The State of Innovation in Vaccines and Prophylactic Antibodies for Infectious Diseases

by David Thomas, CFA
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Bio

Where breakthroughs begin

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Vaccines and Prophylactic Antibodies for Infectious Diseases

Introduction

Vaccines are a compelling solution to emerging and established infectious disease threats. Vaccination is often cited among the 10 greatest public health achievements of the 20th century[1] — only access to safe and clean water has had a greater impact on human health by preventing disease and extending lifespans.[2] The U.S. Centers for Disease Control and Prevention (CDC) estimate that U.S. children born between 1994 and 2021 who are vaccinated according to the recommended immunization schedule will prevent 472 million illnesses and 29.8 million hospitalizations over the course of their lifetimes.[3]

The overall impact on mortality reduction can be seen in **Figure 1**, which illustrates numerous vaccines yielding a 100%, or near 100%, reduction in the risk of death. Prior to the introduction of vaccines, these diseases caused significant morbidty and mortality. Examples include the eradication of polio and the recent reduction in deaths due to the SARS-CoV-2 pandemic. In addition to these examples, vaccines have been shown to reduce the risk of cancer and other longer-term diseases. For example, the percentage of cervical lesions (precancers that could progress to invasive cervical cancer) dropped by 40% in women vaccinated against human papillomavirus (HPV).[4]

Unfortunately, not all diseases have been amenable to prevention with efficacious vaccines. For example, human immunodeficiency virus (HIV) vaccines have been researched and developed for nearly 40 years with no success. Further, tuberculosis, *Streptococcus* A, Schistosomiasis, Chagas, Nipah, Lassa, MERS, Zika, Hepatitis C, Gonorrhea, Plague (*Yersinia*), *Salmonella*, *Shigella*, *E. coli*, *Klebsiella pneumoniae*, Chlamydia, Coxsackie virus, Norovirus, Chikungunya, CMV, HSV-2, EBV and other infectious diseases with significant human burden remain without a vaccine. Biotechnology companies today continue to search for innovative ways to elicit an enduring immune response for these infectious pathogens. The most advanced, novel pipeline candidates developed by biopharmaceutical companies are outlined in this report.[6]

EXAMPLES OF VACCINE IMPACT ON MORTALITY

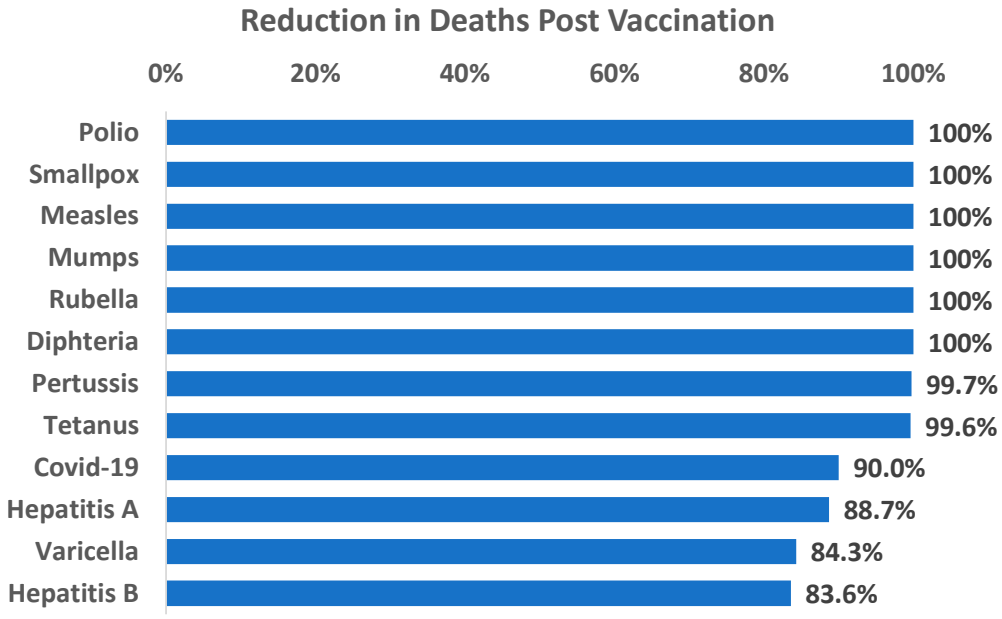


Figure 1. Reduction in death due to vaccination for various diseases. Diseases with vaccination and the percent reduction in deaths post vaccination. See footnotes for sources.[5]

Executive Summary

Pipeline & Investment

- The global clinical pipeline for infectious disease vaccines consists of 249 active novel clinical-stage programs that are company sponsored. There are 31 infectious diseases represented in the clinical pipeline for which there is no currently available approved vaccine. The clinical pipeline has breadth, but lacks the depth likely required for successful product development for many important pathogens.
    - For programs against viral pathogens, there are 187 clinical-stage programs. This consists of 69 SARS-CoV-2 vaccines, 84 for other RNA viruses (more than half of these for influenza, RSV, and HIV), and 34 DNA virus vaccines (half of these target HPV and Varicella-Zoster).
    - For programs against bacterial pathogens, there are 44 clinical-stage programs. Although 18 total bacterial pathogens are targeted, more than half of the programs target Streptococcus pneumoniae, Mycobacterium tuberculosis, and meningococcus.
    - For programs against parasitic pathogens, there are eight clinical-stage programs for malaria and schistosomiasis.
    - There are 10 novel combination vaccines in development covering a total of 10 pathogens.
- There is a wide range of vaccine modalities in the clinical pipeline, including 87 protein-based vaccines, (24 are part of virus-like particles (VLPs), 53 RNA-based vaccines (40 mRNA and 13 saRNA), 27 recombinant viral vector-based vaccines, 24 glyco-conjugate vaccines, 14 inactivated and 14 live attenuated viral vaccines, 12 DNA vaccines, 12 whole cell vaccines, and seven peptide vaccines.
- Clinical success rates have been above average for vaccines during the period 2013-2022. With an 11% likelihood of FDA approval (LOA) from Phase I, vaccines outperformed non-vaccine biologics, which have a 7.6% LOA over the same time frame. By comparison, novel small molecules across all diseases had only 5.6% LOA.
- Venture capital investments in global companies with infectious disease vaccine programs totaled $6.5 billion over the last 10 years. This represents 3.4% of total venture capital raised for biopharmaceutical companies during the same period. By contrast, oncology drug development companies raised $72.6 billion over the last decade, a 12-fold greater investment than in vaccines. Public companies with infectious disease vaccine programs raised $8.7 billion, $3.2 billion from IPOs and $5.5 billion from secondary offerings. $6 billion of the $8.7 billion was raised during the COVID-19 pandemic.
- The clinical pipeline for prophylactic antibodies is small relative to vaccines, with only 16 in clinical-stage development. However, the antibody pipeline targets 11 different pathogens.
- Prophylactic antibodies have been used in broad populations to protect against seven unique pathogens.
- In total, vaccines for 34 unique pathogens have been approved in the U.S. or globally. Licensed vaccines utilize a wide range of modalities: direct antigen delivery (protein, carbohydrate, pathogen inactivation and pathogen attenuation) and indirect antigen delivery (mRNA and viral vector-based vaccines).

Proposed Solutions to Expand the Depth/Breadth of the Vaccine Pipeline

- Capitalize on use of Platform Technologies: Platform technologies can speed development of novel approaches to improve efficacy and/or safety of vaccines, spur investment in new technologies in disease areas that have been difficult to tackle and help in pandemic preparedness. The policy environment must facilitate the use of platform technologies to spur investment in R&D across viral families.
- Expand Access to Vaccines: Given the broad benefits of primary prevention to individuals and society, especially for persons with underlying chronic conditions, facilitating access to immunizations through both financial policies and policies that increase the types of vaccinators (for example pharmacists) will have a significant impact on overall healthcare outcomes and costs.
- Rebuild Vaccine Confidence Worldwide: Combatting vaccine misinformation and disinformation and bolstering vaccine confidence is crucial to realizing the broadest benefits of vaccines and a stronger vaccine infrastructure overall.
- Evolving ACIP and NITAG Review Processes: Evaluation and recommendation by ACIP and other NITAGs define the size and patient utilization for the vaccine market. This process must adapt to the changing vaccine landscape and create a predictable review environment that encourages increased investment in the space.

Methodology

Part I of this report focuses on vaccine innovation and success at the clinical stage, as well as funding of companies with lead vaccine programs. Part II focuses on prophylactic antibodies in clinical trials. For context on modalities and disease areas of unmet need, a brief summary of approved vaccines and prophylactic antibodies is provided prior to the discussion. A more detailed description of previously licensed vaccine technologies is provided in the Appendix. This report does not contain data or discussion on other important topics related to vaccines including: storage, distribution, clinical safety and efficacy data, real-world evidence, pricing, or global market access.

The initial sources for clinical candidates are the Biomedtracker and Pharmaprojects databases, with subsequent details and updates from company websites and peer-reviewed articles. For international vaccine approvals, the EvaluatePharma database was used as a primary resource. The COVID-19 pipeline data is based on the Biotechnology Innovation Organization (BIO) COVID tracker (www.bio.org/iareports), which relies on multiple sources including Biomedtracker and Biocentury.

List of Figures and Charts

Intro

Part 1. Vaccines

Part II. Prophylactic Antibodies

Part I. Vaccines

History of Vaccines Approved for Human Prophylaxis

Vaccination utilizes a component of a pathogen or an intact pathogen (live and inactive), to actively train the immune system for defensive action against a fully infectious version of a pathogen.[7] This is distinct from variolation, used prior to the 19th century, where limited exposure to the infectious pathogen itself was used.[8] Although the first true vaccine used in a broad population originated in the 1790s, this was by no means a purified vaccine that would classify as an approvable vaccine candidate today. Early vaccines were crude mixtures of pathogen variants and often came with contamination, mixed strains, and reproducibility issues. In the second half of the 20th century, progress in biotechnology allowed for the development of purified vaccines with high reproducibility using clonal strains or recombinant antigens. The first two decades of the 21st century have led to even greater innovation, with new modalities, higher quality manufacturing, and broader applicability.

Figure 2 lists the breadth of pathogens for which a vaccine license has been granted and used in a large population either in the U.S. or abroad since the 1800s.

Figure 3 illustrates the technologies used to achieve these vaccine approvals for human use.

In the **Appendix**, we expand on the history of approved vaccines and prophylactic antibodies in further detail. This historical context was used to assess the novelty of the current pipeline, with a focus on the primary antigen source, technology type, and production methods (with less emphasis on adjuvants, preservatives, dosages, or intended populations).

TIMELINE OF APPROVED VACCINES AGAINST INFECTIOUS DISEASES

First Broad Usage	Disease	Pathogen Type
1800s	Smallpox	DNA virus
1800s	Cholera	bacteria
1910s	Rabies	RNA virus
1920s	Tuberculosis (TB)	mycobacteria
1930s	Diphtheria infection	bacteria
	Yellow fever	RNA virus
1940s	Tetanus	bacteria
	Whooping Cough	bacteria
	Infleunza (Flu)	RNA virus
1950s	Polio	RNA virus
1960s	Measles	RNA virus
	Mumps	RNA virus
	Rubella	RNA virus
1970s	Anthrax	bacteria
	Adenovirus	DNA virus
	Tick-borne Encephalitis	RNA virus
	Pneumococcal Disease	bacteria
1980s	Hepatitis B	DNA virus
	H. Influenza	bacteria
	Typhoid Fever	bacteria
1990s	Japanese Encephalitis	RNA virus
	Chickenpox	DNA virus
	Hepatitis A	RNA virus
	Lyme Disease (withdrawn)	bacteria
2000s	Meningococcal Disease	bacteria
	Shingles	DNA virus
	Rotaviral enteritis	RNA virus
	HPV	DNA virus
2010s	Dengue Fever	RNA virus
	Hand, Foot, Mouth Disease	RNA virus
	Ebola	RNA virus
2020s	Covid-19	RNA virus
	Malaria	Parasite
	RSV	RNA virus

Figure 2. List of diseases for which vaccines have been developed and approved by a government agency. The order is based on the time period of first broad use (not year of discovery or clinical trials). The Lyme disease vaccine was only marketed 1998-2001 and is included for historical purposes and assessment of current pipeline novelty.

TYPES OF INFECTIOUS DISEASE VACCINES

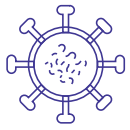
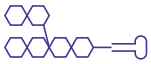
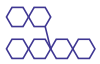
Class	Type	Examples	Illustration
Viral	Live Attenuated Pathogen	Measles, Mumps, Rubella, Smallpox, Yellow Fever, Chickenpox, Influenza, Rotavirus, Dengue	
	Inactivated Pathogen	Polio, Rabies, Influenza, TBE, JEV, Enterovirus, COVID-19	
	Recombinant Viral Vector, Replicating	Ebola	
	Recombinant Viral Vector, Nonreplicating	COVID-19 (EUA)	
Nucleic Acid	mRNA	COVID-19	
Protein	Purified Antigen Protein	Influenza, Diptheria, Pertussis, Tetanus, Anthrax, Influenza, COVID-19, RSV	
	Protein-VLP (Virus Like Particle)	Meningococcus Group B, Shingles, Hepatitis B, HPV, Malaria, COVID-19	
Carbohydrate	Carbohydrate-Protein Conjugate (glyco-conjugate)	Pneumococcal, Hemophilus Influenza (Hib)	
	Capsid Carbohydrate	Pneumococcal	
Cell	Live Attenuated Bacteria	Tuberculosis (BCG), Cholera	
	Inactivated Bacteria	[Typhoid Fever]	

Figure 3. Types of vaccines that have been approved historically. Examples given are not an exhaustive list. Typhoid fever inactivated whole Salmonella Typhi cell is no longer licensed, but rather an extraction of polysaccharides from Salmonella Typhi cells.

Current Novel Clinical Pipeline for Vaccines

The current company-sponsored clinical pipeline for infectious disease vaccines worldwide contains 249 novel clinical programs based on analysis of the Biomedtracker and PharmaProjects databases.[9] There are 31 infectious diseases represented in the clinical pipeline for which there is no currently available approved vaccine.

As shown in **Figure 4**, there are ongoing vaccine programs for RNA viruses, DNA viruses, bacteria, and parasitic pathogens. RNA viruses make up the largest group with 153 clinical programs (61.4% of all vaccine programs). As there were far more SARS-CoV-2 vaccine programs compared to other indications, SARS-CoV-2 RNA virus programs are grouped separately from the other RNA virus vaccines in **Figure 4**. After 109 suspended programs over the last few years, there are now 69 ongoing company-sponsored clinical programs for SARS-CoV-2, accounting for 27% of all vaccine programs.[10] Bacterial programs rank second by pathogen group after RNA viruses, with 44 programs (16.5% of all vaccine clinical programs). DNA virus vaccines have a total of 34 clinical-stage programs (13.7% of all vaccine clinical programs). There are 8 parasitic clinical-stage vaccine programs, most of these for malaria. Lastly, 10 vaccine programs are combination products with first-in-class antigenic approaches.

Clinical trial phases of the vaccine pipeline are also shown in **Figure 4**. Phase I has the highest number of programs with 119 clinical programs or 48% of the total vaccine pipeline. Fewer programs are found in Phase II, with 85 comprising 34% of the pipeline. This is the opposite proportion than what is seen in the overall industry pipeline (n=7,111 clinical programs), where more programs are in Phase II (49%) than in Phase I (33%). Late-stage trial status percentages mirror the overall industry pipeline composition: Vaccine Phase III and BLA clinical programs make up 16% and 2%, respectively.[11]

In terms of the types of pathogens targeted by Phase, the distribution is similar across Phases I-III except that parasitic vaccines and new combination vaccines are in Phase I and II only.

The pipeline within each pathogen group, by individual pathogen species, is described below. Each group has a breakdown by phase and a breakdown by modality of the vaccine approach.

