VACCINES: HARNESSING SCIENCE TO DRIVE INNOVATION FOR PATIENTS

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INTRODUCTION

Advances in science and technology are driving increases in survival and improved quality of life for people around the world. Vaccines represent some of the most impactful public health advances, helping to prevent the spread of many infectious diseases and, in many parts of the world, eliminating some of the most devastating conditions.

Examples of vaccine successes are numerous and significant:

- **Smallpox**, at one point one of the deadliest diseases in existence, has been eradicated around the world as a result of vaccination.[1]
- Following the introduction of the first **polio** vaccine in 1955, the crippling infectious disease has been eliminated in the United States (U.S.) and by 2015 just 74 cases of the disease were reported around the world.[2,3]
- The recent introduction of the **human papilloma virus** (HPV) vaccine has changed the trajectory of cervical cancer, by preventing infection of the HPV strains most likely to cause cancers.[4]
- A new wave of therapeutic vaccines has the potential to treat diseases, including many **cancers.**[5]

As our understanding of the science grows, uncovering the complex biological drivers of many diseases, and regulatory requirements expand, the research and development (R&D) process to develop medicines also grows more challenging.

Innovative biopharmaceutical companies are working with stakeholders from across the research and development ecosystem to develop new ways of preventing and treating illnesses, with vaccines at the forefront. As of October 2017, there are more than 260 vaccines in development by biopharmaceutical companies for the treatment or prevention of disease. There is significant hope for the future, with the pipeline containing new vaccine technology that has the potential to prevent the transmission of the human immunodeficiency virus (HIV), protect against malaria and treat pancreatic cancer.[6]

"Discovering and developing breakthrough vaccines that help address unmet needs is more complex and challenging than ever before. We embrace cutting-edge technologies and the most promising science in our quest to help protect current and future generations from preventable infectious diseases."

—Paula Annunziato, M.D., Vice President Vaccines Clinical Research, Merck & Co., Inc.

UNDERSTANDING VACCINES

The human immune system is incredibly powerful and versatile, working continuously to keep a variety of invaders from causing infection and disease.[7] From bacteria to viruses to parasites, the immune system recognizes invading threats and triggers a response in the body to contain and combat invaders.[8] 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.[9] 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 supply of immune cells that will remember how to fight an invading pathogen in the future.

A new era of therapeutic vaccines is also emerging, as researchers learn more about ways to harness the immune system in fighting disease. For example, recent studies are demonstrating early success in vaccines that could treat HIV, Alzheimer's disease and various cancers.[10, 11]

In oncology, building on the success of the first cancer vaccine in 2010 (approved for metastatic prostate cancer), scientists are opening new avenues for immunotherapy, or immuno-oncology, where vaccines are showing promise in boosting the immune system or helping the immune system recognize cancer cells. [12 13] Many of these potential vaccines to treat cancer that are showing early promise can be individualized to each patient.[14 15]

"The development of a vaccine is a long, complex and expensive process, and one that requires experienced R&D organizations with a track record of success. But when it comes to emerging infectious diseases, this is not enough. The vaccine industry requires partnerships with governments and other funders to share the investment and the risk, with a goal of protecting populations everywhere against the inevitable infectious disease threats of the future."

—Rajeev Venkayya, MD, President of the Global Vaccine Business Unit, Takeda

HOW DO VACCINES WORK?

The primary component of a vaccine is antigens – the cellular elements that replicate or mimic key parts of invading pathogens, thus "sounding the alarm" and triggering an immune response in the body.[16] A vaccine also contains other substances that are used to ensure the vaccine can be safely stored, prevent contamination and promote its efficacy.

A variety of cells in the immune system play a key role in driving a vaccine's efficacy. When a vaccine is administered, the antigens are recognized as foreign by specific types of immune cells, called antigen-presenting cells, which alert the immune system to the invader.[17] The system then produces B-lymphocyte cells, which produce antibodies that recognize and attack the vaccine antigen (which mimics invading microbes or key properties of microbes), as well as cytotoxic T-lymphocytes, also called "killer T-cells," which detect cells within the body that may have already been infected and destroy them.[18] The immune system learns this response to the antigens and is ready to mount a response to the real disease if exposed in the future.

Therapeutic vaccines work to leverage or boost various elements of the immune system as well, helping the body better identify or target diseased cells.

