Review article

CLINICAL AND EXPERIMENTAL VACCINE RESEARCH

Perspective vaccines for emerging viral diseases in farm animals

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The world has watched the emergence of numerous animal viruses that may threaten animal health which were added to the perpetual growing list of animal pathogens. This emergence drew the attention of the experts and animal health groups to the fact that it has become necessary to work on vaccine development. The current review aims to explore the perspective vaccines for emerging viral diseases in farm animals. This aim was fulfilled by focusing on modern technologies as well as next generation vaccines that have been introduced in the field of vaccines, either in clinical developments pending approval, or have already come to light and have been applied to animals with acceptable results such as viral-vectored vaccines, virus-like particles, and messenger RNA-based platforms. Besides, it shed the light on the importance of differentiation of infected from vaccinated animals technology in eradication programs of emerging viral diseases. The new science of nanomaterials was explored to elucidate its role in vaccinology. Finally, the role of Bioinformatics or Vaccinomics and its assist in vaccine designing and developments were discussed. The reviewing of the published manuscripts concluded that the use of conventional vaccines is considered an out-of-date approach in eliminating emerging diseases. However, these types of vaccines are considered the suitable plan especially in countries with few resources and capabilities. Piloted vaccines that rely on genetic-based technologies with continuous analyses of current viruses should be the aim of future vaccinology. Smart genomics of emerging viruses will be the gateway to choosing appropriate vaccines, regardless of the evolutionary rates of viruses.

Keywords: Vaccines, Synthetic vaccines, mRNA vaccine, Virus-like particle vaccines, Nanoparticle drug delivery system, Computational biology

Introduction

The science of vaccination and immunology spans many centuries back even in 17th century when Buddhist monks in China drank snake venom to accord immunity to snakebite. In Latin, vacca means cow, praising Edward Jenner's trial. In 1798, he injected humans with cowpox pustule fluid that prompt protection against smallpox [1]. Later, Louis Pasteur produced the attenuated fowl cholera and learned that the pathogenicity reduced with age [2]. Attractively, the early development of human vaccines was genuinely linked to animals. Vaccinology was shaped 2 centuries ago by the late 19th and early 20th century where this rudimentary beginning was widely emerged based on the biomedical sciences [3] (Fig. 1). Early, 1930s to 1950s, the chick embryos and minced tissues were introduced for propagating viruses *in-vitro* for vaccine pro-

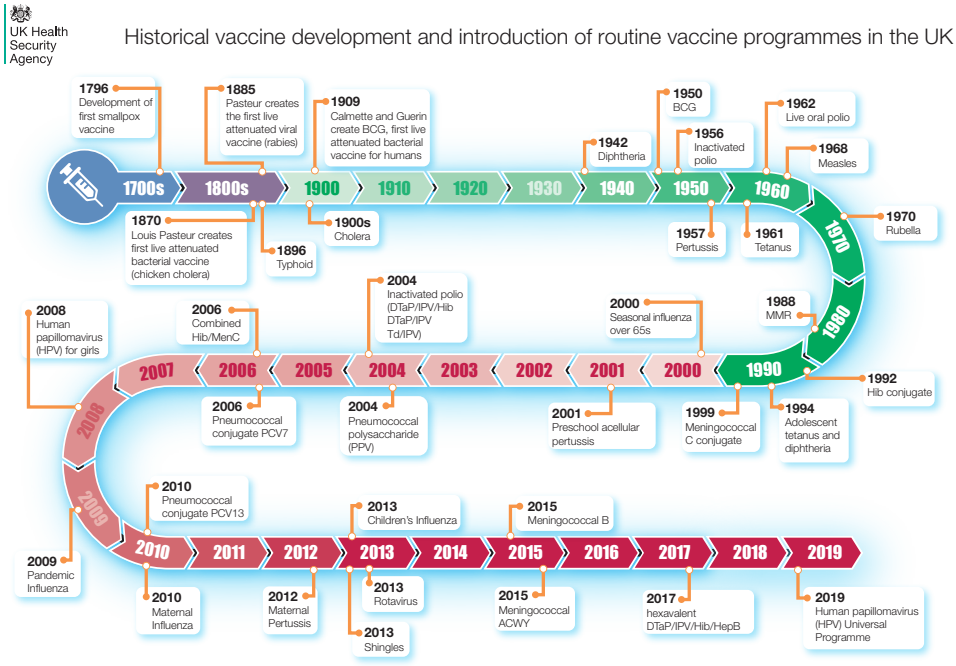

Fig. 1. Historical vaccine development and introduction of routine vaccine programs in the UK. From UK Health Security Agency. Promotional material: vaccination timeline: historical vaccine development and introduction of vaccines in the UK [Internet]. London: UK Health Security Agency; 2013 [cited 2021 Mar 16]. Available from: https://www.gov.uk/government/publications/vaccination-timeline [3]. BCG, bacillus Calmette-Guérin; MMR, measles-mumps-rubella; Hib, Haemophilus influenzae type b; DTaP, diphtheria-tetanus-pertussis; IPV, inactivated polio vaccine; Td, tetanus-diphtheria; PPV, pneumococcal polysaccharide vaccine; MenC, meningococcal group C; PCV, pneumococcal conjugate vaccine; HPV, human papillomavirus; HepB, hepatitis B.

duction [4]. Modern vaccinology began around 1950 and has been founded largely on innovations in cell culture as well as molecular biology which have yielded the traditional live and killed viral vaccines in addition to the recombinant-expressed vaccines [5]. These developments led to the advent of the Salk and the Sabin polio vaccine [6], which was able to eradicate poliomyelitis nearly from most of the landmass.