COMPANY-SPONSORED GLOBAL CLINICAL PIPELINE FOR NOVEL VACCINES

Pathogen Type	Phase I	Phase II	Phase III	BLA	Total
Non-CoV-2 RNA viruses	49	22	10	3	**84**
SARS-CoV-2 RNA virus	32	23	14	0	**69**
DNA viruses	14	14	6	0	**34**
Bacteria	12	20	11	1	**44**
Parasites	4	4	0	0	**8**
Multiple Pathogen Types	8	2	0	0	**10**
Total	**119**	**85**	**41**	**4**	**249**

Figure 4. The company-sponsored global vaccine clinical pipeline by pathogen type (top) and phase (bottom) as of July 2023. Only novel vaccines for infectious disease are included.

Vaccine Clinical Pipeline for RNA Virus Pathogens

For the 153 company-sponsored clinical programs for RNA viruses worldwide, three are in registration-stage for approval, 24 are in Phase III, 45 in Phase II, and 81 in Phase I. There are 18 different pathogens being targeted in the vaccine pipeline as listed in **Figure 5**. The types of programs and modalities within each will be described below.

COVID-19 vaccine pipeline (Vaccine types: protein, protein-VLP, conjugate, peptide, mRNA, saRNA, viral, DNA, recombinant bacteria, recombinant human cell)

Although there are now 39 vaccines authorized or approved for COVID-19 worldwide, there is still robust activity with 69 COVID-19 vaccines in the clinical pipeline, comprising a wide range of modalities. Most of these vaccines are now in development as updated versions, targeting newer variants or for pan-coronavirus protection.

Protein-based vaccines outnumber all other COVID-19 vaccine types with 20 programs. Of these 11 are in Phase I, 6 are in Phase II, and 3 in Phase III development. All but one of the protein-based vaccines are targeting the spike protein of COVID-19. One of the Phase I programs targets multiple epitopes, however, it is not disclosed which ones. The majority (12) of the protein-based vaccines are manufactured using mammalian cells, while others use insect (2), plant (1), or fungal (1) cells (four of the protein programs do not disclose expression systems for manufacturing).

mRNA programs have the second highest number of clinical programs with 13. Of these 13 programs, seven are in Phase I, five are in Phase II, and one is in Phase III. All but one of the mRNA vaccine programs codes for the spike protein, with one program designed with a non-spike protein that is not disclosed.

The third largest group of COVID-19 clinical-stage vaccine programs are the non-replicating recombinant viral-vector vaccines. Four of the programs are in Phase I, three are in Phase II, and three are in Phase III. Of the 10 programs, five use an adenovirus vector as the backbone for engineering, two of which are single cycle adenoviruses, one an adenovirus 5 vector, one a gorilla adenovirus, and one is undisclosed. Two other programs use the Newcastle virus (NDV) vectors, another uses a Parainfluenza virus 5 (PIV5) vector, one is derived from the human respiratory syncytial virus (RSV), and the final uses a modified vaccinia Ankara vector (MVA). All 10 of these programs are designed to express the spike protein while the MVA program also encodes the nucleocapsid protein of SARS-CoV2.

The fourth largest group of COVID-19 clinical-stage vaccine programs are the DNA-based vaccines with 7 programs. All these DNA-based vaccines use DNA plasmids, with four of them targeting the spike protein while the other three do not disclose the target.

The next largest group is self-amplifying RNA (saRNA) vaccines with six programs. For these programs, two are in Phase I, three are in Phase II, and one is in Phase III. All six programs target the spike protein, but one also targets other T-cell epitopes that are not disclosed, and another also targets the nucleocapsid.

The Virus-like particles (VLP) modality comes next with five programs. Two of the VLP programs are in Phase I, two are in Phase II, and one is in Phase III. All six programs target the spike protein.

The remaining programs include two peptide-based vaccines, one each in Phase I and Phase III; two inactivated viral vaccines with one each in Phase II and Phase III; one live attenuated viral vaccine in Phase III; one gene edited bacteria-based vaccine in Phase I; one semi-synthetic glycoconjugate vaccine in Phase I; and one recombinant human cell vaccine in Phase II that is based off dendritic cells.

Influenza vaccine pipeline (Vaccine types: protein, protein-VLP, mRNA, viral)

Influenza vaccines in the pipeline are separated into three different indications: seasonal, universal, and pandemic. Seasonal influenza vaccines work to address the common forms of influenza that follow a seasonal epidemic of the disease. These vaccines may target either Influenza A or B viruses or both. Universal Influenza vaccines aim to be effective against all types of influenza, regardless of strain, without the need to modify the vaccine on a seasonal basis. Pandemic influenza vaccines are vaccines that address new and different influenza strains that could infect a large amount of people causing a pandemic. Influenza A viruses are currently the only influenza viruses that are known to cause pandemics.

Of the 29 influenza vaccines currently in clinical development, over half of the vaccines are seasonal influenza. Thirteen of the seasonal vaccines are utilizing RNA technologies such as mRNA and saRNA. Two are protein and protein-VLP based, a third is an inactivated virus, and a fourth seasonal vaccine candidate is a live attenuated H1N1 strain.

For the remaining 12 influenza vaccines, seven are universal influenza vaccines and five pandemic influenza vaccines, all but two of the vaccines utilize modalities commonly seen in vaccines approved today. The universal influenza candidate vaccines include an HA antigen VLP, nucleoprotein, two attenuated influenza virus strains (made by deleting Ns1 or M2 genes), self-amplifying RNA, and a peptide vaccine.

COMPANY-SPONSORED GLOBAL CLINICAL PIPELINE FOR RNA VIRUS PATHOGENS

RNA virus vaccines	Phase I	Phase II	Phase III	BLA	Total
SARS-CoV-2	32	23	14	0	**69**
Influenza - Seasonal	12	1	3	1	**17**
Influenza - Universal	5	2	0	0	**7**
Influenza - Pandemic	2	3	0	0	**5**
RSV	6	3	2	0	**11**
HIV	6	2	0	0	**8**
Norovirus	1	5	0	0	**6**
Dengue	3	1	1	0	**5**
Rotavirus	1	1	2	0	**4**
Zika	2	1	0	0	**3**
Chikungunya	0	1	1	1	**3**
Nipah Virus	3	0	0	0	**3**
Ebola	1	1	0	0	**2**
Rabies	1	0	1	0	**2**
EEV	2	0	0	0	**2**
Lassa Virus	2	0	0	0	**2**
Coxsackie virus	1	0	0	0	**1**
Enterovirus	0	0	0	1	**1**
Yellow Fever	0	1	0	0	**1**
West Nile Virus	1	0	0	0	**1**
Total	**81**	**45**	**24**	**3**	**153**

RNA virus vaccines	Protein	protein VLP	carbohydrate-protein	peptide	mRNA	saRNA	Viral (inactivated)	Viral (attenuated)	rViral (non-replicating)	rViral (replicating)	DNA	human cell (recombinant)	bacteria (recombinant)	Total
SARS-CoV-2	20	5	1	2	13	6	2	1	10	0	7	1	1	**69**
Influenza - Seasonal	1	1	0	0	8	6	1	0	0	0	0	0	0	**17**
Influenza - Universal	1	1	0	1	0	1	0	3	0	0	0	0	0	**7**
Influenza - Pandemic	3	0	0	0	0	0	2	0	0	0	0	0	0	**5**
RSV	2	3	0	0	2	0	0	3	0	1	0	0	0	**11**
HIV	1	0	0	0	2	0	1	0	2	0	2	0	0	**8**
Norovirus	1	3	0	0	0	0	0	0	2	0	0	0	0	**6**
Dengue	1	0	0	1	0	0	0	3	0	0	0	0	0	**5**
Rotavirus	1	1	0	0	0	0	1	1	0	0	0	0	0	**4**
Zika	1	0	0	0	1	0	1	0	0	0	0	0	0	**3**
Chikungunya	0	1	0	0	0	0	1	1	0	0	0	0	0	**3**
Ebola	0	0	1	0	1	0	0	0	0	1	0	0	0	**3**
Nipah Virus	0	0	0	0	0	0	0	0	1	0	1	0	0	**2**
Rabies	0	0	0	0	1	0	1	0	0	0	0	0	0	**2**
EEV	0	1	0	0	0	0	0	0	1	0	0	0	0	**2**
Lassa Virus	0	0	0	0	0	0	0	0	0	2	0	0	0	**2**
Coxsackie virus	0	0	0	0	0	0	1	0	0	0	0	0	0	**1**
Enterovirus	0	0	0	0	0	0	1	0	0	0	0	0	0	**1**
Yellow Fever	0	0	0	0	0	0	1	0	0	0	0	0	0	**1**
West Nile Virus	0	0	0	1	0	0	0	0	0	0	0	0	0	**1**
Total	**32**	**16**	**2**	**5**	**28**	**13**	**13**	**12**	**16**	**4**	**10**	**1**	**1**	**153**

Figure 5. The company-sponsored global clinical pipeline for novel RNA virus vaccines. Top: pathogen targets and phase of program. Bottom: pathogen target and modality of vaccine.

The five pandemic influenza vaccine clinical candidates target H5N1, H5N6, H7N1, H7N9, and one for all H7 strains. Three of these are protein based and use the HA antigen of the respective influenza strain. Two programs use inactivated viral strains.

RSV vaccine pipeline (Vaccine types: protein, protein-VLP, attenuated virus, recombinant viral vector)

On the heels of the two recent vaccine approvals for RSV as described in **Appendix I**, there are 12 other candidates in clinical trials - six are in Phase I, three in Phase II, and three in Phase III.

Protein-based vaccines account for five of the 11 RSV vaccines in clinical development. Three of the five are protein-based vaccines that use VLPs to display the antigenic portion of the protein. One is a synthetic VLP displaying epitopes for RSV F-protein site II in Phase I, and the other two have VLP displaying the pre-fusion F proteins (similar to the approved vaccine protein conformation). The other two are pure protein vaccines being developed ex-U.S. In China there is an RSV G protein subunit vaccine (purified from *E. coli*) in Phase II, and the other, in Phase II in Japan, uses an undisclosed RSV protein antigen.

Two mRNA programs for RSV are in Phase II and III. The Phase III codes for the prefusion F protein, and the Phase II gene product has not been disclosed (although it is also likely some version of the F protein)

There are four viral vaccines for RSV in clinical development. Three programs are early-stage and use various genetic mutations to achieve attenuation of RSV. The last is a recombinant vector-based vaccine using a PIV5 (canine parainfluenza virus) expressing full length F protein (in Phase I).

Furthermore, there are additional combination vaccines containing RSV in development that will be described below in the section on novel combination vaccines.

HIV vaccine pipeline (Vaccine types: protein, DNA, inactivated virus, recombinant viral vector)

The HIV clinical vaccine pipeline includes eight vaccine candidates, six of which are in Phase I and two in Phase II. Two of the HIV vaccines are DNA-based (using various combinations of g120, gp140, and gag) and two are mRNA-based. Two vaccines are recombinant viral vectors and one is inactivated HIV virus. There is one protein fusion vaccine in Phase I containing the HIV antigenic protein bound to a CD40 antibody.

Norovirus vaccine pipeline (Vaccine types: protein; recombinant viral non-replicating)

Six vaccines are in clinical development for norovirus. The most advanced are in Phase II, of which there are five, and one is in Phase I.

The Phase I program is testing a plant-based protein-VLP vaccine that contains capsid proteins for GI.4 and GII.4 noroviruses. There are two Phase II programs in China: a capsid protein vaccine for GI.1, GII.4 noroviruses using the yeast *Hansenula Polymorpha* for production and a quadrivalent protein-VLP norovirus vaccine using the yeast *Pichia pastoris*. There is another purified protein-vaccine in Phase II with no disclosed details on antigen or source of production.

There are two recombinant nonreplicating viral vaccines in Phase II. The first uses an Ad5 vector to make capsid VP1 antigens for G1.1-NN and GII.4-NS.

Dengue vaccine pipeline (Vaccine types: live attenuated; peptide)

There are five Dengue vaccines in the clinical pipeline in Phase I and II. Three are live attenuated virus vaccines potentially effective against all four serotypes. The other two are peptide vaccines with one vaccine containing dengue protein fragments and the other composed of four salivary peptides isolated from *Anopheles gambiae* (mosquito) salivary glands.

Zika vaccine pipeline (Vaccine types: mRNA, inactivated, peptide)

Of the three Zika vaccine candidates, the most advanced is an mRNA vaccine in Phase II. The other candidates are in Phase I. One is an inactivated Zika virus, and the other is composed of four salivary peptides isolated from *Anopheles gambiae* salivary glands.

Chikungunya vaccine pipeline (Vaccine types: live attenuated, protein-VLP)

There is a live attenuated Chikungunya vaccine in registration with regulatory authorities in the U.S. and Canada. There is also a Phase III VLP vaccine composed of the E1, E2, and capsid proteins of the CHIKV (strain 37997).

Nipah vaccine pipeline (Vaccine types: mRNA)

There is a Phase I mRNA Nipah vaccine encoding a secreted prefusion F protein linked to G monomer of Malaysian strain NiV.

Rabies (Vaccine types: mRNA)

There is an mRNA-based vaccine encoding the rabies virus glycoprotein RABV-G currently in an open-label, dose-escalation Phase 1.

Equine Encephalitis Virus (EEV) vaccine pipeline (Vaccine types: recombinant virus, non-replicating)

A recombinant MVA-BN vector expressing antigens from all three equine encephalitis viruses: western, eastern and Venezuelan is in Phase I.

Lassa vaccine pipeline (Vaccine types: recombinant virus, replicating)

A replicating recombinant vesicular stomatitis virus (VSV) expressing the Lassa virus surface glycoprotein is in Phase I.

Coxsackie vaccine pipeline (Vaccine types: inactivated)

There is one "polyvalent" vaccine for Hand, Foot, Mouth Disease (caused by Coxsackie virus infection) in Phase I. There is also a combination vaccine discussed below that covers coxsackievirus A16 (CVA16) and enterovirus 71 (EV71).

Yellow Fever (YF) vaccine pipeline (Vaccine types: inactivated virus)

There is a serum-free Vero (African green monkey kidney) cell derived yellow fever vaccine in Phase II. This is differentiated from the approved yellow fever viral vaccine which is propagated in chicken eggs.

West Nile Virus (WNV) vaccine pipeline (Vaccine type: peptide)

There is only one clinical-stage vaccine for West Nile Virus. This Phase I vaccine is composed of four salivary peptides isolated from mosquito *Anopheles gambiae* salivary glands.

Vaccine Clinical Pipeline for Bacterial Pathogens

For the company-sponsored clinical pipeline for bacterial vaccines summarized in **Figure 6,** there are 44 clinical-stage programs in total with more than half of those for *Streptococcus pneumoniae* (14 programs), *Shigella* (5), tuberculosis (4), and *Meningococcus* (3). In terms of phases there are 12 in Phase I, 20 in Phase II, 11 in phase III, and only one under BLA review. The majority (80%) of the bacterial vaccines are protein or protein carbohydrate conjugates.

***Streptococcus pneumoniae* (pneumococcal disease) vaccine pipeline** (Vaccine types: inactivated bacteria; protein; carbohydrate-protein conjugate)

Of the targeted bacterial pathogens, *Streptococcus pneumoniae* (pneumococcus) has the most clinical-stage programs in development. Six of those are in Phase I, five are in Phase II, and three are in Phase III. (The pipeline for *Streptococcus agalactiae*, or group B streptococcus, is discussed separately in a later section).

For the early-stage pneumococcal vaccine candidates (Phase I or II), there is one bacterial vaccine, two protein-based and seven protein-conjugate vaccines. The bacterial vaccine uses an engineered pneumococcal strain lacking capsular polysaccharides and inactivated using gamma irradiation. This inactivation method has the advantage of maintaining the structures of the surface protein antigens. One protein-based vaccine candidate is serotype independent, offering an advantage over other serotype specific vaccines as there are more than 100 serotypes. Other early-stage candidates are carbohydrate-protein conjugate vaccines and include vaccines developed mostly outside the U.S. and contain different valences (13, 15, 24, and 25) and different serotypes. Two candidates stand out from the others from a technological standpoint. One utilizes non-native amino acids as conjugation anchors for precise conjugation of saccharides to carrier proteins. The other conjugation technique uses biotin-labeled polysaccharides that bind avidin-like proteins fused to antigen proteins.

