

RECOMBITEK® LYME

MEANS PURE.



**TARGETED
LYME
PROTECTION**

RECOMBITEK® Lyme has all the protection dogs need, and none of the antigens they don't.


RECOMBITEK®
lyme

LYME DISEASE: A GROWING, PREVENTABLE THREAT

Lyme disease: the threat against dogs continues to rise

- Lyme disease cases in dogs have increased between 2012 and 2019¹
- Since the late 1990s, reported human cases of Lyme disease in the US have tripled²
- A positive correlation between Lyme disease incidence in humans and seroprevalence in dogs has been demonstrated³
- Diagnosis of Lyme disease is difficult: Most *Borrelia burgdorferi* seropositive dogs show no clinical signs, and infected dogs do not typically present acutely⁵

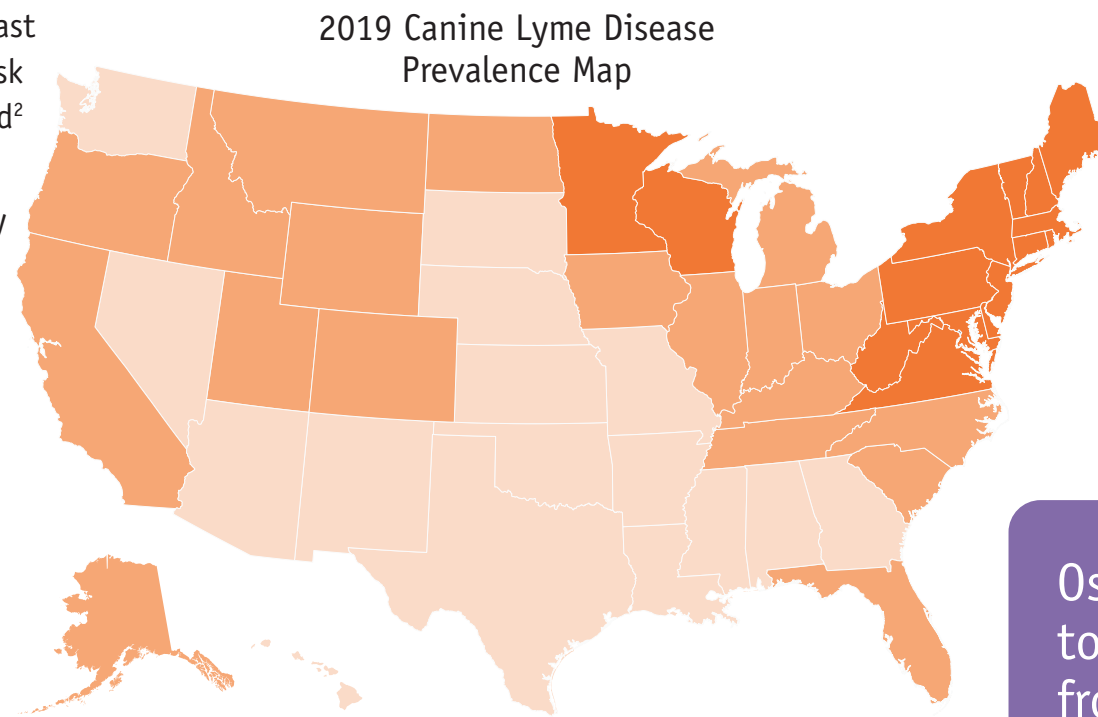
121% Increase In Cases

82% US Tickborne Human Cases⁴

Lyme disease is on the move

Lyme disease has been detected in dogs in all 50 states and is common in the Northeast, upper Midwest, Mid-Atlantic, and West Coast.¹

- The number of counties in the Northeast and upper Midwest considered high-risk for Lyme disease has more than tripled²
- Ticks that transmit Lyme disease have spread to geographic areas where they had not been seen before²
- Lyme disease is transmitted from the bite of what is commonly called the black-legged tick (or deer tick)—*Ixodes scapularis* in the Northeast and Midwest, *Ixodes pacificus* on the West Coast⁶



