

Transient impacts of vaccination on livestock production: A holistic review

A. S. Rajput¹, D. Rajawat², Jisna K. S.³, A. Panwar², M. K. Patra^{1,3*}

¹Livestock Production Management Section, ICAR- Indian Veterinary Research Institute, Izatnagar, Bareilly- 243 122, India; ²Divisions of Animal Genetic, ICAR- Indian Veterinary Research Institute, Izatnagar, Bareilly- 243 122, India; ³Animal Reproduction Division, ICAR- Indian Veterinary Research Institute, Izatnagar, Bareilly- 243 122, India

Abstract

Vaccination is recommended as a cost-effective method for preventing health issues and ensuring the welfare of animals. However, the adoption rate continues to be poor in India, and only 61.4% of dairy farmers consider their livestock vaccination profitable. The poor adoption may be due to the potential negative effects of vaccination, such as transient stress, immune suppression, vaccine reaction, fever, decreased milk production, reproductive performance, and semen quality, respectively. Transient stress is a common occurrence in animals following vaccination. Sometimes, it can cause a brief rise in the number of white blood cells (WBC), especially neutrophils, and an increase in oxidative stress by producing reactive oxygen species (ROS). Vaccination in livestock also leads to a 5.5-16% transient decrease in milk production due to immune response-related stress. Vaccination also has potential effects on semen production and semen quality in bulls. Therefore, proper vaccination practices can help to mitigate these potential drawbacks and ensure that the positive impact of vaccination on animal production is maximized. So, several ameliorative strategies such as trace minerals, levamisole treatment, vitamin E, vitamin C, and selenium supplementation can mitigate this stress and ensure the overall health and welfare of the animals. Furthermore, the long-term benefits of vaccination such as protecting animal and public health, reducing animal suffering, and reducing the need for antibiotics ensuring the better health and production of animals. The future scope to minimize the vaccination-induced stress is the use of recombinant subunit vaccines; DNA and non-pathogenic virus vector vaccines are currently being explored for farm animals.

Keywords: Livestock, Milk production, Stress, Semen quality, Vaccination

Highlights

- Vaccination causes transient stress to animals that negatively impact milk production, semen quality, and pregnancy outcomes.
- Ameliorative measures using trace minerals, levamisole treatment, vitamins E and C, and selenium supplementation mitigate transient stress and ensure animal welfare.

INTRODUCTION

Livestock rearing is a primary livelihood option for smallholder and marginal farmers in India. To make dairy farming successful and sustainable, the farmer must follow a scientific methodology (Bisht *et al.*, 2020). The adoption of scientific dairy farming and production technologies led India to be the largest producer of milk in the world, contributing 24% of global milk production. The milk production of India has registered over 61% increase from 137.7 million tonnes in 2013-14 to 221.1 million tonnes in 2021-22 (Basic Animal Husbandry Statistics- 2022-23). In India, livestock vaccination plays a crucial role in ensuring animal health, well-being, and productivity. Livestock vaccination in India, driven by the need to mitigate economic losses due to diseases, has been instrumental in preventing decreased meat and milk

production, impaired reproduction, reduced work capacity, and increased animal mortality (Randolph *et al.*, 2007). Moreover, some of these diseases are transmitted to humans by infected animals (zoonotic diseases), posing a potential public health risk (Abdelnour *et al.*, 2018).

Furthermore, several transboundary animal diseases (TADs), which are highly contagious or transmissible, are epidemic, with the potential to spread rapidly across the globe and the potential to cause substantial socioeconomic and public health consequences. For instance, FMD alone led to reported losses of 14,000 million Indian rupees (Singh *et al.*, 2014), while other diseases like Hemorrhagic septicemia and Peste-des-Petits Ruminants (PPR) caused estimated losses of 5,255 and 8,895 million Indian rupees, respectively (Singh *et al.*, 2014). Vaccination is recommended as a cost-effective

