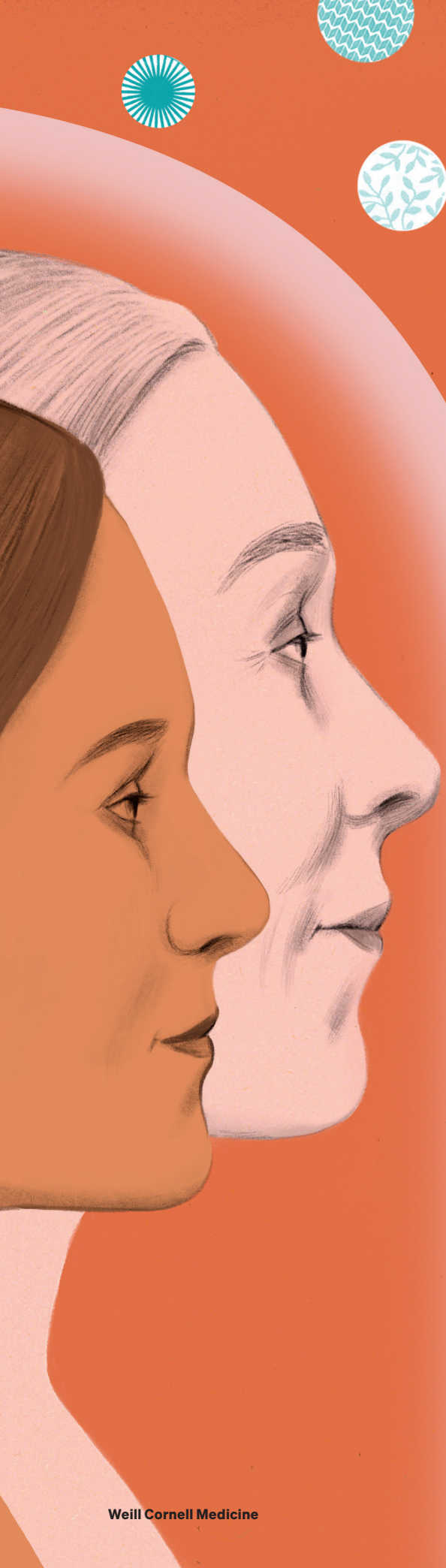

Good Medicine

BY MICHAEL EISENSTEIN

ILLUSTRATION BY SILJA GOETZ

New research aims to extend the power of existing vaccines — and develop even better ones in the future.

At three weeks old, the biggest challenge for most infants is settling into a routine of feeding and sleeping. But Mila Dukes had a more frantic experience, including an exhaustive gauntlet of medical procedures. "She had a spinal tap, she had an MRI, she had a head ultrasound, a stomach ultrasound, a blood test, a vision test and a hearing test — all within a 24-hour period," says her mother, Melanie Dukes.

Mila was diagnosed with congenital cytomegalovirus (CMV) infection last year. CMV is commonplace, and more than half of all U.S. adults over 40 have been infected. Infections are generally asymptomatic in healthy adults, but the virus remains dormant in the body. And in pregnant people, CMV infection or reactivation of latent virus can lead to transmission to their unborn children. Congenital CMV infection affects roughly 1 in 200 newborns in the U.S., putting children at risk of hearing or vision loss, intellectual disabilities and other developmental problems.

Luckily, a statewide pilot CMV screening program in New York caught Mila's infection early. "She is one of those babies who would've been completely missed because she passed the hearing screen," says Dr. Christine Salvatore, chief of pediatric infectious disease. Dr. Salvatore subsequently took the lead on Mila's care, overseeing the tests that ultimately led to her receiving antiviral treatment — the only pharmaceutical treatment available for congenital CMV. It was the start of a medical journey that will span Mila's childhood, but Dukes, of Brooklyn, recognizes that her family was relatively lucky. "It gave me peace just to know that she was being checked more than any other child because of this diagnosis," she says. But she adds that "if there had been a vaccine for pregnant women against CMV, this all could have been prevented."

