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A new successful vaccine against babesiosis: Any use for malaria?

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Merck

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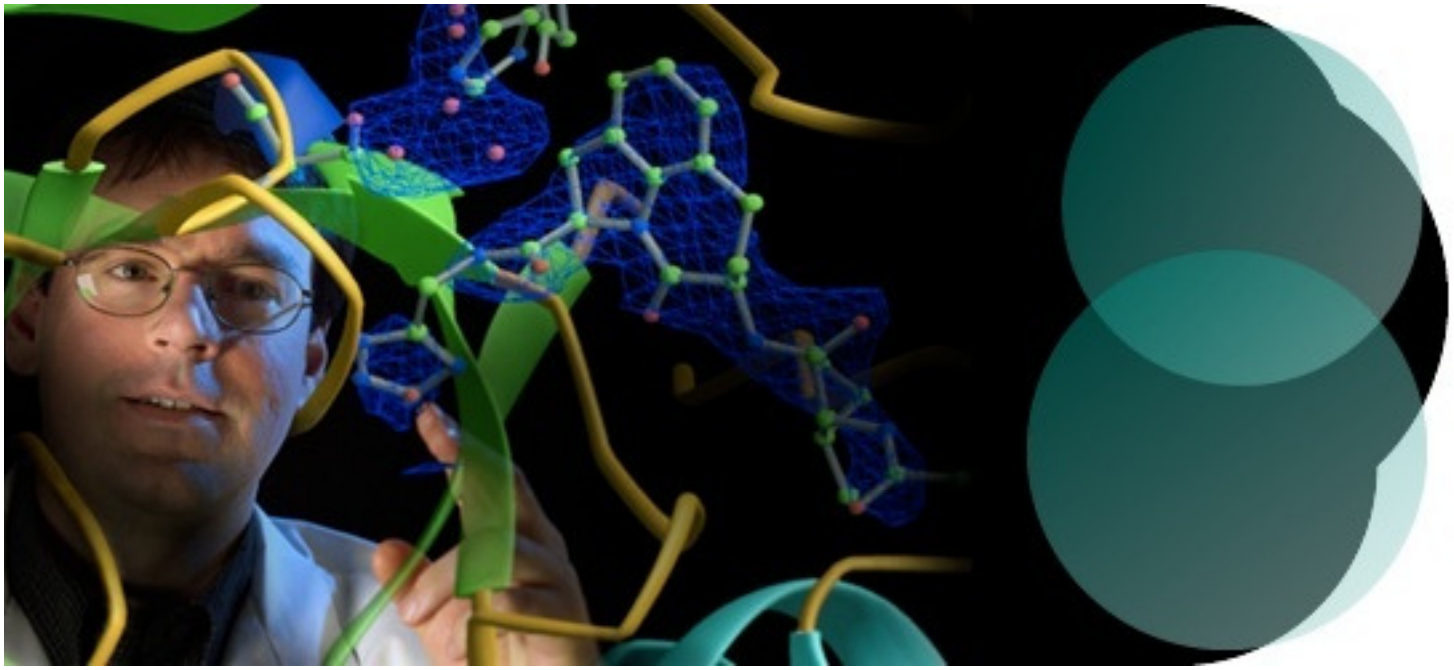
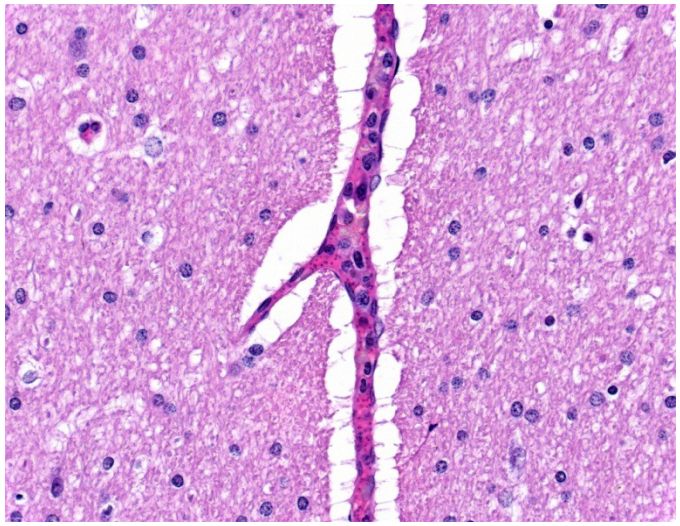