Therefore, the present review aims to explore the perspective vaccines for emerging viral disease in farm animals. This aim was fulfilled by focusing on modern technologies as well as next generation vaccines that have been introduced in the field of vaccines, either in clinical developments pending approval or have already come to light and have been applied to animals with acceptable results.

Emerging Viral Diseases

The World Organization for Animal Health (formerly, Office International des Epizooties) defines an emerging disease as a new infection resulting from the evolution or change of an existing pathogenic agent, or a known infection spreading to a new geographic area. In other words, a previously unrecognized disease diagnosed for the first time and which had a significant impact on animal or public health. Emerging diseases are not restricted to the boundaries present on the continent.

Recent years have witnessed the emergence of several animal viruses that challenge virologists, veterinarians and may threaten animal health. These newly recognized agents were added to the giant list of animal pathogens which draw attention of veterinarians and animal health personnel. These emerged viruses which have shown a constant evolution behavior are comprised of, but not restricted to, Rift Valley fever (RVF), porcine respiratory and reproductive syndrome virus in pigs, the geographical redistribution of West Nile virus and the spreading of new bluetongue virus (BTV) strains [7].

Emerging infections can be caused by previously undetected or unknown infectious agents, namely known agents that have spread to new geographic locations or new populations, previously known agents whose role in specific diseases is unrecognized, and re-emergence of agents whose incidence of disease had significantly declined in the past but have reappeared again.

Legacy of Vaccination

Most preventative viral vaccines consist of attenuated or inactivated viruses that provoke a protective immune response [8]. These types of vaccines are convincingly effective, and in general the use of booster doses in presence or even absence of adjuvants is not essential. However, attenuated vaccines may show negative repercussions and revert to the wild status [9,10].

The inactivated vaccines are a well-established type of vaccination. It can immune the animals against vast diseases such as bovine viral diarrhea (BVD), bovine herpesvirus type 1 (BoHV-1), rotavirus, coronavirus, and others. In presence of adjuvants whether natural or synthetic, the inactivated vaccines can provoke powerful humoral immunity with appropriate long coverage duration. Moreover, the polyvalence concept can increase the potentiality of the prepared vaccine with potentiation of its component to each other. Despite their inexpensive production price compared to that of the others, the inactivated vaccines have been proved to be safer than the live-attenuated vaccines [11]. In Egypt, this type of vaccination is considered a legacy. Most of the vaccines used in the Egyptian veterinary market, if not all, are inactivated vaccines that have been conducted on a wider scale on each species of farm animals.

On the contrary, the live attenuated vaccines induce stronger cellular immunity as well as humoral immunity. One of the drawbacks is the possibility of the vaccine virus strain to convert into the wild form resulting in the infection [12].

Next Generation Vaccines

Advances in recombinant genomic technology have made it possible to design new innovative genetically engineered vaccines with improved safety profiles and greater protective efficacy. These "next generation" vaccines include but not restricted to virus-vectored vaccines, virus-like particle (VLP) vaccines, messenger RNA (mRNA) vaccines, and nano-vaccines [13].

Virus-vectored vaccines

Many viruses have been employed to develop virus vectored vaccines, which provide effective protection against antigens. The number of vectored vaccines licensed for veterinary and human use has increased over time. Initially, vectored vaccines were based on DNA viruses such as herpesviruses, animal poxviruses, and adenoviruses [14,15]. This technology may depend on one of the followings: replication-competent vectors, replication-defective vectors, single-cycle vectors, and multi-segmented vectors [16]. Nowadays, the adenovirus is a viral vector used widely with obvious safety and efficacy. The virus has become one of the most exploited vectors for vaccine development. Major advantages of utilizing it in a vaccine platform can be demonstrated in its ability to infect broad range of hosts and to induce high levels of transgene expression without the potential of viral genes being integrated into the host genome. Coupled with the previously mentioned advantages, due to their ability to grow in high titers in cell culture, adenovirus can be manufactured safely and economically [17].

One of the successful and safe viruses are widely used in production of such type of vaccines is the Newcastle disease virus (NDV). Recombinant NDV (rNDV) vaccine strains infect many mammals but very safe due to restricted host tropism. Nevertheless, NDV is a strong stimulator of humoral and cellular immune responses at both the local and systemic levels. NDV does not establish persistent infection in animals because it replicates only in the cytoplasm [18]. NDV vaccines have been used to develop antigen delivery vaccines for use in cattle and sheep. Antigen delivery vaccines for veterinary use include [13] (Table 1), for example, rNDV-vectored vaccines protect against BoHV-1 [18], bovine ephemeral fever virus [19], and Rift Valley fever virus (RVFV) [20].

Table 1. Recombinant Newcastle disease virus-vectored vaccines of veterinary use

Host	Pathogen	Vaccine type	Seed virus				Efficacy test
			Seed virus	Antigen	Insert site	Animal model	Vaccination[a] (route/time/titer per dose)
Cattle/sheep	BHV-1	Live	rLaSota/gDFL	gD	P/M	Calf	o.n./single/1.5×107 PFU
	BEFV	Live	rL-BEFV-G	G	P/M	Calf	i.m./twice/8×10^{7} $TCID_{50}$
	RVFV	Live	NDFL-GnGc	Gn/Gc	P/M	Lamb	i.m./twice/$10^{7.3}$ $TCID_{50}$

From Choi KS. Clin Exp Vaccine Res 2017;6:72-82 [13].
BEFV-1, bovine ephemeral fever virus-1; P, protein, phosphor; M, matrix; o.n., oro-nasal; PFU, plaque forming units; BEFV, bovine ephemeral fever virus; i.m., intramuscular; TCID, median tissue culture infectious dose; RVFV, Rift Valley fever virus.
[a]Minimum test dose showing efficacy.

