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Rakshavac T: A Cornerstone in the Prophylaxis of Tropical Bovine Theileriosis in India

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Abstract

Tropical bovine theileriosis, caused by the protozoan parasite *Theileria annulata*, represents a significant economic burden on the livestock industry in tropical and subtropical regions, particularly in India. This article examines Rakshavac-T, a live attenuated vaccine developed by Indian Immunologicals Ltd., as a critical tool for the prophylactic management of this debilitating disease. The review explores the etiology and epidemiology of *T. annulata*, the composition and immunological mechanisms of Rakshavac-T, its administration protocols, and its evaluated efficacy and safety. Furthermore, it considers the regulatory framework governing veterinary vaccines in India and the vaccine's market impact. A critical discussion is provided on the inherent challenges associated with live attenuated vaccines and the promising developments in novel vaccine technologies, including subunit and mRNA-based approaches. This comprehensive overview highlights Rakshavac-T's vital role in current disease control strategies while acknowledging the continuous evolution of vaccinology to address emerging challenges.

1. Introduction

1.1 Global and National Significance of Bovine Theileriosis

Bovine theileriosis, a tick-borne lymphoproliferative disease, poses a serious threat to cattle productivity worldwide, particularly in tropical and subtropical regions. Among the various *Theileria* species, *Theileria annulata* is the principal causative agent of tropical theileriosis, resulting in substantial economic losses in the livestock sector. The disease is especially severe in exotic and crossbred cattle, which generally exhibit greater susceptibility than indigenous breeds. Beyond direct animal health impacts, tropical theileriosis adversely affects the dairy industry and, by extension, agricultural economies.

1.2 Economic Burden of *Theileria annulata* in Livestock

The financial repercussions of tropical theileriosis are considerable. In India, the estimated annual economic loss due to bovine tropical theileriosis alone is approximately US$ 384.3 million. Broader estimates for all blood parasite diseases in animals in India indicate an annual loss of around US$ 498.7 million. For comparison, other major infectious diseases also impose substantial economic burdens. For instance, Foot-and-Mouth Disease (FMD) in India was estimated to cause losses of INR 20,897 crore (≈ US$ 2.5 billion) during 2013–2014. While these figures pertain specifically to FMD, they underscore the general vulnerability of the livestock sector to infectious diseases, including protozoal infections such as theileriosis. Losses associated with tropical theileriosis arise from multiple factors, including:

- Reduced milk yield
- Loss of draught power
- Distress sale of infected animals
- Substantial treatment costs

The economic burden is further amplified by high morbidity rates, often approaching 100%, and mortality rates ranging from 60–80% in susceptible populations.

1.3 Overview of Current Control Strategies and the Role of Vaccination

Control of tropical theileriosis requires a multifaceted approach. Historically, chemotherapeutic agents such as buparvaquone have been employed for both treatment and prophylaxis. However, chemotherapy is most effective only when administered during the early stages of clinical disease, is often expensive, and affected animals may take several weeks to fully regain productivity. Tick control using acaricides represents another important component, as *Theileria annulata* is transmitted by *Hyalomma* spp. ticks. Yet, intensive tick control has limitations: it can render cattle populations vulnerable to sudden outbreaks if acaricides become unavailable or resistance develops. Given these constraints, vaccination emerges as a sustainable and highly effective preventive measure. Live attenuated vaccines based on the schizont stage of the parasite have been widely used for decades. These vaccines play a pivotal role in reducing morbidity and mortality, thereby protecting animal health and safeguarding the economic viability of livestock production systems.

2. Understanding Tropical Theileriosis: The Foe We Face

2.1 Etiology: *Theileria annulata* – A Protozoan Parasite

Tropical theileriosis is caused by *Theileria annulata*, an obligate intracellular protozoan parasite belonging to the phylum Apicomplexa. The parasite has a complex life cycle involving both a tick vector and a mammalian host (cattle). The hallmark of the disease is its lymphoproliferative nature, whereby infected lymphoid cells undergo uncontrolled proliferation, contributing to pathology and clinical disease.

