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QUARTERLY
SUMMER 2024 VACCINES

Vaccines
Current and Future
Curbing the Spread of Infectious Diseases

ACCELERATING
Rare Disease Treatments

NOVEL AND NEXT-GENERATION
COVID Vaccines

UPDATE ON TREATING
Neutropenia

Vaccine Resistance:
COUNTERING THE ESCALATION

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High Blood Pressure

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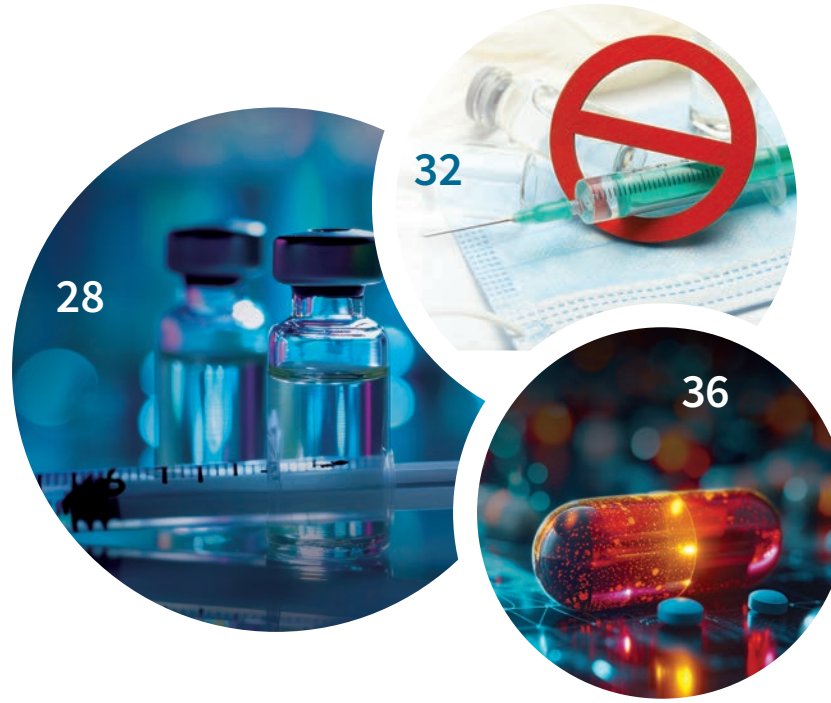

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BioSupply Trends Quarterly is the definitive source for industry trends, news and information for healthcare professionals in the biopharmaceuticals marketplace.

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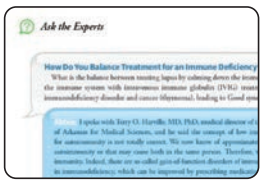

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Increasing Vaccine Development Provides Hope, Despite Resistance

IT'S ALARMING that despite vaccines' proven success, some 40,000 to 50,000 adults die from vaccine-preventable diseases each year. Even diseases that were once-eradicated are making a comeback. A disturbing example of this is measles, which was eradicated in the U.S. in 2000 due to the protective effects of the measles vaccine that was developed in 1963. As of May 30, there have been 146 cases of measles in 2024 alone. So, what's causing the spate of vaccine-preventable disease outbreaks? It's certainly not the fault of research that provides ample evidence of vaccines' safety and effacy or of the vaccine manufacturers that are doing their part to improve upon existing vaccines, as well as develop novel ones for existing and merging infectious diseases. Instead, it's likely due to two factors: 1) Many Americans simply don't understand how important vaccination is, since many diseases are becoming very rare largely because of vaccination, and 2) mistrust among a growing proportion of the public is causing an uptick in anti-vaccine rhetoric.

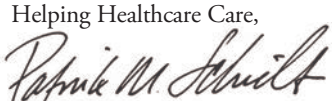
The historic success of vaccines can't be denied. We highlight some of the major diseases that have been eradicated or nearly eradicated as a result of vaccines in our article "Viruses, Variants and Vaccines: Staying Ahead of the Spread" (p.22). We also delve into the different vaccine technologies, including recombinant protein, viral vector, mRNA and DNA, that are critical for stopping the spread of a host of infectious diseases such as hepatitis B virus, human papillomavirus, pertussis, influenza, COVID-19, malaria, Lyme disease, cytomegalovirus, Zika, dengue, typhoid and more. Research into vaccines using these technologies is providing hope in the face of ever-evolving threats.

The most recent threat, the SARS-CoV-2 virus, continues to mutate, evading protection even from existing COVID-19 vaccines. Fortunately, even though the pandemic is officially declared "over" in the U.S., three of the top-10 global vaccine manufacturers are continuing their efforts to protect people from the virus mutations. We take a look at what COVID-19 vaccines are currently available, as well as what these manufacturers are developing in our article "COVID Vaccines: What's Available and What's in the Works" (p.28). Not only are Pfizer-BioNTech, Moderna and Novavax all working to tailor their current COVID vaccines to protect against mutations, but their efforts are also focused on developing next-generation and combination vaccines, including a refrigerator-stable vaccine and a vaccine that will protect against both COVID and influenza.

It can only be hoped that the majority of Americans will embrace these and other vaccines, including the new respiratory syncytial virus vaccines to protect older adults, that we discuss in our article "The Protective Value of RSV Vaccines in Older Adults: A Deeper Dive" (p.50). But that can only be achieved by countering the arguments made by anti-vaxxers that erode public trust in vaccines. We explore the growing political ideology of the anti-vaccine movement in our article "The Anti-Vaccine Movement: Where Are We Now?" (p.32), as well as how it affects herd immunity and how it can be addressed.

As always, we hope you enjoy the additional articles in this issue of *BioSupply Trends Quarterly*, and find them both relevant and helpful to your practice.

Helping Healthcare Care,



Patrick M. Schmidt
Publisher

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

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HHS Finalizes Rule Expanding Access to Care and Increasing Protections for Medicare Part D Plans

The U.S. Department of Health and Human Services (HHS), through the Centers for Medicare and Medicaid Services (CMS), is finalizing policies to ensure Medicare Advantage and Medicare Part D prescription drug plans best meet the needs of people with Medicare.

The 2025 Medicare Advantage and Part D final rule establishes a set amount a plan can compensate an agent or broker to protect Medicare Advantage and Part D plan enrollees and prospective enrollees from anti-competitive steering, and to help these individuals find the plan that best suits their needs rather than being steered into options based on financial incentives to agents and brokers from insurance plans. CMS is also requiring that Medicare Advantage plans include an expert in health equity on their utilization management committees and for the committees to conduct an annual health equity analysis of the plans' prior authorization policies and procedures.

The final rule also promotes access to behavioral health providers and services for people with a Medicare Advantage plan to help ensure they can receive essential treatments for mental health and substance use disorders. It expands network adequacy evaluation requirements to a new outpatient behavioral health specialty type, which includes marriage and family therapists and mental health counselors who are now able to bill under Original Medicare, as well as addiction medicine clinicians, opioid treatment providers and other behavioral health practitioners providing psychotherapy or medication for substance use disorder.

Additionally, the rule finalizes new guardrails for certain types of supplemental benefits, available only to chronically ill enrollees, to ensure these supplemental benefits offered by a Medicare Advantage plan meet the health needs of people with Medicare by being supported by evidence. The rule also requires Medicare Advantage plans to send a mid-year, personalized communication to their enrollees about accessing unused supplemental benefits. These actions ensure that the large federal investment of over $65 billion per year of taxpayer dollars in supplemental benefits will meet enrollee needs and will not be used just for marketing. ❖

Biden-Harris Administration Finalizes Rule Expanding Access to Care and Increasing Protections for People with Medicare Advantage and Medicare Part D. U.S. Department of Health and Human Services press release, April 4, 2024. Accessed at www.hhs.gov/about/news/2024/04/04/biden-harris-administration-finalizes-rule-expanding-access-care-increasing-protections-people-medicare-advantage-medicare-part-d.html.

HHS Releases White Paper Focused on Preventing Drug Shortages

The U.S. Department of Health and Human Services (HHS) has released a white paper highlighting steps the organization has taken to prevent and mitigate drug shortages and proposing additional solutions for policymakers to consider. Specifically, HHS has established a new supply chain resilience and shortage coordinator role to strengthen implementation of strategies to enhance supply chain resilience for pharmaceuticals and other medical products, and has issued guidance to increase supply chain transparency, while continuing to consider additional long- and short-term solutions.

HHS has also taken steps to increase resilience and redundancy within the market. This work includes supporting domestic manufacturing of key ingredients and drugs to address various vulnerabilities. The Administration for Strategic Preparedness and Response has invested $500 million to date to support active pharmaceutical ingredient manufacturing, and is exploring how it can utilize new authorities to promote the onshoring of essential medicines, medical countermeasures and their critical ingredients. Moreover, HHS is developing policies to foster resiliency by considering Medicare payments, and additional requirements, to support a more diverse supply chain. ❖

HHS Releases White Paper Focused on Preventing Drug Shortages. U.S. Department of Health and Human Services press release, April 2, 2024. Accessed at www.hhs.gov/about/news/2024/04/02/hhs-releases-white-paper-focused-preventing-drug-shortages.html.

HHS Releases Final Rules Protecting Consumers Purchasing Short-Term Health Plans

The Departments of Health and Human Services, Labor and the Treasury have released the Short-Term, Limited-Duration Insurance and Independent, Noncoordinated Excepted Benefits Coverage, or "Junk Insurance," final rules. Short-term, limited-duration insurance (STLDI) is a type of health insurance that is typically designed to fill temporary gaps in coverage when an individual is transitioning from one source of coverage to another. Unlike most health insurance plans, STLDI plans are not subject to the Affordable Care Act's critical consumer protections, including guaranteeing coverage for people with preexisting conditions and prohibiting discrimination based on health status, age or gender. The final rules will limit these "short-term" plans to truly short time periods, no more than four months instead of three years.

In addition, the final rule will require health insurance companies to be clear and up front with what consumers are buying. Short-term plans, as well as "fixed indemnity" insurance policies that provide a fixed, cash payment for a healthcare event, will have to include a clear, easy-to-understand consumer notice on marketing, application, enrollment and re-enrollment materials so that consumers can make informed coverage purchasing decisions. The final rules increase transparency while helping to ensure consumers do not mistakenly enroll in these types of insurance plans as substitutes for comprehensive coverage.

"HHS is cracking down on junk insurance plans to help consumers make informed choices and avoid mistakenly paying for a plan that does not provide them the coverage or protection they expect," said HHS Secretary Xavier Becerra. "Over the past three years, we have helped more people gain access to high-quality, affordable coverage — and more than 300 million Americans are covered for the first time ever. We want everyone to have the peace of mind that comes with having coverage that includes the protections and benefits they expect." ❖

Biden-Harris Administration Protects Consumers from Low-Quality Coverage by Limiting "Junk" Health Plans. Centers for Medicare & Medicaid Services press release, March 28, 2024. Accessed at www.cms.gov/newsroom/press-releases/biden-harris-administration-protects-consumers-low-quality-coverage-limiting-junk-health-plans.

CDC Releases New Guide to Address Healthcare Worker Burnout

As part of the first federal campaign to address healthcare worker burnout, the Centers for Disease Control and Prevention's (CDC) National Institute for Occupational Safety and Health (NIOSH) released an evidence-informed and actionable guide for the nation's hospital leaders to improve healthcare worker wellbeing titled "Impact Wellbeing Guide: Taking Action to Improve Healthcare Worker Wellbeing." This guide is the newest addition to the Impact Wellbeing campaign launched in October 2023, and provides a step-by-step process for hospitals to start making organizational-level changes that will impact and improve the mental health of their employees.

The guide outlines six key steps for hospital leaders to take, which were pilot-tested and refined with a working group comprised of six U.S. hospitals:

1) Conduct a review of your hospital's operations to determine how they support professional wellbeing.

2) Build a dedicated team to support professional wellbeing at your hospital.

3) Remove barriers to seeking care such as intrusive mental health questions on credentialing applications.

4) Develop a suite of communication tools that help you share updates with your workforce about your hospital's journey to improve professional wellbeing.

5) Integrate professional wellbeing measures into an ongoing quality improvement project.

6) Create a 12-month plan to continue to move your hospital's professional wellbeing work forward.

CDC/NIOSH began hosting a webinar series in late April 2024 for hospital leaders

to learn how to use each section of the guide. The goal is for participating hospitals to start implementing the guide immediately after the webinar series. ❖

CDC's National Institute for Occupational Safety and Health's Impact Wellbeing™ Campaign Releases Hospital-Tested Guide to Improve Healthcare Worker Burnout. Centers for Disease Control and Prevention news release, March 18, 2024. Accessed at www.cdc.gov/media/releases/2024/p0318-Worker-Burnout.html.

Payment for Medications: It's an Exacting Team Sport!

By Bonnie Kirschenbaum, MS, FASHP, FCSHP

GETTING PAID for drugs demands a robust chain of events linking product procurement, its use within both the clinical framework and payer requirements, and the revenue cycle function of charging, billing and subsequent reimbursement. Payment rules under the Centers for Medicare and Medicaid Services (CMS) are often emulated by private payers in the inpatient prospective payment system (IPPS), outpatient prospective payment system (OPPS) and Inflation Reduction Act (IRA), and apply to every care site.

The IPPS and OPPS rule sets take two very different approaches toward medications: Products used in the inpatient setting are not separately reimbursable but are paid under the all-inclusive diagnosis-related group (DRG), while those in the outpatient setting are paid separately according to status indicators (SI). However, due to their expense and uniqueness, new technology products are the exception, and they are separately reimbursable at a set amount for a fixed period of time, with new technology allowable payments (NTAPs) applying to inpatients and pass-through drugs applying to outpatients.

NTAPs in 2024

In 2024, CMS approved nine new NTAPs for drugs and continued existing applications for two others (Table). In each case, payment is made only when the use of the product is for the very specific ICD-10 code listed and only up to the maximum allowable as stated in the table. This requires very carefully constructed computer physician order entry (CPOE) sets to drive the required documentation, as well as coordination with the revenue cycle team (either in-house or outsourced) who need to be alerted to the somewhat unusual circumstances of billing separately for drugs outside of the DRG.

In 2024, separate reimbursement for 15 products is discontinued because their NTAP status reached a three-year anniversary date prior to April 1, 2024. This includes discontinuing NTAP status for the CAR-T therapies TACARTUS, ABECMA and CARVYKTI.

In 2024, CMS also revised its NTAP policies to require:

- A "complete and active FDA marketing authorization request" at the time of submission
- FDA marketing authorization by May 1 (versus July 1) of the applicable NTAP year

Future rulemaking changes to how the agency assesses NTAP eligibility in the third year of newness such as potentially adjusting the April 1 cutoff to allow for a longer eligibility window might be considered.

Three-Year Transitional Pass-Through Payment

The period for all pass-through drugs, biologicals and radiopharmaceuticals and quarterly expiration of pass-through status was created under the Medicare, Medicaid and SCHIP Balanced Budget Refinement Act of 1999 and requires CMS to make additional payments to hospitals for current orphan drugs, as designated under section 526 of the Federal Food, Drug and Cosmetic Act; current drugs and biologicals and brachytherapy sources used in cancer therapy; and current radiopharmaceutical drugs and biologicals. "Current" refers to the types of drugs or biologicals mentioned previously that are hospital outpatient services under Medicare Part B for which transitional pass-through payment was made on the first date the hospital OPPS was implemented.

Transitional pass-through payments are also provided for certain new drugs and biologicals not being paid for as a hospital outpatient department service as of Dec. 31, 1996, and whose cost is "not insignificant" in relation to OPPS payments for the procedures or services associated with the new drug or biological. For pass-through payment purposes, radiopharmaceuticals are included as drugs.

These products have been assigned SI G and can easily be found in the Addendum A and B updates, which are Excel files and can be found at www.cms.gov/Medicare/Medicare-Fee-for-Service-Payment/HospitalOutpatientPPS/Addendum-A-and-Addendum-B-Updates. SI drugs are paid for as part of a bundle or package of services.

Some nuance of payment for SI G drugs include:

- Payment is at average sales price (ASP) plus 6 percent or at wholesale acquisition cost (WAC) plus 3 percent if no ASP is available.
- All biosimilars are eligible for pass-through, not just the first one for each reference product (as an example, all 11 biosimilar products for Humira, each with its own HCPCS code, are pass-through eligible).
- In 2024, 49 products will keep or gain pass-through status, while pass-through status expired for 43 drugs in 2023 and 25 drugs in 2024.

Table. New Drug NTAPs Approved for FY 2024

Product	ICD-10-PCS Code	Maximum NTAP Payment for FY 2024
CYTALUX	Lung Indication: 8E0W0EN, 8E0W3EN, 8E0W4EN, 8E0W7EN, or 8E0W8EN; Ovarian Indication: 8E0U0EN, 8E0U3EN, 8E0U4EN, 8E0U7EN or 8E0U8EN	$2,762.50
EPKINLY and COLUMVI	XW013S9, XW033P9 or XW043P9	$6,504.07
LUNSUMIO	XW03358 or XW04358	$17,492.10
REBYOTA (fecal microbiota, live-jslm) and VOWST (fecal microbiota spores, live-brpk)	XW0H7X8 or XW0DXN9	$6,789.25
REZZAYO (QDIP)	XW033R9 or XW043R9	$4,387.50
SPEVIGO	XW03308	$33,236.45
taurolidine/heparin (QDIP)	N/A (FDA marketing authorization not yet approved)	N/A
TECVAYLI	XW01348	$8,940.54
TERLIVAZ	XW03367 or XW04367	$16,672.50
XACDURO (QDIP)	XW033K9 or XW043K9 in combination with one of the following: Y95 and J15.61; OR J95.851 and B96.83	$13,680.00
Drug NTAPs Continuing in FY 2024		
RYBREVANT	XW033B7 or XW04B7	$6,405.89
LIVENCITY	XW0DX38 or XW0G738 or XW0H738	$32,500.00

Biosimilars: Melding IRA and OPPS in 2024

It's necessary to be aware of more than one rule set and to understand how each impacts the use of certain products. The goal is to reduce the cost of treatment with the market introduction of biosimilars:

1) Under OPPS, previous policies for biosimilars are continued. Under IRA, new biosimilars furnished before ASP data is available must have a payment limit set not exceeding 103 percent WAC or 106 percent and less of WAC or ASP.

2) Under the OPPS threshold packaging policy, biosimilars are excepted when their reference biologicals are separately paid, with the goal of promoting use as a lower-cost alternative. If the reference product cost/day falls below threshold, all biosimilars related to it would be similarly packaged regardless of whether their cost/day are above it. (For instance, the qualifying biosimilar = product with ASP less the reference product ASP for a calendar quarter during an applicable five-year period.)

3) Under the IRA, payment is ASP plus 8 percent of the reference product ASP.

The IRA Part B reimbursement changes for biosimilars establishes a payment rate for biosimilars under Part B during the initial period:

- For biosimilars furnished on or after July 1, 2024, the initial period payment rate is the lesser of the biosimilar's WAC plus 3 percent or 106 percent of the reference product's ASP.
- For qualifying biosimilars, the Part B add-on payment was increased from 6 percent to 8 percent of the reference product's ASP for a five-year period so that payment for such biosimilars would be the biosimilar's ASP plus 8 percent of the ASP of the reference biologic.

The IRA brings significant changes to U.S. healthcare policies, including provisions to address patient affordability concerns, allowing Medicare to negotiate drug prices, and a redesign of the Medicare Part D benefit. Signed into law on Aug. 16, 2022, it contains three primary components related to prescription drugs: 1) Drug Price Negotiation Program, 2) Medicare Part B and Part D inflation rebates and 3) Medicare Part D redesign.

The Drug Price Negotiation Program applies to certain high-spend Medicare drugs. During the negotiation process, the Secretary of Health and Human Services selects a specified number of drugs for negotiation two years before the negotiated price applies. A specified number of the highest ranked negotiation-eligible drugs

is determined with only Part D drugs selected for 2026 and 2027.

Under the maximum fair price (MFP), a manufacturer of a selected drug will be required to offer a MFP for such drug with respect to Medicare beneficiaries, generally capped at an applicable percentage of non-federal average manufacturer price.

IRA: Inflation-Adjusted Coinsurance

As of Jan. 1, 2023, rebates to Medicare were made from drug companies raising prices for certain Medicare Part B drugs faster than the rate of inflation. CMS adjusts the patient coinsurance so it's based on the lower inflation-adjusted payment amount. This applies to certain Part B single-source drugs/biological products, including biosimilars.

As of April 1, 2023, if the Part B payment amount for a rebate-able drug for a calendar quarter is more than the inflation-adjusted payment amount, 1) the patient coinsurance is based on 20 percent of the inflation-adjusted payment amount for the quarter and reflected as a percentage (less than 20 percent) of the Part B payment amount, and 2) the Medicare portion of the payment is increased to the difference between the Part B payment amount and patient coinsurance, minus any Part B deductible and set-aside.

This means that patients must be charged the correct amount of coinsurance, which may change quarterly. CMS makes up the difference between the usual 20 percent and the co-insurance percent, preventing provider revenue loss.

Inflation Rebates

For Part B and D drugs, manufacturers are required to pay a rebate for a drug paid under Part B or D when the price of the drug increases faster than inflation. Rebates are owed only on Medicare usage and not on commercial or private payer usage.