For late-stage vaccines (Phase III or BLA), the 21-valent carbohydrate-protein conjugate vaccine uses conjugation with CRM197, but with polysaccharides not included in any currently licensed pneumococcal vaccines, (15A, 15C, 16F, 23A, 23B, 24F, 31, and 35B).[12] Another vaccine in Phase III utilizes two carrier proteins instead of one (CRM197 and tetanus toxoid), which may offer advantages over using a single carrier protein.

Tuberculosis (TB) vaccine pipeline (Vaccine types: live attenuated bacteria; protein)

There are four candidate vaccines in clinical development for TB. Three of these are protein based and one is a live attenuated bacteria vaccine. The protein vaccines for TB include: 1) a Phase I fusion protein of four Mb antigens (Rv2608, Rv3619, Rv3620, and Rv1813), 2) a Phase II fusion protein of three Mb antigens (85B, ESAT-6 and Rv2660c), and 3) a Phase II made of individual Mb proteins 85B, ESAT6.

The live attenuated vaccine is in Phase III. It is similar to the BCG vaccine described previously but uses an engineered Mb mycobacteria with deletions of two virulence factors genes.

Meningococcal vaccine pipeline (Vaccine types: carbohydrate-protein conjugate)

There are three novel meningococcal carbohydrate-protein conjugate vaccines in the pipeline. Two of them are pentavalent vaccines with one containing the A, C, Y, W-135, X antigens and the other A, B, C, Y, and W antigens, in Phase II and III. A third is in Phase II with an undisclosed number of component antigens.

***Clostridium difficile* (C. diff) vaccine pipeline** (Vaccine types: live attenuated bacteria; protein)

There are two *Clostridium* vaccines in clinical development. One is a protein vaccine in Phase I with very little specifics disclosed beyond that it is adjuvanted. The other is a Phase III live attenuated *Clostridium difficile* bacteria with deletions of toxin genes tcdA and tcdB.

***E. coli* vaccine pipeline** (Vaccine types: inactivated bacteria; carbohydrate-protein conjugate)

There are two vaccines in clinical development for *E. coli*. One vaccine, in Phase II, contains four inactivated *E. coli* strains over-expressing CFA/I, CS3, CS5 or CS6. In addition, it contains a fusion protein of enterotoxin B subunit (LTB) and CTB-subunit, and a dmLT adjuvant. In Phase III is a 9-valent carbohydrate-protein conjugate vaccine for ExPEC (Extraintestinal Pathogenic *Escherichia Coli*).

***Salmonella* vaccine pipeline** (Vaccine types: protein-VLP; carbohydrate-protein conjugate)

There are two clinical-stage vaccine candidates for *Salmonella*. One is in Phase I and contains outer membrane vesicle (OMV) antigens for both *S. typhimurium* and *S. enteritidis.* The other is a carbohydrate-protein conjugate vaccine in Phase II.

***Shigella* vaccine pipeline** (Vaccine types: carbohydrate-protein conjugate)

Many recent vaccine programs for *Shigella* have been suspended recently. This is in part due to the fact that there are four species and many serotypes of *Shigella*.[13]

COMPANY-SPONSORED GLOBAL CLINICAL PIPELINE FOR BACTERIAL VACCINES

Bacterial vaccines	Phase I	Phase II	Phase III	BLA	Total
Streptococcus pneumoniae	6	5	3	0	**14**
TB	1	2	1	0	**4**
Meningococcus	0	2	1	0	**3**
Shigella	1	3	1	0	**5**
E. coli	0	1	1	0	**2**
Clostridium difficile	1	0	1	0	**2**
Group B Streptococcus	0	2	0	0	**2**
Salmonella	1	1	0	0	**2**
Bacterial - Urinary	0	0	0	1	**1**
Cholera	0	0	1	0	**1**
Staphylococcus	0	0	1	0	**1**
Lyme (Borrelia)	0	0	1	0	**1**
Plague (Yersenia)	0	1	0	0	**1**
Anthrax	0	1	0	0	**1**
Pertussis	0	1	0	0	**1**
Gonorrhea (Neisseria)	0	1	0	0	**1**
Klebsiella pneumoniae	1	0	0	0	**1**
Chlamydia	1	0	0	0	**1**
Total	**12**	**20**	**11**	**1**	**44**

Bacterial vaccines	Protein	protein VLP	car-bohy-drate-protein	bacteria (attenu-ated)	bacteria (inacti-vated)	Total
Streptococcus pneumoniae	2	0	11	0	1	**14**
TB	3	0	0	1	0	**4**
Meningococcus	0	0	3	0	0	**3**
Shigella	0	0	4	1	0	**5**
E. coli	0	0	1	0	1	**2**
Clostridium difficile	1	0	0	1	0	**2**
Group B Streptococcus	1	0	1	0	0	**2**
Salmonella	1	0	1	0	0	**2**
Bacterial - Urinary	0	0	0	0	1	**1**
Cholera	0	0	0	0	1	**1**
Staphylococcus	1	0	0	0	0	**1**
Lyme (Borrelia)	1	0	0	0	0	**1**
Plague (Yersenia)	1	0	0	0	0	**1**
Anthrax	1	0	0	0	0	**1**
Pertussis	0	0	0	1	0	**1**
Gonorrhea (Neisseria)	0	1	0	0	0	**1**
Klebsiella pneumoniae	0	0	1	0	0	**1**
Chlamydia	1	0	0	0	0	**1**
Total	**13**	**1**	**22**	**4**	**4**	**44**

Figure 6. The company-sponsored global clinical pipeline for novel bacterial vaccines.
Top: pathogen targets and phase of program. Bottom: pathogen targets and modality of vaccine.

There are five clinical-stage vaccine candidates for *Shigella*. One is a Phase I genetically modified non-invasive *Shigella* strain that lacks the bacterial surface coat comprised of dominant sugar antigens. Three others are in Phase II, one being a carbohydrate-protein conjugate *for Shigella dysenteriae*, another a carbohydrate-protein conjugate for *Shigella flexneri* 2a, and the third a quadrivalent carbohydrate-protein of four undisclosed *Shigella* bacterial strains. Lastly, there is a Phase III carbohydrate-protein conjugate candidate for both *Shigella flexneri* and *Shigella sonnei*.

Group B *Streptococcus* vaccine pipeline (Vaccine types: carbohydrate-protein conjugate)

Unlike the large clinical pipeline for *S. pneumoniae*, *S. agalactiae* (Group B *Streptococcus*) has only two novel vaccine candidates. One is a fusion protein vaccine in Phase II consisting of AlpCN-RibN and Alp1N-Alp2/3N. The other is a hexavalent carbohydrate-protein conjugate in Phase II.

Anthrax vaccine pipeline (Vaccine type: protein)

Aside from new adjuvants for existing vaccines, there is only one clinical candidate for Anthrax. This Phase II candidate is a protein vaccine with purified protective antigen recombinantly produced in *Bacillus brevis*. As described above, the approved BioThrax® (Anthrax Vaccine Adsorbed) contains cell-free filtrate (which contain PA and other proteins) from *Bacillus anthracis*.

Pertussis vaccine pipeline (Vaccine type: live-attenuated bacteria)

There is one vaccine candidate in human trials for protection against *B. pertussis* infection. It is a live-attenuated bacterial vaccine in Phase II.

Cholera vaccine pipeline (Vaccine type: inactivated bacteria)

There is one vaccine candidate in human trials for protection against *Vibrio cholerae* infection. This Phase III vaccine is an inactivated bacteria expressing approximately 50% each of Ogawa and Inaba O1 LPS antigens.

Bacterial – Urinary vaccine pipeline (Vaccine type: inactivated bacteria)

A combination product for urinary bacterial infection is being developed outside the U.S. and has completed Phase III trials. It is composed of four inactivated bacteria strains: *Escherichia coli; Klebsiella pneumoniae; Proteus vulgaris; and Enterococcus faecalis*.

Gonorrhea (*Neisseria*) vaccine pipeline (Vaccine type: protein-VLP)

One protein vaccine, derived from the outer membrane vesicles of *Neisseria*, is in Phase I for Gonorrhea.

***Chlamydia* vaccine pipeline** (Vaccine type: protein)

There is one vaccine candidate in Phase I for *Chlamydia* that uses a recombinantly expressed CTH522 protein subunit as antigen.

***Staphylococcus* vaccine pipeline** (Vaccine type: protein)

There is one protein-based *Staphylococcus aureus* vaccine being developed. This Phase III candidate contains five Staph proteins purified from *E. coli*.[14]

Plague (*Yersinia*) vaccine pipeline (Vaccine type: protein)

A fusion protein, *Yersinia* F1-V, is in Phase II studies for protection against Plague.

Lyme Disease vaccine pipeline (Vaccine type: protein)

The single clinical-stage Lyme diseases vaccine is a protein-based vaccine in Phase III. The withdrawn marketed vaccine for Lyme (LYMERix®), mentioned previously in **Figure 2**, was also a purified OspA protein vaccine. The main difference is that the new candidate is multivalent targeting six serotypes of *Borrelia*.[15]

Vaccine Clinical Pipeline for DNA Virus Pathogens

There are 34 novel vaccine programs for the prevention of diseases from DNA viruses. As shown in **Figure 7**, 14 of these are in Phase I, 14 are in Phase II, and six in Phase III. Currently, there are no licensing applications under review. Of the seven DNA virus pathogen indications listed in **Figure 7**, only two (HPV and CMV) have Phase III programs. More than half of all programs are for HPV and Varicella (chickenpox), for which there is prior approval precedent.

More than half of the vaccines for DNA viruses are protein-based vaccines. All DNA viral pathogen indications listed in **Figure 7, apart from** EBV, have at least one protein program. HPV has four VLP protein programs in clinical development, whereas the other protein programs utilize purified protein alone.

COMPANY-SPONSORED GLOBAL CLINICAL PIPELINE FOR DNA VIRUS VACCINES

DNA virus vaccines	Phase I	Phase II	Phase III	BLA	Total
Human Papillomavirus	3	4	5	0	**12**
Varicella-Zoster (Chickenpox)	5	3	0	0	**8**
Hepatitis B (HBV)	1	4	0	0	**5**
Cytomegalovirus (CMV)	0	3	1	0	**4**
Herpes Simplex Virus (HSV)	2	0	0	0	**2**
Herpes-Zoster (Shingles)	2	0	0	0	**2**
Epstein-Barr Virus (EBV)	1	0	0	0	**1**
Total	**14**	**14**	**6**	**0**	**34**

DNA virus vaccines	Protein	protein VLP	peptide	mRNA	Viral (attenuated)	rViral (non-replicating)	DNA	Total
Human Papillomavirus	6	4	0	0		1	1	**12**
Varicella-Zoster (Chickenpox)	5			2	1			**8**
Hepatitis B (HBV)	1		1			3	0	**5**
Cytomegalovirus (CMV)	1			1		2		**4**
Herpes Simplex Virus (HSV)	1			1				**2**
Herpes-Zoster (Shingles)	1					1		**2**
Epstein-Barr Virus (EBV)				1				**1**
Total	**15**	**4**	**1**	**5**	**1**	**7**	**1**	**34**

Figure 7. The company-sponsored global clinical pipeline for novel DNA virus vaccines. Top: pathogen targets and phase of program. Bottom: pathogen targets and modality of vaccine.

HPV (Human Papillomavirus) vaccine pipeline (Vaccine type: protein; protein-VLP; DNA; non-replicating viral vector)

There are 12 HPV vaccines in clinical development, five of which are in Phase III studies. All but two are protein-based.

The five HPV vaccines in Phase III are protein-based: One trivalent, three 9-valent, and one 11-valent. One of the 9-valent vaccines uses VLP for antigen display.

In Phase II for HPV there are two protein vaccines and two non-protein vaccines. The protein vaccines are 14-valent and 9-valent. One of the non-protein vaccines uses electroporated DNA to deliver E6 and E7 antigen genes (covering HPV types 16 and 18). The second non-protein vaccine in Phase II is a recombinant viral vector vaccine. It uses a two dose, two vector approach: ChAdOx vector and a second dose using MVA, both engineered with HPV antigen.

Phase I vaccines for HPV are all protein-based. Two are protein-VLP based vaccines in Phase I that use *H. polymorpha*, a methylotrophic yeast species to produce the antigens, unlike the approved protein antigen in Gardasil® which is made using *Saccharomyces cerevisiae*. Other differences are the number of HPV strains added to the vaccine (in this case Type 16 and 18, and Type 6 and 11 for the other). Lastly, there is a Phase I quadrivalent HPV vaccine.

Varicella (Chickenpox) vaccine pipeline (Vaccine type: protein; live attenuated virus, mRNA)

There are eight next generation chickenpox vaccines in the pipeline, all in early-stage human trials. Seven of these (two mRNA, five protein-based) are differentiated from the current marketed chickenpox vaccines which are live attenuated vaccines. There is one new live attenuated vaccine candidate with a new strain of Varicella Zoster.

Hepatitis B vaccine pipeline (Vaccine type: protein; peptide; non-replicating viral vector)

The next-generation Hepatitis B vaccine pipeline includes three viral vector and two protein vaccines. A Phase I viral vector program contains lenti-HBV viral vector with HBV surface antigen (sAg). A prime boost hybrid vaccine is in Phase II with the following components: 1) ChAd155 vector with aAg, modified polymerase and core antigens, 2) MVA vector with similar antigens. The second viral vector vaccine in Phase II is a triple component vaccine with the following components: 1) ChAd155-hIi-HBV vector with truncated HBV core antigen (cAg) and full-length small HBV surface antigen (S-sAg), 2) MVA vector encoding cAg and S-sAg, and 3) the cAg and S-sAg proteins themselves with AS01B-4 adjuvant.[16]

The next-generation protein vaccine in Phase II is a fusion of HBV PreS L-sAg and peptides derived from the grass pollen allergen, Phlp5. And lastly, there is a Phase II peptide vaccine that consists of nine peptides from highly conserved regions of three different HBV antigens (pol, core, and s) common to the majority of genotypes.

Cytomegalovirus (CMV) vaccine pipeline (Vaccine type: protein; non-replicating viral vector)

Four CMV vaccine candidates are in clinical development. Two of these are recombinant viral vector platforms (both in Phase II), one mRNA (Phase III), and one protein (Phase I/II). The most advanced candidate is the mRNA vaccine containing mRNA for six CMV proteins (gH, gL, UL128, UL130, UL131A, and gB). One Phase II viral vector program uses two replication-deficient lymphocytic choriomeningitis virus vectors, one expressing CMV pp65 and one expressing a truncated CMV gB protein. The other Phase II viral vector program uses modified vaccinia Ankara (MVA) to express three CMV antigens (pp65, UL122, and UL123).

Herpes Simplex Virus (HSV-2) vaccine pipeline (Vaccine type: protein; mRNA)

There are two Phase I programs for HSV-2 infection and genital herpes. One is an mRNA vaccine with three HSV-2 glycoprotein mRNAs, and the other is a protein vaccine.

Herpes Zoster (Shingles) vaccine pipeline (Vaccine type: protein; non-replicating viral vector)

There are two Phase I next-generation vaccines for Herpes Zoster (Shingles). One is a protein vaccine containing VZV glycoprotein E (gE), and the other is recombinant vector ChAdOx1 gE.

Epstein-Barr virus (EBV) vaccine pipeline (Vaccine type: mRNA)

A single Phase I program exists for Epstein-Barr virus (EBV). It contains five mRNAs that encode EBV membrane-bound proteins (gp350, gB, gp42, gH and gL).

Vaccine Clinical Pipeline for Parasitic Pathogens

There are two pathogens being targeted in the clinic pipeline for parasites: malaria and schistosomiasis. All of the eight novel candidate vaccines are in early-stage development (**Figure 8)**. There is a wide range of modalities being pursued including protein, protein-VLP, peptide, mRNA, and whole parasite.