2.2 Epidemiology and Transmission: The Tick-Borne Threat

The principal vector of *T. annulata* is the ixodid tick, particularly species of the genus *Hyalomma*, such as *Hyalomma anatolicum*. The disease is widely distributed, occurring across the Mediterranean basin, the Middle East, and large parts of Asia, including India.

Transmission follows a cyclical cycle involving development within the tick vector:

Flowchart: Simplified Life Cycle of *Theileria annulata*

1. Infected tick bite: *Hyalomma* ticks harboring sporozoites in their salivary glands feed on cattle.
2. Sporozoite invasion: Sporozoites are inoculated into the bovine host and invade lymphocytes/monocytes.
3. Schizont development: Within host cells, sporozoites transform into schizonts, inducing uncontrolled proliferation of infected lymphoid cells. These schizont-infected cells disseminate throughout the lymphoid system, causing lymphadenopathy and clinical disease.
4. Merozoite formation: Schizonts differentiate into merozoites, which are released and invade erythrocytes.
5. Piroplasm stage: Within erythrocytes, merozoites develop into piroplasms—the diagnostic stage visible in blood smears.
6. Tick ingestion: Uninfected *Hyalomma* ticks feed on infected cattle, ingesting piroplasm-infected erythrocytes.
7. Sexual reproduction and sporogony in the tick: Piroplasms undergo gametogony and sporogony within the tick, resulting in the formation of sporozoites in salivary glands, completing the cycle.

This intricate cycle highlights the necessity of integrated control strategies, combining both tick management and vaccination.

2.3 Clinical Manifestations and Pathogenesis in Cattle

Tropical theileriosis presents in peracute, acute, subacute, or chronic forms, depending on the virulence of the parasite and the susceptibility of the host. Although cattle of all ages are susceptible, older animals often display more severe clinical signs.

Key clinical manifestations include:

- Pyrexia (fever)
- Generalized enlargement of superficial lymph nodes
- Anemia and anorexia
- Cachexia (progressive wasting)

- Respiratory distress

Other features may include petechiae on conjunctival, oral, and nasal mucosa, and unilateral or bilateral exophthalmia (protrusion of the eyeballs). In severe cases—particularly in exotic and crossbred cattle—the disease may be fatal. The pathogenesis involves uncontrolled proliferation of schizont-infected lymphoid cells, leading to widespread lymphoid destruction. Anemia, a prominent feature, is linked to overproduction of cytokines and reactive oxygen species, which cause oxidative damage to erythrocytes.

3. Rakshavac-T: Unveiling the Vaccine

3.1 Vaccine Type and Composition: A Live Attenuated Approach

Rakshavac-T, manufactured by Indian Immunologicals Ltd. (IIL), is a live attenuated schizont cell culture vaccine designed specifically for the prophylaxis of tropical theileriosis caused by *T. annulata*.

The attenuation process involves:

1. Parasite isolation: Lymphoid cells infected with *T. annulata* schizonts are obtained from an infected animal.
2. Cell culture initiation: These infected cells are cultured in vitro in a suitable medium.
3. Serial passaging (attenuation): The cells are propagated through multiple in vitro passages (≈300 passages for Rakshavac-T), gradually reducing parasite virulence.
4. Quality control and attenuation assessment: Periodic testing is performed by inoculating naïve animals to ensure sufficient attenuation.
5. Cryopreservation: Attenuated schizont-infected cells are cryopreserved with dimethyl sulfoxide (DMSO) in liquid nitrogen at –79°C.
6. Packaging and distribution: Cryopreserved vaccine is packaged in vials with diluent for field use.

3.2 Mechanism of Action: How Rakshavac-T Builds Immunity

Protection induced by Rakshavac-T is primarily cell-mediated, with the schizont stage serving as the main immunogen. Both $CD4^+$ helper T cells and $CD8^+$ cytotoxic T cells contribute to protection; however, $CD8^+$ T cells play the dominant role by targeting parasite antigens expressed on the surface of infected host cells.

