DIVA Strategy in Modern Vaccinology: Shaping Disease Surveillance, Transmission, and Control in the Amrit Kaal Era

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Goat Farming

Goat is a multi functional animal and plays a significant role in the economy and nutrition of landless, small and marginal farmers in the country.

Compared to cow and other livestock farming, goat farming requires less space and additional facilities.

Goats are hence rightly called as "poor man's cow" since it has promises of good return that can serve as investment source.

Goats can adopt themselves with almost all types of agro-climatic conditions.

Goat has been playing multiple role in livelihood of the rural people by providing income, employment, nutrition, supporting crop production and risk aversion in case of crop failure.

Landless men and women are increasingly relying on goat keeping for their socio-economic upliftment.

Hence, maintenance of healthy goat is very important for the healthy family as well as healthy nation.

Economic impact of diseases in sheep and goat

- Estimated annual economic loss due to PPR in goats and sheep is Rs. 8895.12 crores, of which Rs. 5477.48 and Rs. 3417.64 crores respectively are due to the disease in goats and sheep (B. Singh *et al.*, 2014).
- The World Organization for Animal Health has identified PPR as a notifiable and economically important transboundary viral disease of sheep and goats associated with high morbidity and mortality.
- Losses due to PPR in goats are higher (74.88%) as compared to sheep (25.12%)
- The overall order with respect to the number of incidences has been found as:

PPR > FMD > sheep and goat pox > CCP > fascioliasis / distomatosis > enterotoxaemia > anthrax.

- The corresponding ranking order with respect to number of deaths was:

PPR > sheep and goat pox > enterotoxaemia > CCP > anthrax > fascioliasis / distomatosis > FMD.

Common diseases of goats in India

Bacterial diseases	Fungal diseases	Parasitic diseases	Protozoa/Rickettsial diseases	Viral diseases	Metabolic and nutritional diseases
Anthrax	Candidiasis	Endo parasite	Babesiosis	PPR	Mil fever
Brucellosis	Cryptococcosis	Ecto parasite	Coccidiosis	Sheep pox and Goat pox	Ketosis
Caseous lymphadenitis (CLA)	Ring worm		Theileriosis	CAE	Grain overload
CCPP	Aspergilosis		Cowdriosis	Orf	
Dermatophilosis			Anaplasmosis	Blue tongue	
Mastitis				FMD	
Foot rot					

WOAH listed diseases affecting sheep and goats

Caprine diseases	Multiple species diseases affecting sheep and goats
1. Border Disease 2. Caprine Arthritis encephalitis/ and Maedi-Visna 3. Contagious Agalactia 4. Contagious caprine pleuropneumonia 5. Nairobi Sheep Disease 6. Ovine Epididymitis (Brucella ovis) 7. PPR 8. Scrapie 9. Sheep pox and Goat pox	1. Anthrax 2. Aujeszky Disease 3. Blue tongue 4. Brucellosis 5. CCHF 6. Epizootic Haemorrhagic disease 7. FMD 8. Paratuberculosis 9. Rift Valley Fver

