccine effectiveness at specific ages and how the vaccines interact with each other. For instance, the MMR vaccine is timed so children receive it when they lose residual immunity from their mothers. Whereas an unvaccinated child has a nine in 10 chance of contracting measles if he or she walks into a room an infected person has recently left, a child with both recommended doses of MMR has only a 3 percent likelihood of developing measles.[9]

Myth: Any risk concerning vaccines is too risky to justify vaccination.

Fact: The benefits of vaccines are far greater than any risks. Without vaccines, there would be more cases of disease and more serious side effects and deaths. For example, according to an analysis of the benefit and risk of DTaP immunization, without an immunization program in the U.S., pertussis cases could increase 71-fold and deaths due to pertussis could increase fourfold. A child is far more likely to be seriously injured by one of these diseases than by any vaccine.[8]

Dispelling the Myths Now

Public health successes have been directly attributable to vaccines for the past 200 years. Yet, despite the proven lifesaving benefits of preventing diseases rather than treating them after they occur, challenges remain due to parental resistance. Reasons for vaccine resistance include individual rights and public health stances toward vaccination, religious standpoints and vaccine objections, and suspicion and mistrust of vaccines — all of which pose a significant public health problem. But suspicion and mistrust can be overcome. Candid communications between parents and clinicians can play a powerful role in whether parents choose to have their children vaccinated. And, it hinges on dispelling the plethora of myths surrounding vaccines. ❖

References

1. World Economic Forum. A Brief History of Vaccines and How They Changed the World, April 9, 2020. Accessed at www.weforum.org/agenda/2020/04/how-vaccines-changed-the-world.
2. Centers for Disease Control and Prevention. Table 1. Recommended Child and Adolescent Immunization Schedule for Ages 18 Years or Younger, United States, 2021. Accessed at www.cdc.gov/vaccines/schedules/hcp/imz/child-adolescent.html#birth-15.
3. Centers for Disease Control and Prevention. 2021 Recommended Vaccinations for Infants and Children (Birth Through 6 Years) Parent-Friendly Version. Accessed at www.cdc.gov/vaccines/schedules/easy-to-read/child-easyread.html#table-child.
4. Centers for Disease Control and Prevention. Vaccination Coverage by Age 24 Months Among Children Born in 2016 and 2017 — National Immunization Survey-Child, United States, 2017-2019. Accessed at www.cdc.gov/mmwr/volumes/69/wr/mm6942a1.htm.
5. Open Access Government. Child Vaccination Rates Have Declined Since COVID-19 Outbreak, April 16, 2021. Accessed at www.openaccessgovernment.org/child-vaccination-rates-have-declined-since-covid-19-outbreak/108701.
6. Public Health. Vaccine Myths Debunked. Accessed at www.publichealth.org/public-awareness/understanding-vaccines/vaccine-myths-debunked.
7. Centers for Disease Control and Prevention. Vaccine-Preventable Diseases and Childhood Vaccines, Part 1. Accessed at www.cdc.gov/vaccines/parents/tools/parents-guide/downloads/parents-guide-part1.pdf.
8. World Health Organization. Vaccines and Immunization: Myths and Misconceptions, Oct. 19, 2020. Accessed at www.who.int/news-room/q-a-detail/vaccines-and-immunization-myths-and-misconceptions.
9. Roberts C. Myths and Facts About Vaccines for Children. Consumer Reports, Feb. 12, 2019. Accessed at www.consumerreports.org/vaccines/myths-and-facts-about-vaccines-for-children.
10. American Academy of Allergy, Asthma & Immunology. Vaccines: The Myths and the Facts. Accessed at www.aaaai.org/conditions-and-treatments/library/allergy-library/vaccine-myth-fact.
11. Centers for Disease Control and Prevention. Possible Side Effects from Vaccines. Accessed at www.cdc.gov/vaccines/vac-gen/side-effects.htm.
12. Vaccines.gov. Vaccine Side Effects. Accessed at www.vaccines.gov/basics/safety/side_effects.
13. Dubinsky D. Is It True That a Vaccine Can Cause the Disease It Was Meant to Protect Against? BabyCenter, Aug. 2, 2020. Accessed at www.babycenter.com/health/doctor-visits-and-vaccines/is-it-true-that-a-vaccine-can-cause-the-disease-it-was-meant_10310768.
14. Centers for Disease Control and Prevention. Timing and Spacing of Immunobiologics, Nov. 17, 2020. Accessed at www.cdc.gov/vaccines/hcp/acip-recs/general-recs/timing.html.

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

Against the Storm: High-Dose IVIG as an Immunoregulatory Treatment Strategy for Severe COVID-19

By Keith Berman, MPH, MBA

MASS VACCINATION, mask-wearing and social distancing have helped to sharply reduce new U.S. COVID-19 cases from its peak of nearly 250,000 per day in early January. Still, as of early May — 15 months since the beginning of this pandemic — an average of 50,000 new COVID-19 cases were being reported on an average daily basis, with more than 5,000 new hospitalizations per day.[1] And while use of supplemental oxygen, dexamethasone and measures ranging from prone positioning to extracorporeal membrane oxygenation have helped to reduce case mortality, between 10 percent and 15 percent of hospitalized COVID-19 patients continue to succumb to acute respiratory distress syndrome (ARDS), sepsis, multiorgan failure and other disease complications.

We now know that SARS-CoV-2 neutralizing monoclonal antibody preparations and as little as a single unit of high-titer COVID-19 convalescent plasma[2] are effective in reducing the likelihood of severe disease and hospitalization when administered to mildly ill at-risk COVID-19 patients within a few days following first symptoms. Yet in most hospitalized patients, neither these antibody-based treatments nor antiviral drugs such as remdesivir and lopinavir have been shown to reduce mortality or the need for ICU admission or mechanical ventilation.[3]

Numerous clinical and laboratory studies of the immunopathology of severe viral respiratory tract diseases provide the answer to this seeming paradox. Nonsevere respiratory viral infections generally induce physiologic release of inflammatory cytokines and chemokines by endothelial cells, mononuclear macrophages, dendritic cells and natural killer cells, which helps recruit leukocytes and plasma proteins to the infection site to help combat it.[4] But excessive production of proinflammatory cytokines is commonly triggered in patients with severe acute viral pneumonias — most notably severe influenza and the SARS and MERS coronaviruses — resulting in a runaway hyperinflammatory process. Untreated, this "cytokine release syndrome" or "cytokine storm" can rapidly lead to a constellation of severe sequelae, including ARDS, multiorgan failure, disseminated intravascular coagulation, vasodilatory shock and death.[5,6]