Upon vaccination, attenuated schizonts replicate to a limited extent, mimicking natural infection without causing severe disease. This controlled replication allows the host immune system to mount a robust, long-lasting cellular immune response, which provides protection against subsequent exposure to virulent *T. annulata* strains.

4. Practical Application: Administration and Vaccination Protocols

4.1 Dosage and Route of Administration

Rakshavac-T is administered via the subcutaneous (SC) route. Reported dosage recommendations vary slightly across sources:

- One source: 1 mL
- Official product leaflet: 3 mL for cattle and calves (SC)
- Patent on anti-theileriosis vaccines: 0.1–3 million infected cells per dose

This variability underscores the importance of consulting the official product insert or local veterinary guidelines for accurate and up-to-date dosing instructions.

4.2 Vaccination Regimen and Storage Guidelines

Vaccination schedules also vary across references:

- A general guideline in India recommends a single "once in a lifetime" dose for crossbred and exotic cattle ≥3 months of age.
- Another schedule suggests a 3 mL SC dose for cattle and calves ≥2 months of age, followed by revaccination after 1 year.
- The official product leaflet specifies:
    - Primary vaccination: At ≥3 months of age
    - Annual revaccination thereafter

The difference between "once in a lifetime" versus "annual booster" schedules has significant practical implications, highlighting the need for veterinarians to remain updated on local epidemiological conditions and product-specific recommendations. Evidence suggests that immunity may begin to wane after six months, which supports the rationale for annual boosters.

For storage and transport, Rakshavac-T must be maintained at 2–8°C and must not be frozen, as freezing adversely affects vaccine potency. Before administration, the vial should be thoroughly shaken, and only sterile syringes and needles should be used, with strict aseptic precautions to prevent contamination.

5.1. Efficacy of Rakshavac-T

Rakshavac-T, a live attenuated schizont vaccine, is regarded as a promising tool for controlling tropical theileriosis. It provides robust immunity against homologous parasite challenges, with reported protection rates of up to 100%. However, its efficacy is less consistent against heterologous strains (i.e., genetically diverse field isolates). Under experimental conditions, vaccinated animals may survive infection but can still develop clinical signs of acute tropical theileriosis. Field studies have demonstrated variable levels of protection: some calves resisted challenge for up to six months post-vaccination, while others succumbed within 90 days of immunization. This variability indicates that although Rakshavac-T offers significant protection, it may not always be absolute or long-lasting in endemic areas with high parasite diversity. Moreover, immunity induced by the *T. annulata* schizont cell culture vaccine has been observed to decline after approximately six months, highlighting the need for revaccination to sustain protective immunity.

5.2. Safety Profile in Diverse Cattle Populations (Calves, Pregnant Animals)

The safety of Rakshavac-T across cattle populations—including calves and pregnant cows—is a critical consideration. Available evidence presents a nuanced picture, likely reflecting both advances in vaccine formulation and evolving safety assessments over time.

An earlier patent (2005) stated that Rakshavac-T was not recommended for calves younger than two months or for pregnant cows, despite these groups being highly susceptible to tropical theileriosis. This represented a notable limitation.

Conversely, a 1997 study on a *T. annulata* schizont cell culture vaccine (likely an early version of Rakshavac-T) reported extensive use in susceptible calves and pregnant/lactating cows under field conditions, with results confirming the vaccine to be safe, potent, and effective across breeds, ages, and physiological states. This suggests improvements in vaccine production or updated understanding of its safety profile over time. Current product information from Indian Immunologicals Ltd. recommends Rakshavac-T for prophylactic use in cattle without specifying age or pregnancy restrictions. However, explicit claims regarding neonates or pregnant animals are absent, necessitating cautious application in these groups. Importantly, passive transfer of immunity via colostrum from vaccinated dams to their offspring has not been demonstrated. Consequently, calves born to immunized cows remain fully susceptible shortly after birth, underscoring the importance of direct vaccination at the appropriate age.