Infection Risk
 No Data High Risk



Lyme disease mode of transmission

- *B. burgdorferi*, the causative agent of Lyme disease is transmitted by ticks
- Transmission of *B. burgdorferi* typically occurs 36 to 48 hours or more after tick attachment⁷
- Outer surface protein A (OspA), the predominant surface protein expressed on *B. burgdorferi*, is involved in the attachment of spirochetes to the tick's midgut⁸
- During feeding, the warmth of the new environment causes spirochetes to downregulate their expression of OspA and start expressing OspC; spirochetes then migrate from the midgut to the salivary glands and subsequently infect the mammalian host⁸
- The OspA lipoprotein is highly conserved between *B. burgdorferi* species in the US; this homogeneity makes it an ideal vaccine target⁹
- OspC exhibits much greater heterogeneity than OspA: **Over 30 distinct OspC phyletic types** have been identified in the US, and immune responses elicited by OspC epitopes are phyletic specific¹⁰

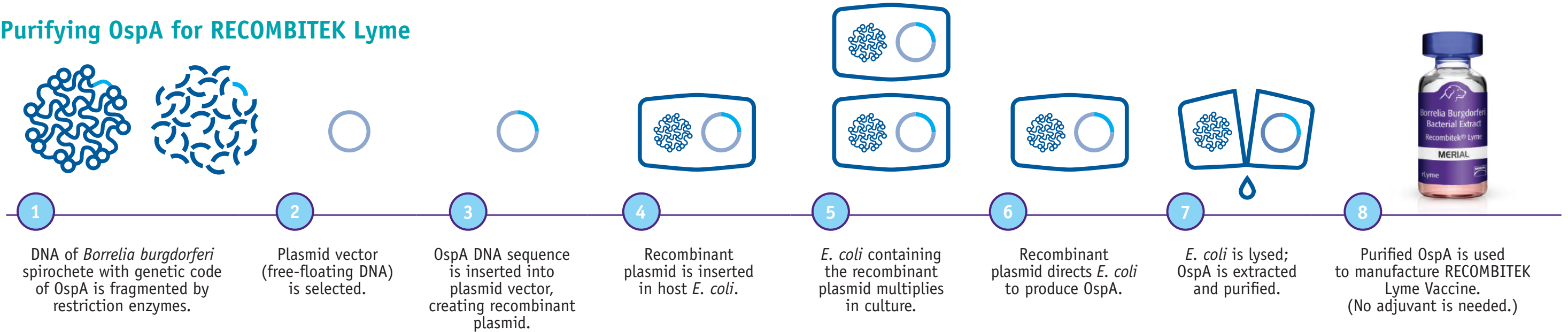
OspA is the only vaccine antigen necessary to block transmission of *B. burgdorferi* from the tick to the dog.¹¹



The only vaccine that contains lipidated OspA in a non-adjuvanted formulation

RECOMBITEK® LYME: TARGETED, PURE PROTECTION


Purifying OspA for RECOMBITEK Lyme





Non-adjuvanted formulation

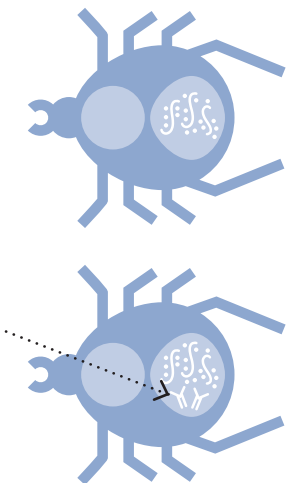
- RECOMBITEK Lyme is the only non-adjuvanted Lyme vaccine
- RECOMBITEK Lyme contains a highly purified lipidated OspA¹²
- RECOMBITEK Lyme uses only a pure protein without an adjuvant to stimulate immunity
- Unlike RECOMBITEK Lyme, whole-cell bacterin canine Lyme vaccines and the chimeric recombinant canine Lyme vaccine contain adjuvants to enhance the immune response⁵
 - Sensitization to an adjuvant may contribute to hypersensitivity reactions¹³
- Whole-cell bacterin Lyme vaccine contains more than 100 *B. burgdorferi* lipoproteins, inducing host inflammatory responses that may lead to pathologic changes responsible for the inflammation associated with infection^{14,15}

What happens when an infected tick bites a dog protected by RECOMBITEK Lyme?

In the unfed tick, *B. burgdorferi* expresses OspA  in the tick midgut.

