RECENT EVOLUTION OF VACCINES:

LEARNINGS FROM PAST OUTBREAKS FOR COVID-19

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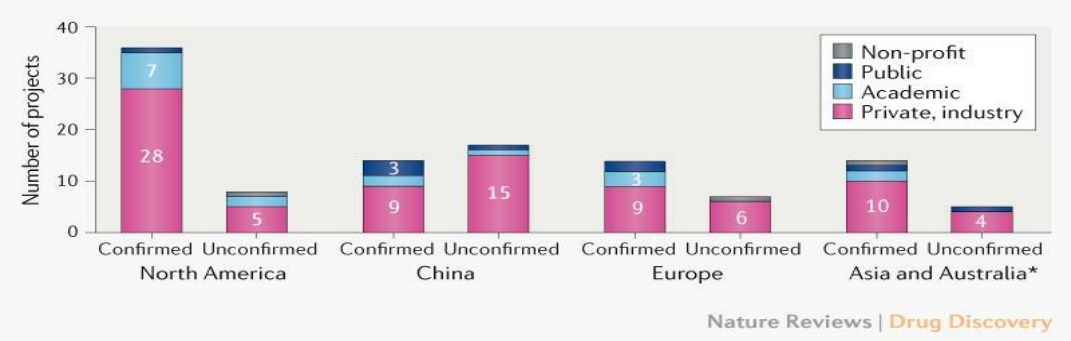
The COVID-19 pandemic has shut down countries across the globe for most of the last year. As we are getting close to the 1-year mark of the pandemic in the United States, we thought it would be judicious to discuss the planning, innovation and rapid development of anti-virals and vaccines that have been created in record time. But first, we must look back almost 7 years to 2013 and the Ebola outbreak that threatened global health and economies.

Ebola is a severe hemorrhagic fever in humans with a high case fatality rate and significant potential to become an epidemic or pandemic. The 2013-2016 epidemic of Ebola in Western Africa was larger than all previous outbreaks combined and was unique in its geographic distribution as well as multi-country spread. This epidemic claimed over 11,000 lives of the 28,000 reported cases and took more than 3 years to bring under control. The enormous amount of money and effort spent ending this epidemic made it extremely clear to the scientific community that zoonotic diseases, like Ebola, pose a threat to humanity's continued existence.

