VACCINES

Biopharmaceutical Companies are Researching and Developing Nearly **260** Vaccines

Over the years, vaccines have played a critical role in reducing the spread of, and, in some cases, eliminating the threat of the world's many devastating infectious diseases. Vaccines represent some of the most impactful public health advances seen to date.

There are several notable success stories in prevention of infectious diseases in the U.S. and worldwide. Smallpox at one point was one of the deadliest diseases in existence. But as a result of American immunization requirements, the last natural outbreak occurred in 1949. And across the globe due to aggressive vaccination programs naturally-occurring smallpox was declared eradicated in 1980. Though many diseases remain threats around the world, vaccination requirements in the U.S. have led to the elimination of once highly contagious infections impacting children, including polio in 1994, measles in 2000 and rubella in 2004.

Prior to the availability of vaccines, each year 48,000 people were hospitalized with measles and 400-500 people died.[5] Polio outbreaks caused more than 15,000 cases of paralysis[6] and during the last major outbreak of rubella, 11,000 women lost babies, 2,100 newborns died and 20,000 babies were born with congenital rubella syndrome causing severe birth defects.[7]

More recent advances in the development of vaccines have built on this progress and provide protection against many of the public health threats facing the world today. For example, as recently as this year, two vaccines against Ebola have been deployed in Africa to combat the latest serious outbreak of this devastating disease. Recent advances in vaccine development are also diverse in aim and scope. These new vaccines protect against infectious diseases ranging from rare to more widespread, from those impacting older adults to those prevalent among young adults, and some vaccines can even protect against some cancers and potential bioterrorist threats.

These public health victories illustrate the major contributions vaccines have made and are continuing to make in saving countless lives in the United States and around the world.

MEDICINES IN DEVELOPMENT / 2020 REPORT

America's Biopharmaceutical Companies

VACCINES

JUST THE FACTS

16

DISEASES ARE NOW PREVENTABLE IN THE U.S. AS A RESULT OF CHILDHOOD VACCINES, DRAMATICALLY REDUCING INFANT DEATH AND DISABILITY [1]

$406

BILLION IN DIRECT MEDICAL COSTS AND $1.9 TRILLION IN TOTAL SOCIETAL COSTS SAVED DUE TO ROUTINE CHILDHOOD IMMUNIZATION OF U.S. CHILDREN BORN BETWEEN 1994-2018[2]

73%

DROP IN MEASLES DEATHS BETWEEN 2000 AND 2018 WORLDWIDE DUE TO MEASLES VACCINATION[3]

MORE THAN

70

VACCINES IN THE WORLDWIDE RESEARCH PIPELINE FOR COVID-19.[4]

Innovative biopharmaceutical companies are working with stakeholders from across the research and development (R&D) ecosystem to develop new ways of preventing and treating illnesses, with vaccines at the forefront. Today, there are 258 vaccines[8] in development by biopharmaceutical companies for the treatment or prevention of disease. These vaccines offer significant hope for the future, with many vaccines in the pipeline using new technologies that have the potential to prevent the transmission of the human immunodeficiency virus (HIV), protect against malaria and even therapeutic vaccines with the potential to treat several types of cancer.

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 in cancer. Currently, outside of infectious diseases, there are five oral therapeutic vaccines approved to treat pollen allergies and peanut allergy, one therapeutic vaccine for prostate cancer, and many more in development.

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.[9] From bacteria to viruses to parasites, the immune system recognizes invading threats and triggers a response in the body to contain and combat invaders.[10] And although the immune system is incredibly robust, it is not invincible.

Preventative 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.[11] While the vaccine itself does not have the capacity to cause full blown disease, its components are sufficient to trigger an immune response, leaving the body with a durable supply of immune cells that will remember how to fight an invading pathogen in the future.

Therapeutic vaccines are designed to treat diseases by provoking a targeted immune response against an existing disease rather than offering lasting protection against infection as traditional vaccines do. In cancer, scientists are opening new avenues for immunotherapy where vaccines are showing promise in boosting the immune system or helping the immune system recognize cancer cells.[12] These vaccines have the potential to provide cancer patients with treatment options with less side effects than more conventional treatments, such as chemotherapies.

