PERSPECTIVE

US Taxpayers Heavily Funded the Discovery of COVID-19 Vaccines

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The world has been elated by the roll-out of multiple highly effective vaccines that prevent coronavirus disease 2019 (COVID-19). Developing effective vaccines in under 12 months after the genome of the novel severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2) was made publicly available is a remarkable scientific tour de force. Over 3.1 billion vaccines against COVID-19 have been administered globally and over 67% of adult Americans have received at least one vaccination.

The origins of this historic accomplishment can be traced back directly to publicly funded innovations in basic science research and biotechnology. Because these critical contributions are often given inadequate attention in public discourse, we sought to review the origins of COVID-19 vaccines and the global implications of the risky, decade-long taxpayer investments that made this moment possible.

Katalin Karikó, a Hungarian-born scientist, came to the United States in 1985. She reports being overlooked and scorned at the University of Pennsylvania[1] as she was trying to develop messenger RNA (mRNA) technology to redeploy cellular mechanisms to create proteins that could be used for a variety of clinical purposes. She faced the challenges of working with synthetic RNA, which was easily destroyed before reaching its target cells and it frequently elicited an overwhelming immune response that could pose a danger to patients. In 2005, after a decade of trial and error, she and her colleague Drew Weissman published a seminal paper[2] showing that modification of select nucleosides could suppress the body's recognition of synthetic RNA, avoiding a dangerous immune cascade. To accomplish this work, Karikó and Weissman were supported by $2.3 million in grants for 6 projects from the National Institute of Allergy and Infectious Diseases (NIAID).

This finding caught the attention of Derrick Rossi, a stem cell biologist who initially thought it may be the key to growing stem cells. He shared it with his colleagues at Harvard and MIT, and they co-founded the biotech startup Moderna in 2010.[1] Meanwhile, a husband-wife duo of Turkish-German physicians, Ugur Sahin and Özlem Türeci, co-founded BioNTech in Germany in 2008.[3] Sahin, an oncologist and inventor, co-founded Ganymed Pharmaceuticals to develop individualized cancer immunotherapies with Özlem Türeci, a physician-immunologist. They sold Ganymed for $1.6 billion in 2016.[3] In 2013, they hired Katalin Karikó as senior vice president at BioNTech to oversee development of their mRNA technology with the goal of pandemic preparedness.[1]

Nearly every vaccine against COVID-19 currently being used to inoculate billions of people globally targets the spike protein of the SARS-CoV-2 virus—a pre-fusion protein used by the virus to infect host cells. The structure of this protein was discovered by Barney Graham, the current deputy director of NIAID Vaccine Research Center, and his colleagues.[4] He started this work by investigating a failed 1966 vaccine against the respiratory syncytial virus (RSV).[5] He and his colleagues isolated the RSV fusion protein and discovered that pre-fusion antibodies were substantially more potent than the post-fusion antibodies used in the unsuccessful vaccine. In 2016, Graham and colleagues, including Jason McLellan, Kizzmekia Corbett, and Andrew Ward, published a description of the complete prefusion spike protein of a human betacoronavirus,[4] HKUI1, which is related to viruses that cause SARS, Middle East respiratory syndrome (MERS), and now to SARS-CoV-2. During this time, Graham received considerable government support for his research. He began in 1991 as a microbiologist and immunologist at Vanderbilt University. In 2000, he was recruited to the NIAID Vaccine Research Center. He and his colleagues received over $8.4 million in NIAID funding for 24 projects that contributed to their spike protein discovery.

While the NIAID was funding these basic science innovations, the US

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Department of Defense was making high-risk investments in RNA vaccine technology through its Defense Advanced Research Projects Agency (DARPA). In 2011, DARPA awarded CureVac (a Sanofi-affiliated company) and In-Cell-Art $33.1 million to advance their vaccine platforms and test candidate products.[6] In 2017, CureVac researchers published the first phase I clinical trial demonstrating that an mRNA vaccine could induce functional antibodies against a viral antigen, the rabies virus.[7] In 2013, DARPA awarded Moderna $25 million toward developing RNA vaccines against the viral diseases Zika and Chikungunya, validating the concept that mRNA sequences could be used to produce a secreted human protein and potentially scale antibody responses against a specific target in the human body.[6]

These foundational advances were funded in part by US taxpayers and laid the groundwork for the COVID-19 vaccines the world is racing to get into as many arms as possible. Without these investments, it would have been far more challenging to achieve the rapid and remarkable success we have seen with mRNA vaccine development during this pandemic.