The rebate formulas are:

- Part B: Total amount of eligible Part B utilization of drug in rebate quarter multiplied by amount (if any) by which rebate quarter Part B payment amount exceeds inflation-adjusted Part B payment
- Part D: Total amount of eligible Part D utilization of drug in rebate year multiplied by amount (if any) by which volume-weighted average annualized average manufacturer price (AMP) for rebate year exceeds inflation-adjusted volume-weighted average annualized AMP for the benchmark period

Effective dates for when rebates take effect are different for Parts B and D. For Part B, the first rebate period began in the first quarter of 2023, and for Part D, the first rebate period began in the fourth quarter of 2022.

Part B Co-Insurance Adjustment

Part B beneficiaries also share in inflation rebates. Their coinsurance for a drug is set at 20 percent of the Part B inflation-adjusted payment amount, such that beginning April 1, 2023, beneficiaries may pay a lower coinsurance for certain drugs if the drug's price increased faster than the rate of inflation in a benchmark quarter. There is no comparable provision for Part D inflation rebates, which are reflected in quarterly ASP payment files.

CMS makes providers whole by reimbursing 80 percent of the Part B payment amount, plus the difference between 20 percent of the Part B payment amount and 20 percent of inflation adjusted payment amount.

505(b)(2) or biologics license application pathway products require delicate coordination between the pharmacy supply chain acquiring the product, the IT/informaticist team, the revenue cycle team and the order entry clinician. This is critical because not all products are interchangeable or considered therapeutically equivalent. Also, not all products have the full range of approvals that their branded counterparts have, and payer requirements/preferences may derail attempts to reduce drug costs both for a facility's department and for patients.

This has a tremendous impact on order entry. Facilities (with pharmacy purchasing) need to determine which products they'd like to use in their healthcare system. Quarterly ASP table crosswalk files can identify correct billing and payment codes for each applicable product. The complexity and nuanced nature of differences between each product should be considered, as well as limitations in approved indications, payer limitations and prior authorization requirements.

Each chosen product should be added to the pharmacy drug master and charge description master using the unique brand-specific HCPCS code assigned. And CPOE entries should be created that reflect these decisions. Lastly, the order entry must be for the actual product that is being purchased. ❖

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Promoting Health Equity

Can true fairness in healthcare be achieved when everyone — regardless of class, color or creed — has the opportunity and agency to pursue their own optimal health?

By Rachel Maier, MS

IT'S A BUZZWORD that shows up everywhere in medicine these days: health equity, a somewhat ambiguous concept that is transforming the healthcare industry from the inside out. Health equity task forces are cropping up everywhere, advocating for equal outcomes and resources to be funneled to policies and procedures that promise to achieve them. Promoting health equity is even part of the Joint Commission's national patient safety goals for 2024.[1] But what exactly is health equity, and how does it affect your practice?

What Is Equity?

A simple Internet search for "health equity" yields about 195 million hits, and yet the meaning of "equity" is easily confused with the meaning of "equality." The two certainly overlap: Equality is the state of being the same in quality, nature or status for each member of a group, class or society; equity is justice according to natural law or right, specifically freedom from bias or favoritism.[2,3]

While equality refers to the *state* of being equal (something one is by virtue of being human), equity seems to refer to the *quality* of being equal (or one's experience of equality). Health equality means treating patients in the same way; health equity means treating patients according to their needs. In other words, health equality seeks to treat all people the same regardless of demographics or background, while health equity seeks to treat people differently based on those exact premises.

A Question of Fairness

Equality is a good starting point in healthcare: All people, by virtue of their humanity, have a natural right to seek and receive medical care when they need it. But not every person needs the same thing or has the same resources to seek and receive medical attention when they need it. That's where health equity comes in.

The World Health Organization (WHO) describes "health equity" as a state in which everyone can attain their full potential for health and well-being regardless of who they are, where they come from, what they believe, etc.[4] The Centers for Disease Control and Prevention says health equity is achieved "when all people have the opportunity to attain their full health potential."[5] Health equity aims to distribute resources according to need in an effort to make outcomes more fair.

Traditionally, the idea of health equity recognizes that some people need more help than others do, and it is right and just to administer help where it is needed without favoritism or bias. On the other hand, an evolving, progressive idea of health equity argues that the healthcare system is inherently biased against some minority groups and asserts that things such as race, gender, sexual preference, age, ability and myriad other demographic details directly affect how equitably patients are treated. It ties health equity to diversity and inclusion, which inevitably ends up conferring favoritism to some populations — which is an inversion of true equity. In trying to eliminate bias or favoritism, this view promotes it in reverse.

Health disparities — health differences linked to demographic differences — are real and they usually aren't fair, but finding the best way to make them more so continues to be a problem, especially when trying to find common ground between the two competing ideologies. According to David A. Kindig, PhD, an emeritus professor of population health sciences and emeritus vice-chancellor for Health Sciences at the University of Wisconsin-Madison's School of Medicine, fairness seems to be the shared ideal at the root of health equity, but finding the means of arriving at the elusive end is a challenge.

"One major ideological difference in population health policy is the role of individual responsibility in producing and maintaining health. Although each of us must take personal responsibility for many of our health choices, we also know that making healthy choices is much harder for people with less education and/or fewer economic or social resources," Dr. Kindig explains.[6] "Many public and population health experts tend to approach this issue of

common ground through a lens of social justice and principles of fairness. But many of our unhealthier communities are in more politically conservative areas of the nation, whose inhabitants have different assumptions about how social programs and population health have affected local, state and national policy for more than a century."[6]

Opportunity vs. Outcome

The traditional view of equity seeks equal opportunity. The question isn't whether or not social determinants of health — the conditions in the environments where people are born, live, learn, work, play, worship and age — affect how easily people can access healthcare or pursue and maintain a healthy lifestyle.[7] We know these things do indeed affect population health. The question is whether or not all people have the opportunity to overcome their own unique set of obstacles. Whether people utilize the opportunities available is a matter of personal choice.

A more progressive view of equity seeks equal outcomes, and whether or not some populations achieve them is directly connected to social determinants of health and the discrimination and bias these populations face. According to WHO, "People's living conditions are often made worse by discrimination, stereotyping and prejudice based on sex, gender, age, race, ethnicity or disability, among other factors." To address this, WHO says "the right mix of government policies" ought to be put in place.[4] However, this view often creates division by emphasizing differences while also taking away individuals' control of their own health.[6] It assumes some groups are unable to make healthcare decisions for themselves and gives bureaucrats the power to make choices for everyone. According to Dr. Kindig, that's a problem, as many of the people whose social determinants of health that lead to health disparities, and ultimately health inequities, still value personal responsibility and decision-making.[6]

Could Agency Be the Answer?

In a 2022 article discussing fairness in healthcare, Daniel H. Johnson Jr., MD, FACR, radiologist and former visiting fellow in health policy at The Heritage Foundation, and Robert E. Moffit, PhD, senior research fellow of the Center for Health and Welfare Policy, posited that the progressive idea of health equity is actually regressive. "This approach is problematic. It creates racial division. It also conflicts with the overarching goal of medicine, which is to provide the appropriate care in the appropriate setting at the appropriate time when a patient presents with illness or injury, with emphasis on preventing illness or injury whenever possible."[8] Dr. Johnson and Dr. Moffit argue that the population at large would be well-served by a patient-centered approach to medicine, one that gives patients agency and seeks to achieve true fairness by creating unity of purpose among healthcare providers and patients alike.

In patient-centered care, a patient's specific health needs and desired health outcomes are the driving force behind all healthcare decisions and quality measurements, according to an article in the *New England Journal of Medicine Catalyst.* "The main goal and benefit of patient-centered care is to improve individual health outcomes, not just population health outcomes, although population outcomes may also improve."[9] Patient-centered care emphasizes agency for single patients and entire populations: It assumes people are able to think for themselves and take action as they so choose. Ultimately, personal agency gives people the opportunity, tools and power to chart their own course in healthcare.

Serve Individuals, Not Ideologies

At its best, health equity aims to achieve equal opportunity for fair treatment and the pursuit of optimal health outcomes for everyone regardless of who they are or where they come from. It's a high, hard calling. But focusing on patients — what they need and what health outcomes they want — could very well evade divisive ideology. People come from all sorts of backgrounds; life circumstances and stories vary from person to person; some populations need more help than others; and many people can't easily change their situation. As Dr. Johnson and Dr. Moffit ask, "Why not just agree to concentrate on delivering the highest level of medical care to each patient, regardless of racial, ethnic or other characteristics?"[8] True health equity that is right and just puts processes in place that make sure everyone gets the care they need regardless of who they are or where they come from. ❖

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RACHEL MAIER, MS, is the associate editor of *BioSupply Trends Quarterly.*

Medicines

FDA Grants wilate Orphan Drug Exclusivity

The U.S. Food and Drug Administration (FDA) has granted orphan drug exclusivity for Octapharma's wilate, von Willebrand factor/coagulation factor VIII complex (human) lyophilized powder for solution for intravenous injection, for routine prophylaxis to reduce the frequency of bleeding episodes in adults and children 6 years of age and older with von Willebrand disease (VWD). Wilate is the first von Willebrand factor (VWF) concentrate indicated for prophylactic treatment across all forms of VWD, a significant patient treatment milestone for the most prevalent bleeding disorder in the United States. VWD affects up to one percent of the U.S. population, including many who are undiagnosed.

"The FDA orphan exclusivity is exciting news for Octapharma and patients who have endured excessive bleeding episodes," said Octapharma USA President Flemming Nielsen. "Patients with severe VWD are recommended to utilize long-term prophylaxis with VWF concentrate, as compared to on-demand treatment for bleeding, to avoid life-threatening bleeding episodes, as well as a better quality of life." ❖

FDA Grants Orphan Drug Exclusivity to wilate®, the First VWF Concentrate for Prophylaxis in All Types of VWD. Octapharma USA press release, April 20, 2024. Accessed at www.prnewswire.com/news-releases/octapharma-usa-fda-grants-expanded-approval-to-wilate-as-the-first-vwf-concentrate-for-prophylaxis-in-all-types-of-vwd-302005285.html.

Research

Blood Test Predicts Multiple Sclerosis Years Before Symptoms Appear

Researchers at the University of California, San Francisco, (UCSF) have identified a specific pattern of autoantibodies in the blood that precedes the clinical onset of multiple sclerosis (MS). The study found that 10 percent of MS patients displayed a unique set of autoantibodies against both human proteins and common pathogens like the Epstein-Barr virus (EBV) years before showing symptoms. These findings could lead to a simple blood test for early detection of MS, allowing for timely intervention with more effective therapies.

In about one in 10 cases of MS, the body begins producing a distinctive set of antibodies against its own proteins years before symptoms emerge. These autoantibodies appear to bind to both human cells and common pathogens, possibly explaining the immune attacks on the brain and spinal cord that are the hallmark of MS.

The finding was a result of a search for autoantibodies in the blood of people with MS. Samples were obtained from the U.S. Department of Defense Serum Repository, which stores blood taken from armed service members when they apply to join the military, from 250 MS patients collected after their diagnosis, plus samples taken five or more years earlier when they joined the military. The researchers also looked at comparable blood samples from 250 healthy veterans. Using a mere one-thousandth of a milliliter of blood from each time point, the scientists thought they would see a jump in autoantibodies as the first symptoms of MS appeared. Instead, they found that 10 percent of the MS patients had a striking abundance of autoantibodies years before their diagnosis.

The dozen or so autoantibodies all stuck to a chemical pattern that resembled one found in common viruses, including EBV, which infects more than 85 percent of all people, yet has been flagged in previous studies as a contributing cause for MS. Years before diagnosis, this subset of MS patients had other signs of an immune war in the brain. Ahmed Abdelhak, MD, co-author of the paper and a postdoctoral researcher in the UCSF laboratory of Ari Green, MD, found that patients with these autoantibodies had elevated levels of neurofilament light, a protein that gets released as neurons break down.

To confirm their findings, the team analyzed blood samples from patients in the UCSF ORIGINS study. These patients all had neurological symptoms and many, but not all, went on to be diagnosed with MS. Once again, 10 percent of the patients in the ORIGINS study who were diagnosed with MS had the same autoantibody pattern. The pattern was 100 percent predictive of an MS diagnosis. Across both the Department of Defense and ORIGINS groups, every patient with this autoantibody pattern had MS. ❖

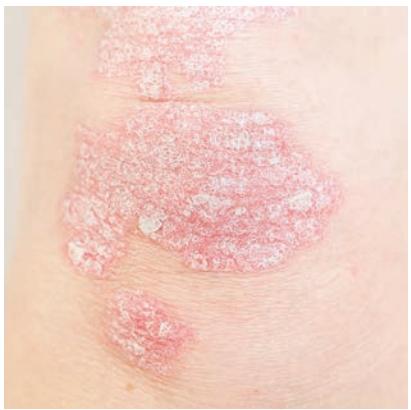
Blood Test Predicts Multiple Sclerosis Years Before Symptoms Appear. Neuroscience News, April 19, 2024. Accessed at neurosciencenews.com/blood-test-multiple-sclerosis-25950.

Medicines

Selarsdi Approved as Biosimilar to Stelara to Treat Plaque Psoriasis and Psoriatic Arthritis

The U.S. Food and Drug Administration (FDA) has approved Selarsdi (ustekinumab-aekn) injection for subcutaneous use, as a biosimilar to Stelara, for the treatment of moderate to severe plaque psoriasis and for active psoriatic arthritis in adults and pediatric patients 6 years and older. Ustekinumab is a human monoclonal antibody (mAb) that selectively targets the p40 protein, a component common to both interleukin (IL)-12 and IL-23 cytokines, which play crucial roles in treating immune-mediated diseases like psoriasis and psoriatic arthritis. Alvotech developed and produces Selarsdi using Sp2/0 cells and a continuous perfusion process, which are the same type of host cell line and process used in the production of Stelara.

FDA approval of Selarsdi, referred to as AVT04 during development, was



based on a totality of evidence, including analytical and clinical data. The clinical development program included data from 1) study AVT04-GL-301, a randomized, double blind, multicenter, 52-week study to demonstrate equivalent efficacy and to compare safety and immunogenicity between Selarsdi and the reference product Stelara in patients with moderate to severe chronic plaque-type psoriasis. The study was conducted in four countries in Europe and enrolled 581 patients. The primary efficacy endpoint was Psoriasis Area and Severity Index percent improvement from baseline to week 12; and 2) study AVT04-GL-101, a Phase I, randomized, double-blind, single-dose, parallel-group, three-arm study to compare the pharmacokinetic, safety, tolerability and immunogenicity profiles of Selarsdi, administered as a single 45mg/0.5mL subcutaneous injection with that of the U.S.-licensed Stelara, as well as EU-approved Stelara. The study was conducted in Australia and New Zealand and enrolled 294 healthy adult volunteers. ❖

FDA Approves Selarsdi. Drugs.com, April 16, 2024. Accessed at www.drugs.com/newdrugs/fda-approves-selarsdi-ustekinumab-aekn-biosimilar-stelara-6247.html.

Medicines

Hizentra Vials to Be Discontinued and Replaced with Prefilled Syringes

CSL Behring is discontinuing all sizes of Hizentra vials in the U.S. by the end of September 2024. The company is advising that all appropriate vial patients should be transitioned to Hizentra prefilled syringes (PFS), and new Hizentra patients should be started on PFS. Customers, providers and patients will receive a final Hizentra vial discontinuation notification once all Hizentra vial inventory has been exhausted.

The following Hizentra Product SKUs are being discontinued:

- Hizentra 1g/5mL vial 44206-0451-01
- Hizentra 2g/10mL vial 44206-0452-02
- Hizentra 4g/20mL vial 44206-0454-04
- Hizentra 10g/50mL vial 44206-0455-10

After discontinuation of these product SKUs, the following available product SKUs will be available:

- Hizentra 1g/5mL PFS 44206-0456-21
- Hizentra 2g/10mL PFS 44206-0457-22
- Hizentra 4g/20mL PFS 44206-0458-24
- Hizentra 10g/50mL PFS 44206-0455-25

"CSL Behring believes it is in the best interest of Hizentra patients to simplify their infusion process, offering them a simple, convenient and ready-to-use option in Hizentra prefilled syringes that eliminates the need for a vial transfer," said Richard Dudek, vice president of healthcare systems. "CSL Behring is committed to putting patients' needs first, and to delivering innovative, lifesaving

medicines to patients."

For additional questions, individuals should contact their CSL Behring associate director of corporate accounts. For any medical/clinical questions, contact CSL Behring's medical information team at (800) 504-5434. ❖

CSL Behring letter to customers titled "Notitice: Hizentra Vials to be Discontinued – All Hizentra Patients to Transition to Prefilled Syringes Hizentra® [immune globulin subcutaneous (human) 20% liquid] Vial SKUs, April 2024.

Medicines

Fresenius Kabi's Tyenne, a Biosimilar of Actemra, Is Approved to Treat Autoimmune Diseases

The U.S. Food and Drug Administration (FDA) has approved Tyenne (tocilizumab-aazg), a biosimilar referencing tocilizumab (Actemra; Genentech), to treat multiple autoimmune diseases, including rheumatoid arthritis and juvenile idiopathic arthritis. Tyenne is the first tocilizumab biosimilar to be approved by FDA for intravenous (IV) and subcutaneous use.

Tyenne is an interleukin-6 receptor antagonist that will be available in prefilled syringes, pen injectors and vial presentations. Serious infections have been reported for individuals receiving the biosimilar, including tuberculosis, bacterial, invasive fungal, viral and other infections.

"Offering the first FDA-approved tocilizumab biosimilar therapy option in both IV and subcutaneous formulations to people living with autoimmune diseases in the U.S. is a moment of great pride for Fresenius Kabi. The FDA's approval of our tocilizumab biosimilar is a breakthrough in bringing high-quality, affordable and accessible autoimmune treatment options to patients and healthcare providers," said Michael Schönhofen, PhD, president of biopharma at Fresenius Kabi. "We are expanding our biosimilars portfolio for immunology and oncology-related diseases, and we are committed to improving the quality of patients' lives and lightening the burden on healthcare systems around the world."

This is Fresenius Kabi's third biosimilar approved in the United States, following Stimufend (pefilgrastim-fpgk), a biosimilar to Neulasta, and Idacio (adalimumab-aacf), a biosimilar to Humira. ❖

Tyenne® (tocilizumab-aazg) Becomes the First IV and Subcutaneous Tocilizumab Biosimilar Approved by the FDA. Fresenius Kabi press release, March 7, 2024. Accessed at www.fresenius-kabi.com/news/tyenne-first-iv-and-subcutaneous-tocilizumab-biosimilar-approved-by-fda.

Medicines

FDA Approves Repotrectinib for Non-Small Cell Lung Cancer

The U.S. Food and Drug Administration (FDA) has approved Bristol Myers Squibb's repotrectinib (Augtryo) for the treatment of adult patients with locally advanced or metastatic ROS1-positive non-small cell lung cancer. Repotrectinib is an orally administered tyrosine kinase inhibitor (TKI) that targets ROS1 oncogenic fusions.

Approval is based on findings from the TRIDENT-1 study, a global, multi-center, single-arm, open-label, multi-cohort Phase I/II clinical trial that evaluated the safety, tolerability, pharmacokinetics and anti-tumor activity of repotrectinib in patients with advanced solid tumors. The primary end point of the study was objective response rate (ORR), or the proportion of patients treated within a certain time frame who experienced either a partial response (tumor size decreased) or complete response (no longer had signs of cancer). The study demonstrated an ORR of 79 percent. The median duration of response (mDOR) was 34.1 months. Additionally, among patients who had been pretreated with one prior ROS1 TKI and no prior chemotherapy (n=56), the ORR was 38 percent, and the mDOR was 14.8 months. Furthermore, among patients who had measurable central nervous system metastases at baseline, responses in intracranial lesions were seen in seven of eight TKI-naïve patients (n=71) and in five of 12 patients who were pretreated with TKIs (n=56).

The most common adverse reactions that occurred in at least 20 percent of patients were dizziness (63 percent), dysgeusia (48 percent), peripheral neuropathy (47 percent), constipation (36 percent), dyspnea (30 percent), ataxia (28 percent), fatigue (24 percent), cognitive disorders (23 percent) and muscular weakness (21 percent). Permanent discontinuation of repotrectinib occurred in eight percent of patients in the study, with serious adverse events occurring in 33 percent of patients. Serious adverse events occurring in at least two percent of patients included pneumonia (5.7 percent), dyspnea (3.8 percent), pleural effusion (3.4 percent) and hypoxia (3 percent). Furthermore, fatal adverse reactions occurred in 4.2 percent of patients, including death, pneumonia, pneumonia aspiration, cardiac arrest, sudden cardiac death, cardiac failure, sudden death, hypoxia, dyspnea, respiratory failure, tremor and disseminated intravascular coagulation. ❖

Steinzor, P. FDA Approves Repotrectinib for Locally Advanced or Metastatic ROS1-Positive NSCLC. *American Journal of Managed Care*, Nov. 16, 2023. Accessed at www.ajmc.com/view/fda-approves-augtyro-for-locally-advanced-or-metastatic-ros1-positive-nsclc#.