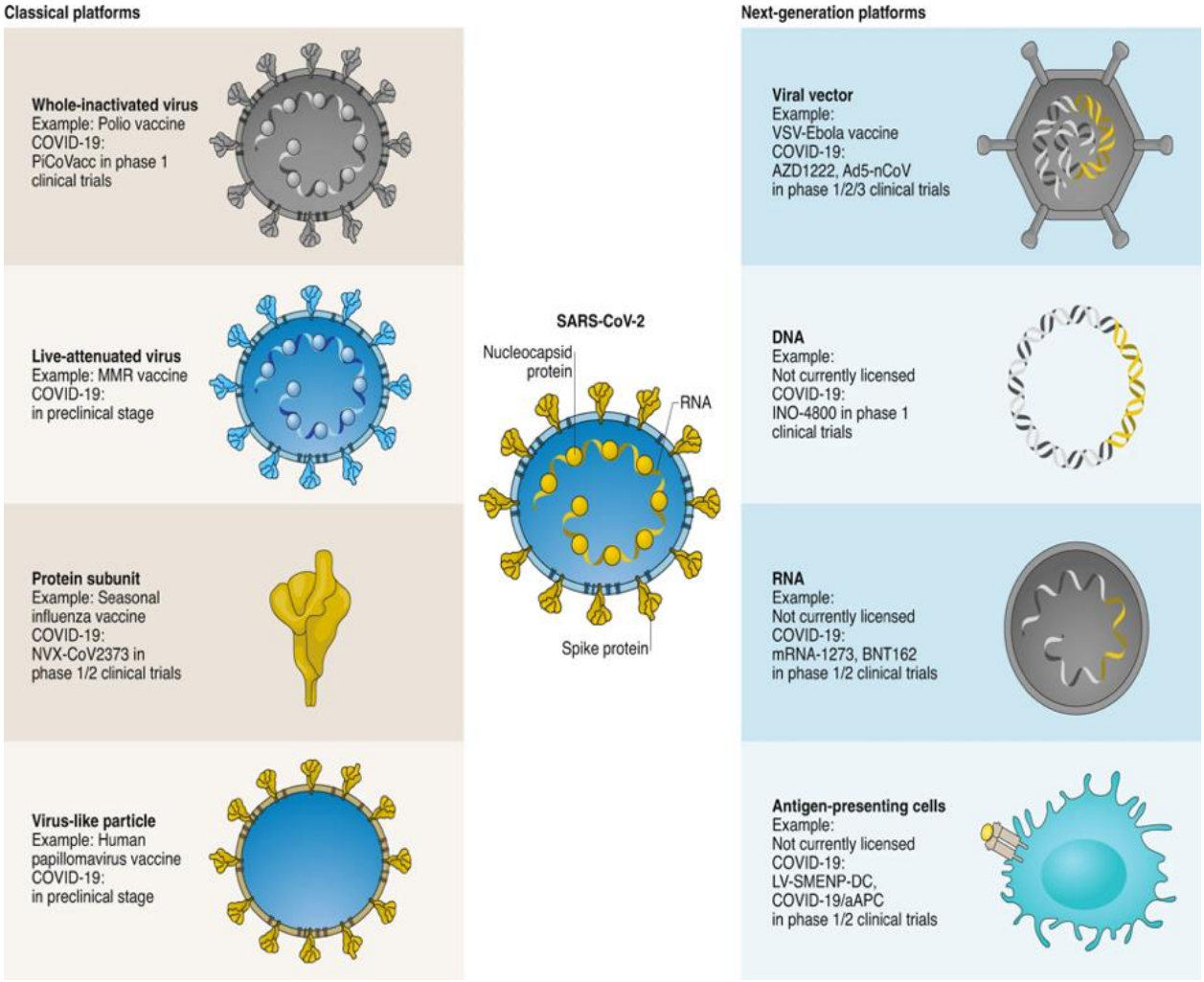
Since the Ebola epidemic, efforts were launched to identify future viruses with epidemic or pandemic potential and large sums of money were invested to develop vaccines against some of them as well as new, rapid vaccine platforms. There are currently over 200 COVID-19 vaccines in development with **Pfizer** and **BioNTech**'s vaccine obtaining FDA emergency use authorization on December 11, 2020 and **Moderna**'s vaccine receiving its emergency use authorization on December 18, 2020. Over 50 of the international vaccines closest to the emergency authorization / approval process can be seen in Appendix 1. There has been significant speculation as well as conspiracies regarding these

Authorized/Approved Vaccines				
Name	Vaccine Type	Primary Developers	Country of Origin	Authorization / Approval
mRNA-1273	mRNA-based vaccine	Moderna	US	US
BNT162b2	mRNA-based vaccine	Pfizer, BioNTech; Fosun Pharma	Multi-national	UK, Bahrain, Canada, Mexico, US, Singapore, Oman, Saudi Arabia, Kuwait
CoronoVac	Inactivated vaccine (formalin with alum adjuvant)	Sinovac	China	China
No name announced	Inactivated vaccine	Wuhan Institute of Biological Products; China National Pharmaceutical Group (Sinopharm)	China	China
Sputnik V	Non-replicating viral vector	Gamaleya Research Institute, Acellena Contract Drug Research and Development	Russia	Russia
BBIBP-CorV	Inactivated vaccine	Beijing Institute of Biological Products; China National Pharmaceutical Group (Sinopharm)	China	China, United Arab Emirates, Bahrain
EpiVacCorona	Peptide Vaccine	Federal Budgetary Research Institute State Research Center of Virology and Biotechnology	Russia	Russia



vaccines, so we thought it prudent to explain the differences between classic vaccine platforms and next-generation vaccine platforms.