*Corresponding Author, E-mail: drmanas01@gmail.com; manas.patra@icar.gov.in

method to protect animal health and welfare from infectious diseases (Roth, 2011). Vaccines are biological agents developed to induce immune reactions specific to pathogenic microbes to prevent or mitigate the spread of infectious diseases (Sander *et al.*, 2020). The continued development and expansion of livestock vaccinations will advance animal health and well-being, efficient food production, producer losses, and the threat of zoonotic diseases. While vaccination plays a critical role in safeguarding animal health and promoting livestock production, certain negative effects can be associated with vaccination (Van Herten and Meijboom, 2019). However, it's essential to be aware of potential drawbacks. The potential negative effects of vaccination on animal production are stress, vaccine reaction, fever, decline in milk production, and immune suppression. It's important to recognize that these negative effects are generally outweighed by the benefits of disease prevention, improved animal welfare, and enhanced livestock production (Mukhtar *et al.*, 2016). Proper vaccination practices, including selecting appropriate vaccines, following recommended administration protocols, using immuno-modulators, and monitoring animal health, can help mitigate these potential drawbacks and ensure that the positive impact of vaccination on animal production is maximized (Sharma *et al.*, 2020). From this perspective, the present review addresses the transient effect of vaccination on health and production in dairy animals and the current trends in prevention to improve production. Furthermore, we also addressed the strategies to mitigate them to enhance livestock production.

Current status of vaccination

The adoption rate for vaccination continues to be poor in India owing to weak research and extension and poor linkages with farmers. It was found that only 61.4% of dairy farmers considered vaccination of their livestock to be profitable (Rathod *et al.*, 2016). However, awareness of regular vaccination against major diseases in the livestock industry is considered a major limitation (McGuffey, 2017), given that the adoption of vaccination at the field level needs to be

improved. Major limitations dairy farmers encounter while practicing vaccination for dairy animals include lack of knowledge, reduced milk production, animal infertility, local reaction, fever, recurrence of disease, non-availability of skilled staff, and poor infrastructure (Hopker *et al.*, 2021). The government spends most public funds allocated to the dairy industry on curative veterinary care compared to preventive measures. There are various initiatives of the central and the state governments; still, farmers vaccinated their livestock only when a veterinarian or para-veterinarian visited their village under government-sponsored schemes (Bardhan *et al.*, 2015).

To enhance vaccination coverage in India, the Union government launched initiatives through a centrally supported Livestock Health and Disease Control Program (LH & DC). The main objective of the LH & DC scheme is to improve the animal health sector by way of the implementation of prophylactic vaccination programs against various diseases of livestock and poultry, capacity building, disease surveillance, and strengthening of veterinary infrastructure (Hopker *et al.*, 2021). In terms of the profitability of vaccination, the difference in perception varies widely between farmers and scientists (38.6%), extension workers and farmers (33.6%), and extension workers and scientists (5%) (Rathod *et al.*, 2016). This influence is due to the need for more awareness or the undervaluation of the risk of livestock diseases compared to the cost of vaccinating the animal (Ashfaq *et al.*, 2015). The disparities between the adoption of vaccination may be due to a lack of knowledge about diseases and poor infrastructure facilities. Scientists have a better perception regarding the adoption of vaccination as compared to extension workers and farmers due to a better understanding of diseases and their effects. This highlights the fact that, although the government of India has made substantial investments in disease control and prevention, there still needs to be better diffusion and adoption of vaccination at the field level. The adoption of vaccination depends on the following factors shown in Fig. 1.

