PhRMA
RESEARCH • PROGRESS • HOPE

Vaccines in Development

Summer 2024

Safeguarding the Future of Vaccines

The eradication of smallpox. The near elimination of diseases like polio and measles. The ability for the world to return to normal after the COVID-19 pandemic. Throughout human history, few innovations have held as much transformative power as vaccines. These innovations provide lifelines to millions of people throughout the world. Each vial at the pharmacy and doctor's office represents many years of research and development by researchers at America's biopharmaceutical companies.

Today's vaccine pipeline holds tremendous promise, too.

In labs around the country, researchers look for a shot that has the power to prevent cancer, E. coli infection and Alzheimer's disease, just to name a few. I hope you find the advances highlighted in this report as exciting as I do.

As we work to protect public health through vaccine development, we need to also protect the ecosystem that makes this innovation possible. Policymakers can help ensure patients have access to new vaccines by:

- *Reauthorizing critical provisions in the Pandemic and All Hazards Preparedness Act;*
- *Protecting intellectual property (IP) to defend American biopharmaceutical research, development, manufacturing and collaboration;*
- *Asserting that U.S. will defend IP rights abroad and reject any proposals to waive those rights.*

Taken together, these policies will help save people and the health care system from the devastation and expense of treatment for preventable diseases.

Stephen J. Ubl
President and Chief Executive Officer
Pharmaceutical Research and Manufacturers of America

PhRMA
RESEARCH • PROGRESS • HOPE

JUST THE FACTS

- More than **1 million** deaths prevented over the last 30 years in the U.S. due to childhood vaccines[i]
- **$2.2 trillion** saved in societal costs in the U.S. because of childhood vaccines[i]
- More than **18 million hospitalizations were prevented, nearly 3 million lives saved and $1.15 trillion** in medical cost savings were realized through the use of COVID-19 vaccines in the first two years they were available[ii]
- Vaccines can reduce the risk and severity of vaccine-preventable diseases which cost nearly **$27 billion** in direct and indirect costs each year among adults over the age of 50[iii]

Vaccines play a critical role in reducing the spread of many infectious diseases and are one of the most effective tools for protecting and promoting public health. U.S. biopharmaceutical leadership in vaccine research and development protects Americans and people around the world from health threats and helps ensure a bright future of continued advances.

Advances in biopharmaceutical science and related technologies are helping drive increases in overall survival and improved quality of life for people around the world. Vaccines represent some of the most impactful public health tools contributing to these advances by preventing the spread of many infectious diseases and, in many parts of the world, eliminating some of the most devastating conditions historically faced by the global populace.

As our understanding of the complex biological drivers of many diseases grows, the research and development (R&D) process to develop vaccines also grows more complex.

This report seeks to capture the dynamic advances happening in vaccine research from innovative biopharmaceutical research companies. The vaccines in development included in this report are in clinical trials or awaiting U.S. Food and Drug Administration (FDA) review.

Throughout history, examples of vaccine successes are numerous and significant:

Smallpox at one point one of the deadliest diseases in human existence, has been eradicated around the world as a result of vaccination.[iv]

Following the introduction of the first **polio** vaccine in 1955, this crippling infectious disease has been eliminated in the U.S. and polio vaccines have prevented an estimated 20 million cases of paralysis in children worldwide since 1988.[v]

The introduction of the **human papilloma virus (HPV)** vaccine has changed the trajectory of cervical cancer incidence, as well as other HPV-related cancers and infections by decreasing viral infection by 88% in teen girls and 81% in young adult women.[vi] Among vaccinated women aged 20 to 24, the incidence rate of cervical cancer dropped 65% from 2012 to 2019.[vii]

Flu vaccination prevented an estimated 7.1 million influenza cases, 3.4 million medical visits, 100,000 hospitalizations and 7,100 deaths, between 2019-2020 in the United States — the last flu season prior to the COVID-19 pandemic.[viii]