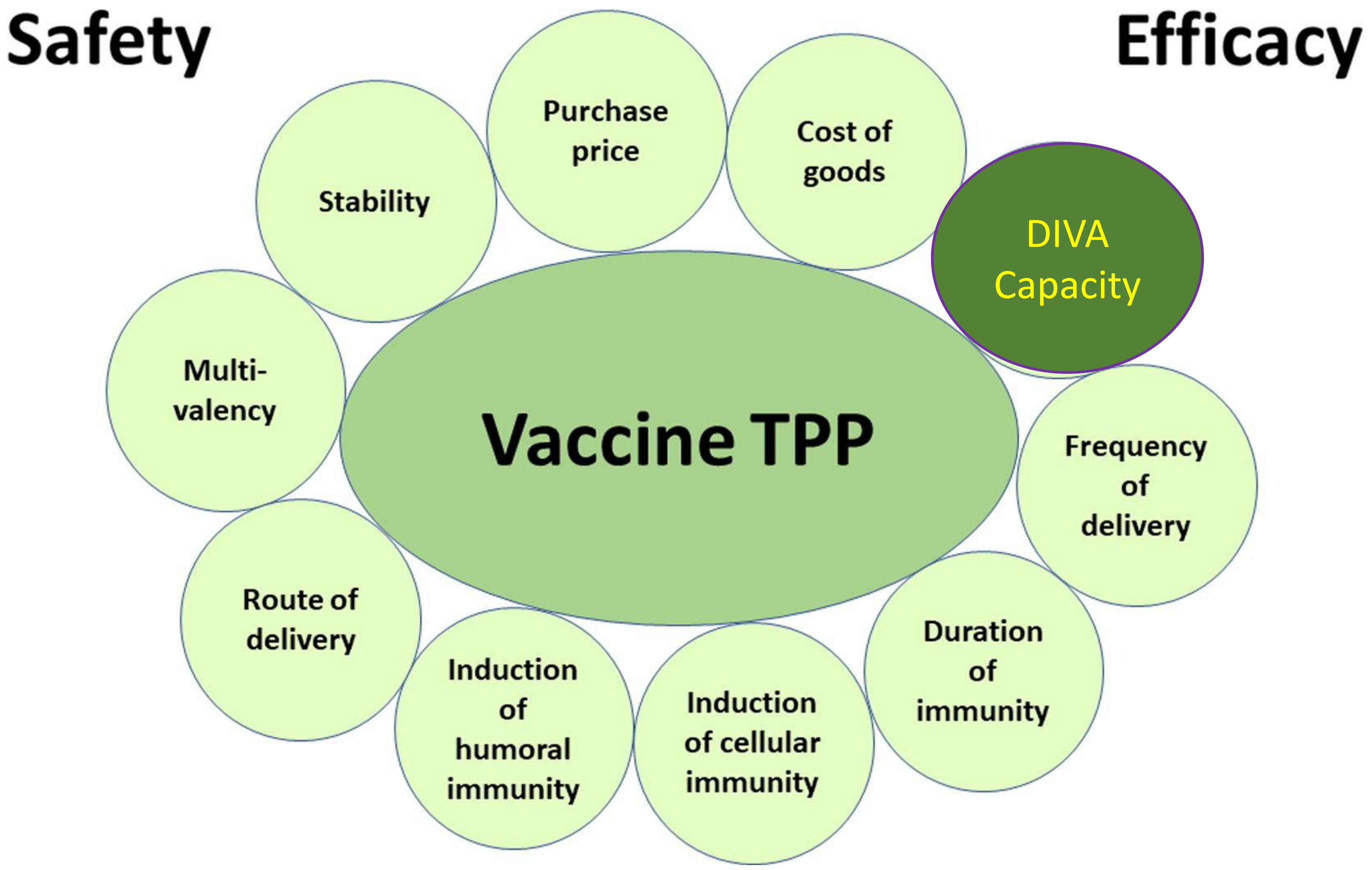
Diseases reported in India is indicated in red colour

As CAE, NSD, RVF are exotic to India, ICAR-NIHSAD is having diagnostic preparedness for effective surveillance and routinely extending its service to AQCS to maintain the country free from them

Roadmap of the key steps in the research phase of vaccine development

Disease → Pathogen identification, characterization and sequencing → Definition of host-pathogen interactions and mechanism of host immunity → Selection and production of target antigen(s) → Selection of platform technology for antigen delivery → Evaluation of safety and efficacy in suitable experimental challenge model → Prototype vaccine

Factors influencing the deployment of platform technologies in Veterinary Vaccinology



The construction of the vaccine target product profile (TPP) sets out the desired features for a successful vaccine and should be established at an early start of research and development.

Safety and efficacy are essential over-arching criteria.