The Unique Challenge of Cytokine Storm

Cytokine storm in COVID-19 patients is characterized by a sudden acute increase in circulating levels of numerous proinflammatory cytokines, growth factors and chemokines, notably including IL-6, IL-1, GM-CSF, TNF and IFN-γ. Also elevated are nonspecific markers of inflammation such as C-reactive protein (CRP), whose levels have been found to correlate with severity. COVID-19 patients with cytokine storm typically have pneumonia that can quickly progress to ARDS and multiorgan failure. It is now apparent that the rapid

clinical deterioration seen in hospitalized patients with SARS-CoV-2 infection is most often the result of injury caused by the exaggerated proinflammatory immune dysregulation, not direct viral damage.[7]

Elevated IL-6 levels, the most frequently reported indicator of cytokine storm in hospitalized COVID-19 patients, have been strongly associated with shorter survival.[8] Accordingly, numerous studies have investigated tocilizumab,* a licensed recombinant anti-IL-6 receptor monoclonal antibody, as a potential treatment. Conflicting results have been reported thus far, with some studies documenting meaningful survival or other clinical benefits with use of tocilizumab,[9,10,11,12] while others show no benefit at all, or even the possibility of increased mortality risk.[13,14,15,16,17]

These tocilizumab trials varied considerably in size, study design and subject illness severity; early trials in particular were underpowered to detect differences in death rates between groups, or excluded critically ill patients.[18] After consideration of all the data, the National Institutes of Health's (NIH) COVID-19 Treatment Guidelines Panel has recommended the use of tocilizumab in combination with dexamethasone solely for certain hospitalized COVID-19 patients exhibiting rapid respiratory decompensation within the first three days of admission.[10] As more evidence comes in, it is becoming increasingly apparent that this highly targeted IL-6 inhibitor offers limited benefit against the multifactorial cytokine storm phenomenon that accounts for severe COVID-19-related complications, ICU admissions and deaths.

Other narrowly targeted immunomodulators continue to be evaluated as potential treatments to limit cytokine storm-mediated injury, among which are interferons, IL-1 inhibitors and Janus kinase inhibitors, including baricitinib. With the exception of baricitinib in combination with remdesivir, which are narrowly approved under an emergency use authorization in hospitalized patients for whom corticosteroids cannot be used, there are currently insufficient data to support their use.[20]

The physiologic inflammatory process that helps clear infections involves a vastly complex interplay between cytokines and cellular immune elements, as does the pathophysiologic process leading to overproduction of inflammatory cytokines in response to a severe, overwhelming or prolonged infection. Thus, it should come as no surprise that highly specific immunomodulators are of modest or no value as means to downmodulate cytokine storm and resulting organ damage.

Multimodal Immunoregulatory Actions Make IVIG Unique

While there may be no "magic bullet" to treat cytokine storm, one widely used immunomodulatory agent in particular — polyclonal intravenous immune globulin (IVIG) purified from healthy donor plasma — is distinguished by the simple fact that it is anything but a narrowly targeted treatment. More than two decades ago, immunologists first proposed the therapeutic effect of IVIG may be related to its demonstrated ability to reduce levels of multiple proinflammatory cytokines.[21,22] While the mechanisms involved remain largely obscure, the potent immunomodulatory activity of high doses of these human IgG concentrates is exploited to treat diverse autoimmune inflammatory disorders ranging from chronic inflammatory demyelinating polyneuropathy to dermatomyositis to Kawasaki syndrome.

Past studies suggest immunoregulatory IgG antibodies address the pathophysiology of cytokine storm in COVID-19 patients through a number of mechanisms, including:

- Direct F(ab)'2-mediated neutralization of inflammatory cytokines, chemokines and complement fragments;
- Inhibition of innate immune cell activation and secretion of proinflammatory mediators;
- Scavenging of complement fragments and inhibition of complement system activation;
- Functional blockade of Fc receptors required to activate immune complexes; and
- Saturation of endothelial FcRn, resulting in increased clearance of pathogenic IgG and other antibodies.

In addition to attenuating excessive production of pathogenic inflammatory cytokines and chemokines, immunoregulatory IgG in standard IVIG may also prevent tissue injury by downregulating overactive mononuclear macrophages, dendritic cells, natural killer cells and lymphocytes.[23]

Expanding Evidence of IVIG Efficacy vs. Cytokine Storm

Prompted by this understanding, Chinese physicians at the Wuhan Third Hospital were the first to report on the use of IVIG to treat COVID-19

** Results from a large placebo-controlled trial of another licensed anti-IL-6 receptor monoclonal antibody, sarilumab, did not support a clinical benefit in hospitalized COVID-19 patients receiving supplemental oxygen. (Lescure FX, Honda H, Fowler RA, et al. Sarilumab in patients admitted to hospital with severe or critical COVID-19: a randomised, double-blind, placebo-controlled, phase 3 trial.* Lancet Respir Med *2021).*

Table 1. Effects of IVIG Dose and Timing on Mortality in 174 Hospitalized COVID-19 Patients with Severe or Critical Illness[25]

Outcome measure	IVIG > 15 g per day (N = 74)	IVIG ≤ 15 g per day (N = 100)	P-value
28-day mortality	5 (7%)	17 (17%)	0.044
60-day mortality	9 (12%)	24 (24%)	0.049

Outcome measure	IVIG started ≤ 7 days after admission (N = 158)	IVIG started > 7 days after admission (N = 16)	P-value
28-day mortality	19 (12%)	3 (19%)	0.441
60-day mortality	26 (17%)	7 (44%)	0.008

in 58 critically ill adult patients with pneumonia admitted to the ICU between January and February 2020.[24] In addition to supplemental oxygen, antiviral agents, antibiotics and other standard therapies, patients received 20 grams of IVIG daily when the absolute lymphocyte count fell to less than 0.5 x 10^9 per liter. In a post-hoc analysis, patients were divided into two groups: those first given IVIG ≤48 hours after admission (n=30) and those first started on IVIG >48 hours after admission (n=28). IVIG administration was delayed by just over one day in the >48 hour group compared to the ≤48 hour group (2.7 vs. 1.6 days).