As the tick feeds, OspA antibodies  in the dog's blood enter the midgut and bind to OspA on the surface of *B. burgdorferi*.

B. burgdorferi  growth is arrested, migration to the salivary gland is blocked, and transmission is prevented.



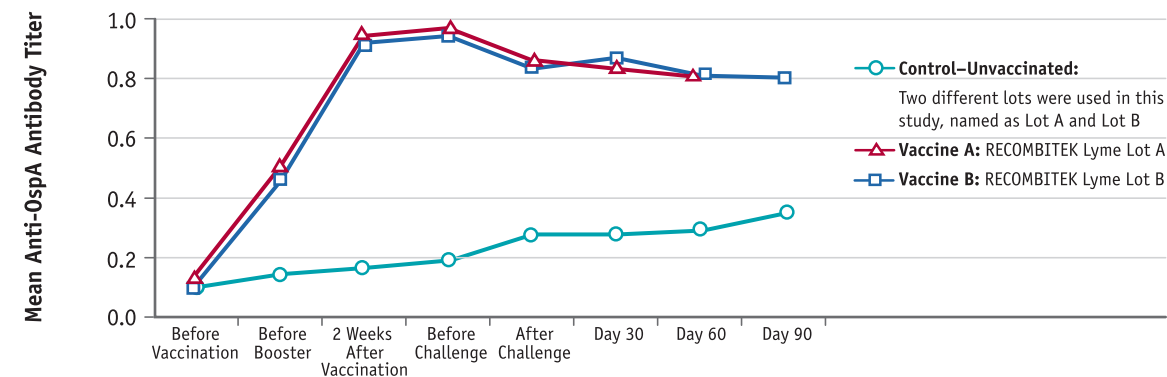
PROVEN EFFICACY

RECOMBITEK Lyme blocked infection before transmission could occur¹¹

- Randomized, blinded, controlled study designed to mimic natural tick challenge
- 100% of control dogs infected post-challenge
- Efficacy of RECOMBITEK Lyme was determined by:
 - Serology (ELISA)
 - Recovery of the infectious agent via skin biopsy culture, PCR analysis, western blot analysis and tick xenodiagnosis