5.3. Reported Post-Vaccination Reactions

Rakshavac-T is generally well tolerated, with adverse reactions being infrequent and mild. Reported reactions include:

- Local reactions: Slight swelling at the inoculation site, which resolves spontaneously within a few days.
- Systemic reactions: Transient fever and swelling of regional lymph nodes, often attributed to the serum component or allogeneic vaccinal cell line. These reactions typically subside without intervention.

- Rare events: Anaphylactic reactions may occur in susceptible animals, though such cases are uncommon. In such instances, epinephrine is the treatment of choice, followed by supportive therapy.

It is recommended to avoid the concurrent administration of immunosuppressive drugs or other vaccines within two weeks before and after bovine theileriosis vaccination to prevent interference with immune response development.

6. Regulatory Landscape and Market Impact in India

6.1. Indian Immunologicals Ltd.: The Manufacturer's Role

Rakshavac-T is produced by Indian Immunologicals Ltd. (IIL), a leading "One Health" company established in 1982 under the National Dairy Development Board (NDDB). IIL was initially created to provide affordable vaccines for livestock health. Over the years, it has expanded into a major manufacturer of veterinary and human vaccines, nutraceuticals, and pharmaceutical formulations. IIL operates state-of-the-art facilities compliant with Good Manufacturing Practices (GMP) and ISO 9001 certification. It is also recognized for its strong research and development (R&D) pipeline. Notably, IIL introduced Rakshavac-T as the world's first commercial vaccine against tropical theileriosis, thereby positioning itself as a pivotal contributor to India's livestock disease control programs.

6.2. Regulatory Oversight by the Central Drugs Standard Control Organization (CDSCO)

In India, veterinary vaccine licensing and regulation are overseen by the Central Drugs Standard Control Organization (CDSCO), under the Drugs and Cosmetics Act (1940) and Rules (1945). The CDSCO ensures that veterinary biologicals meet rigorous standards of quality, safety, and efficacy before market authorization.

The regulatory process involves:

- Evaluation of detailed dossiers in the Common Technical Document (CTD) format.
- Submission of quality control data, non-clinical safety studies, and field efficacy trial results.
- Post-marketing surveillance and periodic inspections of manufacturing facilities.

This framework ensures that Rakshavac-T adheres to national and international standards, safeguarding both animal health and farmer confidence in vaccination programs.

6.3. Commercial Presence and National Significance of Rakshavac-T

Rakshavac-T enjoys a significant commercial presence in India as the sole live attenuated vaccine available for immunoprophylaxis against *T. annulata*. IIL's extensive distribution network enables its availability across both urban and remote rural areas, ensuring broad coverage for dairy farmers.

The vaccine's role is particularly important given the high economic burden of tropical theileriosis in India. National initiatives such as the Livestock Health and Disease Control Programme (LHDCP) support preventive vaccination campaigns against major animal diseases. Although funding details specific to theileriosis vaccination are limited, the government's emphasis on preventive health measures underscores the importance of Rakshavac-T within India's broader livestock disease management strategy.

7. Challenges and Future Directions in Theileriosis Vaccinology

7.1. Limitations of Live Attenuated Vaccines

Despite their success, live attenuated vaccines such as Rakshavac-T face several challenges:

- Infrastructure constraints: Production requires highly specialized cell culture facilities, limiting large-scale availability in many endemic regions.
- Cold chain dependence: Potency is compromised outside 2–8°C, necessitating uninterrupted refrigeration during transport and storage.
- Potential parasite persistence: Attenuated strains could theoretically establish within local tick populations, raising concerns about carrier states and environmental circulation.
- Strain diversity: Efficacy may be reduced against heterologous field strains due to loss of genetic variability during long-term in vitro passaging.
- Waning immunity: Protective immunity often declines within six months, necessitating periodic revaccination.
- Unpredictability of attenuation: The empirical nature of serial passaging can sometimes reduce vaccine effectiveness or lead to inconsistent results.

These limitations highlight the need for alternative, more reliable vaccine technologies.