Altogether, 23 of the 58 patients died within 28 days of admission: seven (23.3 percent) in the ≤48 hour and 16 in the >48 hour IVIG treatment groups. Survivors received their first IVIG infusion a day earlier (2.26 ± 0.20 days) than nonsurvivors (3.39 ± 0.32 days). Both hospital and ICU length of stay was about one-third shorter in the ≤48 hour-treated group. Consistent with the significant difference in mortality, just two patients started on IVIG within the first 48 hours (6.7 percent) required mechanical ventilation, compared to nine patients who started on IVIG more than 48 hours after admission (32.1 percent). While not a proof of IVIG efficacy against COVID-19 cytokine storm, these findings do imply that — if administered early enough — IVIG could potentially blunt possibly lethal hyperinflammatory injury to lungs and other vital organs.

A second larger retrospective study in 325 Chinese COVID-19 patients examined IVIG use compared to nonuse during that same time frame in early 2020.[25] After adjusting for multiple variables (e.g., age, comorbidities, CRP level and baseline clinical status), there was a significant difference in 28-day mortality favoring patients who received IVIG. And strikingly, in the cohort of 174 patients who received IVIG, both higher dose and earlier administration were associated with significantly lower mortality (Table 1).

But further analysis revealed two additional patterns:

1) A survival benefit of IVIG therapy was apparent only in the subset of patients with critical-stage disease with a high risk of death: 28-day mortality was sharply lower in critical-stage patients given IVIG versus those not given IVIG (27 percent vs. 53 percent; P = 0.009) but was not different for patients classified as "severe" with a low mortality risk (3 percent in both IVIG and non-IVIG subgroups).

2) In critical-stage patients, higher IVIG dose was associated with lower mortality: 27 percent for the subgroup receiving more than 15 grams per day, compared with 68 percent for patients receiving ≤15 grams per day.

A third early retrospective study sought to answer whether IVIG therapy might offer clinical benefit in nonsevere hospitalized COVID-19 patients without signs of respiratory distress (respiratory rate <30/minute, pulse oxygen saturation >93 percent at rest) or organ failure.[26] Using propensity score matching, outcomes in 45 nonsevere COVID-19 patients treated with IVIG were compared with outcomes in 90 untreated nonsevere patients. There were no significant differences in any outcomes, including risk of progression to severe disease (6.6 percent vs. 3.3 percent), deaths (1 vs. 0) and length of hospital stay (14 days vs. 13 days). "No benefit was observed with IVIG treatment beyond standard therapy in the treatment of nonsevere patients with COVID-19," the investigators concluded. This finding is entirely consistent with hypotheses that the immunoregulatory properties of IVIG

Table 2. Published Studies Documenting Health Outcomes of High-Dose IVIG in COVID-19 Patients with Severe Disease*

Author	Study design (n)	IVIG dosage regimen	Findings
Herth 2020[31]	Case series (n=12)	0.5 to 2.0 g/kg/day for 1-4 days	All patients (on mechanical ventilation) survived and were discharged. Length of stay shorter in 5 patients receiving IVIG 4 days after admission than 7 others who started on IVIG > 7 days after admission (7 vs. 33 days; p = 0.03).
Mohtadi 2020[32]	Case series (n = 5)	0.3 to 0.5 g/kg/day for 5 days	Oxygen saturation improved in all 5 patients, who had previously been unresponsive to other treatments. All recovered and were discharged.
Muccioli 2020[33]	Case series (n = 5)	0.4 g/kg/day for 4-6 days	IVIG therapy started a mean of 29.8 days after encephalopathy onset led to complete electroclinical recovery in all 5 patients.
Esen 2021[34]	Retrospective two-cohort study (n = 93)	30 g/day for 5 days	Overall survival 61% in IVIG + standard intensive care (SIC) group and 38% in the SIC only group after controlling for baseline imbalances.
Raman 2021[35]	Open-label randomized trial (n = 100)	0.4 g/kg/day for 5 days	IVIG + standard of care (SOC) group had shorter hospitalization (7.7 vs 17.5 days), fewer days to normalization of oxygen saturation (2.5 vs. 4.8 days) and weaning from mechanical ventilation (2.4 vs. 4.5 days).
Gharebaghi[36]	Randomized, placebo-controlled trial (n = 59)	20 g/day for 3 days	In-hospital mortality was significantly lower in IVIG group than control group (20.0% vs. 48.3%). Multivariate regression analysis indicated that IVIG significantly impacted mortality.

*See also studies referenced in text (references 24-26)

can be expected to benefit only more severely affected patients experiencing or at imminent risk for cytokine storm and consequent immune-mediated lung and other organ injury.

A number of case series, case-control studies and small randomized, controlled trials (Table 2) have subsequently added to the body of evidence suggesting administration of high-dose IVIG therapy can importantly reduce mortality, reduce serious morbidity and shorten recovery time in severely ill hospitalized COVID-19 patients.

Next: Answers from Definitive IVIG/COVID-19 Trials

Intent on delineating whether and in whom high-dose IVIG can be beneficial, several major IVIG manufacturers have organized prospective clinical trials that randomize severely ill COVID-19 patients to receive high-dose IVIG or placebo infusions, or alternatively randomly assign patients to high-dose IVIG plus standard medical treatment (SMT) or SMT only.

Subject enrollment has been completed for a multinational Phase III, fully-blinded randomized trial sponsored by Octapharma to compare high-dose Octagam 10% IVIG against placebo in 208 hospitalized COVID-19 patients with severe disease progression.[27] Active treatment group subjects received 2 g/kg of IVIG in four divided doses over four consecutive days. A six-point clinical status scale that includes hospital discharge, increasing levels of hospital treatment intensity and death will be applied to assess the proportion of subjects who improve or are stabilized at days 7 and 14. Results of this trial are anticipated shortly.

Grifols is coordinating two Phase II pilot studies targeting different COVID-19 patient populations. Ten participating centers in Spain very recently completed enrollment and randomization of 100 patients to receive SMT plus 2 g/kg of Flebogamma DIF IVIG over four days to five days, or SMT alone.[28] Primary outcome measures include 1) death or ICU admission and 2) dependency on high-flow oxygen devices or mechanical ventilation at day 29.