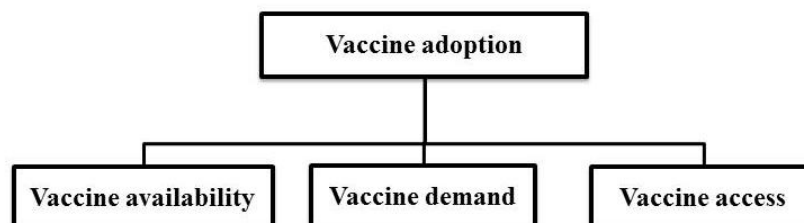


Fig. 1. Factor affecting the adoption of vaccination in field condition

Vaccination-induced stress

Vaccination-induced stress in animals refers to the physiological and behavioral responses that animals may exhibit after administering vaccines. Transient stress is common in animals following vaccination (Richeson, 2015). Vaccines are essential for preventing and controlling disease in livestock, but they can also temporarily activate the immune system and cause various stress-related reactions (Dhabhar and Viswanathan, 2005). Stress may be categorized as either acute or chronic. Acute stress (<24 h) boosts immunity and vaccination potential, while long-term chronic stress (several days to months) impairs the humoral immune response to the vaccine (Roth, 1985). Vaccination stress will directly or indirectly activate the hypothalamic-pituitary-adrenal (HPA) axis (Koolhaas *et al.*, 1999); the HPA axis is a major neuroendocrine system that controls reactions to stress and regulates many body processes. It is the common mechanism for interactions among glands, hormones, and parts of the mid-brain that mediate the general adaptation syndrome (GAS). The HPA axis contributes to the release of an adrenocorticotrophic hormone (ACTH), which stimulates adrenals to secrete and release glucocorticoid hormones, including cortisol into peripheral circulation (Marketon and Glaser, 2008; Lerch *et al.*, 2017). The high glucocorticoid levels over a long period trigger the apoptosis of pre-B cells, reducing the number of B lymphocytes and suppressing immunity (McGregor *et al.*, 2016). It's important to emphasize that vaccine-induced stress is usually short-lived and is a natural part of the immune response. Most animals quickly recover and return to their normal behavior and activity levels. Additionally, the benefits of vaccination in preventing potentially serious diseases and improving overall animal health and welfare far outweigh the transient stress following vaccination.

To minimize vaccine-induced stress, it is advisable to follow proper vaccination protocols, administer vaccines correctly, use immune modulators, and provide appropriate care and monitoring following vaccination (Wang *et al.*, 2023). Veterinarians and animal health professionals play a crucial role in ensuring that vaccines are administered safely and effectively to minimize animal stress and discomfort. To minimize stress and discomfort during vaccination, pain-relieving strategies are followed, such as topical anesthetics, the distraction of animals, the positioning of animals, and the pH of the vaccine. Vaccination stimulates the immune system to recognize and respond

to specific pathogens (Chen *et al.*, 2022). This immune response involves the production of antibodies and the activation of immune cells. This process can be physically and metabolically demanding on the animal body, leading to a transient stress response known as Immune System Activation. The vaccine also causes localized discomfort and pain at the injection site. Animals may exhibit discomfort, such as rubbing, licking, or decreased mobility in the injected area (Hervé *et al.*, 2019). Due to this, some animals may display altered behavior following vaccination. This can include changes in eating, drinking, and activity patterns. In some cases, animals may become more subdued or less active immediately after vaccination. This can impact nutrient intake and growth rates, particularly in young animals (Nakaya *et al.*, 2012; Richeson, 2018). An immune response to vaccination can sometimes result in a mild fever. Elevated body temperature is a common response to inflammation, a key immune response component (Rao *et al.*, 2017). While counterintuitive, the immune response triggered by vaccines can temporarily suppress the immune system's ability to respond to other challenges. This is a natural and temporary phenomenon as the immune system redirects its resources toward the specific pathogens the vaccine targets (Chetia *et al.*, 2017). Animals may respond differently to vaccines based on age, genetics, health status, and previous vaccine exposure. Some animals may be more sensitive to stressors associated with vaccination (Glass, 2004).

Vaccination and body temperature

Vaccination can sometimes lead to a mild increase in body temperature, commonly called a "vaccine reaction fever." Vaccines are designed to stimulate an immune response in the body (Schulze *et al.*, 2016). As the immune system becomes activated, it can lead to a mild inflammatory response associated with a temporary increase in body temperature. The increase in body temperature after vaccination is typically mild and transient (Scott *et al.*, 2001). The degree of temperature increase varies among individual animals. It may depend on factors such as the type of vaccine, age, overall health, and previous exposure to the vaccine or the pathogen. In most cases, the temperature increase remains within the normal range and lasts only a few days. It is a good practice to monitor an animal's body temperature after vaccination, especially in the hours and days following the administration of the vaccine to know the effect of vaccination. Exposure to vaccine antigens results in the production of interleukin 1 β (IL-1 β), IL-6, and tumor necrosis factor

α (TNF α), which are potent pro-inflammatory cytokines that are released by macrophages and other cells (Sivajothi *et al.*, 2018). The production of small amounts of pro-inflammatory cytokines is beneficial to the induction of a protective immune response. However, overproduction of the pro-inflammatory cytokines can have mild to severe adverse side effects (Parihar and Chauhan, 2021). These pro-inflammatory cytokines promote the synthesis of acute-phase proteins and act on the hypothalamus to induce fever and malaise (Roth, 1985).

