Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Commentary

With established safe and effective use, protein vaccines offer another choice against COVID-19

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1. Viewpoint

Approved mRNA and adenovirus vector vaccines against COVID-19 have thus far prevented approximately 2.2 million deaths in the United States. Despite their efficacy, safety, and availability at no cost, according to the CDC, as of September 8, 2022 only 68 % of the total US population has completed a primary vaccine series, among whom only 47 % have received a booster dose [2]. Reasons for COVID-19 vaccine hesitancy include doubts over their safety and efficacy, low perceived disease risk and concerns over the novelty of the available vaccine platforms [1]. In a US-based survey of 400 individuals hesitant to receive currently available vaccines, 55 % stated that they would likely receive a hypothetical protein-based vaccine, and 10 % said that they trusted protein-based vaccines more than the other choices [3]. Therefore, an alternative vaccine platform with a history of safe and effective use has the potential to benefit public health by providing an additional choice to those in the United States who have not received the primary series or have not been boosted.

1.1. Protein-based vaccines: History and advancements

For decades, protein-based vaccine platforms have been used for the prophylaxis of both bacterial (e.g., pertussis, tetanus, diphtheria) and viral (e.g., hepatitis B, HPV) diseases, with the first vaccine containing a surface protein of a virus approved in the United States in 1986 (Fig. 1). Protein-based vaccines are indicated for use in infants, children, and adults, including the elderly, and their favorable safety profile and benefits are well known. Since the availability of the first protein-based vaccine against HPV in 2006, the CDC estimates that HPV infections in teenage girls and young adult women have decreased by 88 % and 81 %, respectively. The success of the HPV vaccination campaign is partly due to the durability of vaccine-induced antibodies, which can persist for over a decade.

Historically, the proteins used in vaccines were purified exclusively from cultures of an infectious agent, but this technique is challenging as the growth of large quantities of virulent organisms poses serious safety concerns and not all pathogens can be cultured [4]. Today, specific immunogenic proteins can be generated via recombinant expression systems. Notably, the use of eukaryotic expression systems, such as yeast, insect, or mammalian cells, represents a major advantage over prokaryotic cells (bacteria) given their ability to endow recombinant proteins with posttranslational modifications that more closely mimic the structure—and thus immunogenicity—of the original pathogen [4,5].

Relative to vaccines composed of live-attenuated or inactivated whole organisms, protein-based vaccines are generally less immunogenic [4,5]. However, their immunogenicity can be enhanced through targeted mutations, the addition of adjuvants and/or the use of nanotechnology. First, intentional mutations made to stabilize the RSV F protein in its prefusion form have been shown to increase the neutralizing activity of vaccine-induced antibodies by 60 % relative to antibodies against the post-fusion form of the F protein [6]. This discovery has influenced the development of several prefusion-stabilized recombinant SARS-COV-2 spike protein vaccines. Second, adjuvants, long used to enhance vaccine immunogenicity, can skew helper T cells toward a Th1 (cell-mediated) or Th2 (antibody-mediated) phenotype. Although vaccines have traditionally sought to trigger predominantly humoral immune responses [4], the U.S. Food and Drug Administration recommends that investigational COVID-19 vaccines stimulate both cellular and humoral immune responses. This guidance was informed, in part, by clinical observations that individuals with a rapid Th1 response present with less severe COVID-19 [5]. Traditional aluminum-based adjuvants bias toward Th2 responses, whereas alternative adjuvants, such as Matrix-M™, MF59 and AS03, provoke more balanced Th1/Th2 cell profiles. Finally, rather than vaccinating with poorly immunogenic proteins alone, nanotechnologies, such as VLPs and protein micelles, are used to mimic the structure and repetitive protein displays of whole pathogens [4]. Licensed vaccines against hepatitis B virus and HPV utilize VLP technology.

Abbreviations: CDC, Centers for Disease Control and Prevention; COVID-19, coronavirus disease 2019; GSK, GlaxoSmithKline; HPV, human papillomavirus; RBD, receptor-binding domain; RSV, respiratory syncytial virus; VLP, virus-like particle.