Scientists have also demonstrated early success in the development of therapeutic vaccines that could treat HIV and Alzheimer's disease as well as infectious diseases.[13,14]

Notable Public Health Vaccine Successes

Vaccines protect against public health threats impacting the world today. Some important examples include:

Ebola: The first vaccine to protect against the Ebola virus disease was approved in the U.S. in 2019. A second vaccine is also under review by the European Medicines Agency (EMA), with a decision expected this year. Both vaccines were advanced in response to the West African Ebola crisis, and both were successfully deployed to help contain the current outbreak in the Democratic Republic of the Congo (DRC). Ebola is a lethal and highly contagious hemorrhagic fever with mortality rate ranging from 40-90%.[15] Though Ebola risk remains low in the U.S., the virus has caused more than 30 epidemic outbreaks in Africa since 1976.[15]

Dengue: The virus is the most prevalent mosquito-borne viral illness in the world. Once individuals are infected with one of four dengue virus serotypes, they are immune to subsequent infections from that serotype; however, subsequent infections with another serotype leads to severe dengue, which can lead to shock, internal bleeding, and even death. Each year 500,000 severe dengue cases occur around the world, which contribute to about 20,000 deaths primarily among children.[16] The first vaccine for those who have confirmed previous dengue infection and can help to prevent severe dengue illness was approved in the U.S. in 2019.

Meningitis B: Meningococcal disease is a life-threatening illness caused by bacteria that infect the bloodstream and lining that surrounds the brain and spinal cord, leading to potentially deadly meningitis. Since 2014, two vaccines have become available in the U.S. to protect against serogroup B Meningococcal disease for at-risk adolescents and young adults.

HPV Driven Cancer: The introduction of the human papilloma virus (HPV) vaccine has changed the trajectory of cervical cancer, as well as other HPV-related cancers and infections by decreasing viral infection by 86% in teens and 71% in young adult women. Among vaccinated women, the percentage of cervical cancer caused by certain HPV infections has dropped by 40%.[17]

Pneumococcal Pneumonia: The U.S. Food and Drug Administration (FDA) first licensed a pneumococcal vaccine in 1977 to protect against 14 different strains of the virus. The vaccine is now licensed to protect against 23 strains. However, it is most effective in adults. A separate vaccine for children was licensed in 2000 and was expanded to include protection against 13 strains in 2010. Since the initial recommendation, invasive pneumococcal disease in children has dropped by nearly 80% in the United States.[18]

Shingles: People aged 50 years and older are at an increased risk for shingles and postherpetic neuralgia (PHN). Shingles is the third most common cause of chronic neuropathic pain with 500,000 cases annually. Vaccines that have become available can reduce the risk of developing shingles and PHN up to 90%.[15]

Bioterrorist threats: Routine U.S. vaccination against smallpox stopped following the eradication of the disease. As a result, a large portion of the U.S. and global population lacks immunity posing a significant bioterrorist threat. A new vaccine became available in 2019 for prevention in those at high risk of smallpox infection and is a part of the Strategic National Stockpile. Though widespread use remains unnecessary, this advance represents efforts to ensure preparedness in the face of public health emergencies.

Vaccines: Research and Development

Researching and developing new medicines and vaccines is a complex and multifaceted process, requiring significant time and resource investment. It can take more than 10 years to develop a novel vaccine from the discovery stage all the way through to approval by the FDA. Although efforts are underway to significantly shorten that timeline for a COVID-19 vaccine. In broader context, the R&D process for vaccines and medicines is beset with dead ends and setbacks, with only 12% of medicines that enter clinical trials eventually being approved by the FDA.

As with any medicine, vaccines undergo a comprehensive research process in order to meet rigorous FDA standards for safety and efficacy. In addition to carefully conducted pre-clinical and clinical studies, this also includes research to establish robust manufacturing and storage plans, in order to ensure the purity and potency of the vaccine.

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 test 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 preventative 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.
- Overcoming stigma and misinformation.
- Compliance with some vaccine regimens that require multiple does or shots to ensure protection.

Manufacturing and Distribution Challenges

- Because vaccines are large biological molecules generated via micro-organisms, manufacturing vaccines 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 vaccine for clinical trials, or in response to sudden increased need, can be very 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 enormous challenges, biopharmaceutical research companies and their partners in the R&D ecosystem are developing vaccines and de-coding viruses faster than ever.

Vaccines in the Pipeline

The 258 vaccines in development by biopharmaceutical research companies are being investigated to treat or prevent infectious diseases, cancers, allergies and Alzheimer's disease. Among the vaccines in development are:

A vaccine to prevent **HIV infection**, which has the potential to teach the patient's immune system to recognize and effectively fight HIV. This vaccine contains mosaic immunogens – molecules designed to induce an immune response against the wide variety of HIV strains responsible for the epidemic. It is currently being tested for efficacy in large-scale clinical trials taking place across four continents.