Rift Valley fever

Successful vectored vaccine was invented against RVFV which was considered one of the emerged diseases that infects cattle and sheep as well as humans [20]. Presently, the live attenuated (Smithburn strain) and inactivated RVFV vaccines are available. However, these vaccines impose a risk on farm animals. To improve efficacy and safety, the rNDV-vectored vaccine (NDFL-GnGc) expressing the Gn and Gc glycoproteins of RVFV was developed [20]. Given that the detected vaccine was aided in neutralizing antibodies against RVFV.

Bovine herpesvirus type1

BoHV-1 is considered a key cause of bovine respiratory disease (BRD) complex in cattle. The modified live vaccines are able to generate latent infection, with the concomitant risk of reactivation. The vectored rNDV was developed (rLaSota/gDFL) expressing the glycoprotein D of BoHV-1. A single shot succeeded to produce pronounced antibody responses both mucosal and systemic [18].

Foot and mouth disease

A recombinant model using rodent virus named Murine respirovirus, formerly Sendai virus containing the P1 gene of foot and mouth disease virus (FMDV) elicited well detected levels of both types of immunity in vaccinated mice [21]. Another virus vectored platform is the bamboo mosaic virus expressing FMDV epitopes and proved its efficacy in swine [22]. Added innovative approach was the immunization of the cattle with recombinant bovine herpesvirus carrying epitopes of FMDV which gave a positive immunity against both agents after virus challenge [23-25]. When adenovirus 5 was used as vector to express the capsid proteins of the FMDV strain A24 (Ad5-A24), it elicited a prompt protection against virus challenge [26]. To sum up, the recorded experimental vector vaccines were able to partially protect against foot and mouth disease (FMD) in their natural host. The replication-defective human adenovirus virus is considered the only vectored vaccine candidate approved to be used in emergency situations and has been shown to induce a full and complete immune response via its delivery of FMDV structural proteins [27]. The top returns associated with these adeno-vaccines are differentiation of infected from vaccinated animals (DIVA) competency which will be discussed later on in this review.

Examples of other veterinary viral vectored vaccines licensed and available for commercial use in the United States are illustrated in Table 2 [16].

Virus-like particles

VLPs are protein-based, nanoscale molecules which have relevant applications in vaccine field. They can be used for the development of vaccines, as well as drug and gene therapy. This platform has wide biomedical applications especially in development of vaccines production [28].

VLPs are not infectious and therefore it will initiate the im-

Table 2. Veterinary viral vectored vaccines licensed and available for commercial use in the United States

Species	Pathogen/diseases	Antigen	Products	Manufacturer
Canarypox vector				
Dog, cat	Canine distemper virus	HA and F glycoproteins	Recombitek	Boehringer-Ingelheim
	Feline leukemia virus	Env, gag, pol	Purevax FeLV	Boehringer-Ingelheim
	Rabies virus	Glycoprotein G	Purevax Rabies	Boehringer-Ingelheim
Vaccinia vector				
Raccoons/coyotes	Rabies virus	Glycoprotein G	Raboral V-RG	Boehringer-Ingelheim
Alphaverpesvirus (HVT) vector				
Chicken	IBD, Marek's disease, ND	VP2 of IBDV, F glycoproteins of NDV	VAXXITEK HVT+IBD+ND Ultifend IBD ND	Boehringer-Ingelheim
	ND and Marek's disease	VP2 of IBDV, F glycoproteins of NDV	NEWXXITEK HVT+ND	CEVA
	IBD and Marek's diseases	F glycoprotein		Boehringer-Ingelheim
	Marek's disease and infectious LT	VP2 of NDV	VAXXITEK HVT+IBD Vectormune HVT IBD	CEVA
		Glycoprotein B	Vectormune LT	CEVA

From Vrba SM, et al. Vaccines (Basel) 2020;8:680 [16].
HA, hemagglutinin; F, fusion; HVT, turkey herpesvirus; IBD, infectious bursal disease; ND, Newcastle disease; IBDV, infectious bursal disease vaccine; NDV, Newcastle disease virus; LT, laryngotracheitis.

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mune system without producing the effect of the real illness of the disease vaccinated against. Its production runs through two main tactics, first via production of chimeric VLP using genetic insertion where the antigen is fused to the coat protein by genetic engineering, and then chimeric VLP is expressed in probable system. Secondly, chimeric VLP is generated by chemical conjugation of foreign peptides to the surface of the VLP. The VLP production can be carried out either on small scale or large scale in presence of good manufacturing procedures [29] (Fig. 2).

VLPs stimulate the immune response through one of the following pathways: (1) stimulation of innate immunity through toll-like receptors and pattern recognition receptors; (2) induction of strong humeral response; and (3) enhancement of the uptake, processing and presentation by antigen presenting cells (APCs). The nano-sized VLPs can be engulfed by APCs and degraded, which leads to T cell activation with inducing strong immune responses even in the absence of adjuvants [30].

The selection of expression vector is one of the major factors in VLP generation. The reports showed the successful production of VLPs indicating that bacterial, yeast, and insect systems are used where the insect platform has a wider utilization compared to the other platforms [31].