In this context, Scott *et al.* (2001) reported that vaccinated animals with 9-way killed vaccines (BHV1, BVDV, PI-3V, BRSV, and 5-way *leptospiral bacterin*) exhibited higher (0.41-0.29°C) temperature than the control. Similarly, Ferreira *et al.* (2016) also state that after FMD vaccination, rectal temperature was higher in the vaccinated group than in the non-vaccinated after 24 h of vaccine administration. Rao *et al.* (2017) also reported higher rectal temperature in the first week of post-vaccination compared to the pre-vaccination, but it became normal from the second week onwards. In Murrah, bulls vaccinated with Raksha Triovac (FMD + HS + BQ oil adjuvant) showed mean rectal temperature (°F) of 102.59±0.04 following vaccination, which is significantly higher than pre-vaccination (Pankaj *et al.*, 2007). Similar trends were also seen in Mithun (*Bos frontalis*) with the FMD vaccine–Raksha-Ovac (trivalent, containing virus types O, A, and Asia 1- strains), which showed a rise in rectal temperature in first five weeks of vaccination, later temperature reduced gradually (Perumal *et al.*, 2013). Schulze *et al.* (2016) reported a rise in body temperature after phase I *Coxiella burnetii* inactivated vaccination (1.0±0.9°C) and observed peaks in the first 24 hours, then declined to normal. The blue tongue vaccine also caused an increase in rectal temperature ranging from 39.4°C to 39.8°C for three days in dairy cows and gradually became normal (Giovannini *et al.*, 2004). This rise in body temperature indicates that the animal immune system recognizes and responds to the vaccine, which helps build immunity. It is generally a body natural defence mechanism working to create immunity.

Vaccination and hematological or serum biochemical parameters

Vaccinations may influence hematological and serum biochemical parameters in animals. However, the effects can vary depending on the vaccine type, animal species, and individual factors (Shawky *et al.*,

2016). Vaccinations can sometimes lead to a temporary increase in white blood cells (WBC), particularly neutrophils, as a part of the immune response. It will not directly affect red blood cell (RBC) counts (Aikhuomobhogbe and Orheruata, 2006). However, stress related to the vaccination process might lead to temporary changes. Some vaccinations may cause a mild decrease in platelet count, but this is usually transient and not clinically significant. Vaccinations can also trigger the release of cytokines, which are small proteins that regulate the immune response (Gualandi, 2022). In some cases, vaccinations can cause a temporary increase in liver enzymes due to the immune response. Vaccinations may lead to shifts in serum protein levels, including acute phase proteins such as C-reactive protein (CRP), as part of the inflammatory response (Bijwal *et al.*, 1999).

Haemato-biochemical alterations related to the use of FMD hexavalent vaccine (O Manisa + O-3039 + A Iran 05 + A Saudi 95 + Asia 1 + Sat2) showed significant elevations in total leucocyte count (TLC), neutrophil, lymphocyte counts, serum activity of aspartate aminotransferase (AST), blood urea nitrogen and ceruloplasmin, respectively. However, there is no significant difference in RBC count, hemoglobin, and packed cell volume (PCV) between the vaccinated and the control animals (Shawky *et al.*, 2016). Moreover, the PPR vaccine in the goat led to increased lymphocyte count, which will consequently increase the phagocytosis ability of WBC and thus confer higher immunity (Aikhuomobhogbe and Orheruata, 2006). Similar trends in swine fever vaccination revealed increased total protein, creatinine, and globulin concentrations in serum compared to pre-vaccination in pigs (Chetia *et al.*, 2017). In earlier studies, an increase in total protein during the post-FMD and FMD-HS vaccination period was also recorded in cattle (Kumar and Singh, 2004) and cross-bred calves (Bijwal *et al.*, 1999). This variation in serum total protein during the post-vaccination period was observed, possibly due to higher levels of γ -globulin and overall transaminase activity (Gualandi, 2022). In context to cortisol, the rabies vaccine showed a substantial rise in blood cortisol levels after receiving the booster vaccination on day 30 compared to control (Reis *et al.*, 2013). Thus, the effect of vaccination on hematological and serum biochemical parameters in animals underscores the complex interplay between the immune system and physiological responses. These alterations are generally short-lived and reflective of the body's natural defence mechanism gearing up to establish immunity. Regular monitoring of these

parameters post-vaccination is essential for assessing the animal's overall health status. Any deviation from normal ranges should be interpreted in the context of the vaccination process and the animal's response.