7.2. Emerging Vaccine Technologies: A Glimpse into the Future

To address the limitations of live attenuated vaccines, research is increasingly focused on next-generation vaccine platforms. Molecular approaches, such as subunit vaccines, DNA vaccines, and mRNA-based strategies, offer several potential advantages:

- Defined antigen targets, improving safety and consistency.
- Enhanced stability, reducing cold chain dependency.
- Reduced risk of parasite persistence or reversion.
- Potential for broader cross-strain protection.

These novel platforms represent promising avenues in the evolution of theileriosis vaccinology, aiming to complement or eventually replace live attenuated vaccines like

Rakshavac-T.

7.2. Emerging Vaccine Technologies: A Glimpse into the Future

Recent advances in immunoinformatics and computational modeling are accelerating the development of novel vaccine candidates. For instance, multi-epitope mRNA vaccines against *Theileria annulata* are being designed through *in silico* identification of antigenic proteins and their epitopes. Such constructs aim to induce both humoral and cell-mediated immune responses, which are essential for controlling intracellular pathogens like *Theileria*. One of the major advantages of mRNA platforms is their ability to encode multiple antigens within a single construct, potentially enhancing the breadth and durability of protective immunity. These innovations hold the promise of revolutionizing preventive strategies by offering safer, more effective, and more stable alternatives to traditional live attenuated vaccines. Beyond vaccination, research has also begun exploring novel therapeutic compounds, such as phytochemicals including plumbagin and thymol, which have demonstrated *in vitro* efficacy against *T. annulata*. These findings highlight the possibility of integrating improved therapeutic options alongside preventive strategies for more comprehensive disease control.

7.3. Integrated Disease Management: Beyond Vaccination

Although vaccination remains the cornerstone of tropical theileriosis control, sustainable disease management requires an integrated approach that combines multiple strategies:

- Chemotherapy: Early and judicious use of anti-theilerial drugs such as buparvaquone for clinical cases.
- Vector Management: Regular application of acaricides to reduce tick populations and interrupt transmission.
- Biosecurity and Farm Management: Implementing practices to reduce tick exposure, control animal movement, and strengthen overall herd health.

The considerable genetic variation observed among *T. annulata* populations in India indicates successful parasite adaptation and spread, which may compromise long-term disease control. Continuous molecular surveillance of parasite diversity is therefore essential. This information can guide the adaptation of vaccine strains or support the development of broad-spectrum vaccines better suited for endemic regions. Ultimately, the integration of vaccination, chemotherapy, vector control, and biosecurity represents the most effective and sustainable defense against tropical bovine theileriosis.

8. Conclusion

Rakshavac-T remains a critical prophylactic tool in the control of tropical bovine theileriosis in India, a disease that imposes severe economic losses on the livestock sector. As a live attenuated schizont vaccine, it induces strong cell-mediated immunity and provides valuable protection, particularly in exotic and cross-bred cattle, which are highly susceptible to the disease. Nevertheless, a critical appraisal highlights important nuances. Variability in dosage recommendations and vaccination schedules across sources underscores the need for veterinarians to rely on the most up-to-date product guidelines. Likewise, evolving insights into the vaccine's safety profile, especially for calves and pregnant cows, illustrate the dynamic nature of veterinary vaccinology and the ongoing effort to ensure suitability across vulnerable populations. While live attenuated vaccines such as Rakshavac-T have played a pivotal role, their inherent limitations—including production complexity, dependence on cold-chain infrastructure, risk of attenuated strain persistence, and inconsistent efficacy against diverse field isolates—highlight the necessity of next-generation alternatives. Advances in subunit, DNA, and mRNA-based vaccine technologies represent promising directions for future research, offering the potential for broader-spectrum, safer, and more durable protection.

Moving forward, the most effective strategy will be integrated disease management: combining vaccination with chemotherapy, vector control, biosecurity, and continuous surveillance of parasite diversity. In this context, Rakshavac-T remains a vital component of current control programs, but its long-term success will depend on synergizing with innovative technologies and adaptive, science-driven disease management practices.