The good news is that multiple CMV vaccines are now in active development, potentially adding to the deep roster of vaccines that have saved the lives of more than 146 million children ages 5 or younger worldwide over the past 50 years and spared many more from pain and disability. "Essentially every decade, new vaccines change the face of pediatrics. This is true even now as we see new vaccines that pediatricians have wished for coming to fruition," says Dr. Sallie Permar, chair of pediatrics, who is actively collaborating with multiple such vaccine programs.

Indeed, Weill Cornell Medicine researchers are collectively engaged in a wide range of research efforts aimed at extending the protection from existing vaccines against diseases like influenza and rotavirus. In parallel, other researchers are focused on targeting other infectious threats like CMV and human immunodeficiency virus (HIV), and better understanding the unique attributes of the immune systems in children and pregnant people that could maximize the effectiveness of vaccines. These efforts have the potential to save millions of lives worldwide and accelerate the development of even better protective measures against infectious diseases in the future — if researchers continue to receive the funding and support they need.

Stacking the Odds Against Flu

By definition, the best time to get a vaccine is early — ensuring robust immune protection well in advance of a person's first encounter with a virus or bacterium. By training antibodies and T cells to recognize these threats during infancy, one can achieve durable — for some diseases, even lifelong — protection. But there are other reasons to prioritize child immunization as well, including the fact that many infections are far more dangerous to babies and small children than adults. For example, children under 5 are the second most likely age group to be hospitalized by influenza after seniors, with 20,000 young children hospitalized in a typical flu season in the United States alone. And in