Vaccination and oxidative stress

Vaccination-induced oxidative stress refers to the potential increase in oxidative stress levels due to receiving a vaccine. Oxidative stress occurs when there is a difference between the generation of reactive oxygen species (ROS) and the body's ability to effectively neutralize them with antioxidants (Rezaie *et al.*, 2007). ROS are molecules that contain oxygen and are natural derivatives of cellular metabolism. While they play a role in various physiological processes, excessive ROS production can lead to cellular damage and contribute to various health issues (Gao *et al.*, 2014). When an animal receives a vaccination, its immune system is stimulated to recognize and respond to the vaccine antigens (Contreras *et al.*, 2020). This immune response involves stimulating immune cells and producing molecules, including ROS, as part of the body defence mechanism. While ROS are involved in signaling and defence against pathogens, their overproduction can lead to oxidative stress.

Recent studies show that ROS significantly influences antigen-antibody interactions, lowering antibody activity and negatively influencing immunological function. The antibody response in tick recombinant antigens was associated with decreased antioxidant biomarkers in cattle (Contreras *et al.*, 2020). To evaluate the oxidative state, serum concentrations of hydrogen peroxide (H_2O_2), advanced oxidation protein products (AOPP), ferrous oxidation-xylenol orange (FOX), and total oxidant status (TOS) were evaluated (Grisham, 2013). Regarding oxidant biomarkers, vaccination shows a drop in TOS, AOPP, and H_2O_2 (Gao *et al.*, 2014; Han *et al.*, 2016). Vaccines that cause less oxidative stress result in a larger concentration of antigen-specific antibodies (Contreras *et al.*, 2020). The production of ROS is specifically linked to immune cell functions, such as those that involve cytotoxic activity and phagocyte microbicidal activity. Therefore, the antioxidant/oxidant balance significantly impacts how well immune cells function, and the antioxidant levels in these cells are crucial for keeping immune cells healthy in a low-oxygen environment, shielding them from oxidative stress, and maintaining optimal function (Aslani and Ghobadi, 2016). The potential effects of oxidative stress in animals following vaccination

include cellular damage. High levels of oxidative stress can damage cellular components, including lipids, proteins, and DNA. This damage may contribute to inflammation and tissue injury (Gessner *et al.*, 2017). Inflammation; oxidative stress can trigger inflammation, a natural part of the immune response. However, prolonged inflammation can be harmful (Han *et al.*, 2016). Antioxidant depletion; the increased ROS production during the immune response can deplete antioxidants, such as vitamins C and E, glutathione, and enzymes like superoxide dismutase. Antioxidants help counteract the damaging effects of ROS (Hu *et al.*, 2018) and immune response modulation; oxidative stress can influence the immune response, potentially affecting the ability of the immune system to function optimally (Contreras *et al.*, 2020). It is important to note that the body antioxidant defence mechanisms usually help mitigate its effects when vaccination-induced oxidative stress occurs. The transient and controlled increase in ROS production during the immune response is a natural part of the vaccination process. In healthy animals, the benefits of vaccination in preventing potentially severe infectious diseases generally outweigh the short-term oxidative stress. If there are concerns about oxidative stress, they may recommend strategies to support the animal antioxidant defence systems. These strategies include providing antioxidant-rich diets, using nutritional supplements, and ensuring proper hydration.

Vaccination and semen quality

Vaccinations in livestock can have potential effects on semen production and semen quality. Semen production and quality are critical factors in animal reproduction, as they directly impact fertility and breeding success (Bhakat *et al.*, 2011). While vaccinations are crucial for preventing infectious diseases and maintaining animal health, it is important to consider their potential impact on reproductive parameters (Perumal *et al.*, 2013). However, the effects can vary depending on factors such as the type of vaccine, animal species, and individual variations. The breeding bulls raised to produce frozen sperm require prompt protection from numerous bacterial and viral diseases. Due to the increased risk of disease in exotic and crossbred bulls, immunization has received special attention (Bhakat *et al.*, 2011). Vaccination increases body and testicular temperatures, lowering sperm quality (Bhakat *et al.*, 2010; Bhakat *et al.*, 2011). It also causes increased cellular damage and testicular degeneration leading to enhanced sperm abnormalities and decreased sperm motility, concentration, and