The well-characterized *Escherichia coli* strains are considered one of the successful used as an expression vector. It has disadvantages which can be overcome, such as inability to produce recombinant proteins with post-translational modifications, inability to generate the proper disulfide bonds which mainly affect the protein solubility problems, and the contamination of the prepared recombinant proteins with endotoxins. *E. coli* systems are a well-accepted technology which fulfills research and industrial requirements [32].

Insect cell-based expression systems are widely used for VLP production on the laboratory or industrial scale due to a number of advantages. It is characterized by its fast growth rates in animal product-free media, the capacity for large-scale cultivations, and the ability of post-translationally modifying the recombinant proteins similarly to mammalian cells [33,34]. The VLPs produced in the insect cells using the baculovirus are facing technical and practical obstacles make its field application is delimited [35]. Moreover, the chance of contamination of VLPs with the baculovirus makes the purification of the final product is expensive due to the downstream bio-separation processing steps [36].

In the veterinary field, although many entities are still inside the laboratories, some of them have been recognized in the veterinary field and became available in the global market such as porcine circovirus type 2 (PCV2) VLP-based vaccines Porcilis PCV (Intervet International, Boxmeer, The Netherlands) [37]. In following sections, some of VLP-based vaccines will be discussed which were applied on some of viral diseases of veterinary importance.

Rift Valley fever

VLP-based vaccines were produced against an important zoonotic virus which is RVFV. Näslund et al. [38] in 2009 were able

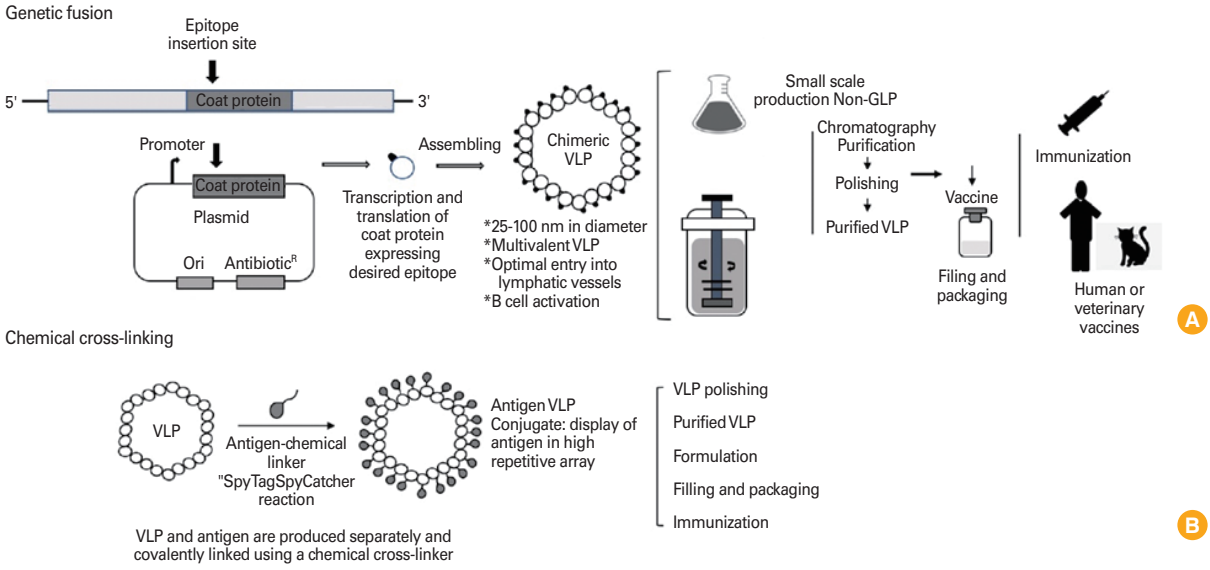

Fig. 2. Illustration of virus-like particles (VLPs) production using different approaches. **(A)** Genetic fusion. **(B)** Chemical cross-linking. From Caldeira JC, et al. Viruses 2020;12:488 [29]. GLP, Good Laboratory Practices; GMP, Good Manufacturing Practices.

to produce the RVFV-VLPs in mammalian cells (293T cells) and expressing the viral structural genes successfully. The vaccine was able to produce high titers of neutralizing antibodies *in-vitro* and would be able to protect mice from the virus challenge. The vaccine showed high profile of safety in mice [38].

Foot and mouth disease

FMDV is one member of the family Picornaviridae which has a distinctive advantage that it could support the VLPs platforms strategy. The family can self-assemble resulting in mature capsid proteins and consequently into VLPs. These VLPs were generated by co-expression of viral proteins (P1 polyprotein, nonstructural protein 2A and protease 3C) using the baculovirus expression systems. The FMDV-VLPs were generated using the baculovirus expression system. FMDV-VLPs were tested in guinea pigs where animals were immunized twice with the VLPs. FMDV-specific neutralizing antibodies were generated in VLP-immunized animals, but their levels were lower than those induced by the conventional vaccine [39-41].