As you can see in the figure below, Classic vaccine platforms can be divided into virus-based or protein-based. These classic platforms have contributed to major breakthroughs in public health such as eradication of polio and measles as well as vaccines for Human Papillomavirus (HPV) that help to prevent cancer.

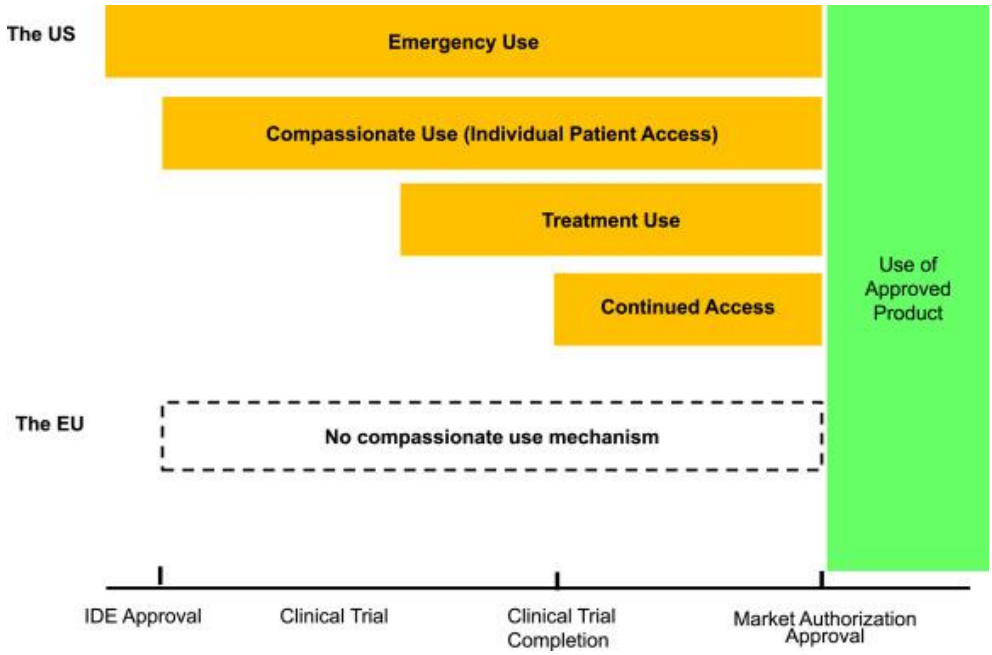


Unfortunately, there are major limitations associated with these platforms that make them unsuitable for fast vaccine production during a pandemic. For SARS-CoV-2 (Severe Acute Respiratory Syndrome–Coronavirus–2), the virus that causes COVID-19, this requires large quantities of the virus to be grown in biosafety level 3 (BSL-3) for inactivated viruses as well as extensive safety testing for live-attenuated viruses to ensure they do not easily revert to their wild type. Virus-like particle vaccines also require many recombinant proteins to be produced simultaneously before they are effective.

The main advantage of the next-generation platforms is that they can be developed solely on the genetic sequence information (DNA or RNA of the virus). This means that only coding sequences for viral proteins important to providing protection from disease are sufficient to start vaccine development instead of the ability to culture the virus. This makes these next-generation platforms extremely adaptable and speeds up development significantly. The **Pfizer-BioNTech (NYSE: PFE, NASDAQ: BNTX)** and **Moderna (NASDAQ: MRNA)** vaccines are both mRNA vaccines. mRNA or messenger RNA is a single-stranded molecule of RNA that is read by a ribosome in a cell for the process of synthesizing a protein. mRNA never enters the nucleus of the cell, which is where human DNA is kept. After uptake into cells, mRNA vaccines work by giving instruction to ribosomes to create spike proteins, which are originally found on the surface of SARS-CoV-2. After this spike protein is synthesized, the mRNA is broken down and destroyed by the cell.