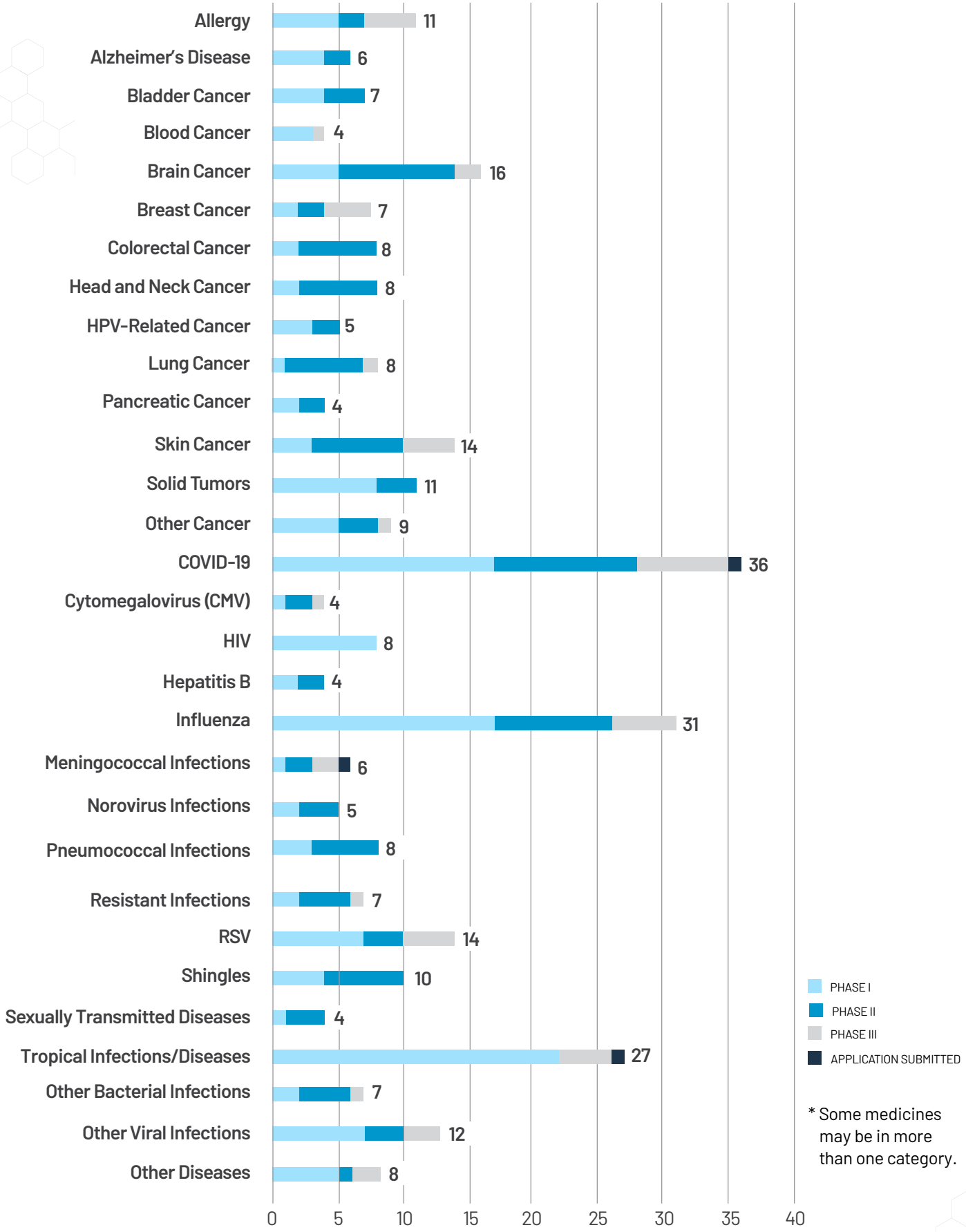
The vaccine for **whooping cough (pertussis)** is effective in reducing severity of a disease that previously killed one in every ten children who became infected prior to the availability of the vaccine. The introduction of routine immunization for pertussis saw a 150-fold reduction in cases.[ix]

Respiratory syncytial virus (RSV) a respiratory illness which causes up to 160,000 hospitalizations in older adults annually, and as many as 80,000 cases in children younger than five years can now be prevented with vaccines.[x]

Innovative biopharmaceutical companies are working to develop new ways of preventing and treating illnesses, with vaccines at the forefront. Today, there are **286** vaccines[xi] in development by biopharmaceutical research companies for the treatment or prevention of disease.

While existing vaccines are powerful tools for preventing disease, a new wave of therapeutic vaccines have the potential to treat diseases. Therapeutic vaccines work by stimulating or restoring the body's immune system to fight infection and disease, such as cancers. Beyond infectious diseases, there are currently five oral therapeutic vaccines approved to treat pollen allergies and peanut allergy, one therapeutic vaccine for prostate cancer and many more in development.

Vaccines in Development



* Some medicines may be in more than one category.

Promise of the Vaccine Pipeline

The vaccines in development by biopharmaceutical research companies are being investigated to treat or prevent infectious diseases, cancers, allergies and even Alzheimer's disease.

Among the vaccines in development are:

A liposomal, therapeutic anti-Tau vaccine is in development for the treatment of **Alzheimer's disease**. The vaccine works by stimulating the patient's immune system to produce conformation-specific antibodies against the Tau protein. Tau proteins form twisted fibers inside neuronal cells and build tangles considered a leading biomarker of Alzheimer's disease, in addition to Abeta-plaques. In preclinical studies, the vaccine showed reduction of Tau aggregation.

A potential first-in-class 9-valent vaccine is being developed for protection against **extraintestinal pathogenic E. coli (ExPEC)**. ExPEC is a leading bacterial cause of sepsis, particularly in older adults, causing approximately 10 million cases of invasive ExPEC disease annually worldwide.[xii] In the bacterium, the outer coating of sugar molecules called polysaccharides are linked with protein carriers to create the vaccine. These protein carriers create a strong immune response against ExPEC.

A messenger RNA (mRNA)-based combination vaccine is being developed for protection against **COVID-19** and **influenza** in adults. mRNA vaccines, which are the result of decades of R&D, provide the blueprint that teaches our cells how to make a protein (in the case of COVID-19, the spike protein on the outside of the virus) that then prompts an immune response inside our bodies. In clinical trials, the combination vaccine demonstrated robust immune responses to influenza A, influenza B and SARS-Cov-2 strains. The vaccine has the potential to lessen the impact of two respiratory diseases with a single injection.