Bluetongue

Bluetongue is a vector-borne disease of ruminants caused by BTV that causes hemorrhages and ulcers in the oral cavity and upper gastrointestinal tract [42]. The immunity of BTV-VLPs produced in baculovirus expression platform was developed for all four major structural proteins (VP2, 3, 5, and 7) and when compared with traditional vaccines, the VLPs candidate proved its superiority and powerful efficacy [43]. In combination with adjuvants, the multiprotein BTV-VLPs have been tested in the susceptible host, sheep. The multivalent adjuvanted VLPs candidate proved its efficacy and succeeded to ward off a virus challenge [43]. The multiprotein BTV-VLPs prompted high neutralizing-antibody titers in comparison to a monovalent protein, the VP2. Moreover, recent studies have revealed that the outer capsid is essential for complete protection regardless of the geographical origin of the BTV for the development of specific serotype vaccine [44].

mRNA based platforms (The Software of Life)

mRNA based vaccines are considered one of the promising types that have become widely used in both the medical and veterinary fields. These vaccines are characterized by the appropriate degree of safety and the speed of the immune response when injected into the body. One of their advantages, that make this type the best, is the speed of its manufacture, and sometimes there is no need for the virus itself, which

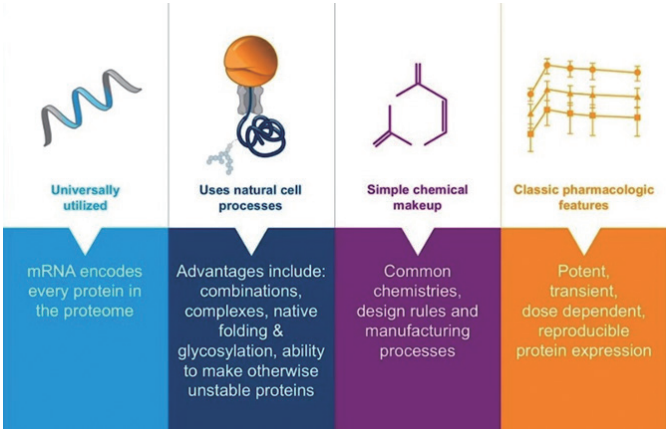

Fig. 3. Advantages of messenger RNA (mRNA) (Moderna Inc., Cambridge, MA, USA; https://www.modernatx.com/power-of-mrna/science-of-mrna).

makes its manufacturing on a large industrial level, is safe (Fig. 3). This feature makes the mRNA-based vaccines the most suitable choice in the situation of emerging diseases and other diseases such as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) which is known publicly by coronavirus disease 2019 (COVID-19) epidemic [45]. Therefore, from the time the dreaded coronavirus epidemic appeared until now, this type of vaccine is the fastest in manufacturing, the most widespread and suitable for these dangerous epidemiological conditions. To stand on the recent applications of this realm, a thorough internet search was conducted in the scientific web pages and its applications in combating emerging animal diseases. The results always were focused on the battle against the coronavirus epidemic that emaciated the world leaving behind more than 11 thousand deaths in Egypt [46] and more than 2.5 million deaths worldwide. The numbers are still on the rise at an unprecedented pace.

There are two main types of mRNA as vaccines, the first is the non-replicating mRNA and the second is self-amplifying RNA (saRNA) [47]. Conventional mRNA-based vaccines encode the proteins of interest with the both untranslated regions, whereas saRNA, beside the target antigen, encode the proteins responsible for viral replication proteins that enables intracellular RNA amplification and profuse protein expression [48]. Recently, this technology has been dramatically innovated and brought out for the scientific community more validated and developed synthetic mRNAs in terms of immunogenicity and efficacy [49]. This type of vaccines may need adjuvants (polymers or lipid nanoparticles) as a ferry carrying mRNA inside the targeted cells to do its instructions. While, other candidates provoke powerful responses in the absence

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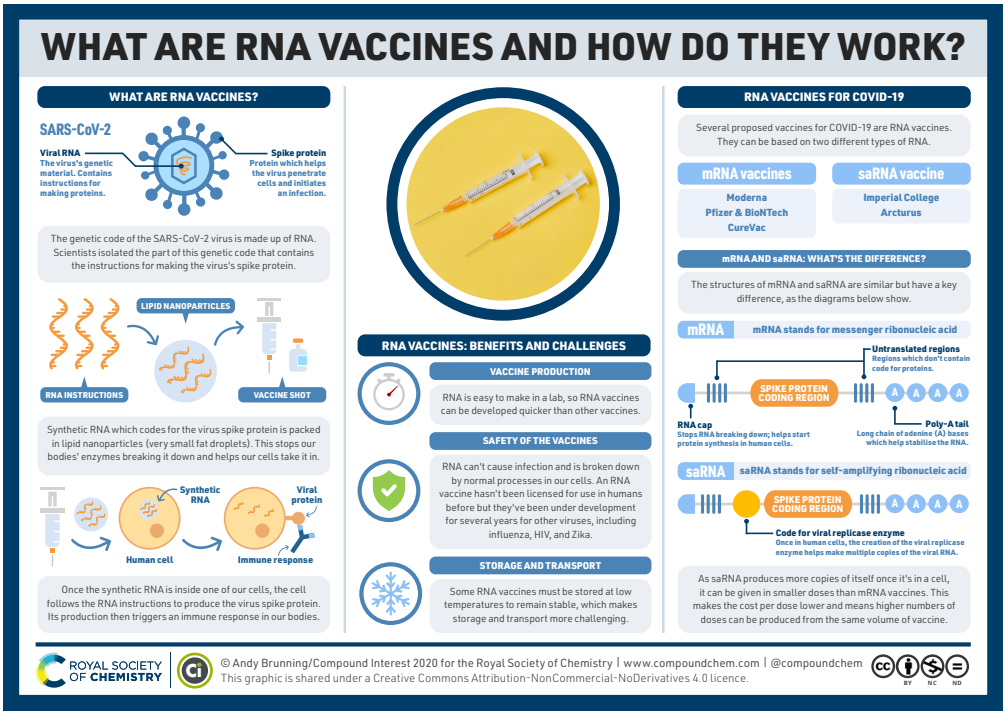

Fig. 4. Messenger RNA (mRNA) vaccines. From Brunning A. What are the COVID-19 RNA vaccines and how do they work? [Internet]. London: Royal Society of Chemistry; 2020 [cited 2021 Mar 24]. Available from: https://www.compoundchem.com/2020/12/02/rna-vaccines/ [54]. mRNA, messenger RNA; COVID-19, coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; sa RNA, self-amplifying RNA.

of adjuvants [50].

