2017. With a better understanding of the incentives that drive development of rare-disease therapies, tax incentives could be better targeted. A return to the provision of tax credits equal to 50% of clinical testing expenses may be appropriate for therapies for ultrarare diseases or those that are useful for a single rare disease, with the 25% rate being applied for all other (including secondary) orphan indications. Alternatively, tax credits could be scaled (e.g., from 25 to 50%) according to the rarity of a disease or conditioned on reasonable-pricing commitments. In all cases, direct subsidies could be clawed back once revenue exceeds $1 billion.

Because patent life now typically persists past the 7-year postapproval period, extended exclusivity has become less relevant to manufacturers and is unlikely to be a meaningful policy lever. We believe a revenue-based incentive cap and scaled tax credits hold more promise for encouraging orphan-drug development.

Many rare diseases remain understudied, and the trajectory of drug prices is increasingly unsustainable. More thoughtfully targeted incentives are therefore required to sustain advances in orphan-drug development for the next four decades.

Disclosure forms provided by the authors are available at NEJM.org.

From the Center for Health Law Studies, Saint Louis University School of Law, St. Louis (M.S.S.); Harvard Business School and the Harvard–MIT Center for Regulatory Science — both in Boston (A.D.S.); Hasso Plattner Institute, University of Potsdam, Potsdam, Germany (A.D.S.); and Duke Law School and the Duke–Margolis Center for Health Policy, Durham, NC (A.K.R.).

This article was published on July 6, 2024, at NEJM.org.

1. IQVIA Institute. Orphan drugs in the United States: rare disease innovation and cost trends through 2019. December 3, 2020 (https://www.iqvia.com/insights/the-iqvia-institute/reports-and-publications/reports/orphan-drugs-in-the-united-states-rare-disease-innovation-and-cost-trends-through-2019).
2. Bagley N, Berger B, Chandra A, Garthwaite C, Stern AD. The Orphan Drug Act at 35: observations and an outlook for the twenty-first century. Innov Policy Econ 2019;19:97-137 (https://www.journals.uchicago.edu/doi/full/10.1086/699934).
3. Miller KL, Lanthier M. Orphan drug label expansions: analysis of subsequent rare and common indication approvals. Health Aff (Millwood) 2024;43:18-26.
4. Tu SS, Nagar S, Kesselheim AS, Lu Z, Rome BN. Five-year sales for newly marketed prescription drugs with and without initial Orphan Drug Act designation. JAMA 2023;329:1607-8.
5. Beall RF, Quinn AE, Kesselheim AS, Tessema FA, Sarpatwari A. Generic competition for drugs treating rare diseases. J Law Med Ethics 2020;48:789-95.

DOI: 10.1056/NEJMp2401487

Funding Postauthorization Vaccine-Safety Science

Daniel A. Salmon, Ph.D., M.P.H., Walter A. Orenstein, M.D., Stanley A. Plotkin, M.D., and Robert T. Chen, M.D.

The United States benefits from a robust federal immunization program that has been successful in controlling and eliminating many diseases. However, the widespread vaccine hesitancy observed during the Covid-19 pandemic suggests that the public is no longer satisfied with the traditional safety goal of simply detecting and quantifying the associated risks after a vaccine has been authorized for use. The public also wants public health authorities to mitigate and prevent rare but serious adverse reactions — which no longer seem rare when vaccines are given to millions or billions of people.

Postauthorization studies are needed to fully characterize the safety profile of a new vaccine, since prelicensure clinical trials have limited sample sizes, follow-up durations, and population heterogeneity.[1] It is critical to examine adverse events following immunization (AEFIs) that have not been detected in clinical trials, to ascertain whether they are causally or coincidentally related to vaccination. When they are caused by vaccines (vaccine adverse reactions), the risk attributable to vaccination and the biologic mechanism must be ascertained. That science becomes the basis for developing safer vaccines, if possible, and for determining contraindications to vaccination and the compensation that should be offered for AEFIs. Currently in the United States, when the Advisory Committee on Immunization Practices (ACIP) recommends a new routine vaccine, the only automatic statutory resource allocations that follow are for vaccine procurement by Vaccines for Children (VFC) and for the Vaccine Injury Compensation Program (VICP). Although the ACIP acknowledges the need,[2] there are currently no resources earmarked for postauthorization safety studies beyond annual appropriations, which must be approved by Congress each year.

Understanding of the Biologic Mechanisms of Vaccine Adverse Reactions.*

Year Identified	Vaccine	Vaccine Adverse Reaction	Understanding of Biologic Mechanism
1969	Oral polio vaccine	Vaccine-associated paralytic polio	Understood
1976	Swine influenza vaccine	Guillain–Barré syndrome	Not understood
1998	RotaShield	Intussusception	Not understood
2000	Inactivated intranasal influenza vaccine	Bell's palsy	Hypothesized but uncertain
2009	Pandemic influenza vaccine	Narcolepsy	Not understood
2021	mRNA Covid-19 vaccine	Myopericarditis	Not understood
2021	AZ–J&J Covid-19 vaccine	Thrombosis with thrombocytopenia syndrome	Hypothesized but uncertain
2021	AZ–J&J Covid-19 vaccine	Guillain–Barré syndrome	Not understood
2024	GSK–Pfizer RSV vaccine	Guillain–Barré syndrome	Not understood

* Updated from Salmon et al.[1] AZ denotes AstraZeneca, GSK GlaxoSmithKline, J&J Johnson & Johnson, and RSV respiratory syncytial virus.