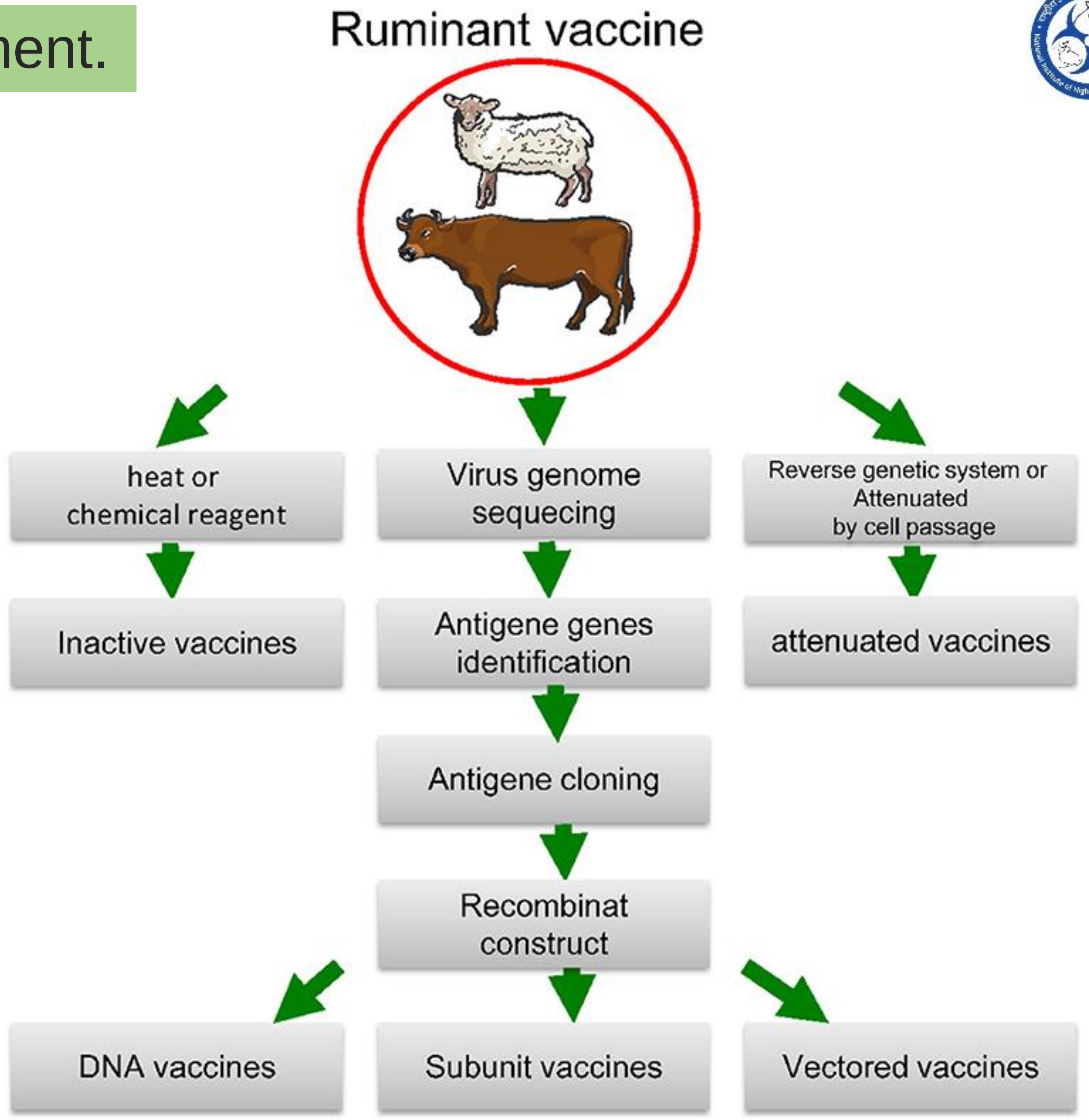
Once the TPP is defined, multiple factors influence the design and ultimate uptake of a new vaccine by end-users

Approaches to vaccine development.