In addition to decades of government funding for research prior to the pandemic, the US taxpayers added significantly more support during the pandemic to further accelerate vaccine development and capacity. Operation Warp Speed (OWS) invested billions of dollars in conducting rigorous clinical trials and in manufacturing with the participation of Moderna, AstraZeneca/Oxford, Johnson and Johnson, and Sanofi/GSK. In total, over $18 billion dollars of US public funds have been invested in 6 vaccine candidates.

The National Institutes of Health (NIH) has joint ownership of the Moderna vaccine patent because of its fundamental role in research and development, starting from the inception of that work and continuing to the present. This includes the nearly $6 billion from US public funds, which supported an enormous proportion of the development costs of the Moderna vaccine from bench to bedside. Public funding vastly exceeded private donations but has often received less attention than such high-profile private investments, including the $1 million donation made by Dolly Parton to Vanderbilt University Medical Center to support this work.

In addition to US federal investment, there were substantial contributions by numerous other scientists, clinical trialists, research support staff, and tens of thousands of diverse volunteer clinical trial participants, all of whom were instrumental in advancing mRNA vaccines from their initial discovery to the inoculation of millions globally. Pfizer's often-repeated statement that it invested ~ $2 billion and did not receive any government research funding to develop its vaccine paints an incomplete picture, because its partner BioNTech received $445 million in funding from the German government to assist with COVID-19 vaccine development. BioNTech is now licensing the NIH's patented pre-fusion spike protein technology.

The decades of foundational government funding in vaccine innovation and the massive influx of money during OWS have benefited the entire biopharmaceutical and scientific community, raising important questions about what should constitute a fair return on this substantial public investment. At present, Americans are not paying out-of-pocket to get the COVID-19 vaccine, largely because the United States has already purchased 400 million doses of the Pfizer-BioNTech vaccine at $39 per person, and 200 million doses of the Moderna vaccine at $30 per person. For comparison, the influenza vaccine costs the Centers for Disease Control (CDC) between $13 and $14 per dose.

By contrast, the Gardasil vaccine against human papillomavirus costs the CDC ~ $141 per dose.[8] Reports indicate the European Union is paying less than the United States for nearly all current and future vaccines, except Moderna's.[9] The public funding of the vaccine could provide the United States with additional authority to negotiate fair vaccine prices for all Americans. In the United States, manufacturers currently set prices at any level they choose; the only reason that COVID-19 vaccine prices have been manageable is that purchasing contracts were negotiated before the products were demonstrated to be effective. Now that the products are approved, future prices are likely to rise; indeed, Pfizer-BioNTech executives have already discussed future price increases for COVID-19 vaccines post-pandemic with their investors. With such price hikes looming, Congress needs to pass legislation to provide the US government with the authority to negotiate prices for approved products so that patients can benefit from a price that reflects the substantial reduction in risk provided by the upfront public investment.

Considerable public funding at each stage of vaccine development gives the United States the moral obligation to take necessary steps to end the global pandemic faster. As of mid-April, according to the World Health Organization (WHO), 87% of globally distributed vaccines were received by high-income countries, whereas the WHO global initiative for low-income countries (COVAX) received just 0.2%. The Biden administration took steps in early June to address this by agreeing to purchase 500 million vaccine doses for COVAX and donating 80 million unused doses, but not until after hundreds of thousands of unvaccinated people in poorer nations such as India died. An analysis of vaccine pre-purchase commitments shows that 51% of doses are likely to go to high-income countries that represent only 14% of the world's population.[10] Given the maldistribution of vaccines between high-income, industrialized nations and low- and middle-income countries, the United States should exercise its authority to manufacture or execute licenses with factories to manufacture these lifesaving vaccines to share with the international community. Whereas we applaud the US government's expressed support for waiving intellectual property protections for COVID-19 vaccines at the World Trade Organization and pledge to purchase and donate 580 million vaccines internationally, these steps represent the beginning of what will be necessary to end the pandemic and stop the propogation of variants. Accelerating domestic and global manufacturing could help end the pandemic faster at home and abroad while taking an important and much-needed step toward global vaccine equity.

Despite ownership of the patents on these lifesaving vaccines lying now mostly in the hands of private companies, US taxpayers funded the fundamental innovations that made mRNA vaccines possible. As the US health care system tries to manage the

daunting logistical challenges of vaccine distribution and public health officials and physicians work to communicate the importance of getting vaccinated, the government should leverage its position, patent rights, and substantial investment to ensure continued vaccine supply at a fair price both domestically and internationally.

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CONFLICT OF INTEREST
The authors have no conflicts of interest to report.

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