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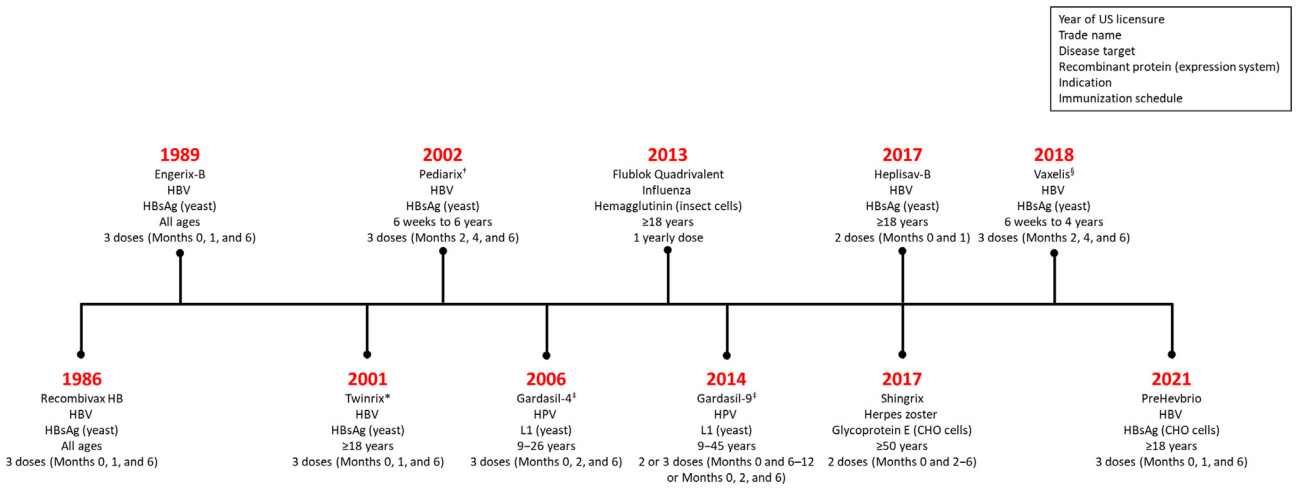

Fig. 1. Overview of Protein-Based Vaccines Targeting Viral Infections Approved by the FDA.
*Combination vaccine against hepatitis A and hepatitis B.
†Combination vaccine against hepatitis B, diphtheria, tetanus, pertussis and poliovirus.
‡Gardasil-4 is no longer available in the United States, as it has been replaced by Gardasil-9, which was approved in 2014 for use in individuals aged 9 to 45 years. Gardasil-9 can be administered on a 2-dose (Months 0 and 6 to 12) or 3-dose (Months 0, 2 and 6) schedule.
§Combination vaccine against hepatitis B, diphtheria, tetanus, pertussis, poliovirus and *Haemophilus influenzae* type b.
Abbreviations: CHO, Chinese hamster ovary; FDA, U.S. Food and Drug Administration; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HPV, human papillomavirus.

Table 1
Recombinant protein COVID-19 vaccines authorized for use.[a]

Vaccine	Manufacturer	Countries where vaccine is authorized for use
Nuvaxovid[b] **(NVX-CoV2373)**	Novavax	Australia, Austria, Belgium, Bulgaria, Canada, Croatia, Cyprus, Czechia, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Liechtenstein, Lithuania, Luxembourg, Malta, Netherlands, New Zealand, Norway, Poland, Portugal, Republic of Korea, Romania, Singapore, Slovakia, Slovenia, Spain, Sweden, Switzerland, Taiwan, United Kingdom, United States
Corbevax (BECOV2A)	Biological E. Limited	Botswana, India
Covovax[b]	Novavax; Serum Institute of India	Bangladesh, India, Indonesia, Philippines, Thailand
Abdala (CIGB-66)	Center for Genetic Engineering and Biotechnology	Cuba, Mexico, Nicaragua, St. Vincent and the Grenadines, Venezuela, Vietnam
Soberana 02	Finlay Vaccine Institute	Cuba, Iran, Nicaragua, Venezuela
Soberana Plus	Finlay Vaccine Institute	Belarus, Cuba
Zifivax (ZF2001)	Anhui Zhifei Longcom Biopharmaceutical	China, Colombia, Indonesia, Uzbekistan
Noora vaccine	Bagheiat-allah University of Medical Sciences	Iran
MVC-COV1901	Medigen	Paraguay, Somaliland, Taiwan
Recombinant SARS-CoV-2 Vaccine (CHO Cell; NVSI-06-08)	National Vaccine and Serum Institute	United Arab Emirates
Razi Cov Pars	Razi Vaccine and Serum Research Institute	Iran
V-01	Livzon Mabpharm Inc	China
SKYCovione	SK Bioscience Co ltd	Republic of Korea
TAK-019	Novavax; Takeda	Japan
SpikoGen (COVAX-19)	Vaxine; CinnaGen Co.	Iran
Aurora-CoV (EpiVacCorona-N)	Vector State Research Center of Virology and Biotechnology	Russia
EpiVacCorona	Vector State Research Center of Virology and Biotechnology	Cambodia, Russia, Turkmenistan, Venezuela