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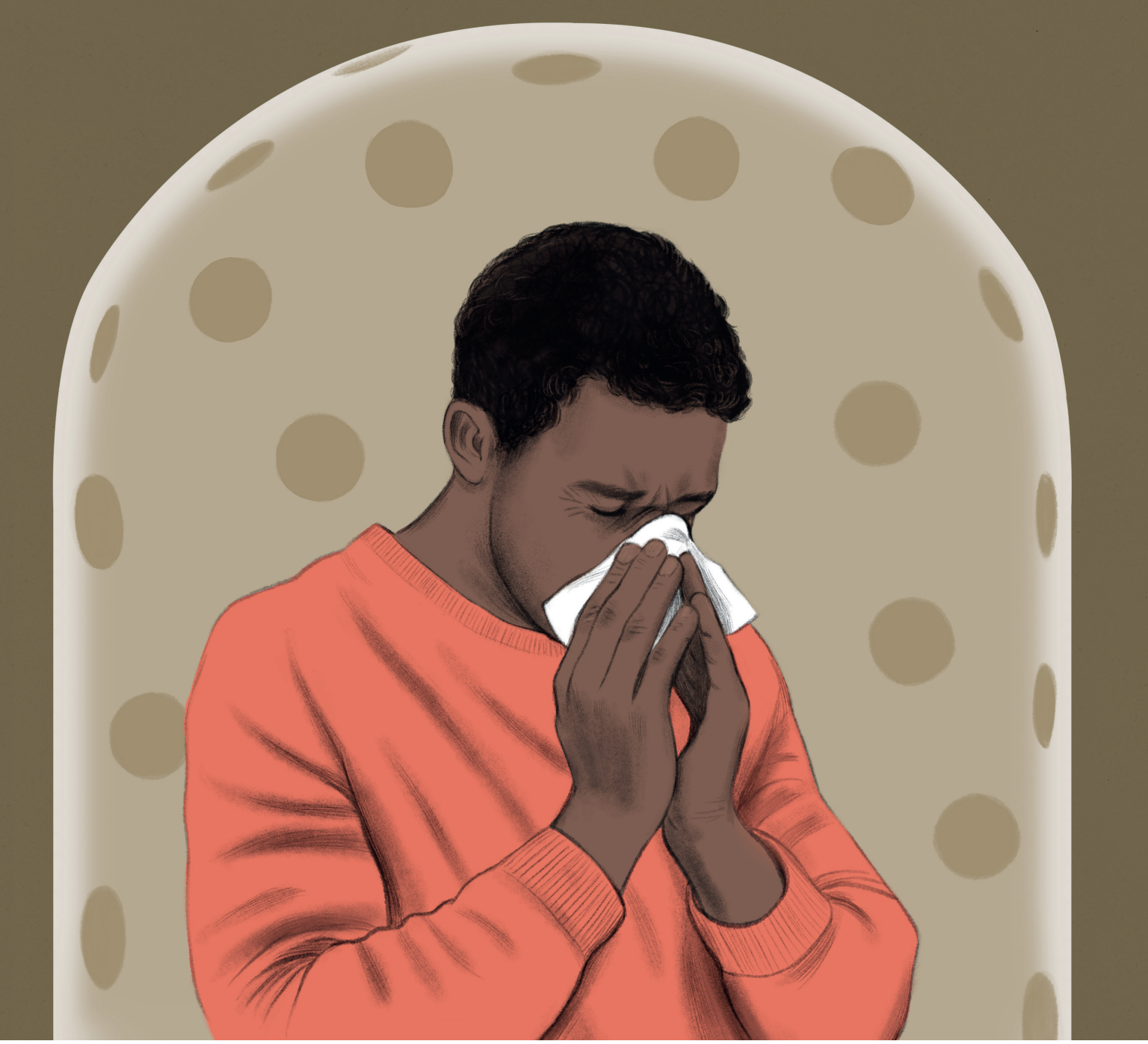
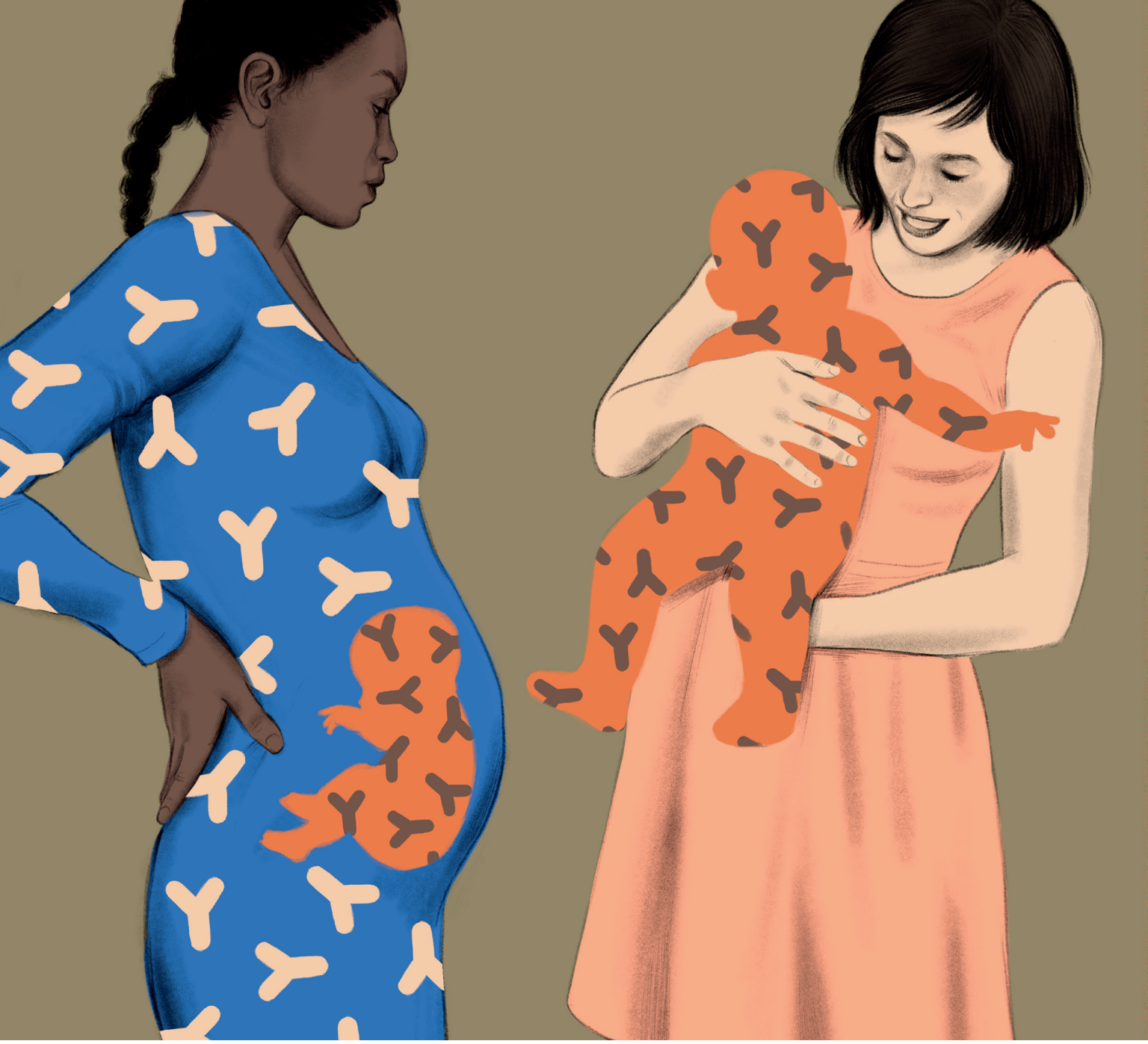