production of live cells (Bane and Nicander, 1966; Rao *et al.*, 2017). Vaccination also causes epididymal dysfunction, which may be the cause of a rise in the number of abnormalities in spermatozoa, resulting in decreased motility. In the Mithun bulls, increased sperm abnormalities, detached sperm heads, and cytoplasmic droplets were reported in the post-FMD-vaccinated period (Perumal *et al.*, 2013). The color of semen in vaccinated bulls was watery due to less sperm in the ejaculate compared to the creamy white pre-vaccinated bull. Alkaline phosphatase (ALP) and acid phosphatase (ACP) concentrations were also decreased in the semen (Perumal *et al.*, 2013). The Frieswal (HF x Sahiwal) bulls vaccinated against FMD, IBR, and HS+BQ had a deteriorating trend in semen quality parameters, with a gradual decline in mean mass and progressive motility (Mathur *et al.*, 2003). Semen characteristics of purebred Holstein Friesian, Jersey, and various grades of Holstein-Friesian or Jersey x

zebu crossbreds after FMD vaccination significantly affected increased variability in ejaculate volume. Semen volume was reduced by 6% post-vaccination period (Sukirman *et al.*, 2020).

It is important to note that vaccination may have transient effects on semen production and quality. Animal breeders often consider the timing of vaccinations during non-breeding to minimize any potential negative effects. To mitigate potential effects and ensure optimal reproductive performance, plan the vaccination strategically to minimize their impact on critical breeding periods. To minimize stress during and after vaccination, provide a balanced diet rich in antioxidants and regularly monitor semen quality. Remember that the overall benefits of vaccinations in preventing diseases and maintaining animal health far outweigh potential short-term effects on reproductive parameters. The effect of vaccination on semen quality in multiple species is documented below in Table 1.

Table 1. Effect of vaccination on semen quality parameters in cattle and buffalo

Breed	Vaccination	Findings	Authors
Buffalo	Rinderpest vaccination	Increase in the proportion of abnormal spermatozoa	Narasimhan <i>et al.</i> , 1970
Crossbred	Rinderpest vaccination	Decline in motility, concentration, and percentage of live spermatozoa	Radhakrishnan <i>et al.</i> , 1975
Murrah	FMD vaccination	Increase in concentration of abnormal spermatozoa and semen preservability declined	Tripathi and Saxena, 1976
Jersey	FMD vaccination	The livability, preservability, and motility of spermatozoa deteriorated	Saxena and Tripathi, 1977
Jersey	Rinderpest vaccination	Mild deleterious effects like pyrexia were noticed post-vaccination.	Gahlot <i>et al.</i> , 1990
Buffalo	Black quarter vaccination	The initial motility and live sperm count declined and total spermatozoal abnormalities increased	Murugavel <i>et al.</i> , 2013
Frieswal	FMD, HS, and BQ vaccination	Decline in mass activity and progressive motility of spermatozoa	Mathur <i>et al.</i> , 2003
Buffalo	FMD vaccination	Sperm concentration, motility, live sperm count, and intact acrosome count were decreased in post-vaccination	Singh <i>et al.</i> , 2014
Murrah and Sahiwal	RakshaTriovac (FMD, HS+BQ)	Decrease in sperm motility and mass activity	Pankaj <i>et al.</i> , 2007
Sahiwal	FMD vaccination	Significant decrease in mass activity and sperm concentration	Bhakat <i>et al.</i> , 2008
Karan Fries and Murrah	FMD vaccination	Significant decrease in mass activity, initial motility, sperm concentration, and total sperm concentration per ejaculate	Bhakat <i>et al.</i> , 2010

Cont. Table 1.

Table 1., Cont. ...

Breed	Vaccination	Findings	Authors
Mithun	FMD vaccination	Increase in protrusion and ejaculation time, whereas, a decrease in volume, mass activity, individual motility, live sperm, sperm concentration	Perumal <i>et al.</i> , 2013
Buffalo	HS and BQ vaccination	Decline in mass activity, sperm concentration, individual motility, and total sperm output per ejaculate	Bhakat <i>et al.</i> , 2015
Buffalo	FMD and HS+BQ vaccine	Libido and sexual behavior scores were decreased and mean reaction time was increased in the vaccinated group	Shelar <i>et al.</i> , 2019

Vaccination and conceptus development or pregnancy

Dairy cattle productivity largely depends on herd reproductive success, as the lactation cycle starts and is renewed by pregnancy (Lucy *et al.*, 1992). Pregnancy losses significantly impact dairy herd reproductive efficiency, with more than half of dairy cows that conceive losing their pregnancy during the first six weeks of gestation (Santos *et al.*, 2004). Infectious diseases such as infectious bovine rhinotracheitis (IBR), bovine viral diarrhoea (BVD), and leptospirosis are responsible for up to 50% of pregnancy losses in cattle (Khodakaram-Tafti and Ikede, 2005; McEwen and Carman, 2005). Infection with *Leptospira* species is known to cause fatal mortality, abortions, and infertility (Mineiro *et al.*, 2007). Vaccination measures established to lessen the burden of reproductive disorders, such as IBR, leptospirosis, and BVD, are not receiving adequate attention (Van Drunen, 2006). It is reported that cows vaccinated against IBR, BVD, and leptospirosis had a higher pregnancy rate and lower pregnancy loss when compared to control cows (Pereira *et al.*, 2013).