VACCINATION AGAINST BABESIA

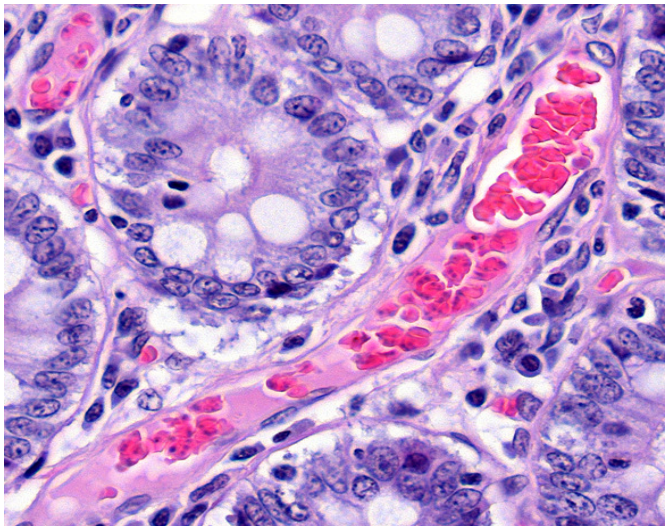
Implications for malaria ?

MSD
Be well

BLOCKED CAPILLARIES-BABESIA



Brain section of B. canis infected dog



Gut section of B. canis infected dog

In clinical babesiosis capillaries become blocked

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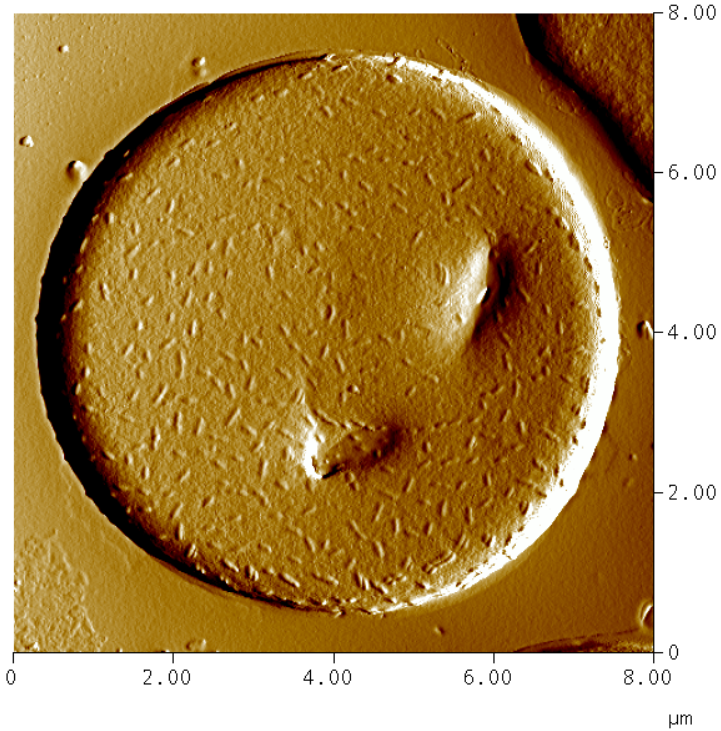
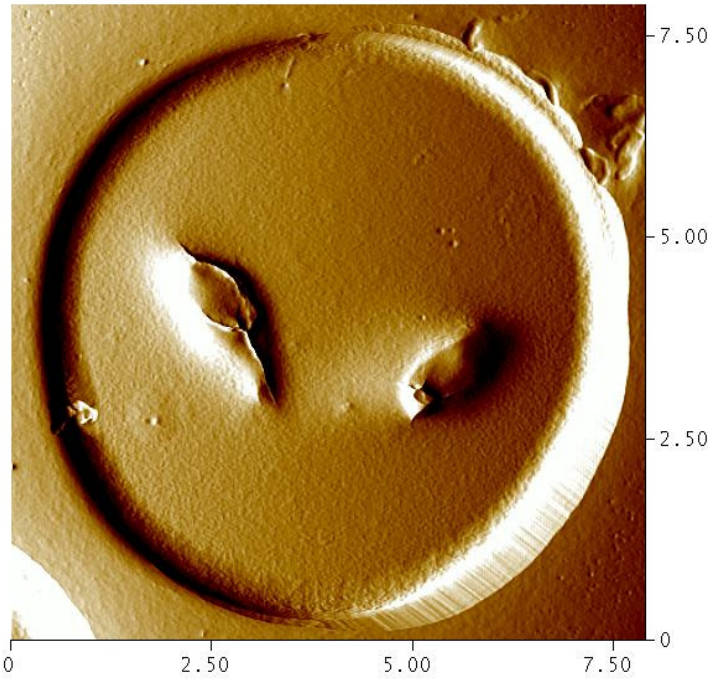
BLOCKED CAPILLARIES-BABESIA