2024, the U.S. saw 207 pediatric deaths from flu — a record for a non-pandemic season.

The annual flu shot can greatly reduce the risk of severe disease, but the robustness of that armor varies from year to year. No vaccine is perfect, of course — efficacy of protection typically ranges from 80–95 percent. But once a community achieves adequate vaccination levels, the resulting "herd immunity" can halt further spread of a given disease.

In contrast, the influenza vaccine offers more modest protection. This is due to the dynamic genome of the influenza virus, which is highly mutation-prone and gradually evolves as the virus spreads. "Globally, there's always multiple influenza strains," explains Dr. Patrick Wilson, professor of microbiology and immunology in pediatrics. "It's not like there's just one strain that changes." Every year, surveillance teams track variants around the globe and attempt to predict which will ultimately predominate. These efforts directly inform vaccine design, but even a good prediction yields a vaccine that is only 40–60 percent effective in preventing flu. As a solution, Dr. Wilson is exploring opportunities to develop "universal" vaccines that deliver durable, broad protection against diverse influenza strains.

"The virus has evolved by selective pressure so that the dominant parts of it that our immune system sees are the parts that it can change really quickly," says Dr. Wilson. This effect is most notable in the protein hemagglutinin, which influenza viruses use to bind to and enter cells. Hemagglutinin is mushroom-



shaped, and both virus and vaccine tend to produce a strong antibody response against the outward-facing "head" domain. This domain is highly mutation-prone and allows the virus to evolve changes that help it elude antibody binding. In contrast, the "stalk" domain that couples the head to the viral shell is more stable and consistent across viruses, as extensive mutation can compromise its function.

One approach being evaluated by Dr. Wilson's group employs "chimeric" viral proteins, which combine the head domain from influenza strains that do not infect humans with stalk domains that are broadly shared by human-infecting strains. In a 2021 study, Dr. Wilson and his collaborators demonstrated that such vaccines could stimulate robust production of stalk-specific antibodies that could potentially fend off a range of seasonal — and some potentially pandemic-causing — viral variants. "We're able to get the targeting we want," says Dr. Wilson. "But is it effective protection? We don't know yet."

The timing of vaccination is also important. The influenza strains we encounter early in life via infection or vaccination are thought to train the immune system to recognize specific viral features. This "imprinting" process can then result in a weaker immune response to subsequently encountered viruses in which those features are heavily mutated or even absent. Accordingly, Dr. Wilson and colleagues are currently studying whether children may have more flexibility in their immune response to new flu strains relative to adults with well-established immune imprinting.