Fifteen U.S. sites participating in the second Grifols-sponsored study are currently enrolling 100 COVID-19 patients requiring ICU admission, who are being randomized to receive either 2 g/kg of GAMUNEX-C plus SMT, or SMT alone.[29] Among the key outcome measures, all through day 29, are all-cause mortality, time to ICU discharge, duration of any oxygen use and change from baseline in Sequential Organ Failure Assessment (SOFA) score. Subject enrollment is projected to be completed this summer.**

While we await the findings of these trials, the NIH COVID-19 Treatment Guidelines Panel continues to recommend against the use of IVIG to treat COVID-19. At this writing, that NIH panel recommendation had not been updated since July 2020.[30] Some clinicians battling to save their severely ill COVID-19 patients with clear indicators of cytokine storm might nevertheless find themselves contemplating IVIG therapy given 1) the volume and consistency of evidence supporting the efficacy of IVIG that has yet to be examined by this NIH panel, 2) an absence of serious safety signals with administration of high-dose IVIG and 3) the paucity of proven available treatments.

IVIG has a long history of being overlooked as a prospective treatment for immune-mediated disorders; many for which IVIG is now commonly used weren't discovered until decades after its initial approval in 1981 for the treatment of immune thrombocytopenic purpura. Forty years later, new clinical applications continue to emerge for what is, in essence, a concentrate of the normal humoral immune system. And given the highly encouraging published evidence thus far, it would be foolish to bet against IVIG as a potentially important new treatment for patients with severe COVID-19. ❖

References

1. U.S. Centers for Disease Control and Prevention. New Admissions of Patients with Confirmed COVID-19, United States. Accessed 4/23/2021 at www.cdc.gov/coronavirus/2019-ncov/covid-data/covidview/index.html.
2. Libster R, Marc G, Wappner D, et al. Early high-titer plasma therapy to prevent severe Covid-19 in older adults. *N Engl J Med* 2020 Feb 18;384(7):610-8.
3. WHO Solidarity Trial Consortium. Repurposed antiviral drugs for Covid-19 — Interim WHO Solidarity trial results. *N Engl J Med* 2021 Feb 11;384(6):497-511.
4. Ragab D, Eldin HS, Taeimah M, et al. The COVID-19 cytokine storm; what we know so far. *Front Immunol* 2020 Jun 16;1446.
5. Liu X, Cao W and Li T. High-dose intravenous immunoglobulins in the treatment of severe acute viral pneumonias: the known mechanisms and clinical effects. *Front Immunol* 2020 Jul 14;11:1660.
6. Fajgenbum DC, June CH. Cytokine storm. *N Engl J Med* 2020 Dec 3;383:2255-73.
7. Newton AH, Cardani A and Braciale TJ. The host immune response in respiratory virus infection: balancing virus clearance and immunopathology. *Semin Immunopathol* 2016;38:471-82.
8. Del Valle DM, Kim-Schulze S, Huang H-H, et al. An inflammatory cytokine signature predicts COVID-19 severity and survival. *Nat Med* 2020;26:1636-43.
9. RECOVERY Collaborative Group, Horby PW, et al. Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): preliminary results of a randomised, controlled, open-label, platform trial. *medRxiv* 2021 Feb 11. Available at www.medrxiv.org/content/10.1101/2021.02.11.21249258v1.
10. REMAP-CAP Investigators, Gordon AC, et al. Interleukin-6 receptor antagonists in critically ill patients with COVID-19. *New Engl J Med* Apr 22;384(16):1491-1502.
11. Gupta S, Wang W, Hayek SS, et al. Association between early treatment with tocilizumab and mortality among critically ill patients with COVID-19. *JAMA Intern Med* 2021 Jan 1;181(1):41-51.
12. Xu X, Han M, Li T, et al. Effective treatment of severe COVID-19 patients with tocilizumab. *Proc Natl Acad Sci USA* 2020 May 19;117(20):10970-5.
13. Rosas IO, Brau N, Waters M, et al. Tocilizumab in hospitalized patients with severe COVID-19 pneumonia. *N Engl J Med* 2021 Apr 22;384(16):1403-16.
14. Veiga VC, Prats J, Farias D, et al. Effect of tocilizumab on clinical outcomes at 15 days in patients with severe or critical coronavirus disease 2019: randomised controlled trial. *BMJ* Jan 20;372:n84.
15. Salama C, Han J, Yau L, et al. Tocilizumab in patients hospitalized with Covid-19 pneumonia. *N Engl J Med* 2021 Jan 7;384(1);20-30.
16. Stone JH, Frigault MJ, Serling-Boyd NJ, et al. Efficacy of tocilizumab in patients hospitalized with Covid-19. *N Engl J Med* 2020 Dec 10;383(24)2333-44.
17. Salvarani C, Dolci G, Massari M, et al. Effect of tocilizumab vs standard care on clinical worsening in patients hospitalized with COVID-19 pneumonia: a randomized clinical trial. *JAMA Intern Med* 2021 Jan 1;181(1):24-31.
18. Gupta S, Leaf DE. Tocilizumab in COVID-19: some clarity amid controversy. *Lancet* 2021 May 1;397(10285):P1599-1601.
19. National Institutes of Health. COVID-19 Treatment Guidelines: Interleukin-6 Inhibitors (April 21, 2021). Available at www.covid19treatmentguidelines.nih.gov/immunomodulators/interleukin-6-inhibitors.
20. National Institutes of Health. COVID-19 Treatment Guidelines: Immunomodulators Under Evaluation for the Treatment of COVID-19 (April 21, 2021). Available at www.covid19treatmentguidelines.nih.gov/immunomodulators.
21. Abe X, Horiuchi A, Miyake M, et al. Anti-cytokine nature of natural human immunoglobulin: one possible mechanism of the clinical effect of IVIG therapy. *Immunol Rev* 1994;139:5-19.
22. Sharief, MK, Ingram, DA, Swash M, et al. Immunoglobulin reduces circulating proinflammatory cytokines in Guillain-Barré syndrome. *Neurology* 1999;52(9):1833-8.
23. Liu X, Cao W and Li T. High-dose intravenous immunoglobulins in the treatment of severe acute viral pneumonia: the known mechanisms and clinical effects. *Fron Immunol* 2020 Jul 14;11:1660.
24. Xie Y, Cao S, Dong H, et al. Effect of regular intravenous immunoglobulin therapy on prognosis of severe pneumonia in patients with COVID-19 [ltr]. *J Infect* 2020 Apr 10 [Epub].
25. Shao Z, Feng Y, Zhong L, et al. Clinical efficacy of intravenous immunoglobulin therapy in critically ill patients with COVID-19: a multicenter retrospective cohort study. *Clin Transl Immunology* 2020 Oct 14;9(10):e1192.
26. Huang C, Fei L, Li W, et al. Efficacy evaluation of intravenous immunoglobulin in non-severe patients with COVID-19: a retrospective cohort study based on propensity score matching. *Int J Infect Dis* 2021;105:525-31.
27. Octapharma. Octagam 10% Therapy in COVID-19 Patients with Severe Disease (NCT04400058). ClinicalTrials.gov: clinicaltrials.gov/ct2/show/NCT04400058?term=Octapharma&cond=COVID-19&draw=2&rank=2.
28. Instituto Grifols, S.A. Study to Evaluate the Safety and Efficacy of High dose IVIG in Hospitalized Participants with Coronavirus Disease (COVID-19) (NCT04432324). ClinicalTrials.gov: clinicaltrials.gov/ct2/show/NCT04432324?term=IVIG%2C+Grifols&cond=covid-19&draw=2&rank=1.
29. Grifols Therapeutics LLC. Study to Evaluate the Safety and Efficacy of High Dose IVIG Plus Standard Medical Treatment (SMT) Versus SMT Alone in Participants in ICU with COVID-19 (NCT04480424). ClinicalTrials.gov: clinicaltrials.gov/ct2/show/NCT04480424?term=IVIG%2C+Grifols&cond=covid-19&draw=2&rank=2.
30. National Institutes of Health. COVID-19 Treatment Guidelines: Immunoglobulins — Non-SARS-CoV-2 Specific (July 17, 2020). Available at www.covid19treatmentguidelines.nih.gov/immunomodulators/ivig---non-sars-cov-2.
31. Herth F, Sakoulas G, Haddad F. Use of intravenous immunoglobulin (Privigen or Octagam) for the treatment of COVID-19: retrospective case series. *Respiration* 2020;99(12):1145-53.
32. Mohtadi N, Ghaysouri A, Shirazi S, et al. Recovery of severely ill COVID-19 patients by intravenous immunoglobulin (IVIG) treatment: a case series. *Virology* 2020 Sep;548:1-5.
33. Muccioli L, Pensato U, Bernabè G, et al. Intravenous immunoglobulin therapy in COVID-19-related encephalopathy. *J Neurol* 2020 Oct 8:1-5.
34. Esen F, Özcan PE, Orhun G, et al. Effects of adjunct treatment with intravenous immunoglobulins on the course of severe COVID-19: results from a retrospective cohort study. *Curr Med Res Opin* 2021 Apr;37(4):543-8.
35. Raman RS, Barge VB, Kuman DA, et al. A phase II safety and efficacy study on prognosis of moderate pneumonia in COVID-19 patients with regular intravenous immunoglobulin therapy. *JID* 2021. Epub Feb 15.
36. Gharebaghi N, Nejadrahim R, Mousavi SJ, et al. The use of intravenous immunoglobulin gamma for the treatment of severe COVID-19: a randomized placebo-controlled double-blind clinical trial. *BMC Infect Dis* 2020 Oct 21;20(1):786.