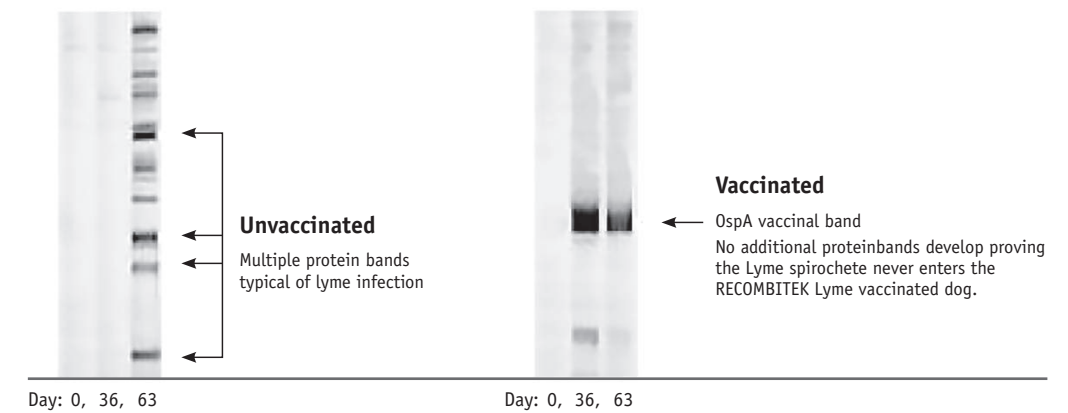


RECOMBITEK Lyme induced a robust antibody response



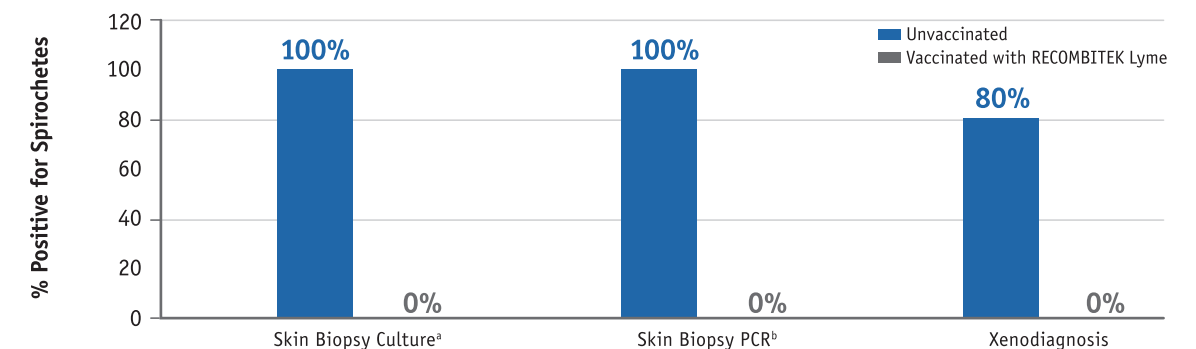
- Relative to controls, vaccinates responded with significantly high levels of anti-OspA antibodies that were maintained throughout the study
- Vaccinates showed no booster effect after challenge, demonstrating solid immunity
- The unvaccinated control group had low titers that increased in response to challenge and were maintained throughout the study

RECOMBITEK Lyme prevented infection in the face of challenge



- All controls (10/10) had antibodies characteristic of infection with *B. burgdorferi* after challenge (day 63), whereas no antibodies developed to antigens that are specific for infection to *B. burgdorferi* in the vaccinates
- Vaccinated dogs demonstrated an OspA antibody pattern following vaccination (day 36) and tick challenge (day 63)
- This confirms that no infection occurred in the vaccinated dogs following challenge with ticks infected with *B. burgdorferi*

RECOMBITEK Lyme showed no evidence of infection in vaccinated dogs



^a Post challenge days 30, 60, and 90

^b Post challenge days 30 and 60

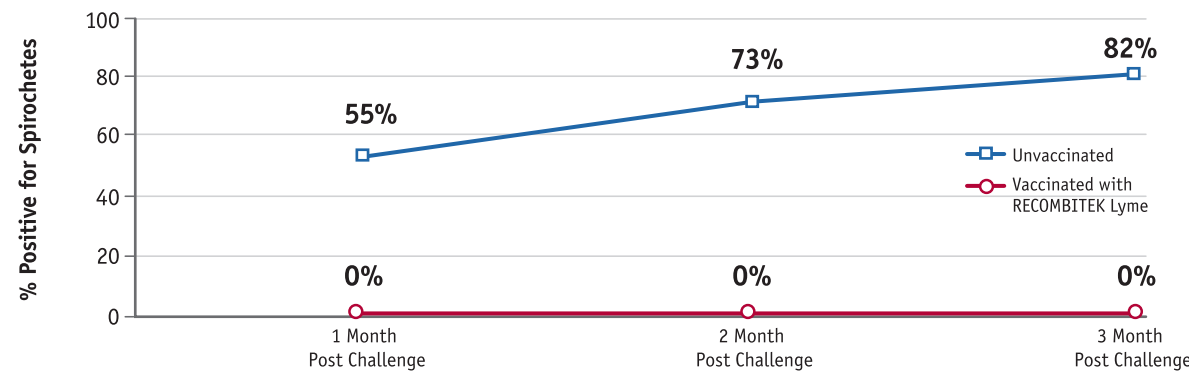
- In contrast to unvaccinated group, vaccinates had no isolation of spirochetes on skin biopsy and had no positive PCR results after challenge for up to 3 months and 60 days, respectively
- Xenodiagnosis demonstrated that all ticks recovered from vaccinated dogs were negative for *B. burgdorferi*, whereas 80% of ticks were positive for *B. burgdorferi* in unvaccinated controls

AAHA recommendation: Lyme vaccination is recommended for dogs with a known risk of exposure due to living in or visiting regions where risk of vector tick exposure is considered to be high, or where disease is known to be endemic.¹⁶

PROVEN 1-YEAR IMMUNITY AND STRONG IMMUNOGENICITY

RECOMBITEK Lyme demonstrated long-lasting protection in a live-tick challenge 366 days after vaccination¹⁷

- Duration of immunity and safety for RECOMBITEK Lyme was evaluated in a randomized, blinded, placebo controlled study
- Dogs were challenged by exposure to naturally infected ticks 1 year (366 days) after initial vaccination series (2 doses administered 3 weeks apart)
- Spirochete reisolation from skin biopsies was used to assess vaccine efficacy at monthly intervals for 3 months after challenge