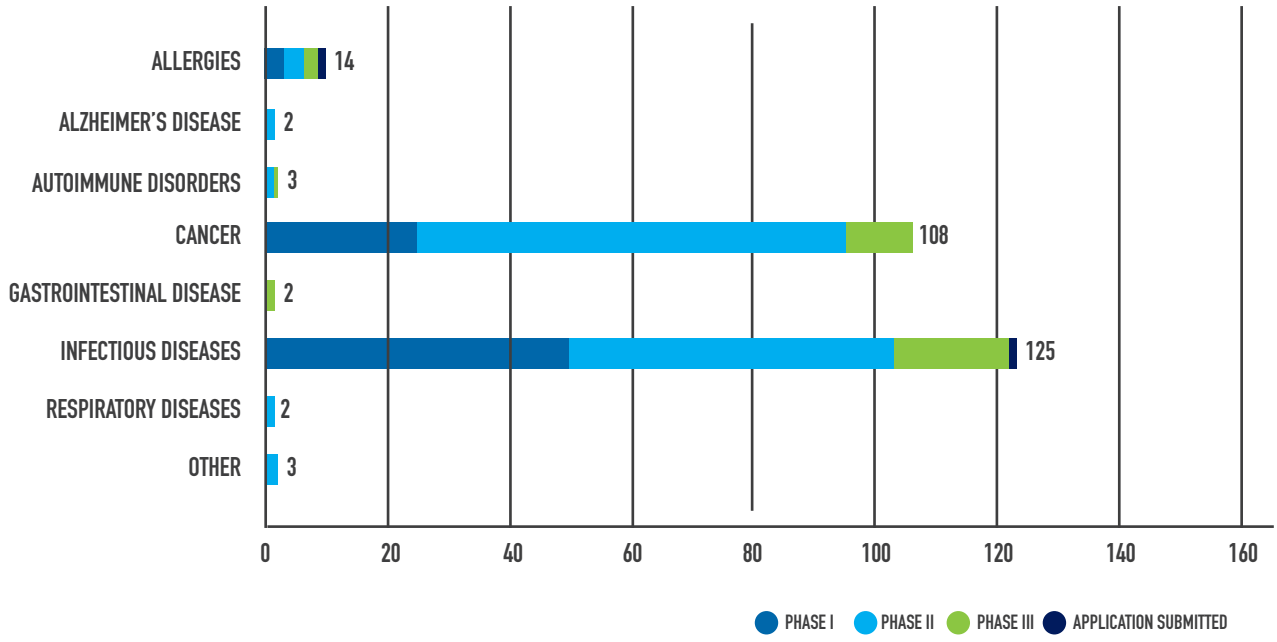
A therapeutic vaccine for **non-small cell lung cancer** (NSCLC) which uses messenger RNA (mRNA) to mobilize the patient's own immune system to fight the tumor(s). mRNA are the instructions to cells that make all proteins and send them to various parts of the body. mRNA medicines take advantage of the body's biological processes to create a desired therapeutic effect. The vaccine in development targets six specific tumor-associated antigens (substances produced in tumors that trigger an immune response) that are overexpressed in lung cancer. It is being studied in combination with cancer immunotherapy.

A therapeutic vaccine for **Alzheimer's disease** targets amyloid beta protein and is designed to induce high B-cell specific responses while avoiding T-cell inflammation, an autoimmune response that can lead to organ damage. In animal studies, the vaccine was shown to generate site-specific antibodies and to reduce amyloid beta.

An adenoviral vector vaccine for the prevention of **respiratory syncytial virus** (RSV) infections in adults over the age of 60 contains gene coding for the fusion protein of the RSV virus as an antigen to induce an immune response in the body, especially the production of antibodies.

A vaccine for the prevention of novel **coronavirus** (COVID-19) recently dosed the first participant in a clinical trial. The messenger RNA-based vaccine is designed to direct the body's cells to produce proteins (intracellular, membrane or secreted proteins) that can have a preventative benefit against the virus.