After the spike protein is synthesized, it is presented on the surface of the cell. Our immune system then recognizes that this protein does not belong in the body and begins to build an antibody response to the protein, similar to the process that occurs during a natural infection of COVID-19. When this process has completed, our immune systems have learned to protect us against future infection.

There are no licensed mRNA vaccines in the United States as the Pfizer and Moderna vaccines have received only FDA Emergency Use Authorization but are not fully approved by the FDA.



Nevertheless, this does not mean that they are an untested platform. Researchers have been working with and studying these vaccines for decades and there has been significant interest in them because they can be created in laboratories using readily available equipment and materials. Because of this, the process to create mRNA vaccines can be standardized and brought to scale quickly and efficiently, allowing for faster vaccine development times than classic methods. mRNA vaccines have been studied for use in flu, Zika and rabies vaccines. This allowed

scientists to begin designing the mRNA instructions for SARS-CoV-2 spike proteins as soon as the genome of the virus was isolated and made available.

The processes described have allowed the creation of one of the fastest and most effective vaccines in the history of humanity. The advancements that have been made for these vaccines have also fueled the funding for future mRNA vaccine development to allow for a single vaccine to provide coverage for multiple diseases. Additional use of the technology to trigger the immune system to target specific cells in the treatment of cancer is on the horizon. One question that keeps us all wondering: "is the FDA approval process more of an obstacle in rapid vaccine approval?"

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Glossary of Terms

1. **Attenuated Vaccine**: Vaccines created by decreasing the ability of a pathogen to harm the host
2. **Biosafety Levels**: A series of protections designed to protect laboratory personnel as well as the surrounding environment and community. Ranked from 1 to 4. A specialized research laboratory that deals with potentially deadly infectious agents like Ebola would be designated BSL-4
3. **Culture**: A method of multiplying microbial organisms by letting them reproduce in predetermined media under controlled laboratory conditions
4. **Endemic**: Something specific to a particular people or country
5. **Epidemic**: A disease that affects a large number of people within a community, population or region
6. **Pandemic**: An epidemic that has spread over multiple countries or continents
7. **Outbreak**: A greater than anticipated increase in the number of endemic[4] cases or a single case in a new area
8. **Recombinant protein**: Artificially produced (often purified) protein
9. **Ribosome**: A component of living cells that performs the synthesis of biological proteins
10. **RNA**: Ribonucleic Acid. A chain of nucleotides that conveys genetic information to direct the synthesis of specific proteins. Many viruses encode their genetic information using an RNA genome
11. **Wild type virus**: The typical form of the virus as it occurs in nature
12. **Zoonotic disease**: an infectious disease caused by a pathogen (bacterium, virus, parasite, or prion) that has jumped from a non-human animal to a human

Appendix 1: SARS-COV-2 Vaccines Candidates under Development

Highlighted rows indicate emergency authorization use in US; / between phases (eg.: Phase 2/3) indicates concurrent trials