- Spirochetes were reisolated from 82% of the unvaccinated dogs at 3 months post challenge, whereas none of the vaccinated dogs had spirochete reisolation at any assessed time
- None of the vaccinated dogs had clinical signs of Lyme disease, whereas 18% of unvaccinated control animals showed clinical signs during the study
- No general adverse reactions to the vaccine were noted at any time during the study
- No vaccinates showed any signs of infection after challenge in both efficacy and duration of immunity study^a

^a Infection with *B. burgdorferi* does not always produce clinical signs in dogs⁸

RECOMBITEK Lyme features a uniquely constructed OspA antigen that provides strong immunogenicity¹²

- Natural spirochete-associated OspA is lipidated at the N-terminus of the amino acid sequence¹⁸
- Lipidation has been demonstrated as a determinant of immunogenicity for OspA¹²

Lipidation assessment of the OspA antigen of 2 recombinant canine Lyme vaccines¹²

RECOMBITEK Lyme
A mix of bi- and tri-lipidated forms

Molecular weight of 418 kDa; diameter: 18 nm

Adjuvanted OspA/chimeric OspC vaccine
Non-lipidated

Molecular weight of 34 kDa; diameter: 6.4 nm

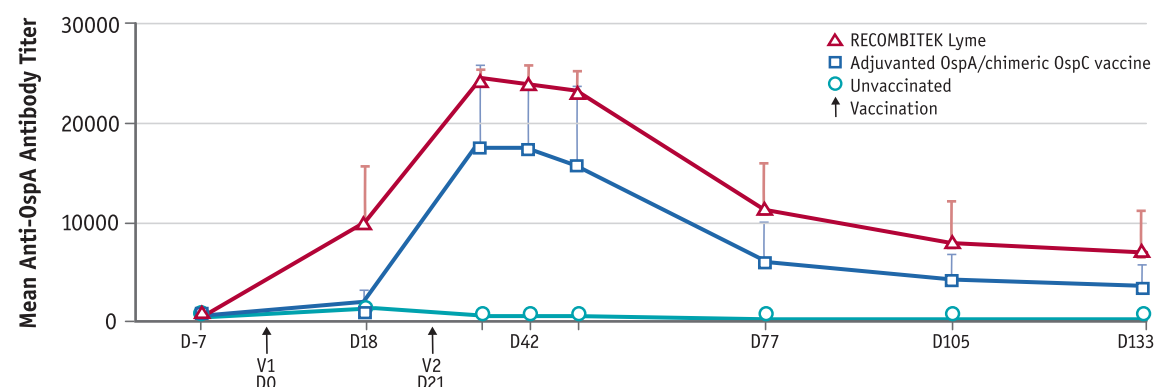
- Recombinant OspA lipidation and subsequent micelle formation might account for superior immunogenic profile of recombinant OspA compared with adjuvanted OspA/chimeric OspC vaccine¹²



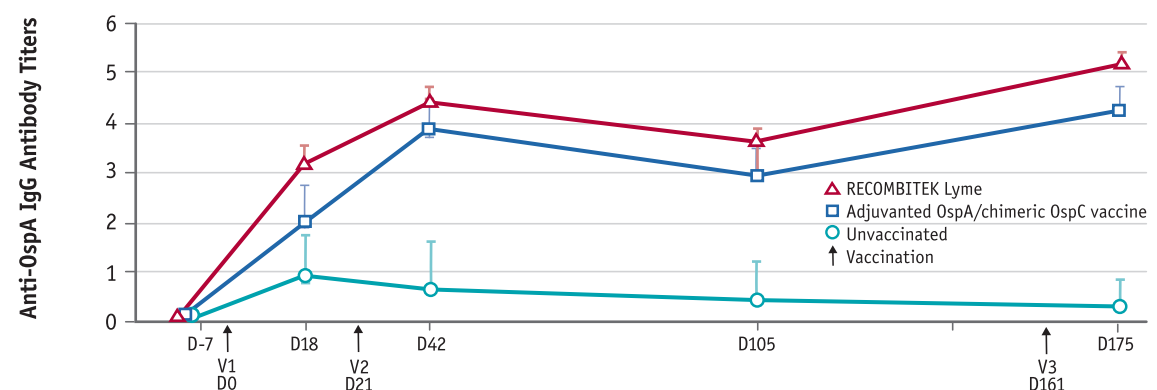
ROBUST, HOMOGENEOUS, AND HIGH-AVIDITY RESPONSE

Serological response and borreliacidal activity of RECOMBITEK Lyme vaccine and adjuvanted OspA/chimeric OspC vaccine¹²