Vaccine Safety

Vaccines undergo a rigorous research and development process in order to ensure safety and efficacy, and continue to be monitored long after U.S. Food and Drug Administration (FDA) approval.[19] Manufacturers and health authorities coordinate to ensure strict manufacturing and delivery schemes, in order to guarantee the quality and purity of vaccines. Data show that the current U.S. vaccine supply is the safest in history, due in part to the U.S. Centers for Disease Control and Prevention's (CDC's) long-standing vaccine safety program, which closely and constantly monitors the safety of vaccines.[20] One important element of the program, the Immunization Safety Office, monitors possible vaccine side effects and works with public health stakeholders to assess possible connections to vaccines.[21] For example, while some have had concerns that autism spectrum disorder might be linked to the vaccines children receive, studies have shown that there is no link between receiving vaccines and developing autism spectrum disorder.[22]

VACCINES: VITAL AT ALL AGES

Vaccines play a critical role in bolstering immunity and fighting disease in people of all ages.[23] In the U.S., sixteen diseases are now preventable as a result of childhood vaccines and the CDC estimates that $1.4 trillion in societal costs have been saved in the U.S. because of childhood vaccines.[24 25]

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.[26]

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.[27]

"Breakthrough vaccine technology will open new doors to effectively help prevent diseases that threaten adults as our immune systems weaken with age. As new vaccines from pioneering research become available, a concerted effort will be needed to improve access to vaccines by reducing financial and other barriers facing adults, in particular older Americans in the Medicare program."

—Patrick Desbiens, Senior Vice President, U.S. Vaccines, GSK

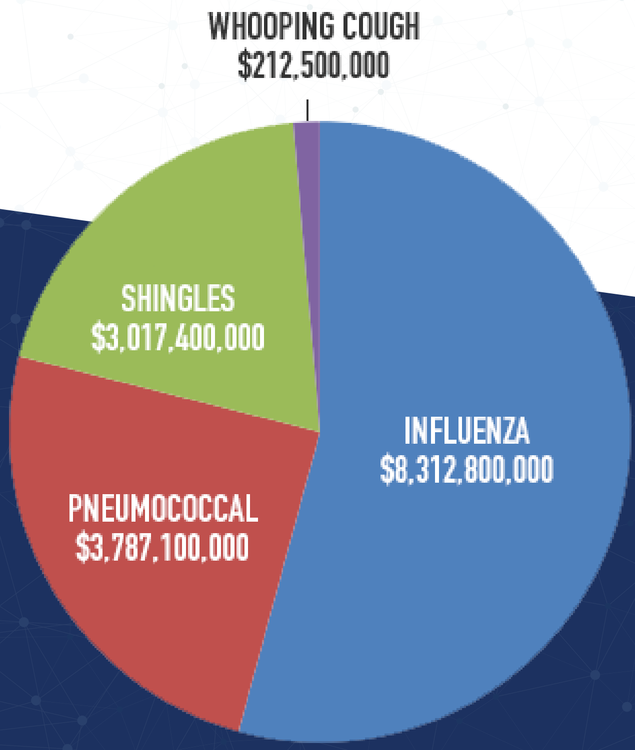
ADULT VACCINES

Despite tremendous advances in vaccines, the prevalence of illnesses attributable to vaccine-preventable diseases remains higher in adults than children.[28] Less than half of adults ages 19 and older received a flu vaccine in 2015, for example, and 30 percent 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.[29] 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.

In 2013, four major vaccine-preventable diseases resulted in $15.3 billion in direct and indirect costs[30]



The following are examples of some of the most important vaccines recommended by the CDC for various stages of life:[31]

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 the Zoster vaccine, which prevents shingles, and people ages 65 and older are recommended to receive vaccines to prevent **pneumococcal infection**.

VACCINES AND TRAVEL

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.[32] 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.