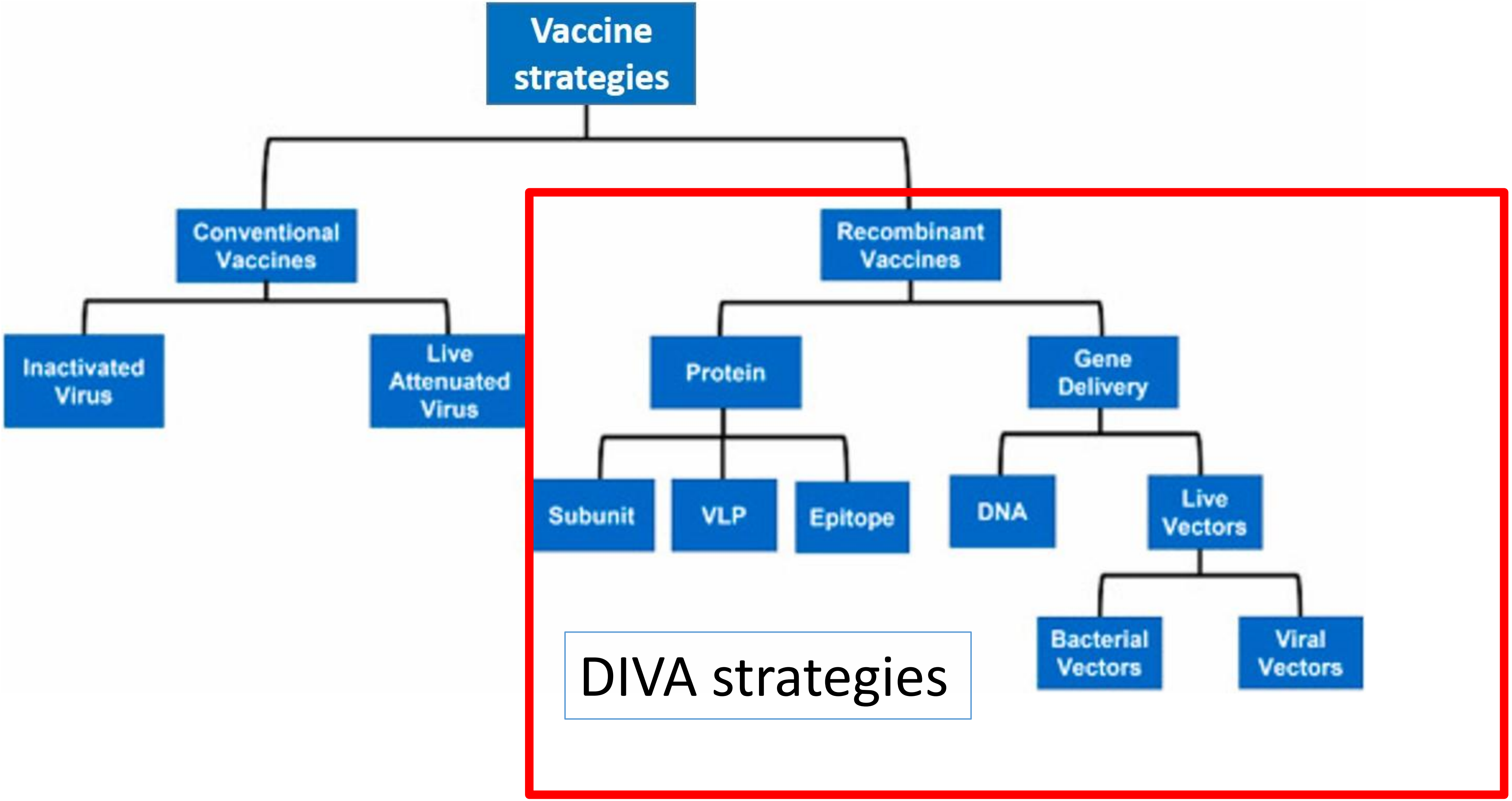
The primary objective of vaccination strategies is to establish immunity by exposing the host to a pathogen or its immunogenic components in a controlled, non-pathogenic form.