RECOMBITEK Lyme produces a greater and more homogenous anti-OspA humoral response



- The response of RECOMBITEK Lyme following a single vaccination was significantly greater than that induced by adjuvanted OspA/chimeric OspC vaccine at day 18
- At subsequent time points the mean anti-OspA antibody titers in RECOMBITEK Lyme remained higher than the adjuvanted OspA/chimeric OspC vaccine (not statistically significant)



- Total IgG titers were significantly higher for RECOMBITEK Lyme vaccinates on days 18, 42, 105, and 175, compared with adjuvanted OspA/chimeric OspC vaccine
- There was a trend of more consistent anti-OspA (less dispersion) response for RECOMBITEK Lyme vaccinates compared with adjuvanted OspA/chimeric OspC vaccine, which was significant at day 175

RECOMBITEK Lyme elicits a higher avidity anti-OspA antibody response

- RECOMBITEK Lyme generated a significantly superior avidity response at days 18, 105, and 175, compared with adjuvanted OspA/chimeric OspC vaccine
- Vaccination with RECOMBITEK Lyme resulted in the production of large amounts of specific, high-avidity antibodies that increased after each vaccination
- Dogs vaccinated with adjuvanted OspA/chimeric OspC vaccine resulted in the production of specific antibodies with lower avidity that did not increase after subsequent vaccination

RECOMBITEK Lyme generates a greater concurrent increase in serum borreliacidal activity

- Post-vaccination borreliacidal activity of sera from dogs receiving RECOMBITEK Lyme vaccine were consistently and significantly higher on days 18, 105, and 175, compared with those from dogs that received adjuvanted OspA/chimeric OspC vaccine

Dogs receiving RECOMBITEK Lyme had higher levels of anti-OspA antibodies, higher avidity of anti-OspA antibodies, and greater concurrent increase in serum borreliacidal activity compared with dogs that received adjuvanted OspA/chimeric OspC vaccine

This vaccine is brought to you by the maker of a full line of vaccine products, including RECOMBITEK®, PUREVAX®, and IMRAB®



RECOMBITEK Lyme Guarantee

In the event that a dog is found to be Lyme positive after being properly vaccinated with RECOMBITEK® Lyme, Boehringer Ingelheim Animal Health USA Inc. will support testing with either the Cornell Canine Lyme Multiplex Assay or the IDEXX™ Quantitative C6 Antibody Test (please contact Veterinary Technical Solutions (VeTS) to set up support for testing preemptively). If a positive diagnosis is confirmed, Boehringer Ingelheim Animal Health USA Inc. will support urinalysis testing and treatment with appropriate antibiotics, such as amoxicillin or doxycycline. More in-depth support will be considered for testing and treatment of definitively diagnosed complications of Lyme disease on a case-by-case basis.

For full details, ask your Representative about our Satisfaction Guarantee on RECOMBITEK or call our Veterinary Technical Solutions team at 1-888-637-4251 opt 1.

RECOMBITEK® LYME MEANS PURE

RECOMBITEK Lyme has all the protection dogs need and none of the antigens they don't

- Effective protection that blocks *Borrelia burgdorferi* while it's still in the tick¹¹
- THE ONLY canine Lyme vaccine that is non-adjuvanted
- THE ONLY recombinant Lyme vaccine that contains lipidated OspA¹²
- Proven 1-year immunity and a robust, homogeneous, and high avidity immune response¹²