Vaccines in Development



Why Vaccines Matter and Access to Immunization

Vaccines play a critical role in bolstering immunity and fighting disease in people of all ages. They also save money and lives. Sixteen diseases are now preventable as a result of childhood vaccines.[1] As a result, the Centers for Disease Control and Prevention (CDC) estimates that among children born between 1994 and 2018 in the U.S., routine childhood vaccinations prevented 419 million illnesses, 26.8 million hospitalizations, and 936,000 early deaths—resulting in $406 billion in direct medical cost savings and $1.9 trillion in total societal cost savings due to childhood vaccination.[2]

Vaccines are critical in order for infants and children to avoid diseases that caused serious illness and deaths in previous generations. Although children inherit immunity to some diseases at birth from their mothers, this wanes quickly over time, making early vaccination vital in providing protection against disease.

In addition to providing individual protection against devastating diseases, individual vaccinations are integral in protecting the health of the community, especially children who may be too young to be vaccinated or who cannot receive vaccines for medical reasons. Additionally, because children's immune systems are somewhat underdeveloped, after receiving a first dose of many vaccines, they need to receive a booster dose as efficacy may wane over time.

It is also important for adults and seniors to receive certain vaccinations as they age to avoid a variety of serious conditions. The immune system naturally weakens over a patient's lifespan and vaccines can be critical to prevent illness among the elderly, who may be particularly vulnerable to infection. For example, shingles is caused by the same virus that causes chickenpox (varicella-zoster) and can occur in adults who had chickenpox as children. It is thought that lowered immunity to infections as people grow older may be the cause.[19]

Despite tremendous advances in vaccines, the prevalence of illnesses attributable to vaccine-preventable diseases remains higher in adults than children. Less than half of adults ages 19 and older received a flu vaccine in 2015, for example, and 30% of adults recommended to receive the herpes zoster, or shingles, vaccine received it in 2015.

In addition to debilitating direct health impacts on individuals, the economic burden of low vaccine uptake among adults is very significant. In 2013 alone, the estimated annual costs for low uptake of vaccines for four major adult vaccine-preventable diseases (influenza, pneumococcal disease, herpes zoster [shingles], and pertussis [whooping cough] totaled $15.3 billion for adults ages 65 or older.[20] This economic burden encompasses both direct medical costs and indirect costs, including decreased productivity, work-loss and lost income.

Ensuring greater uptake of and access to vaccines will improve public health and reduce broader health care costs over time. Increasing awareness of the availability and value of vaccines, particularly among adults, can help improve vaccine rates. It is also important to provide robust insurance coverage for preventative care more broadly, including vaccines, in order to avoid vaccine-preventable diseases.

Low adult immunization rates are due to multiple barriers, including lack of information about recommended vaccines, financial hurdles, as well as technological and logistical obstacles.[21]

Vaccine Recommendations from the CDC

In 2019, a measles outbreak occurred in the U.S., where 1,282[22] individual measles cases were reported from January 1 to December 31, 2019. This is the greatest number of cases reported in the U.S. since 1992 and the majority of those cases were among people who were not vaccinated against measles. The measles, mumps, rubella (MMR) vaccine is part of the list of vaccines recommended by the CDC.

The following are examples of some of the most important vaccines CDC recommends for various stages of life:

Early childhood (birth through age 6)

Vaccines are a central tool for protecting children from a range of dangerous illnesses. Before leaving the hospital, newborn infants receive their first dose of the hepatitis B vaccine. In the first few months, infants will also receive their first doses of vaccines to prevent rotavirus, pneumococcal infection, polio, and Haemophilus influenza type b (Hib), as well as a combination vaccine (called the TDaP) to prevent tetanus, diphtheria and pertussis (whooping cough). When a baby is a year old, they will also receive vaccines to prevent varicella (chicken pox) and hepatitis A, in addition to a combination vaccine that prevents the measles, mumps and rubella (called the MMR vaccine).

Additional doses of these early childhood vaccines are administered a few more times over the course of the first six years of a child's life in order to ensure immunity in their immature immune systems. Young children should also begin receiving their annual dose of the influenza vaccine beginning around the age of 6 months.

Children (ages 7 to 18)

Children should continue to receive an annual influenza vaccine in order to prevent the flu. Pre-teens, ages 11 to 12, should receive a booster of the TDaP vaccine, as well as vaccines that protect against the human papilloma virus (HPV) and bacterial meningitis.