Progress in vaccine-safety science has understandably been slow — often depending on epidemiologic evidence that is delayed or is inadequate to support causal conclusions and on an understanding of biologic mechanisms that is incomplete — which has adversely affected vaccine acceptance. For example, though there were eventually more than a dozen well-conducted epidemiologic studies that led the Institute of Medicine (IOM, now the National Academy of Medicine) to conclude that measles–mumps–rubella vaccines and thimerosal in vaccines were not causing autism, the results were not available until years after these possibilities were raised publicly.[1] The slow speed of science contributed to widespread public concern and consequent decreases in immunization coverage, as well as outbreaks of measles.

In 234 reviews of various vaccines and health outcomes conducted from 1991 to 2012, the IOM found inadequate evidence to prove or disprove causation in 179 (76%) of the relationships it explored, illustrating the need for more rigorous science. In 2024, the National Academies of Sciences, Engineering, and Medicine issued a report on potential harms from Covid-19 vaccines and was unable to find sufficient evidence of a causal relationship in 65 conclusions (76%) (there was sufficient evidence in only 20 conclusions). The growing capacity of large health care databases affords new opportunities to obtain real-world data and conduct rigorous studies to quickly investigate AEFIs. The biologic mechanism remains unelucidated for most vaccine adverse reactions — notably, Guillain–Barré syndrome after administration of the 1976–1977 influenza vaccine and several other vaccines thereafter, myocarditis after mRNA-based Covid-19 vaccines, and intussusception after the first rotavirus vaccine (see table).[1] Identifying the biologic mechanisms of adverse reactions — how and in whom they occur — is critical for developing safer vaccines, preventing adverse reactions by expanding contraindications, and equitably compensating vaccinees for true adverse reactions. Recent advances in genomics, "adversomics," and understanding of the biology of adverse health outcomes have created unprecedented opportunities to elucidate the biologic mechanisms of vaccine adverse reactions.[3]

Historically, the Centers for Disease Control and Prevention (CDC) and the Food and Drug Administration (FDA) have led postauthorization vaccine-safety surveillance and research in that they comanage the Vaccine Adverse Event Reporting System (VAERS) passive-surveillance system, which is used to detect signals that require further investigation. But though VAERS is large and events may be reported to it in a timely fashion, few VAERS reports include the specific laboratory or clinical findings required for determining

causality. In most VAERS cases, establishing a causal link would require rate calculations showing that there is a higher rate of AEFIs in vaccinated groups than in unvaccinated control groups, but VAERS reports lack much of the information needed for such calculations. Active surveillance using health care databases such as the Vaccine Safety Datalink and the FDA's Biologics Effectiveness and Safety (BEST) System managed by the CDC and the FDA has this capacity to ascertain or rule out associations between vaccines and AEFIs. Other government databases (e.g., the Medicare database) have also been used for active surveillance, and the CDC conducts clinical assessment of AEFIs by means of the Clinical Immunization Safety Assessment Network.

Over the past two decades, many new vaccines have been introduced for children and for vulnerable populations such as pregnant women and older adults. However, aside from emergency appropriations for the H1N1 influenza and Covid-19 pandemics, the budget for vaccine-safety monitoring at the CDC (which is responsible for the majority of U.S. federal efforts) has remained stagnant during this period, at about $20 million per year. Although these resources have been used efficiently, this inadequate level of funding has adversely affected the speed and completeness of the science.

Postauthorization vaccine-safety research requires adequate and timely funding directly linked to the introduction of new vaccines, just as VFC and VICP funding is. The VICP is funded by an excise tax on each dose of routinely recommended vaccines ($0.75 per case of disease prevented), which goes to the VICP Trust Fund. Trust fund income has exceeded expenditures by about $120 million per year since 1991, and there was a balance of $4.3 billion as of April 30, 2023. Using this balance for vaccine-safety science and reduction of vaccine reactions would benefit immunization programs and the public, in keeping with the VICP's intent.

During the 5 years of legislative hearings that led to the VICP, Senator Paula Hawkins (R-FL), its sponsor, noted, "Although compensation of the injured children is a key component . . . other provisions of this bill are of equal importance, perhaps more important, because they are designed to improve the entire immunization program to prevent the injuries in the first place."[4] Furthermore, as explained by Senate Bill 827, passed by the Senate Labor and Commerce Committee in August 1986 but never enacted, this activity is a federal (not an industry) responsibility, "because communicable diseases are a national problem, because the primary thrust for childhood vaccination programs has come from the Federal Government, and because childhood vaccine-related injuries which may tend to undermine the public's confidence in these vaccination programs are a national concern."[5]

Postauthorization vaccine-safety research requires adequate and timely funding directly linked to the introduction of new vaccines, just as Vaccines for Children and Vaccine Injury Compensation Program funding is.