Malaria vaccine pipeline (Vaccine type: protein, protein-VLP, peptide, mRNA, attenuated and whole parasite)

The Malaria vaccine clinical pipeline contains six company-sponsored products, three in Phase I and three in Phase II.[17]

Two of six Malaria vaccines use live *Plasmodium falciparum* parasites in the vaccine. One uses non-attenuated PfSPZ, allowing the parasites to multiply briefly and co-administrating with antimalarial drug to kill the parasite, and the other uses an attenuated strain of PfSPZ.

Three of the six Malaria vaccines are protein or peptide based. The two protein-VLP vaccines use Pf circumsporozoite surface protein (CSP), with one expressing it as a fusion with hepatitis B sAg (from the yeast *Hansenula polymorpha*) and the other using alphavirus proteins to create the VLP for CSP display. The third protein-based vaccine uses the same fusion construct but uses a purified protein (from *E. coli*). The peptide vaccine is composed of four salivary peptides isolated from *Anopheles gambiae* salivary glands.

An mRNA vaccine encoding *Plasmodium falciparum* circumsporozoite protein is in Phase I.

Schistosomiasis vaccine pipeline (Vaccine type: protein)

There are two protein-based clinical programs for schistosomiasis, one in Phase I and one in Phase II. The recombinantly-produced p80 protein is in Phase I. A TSP-2 protein expressed using *Pichia* yeast is in Phase II.

COMPANY-SPONSORED GLOBAL CLINICAL PIPELINE FOR PARASITIC VACCINES

Parasitic vaccines	Phase I	Phase II	Phase III	BLA	Total
Malaria	3	3	0	0	**6**
Schistosomiasis	1	1	0	0	**2**
Total	**4**	**4**	**0**	**0**	**8**

Parasitic vaccines	Protein	protein VLP	peptide	mRNA	cell	Total
Malaria	0	2	1	1	2	**6**
Schistosomiasis	2	0	0	0	0	**2**
Total	**2**	**2**	**1**	**1**	**2**	**8**

Figure 8. The company-sponsored global clinical pipeline for novel parasitic vaccines. Top: pathogen targets and phase of program. Bottom: pathogen target and modality of vaccine.

Vaccine Clinical Pipeline for Novel Combinations

There are ten novel combination vaccines in the clinical pipeline. All programs are early-stage, and the majority are mRNA-based as shown in **Figure 9**. These novel combination vaccines target seven pathogens (five viral pathogens: SARS-CoV2, influenza, RSV (Respiratory Syncytial Virus), MPV (Metapneumovirus), PIV3 (Parainfluenza Virus Type 3), enterovirus, and coxsackievirus and two bacterial pathogens: *Shigella* and *E. coli*).

Combination vaccines for SARS-CoV-2 + Influenza (Vaccine types: protein; mRNA)

A protein vaccine combining spike from SARS-CoV-2 and HA from influenza in a VLP structure is in Phase II. There are also two vaccines combining mRNA of similar antigens (spike and HA), one in Phase II and the other Phase I.

Combination vaccine for RSV + Influenza (Vaccine type: mRNA)

There is one Phase I program with a combination mRNA vaccine for RSV (mRNA coding for prefusion F protein) and the influenza (mRNA coding for HA).

Combination vaccine for RSV + Influenza + SARS-CoV-2 (Vaccine type: mRNA)

In April 2023, a Phase I trial completed enrollment for a triple pathogen mRNA vaccine (RSV + Influenza + SARS-CoV-2).[18]

Combination vaccine for RSV + MPV (Vaccine types: protein; mRNA)

There are two combination vaccines for RSV and MPV (metapneumovirus), one protein-based and the other mRNA-based. Both are in Phase I and utilize the F surface protein as antigen.

Combination vaccine for MPV + PIV3 (Vaccine types: mRNA)

There is a Phase I program with an investigational MPV (Metapneumovirus) and PIV3 (Parainfluenza Virus Type 3) mRNA vaccine. The mRNA codes for the F surface protein for each of the two viruses.

Combination vaccine for *Shigella* + *E. coli* (Vaccine types: attenuated bacteria)

A live attenuated combination vaccine is in Phase I for *Shigella* and enteric *E. coli*. The vaccine is an engineered *Shigella* bacteria with deletions of surface O-antigen components of LPS (exposing more conserved epitopes and thus serotype-independent), and additions of ETEC antigen genes (expressing LTB and a mutated ST).

Combination vaccine for EV71 + CVA16 (Vaccine type: inactivated viral)

A combination vaccine for enterovirus 71 (EV71) and coxsackievirus A16 (CVA16) is in Phase I.

COMPANY-SPONSORED GLOBAL CLINICAL PIPELINE FOR NOVEL COMBINATION VACCINES

Muliple Pathogens	Phase I	Phase II	Phase III	BLA	Total
COMBO: COVID + Flu	1	2	0	0	**3**
COMBO: RSV + MPV	2	0	0	0	**2**
COMBO: COVID + Flu + RSV	1	0	0	0	**1**
COMBO: RSV + Flu	1	0	0	0	**1**
COMBO: MPV + PIV3	1	0	0	0	**1**
COMBO: EV + CV	1	0	0	0	**1**
COMBO: Shigella + E. coli	1	0	0	0	**1**
Total	**8**	**2**	**0**	**0**	**10**

Muliple Pathogens	Protein	protein VLP	mRNA	Viral (inacti-vated)	bacteria (recom-binant)	Total
COMBO: COVID + Flu	1	0	2	0	0	**3**
COMBO: RSV + MPV	0	1	1	0	0	**2**
COMBO: COVID + Flu + RSV	0	0	1	0	0	**1**
COMBO: RSV + Flu	0	0	1	0	0	**1**
COMBO: MPV + PIV3	0	0	1	0	0	**1**
COMBO: EV + CV	0	0	0	1	0	**1**
COMBO: Shigella + E. coli	0	0	0	0	1	**1**
Total	**1**	**1**	**6**	**1**	**1**	**10**

Figure 9. The company-sponsored global clinical pipeline for novel combination vaccines. Top: pathogen targets and phase of program. Bottom: pathogen targets and modality of vaccine.

Clinical Development Success Rates for Vaccines

As shown in **Figure 10**, infectious disease vaccines have an above average success rate when compared to novel biologics and novel small molecule drugs. The success rate for all novel drugs, across all diseases, is 6.5% for the period 2013-2022. For novel biologics (ex-vaccines) the likelihood of approval (LOA) from phase I is 7.9%. For novel small molecules, the LOA is only 5.6%. The higher 11.0% LOA for vaccines can be attributed to higher success rates in Phase II and Phase III as well as more successful BLA filings.

Although vaccine success rates for BLA filings for approval are higher than non-vaccines, the number of filings is much lower (38 for vaccines vs. 341 for biologics and 466 for small molecule drugs)

CLINICAL DEVELOPMENT SUCCESS RATES FOR VACCINES

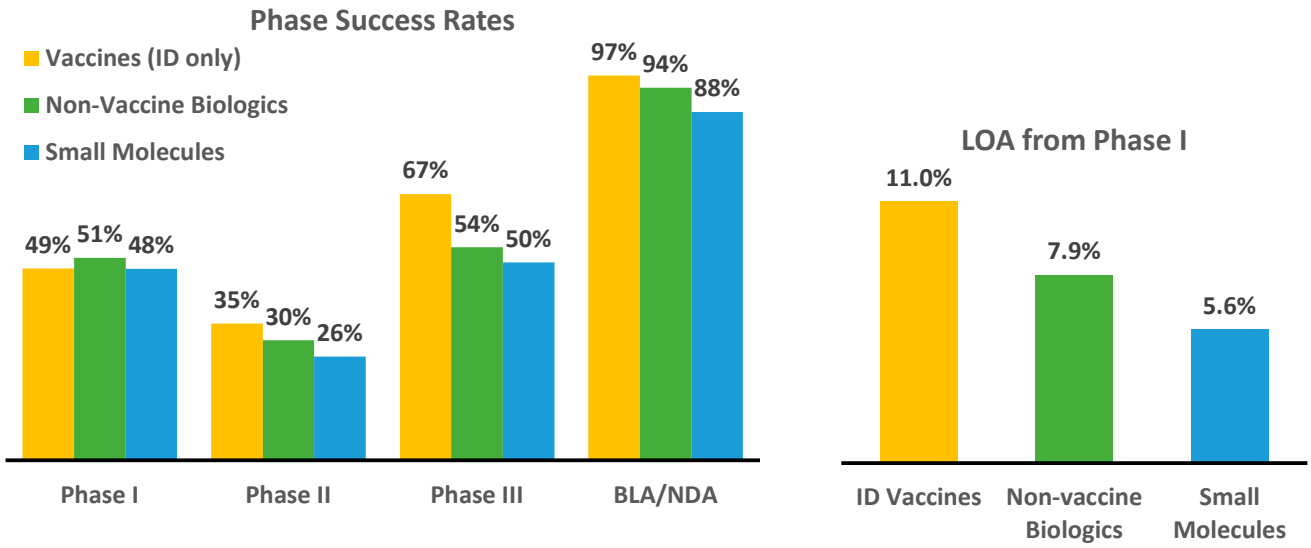


Figure 10. Clinical success rates for vaccine drug programs for infectious disease. Left: Phase success rates for the period 2013-2022. Right: Likelihood of Approval from Phase I to Approval, vaccines vs. all NMEs across all disease areas. Total NME/BLA transitions for 2013-2022: N=324 for vaccine, N=4,633 for biologics, and N=6,048 for small molecules. Data was collected from Citeline's Pharmapremia database.

Investment Trends for Vaccine Companies

Venture capital investment into companies with lead products of infectious disease vaccines from 2013 to 2022 totaled $2.2 billion in the U.S. and $6.5 billion worldwide.[19] This represents 3.4% of total worldwide venture capital raised for biopharmaceutical companies during the same period. By contrast, oncology drug development companies raised $72.6 billion worldwide over the last decade, 12-fold more than investment in vaccines. The peak year for both types of companies was during the COVID-19 pandemic in 2021, with oncology companies raising $17.9 billion and vaccine companies raising $2.4 billion (Figure 11). Between 2020 and 2022 there were fourteen transactions for vaccine companies that exceeded $100 million totaling $3.2 billion compared to two transactions between 2013-2019 equaling $0.6 billion. This large increase of mega-transactions is likely motivated by the COVID-19 pandemic. The top five largest transactions, which range from $200 to $700 million and totaling $2.3 billion, are all associated with companies that developed COVID-19 vaccines.

Between 2013 and 2022, an average of 16 companies with lead products of infectious disease vaccines were financed each year. By comparison, during the same period there was an average of 207 oncology companies financed each year. Breaking the decade into 5-year increments, 63 vaccine companies received investments between 2013-2018 versus 83 between 2019-2022. In 2022, the largest number of companies was financed at 22, closely followed by 2021 with 21. In 2018, there were only eight venture transactions.

Vaccine-focused emerging companies raised a total of $8.7 billion over the last decade through public share offerings (IPOs and follow-on offerings).[20] This compares to $90.7 billion for oncology-focused companies.[21] Roughly 70% of all public emerging company funding for vaccine companies over the past decade came during the COVID-19 pandemic (2020-2022) ($6 billion of $8.7 billion).

GLOBAL VENTURE INVESTMENT INTO COMPANIES 2013-2022 WITH LEAD VACCINE PROGRAMS

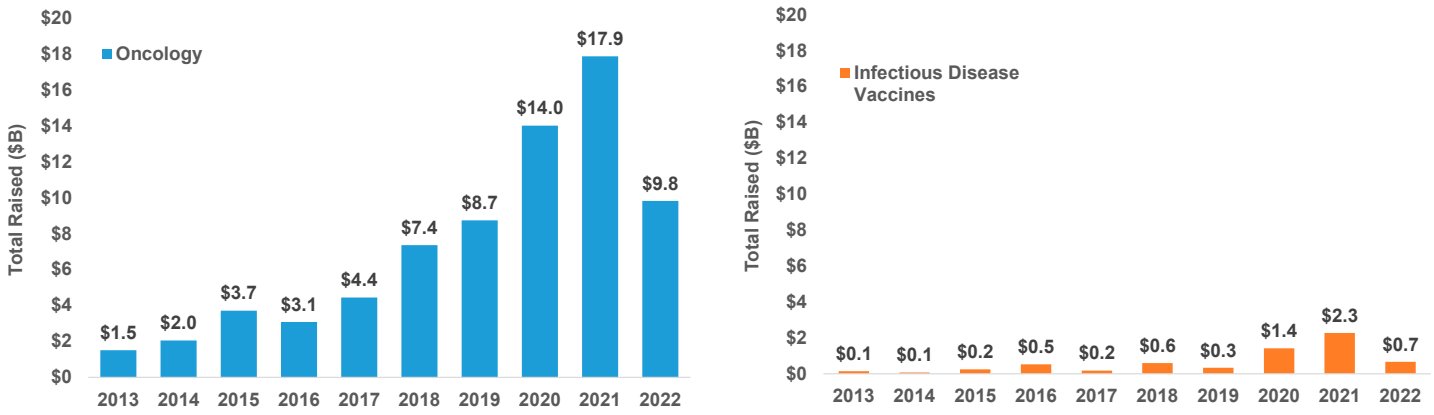


Figure 11. Left: Venture funding of companies with lead products in oncology, 2013-2022. Right: Venture funding of companies with lead products in ID vaccines, 2013-2022.

Part 2. Prophylactic Antibodies

History of Prophylactic Antibodies

Blood serum with anti-toxoid antibodies for tetanus and diphtheria was first used to combat infectious disease in the 1890s. These early blood-derived antibodies were from infected horses, not of high purity, and had protective efficacy for only a few weeks. Contamination and unforeseen side effects in early use of these antibodies eventually led to vaccines being the preferred prophylactic intervention for tetanus and diphtheria. For other infectious diseases there was substantial progress in the development of serum-derived antibodies in the 1890s and by the late 1900s the first monoclonal antibodies were approved for prophylaxis. Today, there are prophylactic serum-derived antibodies available for use in rabies and CMV and monoclonal therapies for RSV, anthrax, and COVID-19.

Appendix II provides a more detailed description of all previously approved prophylactic antibodies.

TIMELINE OF APPROVED PROPHYLACTIC ANTIBODIES

Decade of 1st License or Usage	#	Disease	Pathogen Name	Pathogen Type
1890s	1	Rabies	*Rabies lyssavirus*	RNA virus
1990s	2	CMV disease	*Cytomegalovirus*	DNA virus
	3	RSV	*Respiratory syncytial virus*	RNA virus
2010s	4	C. diff infection	*Clostridioides difficile*	bacteria
	5	AIDS	*Human immunodeficency virus*	DNA virus
	6	Anthrax	*Bacillus anthracis*	bacteria
2020s	7	Covid-19	*SARS-Cov2*	RNA virus

Figure 12. History of prophylactic antibodies listed by date introduced and pathogen name and type.

Clinical Pipeline for Prophylactic Antibodies

There are 17 antibodies in clinical development that have disclosed development programs for prophylactic use against infectious diseases. The majority of the programs (76%) target RNA viruses, and no programs cover DNA viruses nor parasitic infections.

Prophylactic Antibodies for SARS-CoV-2

There are more than 60 antibodies in clinical development for COVID-19, many of which are for pan-coronavirus infection or new variants. However, most of these are antiviral treatments, not prophylactic therapies. We identified four clinical-stage antibodies in development with the stated goal of prophylaxis.

HIV

There are two mAbs for HIV in Phase II. One is a tri-specific antibody specifically for the T-cell CD4 site of envelope glycoprotein gp120, the V1/V2 region of gp120, and gp41. The second Phase II program is testing an anti-gp120 mAb that binds the V3 glycan region specifically and is being tested in combination with other mAbs.

Influenza

There is a single quadrivalent pandemic and seasonal influenza antibody in Phase II. It is a fully human polyclonal antibody against four strains of the influenza virus including both type A and B infections.

Staphylococcus

There are two mAbs for *Staphylococcus*, one in Phase II and one in Phase III. The Phase III mAb is a human IgG1 that binds *S. aureus* alpha-toxin. The Phase II mAb targets bacterial surface polysaccharide, poly-N-acetylglucosamine.