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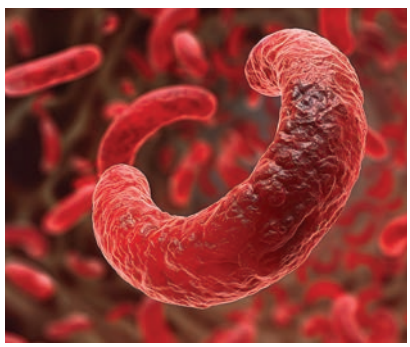
Medicines

World's First Gene Therapies Approved to Treat Sickle Cell Disease



The U.S. Food and Drug Administration (FDA) has approved two treatments, Casgevy and Lyfgenia, representing the first cell-based gene therapies for the treatment of sickle cell disease (SCD) in patients 12 years and older. Casegevy is the first FDA-approved treatment to utilize CRISPR/Cas9, a novel genome editing technology, which signals an innovative advancement in the field of gene therapy.

Patients' hematopoietic (blood) stem cells are modified by genome editing using CRISPR/Cas9 technology. CRISPR/Cas9 can be directed to cut DNA in targeted areas, enabling the ability to accurately edit (remove, add or replace) DNA where it was cut. The modified blood stem cells are transplanted back into the patient where they engraft (attach and multiply) within the bone marrow and increase the production of fetal hemoglobin (HbF), a type of hemoglobin that facilitates oxygen delivery. In patients with SCD, increased levels of HbF prevent the sickling of red blood cells.

Lyfgenia, a cell-based gene therapy, uses a lentiviral vector (gene delivery vehicle) for genetic modification and is approved for the treatment of patients 12 years of age and older with SCD and a history of vaso-occlusive events. With Lyfgenia, the patient's blood stem cells are genetically modified to produce HbAT87Q, a gene therapy-derived hemoglobin that functions similarly to hemoglobin A, which is the normal adult hemoglobin produced in persons not affected by SCD. Red blood cells containing HbAT87Q have a lower risk of sickling and occluding blood flow. These modified stem cells are then delivered to the patient.

Both products are made from the patients' own blood stem cells, which are modified, and are given back as a one-time, single-dose infusion as part of a hematopoietic (blood) stem cell transplant. Prior to treatment, patients' own stem cells are collected, and then patients must undergo myeloablative conditioning (high-dose chemotherapy), a process that removes cells from the bone marrow so they can be replaced with the modified cells in Casgevy and Lyfgenia. Patients who received Casgevy or Lyfgenia will be followed in a long-term study to evaluate each product's safety and effectiveness.

"Sickle cell disease is a rare, debilitating and life-threatening blood disorder with significant unmet need, and we are excited to advance the field especially for individuals whose lives have been severely disrupted by the disease by approving two cell-based gene therapies today," said Nicole Verdun, MD, director of the Office of Therapeutic Products within the FDA's Center for Biologics Evaluation and Research. "Gene therapy holds the promise of delivering more targeted and effective treatments, especially for individuals with rare diseases where the current treatment options are limited." ❖

FDA Approves First Gene Therapies to Treat Patients with Sickle Cell Disease. U.S. Food and Drug Administration news release, Dec. 8, 2023. Accessed at www.fda.gov/news-events/press-announcements/fda-approves-first-gene-therapies-treat-patients-sickle-cell-disease.

Medicines

CSL Behring Adds 4 and 5 Gram Vials of ZEMAIRA

CSL Behring's ZEMAIRA (alpha1-proteinase inhibitor [human]) is now available in 4 gram and 5 gram vials. Previously available only in a 1 gram vial, the new packaging is significant for the alpha-1 community as it will streamline the preparation process for ZEMAIRA and reduce waste.

ZEMAIRA dosing is weight-based: For example, a person weighing 183 pounds would require five 1 gram vials. With the 4 and 5 gram vial sizes, healthcare professionals will need to reconstitute fewer ZEMAIRA vials per dose for their patients with alpha-1. Room temperature storage coupled with the larger vial sizes may also help streamline preparation and administration.

"We have been providing ZEMAIRA to the alpha-1 community for 20 years and are committed to listening and addressing unmet needs through our therapies and patient programs," said Shannen Silvestrini, director of ZEMAIRA marketing at CSL Behring. "With the larger vial sizes, we will continue to provide a safe and effective treatment option while potentially making it easier for healthcare professionals to prepare ZEMAIRA for their patients." ❖

CSL Behring Demonstrates Continued Commitment to Alpha-1 Community with Addition of ZEMAIRA® [Alpha1-Proteinase Inhibitor (Human)] 4- and 5-Gram Vials. CSL Behring press release, Jan. 2, 2024. Accessed at www.prnewswire.com/news-releases/csl-behring-demonstrates-continued-commitment-to-alpha-1-community-with-addition-of-zemaira-alpha1-proteinase-inhibitor-human-4--and-5-gram-vials-302024123.html.

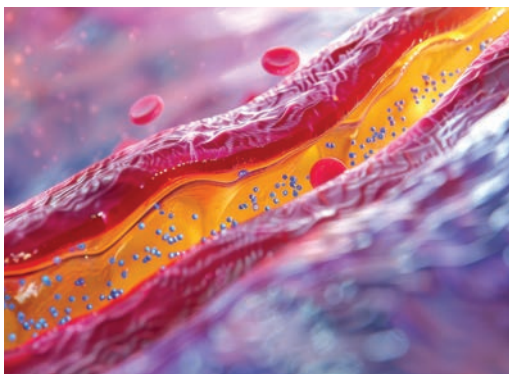
Research

New Vaccine Could Lower 'Bad' Cholesterol by as Much as 30 Percent

A new vaccine currently in development can effectively and affordably lower levels of "bad' cholesterol in the body, a health problem that affects almost two in five adults in the U.S. In tests on mice and monkeys, a team of researchers from the University of New Mexico and the University of California, Davis, were able to reduce low-density lipoprotein (LDL) levels by up to 30 percent by targeting a protein called proprotein convertase subtilisin/kexin type 9 (PCSK9), known to have an important relationship to LDLs. LDL, also known as "bad" cholesterol, is the type of cholesterol that can cause dangerous blockages in the arteries, reducing oxygen flow to the heart or causing blood clots that can lead to a stroke.

"The vaccine is based on a non-infectious virus particle," says molecular geneticist Bryce Chackerian, PhD, from the University of New Mexico. "It is just the shell of a virus, and it turns out that we can use that shell of a virus to develop vaccines against all sorts of different things."

Currently, PCSK9 inhibitors are effective in reducing LDL; however, the vaccine is a solution that could potentially cost much less. Already a decade in development, the next stage for the vaccine is trials in humans, although that will require further study and further financing — all of which will be worth it if it reduces the close to 18 million lives lost globally every year to cardiovascular disease.



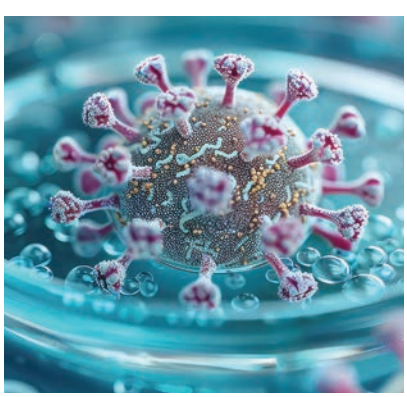
"We hope to have a vaccine in people in the next 10 years," says Dr. Chackerian. ❖

Nield, D. A Game-Changing Vaccine Could Lower 'Bad' Cholesterol by 30%. Science Alert, Dec. 28, 2023. Accessed at www.sciencealert.com/a-game-changing-vaccine-could-lower-bad-cholesterol-by-30.

Research

New Study to Examine COVID-19 Vaccines in People with Weakened Immune Systems

Researchers at the University of Wisconsin (UW) School of Medicine and Public Health are exploring the ideal vaccine booster strategy for immunosuppressed patients to protect those at higher risk of severe illness and complications from COVID-19 infection. The goal of the trial titled Additional Recombinant COVID-19 Humoral and Cell-Mediated Immunogenicity in Immunosuppressed Populations, or ARMOR, is to determine whether a recombinant booster COVID-19 vaccine dose will improve sustained immunity against the virus that causes COVID-19 in people who live with inflammatory bowel disease (IBD) or solid organ transplant recipients and whose medical treatments involve staying on immunosuppressive drugs.



Participants who enroll in this trial will receive the Novavax COVID-19 vaccine, which is a recombinant vaccine and differs from the Pfizer or Moderna drugs in that it directs the immune system to recognize specific pieces of the virus. Studies have shown that those who receive immunosuppressive medications such as corticosteroids are at a higher risk for severe COVID-19 if they are infected, according to Freddy Caldera, DO, MS, associate professor of medicine at the UW School of Medicine and Public Health and gastroenterologist at UW Health.

The trial is taking place at University Hospital in Madison. Participants will receive the Novavax vaccine and have their blood drawn three times, once prior to vaccination, once 30 days after vaccination and once six months after vaccination. Researchers will assess immune system response after vaccination by evaluating levels of antibodies and T cells. The cost of the vaccination is covered by the trial. ❖

New Study Examines COVID-19 Vaccines in People with Weakened Immune Systems. University of Wisconson-Madison School of Medicine and Public Health, Nov. 16, 2023. Accessed at www.med.wisc.edu/news-and-events/2023/november/covid-19-vaccines-immunosuppressed-patients.

Viruses, Variants and Vaccines:

Staying Ahead of the Spread

Although history has proven the success of vaccines in controlling the spread of diseases, emerging threats are concerning. However, hope is on the horizon with studies of newer vaccines.

By Lee Warren

IN THE WAKE of the COVID-19 pandemic, the critical role of vaccines in stopping the spread of infectious diseases has become undeniable. The global response to the pandemic underscores the urgent need for effective vaccines to combat emerging threats and safeguard public health. Despite the challenges the world experienced during the pandemic, researchers worldwide continue to pioneer breakthroughs in vaccine development. From the Zika virus to Lyme disease, ongoing efforts offer promise for the creation of new vaccines.

Before looking at some of the new breakthroughs, here's a summary of historic successes of vaccines in the past.

Vaccine Successes

- *Smallpox.* Smallpox was "one of the most devastating diseases known to humanity," according to the World Health Organization (WHO), as it caused millions of deaths over the course of 3,000 years before it was eradicated. Edward Jenner, MD, first developed a vaccine for smallpox in 1796. WHO

launched an intensified plan to eradicate the virus in 1967. By 1977, the last known natural cause was in Somalia. In 1980, WHO declared the disease eradicated.[1]

• *Polio*. Polio has been in existence for thousands of years. In 1988, the World Health Assembly adopted a resolution for the worldwide eradication of polio. Jonas Salk, MD, is credited with developing the first successful inactivated polio vaccine (IPV), which was announced in 1955. In the 1960s, Albert Sabin, MD, developed the oral polio vaccine (OPV). One estimate says the use of polio vaccines prevented five million cases of paralytic polio between 1960 and 1987 and 24 million cases worldwide between 1988 and 2021, compared to a counterfactual world with no polio vaccines.[2] Just two endemic countries remain: Pakistan and Afghanistan.[3] As such, the world remains at risk, especially those with weak public health and immunization services or whose travel or trade links remain open to endemic countries.

• *Measles.* Measles can spread quickly and can even be fatal in children. WHO reports that before the introduction of the measles vaccine in 1963 and widespread vaccination, major epidemics occurred approximately every two to three years and caused an estimated 2.6 million deaths each year.[4] John Franklin Enders, PhD, a biomedical scientist, developed a measles vaccine along with his team. By 1961, it was considered 100 percent effective and was licensed for public use in 1963. In 2000, measles was declared eliminated (meaning the absence of continuous transmission for more than 12 months) in the United States, largely due to widespread vaccination efforts. With accelerated immunization activities by countries, WHO, the Measles & Rubella Partnership (formerly the Measles & Rubella Initiative) and other international partners, 56 million deaths were successfully prevented between 2000 and 2021.[4]

• *Diphtheria*. Diphtheria was a leading cause of childhood death in the pre-vaccine era.[5] It is fatal in five to 10 percent of cases with a higher mortality rate among young children. Diphtheria was described by Hippocrates in 5th century B.C. prior to epidemics in the 6th century. The diphtheria-tetanus-pertussis (DTP) vaccine was introduced after World War II, resulting in a decreased incidence of the disease in industrialized countries. It should be noted that the decrease in diphtheria morbidity and mortality rates in the United States after 1925 might, in part, be attributed at least to artificial immunization.[6] But that does seem improbable based on the number of people who were immunized. Cases did gradually decline after vaccines were introduced in the 1940s, then rapidly declined after a universal vaccination program. From 2002 to 2022, only six cases were reported in the United States.[7]

Most reported tetanus cases are birth-associated among newborn babies and mothers who have not been sufficiently vaccinated with a tetanus-toxoid-containing vaccine (TTCV). In 2018, approximately 25,000 newborns died from neonatal tetanus, which was a 97 percent reduction from 1988 when an estimated 787,000 newborn babies died within their first month of life.[8] The TTCV vaccine was developed by multiple researchers over several decades. Gaston Ramon, MD, was one of the earliest researchers to develop the TTCV vaccine in the 1920s. Other vaccines are also used to treat tetanus, including Td, Tdap and DTaP. While tetanus is preventable through the administration of vaccines, the disease is not eradicated due to a high prevalence of bacteria in the environment.

Researchers remain vigilant in the face of evolving threats as they use cutting-edge advancements to develop vaccines for current and emerging diseases.

Staying Ahead of the Spread

Conventional vaccines use one or several antigens derived from inactivated or weakened pathogens, or their components such as protein subunits or toxins, to generate an immune response.[9] These vaccines are time-consuming to produce, involve a greater risk of reversion to virulence, and need more customized development against emerging or rapidly evolving pathogens.

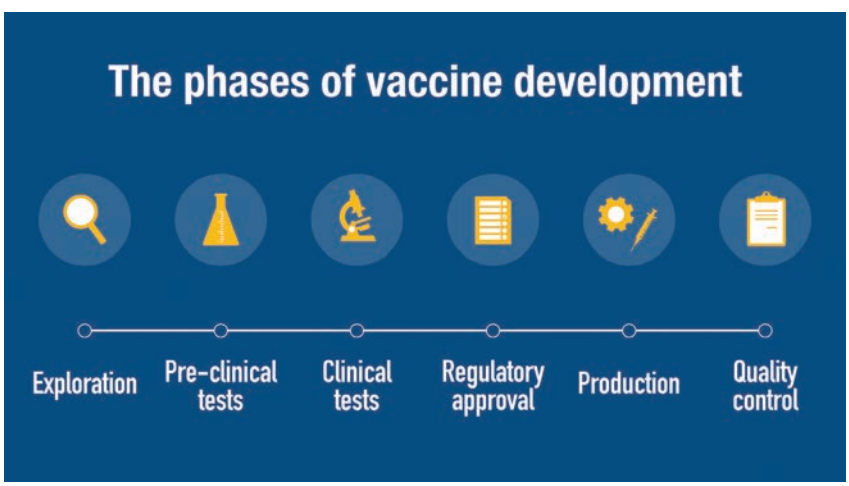
Looking ahead, newer epidemiological surveillance tools are being used for the challenges of new and existing viruses and diseases. Those tools include artificial intelligence and wastewater surveillance; the evolution of rapid, multiplex and easy-to-use diagnostics; and the prompt development and evaluation of novel therapeutics.[10]

As of Jan. 1, 2023, the global vaccine research and development landscape included 966 candidates, among which 23 percent (220) were traditional inactivated or attenuated vaccines. Advances in molecular technologies have led to

the development of other platforms.[11] Following is a look at some of the studies being performed on various vaccines to stay ahead of the spread.

Recombinant Protein Vaccines

Recombinant vaccines can treat hepatitis B virus, human papillomavirus (HPV), pertussis (whooping cough), influenza, COVID-19 (SARS-CoV-2), malaria, Lyme disease and others. Nearly 100 recombinant vaccine candidates are in Phase I development, making it the highest number at this stage among all platforms.[11]



Lyme disease cases have doubled since 2000 to nearly 500,000 per year in the United States. Pfizer anticipates U.S. Food and Drug Administration (FDA) approval in 2026 for the VLA15 vaccine, which is in clinical trials. The vaccine works by targeting an outer surface protein of *Borrelia burgdorferi* — the bacterium that causes Lyme disease. The vaccine blocks the protein OspA, which prevents the spiral-shaped bacterium from being able to leave the tick and infect humans it has bitten.[12]

Two recombinant protein vaccines, PF-06928316 (Pfizer's ABRYSVO) and GSK3844766A (GSK's AAREXVY), have resulted in a greater than 80 percent protection in Phase III trials for respiratory syncytial virus (RSV), and received FDA approval in 2023 to treat RSV in adults age 60 and older.[11]

The first generation of COVID-19 vaccines were less effective against variants, including Omicron. New vaccines developed against variant strains may provide cross-protection against emerging variants when used as boosters. A study of one vaccine in a randomized, double-blind and placebo-controlled Phase III trial in two stages found the vaccine was well-tolerated with an acceptable safety profile.[13] Another study tested a vaccine in a randomized, placebo-controlled Phase I trial of novel SARS-CoV-2 beta variant receptor-binding domain recombinant protein and mRNA vaccines as a fourth dose booster. Both vaccines showed a strong immune boosting response against beta, ancestral and Omicron strains.[14]

Viral Vector Vaccines

Viral vector vaccines employ genetically modified viruses to deliver genetic material-encoding antigens into host cells, prompting the immune system to generate protective responses against the targeted pathogen. Numerous viruses are deemed to be prominent viral vectors, including vesicular stomatitis virus, rabies virus, measles virus, Newcastle disease virus, influenza virus, adenovirus and poxvirus.[15]

RSV can lead to serious disease in infants. Currently, no approved RSV vaccine is available for infants. For adults, the first in-human Phase I clinical trial evaluated a single dose of BLB201, a PIV5-vectored RSV vaccine administrated via intranasal route, for safety and immunogenicity in RSV-seropositive healthy adults in three groups, ranging from 33 to 75 years of age, 70 percent of whom were female. The reported results suggested that BLB201 boosted RSV-specific serum Ab levels in young adults (33 to 59 years old) and elderly adults (61 to 75 years old), although with greater magnitude in young adults versus elderly adults. Runny noses, fatigue, headaches or myalgia were experienced by eight of the 45 participants. Chills, nausea/vomiting and breathing discomfort were reported by one participant. The study researchers concluded that the ability of BLB201 to boost pre-existing cellular, humoral and mucosal responses in adults supported further clinical evaluation.[16]

mRNA Vaccines

mRNA vaccines are used to treat COVID-19 (SARS-CoV-2), influenza, cytomegalovirus (CMV), Zika, cancer and various infectious diseases.

One study examined two Zika virus mRNA-based vaccines (mRNA-1325 and mRNA-1893), both of which were randomized, placebo-controlled, dose-ranging, multicenter, Phase I trials. All three dose levels of mRNA-1325 (10, 25 and 100 µg) were generally well-tolerated, but the vaccine elicited poor Zika virus-

specific nAb responses. On day 57 of the mRNA-1893 vaccine trial, all evaluated dose levels induced robust Zika virus-specific nAb responses, independent of flavivirus serostatus, that persisted until month 13. The findings supported the continued development of mRNA-1893 against Zika virus.[17]

In February 2024, a group of cancer patients at Imperial College Healthcare NHS Trust Cancer UK underwent a new experimental mRNA therapy — a type of immunotherapy treatment called mRNA-4359 — which is being evaluated for safety and its potential for treating melanoma, lung cancer and other "solid tumor" cancers in a global trial. David Pinato, MD, PhD, a consultant medical oncologist at Imperial College Healthcare NHS Trust and a clinician scientist at Imperial College London, is lead investigator of the UK arm of the trial. He articulates the hope of these types of vaccines: "New mRNA-based cancer immunotherapies, such as mRNA-4359, offer a new avenue for recruiting patients' own immune systems to fight their cancer. This research is still in the early stages and may be a number of years from being available to patients, but this trial is laying crucial groundwork that is moving us closer toward new therapies that are potentially less toxic and more precise."[18]

DNA Vaccines

Deoxyribonucleic acid (DNA) vaccines utilize genetically engineered DNA to produce an immunologic response. They are used for cancer, tuberculosis, Edwardsiella tarda, human immunodeficiency virus (HIV), anthrax, influenza, malaria, dengue, typhoid and others.