A first-generation multivalent conjugate vaccine is being developed for protection against **meningococcal infections**. The combination vaccine targets all 5 Neisseria meningitides serogroups (A, B, C, W, and Y). Invasive meningococcal disease (IMD), a major cause of meningitis and septicemia, is an uncommon but serious illness that can cause life-threatening complications or even death, typically among previously healthy children and adolescents.[xiii] Among those contracting meningococcal diseases, one in 10 will die, sometimes in as little as 24 hours, despite treatment.[xiv] If approved, the vaccine will be the first vaccine to offer protection against all 5 serogroups in a single vaccine.

"The strongest contribution that GSK can make to prevent and change the course of disease is being innovative. That's how we've built one of the broadest vaccine portfolios in the industry. Turning vaccine innovation into vaccinations also requires powerful support structures. GSK continues building our arsenal of vaccines through ongoing, transformative innovation to help protect people at all stages of life."

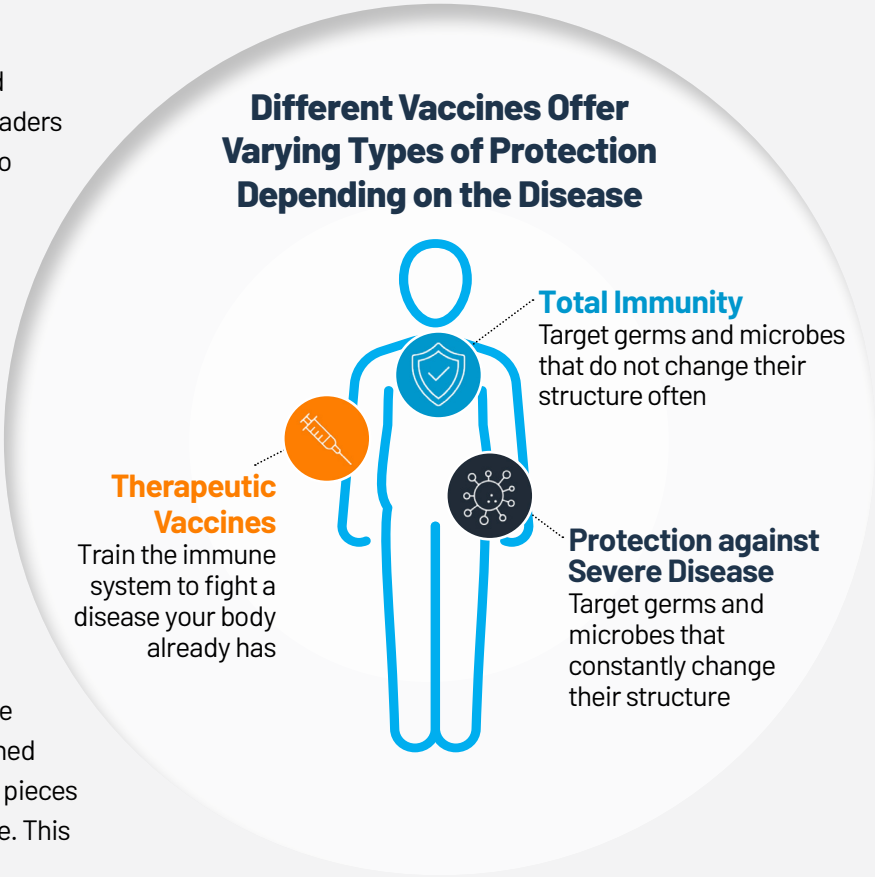
— **Philip R. Dormitzer**, MD, PhD, FIDSA, Senior Vice President and Global Head, Vaccines R&D and Infectious Disease Research, GSK

A mRNA-based therapeutic vaccine is in clinical trials for high-risk (stage IIb-IV) **melanoma**. Melanoma is the most serious form of skin cancer with 100,640 new cases and 8,290 deaths expected in 2024.[xv] The personalized therapeutic vaccine is a synthetic mRNA that can code up to 34 neoantigens that is designed and constructed based on the unique mutations of the patients' tumor. The vaccine neoantigens train and activate an antitumor immune response by generating specific T-cell responses directed at the cancer cells expressing the neoantigens.

An mRNA-based therapeutic vaccine is being studied for the treatment of **pancreatic ductal adrenal cancer (PDAC)**. PDAC is one of the deadliest cancers, with approximately 90% of patients dying within two years of diagnosis.[xvi] The personalized therapeutic vaccine is tailored to a specific patient's tumor and encodes up to 20 patient-specific neoantigens (proteins that are produced by cancer cells that differ from the proteins produced by healthy cells). The targeted delivery of the vaccine stimulates the immune system to target the specific cancer. The vaccine is also being studied in melanoma and colorectal cancer.

How Vaccines Work

The human immune system is incredibly powerful and versatile, working continuously to keep a variety of invaders from causing infection and disease.[xvii] From bacteria to viruses to parasites, the immune system recognizes invading threats and triggers a response in the body to contain and combat invaders.[xviii] And although the immune system is incredibly robust, it is not invincible. Simply put, vaccines work by teaching your body to recognize specific dangerous pathogens, so your immune system is prepared to fight off that infection in the future.