RSV

There is one Phase III RSV antibody in the pipeline. As with the recently approved Beyfortus™ (nirsevimab), this candidate antibody also binds to the pre-fusion conformation of F protein.

Tetanus

There is one Phase II antibody for tetanus that binds the tetanus toxoid**.**

Ebola

Although treatment antibodies have been approved, no prophylactic antibodies have been approved. Two post-exposure antibodies were FDA approved in 2020: Ansuvimab (Ebanga ™) and the triple antibody cocktail of atoltivimab, maftivimab and odesivimab (Inmazeb™). These antibodies target the EBOV trimeric glycoprotein. There is one double antibody cocktail in development. Both antibodies in the cocktail were derived from a patient during the 2013-2016 Ebola outbreak in Africa.

Community-acquired bacterial pneumonia (CAP)

There is a bacterial biofilm disrupting monoclonal antibody in Phase I for community-acquired bacterial pneumonia. A wide range of bacteria can cause CAP, such as *Streptococcus pneumoniae, Haemophilus influenzae, Moraxella catarrhalis, Staphylococcus aureus, Group A Streptococci, Legionella, Mycoplasma, Chlamydia pneumoniae, and C. psittaci*.

Chikungunya

There is one fully human mAb in Phase I for chikungunya infection. It is derived from a patient infected with the chikungunya virus.

Zika

The Phase I antibody product for Zika is a purified gamma IgG fraction of human plasma containing polyclonal antibodies reactive to Zika.

Marburg

A human antibody derived from a survivor of Marburg is in Phase I. This is a potential pan-Marburg virus prophylactic remedy.

COMPANY-SPONSORED GLOBAL PROPHYLACTIC ANTIBODY CLINICAL PIPELINE

Pathogen Type	Phase I	Phase II	Phase III	BLA	Total
RNA virus	6	3	3	0	**12**
Bacteria	1	2	1	0	**4**
DNA viruses	0	0	0	0	**0**
Parasites	0	0	0	0	**0**
Total	**7**	**5**	**4**	**0**	**16**

Pathogen	Phase I	Phase II	Phase III	BLA	Total
SARS-CoV-2	1	1	2	0	**4**
HIV	2	0	0	0	**2**
Influenza - Seasonal	0	1	0	0	**1**
Staphylococcus	0	1	1	0	**2**
RSV	0	0	1	0	**1**
Tetanus	0	1	0	0	**1**
Rabies	0	1	0	0	**1**
CAP	1	0	0	0	**1**
Chikungunya	1	0	0	0	**1**
Zika	1	0	0	0	**1**
Marburg	1	0	0	0	**1**
Total	**7**	**5**	**4**	**0**	**16**

Figure 13. The company-sponsored global prophylactic antibody pipeline. Top: pathogen type and phase of program. Bottom: pathogen target and phase.

Discussion

Vaccine R&D Pipeline in the Context of Vaccine Markets

The clinical pipeline for infectious disease vaccines across the global biopharma industry consists of 249 company-sponsored novel clinical-stage programs. On the surface, this sounds like a significant number of vaccines; however, "infectious disease" is not a single threat, rather it comprises many highly differentiated threats. Unlike oncology, where one drug might work on multiple cancer types, one vaccine will likely only work for a single pathogen. Further, 28% of the total programs (n=69) are for vaccines against SARS-CoV-2. The remaining vaccine programs are spread across 46 different pathogens, many with only one vaccine in clinical development (e.g., Epstein-Barr virus, West Nile virus, chlamydia, gonorrhea, and Lyme disease) and there are many infections without a single vaccine program at the clinical development stage. Resistant bacterial pathogens, for example, are not well represented in the pipeline with only two of the six ESKAPE pathogens having ongoing vaccine programs.[22]

With the likelihood of FDA approval from Phase I calculated at 11%, this means that to statistically ensure approval of a vaccine for each pathogen, 10 programs must enter clinical development. For many infectious diseases, particularly low incidence and tropical diseases that disproportionately affect low- and middle-income countries, there are far fewer than 10 developmental vaccine programs initiated in recent years, signaling that more investment and innovation is needed. Currently, only 10% of the infectious disease threats pursued in the vaccine pipeline have 10 or more ongoing programs, and only 20% have five or more. The lack of breadth may, at least partially, be due to the unique market issues surrounding vaccines.

In comparison to antibiotics, vaccines face a very different type of marketplace. For many vaccine categories there is a relatively clear set of possible populations that would be appropriate for immunization. These populations might be very targeted – occupational risk, travel, specific underlying health risks or conditions – while others may be broader groups, such as all infants or all adults over age 65. However, other vaccines face unique market challenges. For example, vaccines targeting pandemic pathogens face an uncertain future market. For investors and developers, this uncertainty limits the number of vaccines in development that could be leveraged for pandemic preparedness.

Prior to reaching the market, vaccines also endure a hurdle that is not present for antibiotics and other drugs – government advisory recommendations for use. For vaccines, approval by the regulatory authorities is only the first step to their utilization. Once approved, vaccines are evaluated for specific recommendations by National Immunization Technical Advisory Groups (NITAGs) that define where each vaccine will have the most public health, societal and individual benefit. For example, in the U.S., the CDC's Advisory Committee on Immunization Practices (ACIP) conducts these evaluations, advises the Director of the CDC on vaccine recommendations, and creates the nation's immunization schedules. This process is vital to defining the actual market for a vaccine and, in many countries, guides clinician decision-making, leads to mandatory coverage in both public and private insurance programs, and ultimately drives access for patients. Because of this important two-step process (approval and recommendation), innovation in vaccines is partly driven by vaccine developers' and investors' confidence and understanding of how a novel vaccine might be recommended by these Advisors.

Once these recommendations are in place other key areas also contribute to market adoption. National infrastructure that provides and facilitates access to vaccines across many different types of providers, rapid coverage implementation by insurance programs, and clear messages that build vaccine confidence among the public all impact the market for vaccines.

Historically, investment into infectious disease vaccine companies has been a small percent of the total emerging biopharmaceutical funding. For example, only 3.4% of total venture capital raised for biopharmaceutical companies during the last 10 years went to companies with infectious disease vaccine programs. That includes the peak funding years during the COVID-19 pandemic. By contrast, oncology drug development companies receive 38% of venture capital and 12-fold more dollars than vaccine companies.

Although more investment is needed to cover future and emerging pandemic threats, as well as regional and tropical infections, much has been achieved through innovations in vaccine science. The recent approvals of the first RSV vaccines are just one example. COVID-19 gave us a new benchmark for how vaccines can be developed using new molecular technology, quickly translated into clinical studies and move through the development, approval and manufacturing processes. In the last few years, achievements have also been made with Ebola and malaria vaccines. Given recent approvals, there are currently vaccines approved for 34 unique pathogens. Furthermore, recent licensed vaccines utilize a wide range of modalities: direct antigen delivery *(e.g.*, protein, carbohydrate, pathogen inactivation and pathogen attenuation) and indirect antigen delivery (*e.g.*, mRNA and viral vector-based vaccines). There are now 53 RNA-based and 11 DNA-based vaccines in the clinic, 27 recombinant viral vector-based vaccines and 65% of the protein-based vaccines now use virus-like particles (VLPs) that more efficiently display epitopes to immune cells. Furthermore, innovation in the vaccine space over the last decade has had above average clinical success rate for approval from Phase I, 11% for vaccines compared to only 5.6% for novel small molecules.

There is also progress being made with prophylactic antibodies. Although the clinical pipeline for prophylactic antibodies is small relative to vaccines, with only 16 in clinical-stage development, the antibody pipeline targets 11 different pathogens. With historic precedent and recent successes, such as the RSV monoclonal antibody approval this year, the sector could grow beyond the current seven prophylactic antibody approvals for viral and bacterial pathogens.[23]

Development of vaccines is often cited as one of the greatest public health successes of the 20th century. Infectious diseases, such as smallpox and measles, were once great causes of morbidity and mortality worldwide. As an example, decades of broad immunization against measles led to a 99% reduction in related complications like encephalitis and death when compared to the pre-vaccine era.[24] We now have a comprehensive routine childhood vaccine schedule as well as a schedule for adult immunizations in the U.S. that provide protection against 20 pathogens. Most of the current vaccines on the market prevent infectious diseases with well-established incidences of disease in children, adolescents and adults. This makes their potential market and utilization more predictable for vaccine developers and their investors. Vaccinations across people's life span offers many direct and indirect benefits to individuals, communities, society and the economy. Childhood immunization has had the largest impact to date. A CDC analysis of childhood vaccination showed that U.S. children born between 1994 and 2018 who were fully vaccinated would benefit from the prevention of 419 million illnesses, 26.8 million hospitalizations and 936,000 deaths. These reductions save an estimated $406 billion in direct healthcare costs and nearly $1.9 trillion in total societal costs. The high levels of vaccination in children demonstrated benefits for the overall U.S. population, preventing more than 24 million illnesses spanning all ages and decreasing hospitalizations related to multiple different infectious diseases.

Solutions to Strengthen Innovation

BIO posits there are four main policy areas that can help stimulate innovation, increase investment, and close gaps in remaining unmet medical need for vaccines which, if unresolved will result in continued underfunded levels of investment in vaccine development. With the policy areas discussed below, we believe there is a way to make vaccines a more predictable venture, spurring innovation and investment and curing or protecting the world from diseases that debilitate (acutely or chronically) or shorten life spans.

1. Evolve ACIP Processes

The first policy area that will have a vital effect on vaccine innovation is the NITAG recommendation process. In particular, the CDC's ACIP evaluation and recommendations fundamentally shape one of the largest vaccine markets in the world. As we look across the vaccine pipeline, we must understand the impact an ACIP (and other global NITAGs) recommendation will have in defining the potential market size and patient utilization for every vaccine currently in development. Clarifying what data can lead to the most impactful recommendation for each type of vaccine-preventable disease will increase the predictability and confidence in terms of product characteristics and forecasted market size. Many novel vaccines will focus on providing protection to eligible subpopulations at risk, for example prevention of pre-operative bacterial infections in persons at risk of recurrent antimicrobial infections. These vaccines are designed to reduce the infectious disease burden in a target group rather than the entire population.

ACIP proved during the pandemic that it could appropriately evaluate data in a timely fashion to ensure access, as well ass communicate to clinicians critical data. While the urgency of a pandemic is now in the rear view mirror, there are best practices from the pandemic that should be maintained. Indeed, the CDC has taken steps to formalize some of those processes For example, the CDC now stipulates that ACIP recommendations are considered final upon CDC Director adoption. This is a critical signal to payers that coverage of these products is effective. At the same time, the CDC is taking steps to post clinical guidelines faster, through new ACIP updates, rather than waiting for publication in the MMWR. This is also a promising development in ensuring that novel products reach patients faster. However, it is critical that this new process is sustained for all products.

Creating an environment where novel vaccine candidates can be reviewed and recommended is a vital part of stimulating innovative vaccine development. To do this, the ACIP process must adapt to the changing development landscape. The CDC can help create an environment that encourages innovation by implementing some new approaches to the review process.

- The CDC should add more expertise in sub-populations such as geriatrics and complex chronic diseases to the voting committee. The addition of such experts will provide important medical perspective on how infectious diseases affect key individuals and populations of interest.
- CDC staff should increase their understanding of the vaccine pipeline and the new technologies being deployed by industry. Deepening CDC's awareness of the vaccine pipeline will allow them to better plan reviews, resource review committees appropriately and provide valuable guidance to industry related to the types of data needed for clear recommendations.

- CDC should create an infrastructure within the ACIP process that evaluates issues important for the evaluation of *all* vaccines. These topics might include guidelines on best approaches for health economics analysis, especially for more niche vaccines, or shared evaluations of vaccines using platform technologies, or guidance for working groups and industry on the data required for preferential recommendations.

Changes such as these will provide more clarity for vaccine developers on the ACIP processes thereby providing clear recommendations for new vaccines. Vaccine developers and their investors would then be more likely to pursue vaccines for more narrow populations or unique infectious diseases. In addition, refinment of this process may serve as indicator for other NITAGs around the world. Adding more predictability to the recommendation process for new categories of vaccines can increase the likelihood of successful access, uptake and use in many countries.

BIO has been working with leaders and stakeholders to continue to strengthen the ACIP recommendation process and to consider what factors for recommendations will be important for evaluation as the vaccine pipeline becomes more diverse and impacts more sub-populations.

2. Access to Vaccines

Continued increases in vaccination across the life span could prevent even more illness, hospitalization and death while saving healthcare expenditures.

Of course, the reductions in disease and the economic benefits can only be maximized if immunization rates are high for children, adolescents, pregnant people, adults and seniors. One of the most important policy areas relates to increasing access to vaccines across the life span of every person. Over the last few years significant gains have been made related to access to vaccines for adults. The Affordable Care Act (ACA) of 2010 contained provisions that require ACIP-recommended vaccines be made available in most private insurance plans and Medicaid expansion populations with no cost-sharing ($0 out-of-pocket patient cost). Passage of the Protecting Seniors Through Immunization Act and the Helping Adults Protect Immunity (HAPI) Act, both passed as part of the Inflation Reduction Act of 2022, helped provide this same important benefit for seniors with Medicare Part D plans and Medicaid adults not covered through the ACA. These legislative changes mean that approximately 9 of every 10 Americans now have access to vaccines in private and public insurance programs with no out-of-pocket costs for the individual. But work still needs to be done on the access front so that all Americans, especially uninsured adults between 19 and 64 years old, can access vaccines with no out-of-pocket cost. Given the broad benefits of primary prevention to individuals and society, especially for persons with underlying chronic conditions, facilitating access to immunizations through both financial policies and policies that increase the types of vaccinators (for example pharmacists) will have a significant impact on overall healthcare outcomes and costs. So, while progress on financial and access pressures are improving there is still more work to be done to remove all barriers to equitable access to these preventative interventions.

BIO continues to work closely with stakeholders to put forward both legislative and regulatory solutions that will reduce both financial and physical barriers to immunizations for everyone.

One important policy area focuses on policy solutions that increase the reimbursement for vaccine providers across public and private insurance programs. Some solutions focus on broadening the types of medical professionals that can administer vaccines, from nurse practitioners to pharmacists. Lastly, BIO is evaluating policy solutions that increase funding and authorities that allow state and federal programs to purchase vaccines for uninsured adults. The goal is to ensure those who desire vaccines can receive them with no or very low out-of-pocket cost at the immunization site best suited to them.

3. Platform Technologies

The advances made before and especially during the COVID-19 pandemic offer an opportunity to increase investment in new technologies that can conquer infectious diseases that have been scientifically challenging, like HIV and malaria. These new platform technologies can speed development of novel approaches to improve efficacy and/or safety in areas where there are already vaccines. They also offer important advantages as we prepare for the next infectious disease outbreak or pandemic as they could facilitate investment in R&D across viral families – pan coronaviruses, filoviruses, orthopox viruses, etc. – so that we can pivot from a vaccine developed for commercial purposes to quickly develop and use a vaccine platform for another pathogen in that same family. Although records were broken with COVID-19, this may not be the case in the next pandemic. Early preparation, better cataloging and understanding of the characterization of viral families, advanced approaches using new biotechnological platforms, and more funding of translational research will be required.

Recent U.S. legislation created a formal "Platform Technology Designation" program at the FDA. BIO and its members have advocated for broad interpretation and implementation of the program to be forward thinking and allow for the greatest impact on the development of vaccines in and outside public health emergency situations. BIO has also strongly supported legislative efforts to fund a pandemic development program that would leverage platform technologies to do R&D on vaccines for viral families that include pathogens of pandemic potential.