Challenge arises when the immune response from vaccination mimics that of a natural infection, complicating subsequent serological surveillance efforts essential for disease control and eradication.

This issue can be effectively addressed by DIVA (Differentiating Infected from Vaccinated Animals) vaccines, also known as marker vaccines, which are designed to produce an immune response distinct from that of natural infection.



Strategies to develop DIVA vaccines



Marker Vaccine

- A **marker vaccine** is a vaccine which allows for immunological differentiation of infected from vaccinated animals (DIVA) or Segregation of infected from vaccinated animals (SIVA) in veterinary medicine.

- Practically, omitting an immunogenic antigen present in the pathogen being vaccinated against, thus creating a negative marker of vaccination.

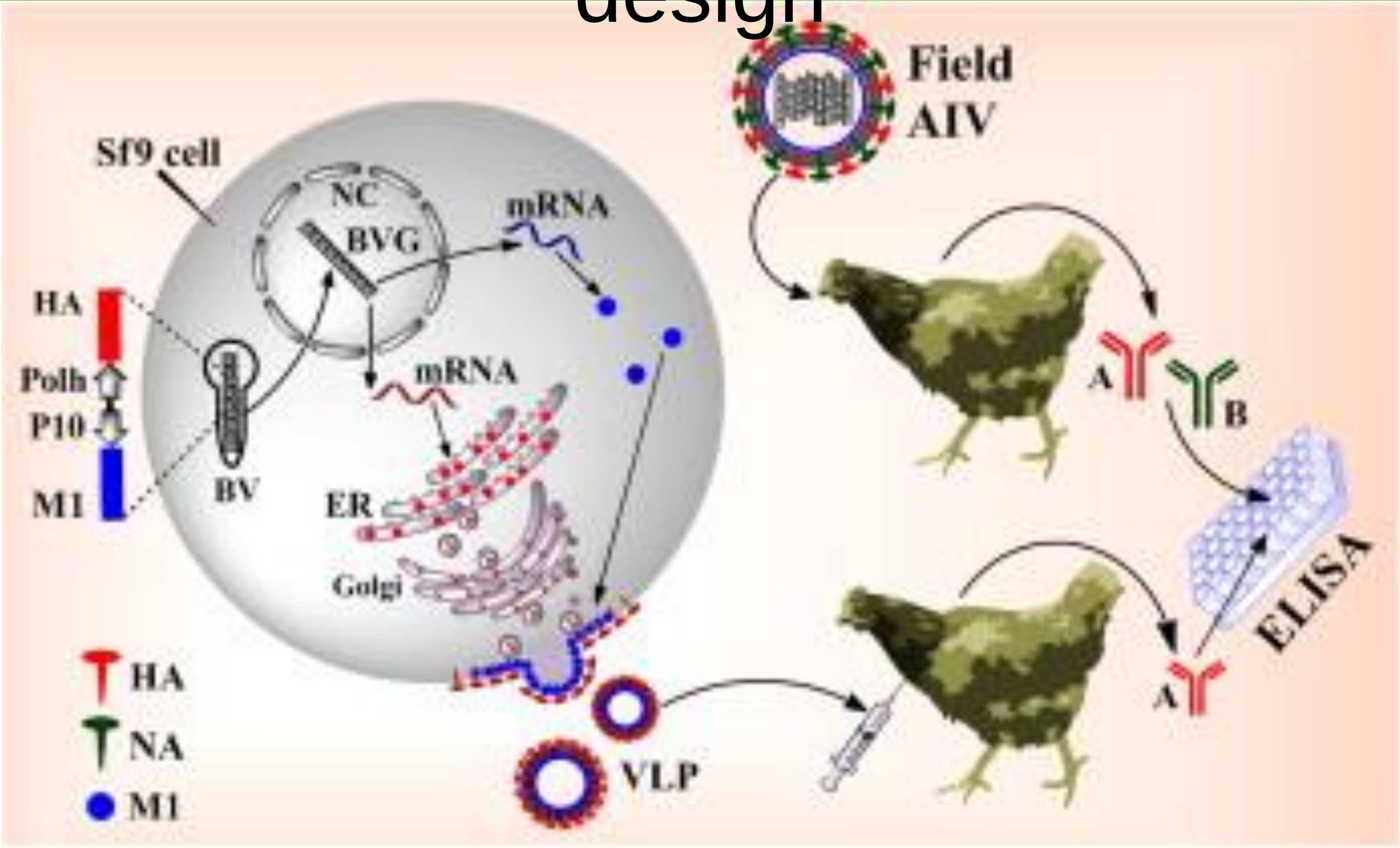
- In contrast, vaccination with traditional vaccines containing the complete pathogen, either attenuated or inactivated, precludes the use of serology (e.g. analysis of specific antibodies in body fluids) in epidemiological surveys in vaccinated populations.