Preventive vaccines help the body develop immunity to a disease by imitating an infection, teaching the immune system how to identify and target microbial invaders (including viruses and bacteria) without actually causing an infection.[xix] Some vaccines are made with very small amounts of weakened or inactive parts of dead germs. Others are made with pieces from the virus that best stimulate an immune response. This means you can't "catch" the virus from the vaccine.[xx]

Some vaccines deliver long-lasting immunity from microbes which can make us sick and that are unlikely to change their structure, like measles, smallpox and polio vaccines. Other vaccines target microbes that are constantly changing their structure, like flu and mRNA COVID vaccines. These vaccines cannot completely prevent infection but are instead designed to decrease the severity of an infection and prevent deaths.[xx]

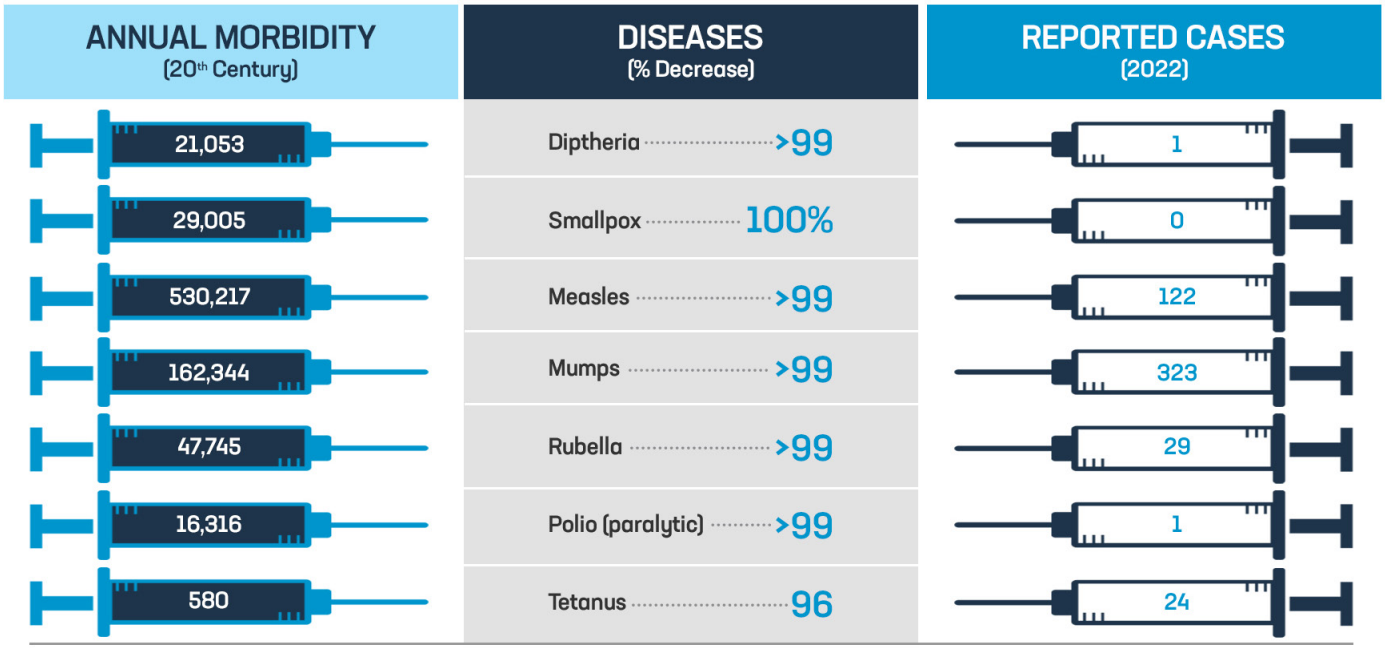
Therapeutic vaccines are designed to fight diseases that a person may already have, such as a cancer. These vaccines work by training the body's immune system to identify and attack cancer cells or diseased cells after a naturally-acquired infection.[xxi] Scientists have demonstrated early success in the development of therapeutic vaccines that could treat HIV and Alzheimer's disease, as well as infectious diseases.[xxii, xxiii]

Why Vaccines Matter

Vaccines are one of the most impactful and cost-effective tools we have for preventing and mitigating diseases and supporting healthy aging. Over the last 30 years in the U.S., childhood vaccines have prevented more than one million deaths.[i] And, in the U.S. alone, vaccines are available to prevent 18 dangerous or deadly diseases.[xxiv] Vaccines have greatly reduced the severity and toll of some diseases across patients' lifespan. For example, in meningitis, up to one in six people who develop bacterial meningitis will die, while up to one in five will suffer severe complications. Today, there are vaccines available to prevent against most forms of invasive meningitis disease – leading to better health outcomes for people.[xxv]