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References: 1. The Companion Animal Parasite Council (CAPC). Parasites Prevalence Maps. US Canine Positive Lyme Results. <https://capcvet.org/maps/#2019/all/lyme-disease/dog/united-states/>. Accessed April 2, 2020. 2. The Centers for Disease Control and Prevention (CDC). Lyme and other tickborne diseases. <https://www.cdc.gov/media/dpk/diseases-and-conditions/lyme-disease/index.html>. Accessed April 2, 2020. 3. Mead P, Goel R, Kugeler K. Canine serology as adjunct to human Lyme disease surveillance. *Emerg Infect Dis*. 2011;17(9):1710-1712. 4. The Centers for Disease Control and Prevention (CDC). Vital Signs: Trends in Reported Vectorborne Disease Cases — United States and Territories, 2004–2016. <https://www.cdc.gov/mmwr/volumes/67/wr/mm6717e1.htm>. Accessed April 2, 2020. 5. Littman MP, Gerber B, Goldstein RE, et al. ACVIM consensus update on Lyme borreliosis in dogs and cats. *J Vet Intern Med*. 2018;32:887-903. 6. The Merck Veterinary Manual website. Overview of Lyme borreliosis. Available at: http://www.merckmanuals.com/vet/generalized_conditions/lyme_borreliosis/overview_of_lyme_borreliosis.html?qt=lyme&alt=sh. Accessed August 1, 2019. 7. The Centers for Disease Control and Prevention (CDC). Lyme disease transmission. <https://www.cdc.gov/lyme/transmission>. Accessed April 2, 2020. 8. Greene CE, Straubinger RK, Levy SA. Borreliosis. In: Greene CE, ed. *Infectious Diseases of the dog and cat*. 4th ed. St. Louis, MO: Saunders, an imprint of Elsevier, Inc.;2012. 9. Appel MJG. Lyme disease vaccination, in Bonagura JD (ed): *Kirk's Current Veterinary Therapy XIII*. Philadelphia, WB Saunders Co. 1999;256-258. 10. Rhodes DV, Earnhart CG, Mather TN, Meeus PF, Marconi RT. Identification of *Borrelia burgdorferi* OspC genotypes in canine tissue following tick infestation: Implications for Lyme disease vaccine and diagnostic assay design. *Vet J*. 2013;198(2):412-418. 11. Conlon JA, et al. Efficacy of a nonadjuvanted, outer surface protein A, recombinant vaccine in dogs after challenge by ticks naturally infected with *Borrelia burgdorferi*. *Veterinary Therapeutics*. 2000;1:96-107. 12. Grosenbaugh DA, De Luca K, Durand P-Y, et al. Characterization of recombinant OspA in two different *Borrelia* vaccines with respect to immunological response and its relationship to functional parameters. *BMC Vet Res*. 2018;14:312. 13. Greene CE, Straubinger RK, Levy SA. Immunoprophylaxis. In: Greene CE, ed. *Infectious Diseases of the dog and cat*. 4th ed. St. Louis, MO: Saunders, an imprint of Elsevier, Inc. 2012;1163-1205. 14. Giambartolomei GH, Dennis VA, Lasater BL, Philipp MT. Induction of pro- and anti-inflammatory cytokines by *Borrelia burgdorferi* lipoproteins in monocytes is mediated by CD14. *Infection and Immunity*. 1999;67(1):140-147. 15. Appel MJG, Jacobsen RH. CVT Update: Canine Lyme Disease, in Bonagura JD (ed): *Kirk's Current Veterinary Therapy XII*, Philadelphia, WB Saunders. 1995;303-309. 16. American Animal Hospital Association (AAHA). AAHA 2017 Vaccination Guidelines. https://www.aaaha.org/globalassets/02-guidelines/canine-vaccination/vaccination_recommendation_for_general_practice_table.pdf. Accessed April 2, 2020. 17. Winkle RE, et al. Canine Lyme disease: One-year duration of immunity elicited with a canine OspA monovalent Lyme vaccine. *Intern J Appl Res Vet Med*. 2006;4(1):23-28. 18. Jiang W, Gorevic PD, Dattwyler RJ, Dunn JJ, Luft BJ. Purification of *Borrelia burgdorferi* outer surface protein A (OspA) and analysis of antibody binding domains. *Clin Diagn Lab Immunol*. 1994;1(4):406-12.

To learn more about RECOMBITEK vaccines and how they can benefit your patients, contact your Sales Representative or your Distributor Representative, call Customer Care at 1-888-637-4251 or visit BI-CONNECT.com

Ask your Representative about our Satisfaction Guarantee on RECOMBITEK.



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