Vaccine Candidates under Development					
#	Candidate	Mechanism	Sponsor	Trial Phase	Institution
1	BNT162	mRNA-based vaccine	Pfizer, BioNTech	Phase 1/2/3	Multiple study sites in Europe, North America and China
2	mRNA-1273	mRNA-based vaccine	Moderna	Phase 3	Kaiser Permanente Washington Health Research Institute
3	Ad5-nCoV	Recombinant vaccine (adenovirus type 5 vector)	CanSino Biologics	Phase 3	Tongji Hospital; Wuhan, China
4	AZD1222	Replication-deficient viral vector vaccine (adenovirus from chimpanzees)	The University of Oxford; AstraZeneca; IQVIA; Serum Institute of India	Phase 3	The University of Oxford, the Jenner Institute
5	Covaxin	Inactivated vaccine	Bharat Biotech; National Institute of Virology	Phase 3	
6	JNJ-78436735 (formerly Ad26.COV2.S)	Non-replicating viral vector	Johnson & Johnson	Phase 3	Johnson & Johnson
7	NVX-CoV2373	Nanoparticle vaccine	Novavax	Phase 3	Novavax
8	Bacillus Calmette-Guerin (BCG) vaccine	Live-attenuated vaccine	University of Melbourne and Murdoch Children's Research Institute; Radboud University Medical Center; Faustman Lab at Massachusetts General Hospital	Phase 2/3	University of Melbourne and Murdoch Children's Research Institute; Radboud University Medical Center; Faustman Lab at Massachusetts General Hospital
9	INO-4800	DNA vaccine (plasmid)	Inovio Pharmaceuticals	Phase 2/3	Center for Pharmaceutical Research, Kansas City. Mo.; University of Pennsylvania, Philadelphia
10	VIR-7831	Plant-based adjuvant vaccine	Medicago; GSK; Dynavax	Phase 2/3	Medicago
11	No name announced	Adenovirus-based vaccine	ImmunityBio; NantKwest	Phase 2/3	
12	CVnCoV	mRNA-based vaccine	CureVac	Phase 2b/3	CureVac
13	No name announced	Recombinant vaccine	Anhui Zhifei Longcom Biopharmaceutical, Institute of Microbiology of the Chinese Academy of Sciences	Phase 2	Various
14	ZyCoV-D	DNA vaccine (plasmid)	Zydus Cadila	Phase 2	Zydus Cadila
15	IIBR-100	Recombinant vesicular stomatitis virus (rVSV) vaccine	Israel Institute for Biological Research	Phase 1/2	Hadassah Medical Center; Sheba Medical Center Hospital
16	No name announced	SF9 cell vaccine candidate	West China Hospital, Sichuan University	Phase 1/2	West China Hospital, Sichuan University
17	Soberana 1 and 2	Monovalent/conjugate vaccine	Finlay Institute of Vaccines	Phase 1/2	Finlay Institute of Vaccines
18	VLA2001	Inactivated vaccine	Valneva; National Institute for Health Research (NIHR)	Phase 1/2	Multiple NIHR testing sites
19	No name announced	Adjuvanted protein subunit vaccine		Phase 1/2	
20	AG0301-COVID19	DNA vaccine	AnGes, Inc.	Phase 1/2	AnGes, Inc.; Japan Agency for Medical Research and Development
21	GX-19	DNA vaccine	Genexine	Phase 1/2	
22	LNP-nCoVsaRNA	Self-amplifying RNA vaccine	Imperial College London	Phase 1/2	Imperial College London
23	ARCT-021 (LUNAR-COV19)	Self-replicating RNA vaccine	Arcturus Therapeutics and Duke-NUS Medical School	Phase 1/2	Duke-NUS Medical School, Singapore
24	No name announced	Protein subunit vaccine	Sanofi; GlaxoSmithKline	Phase 1/2	Various
25	No name announced	Inactivated vaccine	Chinese Academy of Medical Sciences, Institute of Medical Biology	Phase 1/2	West China Second University Hospital, Yunnan Center for Disease Control and Prevention

Appendix 1 (cont.)