> ***"Through the technologies that we have available to us today to design and develop vaccines, Pfizer is positioned to select the platform for the target pathogen from a toolbox of vaccine innovation that spans mRNA, subunit and conjugate approaches. As we harness breakthroughs in research, our commitment remains steadfast to provide global, equitable access as we pave the way for the future of care."***
>
> —**Annaliesa Anderson, Ph.D.**, Senior Vice President and Head, Vaccine Research & Development, Pfizer

Then and Now: Vaccines Help Leave Serious Diseases in the Past



Vaccines Drive Prevention and Savings

Vaccines help drive significant savings for the health care system and society. The U.S. Centers for Disease Control and Prevention (CDC) estimates that over the last 30 years in the United States, childhood vaccines have saved the health system in America nearly $2.2 trillion, making them one of the most cost-effective public health tools we have at our disposal.[i] Another study found that for each dollar invested in pediatric immunization results in $7.50 in savings for the health care system and society.[xxvi] Vaccines can also reduce the risk and severity of vaccine-preventable diseases like flu, pneumococcal disease, shingles and whooping cough, which cost $27 billion in direct and indirect costs each year among adults over the age of 50.[xxvii]

Vaccines Contribute to Healthy Aging

Worldwide, people are living longer. By 2030, the number of people aged 60 and over is expected to increase by more than a third, to 1.4 billion people[xxviii] and by 2050, projections indicate that there will be more older persons aged 60 and over than adolescents and youth at ages 10-24.[xxix]

Living longer can offer opportunities for individuals and society. A longer healthy life offers the chance for people to perhaps pursue new activities, new careers and contribute positively to society. And healthy aging is a major contributor to workforce participation, productivity, socio-economic resilience and gross domestic product (GDP) growth.

But these opportunities can be limited if these additional years are spent in physical and mental decline. In addition to exercise, healthy diet, regular visits to the doctor and positive mental health strategies — medicines and vaccines can help make those additional years healthier.

> *"I'm grateful for vaccines, like the one for shingles that offers older adults like me a chance to avoid serious complications and live a healthier life."*
>
> – Suzanne T., Patient, Delaware

As people age, their immune system declines in strength and becomes less effective, making adults aged 50+ more susceptible to infectious diseases (such as COVID-19, shingles, influenza, pneumococcus, whooping cough and RSV) and related complications. Vaccine preventable diseases can lead to increased risk of other conditions in adults aged 50-64 that could have otherwise been avoided by timely vaccination.[xxx] For example, influenza and shingles infections have been shown to increase the risk of cardiovascular and neurovascular complications, such as heart attack and stroke, in the months following acute infection.[xxxi]

> *"As a new parent, it is important that my newborn daughter stays healthy during this time of critical growth. Vaccines give our kids the chance for healthier lives so they can be setup for success."*
>
> – Vic S., Patient, Georgia

Vaccines Boost Population Immunity

Vaccines work by helping the body identify specific dangerous pathogens, such as bacteria, viruses and parasites, so that the immune system can fight diseases faster and more effectively when exposed.[xxxii]

When not enough people in communities have immunity against a certain infectious disease, it can spread quickly and make many people sick. Herd immunity occurs when a large portion of people in communities develop immunity and the spread of disease from person to person becomes less likely. This can then lower the burden on the health care system. Herd immunity has effectively slowed the spread of measles, polio and smallpox. However, there have been outbreaks of measles in communities where vaccination rates have declined, and they have subsequently "lost" herd immunity.

Vaccines Help Combat Antimicrobial Resistance (AMR)

AMR occurs when microorganisms such as bacteria, viruses, fungi and parasites develop the ability to survive against the drugs designed to kill them. Addressing AMR starts with preventing infections, which makes vaccines a critical tool in fighting AMR. Vaccines help us prepare for the future by protecting against the next pandemic or emerging threats like AMR pathogens. AMR infections pose a significant challenge to health worldwide. In 2019, AMR attributed to an estimated 1.95 million deaths and 47.9 million lost disability-adjusted life-years. Over the last 30 years, there has been a decline in the development of new antibiotics while incidence rates of AMR climb and globally, AMR is expected to cause approximately 10 million deaths annually by 2050.[xxxiv]