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.

*** A French IVIG manufacturer, LFB, is also sponsoring a double-blinded, randomized Phase III trial of 2 g/kg of IVIG in 138 patients with COVID-19-related ARDS who newly require mechanical ventilation (NCT04350580).*

MINIBAR®
A subsidiary of FFF Enterprises, Inc.

Schedule a live demo or webinar today:
(855) 544-2122

- **Ready to provide your patients treatment NOW**
- **Improve the quality care of your patients**
- **Improve the patient experience; no waiting or rescheduling of treatment**

Through our solution...

- Forward-Deployed Inventory (FDI)
- Reduce financial acquisition and inventory costs
- Invoice on dispense
- Right-sized inventory
- Effortless and seamless technology
- Enhanced data granularity
- State-of-the-art temperature control and monitoring
- Full suite of smart management tools

... and much more!

FFF enterprises
Helping Healthcare Care®

info@MinibarRx.com | MinibarRx.com

Jewel Rogers, who was 41 years old when she contracted a serious case of influenza that left her hospitalized for three months, advises others to do their research before deciding not to get a flu vaccine.

Influenza: *A Patient's Perspective*

By Trudie Mitschang

IN 2016, Jewel Rogers was a healthy 41-year-old wife, mother and grandmother. But all of that changed in late March of that year, when Jewel and her husband, Jason, both became ill. She was diagnosed with acute bronchitis and given antibiotics at her local urgent care, but two days later Jewel's symptoms worsened, and she made the wise decision to head to the emergency room. When her influenza (flu) test came back negative, she was once again diagnosed with bronchitis and sent home. Unfortunately, over the course of the next few days, her condition deteriorated, and she returned to the hospital for further tests. "This time, I was diagnosed with pneumonia and admitted to the hospital for treatment due to low oxygen saturation, fever and difficulty breathing," she says. "After two days of standard treatment, I was admitted to the intensive care unit (ICU) for additional care."

Based on her worsening condition in the ICU, the medical staff quickly decided Jewel needed to be transferred to a larger medical facility. The next day, she was transferred to Fort Wayne Lutheran Hospital in Indiana. There, the medical team determined it would be best to place her in a rotating hospital bed that would put her in a prone position to improve her ability to breathe. As her health continued to fail, she was eventually intubated and put into a medically induced coma. That was when the medical team at Fort Wayne transferred her to the ICU at University of Michigan as a last-resort effort to save her life. The staff told Jewel's stunned family that despite their lifesaving efforts, she was not likely to survive.

Once she was admitted at the University of Michigan, a sample from Jewel's lungs showed she had in fact been suffering from complications of H1N1 influenza. This was the first time she was accurately diagnosed with flu. Over the course of the next few weeks, Jewel received numerous interventions that included inserting a tracheostomy tube through her windpipe to improve her breathing. Slowly, over the course of the next seven weeks, Jewel turned a corner and her prognosis began to improve. "My memory of my time at the University of Michigan Medical Center is very vague," says Jewel. "I really only remember the last week of being there, and those memories aren't even clear. At one point close to the end of my stay, I recall having a team of nurses who took me outside for a short time. They said it would do me good to see the sun and the tulips that were blooming. I also remember them getting me ready for the four-hour transport to the rehabilitation facility that would put me thankfully closer to my home and family."