“Almost every new pandemic threat has a higher chance of more severe disease in pregnancy and an impact on our next generation — the fetuses and newborns — than it does for non-pregnant individuals.”

Dr. Sallie Permar

This could offer a golden opportunity to establish broad protection. “That will be a goal of a universal flu vaccine — to get it to the youngest children, so that you have that lifelong immunity,” says Dr. Permar, who is also the Nancy C. Paduano Professor in Pediatrics and pediatrician-in-chief at New York-Presbyterian/Weill Cornell Medical Center and Komansky Children’s Hospital.

Protecting Pregnancy

More generally, clinicians aim to vaccinate as early as possible in order to establish immune protection well in advance of a child’s first exposure to infection. But there are limits to how early they can act. This is because the fetus does not have a fully functioning immune system but instead relies on antibodies produced by its mother.

“In humans, the placenta allows certain antibodies to be transferred over,” explains Dr. Sarah Caddy, an assistant professor in Cornell University’s Baker Institute for Animal Health. “In normal pregnancies, infants are born with almost the same range of antibodies that their moms have.” The capacity to produce their own antibodies will develop in the months after birth, but this leaves a critical window during which babies rely on protection received *in utero*.

Vaccination during pregnancy can fill this gap. Maternal vaccination against influenza and COVID-19 are now commonplace, although these are both primarily focused on the mother. “We know these diseases are worse in pregnancy,” says Dr. Laura Riley, chair of obstetrics and gynecology. But other maternal vaccines are being developed specifically to protect newborns.

For example, most children get infected with respiratory syncytial virus (RSV). Typical infections lead to days of wheezing, coughing and fever, but RSV can be far more dangerous to babies and is the leading cause of infant hospitalization in the U.S. The danger is greatest during the first six months of life, and Pfizer developed a maternal vaccine to protect newborns during this critical period. Clinical trials showed that children born to women vaccinated during pregnancy were almost 70 percent less likely to develop severe respiratory disease in the first six months after birth, and the U.S. Food and Drug Administration (FDA) approved Pfizer’s Abrysvo in August 2023.

Dr. Permar believes that maternal vaccination will only become more essential as a safeguard against future threats. “Almost every new pandemic threat has a higher chance of more severe disease in pregnancy and an impact on our next generation — the fetuses and newborns — than it does for non-pregnant individuals,” she says. But the bar for safety must also be set higher in pregnant individuals, making research demonstrating perinatal vaccine safety especially important. A follow-up 2024 study conducted by Dr. Riley and other Weill Cornell Medicine researchers, for example, supported the safety of Abrysvo and found no evidence for increased risk of birth complications.

However, while maternal antibodies can protect newborns, they also can impede immunization. For example, a 2020 study by Dr. Permar and colleagues examined why infant vaccination against the diarrheal disease-causing pathogen rotavirus is less effective in low- and middle-income countries than in wealthier regions. They traced the problem to a phenomenon called “maternal antibody interference,” wherein antibodies received via breast milk bind to and eliminate the viral particles used for the infant vaccine, preventing it from inducing a proper immune response.

Dr. Caddy, who is also an assistant professor in Cornell University’s Department of Microbiology and Immunology, is now working with Dr. Permar to investigate this problem and the factors contributing to it, using both preclinical models and clinical samples collected by collaborators at the Centre for Infectious Disease Research in Zambia. Dr. Caddy notes that a rotavirus vaccine that achieves 90 percent efficacy in the U.S. delivered a far poorer efficacy of 28 percent for Zambian children, and the underlying biology for this disparity

remains enigmatic. "We're really interested in studying the antibodies and all the samples they've collected to say: Is it a particular type of maternal antibody that's causing a problem? Is it more placental? Is it more breast milk?" The results could guide development of vaccines that offer more effective protection against this often lethal viral infection, which claimed the lives of 440,000 children under 5 in 2021 alone — almost exclusively in lower-income settings.