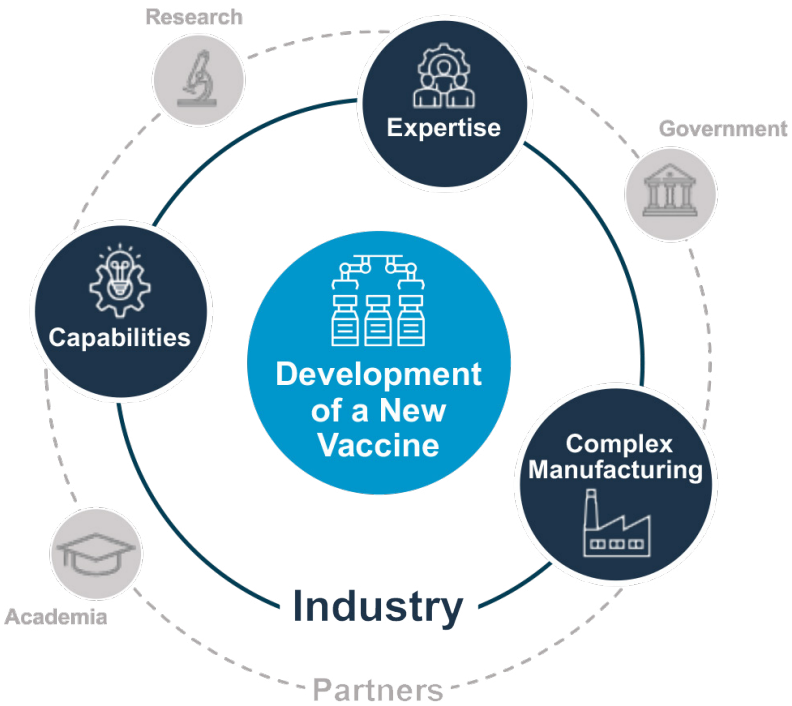
The Future of Vaccine Development

U.S. leadership in researching and developing vaccines has helped bring earlier access to new vaccines for Americans and economic benefits to society. The U.S. biopharmaceutical industry leads the world in researching and developing new vaccines and accounts for more than half of global biopharmaceutical R&D medicine spending, including vaccines.[xxxiv] Additionally, most new vaccines approved worldwide in the last 20 years were developed in the U.S.[xxxv]

The biopharmaceutical industry is working to overcome unique scientific, clinical and logistical hurdles to translate rapid scientific progress into the next generation of preventive and therapeutic vaccines. The work being done today within the R&D ecosystem will also prepare the U.S. and the world for future outbreaks.

To deliver on the promise of the current vaccine R&D, maintaining robust intellectual property protections is essential to providing incentives for entering the lengthy, costly and complex vaccine research and development process.

Vaccines: Research and Development (R&D)



https://www.hhs.gov/sites/default/files/HHS-Vaccines-Report.pdf
U.S. Department of Health and Human Services. 2021. Vaccines National Strategic Plan 2021-2025. Washington, DC

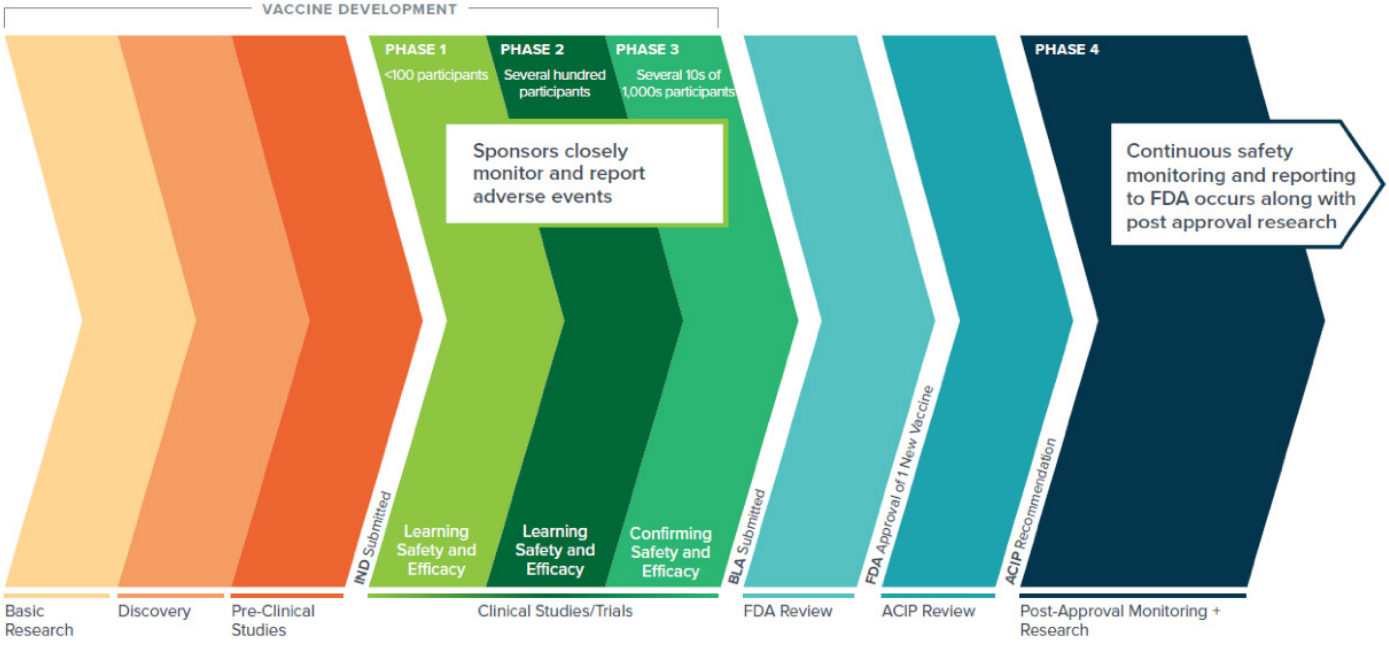
As with any medicine, vaccines undergo a comprehensive R&D process, including large clinical trials which include thousands of volunteers participating to help establish the safety and efficacy of a vaccine. This work builds on a foundation of ongoing research and innovation that can take decades and continue to be monitored long after FDA approval.