Once at the rehabilitation facility, Jewel began a rigorous four-week program of physical and occupational therapy that was needed to help her regain enough strength to perform even the most basic daily tasks. "It was a very slow process," she says. "After being sedated for so long, I was very weak. I had to gain enough strength back in my legs to stand on my own and then to take steps. It was a chore to even dress myself or brush my teeth. While I was there, I remained on high-flow oxygen, and I remember I had to have help just to pull myself up in bed."

Ten weeks after it was initially placed, Jewel had her tracheostomy tube removed, and a short time later, she was finally discharged to go home. But her health problems were far from over. Today, Jewel still suffers complications from her horrific bout with the flu. She often experiences shortness of breath and requires oxygen at night when lying in bed. Additionally, after spending three months in five different hospitals, she feels anxious around people who are visibly ill, and she is uncomfortable in small, enclosed spaces. "My health is 90 percent better, but vigorous exercise is still very taxing on my lungs," Jewel says. "My lungs remain damaged and may never be back to what they were prior to my sickness."

After surviving the flu and its severe complications, Jewel and her family have become advocates of the annual flu vaccination. "Prior to this experience, I had no clue just how serious the flu could be. I did not get the flu vaccine. I just didn't think it was important," says Jewel. "My advice to someone who remains unsure about the flu vaccine is do your research. Talk to those who have experienced it first-hand. Talk to their families to see what it was like for them when they thought they could lose their loved one." ❖

Influenza: *A Physician's Perspective*

Dr. Andrew Eisenberg is a family physician who is dedicated to promoting influenza awareness and prevention, and envisions a future when "no one needs to be hospitalized due to the flu or other vaccine-preventable illnesses."

Andrew C. Eisenberg, MD, is a board-certified family physician with years of emergency department experience. He currently serves as the liaison from the American Academy of Family Physicians (AAFP) to the American Academy of Pediatrics Committee on Pediatric Emergency Medicine. His background also includes a position as past chair of the Council on Quality and Practice for AAFP, and he served for five years on the American Medical Association's steering committee commission to end healthcare disparities. Dr. Eisenberg has been a medical advisor for Families Fighting Flu since October 2007.

BSTQ: What drives you to promote influenza (flu) awareness and prevention?

Dr. Eisenberg: As a family physician, I have spent my career working to prevent illness and disability and keep people and their families and communities well. I work toward a future where no one needs to be hospitalized due to the flu or other vaccine-preventable illnesses.

BSTQ: What tactics are most effective when it comes to promoting flu vaccine compliance?

Dr. Eisenberg: I think we are doing everything we can at Families Fighting Flu to get the word out using stories and anecdotes. This approach has a far greater effect than statistics. People who have become very ill from influenza or have lost loved ones due to flu complications are very passionate about what's happened to them and eager to share their stores.

BSTQ: How do you address flu vaccine questions with your patients?

Dr. Eisenberg: Trying to teach people how to take better care of themselves is a big emphasis for me, and getting an annual vaccine is part of that. I like when people ask questions because it means they are open, and as a physician, I can hope to get one point across: The flu is an infectious disease, and immunizations are your best line of defense.

BSTQ: What are the most dangerous misperceptions about flu?

Dr. Eisenberg: People often assume the flu is only a mild respiratory illness, but this just isn't true. Having influenza can worsen diabetes, stress the heart, leading to heart failure and heart attacks, increase the risk of stroke and overwhelm the immune system, leading to many major health calamities.

BSTQ: How do you respond to patients who say they "got the flu from the vaccine"?

Dr. Eisenberg: The advantage of that question is it gives you an opening to educate. The fact is you can't get an influenza infection from the influenza vaccine. If you develop a reaction to a vaccine does not mean you got an infection from the vaccine. The reaction is just a sign the vaccine is working and your body is actively developing antibodies.

BSTQ: Tell us about your recent efforts to educate the public about influenza.

Dr. Eisenberg: I recently presented a webinar with my fellow Families Fighting Flu medical advisor Jeb Teichman, MD, titled "Influenza: Acting Beyond Treatment to Protect Everyone." In the webinar, we highlight the Centers for Disease Control and Prevention's (CDC) Take 3 approach to fighting the flu: #1 — Get vaccinated annually; #2 — Stop the spread; and #3 — Take antiviral medications if prescribed.

BSTQ: Is there an optimal time of year to receive a flu vaccine?

Dr. Eisenberg: It's best to receive your annual flu vaccine by the end of October, but vaccination even earlier or later in the season is just as beneficial, especially if it's before flu starts circulating in your community. So if the vaccine is available in August, I suggest being proactive and getting it then.

BSTQ: Any closing thoughts on flu prevention?

Dr. Eisenberg: I'm old enough to remember when people contracted polio and other vaccine-preventable diseases. Infectious diseases were the No. 1 killers of people up until just the last century when brilliant scientists and technology helped develop immunization techniques. More lives were saved and illnesses prevented by vaccinations than by any other health intervention besides clean water. Many people simply don't realize what a huge, positive impact vaccines have had on public health, so education is definitely key. We have tools to prevent and lessen the effects of the flu, and vaccines are by far the greatest tool in our prevention toolbox. In closing, I would say let's work together and do our part to prevent the flu and protect our families. Get vaccinated. Stop the spread. ❖

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

Well-Child Primary Care Pocket Guide: A Quick Reference for Physician Assistants and Nurse Practitioners, 1st Edition

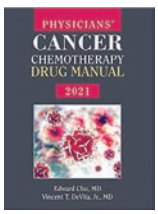
Author: Tanya L. Fernandez, MS, PA-C

This pocket guide has everything healthcare professionals need to ensure a thorough well visit for pediatric patients from newborn to adolescence. With the author's unique NEST & FLY mnemonic applied throughout, physician assistants, nurse practitioners and other healthcare providers are methodically guided through each well visit to ensure a consistent and complete exam. The guide is uniquely designed in easy-to-navigate color-coded tables to quickly find the information needed to evaluate pediatric patients' nutrition, elimination, growth, family and social environment, and physical and cognitive development. Also included are interviewing strategies and questions to gather an updated history, as well as step-by-step guidelines for the head-to-toe physical examination.