HIV in the Crosshairs

HIV is another major public health scourge in these same regions of the world and has proven a stubbornly difficult target for vaccine development; without effective, durable protection, it will remain impossible to eradicate entirely. Like influenza, HIV takes advantage of a sloppy genome replication process that produces lots of mutations and variability, enabling it to readily evolve strategies for bypassing host immune response and efficiently infiltrating T cells. Acting early is of the essence; mothers who keep their HIV infection under control with antivirals can still unknowingly infect their children while breastfeeding, and establishing immune protection before sexual maturity could greatly reduce the odds of contracting HIV as an adult.

As with influenza, WCM researchers are identifying strategies that allow them to target the immune system against components of HIV that are too functionally important to mutate extensively. Dr. Genevieve Fouda, a professor of pediatrics and of microbiology and immunology, says that the HIV vaccine field has been transformed over the past two decades by the discovery of numerous broadly neutralizing antibodies (bNAbs). "When someone is infected, the virus evolves, and as this virus evolves and diversifies, then your antibody repertoire will also evolve and diversify," says Dr. Fouda. "There is this race between the virus and the antibody, and eventually you have these broadly neutralizing antibodies."

This evolution might not occur quickly enough to prevent AIDS in these individuals, but the right vaccine could selectively stimulate the production of these antibodies and thereby prepare the immune system to defend against future infection. This requires careful design of viral protein-derived antigens that can consistently steer the immune response away from strain-specific targets and towards viral protein components shared across most virus variants.

Protecting children — both against transmission from an HIV-positive mother and from future exposure after sexual maturity — is a top priority. And as luck would have it, human and animal studies indicate that childhood is also the best opportunity to elicit the potent antibodies needed for broad immunity against HIV. In a study published last summer, Dr. Permar and colleagues including Dr. Ashley Nelson, assistant professor of immunology research in pediatrics, inoculated nonhuman primates beginning in infancy with a vaccine based on an engineered version of the HIV envelope protein, which encapsulates the virus genome. "If you start immunizing at birth… you can elicit those early precursor bNAbs," says Dr. Nelson. "It still takes multiple doses, but you can elicit them at a pretty high frequency." The finding is encouraging, as it could allow a future HIV vaccine to be embedded in the existing early childhood immunization schedule.

In parallel, Dr. Nelson and Dr. Fouda are investigating "passive immunization" strategies, in which newborns and infants are directly dosed with bNAbs to protect against HIV exposure via breastfeeding. This approach has already proven effective as an alternative to vaccination for RSV, and two recent clinical trials evaluated a single HIV bNAb in adults — with mixed results. "There was not the protection that we were hoping for — the viruses that were transmitted were generally resistant to the bNAb, indicating that you may need to immunize with a combination of bNAbs targeting different regions of the virus envelope," says Fouda. But a 2024 study by Dr. Fouda and colleagues showed that they could safely inoculate young nonhuman primates with a trio of antibodies that collectively neutralize