4. Rebuilding Vaccine Confidence Worldwide

Innovations in vaccine development and successful vaccine candidates are only worthwhile if the population is willing to receive vaccines. In 2018, 13.5 million children across the globe were not vaccinated.[25] The COVID-19 pandemic had a negative impact on routine immunization for children, adolescents and adults worldwide, due to missed or delayed health services, and school and facility closures.. In addition to vaccine access (the ability for individuals to get vaccines if they wish), vaccine acceptance (the willingness to take a vaccine) is crucial. Improving vaccine confidence requires a coordinated effort of clear communication, from trusted community and public health messengers, describing the benefits and risks to people that is supported by thorough data collection and analyses. In recent years, there have been increases in vaccine hesitancy – seen most glaringly through the COVID-19 pandemic – that threaten the important advances in disease burden and reduction due to vaccines and future vaccine candidates. Combatting vaccine misinformation and disinformation and bolstering vaccine confidence is crucial to realizing the broadest benefits of vaccines and a stronger vaccine infrastructure overall. Efforts for effective communication on who needs a vaccine, when, and why they are important, should be prioritized to ensure that the vaccines we currently have available reach individuals, and an environment exists for strong investment in future vaccine development.

As more vaccines are approved for adult populations, efforts to strengthen vaccine confidence are of particular importance. Historically, adults have had lower vaccination rates than children in the U.S., likely due, in part, to inconsistent and unclear messaging and lack of a published adult vaccination schedule by the CDC. Partnerships between community- based organizations, governments, medical leaders, policymakers, industry and non-governmental groups have proven track records in providing and arming communities with vaccine knowledge. Empowering individuals and families with scientifically valid information they can trust is key to ensuring both individuals/families and governments are making the best decisions for themselves and their communities. These partnerships need to proliferate and be coordinated if we want to see a meaningful increase in the acceptance and uptake of vaccines.

We must enact policies and support community engagement and educational activities that will help prevent and/or mitigate the life-altering consequences of pathogens discussed in the paper and the unknown threats on the horizon. BIO has and continues to support community-based organizations in their educational efforts.

Conclusion

The Biotechnology Innovation Organization (BIO) and member companies view innovation as the key to combating current and future threats in infectious disease. Small emerging biotechnology companies are developing 62% of the vaccines and prophylactic antibodies described in this report. Maintaining this trend where from entrepreneurs and early-stage investors are willing to take on substantial risks, will require continued funding for basic and translational research, a health care system that values solutions to potential threats, and a policy environment that incentivizes innovation.

Appendix I – Approved Vaccines

Smallpox Vaccines (Pathogen type: DNA Virus. Vaccine type: live attenuated)

The earliest mass vaccinations for smallpox trace back to the early 1800s. However, these smallpox vaccines were not purified, nor derived from a single source. For 130 years, different crude extracts from blister pus were used around the world in arm-to-arm transfer.[26] These vaccines likely included cowpox, horsepox, or polyclonal variants of similar viruses.[27] The heterogeneity and sourcing of these vaccines, while efficacious, raised safety concerns in multiple countries. In the U.S., it was not until 1931 that the FDA licensed a single pooled strain of "vaccinia" virus for the smallpox vaccine (Dryvax®). Other countries had different pools of vaccinia virus, some more pathogenic than others. We now know through sequencing historic samples that these pooled poxviruses used for mass vaccination were closer to horsepox than the cowpox strains used in the original Edward Jenner clinical experiments dating back to 1796.

Production of the vaccines at scale in the early 1900s was carried out by growing the virus on the skin of calves, which risked contamination. By the 1940s, vaccinia virus vaccine could be grown in eggs for more control over contamination. However, it was not until 2007, that a single, purified isolate of the vaccinia virus, ACAM2000™, received an FDA license.[28] This vaccine is produced in Vero cells, a commonly used cell line derived from an African green monkey kidney in 1962.[29]

Other versions of the smallpox vaccine are based on lab generated mutations of vaccinia strains using serial passaging, the process of growing a pathogen in cells or whole animal in iterations. In the 1960s, the Modified Vaccinia Ankara (MVA) mutant poxvirus was developed by German researchers after serial passaging Turkish vaccinia strains in chicken embryo cells. This MVA strain had the advantage of being *non-replicating* due to attenuating DNA mutations and was used successfully in the 1970s vaccination campaign in Germany.[30] Around the same time, a *replicating* attenuated strain of vaccinia was developed and manufactured by Kaketsuken in Japan.[31] A further passaged clonal strain of MVA, known as MVA-BN (used in Jynneos®, Imvanex®, and Imvamune®) was approved in Europe in 2013 and in the U.S. in 2019.[32] MVA-BN is non-replicating and manufactured using chicken embryo cells.

In **Figure 2** the smallpox vaccine type is categorized under live attenuated vaccine type. All of the smallpox vaccine examples above, whether replicating or non-replicating, lab attenuated or naturally attenuated (by using a cowpox or horsepox relatives), fall into the live viral category. The main differences throughout the history of smallpox vaccination are the purity of the virus, the move from polyclonal to clonal, and the degree of attenuation.

Rabies Vaccines (Pathogen type: RNA Virus. Vaccine type: attenuated, inactivated)

Louis Pasteur is credited with developing an "attenuated" rabies virus in 1885 through the method of serial passaging in rabbits. For this rabies vaccine, he extracted suspensions of infected rabbit spinal cord tissue and inactivated them by air drying and later via chemicals.[33] Due to longer onset of the viral disease, post-exposure vaccination was possible for rabies. Improved versions of the original method, such as modifying the inactivation process, allowed for use in large populations in the early 1910s.

In the mid-20th century, production techniques moved from rabbit nerve tissue to chicken eggs, and later to human diploid cells in the 1970s. Various methods of viral inactivation or production evolved during this time such as the use of B-propiolactone, adsorption to aluminum phosphate, and the use of duck embryo cells (Lyssavac N®). By the 1980s, continuous Vero (African green monkey kidney) cell lines were used.[34] This version is known as the Purified Vero Cell Rabies Vaccine (PVRV) due to the required DNA removal step from the Vero cells. It is used primarily outside the U.S. under trade names such as Verorab®, Imovax® – Rabies vero®.

Currently licensed vaccines in the U.S. use attenuated, inactivated vaccine types: RabAvert®, grown in primary cultures of chicken fibroblasts, and Imovax®, made using human lung fibroblast diploid cells.[35]

Cholera Vaccine (Pathogen type: bacteria. Vaccine type: live attenuated whole cell; [inactivated])

The earliest cholera vaccines for prevention of the disease caused by the bacterium *Vibrio cholerae* date back to the late 1800s. These were inactivated whole cell vaccines used only in limited populations as they were reactogenic and had limited efficacy. Broader vaccination only came a century later with the advent of second-generation vaccines that utilized modern cloning techniques. Starting in the 1990s, efficacious oral cholera vaccines were licensed. The first was a monovalent, killed whole-cell bacteria (O1 serogroup) mixed with cholera toxin B subunits (Dukoral™). The toxin B subunits (called CTB or rBS) are made recombinantly in a strain of *Vibrio cholerae* that lacks the gene for subunit A (both subunits are required to form the toxin).[36] The second widely used cholera vaccine is a bivalent vaccine using the O1 and O139 serogroups, both with deleted CTB genes (Shanchol™/Euvichol™). Although the toxin gene deletion had been used in the Vietnamese mORC-Vax™ vaccine, the Shanchol™/ Euvichol™ vaccine is prepared in a new way. Two of the original O1 strains (with CTB gene deletions) are grown and killed by heat, which allows lipopolysaccharides (LPS) to develop at higher levels. Separately, a O139 strain, one additional O1 strain, and the two

classical O1 strains are each inactivated using formalin and added to the final product.[37]

A live, attenuated cholera vaccine was also developed. This vaccine was licensed around the world as Orochol®, and later as VAXCHORA® in the U.S. This live bacteria vaccine is the first and only cholera vaccine approved in the U.S. (2016). Unlike the majority of attenuated viral vaccines, the live attenuated cholera vaccine was not created by serial passage. The attenuation was designed using genetic engineering by deleting the catalytic domain of cholera toxin. Selective targeting of the deletion allows the non-toxic subunit of CTB to remain available for immunogenic response.[38]

Tuberculosis Vaccines (Pathogen type: mycobacteria. Vaccine type: live attenuated cell)

The attenuated *Mycobacterium tuberculosis* cell has been used as an oral tuberculosis (TB) vaccine since the early 1920s. However, this BCG vaccine (named after Calmette-Guerin who attenuated the original Bacilli strain) had many twists and turns in its history before, and even after its administration to more than 4 billion individuals worldwide.[39] Widespread vaccination outside the U.S. did not occur until the 1950s. Prior to that, results from clinical studies in different regions showed conflicting efficacy data. This is in part due to different regions having various levels of background mycobacteria exposure in their respective environments, thus casting doubt on the control group's naïve immunity. Furthermore, as seen with early smallpox vaccination campaigns, different strains of *Mycobacterium tuberculosis* were being used in different regions of the world (in the 1920s-1960s, there was not a method technologically capable of differentiating bacterial strains).

Eventually, single strains of *Mycobacterium tuberculosis* were used in the attenuated vaccines. The BCG vaccine licensed in the U.S. uses the TICE strain developed at the University of Illinois. Outside the U.S. various strains are used, such as the Danish, Japanese, Bulgarian, and Indian strains, each with varying immunogenic properties in lab studies.[40]

Diphtheria Vaccines (Pathogen type: bacteria. Vaccine type: protein subunit)

Vaccines for *Corynebacterium diphtheriae* bacterial infection (diphtheria) use the secreted toxin (capable of shutting down human cell translation) as the antigenic component.[41] A diphtheria anti-toxoid serum was first used to combat the bacterial disease in the 1890s and included a mixture of antibodies and other blood components derived from infected horses. This mixture was inconsistently produced and of low purity. As a result, contamination and unforeseen side effects were discovered creating a need for a vaccine alternative.[42] In the early 1900s, the diphtheria toxoid itself was isolated as a toxin-antitoxin (TAT) mixture and used as a vaccine. Later versions of the vaccine, some that remain in use today, include mutated variants of the diphtheria toxin alone. The common production method involves growing *Corynebacterium diphtheriae* in cow extracts, detoxification with formaldehyde, followed by purification using ammonium sulfate fractionation, dialysis or column chromatography and finally adsorption onto aluminum phosphate.[43]

Today, the diphtheria vaccine is only available in combination products in the U.S. and most other countries. The combinations have expanded to include up to six components, including acellular Pertussis (aP), haemophilus influenza type B (Hib), hepatitis B (HepB), tetanus (T). For example, it is in combinations such as the bivalent (DT), trivalent (DTaP), quadrivalent (DTaP + Hib or DTaP+ HepB), pentavalent (DTaP+Polio + Hib or DTaP + Polio+ HepB), or hexavalent (DTaP + Polio + Hib + HepB) combinations as well as the quadrivalent adult formulation TdaP. Name brand vaccines in the United States include Daptacel®, Infanrix®, Kinrix™, Pediarix®, Pentacel®, Quadracel®, and Vaxelis®.[44]

Yellow Fever Vaccines (Pathogen type: RNA virus. Vaccine type: live attenuated)

A live attenuated vaccine against yellow fever (YF) was deployed for broad use in the 1930s. The original vaccine was made via serial passaging in chicken and mouse tissue to attenuate the YF RNA virus. The 17D strain had the added advantage of not mutating as rapidly as its ancestral strains, allowing for more homogeneity once replicating in vivo. There are now three substrains of 17D manufactured in various parts of the world (known as 17DD, 17D-213, and 17D-204.[45] The currently licensed yellow fever vaccine for the U.S. is YF-VAX®, a 17D-204 strain grown in chicken embryos and purified by centrifugation.[46]

Pertussis vaccines (Pathogen type: bacteria. Vaccine type: protein; [inactivated])

A vaccine against the bacterium *Bordetella pertussis* (the causative pathogen of whooping cough) was developed in the 1920s-1930s and approved for broad use in the 1940s. The original vaccine used inactivated whole cell *pertussis* bacteria (wP) as the inoculant and quickly became part of the combination vaccine product, DTwP (diphtheria, tetanus, and whole cell pertussis). Decades later, in the 1990s, acellular forms of the pertussis vaccine were used broadly as companies discontinued the whole cell formulations. These acellular pertussis (aP) vaccines are multivalent and combine multiple proteins of the bacterium *Bordetella pertussis*, such as the large pertussis toxin (PT), Filamentous Hemagglutinin (FHA), Pertactin (PRN), and Fimbriae (FIM). The aP vaccine was combined with

diphtheria and tetanus comprising the DTaP vaccines used today, such as Adacel® and Boostrix® in the U.S.[47]

Tetanus Vaccines (Pathogen type: bacteria. Vaccine type: protein)

The *Clostridium tetani* bacteria secretes a toxoid protein that infiltrates motor neurons causing the disease known as tetanus, commonly referred to as lockjaw. As was the case with *Corynebacterium diphtheriae* described, the original vaccine was comprised of this toxoid protein itself. It was developed in the 1920s and used broadly in the 1940s. This highly efficacious version remains the only tetanus vaccine today. It is produced as a monovalent form, but more commonly in combination with other vaccines. For example, bivalent (DT), trivalent (DTaP), quadrivalent (DTaP + Hib or DTaP+ HepB), pentavalent (DTaP+Polio + Hib or DTaP + Polio+ HepB), and even hexavalent (DTaP + Polio + Hib + HepB).

A common production method for the tetanus toxoid protein vaccine involves growing *Clostridium tetani* in cow extracts, detoxification with formaldehyde, followed by purification using ammonium sulfate fractionation, dialysis or column chromatography and finally adsorption onto aluminum phosphate.[48]

Polio Vaccines (Pathogen type: RNA virus. Vaccine type: inactivated)

The first inactivated polio virus (IPV) vaccine was developed and approved in the 1950s. However, production issues for inactivating the polio virus were discovered in the early launch of these products and other vaccine approaches were developed.[49]

In 1961, a live-attenuated oral vaccine for polio (OPV) was approved for use.[50] The attenuated viral strains were developed in the 1940s via serial passage, first in cell cultures then in rats and mice.[51] Production, like IPV described above, is done with attenuated virus particles purified; however, without the inactivation step. Due to it being a live virus, the vaccine could be given orally, including on sugar cubes for children. This oral polio vaccine has not been used in the U.S. since 2000.

In the 1980s, scientists discovered that purification of the polio virus before inactivation with formaldehyde was more efficient, and the addition of various purification techniques could enhance potency. An enhanced inactivated polio vaccine (eIPV) was approved in the U.S. in 1987.[52]

In the U.S., there is one licensed inactivated trivalent polio vaccine that is not combined with DTaP: IPOL®, type 1,2,3 polioviruses grown in Vero (African green monkey kidney) cells. A previously approved inactivated viral vaccine made from human diploid cells (Poliovax®) has been discontinued. The trivalent approach has been the standard since the 1960s. Other polio vaccines are in the four combinations with DTaP described above, either with or without rHepB or HIB, or both.[53] Similar products are manufactured outside the U.S. by 15 companies.[54]

Measles vaccines (Pathogen type: RNA virus. Vaccine types: live attenuated; [inactivated virus])

Two types of viral vaccines for measles were approved in the early 1960s, one inactivated and the other a live attenuated viral vaccine. The inactivated form was withdrawn from the market due to low efficacy compared with the live attenuated vaccine. The live attenuated vaccine was created through serial passaging measles virus in chicken embryo tissue culture, and later chicken embryo fibroblasts.[55] Historically, multiple attenuated strains derived from a single seed virus (Edmonston and Schwarz strains) were tested in Europe and the U.S. until an improved less virulent version was identified in 1968 (Edmonston-Enders strain). In Asia, attenuated measles virus from different seed isolates have been used (e.g., Leningrad 4 and 16 in Russia, Shanghai-190 in China, and CAM-70 in Japan).[56] These live strains are manufactured using chicken embryos and standard viral purification.