In February 2024, researchers in one AIDS study found that the PD-1-enhanced DNA vaccination can induce sustained virus-specific CD8+ T cell immunity in an AIDS monkey model, and the vaccinated monkeys remained free of AIDS for six years and achieved virologic control without the need for combination antiretroviral therapy (cART) — a treatment used to suppress viral replication in individuals living with HIV. Study researchers say that if this efficacy can be replicated in humans, a therapeutic vaccine for cART-free HIV-1 control will be on the horizon.[19]

Typhoid remains a major health problem in the developing world. And it, too, has seen advances in a vaccine, one of which uses bacterial ghost (BG) technology, prepared by both genetic and chemical means. One report that showed improved preparation of high-quality BGs of *Salmonella typhi*, visualized by scanning electron microscope, revealed punctured cells with intact outer shells. Moreover, the absence of vital cells was confirmed by subculturing. At the same time, the release of respective amounts of proteins and DNA is another evidence of BGs' production. Additionally, the challenge test provided evidence that the prepared BGs are immunogenic and have the same efficacy as the whole cell vaccine.[20]

Hope for the Future

The remarkable achievements in successfully eradicating or in greatly curbing deadly diseases through vaccines in the past serve as a testament to the power of scientific innovation and collective action. Researchers remain vigilant in the face of evolving threats as they use cutting-edge advancements to develop vaccines for current and emerging diseases. By prioritizing global collaboration, innovation and equitable access to vaccines, hope is on the horizon for a healthier world. ❖

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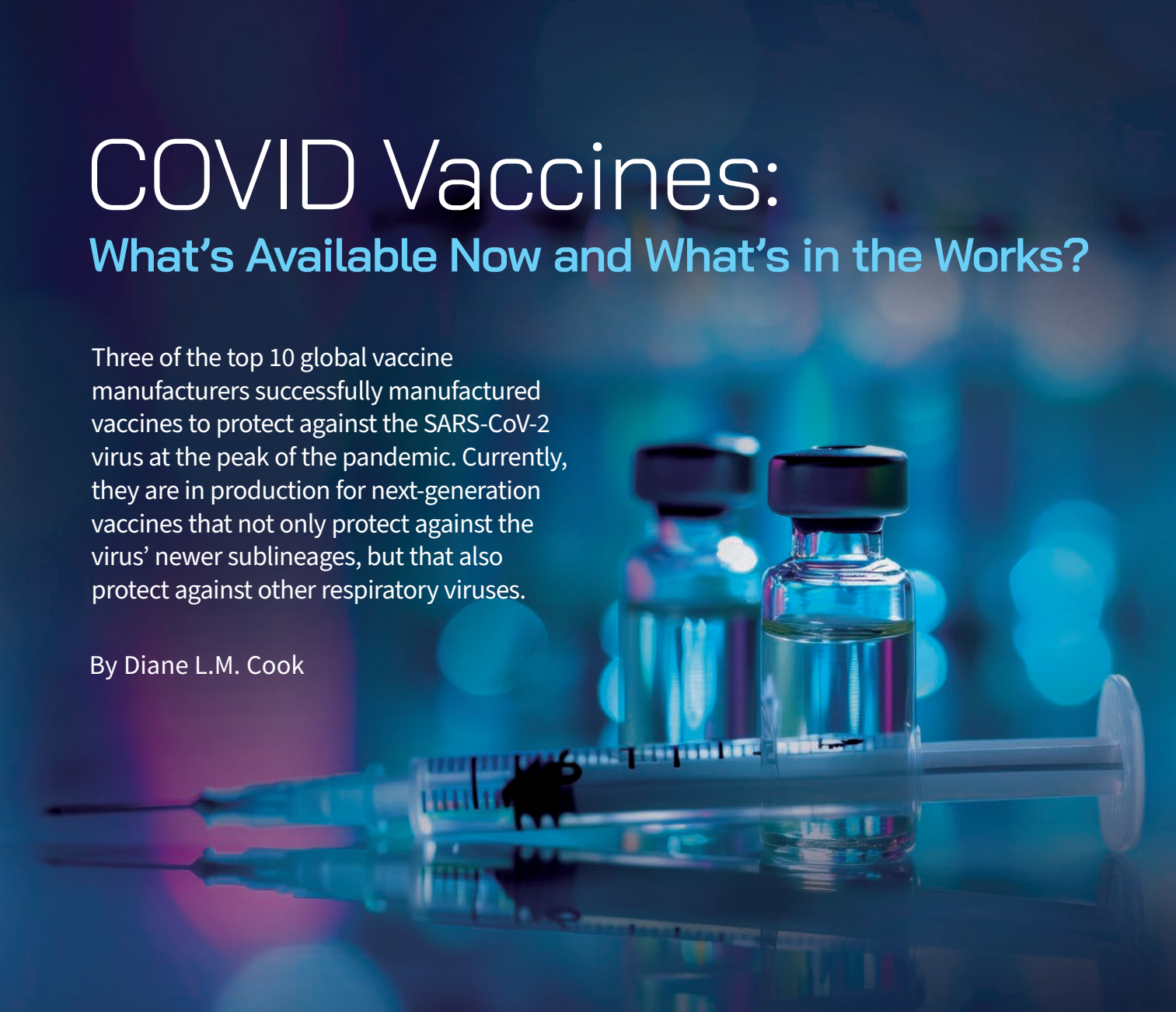
COVID Vaccines:

What's Available Now and What's in the Works?

Three of the top 10 global vaccine manufacturers successfully manufactured vaccines to protect against the SARS-CoV-2 virus at the peak of the pandemic. Currently, they are in production for next-generation vaccines that not only protect against the virus' newer sublineages, but that also protect against other respiratory viruses.

By Diane L.M. Cook



IT HAS BEEN more than a year since the World Health Organization (WHO) and the U.S. Department of Health and Human Services (HHS) declared the end of the COVID-19 pandemic, but COVID-19 vaccines are still prominent in the preventive healthcare space.[1] "COVID-19 is here to stay, and the world will continue to need tools to prevent it, test for it and treat it," says Tedros Adhanom Ghebreyesus, director-general of WHO.[2]

According to WHO and HHS, "While clinical and real-world data still show that existing COVID-19 vaccine options can help protect against the virus, we are continuing to follow the science by exploring new vaccine approaches that may be needed as the virus evolves."[1] Indeed, not only are vaccine manufacturers still making COVID-19 vaccines to prevent the severe acute respiratory syndrome corona virus 2 (SARS-CoV-2), but they are now making next-generation and combination vaccines that prevent the ever-mutating SARS-CoV-2 virus, as well as other respiratory viruses such as seasonal influenza and respiratory syncytial virus (RSV).

Following are the currently available COVID-19 vaccines and a look at what is in the works from three of the top 10 global vaccine manufacturers.

Pfizer-BioNTech

Pfizer-BioNTech's current COVID-19 vaccine — COMIRNATY 2023-2024 Formulation — is an updated vaccine tailored to the SARS-CoV-2 XBB.1.5 sublineage, and is indicated as a single dose for individuals 5 years of age and older.

Preclinical data showed this updated COVID-19 vaccine generated improved neutralizing antibody responses against multiple circulating Omicron-related sublineages, including XBB.1.5, BA.2.86 (Pirola) and EG.5.1 (Eris). Data from real-world studies complement the Phase III clinical trial data and provide additional evidence that the vaccine

provides effective protection against severe disease. The companies' COVID-19 vaccine differs from its earlier COVID-19 vaccines only in that it contains messenger RNA (mRNA) coding for the spike protein of a different SARS-CoV-2 sublineage.

The U.S. Food and Drug Administration's (FDA) approval of Pfizer-BioNTech's updated COMIRNATY vaccine was based on the full body of previous clinical, preclinical and real-world evidence supporting the safety and efficacy of the companies' COVID-19 vaccines. The companies' FDA application included preclinical data showing improved responses against multiple Omicron XBB sublineages, including XBB.1.5, XBB.1.16 and XBB.2.3, compared to the Omicron BA.4/BA.5-adapted bivalent vaccine.

The Pfizer-BioNTech collaboration is currently working on an mRNA-based combination vaccine for COVID-19 and influenza. Based on positive results from a Phase I/II clinical trial among healthy adults 18 to 64 years of age, the vaccine candidate showed robust immunogenicity against all targeted influenza and SARS-CoV-2 strains. The vaccine candidates were compared to a licensed influenza vaccine and the companies' Omicron BA.4/BA.5-adapted bivalent COVID-19 vaccine given at the same visit.

Data from this clinical trial showed the companies' lead formulations demonstrated robust immune responses to influenza A, influenza B and SARS-CoV-2 strains. Pfizer-BioNTech plan to start a Phase III trial soon. The companies have also received fast track designation from FDA for this vaccine.

With its robust vaccine pipeline, Pfizer says it aims to deliver multiple innovative vaccines in the near future. "We have an ambitious and comprehensive program exploring combination vaccines for multiple respiratory viruses including COVID-19, respiratory syncytial virus and influenza," said a Pfizer spokesperson.

Pfizer-BioNTech's COMIRNATY vaccine is based on the companies' proprietary mRNA technology. The versatile and flexible mRNA technology is a molecule that contains the instructions that direct the cells to make a protein using its natural machinery. mRNA-based vaccines have demonstrated their ability to induce robust antibody and T-cell responses. "mRNA is likely to be at least one of the waves of the future for vaccines. Overall, it is a very powerful technique to be able to create a lot of a vaccine fast," explained a Pfizer spokesperson. "The benefit is that the technology is very adaptable. We can potentially go in and change the mRNA in the formulation to target a new antigen, and we can make a lot of high-quality vaccine material relatively quickly. We utilize the mRNA platform for vaccine targets, which gives us the flexibility to explore combinations of different vaccine modalities for COVID-19, influenza, varicella zoster virus and combinations."

Unlike conventional vaccines — which can take many months or even years to cultivate — mRNA vaccines can be developed quickly using the pathogen's genetic code. By having the vaccine recipient make the antigen via the instructions encoded in the mRNA, the antigen can look more like it does during a live infection versus when engineered in a laboratory or produced in eggs, which may improve protection.

"We are encouraged by early results in our Phase I/II study of our combination vaccine candidates against COVID-19 and influenza. This vaccine has the potential to lessen the impact of two respiratory diseases with a single injection and may simplify immunization practices for providers, patients and healthcare systems all over the world. mRNA-based vaccines have demonstrated their ability to induce robust antibody and T-cell responses, and we look forward to starting Phase III clinical development. This is an important achievement toward our ambition of providing a broad portfolio of respiratory combination vaccines," said Annaliesa Anderson, PhD, senior vice president and head of vaccine research and development at Pfizer.

Vaccines Under Development

Company	Vaccine Candidate	Clinical Trial Data
Pfizer-BioNTech	mRNA-based combination vaccine for COVID-19 and influenza	• Phase I/II clinical trial among healthy adults 18 to 64 years old showed robust immunogenicity against all targeted influenza and SARS-CoV-2 strains • Phase III clinical trial to begin soon under FDA fast track designation
Moderna	Refrigerator-stable next-generation COVID-19 vaccine	• Currently in a pivotal Phase III study with results expected in first half of 2024
Moderna	Seasonal flu plus COVID combination vaccine (mRNA-1083)	• Phase III clinical trial is fully enrolled with results expected in 2024
Novavax	Combination protein-based nanoparticle vaccine providing coverage for influenza and SARS-CoV-2	• Phase I/II clinical trial supported advancement to a Phase III clinical trial • Phase III clinical trial to begin in second half of 2024

Moderna

Moderna's current COVID-19 vaccine is Spikevax, which uses its proprietary mRNA technology platform. In June 2023, FDA advised that COVID-19 vaccines should be updated to a monovalent XBB.1.5 composition for the 2023-2024 vaccination season. At the June Vaccines and Related Biological Products Advisory Committee meeting, Moderna presented clinical data showing that its updated Spikevax vaccine resulted in robust immune responses across multiple XBB sublineages, including XBB.1.5 and XBB.1.16.

In September 2023, Moderna announced that FDA had approved its supplemental biologics license application (sBLA) for Spikevax for ages 12 years and older. Emergency use authorization (EUA) for Spikevax was also received by FDA for individuals 6 months through 11 years of age. Moderna's updated COVID-19 vaccine contains spike proteins for the XBB.1.5 sublineage of SARS-CoV-2 to help prevent COVID-19 in individuals 6 months of age and older.

The Centers for Disease Control and Prevention (CDC) says people who were vaccinated with Moderna's updated COVID-19 vaccine, which includes a component that corresponds to the XBB lineage of the Omicron variant, showed a strong immune response against some of the variants that are common now such as XBB.1.5, EG.5.1 and FL.1.5.1. They also had an overall boost in COVID-19 immunity that may have waned since their last vaccination or infection. Their antibody responses after vaccination were about 17 times higher against XBB 1.5 and about 10 times higher against BA.2.86 (a rare new variant) compared to before vaccination. CDC also says these data signal that the updated 2023-2024 COVID-19 vaccine likely provided strong protection against COVID-19 during the 2023-2024 virus season.[3]

Moderna says its upcoming Spikevax vaccines would be determined by strain selection in Spring 2024, which is set by regulatory authorities, for the 2024-2025 vaccination season.

Moderna is currently working on two new types of COVID-19 vaccines. Its next-generation COVID-19 vaccine is a refrigerator-stable (mRNA-1283) vaccine that is currently in its pivotal Phase III study. The company anticipates data from the study in the first half of 2024.

Moderna is also working on a seasonal flu plus COVID combination vaccine (mRNA-1083). Its Phase III trial of this combination vaccine is fully enrolled. The company anticipates data from the study in 2024.

"COVID-19 remains a leading cause of death in the U.S. and poses a significant threat to vulnerable populations. As the primary circulating strain continues to evolve, updated vaccines will be critical to protecting the population," said Stéphane Bancel, CEO of Moderna.[4]

Novavax

Novavax's current COVID-19 vaccine is the Novavax COVID-19 Vaccine (its commercial name is not yet approved for use in the U.S.), adjuvanted (2023-2024) Formula (NVX-CoV2601), for use in individuals 12 years and older. The vaccine is under FDA EUA, and it is recommended by CDC. Currently, the company is working toward full BLA. Novavax's COVID-19 vaccine is the only protein-based, non-mRNA COVID-19 vaccine option available in the U.S.

Non-clinical data showed that Novavax's COVID-19 vaccine induced functional immune responses against XBB.1.5, XBB.1.16 and XBB.2.3 variants. Additional non-clinical data demonstrated Novavax's vaccine induced neutralizing antibody responses to newly emerging subvariants JN.1, BA.2.86, EG.5.1, FL.1.5.1 and XBB.1.16.6, as well as robust CD4+ polyfunctional cellular (T-cell) responses against EG.5.1 and XBB.1.16.6. These data indicate Novavax's vaccine can stimulate both arms of the immune system and may induce a broad response against currently circulating variants.

The latest updated Novavax COVID-19 vaccine targets the XBB subvariants. Additional non-clinical data has demonstrated that this vaccine-induced neutralizing antibody responds to subvariant JN.1 in addition to the previous variants.

Novavax uses adjuvanted protein-based technology to develop vaccines, which combines the power and speed of genetic engineering to efficiently produce protein-based nanoparticles. These protein-based nanoparticles work with Novavax's propriety Matrix-M adjuvant, which helps to enhance immunogenicity. The Matrix-M adjuvant comes from saponins, naturally occurring compounds in the bark of the Quillaja Saponaria (soapbark) tree, commonly found in Chile. This adjuvant is a key element in the company's technology platform. When saponins are mixed with Novavax's vaccine nanoparticles, the combination of ingredients has been shown to enhance the immune system response to the company's vaccines.

Novavax's vaccine technology is disease-agnostic and adaptable. As the SARS-CoV-2 virus evolves, the vaccine can be adjusted to use the version of the spike protein found in new variants.

Vaccine Manufacturer Websites:

- Pfizer: www.pfizer.com
- Moderna: www.modernatx.com
- Novavax: www.novavax.com

Therefore, if a new SARS-CoV-2 variant appears and Novavax's COVID-19 vaccine does not provide sufficient protection, the genetic sequence of the new variant is used to produce a new version of the recombinant spike protein.

Novavax is currently working on combining more than one type of protein-based nanoparticle into a single vaccine candidate to help provide coverage for two or more strains of the same virus. The company's nanoparticle technology is now also being used to combine antigens from different pathogens to help immunize against more than one disease with a single vaccine. For example, Novavax is studying the combination of seasonal influenza with SARS-CoV-2, which may allow protection for individuals against influenza and COVID-19 through a single vaccine. According to the company, data from preclinical trials in animals have shown that a single shot of the combined vaccine successfully generated antibodies against both viruses at comparable levels to using either vaccine alone.

Novavax announced positive data from a Phase I/II clinical trial that evaluated the safety and immunogenicity of this investigational combination vaccine, which supported the advance and development of this candidate into its Phase III trial. Novavax expects to initiate the Phase III trial in the second half of 2024.

Robert Walker, MD, vice president and chief medical officer of Novavax, said, "Vaccination is one of the most cost-effective preventive health investments we can make as an industry and a society. As I look to 2024, I am excited to see years of innovation and hard work on the development of new vaccines pay off even more with a profound impact on public health."

Looking Forward

These three global vaccine manufacturers are continuing their work on novel vaccines for new strains of the SARS-CoV-2 virus, as well as next-generation and combination vaccines to ensure the population has the right vaccine at the right time to prevent serious illness or death from SARS-CoV-2 and other respiratory viruses. ❖

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The Anti-Vaccine Movement: Where Are We Now?

Despite scientific evidence to the contrary, doubts about vaccine safety and efficacy have not only persisted, but escalated. Counteracting this wave of mistrust will require targeted tactics and networked, community involvement.

By Trudie Mitschang

IN THE REALM of public health, few topics have garnered as much attention and sparked as much controversy as the subject of vaccines. In our post-pandemic world, the anti-vaccine movement has not only persisted but seemingly thrived, presenting challenges for public health officials, policymakers and communities worldwide. Despite advances in medical science and overwhelming evidence supporting the safety and efficacy of vaccines, skepticism and hesitancy persist, fueled by misinformation, distrust and ideological beliefs.

The anti-vaccine movement, which gained significant momentum in recent decades, is characterized by individuals and groups who question the value of vaccines. While concerns about vaccines are not new, the proliferation of social media and online platforms as sources of misinformation has significantly contributed to the growth of the movement. From conspiracy theories alleging government cover-ups to unfounded claims linking vaccines to autism or other adverse health effects, anti-vaccine rhetoric has permeated public discourse, sowing doubt and confusion among the general population.

The Spread of Misinformation — and Disease

One of the enduring myths perpetuated by anti-vaccine proponents is the debunked link between vaccines and autism. Despite numerous studies discrediting this claim and the retraction of the original paper that suggested a connection, this misinformation continues to circulate widely, perpetuating fear and distrust among parents. In fact, Andrew Wakefield, the discredited United Kingdom physician who authored the original article linking autism to the measles, mumps and rubella (MMR) vaccine has seen a resurgence in his personal celebrity. Wakefield now resides in the U.S. and makes anti-vaccine film documentaries for a living.

In the face of persistent anti-vaccine propaganda, the scientific community continues to push back. A 2019 study from Denmark found no association between being vaccinated against MMR and developing autism. The work, published in the *Annals of Internal Medicine*, was conducted by researchers at the Statens Serum Institut in Copenhagen.[1] "The idea that vaccines cause autism is still going around, and the anti-vax movement, if anything, has perhaps only grown stronger over the last 15 years," said Anders Hviid, one of the researchers involved in the study. "The trend that we're seeing is worrying."

That trend has caused a steady uptick in infectious diseases that were previously contained. In fact, measles cases in the U.S. continue to increase, so much so that this year's numbers surpassed 2023's total within the first three months of the year, according to the Centers for Disease Control and Prevention (CDC).[2]

Media's Role in Public Opinion

The public health crisis created by the COVID-19 pandemic further fueled vaccine skepticism and provided fertile ground for anti-vaccine sentiment to flourish. The rapid development and deployment of vaccines to combat the virus were immediately met with suspicion and resistance by some segments of the population. Misinformation about the COVID-19 vaccines, including baseless claims about their long-term effects or their role in government surveillance, spread rapidly on social media platforms, undermining efforts to control the pandemic. Media outlets soon became

powerfully influential when it came to shaping the public view of vaccine safety.

A 2023 report by researchers from several American universities found that vaccine-resistant people tend to mistrust mainstream media; they either turn to conservative news outlets such as Fox and Newsmax or they avoid traditional news media altogether. The study reported that as many as 36 percent of those who opposed the COVID vaccine relied on Facebook as their only pandemic information source in the first half of 2020.[3]

The study's findings may be useful to public health officials who are trying to reach as broad an audience as possible, including those who lack trust in mainstream media, says one of the seven authors, Matthew Baum, professor of Global Communications at Harvard Kennedy School. "While we cannot make causal claims with these data, we do see a clear positive association between vaccine resistance and reliance on conservative media outlets, like Fox and Newsmax, or on social media — most notably Facebook — as sources of COVID-related information."

To understand where vaccine-hesitant people go for their health information, the scholars looked back at data from several of the project surveys, as well as related surveys by other academic and political pollsters. The resulting paper, "Media Use and Vaccine Resistance," was published in the journal *PNAS Nexus* in May 2023.[3]

The paper looked closely at Facebook as a source of virus information — and as a way to reach vaccine resistors. The data shows that respondents who rely only on Facebook are "consistently among the most vaccine-resistant" — between a quarter and a third of them resisted vaccination. Those who relied on the conservative news site Newsmax were the least likely to get vaccinated, but the number of individuals in this group was small, at just two percent of those surveyed, whereas Facebook was the sole source for between 12 and 16 percent of respondents.[4]

A Growing Political Ideology

There is increasing concern that the 2024 U.S. presidential election will fuel the fires of the anti-vaccine movement. Currently, candidates from both parties are leaning into a growing movement that marries traditional vaccine skepticism with a broader distrust of big institutions — be they the government, the pharmaceutical industry or the scientific community.

According to an article in Politico,[5] it's a movement focused on anti-vaccine and anti-science. The ideology is pro-medical freedom and pro-alternative medicine, but growth in the movement's ranks has many in and out of government fearful that this campaign cycle will accelerate its spread, consolidate its strength and cement its place in the political milieu. "It's going to get worse before it gets better," said Jerome Adams, MD, U.S. surgeon general during the Trump administration. "Many of us in public health are deeply concerned that distrust in government and health entities, and a political campaign in which candidates are openly and vigorously arguing that people should ignore the advice of health experts, could have detrimental impacts for years to come — no matter who wins."