Coronaviruses, including SARS-CoV, Middle East respiratory syndrome coronavirus, and SARS-CoV-2 have four structural proteins where the structural (S) protein is considered the key protein which responsible for activating the immune response during infection [51]. One of the common features among these strains is sharing mostly the same antigenicity with very little variations with the bovine coronavirus [52]. The receptor-binding domain, a fragment of S protein, initiates both the humoral and cellular immune responses [53]. Hence, this protein is considered an ideal candidate to produce an mRNA vaccine. However, the structural features of this vaccine may affect its behavior inside the body, in addition its safety and efficacy in humans is undetermined [54,55] (Fig. 4).

Differentiation of Infected from Vaccinated Animals Technology

A vaccine which able to differentiate (or segregate) between infected and vaccinated animals can be referred as a DIVA vaccine and SIVA (segregation of infected from vaccinated animals) vaccine. This is mostly accomplished by deleting an immunogenic antigen being vaccinated against. One of the important benefits of this approach is establishment of disease eradication programs coupled with limiting the spread of a disease, though the infected animal is not being serologically mixed with vaccinated ones.

Foot and mouth disease

Three strains of the FMDV (A, O, and SAT 2) were detected in Egypt. Genetic variation was recorded between the isolates within the same season. The evolution rate of the SAT2 strain was the highest while serotype A had less, and serotype O the least [56]; therefore, there is necessity to establish varied strategies for vaccination in Egypt. Globalization, international trade, and vast animal movements introduce a lot of threats where some imported strains are detected taken in consideration that it is not included in the vaccine [57]. That is why scientific research groups always recommend that modern vaccines should differentiate between infected and vaccinated animals. Lubroth et al. [58] in 1996 formulated a FMDV vaccine from 2C protein which become a basis for differentiation between vaccinated and carriers. Many other DIVA vaccines have been produced with different methods and one concept, where results varying between success and failure [27]. By 2004, several commercial enzyme-linked immunosorbent as-

say (ELISA) test kits, that functioning as DIVA tests, were commercially available. Some of which are species-specific (Ceditest FMDV-type O; Cedi Diagnostics B.V., Leystad, The Netherlands) and others work for all species (Ceditest FMDV-NS; Cedi Diagnostics B.V.). NSP antibodies are induced by infection but not by immunization [59]. These tests were found to have 90% sensitivity and 99% specificity rates to differentiate between infected and vaccinated.

Bovine respiratory syncytial virus

The viral RNA genome consists of ten genes encoding eleven proteins. Among these proteins, the fusion protein F and the glycoprotein G induce detectable neutralizing antibodies and mucosal immunoglobulin A (IgA). Besides, F, N, M2, and P proteins are recognized by memory CD8+ T lymphocytes from bovine respiratory syncytial virus (BRSV)-infected calves [60]. The small hydrophobic protein (SH) gene deleted recombinant BRSV vaccine (ΔSHrBRSV) was evaluated concurrently with two subunit candidates that proved to be advantageous as they aided in DIVA. These vaccines were adjuvanted by oil emulsion or immune-stimulating complex compounds. The recombinant vaccine (ΔSHrBRSV) showed nearly complete coverage in the vaccinated calves that lasted for more than a month [61].

Bluetongue virus

The traditional vaccines of BTV can interfere with the epidemiological surveys and to make the differentiation between vaccinated and infected animals with BTV is complicated. Modern vaccines which used the concept of DIVA depend mainly on eliminating at least one viral protein form the produced vaccine. Hence, these types of vaccines are protein-based using expression systems such as recombinant capripox and canarypox viruses [62,63]. Recombinant VP2 of BTV-8 and NS1&2 of BTV-2 were produced, expressed in a baculovirus expression system and adjuvanted with an immune-stimulating complex. The subunit vaccine showed both cellular and humoral immunity with full protection against virulent BTV challenge in calves with detection of high level of VP7 antibodies in challenged animals in comparison of its low level in vaccinated animals [64,65].

Bovine herpesvirus type 1

Production of the DIVA vaccines needs the development of diagnostic assays alongside. In German, 1997, authorities adopted Legislation for the protection of cattle holdings from an infection with BoHV-1. This approach was established by using glycoprotein E (gE; non-essential protein) deleted BoHV-1 or DIVA vaccines along with the necessity of recognizing of gE-specific antibodies by gE-blocking ELISAs [66]. The prosperous applications of the novel approach towards DIVA concept successfully revealed the precious technology to obtain the required results. Chowdhury et al. [67] in 2021 designed a recombinant BoHV-1 triple mutant virus in parallel with gE cytoplasmic tail specific blocking ELISA as a diagnostic test used to differentiate between the vaccinated and infected calves. This mutant vaccines and ELISA required the production of mouse monoclonal antibody which was expressed in *E. coli*. These vaccines would be cost effective and less laborious since the viruses need propagation on the mammalian cell lines.