www.amazon.com/Well-Child-Primary-Care-Pocket-Guide-ebook/dp/B08TQMNY59

Physicians' Cancer Chemotherapy Drug Manual 2021, 21st Edition

Authors: Edward Chu, MD, and Vincent T. DeVita Jr., MD



Completely revised and updated for 2021, the *Physicians' Cancer Chemotherapy Drug Manual* is an up-to-date guide to the latest information on standard therapy and recent advances in the field. Written by world-class experts in clinical cancer therapeutics, this reference provides a complete, easy-to-use catalog of more than 100 drugs and commonly used drug regimens — both on- and off-label — for the treatment of all the major cancers. Key features include the addition of 16 new agents and several new supplemental indications that have been approved by the U.S. Food and Drug Administration within the past year; updated new indications for previously approved agents; indications, drug doses and schedules, toxicities and special considerations for each agent expanded and revised; antiemetic treatment regimens for both acute and delayed nausea/vomiting; diagrams of drug structures and pathways; a discussion of clinical pharmacology, special considerations, indications and dosages; chemotherapy regimens for all major cancers; and an overview of the basic principles of cancer drug therapy.

www.amazon.com/Physicians-Cancer-Chemotherapy-Drug-Manual/dp/1284230139

The Unimaginable Storm: A Doctor's Journey Through a Modern Pandemic

Author: Daniela Lamas, MD

In *The Unimaginable Storm*, Dr. Lamas offers a gripping, frontline account of the COVID-19 response in Boston's Brigham and Women's hospital — beginning with the emergence of the virus through its first spike and beyond — and tells the stories of the doctors, caregivers, patients and families affected by this merciless disease. With remarkable insight and intimacy, Dr. Lamas shares stories of devastation and heartbreak, but also of miraculous survival, resilience, teamwork, perseverance and tenderness, all with an eye toward the human side of medicine that is so frequently obscured by an industry, government and media culture obsessed with data. It is a compassionate, uncompromising look at the human cost of the coronavirus pandemic and the people who've done everything in their power to help.

www.amazon.com/Unimaginable-Storm-Doctors-Journey-Pandemic-ebook/dp/B08PV5Y223

The Power of the Patient Voice: How Health Care Organizations Empower Patients and Improve Care Delivery

Author: NEJM Catalyst

This eBook examines how leading healthcare organizations have given patients a more prominent voice so they can take greater responsibility and be more accountable for their own care. Data gathered throughout the past year from NEJM Catalyst Insights Council surveys and one-on-one interviews with Insights Council members are used to illustrate the need for healthcare professionals and health systems to listen more intently to patients to strengthen engagement and adherence to care plans. Insights Council members — a qualified group of executives, clinical leaders and clinicians directly involved in healthcare delivery — share firsthand their challenges and experiences in evolving care delivery to empower patients.

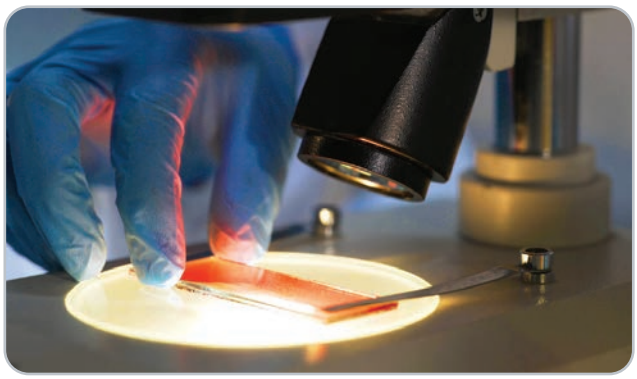
store.nejm.org/signup/catalyst/ebook2021?promo=OCFEDN05

Low Rate of Inhibitor Development in Previously Untreated Hemophilia A Patients Managed with Simoctocog Alfa (Nuwiq)

Final results from Octapharma's Phase III open label, uncontrolled NuProtect study demonstrated a low risk of inhibitor development in previously untreated patients (PUPs) with severe hemophilia A started on prophylaxis or on-demand treatment with simoctocog alfa (Nuwiq). Simoctocog alfa is a fourth-generation recombinant factor VIII (FVIII) produced in a human cell line. Initiated in March 2013, this study recruited patients of any age and ethnicity at 38 sites in 17 countries, and followed them for 100 exposure days or five years, whichever occurred first.

All patients were true PUPs with no prior exposure to FVIII concentrates or blood components. Inhibitor titers were measured with the Nijmegen-modified Bethesda assay. The cut-off for inhibitor positivity was 0.6 Bethesda units (BU), with ≥0.6 to <5 BU defining low-titer inhibitors, and ≥5 BU defining high-titer inhibitors.

Of 105 evaluable PUPs who received simoctocog alfa for the prevention and treatment of bleeding, 28 (26.7 percent) developed inhibitors, including 17 (16.2 percent) who developed high-titer inhibitors and 11 (10.5 percent) who developed low-titer inhibitors. Twenty-seven of 90 PUPs with known null FVIII mutations developed inhibitors, of which 17 (18.9 percent) were high-titer inhibitors. None of 12 PUPs with non-null FVIII mutations developed inhibitors.



Based on a review of recent published clinical trial findings, the investigators concluded PUPs treated with simoctocog alfa had a lower high-titer inhibitor rate than PUPs initially treated with hamster-cell-derived recombinant FVIII products.

Liesner RJ, Abraham A, Altisent C, et al. Simoctocog alfa (Nuwiq) in previously untreated patients with severe haemophilia A: Final results of the NuProtect study. Thromb Haemost *2021 Feb 13. Online ahead of print.*

Subcutaneous Immune Globulin May Be a Treatment Option in Stiff Person Syndrome Patients Intolerant to Intravenous Immune Globulin

Stiff person syndrome (SPS) is a rare immune-mediated neurological disorder characterized by rigidity in the trunk and limbs, muscle spasms and heightened sensitivity to outside stimuli, which has been shown to respond to intravenous immune globulin (IVIG). However, IVIG therapy can be associated with a number of challenges, including poor tolerability, a requirement for intravenous access, the need for monthly infusion visits, and serious adverse events that can include aseptic meningitis, renal complications and thrombosis. For certain other chronic neurological conditions, subcutaneous immune globulin (SCIG) has emerged as an alternative to IVIG with comparable efficacy.

The Johns Hopkins Stiff Person Syndrome Center identified five SPS patients, with a mean duration of illness of 5.9 years (range 2.5 to 7 years), who switched to SCIG from IVIG as the result of IVIG-related side effects. All patients were treated with IVIG for at least two months (maximum 18 months) prior to switching to SCIG.