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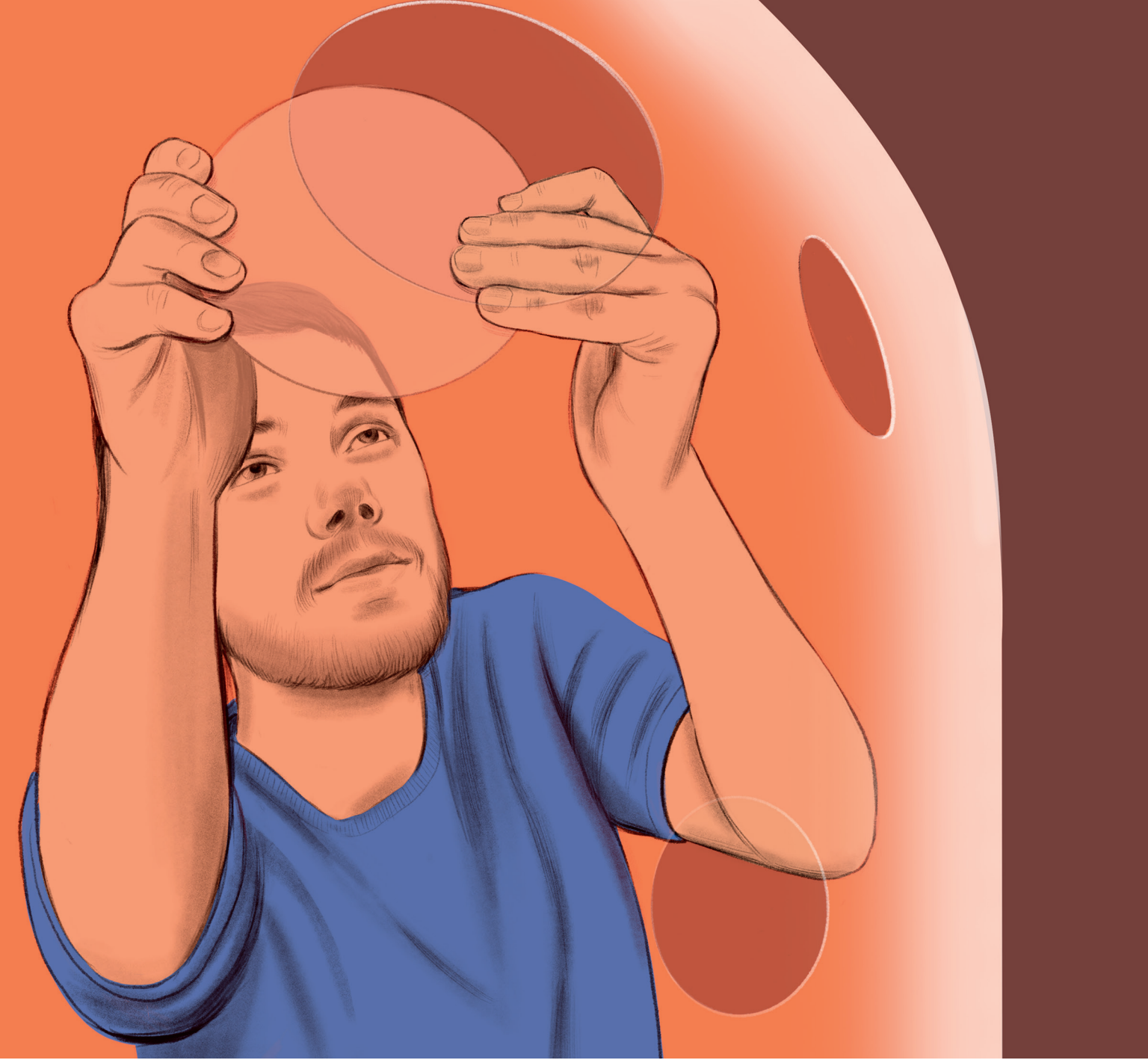

a wide range of viral variants, suggesting a promising road forward. "The next steps would be to test a combination of two to three different bNAbs in children. Phase 1 studies to achieve this goal are in preparation," says Dr. Fouda.

A Vaccine Decades in the Making

The stakes in the fight against CMV are lower than with HIV, but the virus has proven equally challenging for vaccine development. For most people exposed to CMV after birth, the virus slips silently into the body and stays there without triggering meaningful symptoms — or an immune response. "Natural immunity is not protective," says Dr. Permar, and that means that researchers need to find a way to coax the human immune system to do something it cannot achieve on its own.

There are very few screening programs in place for neonatal CMV — the one in New York state that led to Mila Dukes' diagnosis was only funded for a single year. Most of the roughly 20,000–30,000 children born with congenital CMV in the U.S. every year will go undetected, with 10–15 percent manifesting potentially severe sensory or neurological deficits as they grow older. Unfortunately, there is only a narrow window for antiviral treatment — preferably within the first month of life, and no later than 13 weeks — and the benefits are uncertain. "You still could progress and have hearing loss," says Dr. Salvatore.