Nano-vaccinology

Nanotechnology was ubiquitous since early 70s and would be defined as the materials with a nanoscale size range 1–100 nm [68]. Later, other terms were reformed such as nano-vaccines, nanomedicine, and nano-theranostics, i.e., diagnostic and therapeutic [69].

Nano-vaccines are evolving and novel technology in the field of vaccine manufacturing. This emergence comes from its invigorating superiority over the traditional vaccines where nano-vaccine is able to stimulate both types of immunity, with long lasting solid immunity plus wide safety margins [70,71]. In terms of storage and transportation, these types of vaccines are characterized by its stability at room temperature and no need for deep freezing [72]. One of the best advantages is the diversity of delivery routes administration which includes parenteral, oral, and respiratory airways [73,74]. The size of the nanomaterial is crucial in determining the applicability of the nanoparticle used in vaccine production. For instance, nanoparticle with size range 20–100 can enter the lymphatic system directly in comparison to the size range 200–500 nm particles [75]. Other physical and chemical properties of the used nanoparticles are important in selection of the material. Nanoparticle shape, surface charge, and hydrophobicity characteristics are also important aspects must be taken in consideration when selecting a nanoparticle in nano-vaccine design [76]. There are plenty of nano-vaccines that are readily available which utilize variable particle formulations in bovine and other animal models [77] (Fig. 5).

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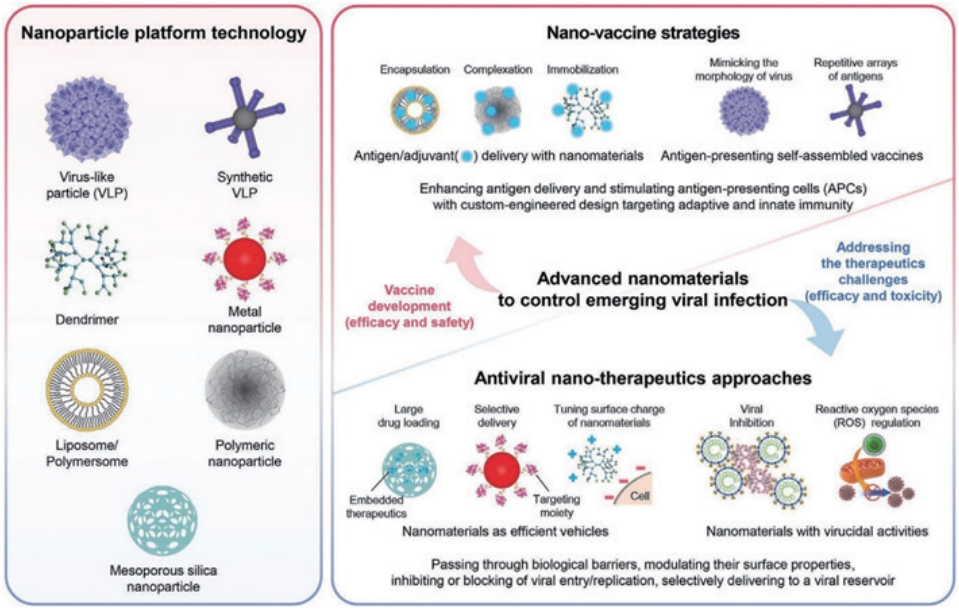

Fig. 5. Nanomaterial-based vaccines strategy and approaches. Overview of nanomaterial-based vaccines and therapeutics for the prevention of emerging viral diseases. Nanovaccines show the feasibility of nanomaterials with multiple modalities to potentiate and enhance immune responses by taking advantage of their use as delivery vehicles or antigen-presenting, self-assembled vaccines. Antiviral nanotherapeutics highlight the versatile use of nanomaterials by mimicking the biochemical and structural features of viral particles. From Kim E, et al. Adv Mater 2021;33:e2005927 [77].

Foot and mouth disease virus

PLGA, PLG, or poly (lactic-co-glycolic acid) is a copolymer nanoparticle used as a vehicle. Two types of PLGA, chitosan-coated and chitosan-trehalose loaded with plasmid encoding precursor protein P1-2A and 3C protein and the whole inactivated FMDV were designed. The PLGA nanoparticles induced strong IgA and weak immunoglobulin G responses. Neither group of vaccinated animals was fully protected against viral shedding or clinical disease [78].

Bovine respiratory disease complex

BRD is a worldwide health concern in the feedlot cattle causing morbidity and mortality in the young livestock with major economic losses to the producer. The viruses involved are bovine viral diarrhea virus, BoHV-1, bovine parainfluenza virus type 3 (BPI3V), and BRSV [11].

Bovine viral diarrhea virus

Mesoporous silica nanoparticles have been used as a carrier for E2 glycoprotein as well as an adjuvant. This nano-vaccine proved its efficacy *in-vivo* in mice [79], with prolonged cellular immunity lasted up to 6 months after immunization which resembles that obtained by traditional inactivated vaccines. After lyophilization of the prepared nano-vaccine, it elicited immunity lasted up to 14 months exceeding the live attenuated vaccines [80].

Bovine respiratory syncytial virus

Nano-vaccine containing polyanhydride nanoparticles encapsulating the recombinant BRSV-F/G (F and G proteins from BRSV) were developed. The nanoparticle was able to maintain the immunogenicity of the antigens resulting in steady release of the antigens for more than a month in the neonatal calves [73]. Another protein target was used to design a nano-vaccine is the N nucleoprotein. In cattle, vaccination with the N nano-vaccine delivered appropriate protection against experimental virus challenge with good cellular immunity [81]. When cattle were immunized with both F and N nucleoprotein nano-vaccine, it induced complete protection after an experimental challenge [82].