Though the clear intent of the law creating the VICP included improving vaccine-safety monitoring and reducing vaccine injuries, the funding to implement it was established by a separate tax code, which permits funds to be used only for payment of compensation and administrative costs of operating the compensation program — not for vaccine-safety monitoring and science. This omission may have been somewhat understandable in 1986, when capacity for safety monitoring and science were less mature, but they have since evolved.

We propose amending the VICP tax code to link funding for vaccine-safety monitoring with vaccine usage. Doing so would not interfere with existing funding for vaccine-injury compensation, since the program has always run a substantial surplus, using only about a third of available funds. Thus, a budget-neutral path is feasible even if the remaining funds are used for vaccine-safety research conducted both within and outside of federal agencies and departments. Expanded activities could include capacity building, epidemiologic studies, and investi-

gations (including genomic studies) of the biologic mechanisms of adverse reactions. A research agenda could be developed to focus efforts on meeting the needs of federal agencies, the medical and public health communities, and the public. The independent National Academies of Sciences, Engineering, and Medicine could be charged with reviewing the vaccine-safety system and recommending the optimal structure and governance for an adequately funded system. Allowing the use of a portion of the existing federal excise tax to fund vaccine-safety research would ensure that the United States has the surveillance, science, and rapid-response capacity to both detect and prevent vaccine injuries. This long-overdue action would be an important step toward rebuilding public confidence in the immunization system.

Disclosure forms provided by the authors are available at NEJM.org.

From the Institute for Vaccine Safety, Johns Hopkins Bloomberg School of Public Health, Baltimore (D.A.S.); Emory University, Atlanta (W.O.); the University of Pennsylvania, Philadelphia (S.A.P.); and the Brighton Collaboration, Task Force for Global Health, Decatur, GA (R.T.C.).

This article was published on July 6, 2024, at NEJM.org.

1. Salmon DA, Chen RT, Black S, Sharfstein J. Lessons learned from COVID-19, H1N1, and routine vaccine pharmacovigilance in the United States: a path to a more robust vaccine safety program. Expert Opin Drug Saf 2024;23:161-75.
2. Oliver SE, Gargano JW, Marin M, et al. The Advisory Committee on Immunization Practices' interim recommendation for use of Pfizer-BioNTech COVID-19 vaccine - United States, December 2020. MMWR Morb Mortal Wkly Rep 2020;69:1922-4.
3. Top KA, Chen RT, Levy O, et al. Advancing the science of vaccine safety during the coronavirus disease 2019 (COVID-19) pandemic and beyond: launching an International Network of Special Immunization Services. Clin Infect Dis 2022;75:S11-S17.
4. United States Senate. National Childhood Vaccine-Injury Compensation Act Hearing (S2117). Committee on Labor and Human Resources. 98th Congress; Second Session. Washington DC: U.S. Government Printing Office; May 3, 1984 (https://files.eric.ed.gov/fulltext/ED255480.pdf).
5. National Childhood Vaccine Improvement Act of 1986, S. Rep. no. 483, 99th Cong., 2d Sess. (1985-1986).

DOI: 10.1056/NEJMp2402379

On Her Own Two Feet

Michael A. Incze, M.D., M.S.Ed., and Laura Stolebarger, B.S.N.

It was 13 minutes past the start of her appointment, and we were getting worried that Ms. S. wouldn't show. We were accustomed to waiting; in the past, Ms. S. had often been hours late to her visits. Of course, once one had seen the hill she had to climb in her wheelchair to get to our clinic — often in snow or broiling heat — any twinge of annoyance at her tardiness would vanish. Today was different, though. For the first time in the 4 years we had known her, we expected Ms. S. to walk through the door.

We first met Ms. S. in 2019, just weeks after she had a below-the-knee amputation because of osteomyelitis, most likely stemming from injection-drug use. At our first visit, her proximal goal was clear: to get out of the wheelchair she had been relying on since discharge and start walking again. Working together as patient and primary care team, we quickly got her established with a rehabilitation specialist and fit for a prosthesis. She was seeing us regularly for buprenorphine treatment of her opioid use disorder as well. But after a couple of visits with a physical therapist, she was having trouble. Her opposite knee was so arthritic that she couldn't walk with the prosthesis. We referred her to an orthopedist who said the knee needed to be replaced. There was just one catch: she would have to be abstinent from all illicit drugs for a year before he would consider operating.

Unable to find any evidence to support this stipulation, we first inquired about it and then pleaded with the surgeon for a meeting to discuss his rationale and openness to a more patient-centered plan. He was concerned about the increased risk of postoperative complications given the patient's history of injection-drug use,[1] and despite the fact that Ms. S. had been actively engaged in addiction treatment for nearly 3 months, the surgery would have to be deferred. The news was a crushing blow for our patient. Facing the reality of a year confined to a wheelchair, she gave up. Her substance use spiraled, she stopped engaging with her specialists altogether, and we never saw her prosthesis again.

For the next 3 years, Ms. S. was stuck in a pattern of erratic substance use, depression, and pain. Through all that adversity, and despite the stigma she encountered regularly in health care settings, she still came to see us in