Vaccine Candidates under Development					
#	Candidate	Mechanism	Sponsor	Trial Phase	Institution
26	HDT-301 (HGCO19)	RNA vaccine	University of Washington; National Institutes of Health Rocky Mountain Laboratories; HDT Bio Corp; Gennova Biopharmaceuticals	Phase 1/2	
27	AdCLD-CoV19	Adenovirus-based vaccine	Cellid; LG Chem	Phase 1/2a	Korea University Guro Hospital
28	COVI-VAC	Intranasal vaccine	Codagenix; Serum Institute of India	Phase 1	
29	CORVax12	DNA vaccine (plasmid)	OncoSec; Providence Cancer Institute	Phase 1	Providence Portland Medical Center
30	MVA-SARS-2-S	Modified vaccinia virus ankara (MVA) vector vaccine candidate	Universitätsklinikum Hamburg-Eppendorf; German Center for Infection Research; Philipps University Marburg Medical Center; Ludwig-Maximilians - University of Munich	Phase 1	University Medical Center Hamburg-Eppendorf
31	COH04S1	Modified vaccinia virus ankara (MVA) vector vaccine candidate	City of Hope Medical Center; National Cancer Institute	Phase 1	City of Hope Medical Center
32	pVAC	Multi-peptide vaccine candidate	University Hospital Tuebingen	Phase 1	University Hospital Tuebingen
33	AdimrSC-2f	Protein subunit vaccine	Adimmune	Phase 1	Adimmune
34	bacTRL-Spike	Monovalent oral vaccine (bifidobacteria)	Symvivo	Phase 1	Symvivo Corporation
35	COVAX-19	Monovalent recombinant protein vaccine	Vaxine Pty Ltd.	Phase 1	Royal Adelaide Hospital
36	DelNS1-2019-nCoV-RBD-OPT1	Replicating viral vector	Xiamen University, Beijing Wantai Biological Pharmacy	Phase 1	Jiangsu Provincial Centre For Disease Control and Prevention
37	GRAd-COV2	Adenovirus-based vaccine	ReiThera; Leukocare; Univercells	Phase 1	Lazzaro Spallanzani National Institute for Infectious Diseases
38	UQ-CSL V451	Protein subunit vaccine	CSL; The University of Queensland	Phase 1	
39	SCB-2019	Protein subunit vaccine	GlaxoSmithKline, Sanofi, Clover Biopharmaceuticals, Dynavax and Xiamen Innovax; CEPI	Phase 1	Linear Clinical Research (Australia)
40	UB-612	Multitope peptide-based vaccine	COVAXX	Phase 1	United Biomedical Inc. (UBI)
41	V590	Recombinant vaccine (vesicular stomatitis virus)	Merck; IAVI	Phase 1	
42	V591	Measles vector vaccine	University of Pittsburgh's Center for Vaccine Research	Phase 1	University of Pittsburgh; Themis Biosciences; Institut Pasteur
43	VXA-CoV2-1	Recombinant vaccine (adenovirus type 5 vector)	Vaxart	Phase 1	Vaxart
44	AAVCOVID	Gene-based vaccine	Massachusetts Eye and Ear; Massachusetts General Hospital; University of Pennsylvania	Pre-clinical	
45	AdCOVID	Intranasal vaccine	Altimmune	Pre-clinical	University of Alabama at Birmingham
46	ChAd-SARS-CoV-2-S	Adenovirus-based vaccine	Washington University School of Medicine in St. Louis	Pre-clinical	Washington University School of Medicine in St. Louis
47	HaloVax	Self-assembling vaccine	Voltron Therapeutics, Inc.; Hoth Therapeutics, Inc.	Pre-clinical	MGH Vaccine and Immunotherapy Center
48	LineaDNA	DNA vaccine	Takis Biotech	Pre-clinical	Takis Biotech
49	MRT5500	Recombinant vaccine	Sanofi, Translate Bio	Pre-clinical	
50	No name announced	Ii-Key peptide COVID-19 vaccine	Generex Biotechnology	Pre-clinical	Generex
51	No name announced	Protein subunit vaccine	University of Saskatchewan Vaccine and Infectious Disease Organization-International Vaccine Centre	Pre-clinical	University of Saskatchewan Vaccine and Infectious Disease Organization-International Vaccine Centre

Appendix 1 (cont.)

Vaccine Candidates under Development					
#	Candidate	Mechanism	Sponsor	Trial Phase	Institution
52	No name announced	mRNA-based vaccine	Chulalongkorn University's Center of Excellence in Vaccine Research and Development	Pre-clinical	
53	No name announced	gp96-based vaccine	Heat Biologics	Pre-clinical	University of Miami Miller School of Medicine
54	No name announced	Inactivated vaccine	Shenzhen Kangtai Biological Products	Pre-clinical	
55	PittCoVacc	Recombinant protein subunit vaccine (delivered through microneedle array)	UPMC/University of Pittsburgh School of Medicine	Pre-clinical	University of Pittsburgh
56	T-COVIDTM	Intranasal vaccine	Altimmune	Pre-clinical	

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