B. bovis infected red blood cell



B. canis infected red blood cell

Infected red blood cells adhere to the lining of blood vessels (margination), but ridges are not absolutely required

Courtesy of Brian Cooke

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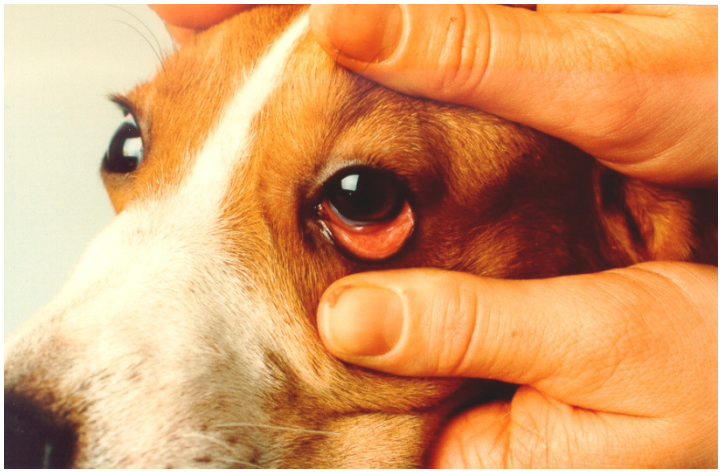
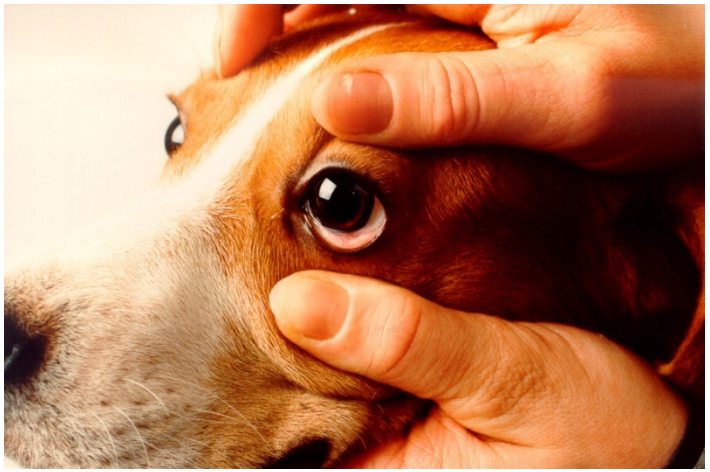
CIRCULATORY DISTURBANCES-BABESIA



Not-infected control dog



B. canis infected dog

- Anaemia
- Prolonged capillary refill time
- Poor tissue perfusion
- Sharp pulse (decreased capillary resistance)