While the anti-vaccine movement has historically found a home among both libertarians and the far-left, recent data is clear that mistrust in vaccines and science in general is significantly higher among Republicans than Democrats. An Associated Press-NORC study showed overall major declines in the public's confidence in science in the wake of the pandemic.[6]

As a modern political force, the anti-vaccine movement has gained visibility and funding, enabling them to expand their public reach, sue federal agencies and organize like-minded activists at the state level, as well as expand their reach abroad. Last year, a lawsuit funded by the anti-vaccine group Informed Consent Action Network forced the state of Mississippi to allow religious exemptions for mandatory childhood vaccinations for the first time in more than four decades.[7]

Informed Consent Action Network was already one of the most well-funded anti-vaccine groups prior to the pandemic, pulling in $1.4 million in 2017. By 2021, its annual revenue topped $13.3 million, according to tax documents. And the group was not alone. Children's Health Defense, a longtime anti-vaccine group launched in 2011 under the name World Mercury Project, also saw its revenue skyrocket, going from just over $1 million in 2018 to more than $15 million in 2021, according to the nonprofit's federal tax filings.[7]

Public health experts believe groups that predated the pandemic have provided a "template" for newer anti-vax efforts, creating an environment in which such groups can proliferate and expand their reach. "Increasingly, there's less and less difference between old school and new school anti-vaxxers," said Dave Gorski, MD, PhD, a Michigan-based oncologist who has been tracking anti-vaccine efforts for two decades. "New anti-vaxxers are lapping up the same old conspiracy theories and pseudoscience."[7]

The Erosion of Herd Immunity

The increase in vaccine hesitancy and vaccine resistance has not only caused an uptick in vaccine-preventable diseases such as measles and whooping cough, it has also led to the erosion of herd immunity. Herd immunity occurs when a large part of a population is immune to a particular disease due to vaccination or previously contracting the illness and developing antibodies. This indirectly also helps ensure the protection of the remaining population and offers a higher chance of combating and reducing transmission.[8]

In many cases, herd immunity ensures that while not everyone is immune to the disease, everyone can enjoy protection from it. Higher numbers of immune people within a population lowers the risk of contracting a disease or virus for everyone. In particular, herd immunity offers protection for a community's most vulnerable demographics, including:

- Those with weak immune systems
- People undergoing chemotherapy
- Newborn babies
- The elderly
- People living with HIV

In every community, there are individuals who fall under the above categories, making herd immunity that much more important. These vulnerable populations depend on others getting vaccinated to be indirectly protected by them.

When it comes to the evolving coronavirus, researchers are increasingly worried that herd immunity is an unattainable goal. In an ideal scenario, reaching high levels of vaccination would mean new outbreaks of the coronavirus would die down quickly, as opposed to growing and spreading. "Vaccine hesitancy is a big problem for all of us," says Ali Mokdad, who tracks coronavirus trends at the Institute for Health Metrics and Evaluation at the University of Washington. "We need to vaccinate as much as possible right now, stop the circulation of this virus in the U.S. and elsewhere. Then we can control it."[9]

Finding a Path Forward

Addressing the anti-vaccine movement requires a multifaceted approach that acknowledges the complex factors driving vaccine hesitancy and skepticism. It is essential to combat misinformation with accurate, evidence-based information and to engage with hesitant individuals and communities with empathy and understanding. Building trust in vaccines and the institutions that promote them necessitates transparency, accountability and open dialogue among public health authorities, healthcare providers and the public. Increasingly, it's clear that addressing the root causes of vaccine hesitancy must extend beyond simply sharing scientific facts. Addressing underlying socioeconomic disparities, improving access to healthcare services and fostering community engagement are critical components of promoting vaccine acceptance.

According to a recent *Time* magazine article, "It should be clear by now that neither persuasion nor coercion is sufficient to change the minds or the behavior of people who are determined to refuse vaccines. Education and research cannot defeat coordinated misinformation. And government efforts — at federal, state and local levels — are stymied by a combination of inadequate power, insufficient political will and a lack of perceived legitimacy by vaccine refusers. One of America's core lessons from the COVID-19 pandemic is that a heavy-handed response to vaccine refusal can make things worse."[10]

So where do we go from here? In a detailed piece by *The Lancet*, contributors recommend a networked approach in which public health agencies collaborate with diverse academic, civic and private sector stakeholders. The proposal suggests the development of connected communities capable of reaching the public at the right time, at the right place and with the right messenger about vaccine-related information — especially aimed at preempting well-funded and amplified messages disseminated by the anti-vaccine movement.[11]

"This action entails a shift in approach for the U.S. public health communication model, from the use of one credible messenger (that is vulnerable to discrediting attacks), to a broad, diverse and coordinated network of expert messengers and influencers. These stakeholders — including leaders of local marginalized or faith communities — can simultaneously share similar messages of factual information to their specific audiences."

The article's authors acknowledge that building networked, coordinated initiatives will be challenging, but suggests the stakes are too high to ignore: "Without concerted efforts to counter the anti-vaccine movement, the USA faces an ever-growing burden of morbidity and mortality from an increasingly undervaccinated, vaccine-hesitant society."[11] ❖

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How FDA Is Working to Accelerate Rare Disease Treatments

Through regulatory pathways and patient engagement, FDA is helping to advance treatment innovations for rare diseases.

By Amy Scanlin, MS

MORE THAN 7,000 rare diseases directly affect more than 30 million patients in the U.S. Although each rare disease, as defined by the Orphan Drug Act of 1983, affects fewer than 200,000 individuals in the U.S., or about one in 10, their effects can be devastating, and the path to diagnosis is often long. In some cases, it can take as many as five or more years to diagnose a rare disease, and the process can involve multiple specialists. This is because for each rare disease, the patient pool is small and symptoms can be confused with other conditions. Today, it is estimated that one in 13 of those with rare diseases remain undiagnosed, and most rare diseases, at present, have no approved U.S. Food and Drug Administration (FDA) treatment.[1]

Efforts to advance treatment innovations for rare diseases, however, are producing exciting collaborations and discoveries. Led by the FDA's Center for Biologics Evaluation and Research (CBER) and Center for Drug Evaluation and Research (CDER), FDA works with external collaborators such as the National Organization for Rare Disorders and others to further understanding of not only the biology and etiology of rare diseases but therapeutics that may provide the greatest benefit.

These efforts have led to more than 800 investigational new drug (IND) applications submitted to FDA for cell and gene therapy products. As recently as December 2023, two cell-based gene therapies, Casgevy and Lyfgenia, were approved to treat sickle cell disease in patients 12 years and older.[1]

On the pharma side, CDER's Accelerating Rare disease Cures (ARC) program, launched in May 2022, is managed by CDER's Rare Disease Team and is a collaborative effort within CDER that brings together CBER, the Center for Devices and Radiological Health and other offices within FDA. ARC provides strategic overview of the center's rare disease initiatives and activities, and by May 2023, had approved 22 new rare disease drugs. Combined, CBER and CDER have approved more than 550 unique drugs and biologics for over 1,100 rare diseases. Yet, even with these exciting numbers, the majority of rare diseases have no available treatments.[2]

Regulatory Pathways for Rare Disease Products

FDA supports numerous initiatives in the quest to develop treatments for rare diseases. It works collaboratively with internal and external stakeholders to exchange scientific and regulatory information pertaining to disease states and the latest research. One example of this collaboration is CBER's Office of Therapeutic Products (OTP) that

works with investigational product sponsors to provide input on chemistry, manufacturing and controls, preclinical study design and clinical development. Another example is the Orphan Drug Grants Program, which helps to fund clinical investigators researching safe and effective orphan drug products used to treat rare diseases. Since the Orphan Drug Act was enacted in 1983, 40 percent of novel drug approvals are for treatments of rare diseases.[2]

From a review and approval perspective, product applications for rare diseases receive the same scrutiny as products used to treat other conditions. FDA will consider whether a drug is safe for its intended use and if the benefits to the population outweigh the risks. According to FDA, "Rare diseases are highly diverse, and the scientific considerations in specific diseases are unique and require case-by-case considerations for the particular development program at issue such as the natural history, the defined pathophysiology, the mechanism of action and other aspects of the disease or product. As such, no one program can be designed exactly like another. FDA is committed to helping sponsors create successful drug development programs that address the particular challenges posed by each disease and encourages sponsors to engage early with the agency to discuss their drug development program."[3]

Post-market reviews are often lengthier for rare disease therapies, particularly for biologics. This lengthier surveillance is needed to evaluate any possible risks associated with gene and cellular therapy such as genetic mutations and immune reactions that may lead to rejection. One example of gene therapies with a lengthier post-approval monitoring requirement is those that use integrating viral vectors, which call for 15 years of patient monitoring.[4]

CBER reviews INDs and biologics license applications (BLA) using regulatory approval pathways of BLAs, premarket approvals, new drug applications and 510(k)s for medical devices. FDA may also award priority reviews to sponsors of rare pediatric disease product applications in cases in which sponsors had earlier product approvals in the same category.

Patient Engagement to Inform Investigators

Engaging patients, caregivers and other non-industry stakeholders helps FDA determine desirable treatment outcomes for specific conditions like rare diseases. As part of the 2016 21st Century Cures Act, the 2022 Food and Drug Omnibus Reform Act and the Prescription Drug User Fee Act (PDUFA) VI (in 2017) and VII (2022), FDA encourages communications through many public meetings through a number of forums. (A listing of upcoming meetings and transcripts of past meetings is found on FDA's website.) These perspectives are captured and incorporated as FDA considers sponsor drug development and evaluation.

Patients Ask FDA is a web-based central entry point for patients and advocates to submit inquiries and meeting requests to enable FDA's understanding of patient experiences and determine how patients define their own meaningful change outcomes so that treatments can be best balanced with risks.

OTP hosts virtual educational sessions on regenerative medicine, called RegenMedEd, bringing together patients, caregivers, patient advocates, FDA staff, researchers and other experts to discuss regenerative medicine therapies, including gene and cell therapies, to explore opportunities for stakeholders to work together to advance research and development of promising products.

CDER's Rare Disease Team has also launched the Learning and Education to Advance and Empower Rare Disease Drug Developers, LEADER 3D, Initiative. Under LEADER 3D, input from stakeholders who design and conduct rare disease drug development programs is obtained and used to identify knowledge gaps related to regulatory considerations for rare disease drug development.

Information on efforts in rare disease research can be found on the ARC website and in the ARC program quarterly newsletter. This aggregated listing of resources is easily searchable with links to FDA guidances for rare disease drug development (searchable by topic area) and upcoming and recent events relevant to rare disease topics (e.g., workshops and webinars), including the recently added recording of panel 4 of FDA's Rare Disease Day that took place on March 1, 2024.[5]

Additionally, Patient Listening Sessions are small, informal, nonregulatory, nonpublic meetings between patients and FDA that focus on patient experiences, perspectives and needs related to their health or a disease. These are particularly helpful in the case of understanding rare diseases, in which both patients' experiences and priorities are less understood. These sessions have informed FDA meetings with medical product developers (though FDA is clear that the sessions are not about specific medical products) and, along with other supporting information, have provided therapeutic context for medical product reviews.

In one such example, in an October 2018 Patient Listening Session, CBER learned of specific thoughts and concerns of patients with hemophilia regarding participating in gene therapy clinical trials. Their input helped to shape the agenda for the "Product Development in Hemophilia" public workshop.[3]

Challenges in Rare Disease Product Development

By some estimates, the orphan drug market is growing at 11 percent annually, compared to a six percent growth in the non-orphan drug market.[6] Yet, when it comes to drug design for rare disease therapeutics, establishing endpoints can be challenging. With phenotypic and genotypic diversity of these diseases, they can be difficult to accurately diagnose, and finding investigators who are able to commit resources to drug development is also challenging.

Rare disease advocacy groups play a role in advancing the development of therapies for rare diseases through research support and coordination in patient-focused drug development and Patient Listening Sessions, and they may also collaborate with sponsors to help with clinical trial recruitment. In fact, FDA finds that many patient advocacy groups for rare diseases are adept at developing contacts and relationships with researchers whose research may be an eventual inroad toward a needed therapy. That being said, FDA also acknowledges that not all rare diseases have well-established advocacy groups, particularly those affecting very small numbers of individuals. Therefore, FDA strives to engage with all rare disease advocacy groups in a variety of ways.[3]

Rare disease drug developers may benefit from additional programs that have the potential to contribute to regulatory knowledge, practice or methodology for clinical studies to benefit rare disease drug development programs. Examples of these programs include:

Complex Innovative Trial Design Paired Meeting Program: This program is designed to facilitate the use of complex innovative design approaches with an emphasis in late-stage drug development. It promotes innovation by allowing FDA to publicly discuss the trial designs accepted by the paired meeting program, including trial designs for medical products that have not yet been approved by FDA. The application of these innovative methodologies in clinical studies for small populations is of particular interest for rare diseases.

Rare Disease Endpoint Advancement Pilot Program: This program is a joint CBER and CDER pilot program with PDUFA VII commitment mandated under the Food and Drug Omnibus Reform Act of 2022 that supports novel endpoint efficacy development for drugs and biologics that treat rare diseases by providing a mechanism for sponsors whose proposals are admitted to the pilot to collaborate with FDA throughout the efficacy endpoint development process.

Support for clinical Trials Advancing Rare disease Therapeutics (START) Pilot Program: This program gives a limited number of sponsors the opportunity for more frequent communication with FDA regarding clinical development issues.

On a global scale, FDA is also supporting work toward a global regulatory convergence and ultimately global harmonization of regulations for products to treat rare diseases. Although still in the planning stages, the Collaboration on the Gene Therapies Global Pilot (CoGenT Global) would be a collaboration with international partners, global regulators and the World Health Organization in which a concurrent collaborative application review could potentially be established.[3]

Helping Patients Identify Clinical Trials

Patient participation in clinical research helps to inform and prioritize development of new therapies, including determining desired treatment outcomes and acceptable risks. Prior to COVID-19, the small patient pool of those with rare diseases made clinical trials challenging, particularly with the geographic spread of potential study participants. The pandemic, however, further and severely limited patients' ability to access study centers.

Although FDA does not itself conduct trials, it's webpage Clinical Trials: What Patients Need to Know includes a searchable database of available trials by medical condition or intervention. It also includes patient-centric information on informed consent, diversity in clinical trial participation and the differences between clinical research and medical treatments.[7] Providers can help patients identify potentially appropriate studies through this webpage, as well as through engagement with patient advocacy organizations.

Looking ahead, technological innovations such as wearables that allow for remote data collection may enable participation from a geographically diverse population. That data could be used to complement assessments of a drug's positive or negative effect. Transportation assistance services to study sites might also be an important factor in patient recruitment, particularly for those who live a greater distance away. ❖

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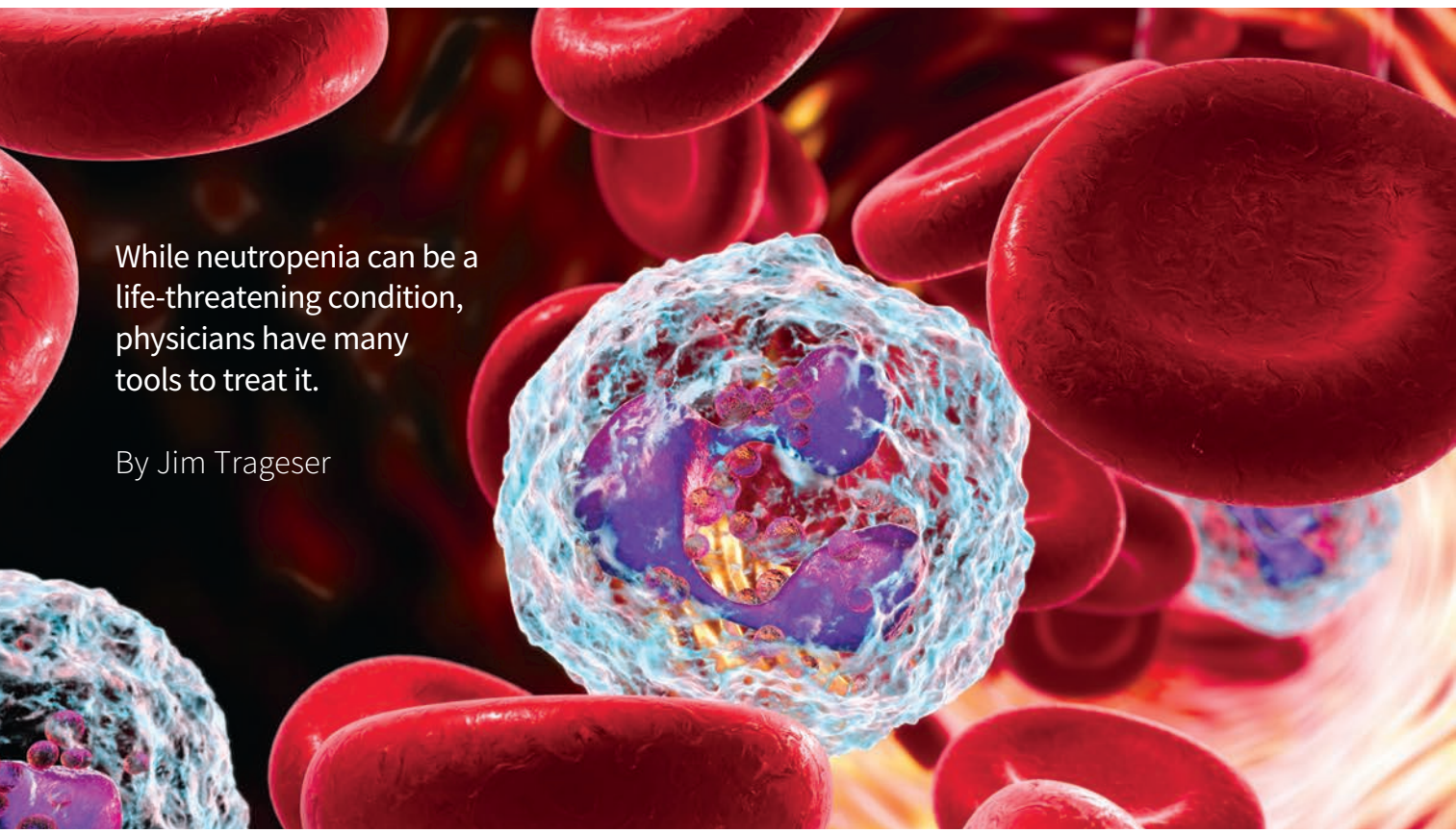
Update on Treating Neutropenia



While neutropenia can be a life-threatening condition, physicians have many tools to treat it.

By Jim Trageser

IT MAY SEEM counterintuitive at first glance (particularly for patients and their families), but a low white-blood count can be as much a sign of infection as a high count, or at the very least a warning of potential infection.

"Neutropenia" is a broad classification that accounts for several diseases and conditions — all of which are marked by a low count of neutrophils in the blood. Neutrophils are a subset of granulocytes, a type of white blood cell that releases enzyme-packed granules when they detect a bacterial or fungal infection. The most common type of white blood cell in healthy patients (accounting for 50 to 80 percent of all white blood cells), neutrophils first detect invading bacteria, fungi and parasites, and then attack the invaders. The absence of enough neutrophils puts patients at increased risk for bacterial and fungal infections.

It can be a challenging condition to monitor and treat because there are no overt symptoms for neutropenia itself — and it is often only discovered during attempts to diagnose resultant infections. And, because serious cases leave patients' immune systems compromised, immediate treatment and even hospitalization may be required.

The Different Types of Neutropenia

Neutropenia is classified according to the underlying cause such as infection, genetics, immunological disease or drugs used to fight cancer, to name a few. Within each classification, cases will range from mild to severe; some cases are lifelong, while most will resolve in a matter of weeks.

There are also three manifestations of neutropenia: temporary, chronic and cyclic. Most cases of neutropenia are short-term, caused by an infection or medication, and resolve in three to six weeks. In chronic cases, the low counts of neutrophils are consistent for more than eight weeks.[1] In cyclic, the neutrepenia occurs roughly every three weeks and lasts three to six days at a time; this is most common in children, and usually resolves itself during adolescence.[2]

Some of the causes of neutropenia are:

- Chemotherapy
- Radiation therapy
- Some cancers
- Congenital (including both Kostmann disease and benign ethnic neutropenia, or BEN)
- Autoimmune disorders
- Some viral or bacterial infections
- Drugs used to treat other diseases
- Nutritional deficiency
- Idiopathic (the cause cannot be determined)

The most common form is chemotherapy-induced neutropenia, a side effect of drugs used to treat cancers. Studies indicate that about half of all patients receiving chemotherapy will develop neutropenia.[3] A more serious version of this is neutropenic fever, which affects roughly 30 percent of patients receiving chemotherapy.[4]

Fortunately, other forms of neutropenia are relatively rare, with an incidence of less than 1.5 percent of the overall U.S. population.[5] It is more common in people of African and Middle Eastern heritage,[6] and affects men and children more than women.