In 1971, the live attenuated measles vaccine was combined with mumps and rubella vaccines, creating a trivalent MMR vaccine (examples in the U.S. today are PRIORIX® and M-M-R II®). More recently, the varicella vaccine was combined with MMR, creating the quadrivalent MMRV (live ProQuad® in the U.S.).[57]

Mumps Vaccines (Pathogen type: RNA virus. Vaccine type: live attenuated, [inactivated])

As was the case with measles, the original mumps vaccine contained an inactivated virus (approved in 1948); however, was discontinued as more effective versions were developed.[58] A superior mumps vaccine was licensed in 1967 in the U.S. The improved vaccine contains a live attenuated virus (Jeril Lynn strain), created by serial passaging in chicken eggs and chicken embryo cell cultures.[59] This live attenuated vaccine has been part of the MMR vaccine since 1971 and the monovalent vaccine is no longer in production. Outside the U.S., several different strains have been developed using similar methods and used for broad vaccination (e.g., Leningrad-3 in Russia, Rubini strain in Switzerland, Urabe in Japan, L-Zagreb in India).[60]

Rubella Vaccines (Pathogen type: RNA virus. Vaccine type: live attenuated)

Unlike measles and mumps, early development attempts at inactivated rubella viral vaccines were unsuccessful and never licensed for use.[61] The first rubella vaccine, which contained a live attenuated virus, was licensed in 1969. The original strain was created by serial passaging the rubella virus in vervet monkey kidney cells and duck embryo fibroblasts.[62] This strain

(HPV77, DE5) and another similar (Cendehill) were used until 1979 when a newer strain was developed (RA27/3, isolated from a human fetus kidney and serially passaged in lung fibroblast cells). Outside the U.S., Japan and China each developed their own attenuated strains of the rubella virus for inclusion into regional vaccines in the 1970s.[63]

In 1971, a combined measles, mumps, and rubella (MMR) vaccine was licensed for use in the United States. In 2005, a combination measles, mumps, rubella, and varicella (MMRV) vaccine was licensed.[64]

Varicella Zoster and Herpes Zoster Vaccines (Pathogen type: DNA virus. Vaccine type: live attenuated; protein VLP)

Although varicella zoster (chickenpox) and herpes zoster (shingles) are caused by the same virus, differences in vaccination are required. Primary infection with varicella-zoster virus (human herpesvirus 3, HHV-3), often in young children, causes varicella (often referred to as "Chickenpox"). Herpes Zoster (often referred to as "Shingles") is caused by the reactivation of the same varicella-zoster virus and is differentiated by the latency period in the central nervous system (CNS) and reactivation in adults, as well its common complication of postherpetic neuralgia (PHN). The herpes zoster (shingles) vaccines are given only to adults, whereas the varicella (chickenpox) vaccines are primarily given to children.

The original varicella-zoster live attenuated virus vaccine (Varivax®) was FDA approved in the 1990s for chickenpox. Other monovalent versions today are also live attenuated vaccines and based on the Oka strain (VARILRIX™, Okavax™). Combination vaccines containing the varicella strains include ProQuad™ (approved by FDA in 2005) and Priorix Tetra™ (approved outside the U.S., beginning with Australia in 2005). Four different Oka varicella vaccines are used in China.[65] There is also a monovalent MVA/06 strain developed in the 1990s in South Korea (Suduvax®).[66]

The herpes zoster (shingles) vaccine Shingrix™ was licensed in 2017 in the U.S. and globally thereafter. It is the only shingles vaccine for U.S. adults, as Zostavax™ was removed in 2020.[67] Shingrix™ is a protein VLP that incorporates a truncated, soluble form of surface glycoprotein E (gE) into liposomes. The liposomes are composed of dioleoyl phosphatidylcholine (DOPC) and cholesterol which mimic some of the lipid characteristics of cell and viral membranes. A lipid-based adjuvant (AS01B) containing monophosphoryl lipid A (MPL) and saponin is also included. The antigenic protein (gE) is produced recombinantly in Chinese Hamster Ovary cells and purified before inclusion into the liposomes.[68]

Anthrax Vaccines (Pathogen type: bacteria. Vaccine Types: protein; live attenuated)

In the U.S., the anthrax vaccine adsorbed (AVA) was licensed in 1970 for the first time. For 30 years, this single attenuated strain of *B. anthracis* was used to prepare cell-free filtrate adsorbed onto aluminum hydroxide.[69] Its parental strain (Sterne 34F2), has been used globally for animal livestock vaccination since the 1930s, and for a U.K. vaccine manufactured using similar techniques.[70] The vaccine's final filtrate contains three toxin components: protective antigen (PA, the most significant antigen for immune response), lethal factor, and edema-forming protein. In the U.S. today, BioThrax®, based on these original methods and formulated with aluminum and formaldehyde, remains the only licensed vaccine for anthrax exposure.[71] Prior to this, the Russians used an unrelated strain to make a live attenuated anthrax vaccine, with and without the addition of protective antigen, PA.[72]

Adenovirus Vaccines (Pathogen type: DNA virus. Vaccine Types: live pathogen, inactivated)

The first adenovirus vaccine in the U.S. was an inactivated viral vaccine (a bivalent mix of Ad4 and Ad7) grown in monkey kidney cells and inactivated with formalin. This was used primarily for the military, but only for a few years in the early 1960s. Production of this inactivated vaccine was withdrawn due to mutations and contaminations during propagation.[73]

A live (non-attenuated) viral Ad4 vaccine was licensed in the 1970s. It was produced in human diploid fibroblast strains as the original kidney cells were not scalable. This was followed years later with an Ad7 live vaccine. Both vaccines are given simultaneously now in separate tablets to be swallowed.[74] Although this live pathogen method can induce a brief, local intestinal infection, it allows for a strong immune response that protects against future respiratory exposure.

Tick-borne Encephalitis (TBE) Vaccines (Pathogen type: RNA virus. Vaccine types: inactivated)

The first widely available TBE vaccine, FSME-IMMUN®, was licensed in Europe beginning in the 1970s. It is an inactivated viral vaccine made by propagating the Neudörfl TBE virus strain in chick embryo fibroblast cells, inactivated with formaldehyde, purified then adsorbed onto aluminum hydroxide. It only became licensed in the U.S. in 2021 as TICOVAC™. In 1991, Encepur® was licensed in Europe. Encepur® used a different strain but was produced using the same production, purification, and inactivation steps.[75]

Pneumococcal Vaccines (Pathogen type: bacteria. Vaccine types: saccharide, saccharide-protein conjugate)

There are currently four pneumococcal vaccines approved in the U.S. (PNEUMOVAX 23® (as of 1983), Prevnar 13® (2010), Prevnar 20® (2021), VAXNEUVANCE® (2021)).[76] The first pneumococcal vaccine contained purified capsular

polysaccharides from 23 individually grown serotypes of *Streptococcus pneumoniae* (serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F). The conjugate vaccines, Prevnar 13®, Prevnar 20®, and VAXNEUVANCE® (15 serotypes), are made by growing each bacterial serotype in soy broth, purifying the polysaccharides, converting to saccharides, then individually linking the saccharides to diphtheria CRM197 protein. Each saccharide-protein conjugate is then compounded to make the final mix of protein-carbohydrate antigens, and aluminum is added as an adjuvant.

Prior to these vaccines, Prevnar®, a 7-valent PCV, was licensed in 2000, but has since been replaced by the newer versions listed above. Outside the U.S., these and similarly produced vaccines are licensed (e.g., PCV-10 vaccines Synflorix™ and Pneumosil™).

Hepatitis B Vaccines (Pathogen type: DNA virus. Vaccine types: protein subunit)

Prior to the advent of recombinant vaccines, plasma derived hepatitis B vaccines were licensed in the early 1980s. These contained the small surface antigen, HBsAgS, purified from the plasma of chronic HBsAg carriers. By the late 1980s, two recombinant protein subunit vaccines were approved in the U.S. For these recombinant vaccines, the small HBsAg is expressed intracellularly in S. *cerevisiae* yeast, purified using standard protein purification techniques, then adsorbed onto aluminum. In 2017, a similar recombinant antigen product was licensed, but this time expressed in *Hansenula polymorpha* yeast and combined with a non-aluminum adjuvant. More recently, in 2021, a fourth recombinant hepatitis B vaccine gained FDA approval. This latest vaccine differs from prior vaccines in that it includes all three surface antigen forms (small, middle, and large). These proteins are expressed extracellularly in Chinese hamster ovary cells, purified from the supernatant, then adsorbed onto aluminum.

Outside the U.S., there are more than 30 individual hepatitis vaccines. Most of these are similar to those described above with some using different yeast strains (e.g., pichia), mammalian cell lines (e.g., mouse c127), or longer forms of the HBsAg (i.e., Middle or Large). The latter change is significant in that additional post translational modifications exist in those longer forms (such as glycosylation and myristylation). Additionally, some of the manufactures outside the U.S. use different viral subtypes. The *adw* subtype is used globally, while some ex-U.S. vaccines contain the *adr* or *ayw* antigen.[77]

In addition to the four licensed hep. B vaccines in the U.S., (Recombivax HB™, Engerix-B™, Heplisav-B™, and PreHevbrio™), hep B vaccines have also been combined with DTaP, as discussed above under the Diptheria vaccine description.

Haemophilus Influenza Type B (Hib) Vaccines (Pathogen type: bacteria. Vaccine type: saccharide-protein conjugate)

In the U.S. there are three monovalent vaccines for preventing Haemophilus Influenza Type B (Hib): PedvaxHIB®, ActHIB®, Hiberix®, which were approved in 1989, 1993, and 2009 respectively. PedavaxHib® is a carbohydrate-protein conjugate vaccine that covalently links capsular polysaccharide purified from the *Haemophilus* bacteria to an outer membrane protein complex (OMPC) purified from Neisseria meningitidis serogroup B (B11). ActHIB® and Hiberix™ are made by covalently linking the purified capsular polysaccharide to purified tetanus toxoid. Unlike PedvaxHIB®, ActHIB® and Hiberix™ do not contain aluminum in the final product. ActHIB® and Hiberix™ use different strains of Hib (1482 and 20,752 respectively).[78]

Additionally, there are combination vaccines that include Hib. In the U.S., there is a pentavalent vaccine (Pentacel®, FDA approved in 2008) and a hexavalent vaccine (Vaxelis™, FDA approved in 2018) combination vaccine given to children that contains the pentavalent antigens plus the hepatitis B antigen.[79]

Influenza (flu) Vaccines (Pathogen type: RNA virus. Vaccine types: inactivated; live-attenuated; protein)

Thirteen years after identifying the virus responsible for influenza in 1933, the first flu vaccine was licensed for civilian use in the U.S. This vaccine was a bivalent, inactivated viral vaccine that included Type A and Type B strains of influenza virus. It was made by growing both viral strains in embryonated chicken eggs, followed by isolation of the virus by red blood cell agglutination and centrifugation, then chemical inactivation using formaldehyde.

Starting in 1973, seasonal variants of Type A and Type B were incorporated into the inactivated flu vaccine, but in 1978, a second Type A strain was introduced making the annual flu vaccine trivalent.[80] Since 2012, quadrivalent vaccines, which include a second Type B strain in addition to the two Type A strains, have been used globally. The 2023-2024 Northern Hemisphere influenza vaccine formulation contains two Type A strains (H1N1 2019 variant and H3N2 2021 variant) and two Type B strains (2013 and 2021 regional variants).[81] Traditional egg propagation and inactivation methods can be found in marketed vaccines such as Afluria® Quadrivalent, Fluad® Quadrivalent and Fluzone® Quadrivalent.

Inactivated vaccines such as Flulaval®/Fluarix® Quadrivalent are inactivated using split technology. This splitting process uses detergent to break the virus (grown in eggs) into separate proteins, nucleic acids, and lipids, then removes the detergent from the final product. The inactivated vaccines have fewer adverse reactions as they are no longer intact virus particles.[82]

Inactivated flu vaccines can also be made using cell cultures instead of eggs, as of 2016. For example, Flucelvax® Quadrivalent uses mammalian cell lines to propagate seasonal viral strains. As of 2021 in the U.S., all four seed virus strains originate in mammalian cells and are delivered to manufacturers by the CDC.[83]

FDA approved a second influenza vaccine type – live attenuated – in 2003. Originally developed as a trivalent seasonal vaccine and the first flu vaccine delivered by intranasal mist, it is now sold in the quadrivalent formulation (FluMist® Quadravalent, Fluenz® Tetra). Outside the U.S., there are two additional live attenuated flu vaccines marketed.

A third type of flu vaccine is the purified protein subunit vaccine, approved for use in 2013 by the FDA. This was also originally trivalent but contained only the hemagglutinin (HA) proteins from each seasonal strain, recombinantly generated in insect cells and purified. A quadrivalent protein subunit formulation is now used broadly (Flublok® Quadrivalent).

The fourth type of influenza vaccine, marketed outside the U.S., is a virosomal vaccine which we categorize as protein-VLP. The Inflexal® V vaccine is propagated in chicken eggs, HA and neuraminidase proteins purified and combined with a liposome preparation. This creates a virus-like display of liposome embedded proteins, hence the protein-VLP categorization. Inflexal® V was first licensed in 1997.

Outside of seasonal flu vaccines, single strain vaccines have been produced for pandemics, such as the 2009 H1N1 swine flu pandemic. The pandemic influenza vaccines were developed leveraging all of the different technologies described above. Companies that develop seasonal flu vaccines often develop vaccines containing pandemic strains but reserve them in bulk in order to be prepared in case of a pandemic. This was done, for example for H5N9 and other pandemic strains.

Typhoid Fever Vaccines (Pathogen type: bacteria. Vaccine type: inactivated; attenuated; conjugate)

The original vaccine for the prevention of *Salmonella typhi* bacterial infection was a heat inactivated vaccine developed in the late 1800s. Inactivated vaccines for typhoid fever improved in the 1950s and have since been replaced with newer technologies.[84] In the U.S., there are two typhoid vaccine types: one is a purified polysaccharide antigen (Typhim Vi®) administered via injection (which is often referred to incorrectly as an "inactivated" vaccine),the other is a live, attenuated vaccine (Vivotif®), administered orally.[85] Outside the U.S., there are two injectable conjugate typhoid vaccines: Typbar-TCV®, which links the Vi polysaccharide antigen to tetanus toxoid protein, and the other, TYPHIBEV®, conjugates the saccharide to CRM197 protein.[86]

Japanese Encephalitis (JE) Vaccines (Pathogen type: RNA virus. Vaccine type: inactivated; live attenuated)

In 1954, Japan licensed the first JE vaccine, an inactivated viral vaccine using the Nakayama strain propagated in mouse-brains.[87] Cell-based production of JE vaccines eventually replaced animal produced vaccines. In 1968, China licensed a Beijing-3 strain manufactured in hamster kidney cells.[88] Later versions of inactivated JE vaccine were grown in Vero cells (derived from African Green Monkey kidney in 1962).

Currently, only one JE vaccine is licensed in the U.S. (Ixiaro®, 2009) and it is manufactured using Vero cells, inactivated with formaldehyde and adsorbed onto aluminum hydroxide.[89] Ixiaro® uses an attenuated strain (SA14-14-2) created in China by serial passaging the virus in hamster kidney cell cultures.

In 1988, the SA14-14-2 attenuated strain was licensed in China as a live viral vaccine. It was later licensed to other countries.[90] In 2010, a second live-attenuated vaccine, with very different properties, was licensed in Australia. Unlike the original SA14-14-2 attenuated vaccine, this latest JE vaccine, IMOJEV®, uses yellow fever virus as the backbone RNA virus into which are inserted the prM and E genes of SA14-14-2 JE vaccine. It is thus referred to as a recombinant chimeric live attenuated viral vaccine.

Hepatitis A Vaccines (Pathogen type: RNA virus. Vaccine type: inactivated; live attenuated)

In the 1990s, the U.S. FDA granted licenses for two inactivated viral vaccines for hepatitis A (Havrix™ and Vaqta®). For these vaccines, the virus is propagated in human diploid cells, purified, and inactivated with formalin. In 2001, a combination vaccine incorporating the Havrix™ hepatitis A components with inactivated hepatitis B vaccine was approved by the U.S. FDA (Twinrix®).[91]

Outside the U.S., a live attenuated vaccine is licensed throughout southeast Asia. The Chinese strains H2 and L-A-1 were derived from infected children and serial passaged in cells to achieve attenuation. It is manufactured using human diploid lung fibroblast cells.[92]

Additionally, there is a virosome vaccine marketed outside the U.S. (Epaxal®, approved in Europe in the mid-1990s).[93] The virosome vaccine differs from the inactive recombinant vaccines described above in that it encapsulates and embeds the antigen protein into liposomes. These are grouped as VLPs in **Figure 3**, as they are lipid/antigen nanoparticles roughly 150 nm in size that mimic the size and antigen presentation of the

hepatitis B virus). Due to its protection and stability in the lipids, the antigen protein can last longer in circulation.