- For example, Avian influenza, this can be achieved by using a vaccine based on a different strain (e.g. H5N2) than the current field strain (e.g. H5N1) and using a serological test that can differentiate between vaccine-induced antibodies (e.g. against N2) and antibodies against the field virus (N1).

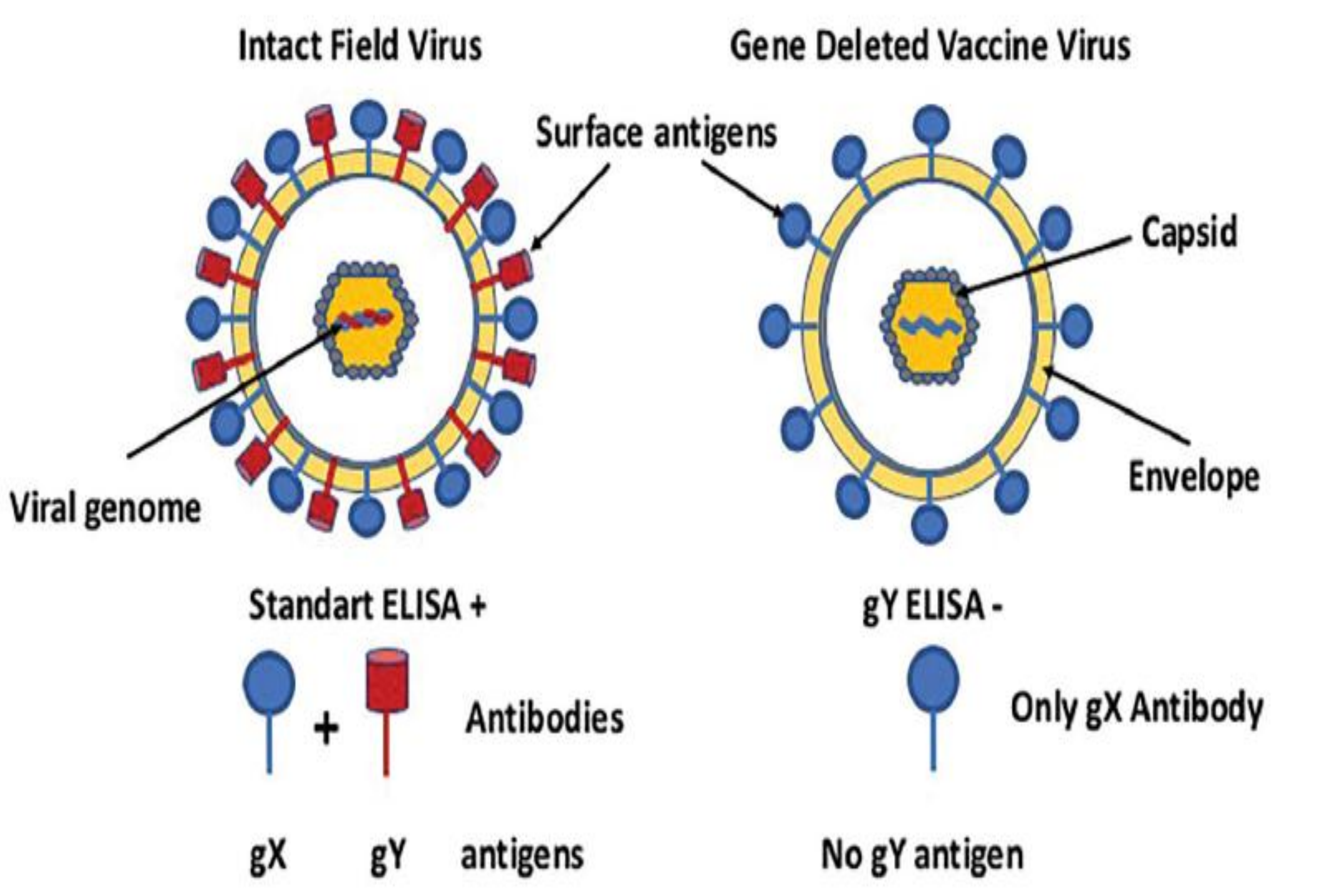
Marker Assay

- Marker assays or companion tests allow the serological differentiation between vaccinated and infected animals.
- The differentiation of vaccinated and infected animals is based on the absence of one or more proteins in the vaccine that are present in the wild type microorganism.