The duration of use of SCIG ranged from four months to six years (mean, 19.2 months). SPS symptoms remained stable in all patients following crossover to SCIG therapy. The treatment was well-tolerated in four of the five patients, one of whom reported mild tolerable injection site reactions. A fifth patient, with a history of asthma and bronchospasm reactions to IVIG treatment, developed escalating side effects, including breathing issues suggestive of a hypersensitivity reaction, which resulted in discontinuation of SCIG treatment after four months.

The study authors concluded that SCIG may be a reasonable and safe alternative for SPS patients who do not tolerate IVIG, with the caveat that allergic and injection site reactions can be a limiting factor for some patients. They called for controlled studies to confirm SCIG treatment durability and efficacy in this patient population.

Aljarallah S and Newsome SD. Use of subcutaneous immunoglobulin in stiff person syndrome. Medicine *(Baltimore) 2021 Mar 26;100(12):e25260.*

Medicare Immune Globulin Reimbursement Rates

Rates are effective July 1, 2021, through Sept. 30, 2021

	Product	Manufacturer	J Codes	ASP + 6% (before sequestration)	ASP + 4.3%* (after sequestration)
IVIG	ASCENIV	ADMA Biologics	J1554	$963.54	$948.09
	BIVIGAM	ADMA Biologics	J1556	$140.98	$138.72
	FLEBOGAMMA DIF	Grifols	J1572	$69.43	$68.31
	GAMMAGARD SD	Takeda	J1566	$131.77	$129.66
	GAMMAPLEX	BPL	J1557	$99.62	$98.02
	OCTAGAM	Octapharma	J1568	$83.21	$81.87
	PANZYGA	Octapharma/Pfizer	90283/J1599	**	**
	PRIVIGEN	CSL Behring	J1459	$86.36	$84.97
IVIG/SCIG	GAMMAGARD LIQUID	Takeda	J1569	$95.42	$93.89
	GAMMAKED	Kedrion	J1561	$95.55	$94.01
	GAMUNEX-C	Grifols	J1561	$95.55	$94.01
SCIG	CUTAQUIG	Octapharma	90284/J3590	**	**
	CUVITRU	Takeda	J1555	$142.09	$139.81
	HIZENTRA	CSL Behring	J1559	$112.33	$110.53
	HYQVIA	Takeda	J1575	$148.34	$145.96
	XEMBIFY	Grifols	J1558	$133.89	$131.74

* ASP + 4.3% applies only after Jan. 1, 2022, unless the Medicare Fee-for-Service sequestration payment adjustment suspension is ended.

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	ASCENIV LIQUID, 10%	ADMA Biologics	PI	5 g
	BIVIGAM LIQUID, 10%	ADMA Biologics	PI	5 g, 10 g
	FLEBOGAMMA 5% DIF Liquid	Grifols	PI	2.5 g, 5 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%	Octapharma/Pfizer	PI, ITP, CIDP	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, 1.65 g, 2 g, 3.3 g, 4 g, 8 g
	CUVITRU Liquid, 20%	Takeda	PI	1 g, 2 g, 4 g, 8 g, 10 g
	HIZENTRA Liquid, 20%	CSL Behring	PI, CIDP	1 g, 2 g, 4 g, 10 g 1 g PFS, 2 g PFS, 4 g PFS
	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
PFS Prefilled syringes

2021-2022 Influenza Vaccine

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

Product	Manufacturer	Presentation	Age Group	Code
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	90685/90687
FLUAD (IIV4)	SEQIRUS	0.5 mL PFS 10-BX	65 years and older	90694/90654
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	2 years and older	90674
FLUCELVAX (ccIIV4)	SEQIRUS	5 mL MDV	2 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

ccIIV4 Cell culture-based quadrivalent inactivated injectable
IIV4 Egg-based quadrivalent inactivated injectable
LAIV4 Egg-based live attenuated quadrivalent nasal spray

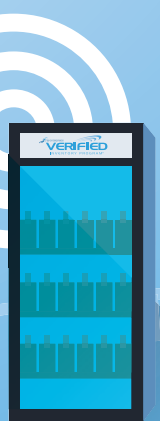
* Providers should check with their respective payers to verify which code they are recognizing for Flucelvax Quadrivalent 5 mL MDV product reimbursement for this season.

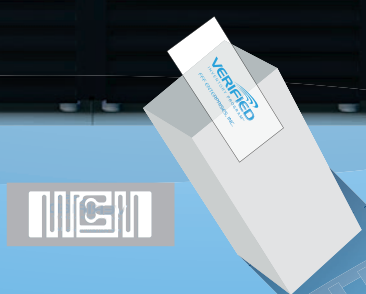
FFF enterprises

VERIFIED

INVENTORY PROGRAM®

WHEN MINUTES MATTER





VIPc CABINET INSTALLATION

REAL-TIME 24/7 MONITORING & INVENTORY VISIBILITY

RFID TAG TECHNOLOGY

PRODUCT SAFETY

The VERIFIED

Spend less time managing inventory

Emergency Ordering 24/7

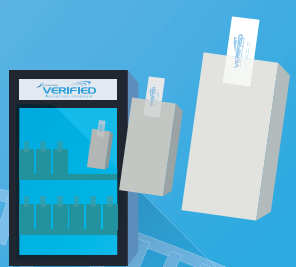
THE PRODUCTS YOU NEED

ARE ALREADY THERE

With FFF's Verified Inventory Program (VIPc)® Forward-Deployed Inventory (FDI) System, you have plenty of time to care for your patients.

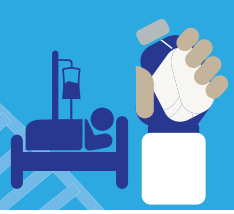
- Eliminate carrying costs
- Real-time 24/7 monitoring
- Inventory PAR levels
- Increased visibility
- Accurate reporting
- Temperature alerting
- High-touch service
- Integrated split-billing

CONVENIENT WEB PORTAL & AUTOMATED ALERTS



CUSTOMIZED INVENTORY

NATIONWIDE COVERAGE



Advantage

and more time focusing on patient care.

(800) 843-7477 | FFFenterprises.com

BioSupply Trends Quarterly
44000 Winchester Road
Temecula, CA 92590-9760

PRSRT STD
US POSTAGE PAID
LEBANON JUNCION, KY
PERMIT NO. 714