Severe congenital neutropenia is even more rare, occurring about four times per one million births.[7] Kostmann syndrome was the first congenital neutropenia to be identified and named in 1950.[8] A series of unrelated genetic abnormalities can prevent the body from creating enough healthy neutrophils: the most widespread mutation (responsible for about half of all congenital neutropenia) affects the ELANE/ELA2 gene, another the HAX1 protein in the mitochondria and a third the AK2 protein, also in the mitochondria.[9]

Milder congenital neutropenia is more common, but in many cases is an asymptomatic version (BEN) that for reasons researchers do not fully understand is not associated with an increased risk of infection.[6] (Canadian researchers note that this form of neutropenia, seen mostly in populations with African or Middle Eastern ancestry, is strongly associated with the presence of red blood cells that protect against malaria.)

Autoimmune disorders can lead to autoimmune neutropenia. It is divided into a primary form, found mostly in children, and a secondary form, which tends to affect adults.[10] Among the autoimmune diseases that can lead to neutropenia in adults are rheumatoid arthritis, Sjögren's syndrome, granulomatosis with polyangiitis, inflammatory bowel disease, lupus and autoimmune hepatitis. Childhood autoimmune diseases associated with neutropenia include hyper IgM syndrome (HIgM), common variable immunodeficiency and severe combined immunodeficiency.

Malnutrition can also predispose a patient to develop neutropenia, although it is thought to be a contributing factor and rarely the sole trigger.[11]

Congenital neutropenia can be diagnosed via genetic testing to look for one of the 20 known mutations that can cause the condition.

Although drugs used to treat cancer can cause neutropenia, some types of cancer can lead directly to neutropenia. This is particularly true of cancers that attack the bone marrow such as leukemia, lymphoma and multiple myeloma. In addition, neutropenia can also be caused by metastatic cancers.[3]

While neutropenia increases a patient's susceptibility to infection, it can also result from an infectious disease. It can take the body some time to rebuild its supply of neutrophils after fighting off an infection, and even though this is usually a temporary condition, it still places patients at heightened risk.[12]

Other infections, however, can cause a more serious form of neutropenia by weakening the body's ability to make new neutrophils. These include not only HIV, but hepatitis (A, B and C), measles, chicken pox, Epstein-Barr and salmonella.[13]

Not only can cancer and drugs used to treat cancer cause neutropenia, but so can radiation therapy. Radiation directed at the bones that create neutrophils is a particular risk for triggering neutropenia.[3]

There are also drugs other than those used in chemotherapy that can cause neutropenia. Termed non-chemotherapy drug-induced neutropenia, the condition is linked to amoxicillin, carbimazole, cotrimoxazole, ganciclovir, metamizole, penicillin G, quinidine, sulfasalazine, thiamazole, ticlopidine, valganciclovir and others.[14] It is thought to affect fewer than 15 patients out of one million. In addition, drugs used to suppress the immune system following a transplant can also lead to neutropenia.[10] And, some patients receiving high-dose intravenous immune globulin (IVIG) therapy have developed neutropenia, although it seems to be mild and short-lived.[15]

When patients experience three months or more of neutropenia and no underlying cause can be identified, this is considered to be idiopathic.[15]

Symptoms and Progression

While neutropenia itself is asymptomatic, it can lead to recurring infections, and the symptoms of those infections often represent the

first indication of neutropenia. The most common infections associated with neutropenia are skin infections, pneumonia and, in the most serious cases, sepsis.[16] Skin infections are often caused by opportunistic pathogens, including streptococci or staphylococci. Other symptoms that may present can include painful swallowing, frequent sinus infections, swollen gums, general fatigue or a low-grade fever.[17]

If neutropenia is left untreated, the patient is likely to suffer a series of increasingly more severe infections, which can lead to life-threatening sepsis, organ failure and death. With children, even milder cases can slow growth and development.[18]

Diagnosis and Treatment

Diagnosis of neutropenia is made strictly on the results of a blood test looking at the neutrophil count:[16]

- 1,000-1,500 mcL = mild neutropenia
- 500-1,000 mcL = moderate neutropenia
- <500 mcL = severe neutropenia

However, neutrophil counts are not as stable as other blood cells, and can vary over days or weeks. A diagnosis of chronic neutropenia can be made if the levels are consistently low for more than three months. Cyclic neutropenia will, as noted above, manifest with a count that varies regularly in a roughly three-week pattern. Also, patients with an African or Middle Eastern ancestry will naturally have a lower count, which should be accounted for.[16]

Before considering the cause of neutropenia, the seriousness of a patient's condition must be considered. An acutely ill patient with a positive diagnosis of neutropenia should be treated as a medical emergency.[19] Any infection will have to be addressed, either before the underlying condition or simultaneously.[17]

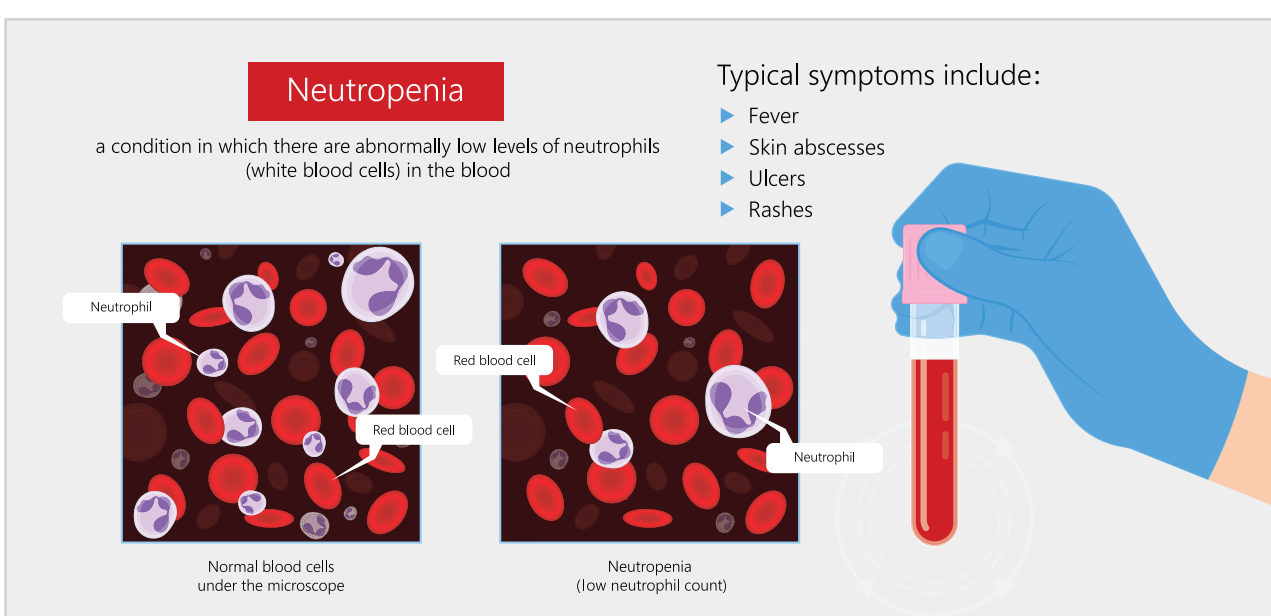
Diagnosis of the underlying cause of the neutropenia will be made by considering the patient's overall health and associated risk factors. If the patient has cancer and is undergoing chemotherapy or radiation therapy, the oncologist may temporarily suspend treatment until the neutrophil count increases. The oncologist may also prescribe the bone marrow stimulant filgrastim (Neupogen) to maintain or increase the neutrophil levels.[20] In general, the neutrophil count will hit its lowest point, or nadir, in one week to 10 days after chemotherapy begins.

Patients with a newly discovered cancer that may be causing or contributing to neutropenia will need to have their cancer treatment balanced against their neutropenia and any resultant infections.

In addition to any other treatment, cancer patients with neutropenia should also be taught how to protect themselves from infection through good hygiene:[21]

- Avoiding large crowds
- Wearing a mask when out in public
- Washing hands often
- Delaying some vaccines, if possible
- Keeping pets from licking their face
- Not sharing utensils or toothbrushes

Congenital neutropenia can be diagnosed via genetic testing to look for one of the 20 known mutations that can cause the condition.[22] Most children with the cyclic form of congenital neutropenia will grow out of it after puberty; treatment will consist of monitoring and treating infections. More serious cases will not only require



antibiotics to treat any infections, but physicians will also want to try to prevent future infections. This may be attempted with a daily dose of sulfamethoxazole/trimethoprim sulfate (Bactrim), possibly combined with metronidazole.[8]

As with patients on chemotherapy, it may be useful to try blood marrow stimulants such as the granulocyte colony-stimulating factor (G-CSF), including filgrastim or lenograstim. In severe cases where other treatment options have failed, a bone marrow transplant or stem cell therapy may be considered.[2]

Autoimmune neutropenia (AIN) occurs when the body's own immune system attacks white blood cells. Primary AIN mostly affects infants and young children, and generally resolves within a few years. Secondary AIN tends to show up in older children and adults, and will most often be chronic.

AIN will be diagnosed with a battery of tests:

- Flow cytometry
- Indirect granulocyte immunofluorescence
- Granulocyte agglutination

Flow cytometry uses a laser to measure the chemical characteristics of cells — often used to check the health of bone marrow. The other two are blood tests that look for specific antibodies known to attack neutrophils.

Treatment will differ for primary vs. secondary AIN. Since primary AIN tends to be milder, treatment may consist of monitoring the patient and prescribing prophylactic antibiotics to prevent infections. With secondary AIN, the physician may be more aggressive in treating the autoimmune disease itself, including corticosteroids to reduce the attacks on the neutrophils. Other treatments that have shown success in fighting secondary AIN are rituximab, alemtuzumab and IVIG.[23]

Post-infectious neutropenia is more common in children, and is more highly associated with viral infections than bacterial infections. However, brucella, rickettsial and mycobacterial infections have also been linked with subsequent neutropenia. In most cases, excepting HIV and Epstein-Barr, neutropenia will disappear in a few weeks. With HIV and Epstein-Barr, neutropenia is likely to be chronic and require treatment similar to that in autoimmune cases: close monitoring and treatment for any infections.

If no other cause has been established, then consideration should be given to a drug being the culprit. If possible, all prescriptions should be halted to see if that helps bring the neutrophil count back up.[24]

Some specific nutritional deficiencies are suspected of contributing to neutropenia: Vitamin B-12, folate and copper deficiencies have appeared in some patients with neutropenia, but usually with another correlating condition.[19] These deficiencies can be addressed through dietary changes.

In cases in which no underlying cause is ever identified, yet the conditions for a diagnosis of chronic neutropenia are present, a diagnosis of chronic idiopathic neutropenia can be made; treatment will consist of ongoing monitoring and, if recurring infections are noted, low doses of G-CSF to prevent future infections.[19]

Looking Ahead

Due to the varied causes of neutropenia, a single cure or vaccine is highly unlikely. Stand-alone cases of isolated neutropenia are extremely rare and, in most instances, can be readily controlled with antibiotics. For those cases caused by autoimmune disease, several effective treatments are available, as outlined above.

While untreated neutropenia remains a life-threatening condition, current treatment options offer physicians the tools to treat the overwhelming majority of cases. ❖

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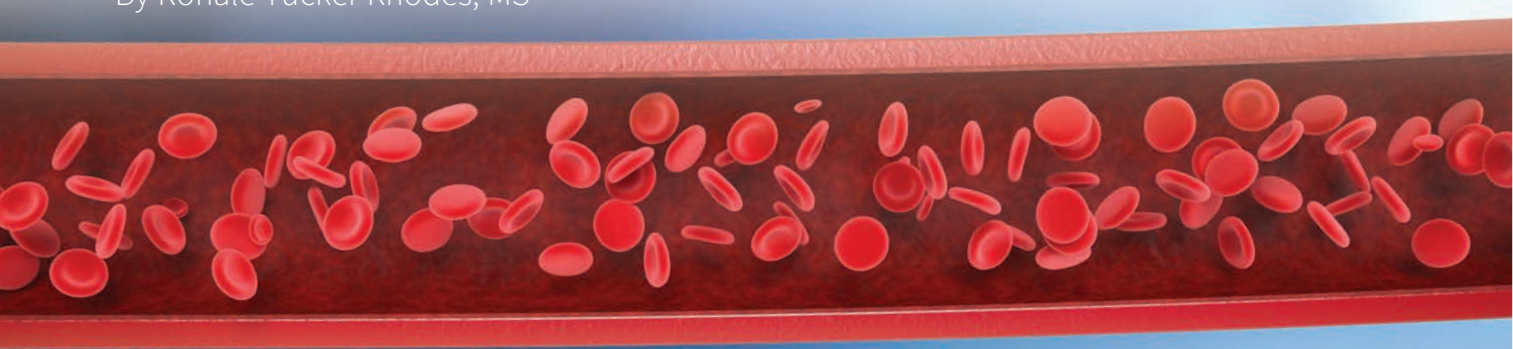
Myths & Facts: High Blood Pressure

Known as the silent killer, hypertension often goes undetected in individuals until a serious event occurs. However, with a better understanding of the condition and regular monitoring, it can be managed with treatment.

By Ronale Tucker Rhodes, MS



HIGH BLOOD PRESSURE, also called hypertension, is blood pressure (the force of blood flowing through blood vessels) that is higher than normal. While blood pressure changes throughout the day based on an individual's activities, consistent blood pressure measures above normal may result in a diagnosis of elevated blood pressure or hypertension.

According to the Centers for Disease Control and Prevention (CDC), nearly half of adults age 30 to 79 years of age have hypertension (48.1 percent, 119.9 million), defined as a systolic blood pressure greater than 130 mmHg or a diastolic blood pressure greater than 80 mmHg, or are taking medication for hypertension.

High blood pressure affects more men (50 percent) than women (44 percent), and it is more common in non-Hispanic black adults (56 percent) than in non-Hispanic white adults (48 percent), non-Hispanic Asian adults (46 percent) or Hispanic adults (39 percent). In addition, rates of high blood pressure vary by geography.[1]

Hypertension is no joke. It puts individuals at risk for heart disease and stroke, which are leading causes of death in the United States. Indeed, in 2021, hypertension was a primary or contributing cause of 691,095 deaths in the United States.[1] And yet, an estimated 46 percent of adults with hypertension are unaware they have the condition,[2] which is why it is called the silent killer. The only methods to curtail the dangers of high blood pressure are to educate the public, encourage regular blood pressure monitoring and to dispel the many myths surrounding it.

Separating Myth from Fact

Myth: A person doesn't have high blood pressure if he or she feels fine.

Fact: It is true that people with severe high blood pressure may experience difficulty breathing, headaches, vision changes, chest pain and more. But others may never feel a thing.[3] The reason high blood pressure is called the silent killer is because most people are unaware they have it, which means they are unaware it is damaging their arteries, heart and other organs.[4] The only way to detect hypertension is to measure blood pressure.

"Unless your blood pressure is dangerously high, you will not have any symptoms," explains Parveen Garg, MD, a cardiologist at Keck Medicine of the University of Southern California (USC) and associate professor of clinical medicine and population and public health sciences at the Keck School of Medicine of USC. "The long-term damage high blood pressure has on your arteries, however, occurs regardless of whether you have symptoms or not."[5]

Myth: High blood pressure is inevitable with age.

Fact: Actually, it is not inevitable, and it is not a normal part of aging. Hypertension *is* more common among

older adults, but it occurs in middle-aged and young adults, too. Statistics show that hypertension affects around 7.5 percent of people aged 18 to 39 years, 33.2 percent of people aged 40 to 59 years and 63.1 percent of individuals over the age of 60 years.[6]

Myth: High blood pressure is OK as long as one number is normal.

Fact: Both numbers matter. Blood pressure is measured using two numbers. The top number is systolic blood pressure, which is the pressure in blood vessels when the heart beats. If the number is higher, the blood exerts more pressure against the artery walls during each contraction of the heart muscle. The bottom number is diastolic blood pressure, which is the pressure in the blood vessels in between heartbeats. A normal diastolic number is lower than 80.

According to United Healthcare, the top and bottom numbers in healthy adults usually add up to around 120 over 80. If these numbers are too low or too high, there might be a problem. For example, someone with high blood pressure may have a systolic reading of 130 to 139 or a diastolic reading of 80 to 89. The higher the numbers go, the more at risk individuals may be for heart attack or stroke. However, it is true that the top number (systolic) is given more attention as a way to figure out if an individual may be at risk for heart disease.[7]

"While high blood pressure used to be defined as over 140/90 mm Hg, that definition has changed in the past few years," explains Dr. Garg. "Today, if someone has blood pressure over 130/80 mm Hg and has a history of cardiovascular disease — or, if they are at high risk for having a cardiovascular event — their physician may recommend taking blood pressure medication."[5]

Myth: High blood pressure can't be prevented.

Fact: Many people believe if parents or close blood relatives have had high blood pressure, they are more likely to develop it, too. But high blood pressure *can* be avoided by engaging in healthy lifestyle changes, including:

- *Keeping weight at a healthy level.* Being overweight puts extra strain on the heart, increasing the risk for developing high blood pressure and damage to blood vessels. Even losing as few as 10 pounds can help manage or prevent high blood pressure in many overweight people (those with a body mass index, or BMI, of 25 or greater).[8]
- *Eating a healthy diet, and limiting salt intake.* Sodium (salt) encourages the body to retain fluid, which can increase the fluid volume of blood and raise blood pressure. According to Amanda Stathos, a clinical dietitian at Johns Hopkins' Sibley Memorial Hospital, the recommended minimum daily sodium intake requirement is about 1,500 milligrams a day, with the upper limit at 2,300 mg, which is equal to only about one teaspoon of salt. Lowering salt intake can be accomplished by cooking low-sodium dishes; substituting salt (including kosher and sea salt[4]) with spices such as garlic, turmeric and paprika, which add flavor and other health benefits; avoiding processed foods (or when using, checking the nutrition labels[4]); and using the DASH (dietary approaches to stop hypertension) diet, which is not only low in sodium, but very high in nutrition, or the Mediterranean diet, which is based on a diverse range of unprocessed foods.[9]
- *Limiting alcohol intake.* Blood pressure can be raised to unhealthy levels from drinking too much alcohol. According to Francisco Lopez-Jimenez, MD, chair of the division of preventive cardiology at Mayo Clinic, consuming more than three drinks in one sitting temporarily raises blood pressure, and repeated binge drinking can lead to long-term increases in blood pressure.

Following are the definitions of excessive drinking:

1) Binge drinking is defined as four or more drinks within two hours for women and five or more drinks within two hours for men.

2) Moderate drinking is up to one drink a day for women and two for men.

3) Heavy alcohol use is defined as more than three drinks a day for women and four for men.

Also, individuals should keep in mind that alcohol contains calories and may cause weight gain, which as mentioned previously, is a risk factor for high blood pressure.[10]

- *Not smoking tobacco or avoiding exposure to it.* According to an article in MedicalNewsToday, every time a person smokes, it produces a temporary increase in blood pressure. Typically, smoking one cigarette raises a person's heart rate and blood pressure for 15 to 30 minutes. So, when people smoke frequently, this effect happens over and over throughout the day. Smoking two cigarettes per hour can lead to a 5 to 6 mm Hg increase in daytime blood pressure.

Studies show that nicotine can raise blood pressure because it stimulates the release of epinephrine and norepinephrine — hormones that underlie a person's fight-or-flight response. Epinephrine and norepinephrine can cause the smooth muscles in certain blood vessels to contract, narrowing the opening and reducing the space through which blood can flow, which results in increased blood pressure.

Smoking — as well as exposure to secondhand smoke — can also damage the walls of blood vessels and raise the likelihood of atherosclerosis — the accumulation of fatty substances called plaque inside the arteries. Consequently, plaque buildup can narrow the blood vessels and contribute to

high blood pressure.[11]

• *Getting regular exercise.* Exercise can actually lower blood pressure. According to the Mayo Clinic, "Regular exercise makes the heart stronger. A stronger heart can pump more blood with less effort. As a result, the force on the arteries decreases. This lowers blood pressure."[12]

The simple rule is to move more and eat well. The American Heart Association recommends people gradually increase their level of physical activity beyond the recommended 150 minutes of moderate-intensity aerobic activity per week, decrease the number of calories taken in and eat a healthy diet.[8]

• *Not letting stress build up.* Both acute (short-term) and chronic (long-term) stress can affect the cardiovascular system by changing hormone levels. While temporary spikes in blood pressure in response to acute stress are normal and expected, chronic stress may lead to high blood pressure. The American Heart Association suggests managing stress by exercising regularly, making time for friends and family, getting enough sleep, maintaining a positive attitude, practicing relaxation techniques and finding a stimulating hobby.[13]

Myth: A person doesn't need to check his or her blood pressure regularly if it's being monitored by a physician.

Fact: While home monitoring, or self-measured blood pressure, is not a substitute for regular visits to a physician, the American Heart Association recommends home monitoring for all people with high blood pressure to keep their healthcare professional aware of whether treatments are working.[14]

Individuals should follow these American Heart Association's tips to ensure their blood pressure readings are correct:[14]

• Be still; don't smoke, drink caffeinated beverages or exercise within 30 minutes; empty the bladder; and ensure at least five minutes of quiet rest before measurements.

• Sit correctly with the back straight and supported, feet flat on the floor, legs uncrossed and the arm supported on a flat surface such as a table with the upper arm at heart level.

• Measure at the same time every day, ideally beginning two weeks after a change in treatment and during the week before the next doctor appointment.

• Take multiple readings, and record the results each time.

• Don't take measurements over clothes.

Myth: High blood pressure treatments don't work and cause too many adverse side effects.