After nearly 60 years of efforts to develop an effective CMV vaccine, the field is finally turning a corner. Since 2017, Dr. Permar has been collaborating with Moderna on the development of a vaccine that uses mRNA strands encoding glycoprotein B and the pentameric complex — a set of proteins that CMV uses to infect cells. After immunization, the mRNA is taken by host cells and translated into viral proteins that train the immune system to rapidly recognize and eliminate the virus. A recent clinical trial whose samples were evaluated by Dr. Permar's team confirmed that this vaccine can consistently elicit neutralizing antibodies against this normally elusive pathogen, and another major trial to assess the vaccine's protective efficacy in nearly 7,500 CMV-negative women is now underway.

Progress in this battle has been powered by sophisticated experimental strategies for understanding the immune response to CMV and opportunities to amplify that response. Dr. Permar's group has developed multiple animal models that replicate scenarios in which there is either high or low risk of CMV transmission to a developing fetus. In parallel, they are assessing the similarities and differences in the human immune response by analyzing samples of placental and umbilical cord blood donated by CMV-positive women after giving birth. "We can measure where the virus was transmitted versus not transmitted, and then how that relates to the results we're getting in an experimental model," says Dr. Permar.

Maintaining Momentum

A more comprehensive understanding of immune system function in both pregnant people and young children will be essential for advancing the development of vaccines that are appropriately designed and dosed for maximum safety and efficacy. "Children are not small adults," says Dr. Fouda, and the differences between the two age groups can be difficult to predict.

For example, Dr. Virginia Pascual, professor of pediatrics and director of the Drukier Institute for Children's Health Research, points out that infants need two doses of flu vaccine to achieve even the modest protection achieved with a single dose in older children and adults. Pediatric patients may also be susceptible to unexpected complications of influenza infection.

Dr. Pascual's team aims to get a better handle on immune system development and how it evolves over time as part of an ongoing collaboration with St. Jude Children's Research Hospital. "We are studying infants from birth and following them through exposures not only to vaccinations but also to [common] infections," she says. Their findings should reveal factors that contribute to successful establishment of immune protection against disease, or which leave children more susceptible to getting sick or responding poorly to immunization.

Prioritizing children and pregnant people for clinical trials will also be essential. Dr. Permar looks back to the studies that led to the clinical approval of the first-generation COVID vaccines, which involved tens of thousands of study participants.

"Not a single of the thousands of enrollees was a child, not a single one was pregnant," she says. "And this meant that when the vaccine was available, pregnant people had to decide with their provider — with no data in hand — whether or not to take the vaccine." She and Dr. Riley, obstetrician and gynecologist-in-chief at NewYork-Presbyterian/Weill Cornell, have developed a set of policy guidelines that could accelerate development and testing of maternal vaccines, including strategies for incentivizing pharmaceutical companies to take on the added risk of focusing on these highly vulnerable populations. Dr. Fouda suggests that pediatric vaccine development could also be accelerated by conducting initial efficacy studies in children alongside — rather than after — adults once safety has been established, using data from appropriately chosen preclinical studies to guide dosing and formulation.

But the most immediate challenge comes from the spending and staffing cuts that threaten to reduce America's federal research, public health and international aid programs. For example, Dr. Wilson notes that the planned U.S. withdrawal from the World Health Organization will challenge efforts to surveil and prepare for influenza and other emerging pandemic threats. "It's a dangerous game," he says. And amid outbreaks of measles around the United States, cancellations of vaccine-related expert meetings and shifts in public messaging emphasizing personal choice in vaccination portend a tough fight to protect the health of children both in the United States and abroad.

The CMV vaccine will inevitably arrive too late for Mila Dukes, but for her mother, it's imperative that vaccine science continue to progress for all children. "It's not just 'nice to have,'" she says. "Investing in the health of our nation is a must."