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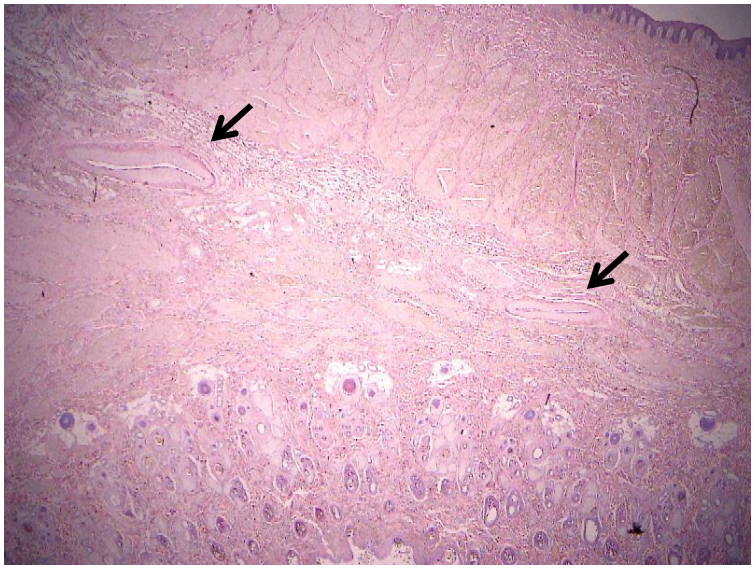
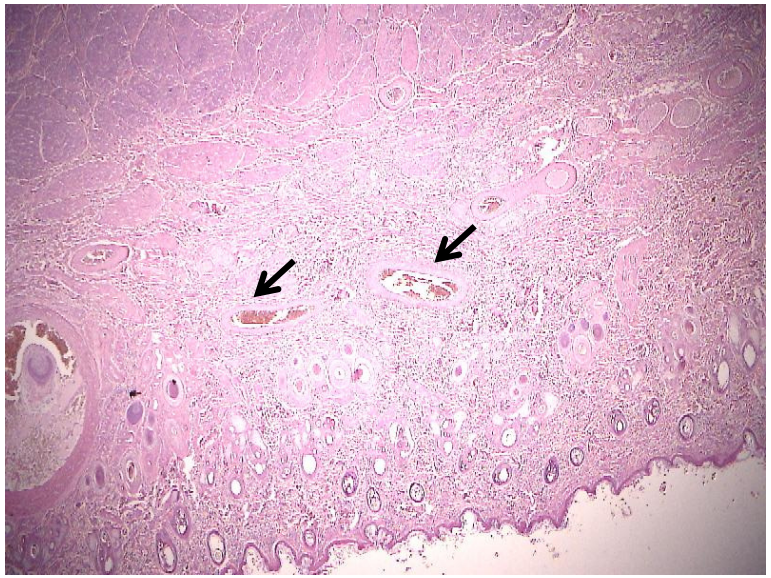
CIRCULATORY DISTURBANCES-BABESIA





Collapsed arterioles in the mucosae of a B. canis-infected dog (left). Control on the right. Note absence of filled arterioles in infected dog

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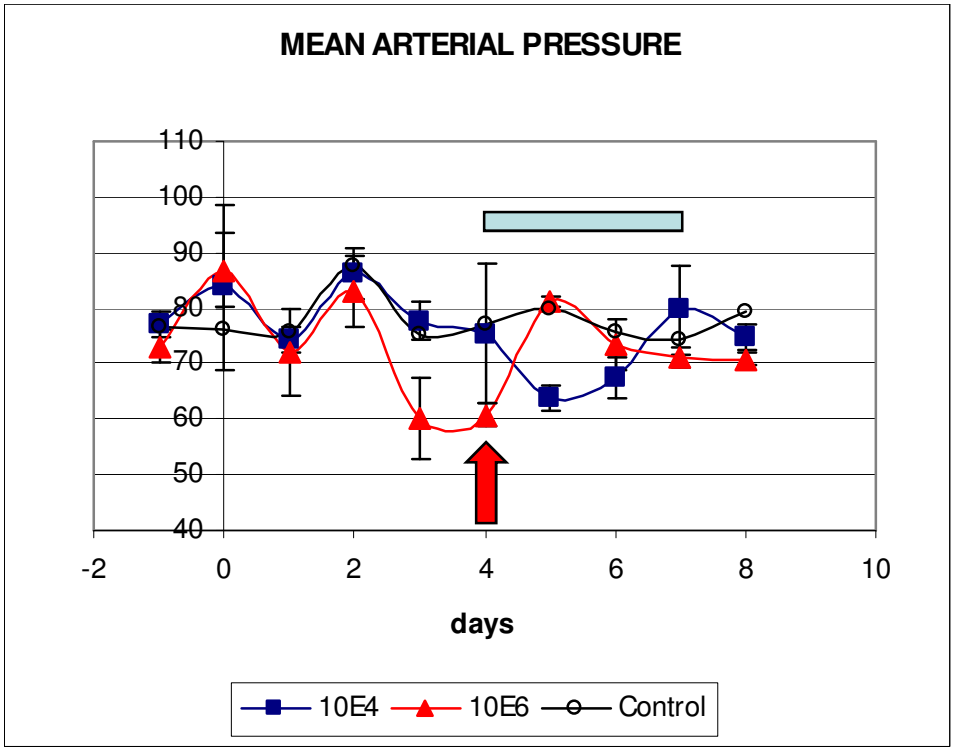
COMPENSATED HYPOTENSION-BABESIA