Fact: In some instances, blood pressure treatments don't work, and if that's the case, the physician will often recommend a hypertension specialist to look for potential causes.[15] However, in most instances, blood pressure medications do work, and most of the time, only a single drug will be used at first, while two drugs may be started for stage 2 high blood pressure, which is when blood pressure is equal to or higher than 140/90 mm Hg. Medline Plus says one or more of these blood pressure medicines are often used to treat stage 2 blood pressure:

• Diuretics, also called water pills, help kidneys remove some salt (sodium) from the body so blood vessels don't have to hold as much fluid and blood pressure goes down.

• Angiotensin-converting enzyme inhibitors (also called ACE inhibitors) reduce the production of angiotensin II in the body, helping to relax blood vessels, which lowers blood pressure.

• Angiotensin II receptor blockers

High Blood Pressure (Hypertension) Treatments[16]

Medications Most Often Prescribed	
Diuretics (also called water pills)	Help the kidneys remove some salt (sodium) from the body so blood vessels don't have to hold as much fluid and blood pressure goes down
Angiotensin-converting enzyme inhibitors (also called ACE inhibitors)	Reduce the production of angiotensin II in the body, helping to relax blood vessels, which lowers blood pressure
Angiotensin II receptor blockers (also called ARBs)	Reduce the action of angiotensin II in the body, helping to relax blood vessels, which lowers blood pressure
Calcium channel blockers	Relax blood vessels by reducing calcium entering cells in the wall of the blood vessels
Beta-blockers (only used if the drugs above are not adequate or cannot be used)	Make the heart beat at a slower rate and with less force
Medications Not as Often Prescribed	
Alpha-blockers	Help relax blood vessels, which lowers blood pressure
Centrally acting drugs	Signal the brain and nervous system to relax blood vessels
Vasodilators	Signal the muscles in the walls of blood vessels to relax
Renin inhibitors	Reduce the amount of angiotensin precursors, thereby relaxing blood vessels

(also called ARBs) reduce the action of angiotensin II in the body, helping to relax blood vessels, which lowers blood pressure.

- Calcium channel blockers relax blood vessels by reducing calcium entering cells in the wall of the blood vessels.
- Beta-blockers make the heart beat at a slower rate and with less force; these have been commonly used, but are now usually only used if the drugs above are not adequate or cannot be used.

Blood pressure medicines that are not used as often include:

- Alpha-blockers that help relax blood vessels, which lowers blood pressure.
- Centrally acting drugs that signal the brain and nervous system to relax blood vessels.
- Vasodilators that signal the muscles in the walls of blood vessels to relax.
- Renin inhibitors that act by reducing the amount of angiotensin precursors, thereby relaxing blood vessels.

All of these medicines have side effects, but most are mild and may go away over time. Some common side effects of high blood pressure medicines include:

- Cough
- Diarrhea or constipation
- Dizziness or lightheadedness
- Erection problems
- Feeling nervous
- Feeling tired, weak, drowsy or a lack of energy
- Headache
- Nausea or vomiting
- Skin rash
- Weight loss or gain without trying

If side effects cause problems, making changes to the dose of medicine or the time it's taken can help reduce side effects.[16]

Myth: Treatment for high blood pressure can be stopped if it's working.

Fact: While blood pressure readings may turn to normal when taking medication, hypertension is a lifelong condition so it's important for individuals to follow their doctors' recommendations and only reduce or stop taking the medication when they have confirmed that this is the best course of action.

The American Heart Association says, "Expect to treat high blood pressure for life. Doctors will sometimes reduce a [person's] drug dosages after achieving normal blood pressure and maintaining it for a year or more, although it is rare for the treatment to be stopped entirely. Some form of treatment must be continued over a lifetime for good results."[6]

Dispelling the Myths Now

Researchers continue to explore ways to prevent and manage high blood pressure and its effects. At Johns Hopkins Medicine, researchers are studying antihypertensive drugs to see if they may help preserve cognitive function in people with high blood pressure. Researchers are also studying the link between higher weight and weight gain and the risk of high blood pressure.[17]

The National Heart, Lung and Blood Institute is another organization that leads and supports research and programs on high blood pressure. It has funded studies and programs to help develop new treatments for high blood pressure, many of which focus on women's health, lifestyle interventions and health disparities. Current studies aim to prevent pregnancy complications and improve blood pressure among people in high-risk groups.[18]

One of the global targets for noncommunicable diseases is to reduce the prevalence of hypertension by 33 percent between 2010 and 2030. In 2021, the World Health Organization released a new "Guideline for the Pharmacological Treatment of Hypertension in Adults," which provides evidence-based recommendations for the initiation of treatment of hypertension, and recommended intervals for follow-up. The document also includes target blood pressure to be achieved for control, and information on who, in the healthcare system, can initiate treatment.[2]

With more research, greater understanding and dispelling the myths about this silent killer, it is hoped that healthcare providers can help to save a growing number of patients succumbing to hypertension. ❖

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HIV: *A Patient's Perspective*

By Trudie Mitschang

AS A WOMAN and activist living with HIV/AIDS, Maria Mejia's mission is to give hope to the hopeless and send the message that she is far more than just a condition. She is currently the co-chair of the Women and Minorities Outreach for the Dab the AIDS BEAR project; an ambassador for the Centers for Disease Control and Prevention's Let's Stop HIV Together campaign; The Stigma Project; The Well Project; and the Greater than AIDS Empowered campaign. Maria is also co-author of *From a Warrior's Passion and Pain*, a real-life account of her decades-long battle with HIV/AIDS. She lives in Florida with her wife, Lisa.

BSTQ: When were you diagnosed with HIV?

Maria: I was infected at age 16 and diagnosed in 1991 at the age of 18. After 10 years of refusing treatment, I was diagnosed with AIDS and uterine cancer. I was given one month to live if I didn't start my medications. I am so glad I chose to live because I love life.

BSTQ: What do you think is the biggest misconception about living with HIV/AIDS?

Maria: That it is a guaranteed death sentence and that your life is over and no one will ever love you with this condition. The truth is you can live a full life with HIV/AIDS if you follow your treatment plan and do not let a virus define you.

BSTQ: How can we reduce the stigma around HIV/AIDS?

Maria: A big part of the reason I serve as an activist and educator is to encourage people to come out of the HIV/AIDS closet. The more we come out and show our faces with no shame, the more we humanize this condition.

BSTQ: What do you want girls and women to understand about HIV?

Maria: I want them to understand that there is life after an HIV or AIDS diagnosis. I want them to remember to love themselves, follow their treatment plan and live a very healthy lifestyle. If there is any personal experience I can share it is that even on my hardest days, I know my spirit is stronger than my body. I am a very spiritual human being, and this helps me keep going.

BSTQ: What medications, treatments and/or studies are positively impacting the HIV community now?

Maria: As a 35-year long-term survivor of HIV/AIDS, I never thought I would see the day with so many options of medication, because I come from a time when we had nothing but a death sentence. I never thought I would see the day when we could take medications in small dosages that actually save lives and make HIV undetectable so it cannot pass on to sexual partners or babies who are breastfeeding. These breakthroughs make me feel the cure is coming very soon and there is renewed hope. At this point, though, I will be content with any treatment that oppresses the virus, like the long-term injectables currently available. This is such a huge advancement in the history of HIV and AIDS.

BSTQ: As you look back on your journey, what are you most proud of?

Maria: I am proud of many things. I am proud of all the people who I have helped since my own diagnosis. I continue to advocate and fight against any form of discrimination as an international human rights activist and a very proud member of The Well Project, a global women's organization. As we know, there are very few organizations that cater specifically to women and girls who are living with HIV, so that is very near and dear to my heart. I am also very proud of being the founder of the two largest international support groups for people living with HIV or affected by it. My work has helped pass legislation for the LGBTQI community's HIV policies in the state of Florida. And most importantly, I'm proud that I've been able to lead by example and show those who are starting this journey and living in the shadows of stigma that I will fight for them, that I will continue to show my face to fight against the shame and stigma. I want to continue being the voice that says you cannot only survive but thrive.

BSTQ: What's next for you?

Maria: Personally, to be a better human being every day, to continue to fight for human rights and to live a healthy and productive life. My mission is still to continue to give hope to the hopeless. Professionally, there's a lot of different things I'm involved in as I continue to grow and get more seasoned as an activist, which is the core of who I am. I am a fighter. ❖

HIV: *A Physician's Perspective*

MARK BLOCH, MD, has been working in the field of HIV medicine since 1983, and he is now the director of clinical research at Holdsworth House in Sydney, Australia. Dr. Bloch is actively involved in research surrounding HIV and sexually transmitted diseases. He completed his medical degree at the University of Western Australia and Master of Medicine in HIV and Sexual Health at the University of Sydney.

BSTQ: Is there still a stigma attached to an HIV diagnosis?

Dr. Bloch: Getting an HIV-positive diagnosis typically comes as a shock, and patients find it hard to fully absorb the news. It can take time to adjust to their new reality and, yes, with the perceived stigma, people experience a range of emotions, including anger toward whomever may have transmitted the virus to them, feelings of shame about the diagnosis itself and, of course, fear about the future.

BSTQ: What is the biggest misconception about HIV today?

Dr. Bloch: Many people simply don't know that HIV has become a manageable condition and not a death sentence. Thanks to medical advances, we can now control symptoms extremely effectively, so much so that the virus can actually be suppressed. That means a person diagnosed with HIV today can not only expect to enjoy a normal life span, they also can avoid passing HIV on to others.

BSTQ: What can you share about HIV treatment?

Dr. Bloch: Research has shown that starting antiretroviral treatment early in the course of a diagnosed HIV infection when the immune system is stronger results in better long-term health outcomes compared with delaying it. When HIV diagnosis and treatment are delayed, HIV continues to replicate, and this can not only negatively impact the infected individual's health, it also increases the risk of transmitting the virus to others.

BSTQ: What types of medications are used to treat HIV?

Dr. Bloch: Antivirals or antiretrovirals work by stopping the HIV virus from multiplying in the body and preventing the damage that the infection can cause. Typically, the treatments include a menu of medications that, when combined, help prevent the virus from becoming treatment-resistant. In most cases, treatment can be combined into a single pill, taken once daily. From a long-term perspective, HIV treatment must be taken indefinitely to control the HIV infection. In the future, there will be longer-acting treatments in pills or injections that need to be taken only every few months. Research is also looking at finding a cure for HIV.

BSTQ: What side effects do patients undergoing HIV treatment experience?

Dr. Bloch: Obviously, people react differently to specific medications, but on the whole, the currently available treatments for HIV are simple, highly effective and very well-tolerated. If side effects do occur, they tend to be on the mild side. The other positive news for newly diagnosed HIV patients is that there are multiple treatment options, so if one is not tolerated, we can try something different. For those who are hesitant about moving forward with treatment, I remind them that the effects of living with an untreated HIV infection are much, much greater than any side effects from the treatments themselves.

BSTQ: What lifestyle changes do you suggest to HIV patients?

Dr. Bloch: HIV treatment alone can make a huge difference in the quality of life for HIV patients, but adopting a healthy lifestyle is also a key component for long-term health. For example, it's important to mitigate the risk of developing other conditions such as diabetes or heart disease, which can worsen HIV symptoms and compromise treatment plans. In my experience, an HIV diagnosis can often serve as a wake-up call and motivate someone to pursue more health-conscious lifestyle choices.

BSTQ: What support do HIV-positive patients usually require after finding out their diagnosis?

Dr. Bloch: HIV-positive patients require medical support that includes ample factual information about their condition. There is still a lot of misinformation out there, so getting the facts can actually be a relief and, in some cases, even empowering. They will also need additional testing to confirm the diagnosis and find out their viral load (how much virus is circulating in the body) and CD4 count (the condition of the immune system that fights infection). Equally important is mental health support from either a counselor or peer support group. Patients often benefit from the opportunity to discuss their diagnosis with others who have HIV and understand the unique issues associated with it. ❖

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

The Protective Value of RSV Vaccines in Older Adults: A Deeper Dive

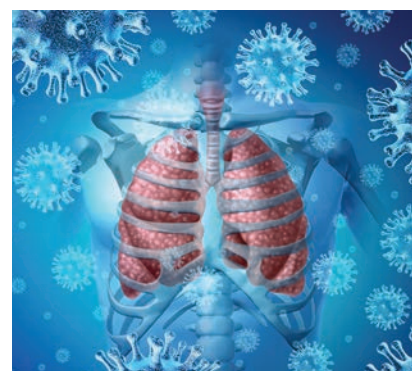
By Keith Berman, MPH, MBA

IN JUST over a year, not one but three novel vaccines that reduce the risk of respiratory syncytial virus (RSV) infection-associated lower respiratory tract disease (LRTD) — GSK's AREXVY, Pfizer's ABRYSVO and most recently Moderna's mRESVIA — have been approved for marketing and will be available for the upcoming 2024-2025 RSV season.* Large-scale clinical trial results have demonstrated that each has robust vaccine efficacy against development of LRTD in persons aged 60 years and older; all three vaccines are indicated solely for prevention of RSV-caused LRTD solely in this older 60-plus age group.[1,2,3]

A consumer fact sheet prepared by the U.S. Centers for Disease Control and Prevention (CDC) also warns older adults, in large block letters, that RSV can cause pneumonia and other serious illness, and annually accounts for 60,000 to 160,000 hospitalizations and 6,000 to 10,000 deaths.[4]

Yet for the majority of adults aged 60 years and older, an RSV infection will result in only mild cold-like symptoms. "Talk to your healthcare provider to see if vaccination is right for you," the CDC recommends.[5] This advice obviously diverges from the CDC's far more straightforward recommendation that, with rare exceptions, every adult (as well as every child aged 6 months and older) should get a seasonal influenza vaccination.

As of mid-May of this year, nearly



three-quarters of adults aged 65 and older have received a seasonal influenza vaccine, while only about one-quarter of those aged 60 years and older report receipt of an RSV vaccine.[6] While this comparatively low rate of RSV vaccine adoption can be explained in part by its newness, leaving the vaccination decision to the discretion of the individual and his or her healthcare provider likely plays a part as well.

This elective aspect of RSV vaccination may be particularly problematic for older adults who:

- Have underlying health conditions that place them at increased risk of severe RSV disease, but are unaware of it because they don't access this information;
- Believe that, because RSV vaccination is elective, they are likely at minimal risk of severe or life-threatening RSV disease; or
- Neglect to inquire with their healthcare provider about the advisability of getting the RSV vaccine.

Marketing materials for ABRYSVO do helpfully alert older adults that "as you age, your immune system weakens, leaving you vulnerable to a serious case of RSV," and "the presence of underlying medical conditions such as asthma, COPD, diabetes or heart disease can put you at increased risk of severe RSV."[7] AREXVY ads similarly explain that "RSV can be serious for those aged 60 years and older, including those with asthma, diabetes, COPD or chronic heart failure."[8]

For older adults who prioritize their health and place their trust in their physician and pharmacist for advice, these kinds of broad-based warnings about the risks of RSV infection are undoubtedly helpful to make the decision to get vaccinated. But qualitative cautionary messages of this nature may be less effective in persuading many millions of other older adults who may be hesitant for one reason or another, or who remain skeptical in the absence of hard evidence.

CDC epidemiologists have now addressed this "hard information" gap with the publication of newly completed research identifying which underlying chronic conditions in older adults increase the risk of hospitalization for RSV infection and, more importantly, by how much.

CDC Surveillance Generates Answers

Leveraging data acquired through its Behavioral Risk Factor Surveillance System and its RSV-Associated Hospitalization Surveillance Network

* ABRYSVO and AREXVY received FDA approval in May 2023, and mRESVIA received FDA approval in May 2024.

(RSV-NET) covering nearly nine percent of the U.S. population, CDC investigators calculated RSV-associated hospitalization rates over the 2017-2018 season for community-dwelling adults with nine different chronic conditions in three defined age groups (50-64, 65-74 and ≥75 years):[9]

- Asthma
- Chronic kidney disease (CKD)
- COPD
- Coronary artery disease (CAD)
- Current smoking
- Diabetes mellitus
- Obesity (body mass index 30-39 kg/m²)
- Severe obesity (body mass index ≥40 kg/m²)
- Stroke history

In addition to estimating RSV-linked hospitalization rates for each of these chronic conditions in persons aged 65-74 years (Figure 1) and ≥75 years (Figure 2), for each of these age groups

Figure 1. RSV-Associated Hospitalization Rates and Adjusted Rate Ratios Among Adults Aged 65-74 Years with and Without Examined Chronic Medical Conditions

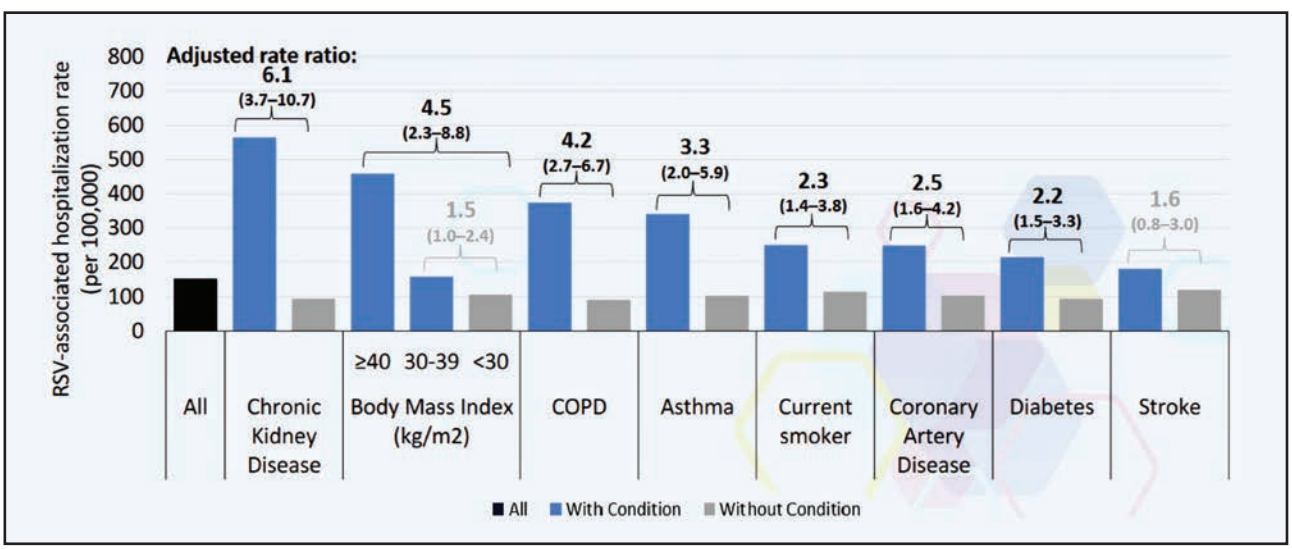
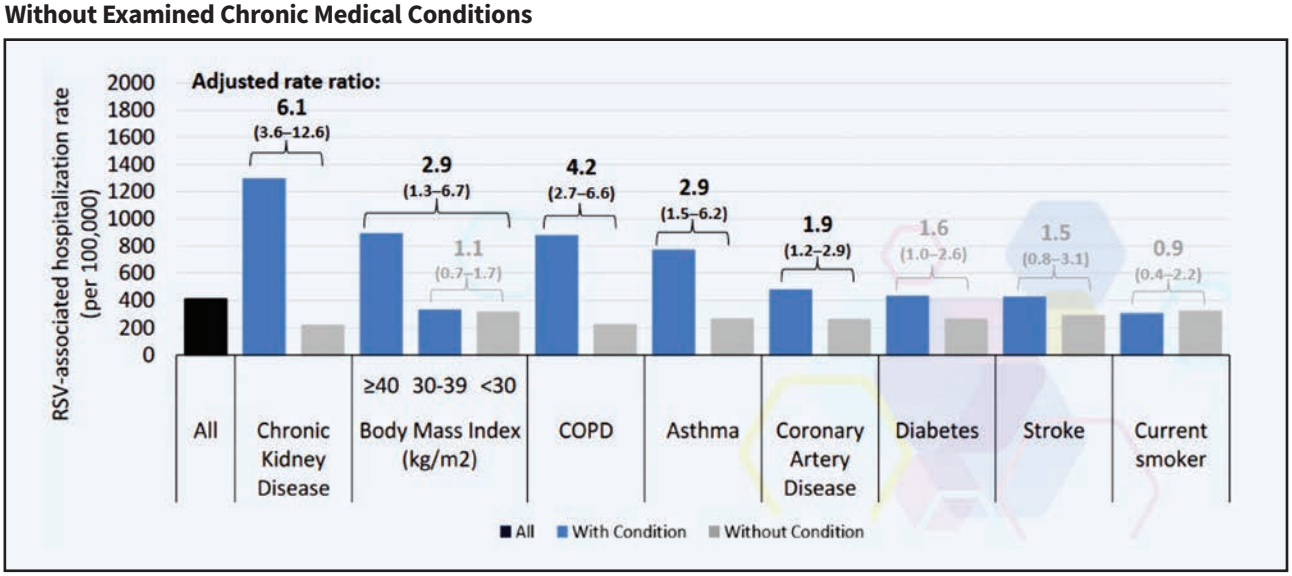


Figure 2. RSV-Associated Hospitalization Rates and Adjusted Rate Ratios Among Adults Aged ≥75 Years with and Without Examined Chronic Medical Conditions



CDC epidemiologists additionally determined adjusted rate ratios (aRRs) relative to their peers without each condition.