- Marker assays detect antibodies against those proteins that are absent in the vaccine. Therefore, naturally infected animals can be detected in a vaccinated population.

Virus-like particles: Promising platforms with characteristics of DIVA for veterinary vaccine design



ELISA in DIVA Vaccines



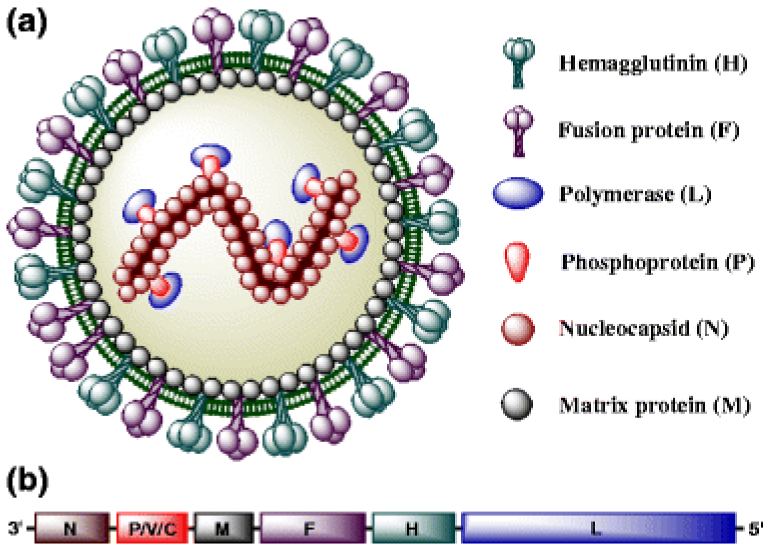
Development of the DIVA vaccines also requires the development of an accompanying diagnostic test

ELISA (Enzyme-Linked Immuno Sorbent Assay) is generally used to test the efficiencies of a vaccination.