COMMON TYPES OF AVAILABLE VACCINES

There are several different types of vaccines, each with different characteristics that are important based on the type of microbe they are targeting (virus, bacteria, etc.), the population that will receive the vaccine and practical considerations regarding the way the vaccine will be delivered and where around the world the vaccine will be used.[33] The following are the most common types of preventative vaccines used today:[34]

Live-attenuated vaccines

- Contain a weakened version of the microbe itself
- More commonly used against viruses than bacteria
- Must be refrigerated
- Examples: Measles, mumps, and rubella (MMR) vaccine, chicken pox vaccine

Inactivated vaccines

- Contain dead microbes
- Confer weaker immunity than a live-attenuated vaccine, so often require a booster shot
- Do not usually require refrigeration
- Examples: Influenza vaccine, hepatitis A vaccine
- A subset of inactivated vaccines, called toxoid vaccines, contain inactivated toxins that are known to cause the immune response (diphtheria and tetanus vaccines, for example)

Subunit/recombinant vaccines

- Contain only the parts of a microbe that stimulate an immune response, rather than a whole microbe
- Can be manufactured using chemicals to break apart a microbe and isolate key components, or by modifying the genetic code of a microbe
- Examples: Pertussis (whooping cough) vaccine, hepatitis B vaccine, some flu vaccines
- A subset of these vaccines, called conjugate vaccines, may have an additional protein connected to the antigen in order to help the immune system recognize them (pediatric pneumonia and Hib vaccines, for example)

There is currently one type of therapeutic vaccine that is approved by the U.S. FDA. This vaccine, a type called a dendritic cell vaccine, uses a patient's own immune cells to produce an immune response to cancer cells (in this case, prostate cancer).[35]

NOTABLE VACCINE ADVANCES

Vaccines have had a tremendous public health impact, preventing some of the most devastating and deadly diseases, and in some cases even eradicating them in certain parts of the world. Below are just a few examples of notable vaccine innovations.

1796:

First Vaccine to be Developed[36]

Smallpox, once considered one of the deadliest infectious diseases, is the only disease to have been eradicated as a result of vaccines.

1955:

Vaccine Prevents Paralyzing Disease[37, 38]

The polio vaccine has eliminated this devastating viral disease in the U.S. and there are only three countries in the world where polio transmission has not been eliminated.

1963:

Vaccine Halts Spread of Highly Contagious Disease[39, 40]

One of the most contagious diseases, measles afflicts people with fever, respiratory problems, and a signature red rash. Today, measles is nearly eliminated in the U.S. and it is estimated that more than 17.1 million lives have been saved around the globe since 2000 as a result of the vaccine.

1967:

Vaccine Stops Spread of Painful Illness[41, 42]

The mumps virus at one time was one of the leading causes of childhood deafness. Since the introduction of the vaccine in 1967, incidence of the disease has decreased more than 99 percent in the U.S.

1991:

Recombinant Vaccine Halts Liver Disease[43]

Introduction of a newly formulated vaccine to prevent hepatitis B has driven incidence of the disease down 82 percent, preventing acute liver failure and chronic illness, which can lead to liver cancer.

2006:

Vaccine Prevents Painful Rash[45, 46]

Caused by the same virus behind chicken pox, shingles is predicted to impact one in three Americans over the age of 60. A vaccine now has the potential to cut incidence in half and reduce the risk of long-term, lingering pain.

2006:

First Cancer-Preventing Vaccine Introduced[44]

Vaccines are now available to prevent the strains of human papilloma virus (HPV) most likely to cause cervical cancers, as well as other cancers. Incidence of HPV in the U.S. has decreased 64% in girls ages 14 to 19 years old since the vaccine was introduced and the vaccine is now recommended for all children and young adults.

2010:

First Therapeutic Cancer Vaccine[47]

A major advance in the field of immuno-oncology, the first vaccine to treat prostate cancer opened doors to new avenues for harnessing the immune system in fighting cancers.

VACCINES: TRANSFORMING PUBLIC HEALTH IN THE UNITED STATES

Vaccines represent some of the greatest advances in public health, resulting in the near elimination of many of the most devastating infectious diseases and eradication of smallpox virus from the U.S.

ANNUAL MORBIDITY (20TH CENTURY)	DISEASES % DECREASE	REPORTED CASES (2013)
21,053	DIPTHERIA 100%	0
29,005	SMALLPOX* 100%	0
530,217	MEASLES >99%	187
162,344	MUMPS >99%	584
47,745	RUBELLA >99%	9
16,316	POLIO (PARALYTIC) >99%	1
580	TETANUS 96%	26
200,752	PERTUSSIS 86%	28,639

Smallpox has been eradicated worldwide.