Bovine parainfluenza virus type 3

Immunization of cattle with an intranasal hemagglutinin-neuraminidase and fusion protein F glycoproteins encapsulated in PLGA nano-vaccine against BPIV3 induced a stronger humoral immunity response [83]. Later, they compared the produced nano-vaccine against the commercial, intranasal live attenuated BPI3V vaccine (Rispoval RS+PI3 intranasal; Zo-

etis, Dublin, Ireland), and found the pronounced immune response of the former over the later [84].

Bioinformatics-Assisted Vaccine Designing (Vaccinomics)

Vaccinomics is a multifaceted field that compromises the computational biology, and biostatistics to provide a comprehensive understanding of the genome of targeted pathogens leading to vaccines development. The basic idea behind this emerging technology is that it seeks to benefit from our comprehending of the immune response and then to precisely target those parts of the virus, the antigen markers, that will enable the immune response to surround the virus.

Reverse vaccinology

This process of developing vaccines was emerged at late 1990s when conventional vaccines against *Neisseria meningitides* B strains (MenB) were not able to protect against the bacterial infection. By the year 2000 a cornerstone in development of the reverse vaccinology was recorded in two main researches done through a consortium between a private biotechnology pharmaceuticals vaccine firm Chiron Corp., The Institute for Genomic Research, and Oxford University. The team succeeded to reveal the whole genome of MenB and became the seed for using a bottom-up approach from genome to vaccine technology [85]. A vaccine containing multiple immunogenic domains against hepatitis B virus was designed by Mobini et al. [86] in 2020. Using 17 web-based bioinformatics tools, Mobini et al. [86] designed and predicted the target genes and evaluated the antigenicity and immunogenicity in silico [87] (Fig. 6).

Fig. 6. Course of Vaccine Development from the point of Reverse Vaccinology. The path to develop a vaccine using this approach could be summarized in the following steps: (1) computer analysis of the whole genome, (2) identify antigens of importance, (3) test its protective response in animals, (4) molecular epidemiology, (5) selected antigens tested in large scale, (6) license from decision-maker agencies, (7) policy-making recommendation on how the vaccine should be used, and finally (8) approved vaccine is commercially available. From Sette A, et al. Immunity 2010;33:530-41 [87].

Conclusion

Epidemics have become inevitable each year, sending a warning to the scientific community that there is an urgent need to work on the developing of vaccines. Nowadays, the interest in vaccinology was dramatically developed around the world as its importance was expected in a manner to enter the era of the second generation with its field applications. It has become necessary to expand understanding of the way the immune system deals with infections, consequently, develop novel vaccines suitable to each virus which is called "type-tailored vaccine." For instance, revealing the complete genomic structure of viruses makes the understanding of the life cycle clearer and thus the epitopes and major proteins responsible for tropism and replication can be discovered. This leads to the development of safe vaccines that do not depend on the complete virus, which can lead to the emergence of the disease, named "vaccinomics." Traditional vaccines are still the most common and widely used, especially in countries with few resources and capabilities. However, it has become necessary to develop these vaccines in order to keep pace with global development.

In term of laboratory research, the potential of VLPs as effective vaccine candidate against some of emerging viral diseases in animals is obvious. Many VLPs vaccines are still in

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the pipeline of clinical trials. The VLPs produced in the insect cells using the baculovirus are facing technical and practical obstacles make its field application is delimited due to interference with the immunogenicity of the VLP-based vaccines. Moreover, the chance of contamination of VLPs with the baculovirus makes the purification of the final product is expensive due to the downstream bio-separation processing steps.

Today, mRNA vaccines are amongst the most sought-after technologies, where they will be likely one of the most key platforms of the vaccinology future. However, it is pessimistic to say that, till now, we do not have an approved mRNA vaccine and scaled up to enter the industrial capacity. This type of vaccines requires thorough studies of its safety, immunogenicity, and efficacy at least in laboratory animals. All these mentioned repercussions proved indefinitely that producing an mRNA vaccine can be tiresome for the vaccinology community. Given that, the time required for developing an employed mRNA vaccine is short perhaps 2 months, but the pertinent biological studies may take longer.

The use of non-replicating viruses as vectors, "viral-vectored vaccines," to carry the synthetic gene that codes the target protein is another approach to develop safe vaccines. The virus vectors were improved on the genomic basis to advance their ability to carry more than one gene, and replication competencies in order to tailor the desired immune responses inducing long-lasting immunity. The global pandemic of COVID-19 shed the light on this novel type of vaccine greatly. Despite the robust immune responses, long history of in-lab achievements, and wide applications in animal models, it puts the financial and technical aspects in the forefront and furthermore it limits their use in farm animal firms. Moreover, hurdles of the presence of past and maternal immunity may inhibit the vector itself or the target antigen.

DIVA capabilities are a cornerstone in eradication programs of emerging diseases. Most of the new technologies introduced in vaccinology can be a tool in the application of DIVA concept. The concept of differentiating between vaccinated and infected was and still successful in eradicating and control of devastating diseases affecting farm animals such as FMD and persistently infected animals with BVD. The main obstacle of FMD is its emergence with new serotypes due to its constant evolution each year, besides deficiencies in submitting outbreak samples to reference laboratories. This annual emergence makes formidable challenges to eradicate FMD.

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