> If the prospect that an RSV infection could lead to hospitalization isn't quite enough to persuade some older at-risk patients to get vaccinated, creating awareness of the most serious adverse outcomes during an RSV-associated hospitalization might change some minds.

In both age groups, the presence of CKD was associated with a six-fold higher aRR of RSV-associated hospitalization relative to persons without CKD. But in adults aged 65-74 years and ≥75 years with comorbid CKD and CAD, the respective aRRs jumped to 10.5 and 7.9 compared to individuals with neither condition, albeit with wide confidence intervals reflecting the limitations of the study sample size.

In both older age groups, presence of COPD, severe obesity and asthma were each associated with a three- to four-fold higher risk that RSV infection would result in hospitalization. Existing CAD, diabetes and current smoking status roughly doubled the risk of hospitalization in adults aged 65-74 years, while only presence of CAD accounted for a similarly increased risk in those aged ≥75 years.

Predictably, the overall RSV-related hospitalization rate was lowest for all adults aged 50-64 years, roughly one-third of the rate for all adults aged 65-74 years and eight-fold lower than the rate for all adults aged ≥75 years. This pattern of increasing RSV hospitalization rates with advancing age applied for each of the examined chronic conditions that commonly affect older individuals (Figure 3).[9]

On close examination, these CDC data also reveal that the risk of RSV-associated hospitalization for persons aged 50-64 years living with CKD, COPD, CAD, asthma and diabetes rivals or exceeds RSV hospitalization risk in the overall population of persons aged 65-74 years.

At present, none of the three vaccines are indicated for any of the roughly two-thirds of individuals in the 50-64 year age cohort who are 50-59 years of age, regardless of whether they have these chronic comorbidities or not. But all three manufacturers are

Figure 3. RSV-Associated Hospitalization Rates Among All Adults Aged 50-64, 65-74 and ≥75 Years, and Among Those with Examined Chronic Medical Conditions

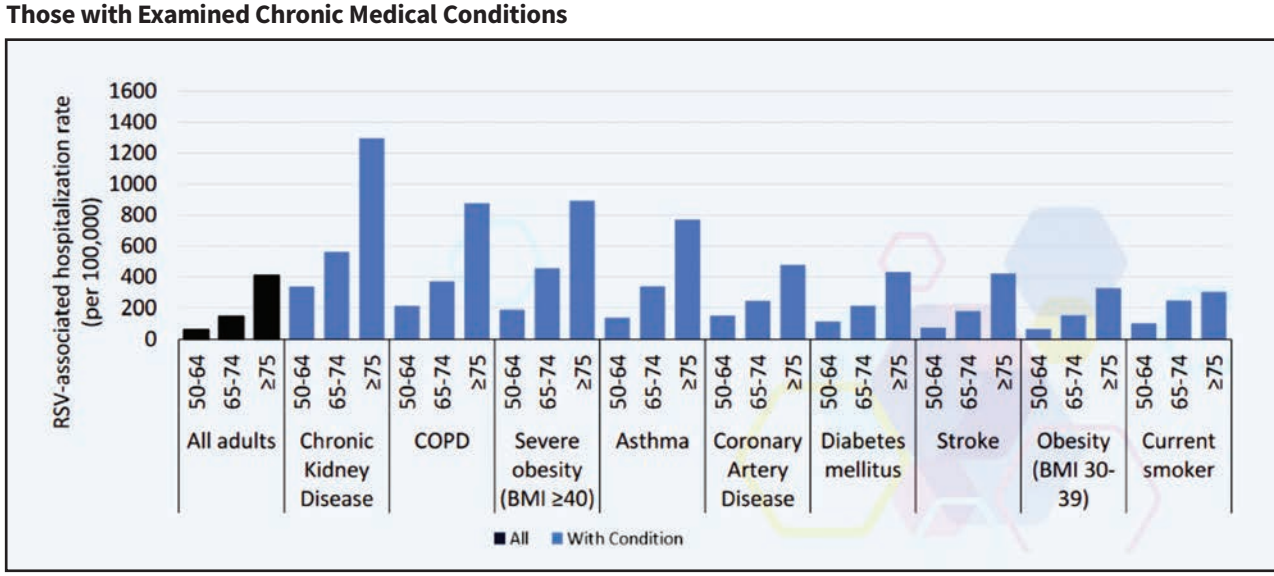


Table. Prevalence of Acute Cardiac Events in Hospitalized Adults with RSV Infection, Both Overall and with and Without Underlying Cardiovascular (CV) Disease

Cardiac event*	Overall prevalence (95% CI) (N = 6,248)	Prevalence in patients without underlying CV disease (95% CI) (N = 2,684)	Prevalence in patients with underlying CV disease (95% CI) (N = 3,564)
≥1 acute cardiac event of any kind	**22.4%** (21.0–23.7)	**8.5%** (7.4–9.8)	**33.0%** (31.0–35.2)
Acute heart failure	**15.8%** (14.6–17.0)	**3.5%** (2.8–4.3)	**25.3%** (23.4–27.2)
Acute ischemic heart disease	**7.5%** (6.8–8.3)	**22.4%** (3.3–5.0)	**22.4%** (9.0–11.5)

* Additionally includes the following acute cardiac events with overall prevalence <2%: hypertensive crisis, ventricular tachycardia, cardiogenic shock, and other unspecified acute cardiac events.

currently conducting clinical trials to investigate the protective effect of their RSV vaccines in adults under age 60 years who have chronic conditions that increase their risk of severe RSV disease.

Acute Cardiac Events in RSV Hospitalizations

If the prospect that an RSV infection could lead to hospitalization isn't quite enough to persuade some older at-risk patients to get vaccinated, creating awareness of the most serious adverse outcomes during an RSV-associated hospitalization might change some minds. To that end, another newly published epidemiologic study by the CDC and state-level public health collaborators has now documented a surprisingly high rate of acute cardiac events in middle-aged and elderly U.S. adults hospitalized with a laboratory-confirmed RSV infection.

The Respiratory Syncytial Virus Hospitalization Surveillance Network (RSV-NET) abstracted medical record data from 6,248 hospitalized persons with RSV aged 50 years or older (median 72.7 years) in 12 states over five RSV seasons, ending in the 2022-2023 season. Just over one-half (56.4 percent) of patients in this cross-sectional sample had underlying cardiovascular disease.

Nearly one-quarter (22.4 percent) of these adults hospitalized with an RSV infection experienced an acute cardiac event, including one in 12 (8.5 percent) adults with no documented underlying cardiovascular (CV) disease and one in three (33.0 percent) with underlying CV disease (Table). Acute heart failure and acute ischemic heart disease were also common occurrences, again at far higher rates in patients with pre-existing CV disease.

Nearly one in five RSV-infected hospitalized adults (18.6 percent) required admission to the intensive care unit, and one in 20 (4.9 percent) died during the course of their hospital stay. Unsurprisingly, older age was associated with increasing risk of an acute cardiac event; compared to hospitalized patients aged 50-64 years, the aRRs for those aged 65-74, 75-84 and ≥85 years were 1.1, 1.2 and 1.44, respectively.

On the Way: More Evidence and Expanded Approvals

Now that safe and effective RSV vaccines are finally available, more evidence of their direct health benefits in older Americans will be forthcoming. It is likely as well that FDA will eventually expand the marketing approvals of these vaccines to include adults under age 60 with chronic conditions demonstrated to importantly increase the risk of RSV-associated LRTD and hospitalization.

For those patients who are initially skeptical or unsure whether to get the RSV jab, sharing epidemiologic data that quantifies risks of severe illness and hospitalization can help make RSV vaccines' protective value clearer and more compelling. And for your patients at increased risk due to underlying chronic comorbidities, it is a conversation particularly well worth having. ❖

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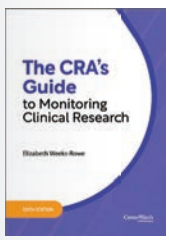
The CRA's Guide to Monitoring Clinical Research, Sixth Edition

Author: Elizabeth Weeks-Rowe



Updated for today's clinical research associates (CRAs), this guide examines the career outlook for CRAs, incorporating the go-to guidance from past editions while reflecting on the growing areas within the clinical research industry. This sixth edition includes tips and strategies, checklists, personal experiences, traveling tips, key takeaways and exercises to help CRAs build job confidence and advance their careers. Topics covered include study initiation, monitoring and closeout; stages of clinical research and phases of trials; adverse events and safety monitoring; statistical methods; IRB review and reporting; inspections and audits; informed consent process; background and principles of good clinical practice; FDA regulations and guidance on clinical trial monitoring; post-COVID adjustments and implications; stakeholders the CRA must work with; new technologies to capture and manage data; and development of new roles in clinical trials.

www.centerwatch.com/products/590-the-cras-guide-to-monitoring-clinical-research-sixth-edition

Key Information and Facilitating Understanding in Informed Consent

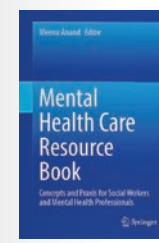
Authors: U.S. Food and Drug Administration (FDA) and the Office for Human Research Protections

This draft guidance provides research sponsors, investigators and institutional review boards with recommendations on how to implement two proposed requirements in the FDA proposed rule "Protection of Human Subjects and Institutional Review Boards" and the corresponding current requirements under the revised Common Rule, including that informed consent begins with key information about the research presented in a clear and concise manner, and informed consent as a whole be presented in a way that facilitates understanding of the reasons why someone might or might not want to participate in the research. It provides recommendations on how to present key information at the beginning of the informed consent document, including topics that are generally important for participants to understand such as the purpose of the research, the possible risks and benefits of the study and the study's length and procedures.

www.fda.gov/regulatory-information/search-fda-guidance-documents/key-information-and-facilitating-understanding-informed-consent-guidance-sponsors-investigators-and

Mental Health Care Resource Book: Concepts and Praxis for Social Workers and Mental Health Professionals, 1st Edition

Editor: Meenu Anand, MBA, MPH



This book takes a strengths-based approach to focus on different aspects of mental health in the post-pandemic world. Three sections each incorporate essential skills and praxis. The first examines the fundamental and conceptual underpinnings of mental health, well-being and wellness to present an overview of mental health from the biopsychosocial perspective. The second section demonstrates using and transforming theoretical principles and perspectives into practice-based skills through detailed narrations and illustrations. The third section combines field-based narratives that reflect multifaceted challenges and efforts toward treating mental disorders and promoting positive mental health, including success stories in diverse settings.

www.amazon.com/ICD-10-CM-2024-Complete-Official-Codebook/dp/1640162909
www.amazon.com/Mental-Health-Care-Resource-Book/dp/9819712025

Let Me Help: The Best Decisions Begin With Kindness

Author: David Trock, MD

The inspiring words of *Let Me Help* include patient narratives, advice for young caregivers, champions of healthcare and stirring accounts of kindness in medical decision-making. Readers will recognize the keys to patient satisfaction and the rewards of helping others. The author, David Trock, MD, served for 30 years on faculty at Yale University School of Medicine and 18 years as chief of rheumatology at Danbury Hospital in Connecticut. His insight into patient care, bedside manner and stoic philosophy will delight anyone who's ever taken a patient by the hand.

www.amazon.com/Let-Me-Help-Decisions-Kindness/dp/B0CNP33JSW

Immune Globulin and Prophylactic Antibiotics Provide Similar Efficacy in Treating Hypogammaglobulinemia Secondary to Hematological Malignancy

Immune globulin replacement and prophylactic antibiotics are commonly used to prevent infections in patients with secondary hypogammaglobulinemia due to hematological malignancies but have never been directly compared.

A randomized controlled feasibility trial conducted in seven hospitals in Australia and New Zealand enrolled patients with secondary hypogammaglobulinemia with either a history of recurrent/severe infection or an immunoglobulin G level <4 g/L. Participants were randomized in a 1:2 ratio to immune globulin (0.4 g/kg per 4 weeks IV) or daily antibiotics (trimethoprim-sulfamethoxazole 160 mg/800 mg or, if contraindicated, 100 mg doxycycline) for 12 months. Participants allocated to antibiotics were allowed to crossover after grade ≥3 infections.

The primary outcome was proportion of patients alive on the assigned treatment 12 months after randomization. Between August 2017 and April 2019, 63 patients were randomized: 42 to antibiotics and 21 to immune globulin. Proportion of participants alive on allocated treatment at 12 months was 76 percent in the immune globulin and 71 percent in the antibiotic arm (Fisher exact test P=.77; odds ratio, 0.78; 95% CI, 0.22-2.52). The lower quartile for time to first major infection (median, not reached) was 11.1 months for the immune globulin and 9.7 months for the antibiotic arm (log-rank test, P=.65). Three participants in the immune globulin and two in the antibiotic arm had grade ≥3 treatment-related adverse events. A similar proportion of participants remained on antibiotic prophylaxis at 12 months to those on immune globulin, with similar rates of major infections.

The researchers concluded that their findings support the feasibility of progressing to a Phase III trial. ❖

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Study Shows Vaccination Decision in IEI Patients Must Be Individualized

Inborn errors of immunity (IEI) increase morbidity and mortality risks, particularly from respiratory tract infections. Hence, vaccination becomes pivotal for IEI patients.

A study examined the vaccination and respiratory tract infection rates in a diverse IEI patient cohort undergoing immune globulin replacement therapy (IGRT) at a tertiary care center. Data on vaccinations and respiratory infections were extracted from medical records. The study included 33 patients (mean age= 37.7 ± 11.4 years; 17 male). The most common clinical phenotype in the cohort was primary antibody deficiencies (90.9 percent). Only two patients had a genetic diagnosis, both of whom were brothers diagnosed with Wiskott-Aldrich syndrome (WAS). Almost half (48.5 percent) of patients had bronchiectasis and 81.8 percent were on prophylactic antibiotics. All patients with IEI included in the study were regularly receiving IGRT.

The vaccination rate of patients against respiratory tract infections was 42.4 percent, 57.6 percent and 78.8 percent for influenza, pneumococcus and COVID-19, respectively. Only one patient (7.1 percent) who received the influenza vaccine developed an upper respiratory tract infection. However, viral panel analysis could not be performed as the patient did not present to the hospital. The COVID-19 vaccination rate was notably higher than that of other vaccines, likely due to increased awareness during the pandemic, aided by public advisories and media influence.

The researchers observed higher vaccination rates for the COVID-19 vaccine compared to other vaccines (influenza and pneumococcal vaccines). Although the researchers acknowledged the

potential impact of social and governmental influence in increasing vaccination rates, they concluded that it is crucial to acknowledge that vaccination decisions in IEI patients must be individualized. ❖

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Medicare Immune Globulin Reimbursement Rates

Rates are effective July 1, 2024, through Sept. 30, 2024

	Product	Manufacturer	J Codes	ASP + 6% (before sequestration)	ASP + 4.3% (after sequestration)
	ALYGLO	GC Biopharma	J1599	*	*
IVIG	ASCENIV	ADMA Biologics	J1554	$982.81	$967.05
IVIG	BIVIGAM	ADMA Biologics	J1556	$150.34	$147.93
IVIG	GAMMAGARD SD	Takeda	J1566	$159.80	$157.24
IVIG	GAMMAPLEX	BPL	J1557	$109.13	$107.38
IVIG	OCTAGAM	Octapharma	J1568	$95.48	$93.95
IVIG	PANZYGA	Octapharma/Pfizer	J1576	$139.53	$137.29
IVIG	PRIVIGEN	CSL Behring	J1459	$97.34	$95.78
IVIG/SCIG	GAMMAGARD LIQUID	Takeda	J1569	$90.14	$88.70
IVIG/SCIG	GAMMAKED	Kedrion	J1561	$99.16	$97.57
IVIG/SCIG	GAMUNEX-C	Grifols	J1561	$99.16	$97.57
SCIG	CUTAQUIG	Octapharma	J1551	$145.34	$143.01
SCIG	CUVITRU	Takeda	J1555	$168.92	$166.21
SCIG	HIZENTRA	CSL Behring	J1559	$131.88	$129.76
SCIG	HYQVIA	Takeda	J1575	$172.39	$169.63
SCIG	XEMBIFY	Grifols	J1558	$144.00	$141.69

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

Calculate your reimbursement online at www.FFFenterprises.com.

Immune Globulin Reference Table

	Product	Manufacturer	Indication	Size
IVIG	ALYGLO	GC Biopharma	PI	5 g, 10 g, 20 g
IVIG	ASCENIV LIQUID, 10%	ADMA Biologics	PI	5 g
IVIG	BIVIGAM LIQUID, 10%	ADMA Biologics	PI	5 g, 10 g
IVIG	GAMMAGARD S/D Lyophilized, 5% (Low IgA)	Takeda	PI, ITP, B-cell CLL, KD	5 g, 10 g
IVIG	GAMMAPLEX Liquid, 5%	BPL	PI, ITP	5 g, 10 g, 20 g
IVIG	GAMMAPLEX Liquid, 10%	BPL	PI, ITP	5 g, 10 g, 20 g
IVIG	OCTAGAM Liquid, 5%	Octapharma	PI	1 g, 2.5 g, 5 g, 10 g, 25 g
IVIG	OCTAGAM Liquid, 10%	Octapharma	ITP, DM	2 g, 5 g, 10 g, 20 g, 30 g
IVIG	PANZYGA Liquid, 10%	Octapharma/Pfizer	PI, ITP, CIDP	1 g, 2.5 g, 5 g, 10 g, 20 g, 30 g
IVIG	PRIVIGEN Liquid, 10%	CSL Behring	PI, ITP, CIDP	5 g, 10 g, 20 g, 40 g
IVIG/SCIG	GAMMAGARD Liquid, 10%	Takeda	IVIG: PI, MMN	1 g, 2.5 g, 5 g, 10 g, 20 g, 30 g
			SCIG: PI , CIDP	
IVIG/SCIG	GAMMAKED Liquid, 10%	Kedrion	IVIG: PI, ITP, CIDP	1 g, 2.5 g, 5 g, 10 g, 20 g
			SCIG: PI	
IVIG/SCIG	GAMUNEX-C Liquid, 10%	Grifols	IVIG: PI, ITP, CIDP	1 g, 2.5 g, 5 g, 10 g, 20 g, 40 g
			SCIG: PI	
SCIG	CUTAQUIG Liquid, 16.5%	Octapharma	PI	1 g, 1.65 g, 2 g, 3.3 g, 4 g, 8 g
SCIG	CUVITRU Liquid, 20%	Takeda	PI	1 g, 2 g, 4 g, 8 g, 10 g
SCIG	HIZENTRA Liquid, 20%	CSL Behring	PI, CIDP	1 g PFS, 2 g PFS, 4 g PFS, 10 g PFS
SCIG	HYQVIA Liquid, 10%	Takeda	PI, CIDP	2.5 g, 5 g, 10 g, 20 g, 30 g
SCIG	XEMBIFY Liquid, 20%	Grifols	PI	1 g, 2 g, 4 g, 10 g

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

2024-2025 Influenza Vaccines

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

Product	Manufacturer	Presentation	Age Group	Code
Trivalent				
AFLURIA (IIV4)	Seqirus	0.5 mL PFS 10-bx	3 years and older	90685
AFLURIA (IIV4)	Seqirus	5 mL MDV	6 months and older	90685
FLUAD (IIV4)	Seqirus	0.5 mL PFS 10-bx	65 years and older	90694
FLUARIX (IIV4)	GSK	0.5 mL PFS 10-bx	6 months and older	90686
FLUBLOK (ccIIV4)	Sanofi	0.5 mL PFS 10-bx	18 years and older	90682
FLUCELVAX (ccIIV4)	Seqirus	0.5 mL PFS 10-bx	6 months and older	90674
FLUCELVAX (ccIIV4)	Seqirus	5 mL MDV	6 months 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	0.5 mL PFS 10-bx	6 months and older	90686
FLUZONE (IIV4)	Sanofi	5 mL MDV	6 months and older	90685
FLUZONE HIGH-DOSE (IIV4)	Sanofi	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.

2024-2025 COVID-19 Vaccines

Product	Manufacturer	Presentation	Age Group	Code
SPIKEVAX COVID-19 Vaccine, mRNA	Moderna	0.5 mL PFS Blister 10-pk	12 years and older	91322
SPIKEVAX COVID-19 Vaccine, mRNA	Moderna	0.5 mL SDV 10-pk	12 years and older	91322
MODERNA COVID-19 Vaccine, mRNA	Moderna	0.25 mL SDV 10-pk	6 months to 11 years	91321
NOVAVAX COVID-19 Vaccine, Adjuvanted	Novavax	0.5 mL SDV 10-pk	12 years and older	91304
COMIRNATY COVID-19 Vaccine, mRNA	Pfizer-BioNTech	0.3 mL PFS 10-bx	12 years and older	91320

2024-2025 Respiratory Syncytical Virus (RSV) Vaccines

Product	Manufacturer	Presentation	Age Group	Code
ABRYSVO	Pfizer	0.5 mL Kit 1-ctn	60 years and older	90678
ABRYSVO	Pfizer	0.5 mL Kit 5-ctn	60 years and older	90678
AREXVY	Pfizer	0.5 mL SDV 10-bx	60 years and older	90679

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.

STEP 3

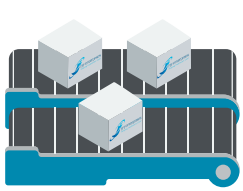
Specialty Packaging

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.

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