The U.S. biopharmaceutical industry leads in developing innovative vaccine technology, helping protect Americans and people around the globe from health threats. On average, researching and developing a new vaccine can be a long and complex process including complex large scale clinical trials. Biopharmaceutical companies contribute capabilities, facilities, resources and the expertise needed to research, develop and manufacture vaccines, but also collaborate with public institutions to advance new vaccines and support the public health infrastructure for ensuring vaccines reach people who need them.

The robust scientific knowledge from the biopharmaceutical industry from decades of experience with viruses such as Zika, MERS and SARS enabled it to quickly respond to the COVID-19 pandemic with safe and effective vaccines in record time. These efforts, including extensive investment from the private sector to develop the technological advances to overcome early technical challenges for mRNA vaccines in particular, helped save millions of people from severe illness and death, and billions in avoidable health care costs.

U.S. biopharmaceutical manufacturers, FDA and CDC closely monitor the safety and effectiveness of available vaccines. Manufacturers are subject to extensive safety monitoring and reporting requirements both during clinical trials and after approval. Additionally, FDA and CDC operate the Vaccine Adverse Event Reporting System to detect possible safety problems and CDC manages the Vaccine Safety Datalink, intended to conduct research on important vaccine safety questions in large populations.

THE VACCINE LIFE CYCLE: SAFETY AT EVERY PHASE



GUIDE

ACIP: Advisory Committee on Immunization Practices, part of the CDC (Reviews to inform recommendations for vaccine use in the U.S.)
BLA: Biologics License Application
CDC: The U.S. Centers for Disease Control and Prevention (Supports medical use and access recommendations and a communication network for vaccine information.)
FDA: U.S. Food and Drug Administration (Reviews to inform recommendations for vaccine use in the U.S.)
IND: Investigational New Drug Application

Source: https://www.cdc.gov/vaccinesafety/ensuringsafety/history/index.html

*"At **CSL Seqirus**, we are committed to investing in and optimizing our unique cell and adjuvant technologies to produce influenza vaccines that for years have improved standards of care for global populations. We are also combining these innovative approaches to develop new vaccine candidates, as well as leveraging the technologies to prepare for and protect against potential pandemics. In addition, we are pioneering the first sa-mRNA COVID vaccine, offering the potential promise of better and longer duration of protection, and establishing a platform from which other vaccines for respiratory infections can be developed."*

— **Dave Ross**, SVP & General Manager, CSL Seqirus

R&D Challenges

Vaccines present a number of unique challenges that make them particularly complicated to research, including scientific, clinical and logistical hurdles throughout the development process. These challenges are made more difficult during public health emergencies. Even with these challenges, some of the newer types of vaccines have the potential to move faster from initial virus identification to a viable vaccine, and faster from there to a licensing application and manufacturing scale up.

Scientific Challenges

- Identifying the particular strain of a virus to target in order to create and evaluate a vaccine. This can take a very long time, particularly when the virus is a new, emerging threat.
- Understanding the complexities of many infectious diseases and how the immune system normally reacts to them, particularly diseases that occur infrequently or in small populations.
- Establishing reliable preclinical models that more closely parallel the human immune system in order to better predict immune response to vaccines.

Clinical Challenges

- Recruitment challenges affect vaccine research because vaccines are usually preventive in nature and, as a result, are tested in healthy people, it can be difficult to recruit sufficient numbers of volunteers for clinical trials.
- When studying emerging infectious diseases, particularly those that occur sporadically and spread through outbreaks, it can be difficult to predict when and where a disease will occur or spread, making it challenging to find the right volunteers for a clinical trial.
- Clinical trial participants compliance with some vaccine regimens that require multiple doses or shots to ensure protection can also be challenging .

Manufacturing and Distribution Challenges

- Because vaccines are biologics, manufacturing is a very complex process. The process entails multiple steps in order to produce the main vaccine component.
- Scaling up manufacturing to make larger quantities of vaccines can be difficult and time-consuming.
- Once manufactured, vaccines need to be packaged, stored and delivered. Then, upon delivery, they need to be stored in appropriate conditions, usually under refrigeration.

But despite these challenges, biopharmaceutical research companies and their partners in the R&D ecosystem are de-coding pathogens and developing vaccines to meet the health needs of society. As we look to the future, it's vital we support the critical R&D needed to advance biopharmaceutical innovation for vaccines.

Sources:

i U.S. Centers for Disease Control and Prevention. www.cdc.gov/vaccines/programs/vfc/protecting-children.html

ii The Commonwealth Fund. Two Years of U.S. COVID-19 Vaccines Have Prevented Millions of Hospitalizations and Deaths. www.commonwealthfund.org/blog/2022/two-years-covid-vaccines-prevented-millions-deaths-hospitalizations

iii National Institutes of Health. Estimated Human and Economic Burden of Four Major Adult Vaccine-Preventable Diseases in the United States, 2013. www.ncbi.nlm.nih.gov/pmc/articles/PMC4486398/

iv World Health Organization (WHO). Smallpox Vaccines. https://www.who.int/news-room/feature-stories/detail/smallpox-vaccines

v U.S. Centers for Disease Control and Prevention. Polio Elimination in the United States. https://www.cdc.gov/polio/about/index.html#:~:text=Polio%20was%20once%20one%20of,called%20immunity)%20in%20the%20population.