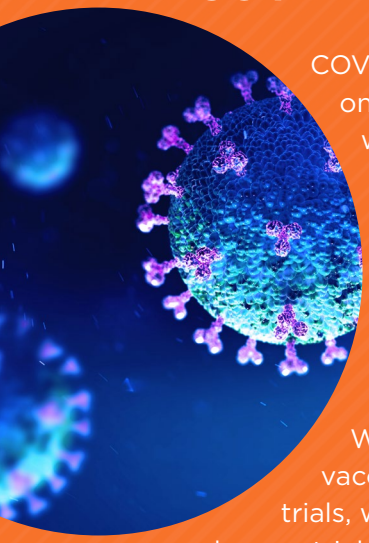
Adults (ages 19 and older)

Vaccines remain an important prevention tool throughout life. Adults should continue to receive an annual influenza vaccine. Additionally, it is recommended that adults receive a booster of the TDaP vaccine every 10 years. Later in life, people ages 60 and older are also recommended to receive vaccination for shingles, and people ages 65 and older and those with compromised immune system, are recommended to receive vaccines to prevent pneumococcal infection.

Travelers

In addition to routine vaccines that are vital to preventing disease, there are also several vaccines that are important to take before traveling abroad, in order to prevent infection by various tropical or infectious diseases. Depending on where one is traveling and which activities are expected, these can include vaccines to prevent typhoid, yellow fever, and cholera, for example. It is also recommended to make sure routine vaccinations are up to date, particularly hepatitis A and hepatitis B.

COVID-19



COVID-19, a disease caused by a novel strain of coronavirus, has caused a pandemic. Based on our current knowledge, the virus is believed to mainly spread from person-to-person when people are in close contact with one another by an infected person's respiratory droplets from coughing or sneezing or from touching surfaces infected with the virus.

Currently there are no approved vaccines or therapeutics to prevent transmission of, or treat, the coronavirus specifically. But treatments approved or cleared by FDA for other uses have been used to help address the symptoms and complications of patients, which include oxygen therapy, ventilators and antibiotics.

While there are no approved vaccines against COVID-19, there are more than 70 vaccines[4] in the worldwide research pipeline. Six vaccines[4] have entered human clinical trials, while several more vaccines are in preclinical development with many planning to begin human trials this year.

The biopharmaceutical industry is uniquely positioned to respond rapidly to the coronavirus and other public health emergencies. Biopharmaceutical companies have long been at the forefront in conducting R&D and providing manufacturing support for global public health emergencies including West Nile virus, SARS, Zika and Ebola. Investments include R&D into new technologies, protocols and facilities to enable companies to develop, test and scale up production for potential vaccines and new medicines. Additionally, industry's R&D programs in infectious diseases and research assets enable researchers to move quickly to screen potentially applicable research from their often-massive compound libraries and to accelerate clinical testing of potential new vaccines and treatments.

While there are enormous upfront costs and risks associated with responding to public health emergencies given the many uncertainties, there are significant efforts underway to prevent, diagnose and treat the novel coronavirus. Several PhRMA member companies are researching and developing new vaccines or treatments, testing existing medicines, or donating medicines and supplies.

Responses to the 2014 and 2018 Ebola outbreaks in Africa are an excellent illustration of how public-private partnerships can affectively meet the needs of the public during a major health crisis. In response to the West African Ebola crisis in 2014, Merck, together with several organizations committed to global health, used a novel vaccination strategy, implemented during the successful eradication of smallpox, to accelerate the development of an Ebola virus vaccine and worked with the Biomedical Advanced Research and Development Authority to support manufacturing of the vaccine. This enabled a record response time to the 2018 outbreak in the Democratic Republic of the Congo (DRC). Nearly 300,000 doses of the vaccine have been administered, the vaccine is already licensed in five African counties and the company is not seeking profit from this vaccine. Similarly, the Janssen Pharmaceutical Companies of Johnson & Johnson also mobilized in response to the West African crisis. Its novel adenoviral vector Ebola vaccine has since been deployed in the DRC and also Rwanda to support outbreak containment efforts, being administered to over 50,000 individuals in the region to date.

"In reality, the global response to the Ebola virus threat is a case study for what science, partnership and trust in one another as global citizens can accomplish. The collaboration that made progress against Ebola virus disease possible is a shining example of what we are already seeing today with the response to the coronavirus outbreak, and should be celebrated and emulated." **—Julie Gerberding, Chief Patient Officer Merck, former CDC director**

Research and Aid Continues Even in Uncertain Times

The R&D ecosystem, including the biopharmaceutical research industry, continues to research new and needed vaccines even when demand varies, people do not vaccinate themselves with approved vaccines when they should, or diseases have very low or disappearing populations.