Moreover, dairy calves vaccinated with the *Leptospira interrogans* serovar hardjo vaccine had a higher first-service conception rate and total conception rate, and the culling rate was much lower (Dhaliwal *et al.*, 1996). In contrast to these findings, vaccination of heifers with the IBR vaccine showed conception rates of 30% and 78% in vaccinated and control heifers, respectively. After breeding, about 10-14% irregular estrous cycles were recorded in vaccinated heifers, higher than in control (Van der Maaten and Miller, 1985). Some studies showed that heifers vaccinated with the IBR vaccine only had 30% and 57% first and second-service conception rates (Chiang *et al.*, 1990). Thus, the vaccination stress on conception in farm animals is evident. Therefore,

ameliorative measures should be taken if vaccination is given at or near the insemination to improve the reproductive efficiency in dairy animals.

Vaccination and milk production

Vaccination in livestock leads to a transient decrease in milk production due to immune response-related stress. However, the effect is usually short-lived, and production typically returns to normal. It is well documented that vaccination is associated with animal stress, and dairy farmers experienced transient losses in milk yield in lactating cows after vaccination (Giovannini *et al.*, 2004; Bergeron *et al.*, 2008; Morgenstern and Klement, 2020). However, less reported literature on the transient loss of milk production after vaccination is available under the Indian scenario (Krishnaswamy *et al.*, 2021). A transient fever could be the cause of the post-vaccination milk decline. The effects of vaccination on milk production seem transitory and are not evident on 305-day yields (Dhaliwal *et al.* 1996). This is supported by Scott *et al.* (2001), vaccinated cows with BHV1, BRSV, BVDV, and PI-3V in combination with a 5-way leptospiral bacterin showed a significant decline in milk production on day 1 of post-vaccination. There was also a significant decline in milk production in dairy cows after vaccination with PI-3, BRSV, BHV-1, and BVDV types 1 and 2 containing the virus (Bergeron *et al.*, 2008). *Escherichia coli* bacterin-toxoid vaccination also showed a decline in milk production for four days (Musser and Anderson, 1996). In the *Coxiella burnetii* vaccine case, vaccinated cows produced lower milk than non-vaccinated cows (Schulze *et al.*, 2016). BHV1 vaccination also showed a decline in milk production per cow, which was only marginal but significant ($P < 0.05$) in the vaccinated group (Bosch *et al.*, 1997). The impact of the LSD (lumpy skin disease) vaccine showed a 5.5-16% loss

in milk yield in a milch cow in Jordan compared to the control (Abutarbush *et al.*, 2016). The short-term effect of the FMD vaccine on milk output revealed a slight drop in Deoni and cross-bred cattle (Krishnaswamy *et al.*, 2021). A bivalent modified-live vaccination against the bluetongue virus showed no significant changes in milk output between the groups that received the vaccine and those that did not (Monaco *et al.*, 2004). However, the average daily milk production increased by up to 3.9% following vaccination. The effects of vaccinations are just transitory (Juste *et al.*, 2009). Once the initial immune reaction subsides, milk production tends to return to its normal levels. The farmer needs to be aware of this potential temporary decline in milk production after vaccination. Still, overall, the long-term benefits of vaccination in ensuring the health and production of animals and the safety of the milk supply outweigh these short-term effects. The loss of milk production after various types of vaccination has been reported in multiple species and documented below in Table 2.

Ameliorative strategy to mitigate vaccination stress

Vaccination-induced stress in animals can have short-term effects on their well-being. Still, several ameliorative strategies can help mitigate this stress and ensure the overall health and welfare of the animals (Berrie *et al.*, 1995). Gentle handling of animals, positive reinforcement, environmental enrichment, vaccinating them individually rather than in groups, and vaccinations at the optimum time are preventive

measures to mitigate vaccination stress. Avoid vaccinating during extreme weather or when animals are already under stress. In some cases, it may recommend using sedatives or anxiolytic medications to help reduce stress and anxiety associated with vaccination.