VACCINE R&D

Researching and developing new medicines is a complex and multifaceted process, requiring significant time and resource investment. It takes an estimated ten to 15 years (on average) and nearly $2.6 billion to develop a novel medicine from the discovery stage all the way through to approval by the FDA.[48] This process is fraught with dead ends and setbacks, with only 12 percent 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.[49] 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.

UNIQUE CHALLENGES OF VACCINE R&D

Vaccines present a number of unique challenges that make them particularly complicated to research. These can include, but are not limited to, scientific, clinical, and logistical hurdles throughout the development process.

Scientific Challenges

Targeting strains that evolve: Identifying the particular strain of a virus to target, in order to create and test a vaccine, can take a very long time (particularly when the virus is a new, emerging threat). During that time, the virus itself may have mutated, requiring scientists to go back to the drawing board.[50]

Understanding the immune system: Rapid scientific advances have accelerated understanding of the immune system in recent years, but there is still much to unravel regarding the complexities of many infectious diseases and how the immune system normally reacts to them, particularly diseases that occur infrequently or in small populations.[51]

Establishing reliable preclinical models: There is a need for preclinical research models that more closely parallel the human immune system in order to better predict immune response to vaccines.[52]

Clinical Challenges

Recruiting patients: Multiple 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 patients for clinical trials.[53] 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.[54]

Overcoming stigma and misinformation: Particularly in areas of the world where people may infrequently visit the clinic or hospital, there are often fears regarding both visiting a medical center and the safety of the vaccine itself.[55, 56] Carefully designed and implemented education and outreach strategies, coordinated through local communities, can be important in overcoming mistrust to conduct research.[57]

Logistical Challenges

Navigating manufacturing complexities: Because vaccines are biologics — 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, isolate and purify it, and mix the purified component in the appropriate solution for storage and delivery.[58] 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.

Storing and transporting vaccines: Once manufactured, vaccines need to be packaged, stored and delivered. Then, upon delivery, they need to be stored in appropriate conditions. Most vaccines require a strict cold-chain to maintain their stability, so must be shipped and stored under refrigeration. Exposure to temperatures outside the recommended ranges can reduce the effectiveness of the vaccine; exposed batches often need to be discarded altogether, resulting in lost time and resources.[59, 60, 61, 62] Maintaining the cold-chain can be challenging in countries that lack a reliable infrastructure so researchers are working on vaccines that do not need to be refrigerated or can be out of refrigeration temporarily.[63]

"We are making important scientific inroads with vaccine candidates to tackle devastating hospital and community acquired infections, and there are opportunities to potentially provide protection to some of the most vulnerable, newly born infants from infectious diseases such as Group B streptococcus and Respiratory Syncytial virus through maternal immunization. But designing effective vaccines for these devastating diseases has challenged scientists for decades. Today, there are a shrinking number of experienced vaccine manufacturers and increased and complex development timelines which require vast resources to advance safe and effective vaccines for a growing global population. At Pfizer, we are not deterred by these challenges and are taking them head-on so that we can continue to have a positive impact on global health."

—Kathrin Jansen, Ph.D., senior vice president and head of Vaccine Research and Development, Pfizer

DRIVING INNOVATION THROUGH COLLABORATION: COMBATTING INFECTIONS AND OUTBREAKS

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. Pandemic threats like Zika and Ebola can spread sporadically and unpredictably, for example, exacerbating an already challenging vaccine research and development process.[64] 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:

GHVCI
GLOBAL HEALTH VACCINE CENTER OF INNOVATION

Global Health Vaccine Center of Innovation:
This collaboration, between 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.[65]

Partnership for Research on Ebola VACcination:
This unique international research partnership leverages the expertise and oversight of the health authorities in countries most impacted by Ebola (Guinea, Liberia, and Sierra Leone) 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 are working hand in hand with partners to design and conduct the research, as well as donate vaccine product for the trial.[66]

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.[67] 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.[68]

"We believe that public-private partnerships are important in new vaccine development and should continue to play a major role in response to emerging public-health emergencies. Policies that encourage such partnerships help the world's ability to quickly respond to these threats."

—Jim Tartaglia, PhD, VP, R&D New Vaccines, Sanofi

ACCELERATING FUTURE VACCINE INNOVATION

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.

In the United States currently, there are more than 260 vaccines in development by biopharmaceutical researchers, aiming to both treat and prevent many illnesses.[69] 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.

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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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