[a] Vaccines that have been approved, authorized, licensed, granted emergency use authorization, or made available for use outside of clinical trials via any pathway by a regulatory agency, a national authority, or another entity.
[b] Granted Emergency Use Listing (EUL) by the World Health Organization.

1.2. The potential of protein-based COVID-19 vaccines

As of late-2022, it is reasonable to ask whether new COVID-19 vaccines are needed. Despite the success of mRNA and adenovirus vector vaccines against COVID-19, some believe that the development of different vaccine platforms remains critically important [7,8]. Global vaccine equity stands to benefit from protein-based vaccines, which typically only require refrigeration; other types of vaccines may need to be kept frozen (at temperatures as low as − 90 °C) until use. Vaccine stability is an important considera-

tion for remote or resource-constrained settings in low- and middle-income countries, where maintaining freezing temperatures may be difficult. Improving overall global vaccination rates would help slow the spread of existing viral strains and the emergence of SARS-CoV-2 variants. Moreover, additional platforms could help to overcome the shortcomings of pandemic-era vaccines, such as poor epitope coverage and durability of protection [8]. For these reasons, it is important to develop multiple vaccine technologies rather than to rely on any individual platform [7].

Protein-based vaccines against COVID-19 are under investigation, several of which have been authorized globally in one or more countries (Table 1) [9]. Examples include NVX-CoV2373 (Novavax®), a self-assembling nanoparticle vaccine composed of recombinant SARS-CoV-2 spike trimers in a polysorbate 80 core, which is now authorized for use in the United States; GBP510 (SK Bioscience/GSK), a self-assembling nanoparticle vaccine that uses the RBD of the SARS-CoV-2 spike protein; Corbevax (Biological E. Limited/Texas Children's Hospital/Baylor College of Medicine) that similarly utilizes spike RBD; subunit D614 vaccine (Sanofi/GSK), which contains a recombinant version of spike; PHH-1 V (HIPRA), a recombinant spike protein RBD fusion heterodimer; SCB-2019 (CLOVER), which employed the Trimer-Tag™ technology platform to develop a stabilized trimeric form of the S-protein (S-Trimer™); and CoVLP-AS03 (Medicago/GSK), a vaccine formulation in which recombinant spike trimers are expressed as VLPs. NVX-CoV2373 is adjuvanted with the saponin-based Matrix-M™ adjuvant. PHH-1V is adjuvanted with an oil-in-water emulsion adjuvant, SQBA. Corbevax and SCB-2019 are adjuvanted with aluminum hydroxide gel and CpG1018. As part of its collaborations with SK Bioscience, Sanofi and Medicago, GSK is contributing its squalene-based adjuvant AS03.

Protein-based vaccines are an example of a well-established vaccine platform that has benefited from recent advancements. Despite a long history of use (Fig.), protein-based vaccines are in line to represent the next generation of vaccine technologies against COVID-19. Given the public's familiarity with protein-based vaccines, this platform could improve uptake by offering individuals, including those who are vaccine-hesitant, an alternative to the COVID-19 vaccines currently authorized in the United States. Any increase in immunization would be a boon to public health, as vaccinations—not vaccines—save lives.

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Author contributions

Anthony Marchese developed the concept and initiated the writing of the manuscript. All authors critically revised the manuscript and approved the final version. All authors attest they meet the ICMJE criteria for authorship.

Data availability

No data was used for the research described in the article.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Anthony M. Marchese and Hadi Beyhaghi are salaried employees of and own stock in Novavax, Inc. Walter A. Orenstein is an uncompensated member of the Moderna Scientific Advisory Board.

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