Numerous studies have proven the effects of trace minerals such as selenium (Se), zinc (Zn), copper (Cu), and manganese (Mn) on immunity (Byrne and Murphy, 2022), health and growth performance of cattle (Berrie *et al.*, 1995). The influence of these minerals on the immune system has been linked to their function in the structure and functioning of antioxidant enzymes like glutathione peroxidase and superoxide dismutase, which enhance neutrophil migration and phagocytic function, lymphocyte proliferation, and antibody production (Bonaventura *et al.*, 2015). Injectable trace mineral administration has also positively affected antibody production and cell-mediated immune response to the bovine respiratory disease vaccine in beef (Roberts *et al.*, 2016) and dairy cattle (Palomares *et al.*, 2016). Levamisole is an immunomodulator that enhances immunity and refreshes the cell-mediated immune response by accelerating T lymphocyte differentiation and macrophage proliferation (Temizel *et al.*, 2012) and stimulating phagocytosis by monocytes. Levamisole treatment also ameliorates the vaccination stress on semen production performance in cross-bred bulls, revealing a significant decrease in reaction time, sperm abnormalities, and higher sperm concentration, total motile spermatozoa, total live spermatozoa, total

Table 2. Effect of vaccination on milk production in cattle and buffalo

Vaccine	Species	Loss	References
<i>Escherichia coli</i> bacterin-toxoid	Dairy cow	0.6 to 1.8 kg/day/animal for 3 days	Musser and Anderson, 1996
Bovine herpes virus-1	Dairy cow	0.54, 0.3, and 0.2 kg per animal/day on days 1-3 after vaccination	Bosch <i>et al.</i> , 1997
9 way killed vaccine	Holstein Friesian	2.53 kg/day	Scott <i>et al.</i> , 2001
Blue tongue vaccine	Cattle	10.5 gm/day/animal	Giovannini <i>et al.</i> , 2004
PI-3, BRSV, BHV-1, and BVDV	Dairy cow	0.63-1.83 kg/cow/day	Bergeron <i>et al.</i> , 2008
Q-fever vaccine	Dairy cow	1.4 kg less milk in the vaccinated group	Schulze <i>et al.</i> , 2016
LSD vaccine	Cattle	5.5-16%	Abutarbush <i>et al.</i> , 2016
LSD vaccine	Cattle	0.41 kg/day/animal for 5 days	Morgenstern and Klement, 2020
<i>Mannheimia haemolytica</i> sub-unit vaccine	Dairy cows	0.7 kg/day/animal for 3 days	Overton and Armfelt, 2020
FMD vaccination	Deoni Crossbred	90 gm/per day 360 gm/per day	Krishnaswamy <i>et al.</i> , 2021

sperm and total dose harvested in vaccinated bulls (Rowe *et al.*, 2014). Zinc content in the semen may thus be a valuable indicator of the possible cause of reproductive dysfunctions; zinc supplementation improved sperm motility in bulls. Vitamin E and C supplementation were also administered to mitigate vaccination stress (Rao *et al.*, 2017). The dietary supplementation with vitamins E and C could down-regulate the elevated ACTH concentration induced by stress and reduce cortisol production, lowering the vaccination-induced stress (Sahin *et al.*, 2002).

Furthermore, recombinant subunit, DNA, and non-pathogenic virus vector vaccines are currently the most cost-effective methods of producing antigens free from the exogenous materials associated with conventional vaccines (Thomson *et al.*, 2017). It's important to note that individual animals may respond differently to stress and vaccination. Additionally, staying informed about current best practices and animal handling and welfare advancements can help improve vaccination experiences and overall animal well-being.

Conclusions

Vaccination is a cost-effective method of preventing infectious diseases in animals. Following vaccination, transient vaccination stress is a part of the physiological immune response, which results in

increased body temperature decline in milk production, semen quality, and reproduction. However, the overall, long-term benefits of vaccination in ensuring the health and production of animals outweigh these short-term effects. Therefore, mitigation strategies such as injectable trace minerals, levamisole treatment, vitamin E, vitamin C, and selenium supplementation have revealed positive effects in dairy cattle following vaccination. The future scope to minimize the vaccination-induced stress using recombinant subunit vaccines; DNA and non-pathogenic virus vector vaccines are currently being explored for farm animals.

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