In addition to vaccine research, biopharmaceutical companies also make donations to developing countries. Most vaccine donations made by the biopharmaceutical industry are in response to emergency situations in developing countries, such as pandemics and usually made through experienced non-governmental organizations (NGOs) operating in the country or through the World Health Organization (WHO). In 2009, 100 million doses of pandemic H1N1 vaccine was donated by Sanofi to WHO to help combat a pandemic in developing countries, who otherwise would not have access to the vaccine.[23]

Innovation Through Collaboration

As advances in science and technology continue, uncovering complex biological drivers of many diseases, and regulatory requirements expand, the R&D process to develop medicines and vaccines also grows more challenging. Recent outbreaks of devastating infectious diseases have highlighted the importance of working together across the research ecosystem to accelerate the development and delivery of vaccines and treatments for people in need. While many different stakeholders are often engaged simultaneously in various vaccine research and delivery efforts, cross-ecosystem collaborations can be essential in overcoming scientific, operational and logistical hurdles. **Recent examples include:**

Biomedical Advanced Research and Development Authority (BARDA) – BARDA is part of the U.S. Health and Human Services (HHS) Office of the Assistant Secretary for Preparedness and Response. It was established to help keep our nation safe and secure from chemical, biological, radiological, and nuclear threats as well as infectious disease pandemics. BARDA supports its mission through public-private partnerships with industry to share risk, improve efficiency and accelerate development while sustaining a marketplace that guarantees continued access to countermeasures vital to our national security. In response to the COVID-19 pandemic, BARDA has launched or expanded vaccine development partnerships with a number of biopharmaceutical companies. For example, BARDA and Johnson & Johnson are together committing more than $1 billion to accelerate a candidate COVID-19 vaccine, with the goal of starting the first clinical studies in humans no later than the fall of 2020.

Gavi (The Vaccine Alliance) – This global collaboration brings together a variety of public health entities, non-profit organizations, and biopharmaceutical companies to accelerate access to vaccines in some of the world's poorest countries. This includes implementing novel strategies to increase utilization of already approved vaccines as well as coordinating to conduct robust clinical research into new vaccines where there are emerging infectious disease threats. Recent estimates indicate that by 2020, 20 million lives will have been saved as well as $350 billion in healthcare costs as a result of Gavi's vaccine initiative work.

Global Health Vaccine Center of Innovation (GHVCI) – A partnership of Sanofi, the Bill & Melinda Gates Foundation and the Infectious Disease Research Institute, focuses on accelerating development of new vaccines and creating efficiencies in production and distribution. The collaboration leverages the partners' collective expertise to advance novel research and development techniques.

Partnership for Research on Ebola Vaccination (PREVAC) – Launched in 2017 following the Ebola outbreak in West Africa, this unique international research partnership leverages the expertise and oversight of the health authorities in countries in the region that were impacted by Ebola (Guinea, Liberia, Sierra Leone and Mali) alongside several health authorities in developed nations (including the U.S. National Institutes of Health) to conduct carefully coordinated clinical studies and advance novel vaccine options. Several biopharmaceutical companies supported this research, donating vaccine product for the trial. The vaccines being tested in the PREVAC trial were supplied by the Janssen Pharmaceutical Companies of Johnson & Johnson, Bavarian Nordic and Merck.

The Future of Vaccine Development

The biopharmaceutical industry is working to overcome unique scientific, clinical and logistical hurdles in order to translate rapid scientific progress into the next generation of preventative 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.

In the United States currently, there are nearly **260** vaccines in development by biopharmaceutical researchers, aiming to both treat and prevent many illnesses. In order to sustain continued innovation in vaccine research and development, it is critical that the policy and regulatory framework keeps pace with evolving science and recognizes the role of vaccines in improving public health and preventing future infectious disease outbreaks.

Maintaining robust intellectual property protections is essential to providing incentives for entering the lengthy, costly and complex vaccine research and development process. Additionally, providing greater clarity on regulatory requirements for vaccine research, including the use of novel trial designs and outcomes measures, can help remove uncertainty and spur innovation in areas where conducting studies has historically been particularly challenging.

It is also important that patients have access to vaccines throughout their lives, as preventative measures like vaccines can be incredibly important in halting the spread of devastating illnesses. Robust coverage and reimbursement policies can play an important role in ensuring that people of all ages can access needed vaccines, resulting in higher rates of vaccination coverage and promoting strong public health.

Through continued collaboration among the public and private sectors, the research community can share and build upon important insights into novel manufacturing and storage techniques, which can accelerate development and delivery of vaccines. Building on the tremendous success of vaccines thus far, there is significant hope for a future further transformed by innovative vaccines.

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