vi U.S. Centers for Disease Control and Prevention. HPV Vaccine. https://www.cdc.gov/hpv/parents/vaccine-for-hpv.html?CDC_AA_refVal=https%3A%2F%2Fwww.cdc.gov%2Fhpv%2Fparents%2Fvaccine.html

vii American Cancer Society. Cancer Statistics, 2023. https://acsjournals.onlinelibrary.wiley.com/doi/full/10.3322/caac.21763

viii U.S. Centers for Disease Control and Prevention. Vaccine Effectiveness: How Well Do Flu Vaccines Work? https://www.cdc.gov/flu/vaccines-work/vaccineeffect.htm

ix GAVI. Vaccine profiles: Pertussis. https://www.gavi.org/vaccineswork/routine-vaccines/routine-vaccines-extraordinary-impact-pertussis

x U.S. Centers for Disease Control and Prevention. RSV in Infants and Young Children. https://www.cdc.gov/rsv/infants-young-children/?CDC_AAref_Val=https://www.cdc.gov/rsv/high-risk/infants-young-children.html

xi Number of vaccines obtained through public government, and industry sources, and the Adis "R&D Insight" database; current as of July 8, 2024.

xii Russo TA and Johnson JR. Medical and economic impact of extraintestinal infections due to Escherichia coli: focus on an increasingly important endemic problem. Microbes Infect. 2003;5:449–456, Rudd KE, Johnson SC, Agesa KM, et al. Global, regional, and national sepsis incidence and mortality, 1990-2017: analysis for the Global Burden of Disease Study. Lancet. 2020;395(10219):200-211. doi:10.1016/S0140-6736(19)32989-7 and Rhee C, et al. Prevalence of Antibiotic-Resistant Pathogens in Culture-Proven Sepsis and Outcomes Associated with Inadequate and Broad-Spectrum Empiric Antibiotic Use. JAMA Netw Open. 2020;3(4): e202899.

xiii ECDC, Factsheet about meningococcal diseases. Accessed March 2023

xiv Bing Wang et al., "Case fatality rates of invasive meningococcal disease by serogroup and age: A systematic review and meta-analysis", in Vaccine, Volume 37, Issue 21, 9 May 2019, Pages 2768-2782. Accessed March 2023.

xv American Cancer Society, Cancer Facts & Figures 2024

xvi Stott, MC et al. Recent advances in understanding pancreatic cancer. Fac Rev. 2022; 11: 9

xvii U.S. Department of Health and Human Services (HHS). What is the Immune System? www.vaccines.gov/basics/prevention/ immune_system/index.html

xviii HHS. How Vaccines Work. www.hhs.gov/immunization/basics/work/index.html

xix CDC. Making the Vaccine Decision. www.cdc.gov/vaccines/parents/vaccine-decision/index.html

xx CDC. https://www.cdc.gov/vaccines/hcp/conversations/understanding-vacc-work.html

xxi NIH. Development of therapeutic vaccines for the treatment of diseases (2022). https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9729511/

xxii Gray, GE, et al. Approaches to preventative and therapeutic HIV vaccines. Curr Opin Virol. April 17, 2016

xxiii Shih-Ya Hung, Wen-Mei Fu. Drug candidates in clinical trials for Alzheimer's disease. J Biomed Sci. 2017; 24: 47

xxiv U.S. Centers for Disease Control and Prevention. https://www.cdc.gov/vaccines/vpd/vaccines-diseases.html

xxv World Health Organization. Meningitis (2023) https://www.who.int/news-room/fact-sheets/detail/meningitis

xxvi https://www.rtihs.org/updates-and-events/impact-routine-childhood-immunization

xxvii McLaughlin JM, McGinnis JJ, et al. "Estimated Human and Economic Burden of Four Major Adult Vaccine-Preventable Diseases in the United States, 2013." J Prim Prev. 2015; 36(4): 259–273.

xxviii World Health Organization. Ageing and health. https://www.who.int/news-room/fact-sheets/detail/ageing-and-health

xxix United Nations. World Population Aging. https://www.un.org/en/development/desa/population/publications/pdf/ageing/WPA2017_Highlights.pdf

xxx U.S. Centers for Disease Control and Prevention. Educating Adults with Chronic Health Conditions: Vaccination Resources. https://www.cdc.gov/vaccines/hcp/adults/for-patients/health-conditions.html#factsheet

xxxi Esposito S, et al. The public health value of vaccination for seniors in Europe. Vaccine. 2018 May 3;36(19):2523-2528 3 CDC. Educating Adults with Chronic Health Conditions: Vaccination Resources

xxxii NIH. How Does the Immune System Work? https://www.ncbi.nlm.nih.gov/books/NBK279364/

xxxiii Mullins LP, Mason E, Winter K, Sadarangani M. Vaccination is an integral strategy to combat antimicrobial resistance. PLoS Pathog. 2023 Jun 15;19(6):e1011379. doi: 10.1371/journal.ppat.1011379. PMID: 37319164; PMCID: PMC10270329

xxxiv National Institutes of Health. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7151793/