Lyme Disease Vaccine (pathogen type: bacteria, Vaccine types: protein)

Although there are no Lyme vaccines available today, there was an FDA approved recombinant protein vaccine marketed from 1998-2001.[94] This vaccine, LYMErix™, is comprised of the outer surface A (OspA) lipoprotein from *Borrelia burgdorferi* expressed recombinantly in *E. coli*, purified, and adsorbed onto aluminum hydroxide.

Meningococcal Disease Vaccines (Pathogen type: bacteria. Vaccine types: carbohydrate-protein conjugate; saccharide)

The first meningococcal saccharide-protein conjugate vaccine (or "glyco-conjugate" for short), Menactra®, was licensed in the U.S. in 2005. Glyco-conjugate vaccines have antigenic sugars (saccharides) bound to a protein substrate to help elicit a strong immune response. Menactra® is made using the polysaccharides from *Neisseria meningitidis* Groups A, C, Y and W-135 conjugated to *Corynebacterium diphtheriae* Toxoid (DT). Another glyco-conjugate vaccine, Menveo®, was licensed in 2010 and is fused to the non-toxic *Corynebacterium diphtheriae* CRM197 protein. In 2020, MenQuadfi® was approved in the U.S. It is similar to the above but conjugated to tetanus toxoid (TT).[95]

There are currently two recombinant protein vaccines approved in the U.S. that target meningococcal serogroup B. Bexsero® contains adhesin A (NadA), heparin binding antigen (NHBA), and factor H binding protein (fHbp) with outer membrane vesicles (OMV) and aluminum.[96] Vaccines based on OMVs were developed more than 20 years ago against *Neisseria meningitidis* serogroup B and have been used with some success to control outbreaks of disease caused by serogroup B meningococci.[97] The second protein vaccine, Trumenba®, contains two lipidated factor H binding proteins (fHbp from subfamily A and B) produced in *E. coli*, purified and combined with aluminum in the final product.[98]

Prior to these five meningococcal vaccines, there was a polysaccharide-only vaccine (MPSV4) licensed in the U.S. in 1978. However, this vaccine is no longer available in the U.S.

Outside the U.S. multiple meningococcal vaccines are available, such as MenAfriVac® (for serogroup A), and Nimenrix (for serogroups A, C, W, Y).

Rotaviral enteritis Vaccines (Pathogen type: DNA virus. Vaccine type: live attenuated)

A live attenuated tetravalent vaccine (RotaShield™) was approved in 1998 but side effects forced it off the market after one year. It used an attenuated rhesus monkey rotavirus backbone with engineered/inserted human genes (for G1, G3, G4).[99] Attenuation of the rhesus monkey rotavirus was gained by passaging in monkey kidney cells then in monkey lung fibroblast diploid cells.[100]

In the 2000s, live attenuated rotavirus vaccines were approved and licensed worldwide. Both RotaTeq® and Rotarix™ contain rotaviruses propagated and purified from Vero (African green monkey kidney) cells. Both are approved for the prevention of rotavirus gastroenteritis caused by G1, G2, G3, G4, and G9 rotavirus types. However, Rotarix™ uses a single attenuated viral strain (human G1/P8 type) while RotaTeq® contains five unique viruses.[101]

The RotaTeq® pentavalent vaccine takes advantage of the segmented nature of the RNA viral genome. Rotavirus A, which infects humans, has a two-strain classification system based on two key surface glycoprotein proteins, VP7 (the G serotype) and VP4 (the P serotype, which encodes the rotavirus Spike protein). There have been more than 30 VP7 G serotypes and more than 50 VP4 P serotypes identified. Because the rotavirus is segmented (it contains 11 RNA molecules), it can undergo swapping of these genes once two distinct serotypes enter a cell.[102] In human infections, P8 is most persistent and is often found paired with G1, G3, G4, G9, G12. G2 is found paired with P4, but other combinations of serotypes exist.[103]. The pentavalent vaccine not only uses human genes, but bovine as well, making for a complex mix of rotavirus serotypes. The first four "reassortant" viruses in the vaccine are human rotaviruses with bovine VP4 P7 genes that match with either of these four human VP7 versions: G1, G2, G3, G4. The fifth rotavirus contains human VP4 P8 gene and bovine VP7 G6 gene.[104]

Two attenuated rotavirus vaccines from India have been licensed locally, although they are very similar to the vaccines described above. For example, Rotasiil™ is a pentavalent vaccine with bovine–human rotaviruses containing human G1, G2, G3, G4, and G9. The other vaccine, Rotavac® is comprised of a monovalent attenuated human G9/P11 virus.[105]

Human Papillomavirus (HPV Vaccines) (Pathogen type: DNA virus. Vaccine type: protein-VLP)

The first human papillomavirus (HPV) vaccine, Gardasil®, was approved in the U.S in 2006 for the prevention of cervical, vulvar, vaginal and anal cancers caused by HPV Types 16 and 18, and genital warts caused by Types 6 and 11.[106] In 2009, a bivalent vaccine, Cervarix®, was approved for Type 16 and 18.[107] A nine-valent version of Gardasil®, which includes an additional 5 HPV Types (31, 33, 45, 52, 58), was approved in 2014 and has replaced the older HPV vaccines in the U.S.[108]

Each vaccine for HPV is comprised of recombinantly expressed HPV capsid L1 proteins for each individual HPV Type. For Gardasil®, yeast (*Saccharomyces cerevisiae*) is used for protein expression. Yeast cells are disrupted and the L1 complexes self-assemble into virus-like particles (VLPs) that are subsequently purified. Cervarix® uses insect cells (*Trichoplusia ni)* for expression. After L1 protein purification, VLPs are formed and combined with AS04 adjuvant.[109] All three vaccine VLP preps are adsorbed onto aluminum.

Dengue Vaccines (Pathogen type: RNA virus. Vaccine type: live attenuated)

Early research and development of the dengue RNA virus beginning in the 1920s was unsuccessful due to there being four virus serotypes.[110] Almost a century later, through the use of recombinant DNA technology, a live attenuated vaccine was developed and licensed.

Today there are two licensed live attenuated dengue vaccines, Dengvaxia® licensed outside the U.S. starting in 2015 (in the U.S. in 2019) and Qdenga® licensed outside the U.S. beginning in 2022 (U.S. BLA is under priority review with the FDA as of this writing).[111] The Dengavxia® vaccine is composed of engineered chimeric viruses that have the prM and E genes from four serotypes (DENV1,2,3,4) integrated into the backbone of yellow fever virus strain 17D.[112] Qdenga® uses an attenuated DENV-2 backbone for insertion of genes encoding prM and E subunit proteins of Type 1,3,4 DENV serotypes.[113]

Enterovirus Vaccines (Pathogen type: RNA virus. Vaccine type: inactivated virus)

In Asia, there have been four inactivated enterovirus A71 vaccines approved since 2015, the most recent of which was approved in 2023 in Taiwan.[114]

Ebola Vaccine (Pathogen type: DNA virus; Vaccine type: recombinant live attenuated replicating virus)

In 2019, ERVEBO® was approved in the U.S. for the prevention of disease caused by Zaire ebolavirus. ERVEBO® is an engineered viral vaccine with the envelope glycoprotein gene from ebolavirus (Zaire Kikwit strain) inserted into a vesicular stomatitis virus (VSV) backbone.[115] VSV is a single-stranded RNA virus that primarily infects animals but is attenuated upon deletion of the native glycoprotein gene and replacement with a foreign glycoprotein gene.[116] The virus is grown in Vero (African green monkey kidney) cell cultures and purified from the growth medium.[117]

A prime/boost combination vaccine for Ebola was approved by the European Medicines Agency (EMA) in 2020. Mvabea® (MVA-BN Filo)/ Zabdeno® (Ad26.Zebov) uses a Modified Vaccinia Ankara vector encoding glycoproteins from the Ebola Zaire, Ebola Sudan and Marburg virus. The second shot contains Ad26 adenovirus encoding a protein from the Zaire strain of Ebola virus.

Malaria Vaccine (Pathogen type: parasite; Vaccine type: VLP)

A malaria virosomal protein subunit vaccine (Mosquirix™) was prequalified by the WHO in 2022. The recombinant vaccine (also known as RTS,S) is made by expressing *Plasmodium falciparum* circumsporozoite protein (regions R and T) fused with hepatitis B surface antigen (S), as well as being combined with hepatitis B surface antigen (S), from yeast cells (*Saccharomyces cerevisiae*).[118] In addition to these proteins forming VLPs, a lipid-based adjuvant (AS01) is added in the final product.[119] Another product has been recently approved in Ghana, Nigeria, and Burkina Faso and recommended by WHO SAGE for use, but this newer vaccine (R21) does not include free surface antigen and includes Matrix-M™ adjuvant.

SARS-CoV-2 Vaccines (pathogen type: RNA virus, Vaccine Types: mRNA; protein VLP; rViral; inactivated)

In the U.S., two mRNA vaccines have received FDA approval (COMIRNATY® and Spikevax™) and two others (Nuvaxovid™ and Jcovden®) have received emergency use authorization (EUA). The mRNA vaccines code for the expression of the full length CoV-2 spike protein and are delivered as lipid nanoparticles (LNPs) that encapsulate the mRNA. The two vaccines under EUA are for the viral (adenovirus Ad26) vaccine harboring the CoV-2 spike gene, and a spike protein VLP vaccine.

Outside of the U.S. there have been 10 unique vaccines approved and 29 others that have been authorized for COVID-19 since the start of the pandemic. Of these vaccines, the largest portion of these are protein-based vaccines containing Spike antigen, with 17 vaccines, and only one, a Russian made vaccine, receiving full approval (EpiVacCorona – approved in Turkmenistan). The 16 other vaccines have been authorized in multiple other countries: Spikogen® (authorized in Iran) Coviccine® (authorized in China), SCB-219 (authorized in China), Sinopharm NVSI (authorized in UAE), V-01 (authorized in China), Zifivax™ (authorized in five countries), Abdala (authorized in six countries), Vidprevtyn™ Beta (authorized in 30 countries), CORBEVAX™ (authorized in India and Botswana), IndoVac (authorized in Indonesia), Noora (authorized in Iran), Razai COV Pars® (authorized in Iran), SKYCovione™ (authorized in South Korea), Bimervax® (authorized in the EU), ReCOV® (authorized in Mongolia), and MVC-COV1901 (authorized in 3 countries). Two other vaccines are slightly different from the single purified protein examples above such as Soberana® 2 (authorized in Iran) which it is a chemically conjugated Spike-Tetanus Toxoid vaccine and COVIFENZ® (approved in Canada)

which uses a virus-like particle (VLP) for Spike antigen presentation.

The second largest group of COVID-19 vaccines are viral based vaccines with five fully approved vaccines: CoronoaVac® (approved in China), Covaxin® (approved in India), Sinopharm BIBP (approved in four countries), Sinopharm WIBP, (approved in China), and VLA2001 (approved in the U.K.). Seven that have been authorized: Covidful (authorized in China), COVIran Barekat (authorized in Iran and Nicaragua), ERUCOV-VAC (authorized in Turkey), FAKHRAVAC (authorized in Iran), KCONVAC™ (authorized in China and Indonesia), KoviVac (authorized in three countries), and QazVac™ (authorized in Kazakhstan and Kyrgystan).

Of the remaining nine vaccines, one is a DNA vaccine (ZyCoV-D®, authorized in India) using plasmid DNA, three RNA based vaccines: two being mRNA vaccines (AWcorna, authorized in Indonesia and Stemirna, authorized in Laos), and one self-amplifying RNA (saRNA) vaccine (Gemcovac®, authorized in India), which is the first saRNA commercialized in the world, and four rViral based vaccines: two using the modified chimpanzee adenoviruses (iNCOVACC®, authorized in India, and Vaxzevria™, approved in five countries) and two others using other adenoviruses (Convidecia®, approved in China and Sputnik V, approved in three countries). iNCOVACC® is the only approved/authorized COVID-19 vaccine that is delivered intranasally.

Respiratory Syncytial Virus (RSV) Vaccines (Pathogen type: RNA virus; Vaccine type: protein subunit)

In early May 2023, the FDA approved the first RSV vaccine, Arexvy. It is an engineered prefusion trimeric RSV F protein expressed and purified from Chinese hamster ovary (CHO) cells, and adjuvanted using AS01 with QS-21 Stimulon™.[120] A second RSV vaccine, Abrysvo™, wasapproved in late May 2023. Abrysvo™ is an unadjuvanted, bivalent RSV prefusion F protein vaccine.[121]

Appendix II – Approved Prophylactic Antibodies

Rabies

Serum-derived antibodies for rabies have been used since the early 1900s. Currently in the U.S. there are three human Rabies Immune Globulin (RIG) products that protect against rabies virus.[122]

RSV

RespiGam®, a polyclonal immunoglobulin cocktail, was approved by the FDA in 1996 for the prevention of serious RSV infection in children.[123] A monoclonal antibody, palivizumab (Synagis®), was approved in 1998.[124] It targets the same RSV fusion protein that is part of the recently approved protein vaccines. However, it binds to the post-fusion conformation of the F protein. In July 2023, nirsevimab (Beyfortus), which binds to the pre-fusion conformation of F protein, was approved for prevention of RSV in infants.

CMV

FDA approved Cytogam, CMV Immune Globulin (CMV-IGIV) in 1998 for the prophylaxis of cytomegalovirus disease associated with transplantation of kidney, lung, liver, pancreas, and heart.[125]

Anthrax

Two monoclonal antibodies have been approved for the prophylaxis of inhaled anthrax. Raxibacumab (Abthrax®) was approved by the U.S. FDA in 2012, and obiltoxaximab (Anthim™) was approved in 2016.[126]

Clostridioides difficile

In 2016, bezlotoxumab (Zinplava™) was approved by the FDA to reduce recurrence of *Clostridium difficile* Infection.[127] Bezlotoxumab binds to C. diff enterotoxin B.

HIV

Although not a pathogen epitope binding antibody, ibalizumab (Trogarzo™) was approved in 2018 for HIV prevention. Rather than target HIV directly, the human CD4 is the target. This would be akin to an anti-ACE2 mAb for COVID-19.

COVID-19

During the COVID-19 pandemic, FDA authorized Evusheld™ (tixagevimab + cilgavimab) for pre-exposure prophylaxis. However, in January 2023 authorization for use was rescinded due to antigenic drift of new variants. Similarly, the bamlanivimab/etesevimab combination and the casirivimab/imdevimab combination were authorized for post-exposure prophylaxis of COVID-19 but are no longer authorized.[128]

Endnotes

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7 This can also be viewed as passive when the recipient of the immune benefit is a developing fetus receiving antibodies generated by the active immune system of the mother after vaccination.

8 Variolation, the process of inoculation with a pathogen to building immune defense for later infection by the same pathogen, had been used in ancient times.

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20 Vaccine company IPOs (2013-2022) raised $0.7 billion in the U.S. and $2.5 billion Ex-U.S, from 20 transactions. For ex-U.S. IPOs the majority ($1.9 billion) was raised by companies located in Asia. Vaccine company secondary offerings (2013-2022) were $4.6 billion in the U.S. and $0.9 billion Ex-U.S., from 36 transactions. The majority (84%) of secondary offerings were raised during the COVID-19 pandemic, with one company receiving $1.9 billion (35% of all the funds raised in the recent decade)

21 Oncology IPOs (2013-2022) raised $18.4 billion in the U.S. and $12.2 billion Ex-U.S. Oncology secondary offerings (2013-2022) raised $46 billion in the U.S. and $14.2 billion Ex-U.S.

22 The ESKAPE pathogens are six nosocomial pathogens that exhibit multidrug resistance: *Staphylococcus aureus*, *Klebsiella pneumoniae* have ongoing clinical vaccine programs, but *Enterococcus faecium, Acinetobacter baumannii, Pseudomonas aeruginosa,* and *Enterobacter* species do not.

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