These serologic tests can detect antibody response to specific protein(s) after infection

DIVA for PPR

- In the virion (**a**), the **N, P and L proteins** constitute the nucleocapsid that encloses the viral genome, while the **H and F proteins as two glycoproteins** along with the M protein form the viral envelope.
- The PPRV genome (**b**) encodes for eight proteins, and each gene encodes for a single protein except the P gene, which is translated into two nonstructural proteins, namely V and C proteins



Vaccine Strategy followed for PPR

Olden days:

1. Immunization with hyper immune serum
2. Heterologous vaccination (using rinderpest due to high homology

Current Prophylaxis:

1. Homologous virus vaccine-Live attenuated lyophilized vaccine
2. PPR and Sheep pox/goat pox combined vaccine

DIVA strategies for development of novel PPR vaccine candidates

- "Positive marker", by containing at least one heterologous protein or epitope in a potent vaccine, and
- "Negative marker", by the absence of at least one homogenous protein or epitope compared with a corresponding wild-type PPRV
- N protein serving as a negative marker plays a potential role in the development of DIVA vaccines.
- **Poxvirus vector vaccine-**CPV is an excellent vector for the development of recombinant multivalent vaccines to enable delivery of immunogenic genes from the host-specific PPRV sharing the same geographical distribution as the CPV.
- **Adenovirus vector vaccine- AdF + AdH (F and H surface glycoproteins)**
- **Recombinant PPRV-based vaccine**
- **Chimeric baculovirus vaccine**
- **Edible subunit vaccine**
- **Virus-like particle-based vaccine**
- **Nucleic acid vaccine (Naked DNA vaccines)**

The purpose of vaccination with DIVA vaccines is not only to prevent the disease, but also for the implementation of a serological surveillance system

DIVA tests for FMD

- Foot-and-mouth disease is a highly contagious disease of domestic and wild cloven-hoofed animals, including cattle, sheep, goats, buffalo and pigs.
- FMD causes substantial economic damage as a result of production losses, costs of control measures and trade impacts.
- The viral open reading frame encodes a single poly- protein that is cleaved by viral proteases into four structural (VP4, VP2, VP3 and VP1) and eight (L, 2A, 2B, 2C, 3A, 3B, 3C and 3D) nonstructural proteins (NSPs).
- An effective vaccination policy will reduce FMDV transmission and clinical signs of FMD, giving rise to concerns that FMDV might continue to circulate undetected in a vaccinated or partly vaccinated population where surveillance relies on clinical detection of the disease.
- Therefore, countries wishing to rapidly regain their FMD-free status after emergency vaccination must substantiate the absence of virus circulation (in the case of ongoing vaccination) and also the absence of any persistently infected animals (in the case of short-lived emergency vaccination).
- This requires a DIVA testing strategy employing serological tests to detect infection in vaccinated animals.

Role of DIVA in eradication scenario

- Emergency vaccination using DIVA vaccines could be one control tool for disease outbreaks in densely populated livestock areas.
- DIVA vaccination might limit the number of culled animals in the process of disease eradication, thereby enhancing public acceptance for disease control measures and limiting economic damage.
- In contrast to conventional vaccination, DIVA vaccination should always be used as protective vaccination meaning that vaccinated animals are kept to the end of a normal production cycle and their meat eventually marketed.

DIVA (differentiating infected from vaccinated animals) vaccines can reduce the transmission of viruses in animals and help to eradicate them:

- Virus transmission begins with shedding from the infected host through oronasal secretions, respiratory aerosols, faeces, or other se- and excretions.
- The routes of shedding are important for transmission that vary with the infectious disease.
- The amount and duration of virus shedding appear to largely determine the infectivity of an infected host.
- The fourth determinant of transmission, in addition to infectivity, contact features and environmental stability, is susceptibility of the recipient animal for a given virus
- **DIVA vaccines** along with their companion diagnostic tests can play a role in control of infections, ultimately leading to **eradication** of **viruses.**

Disease	How DIVA vaccines help
Pseudorabies virus	Reduces the amount and duration of virus shedding in pigs
Bovine herpesvirus 1	Reduces the infectivity of cattle
Classical swine fever virus	Prevents congenital infection
Bovine diarrhea virus	Prevents the transmission of virus from mother to foetus

Prompt diagnosis and treatment, prophylaxis, control and eradication of infectious diseases are certainly essential to achieve the goal of doubling farmer's income in goat sector.

Thank you