B. canis infected dogs (n=3). Arrow indicates day of cure of 10^6 group

Dogs develop hypotension upon B. canis infection. Non-cured dogs restored blood pressure in two days (blue bar)

Schetters et al. 2009 Vet Parasitol. 162, 7-15

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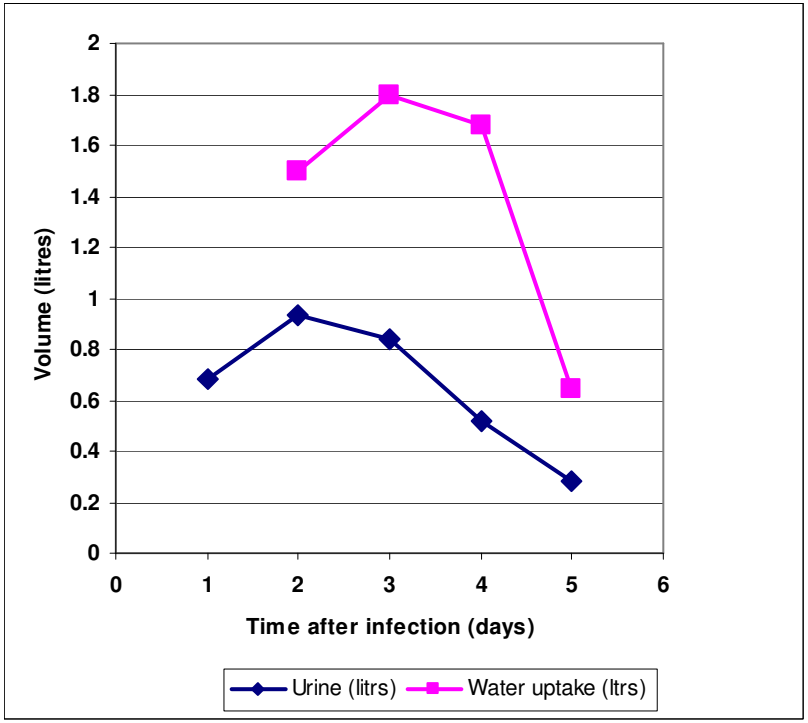
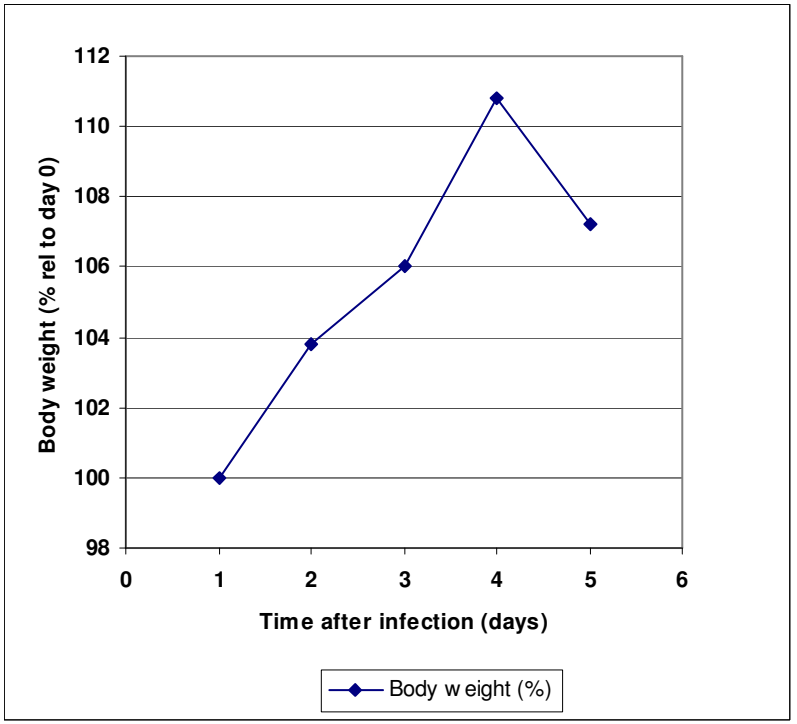
COMPENSATED HYPOTENSION-BABESIA



Water balance in B. canis infected dogs (n=2)



Body weight increase in B. canis infected dogs (n=2)

During the phase of hypotension water is retained, reflected in increased body weight
-dogs were kept in metabolic cages after B. canis infection-

Schetters et al. 1998 Ann. Trop. Med. & Parasitol. 513-519

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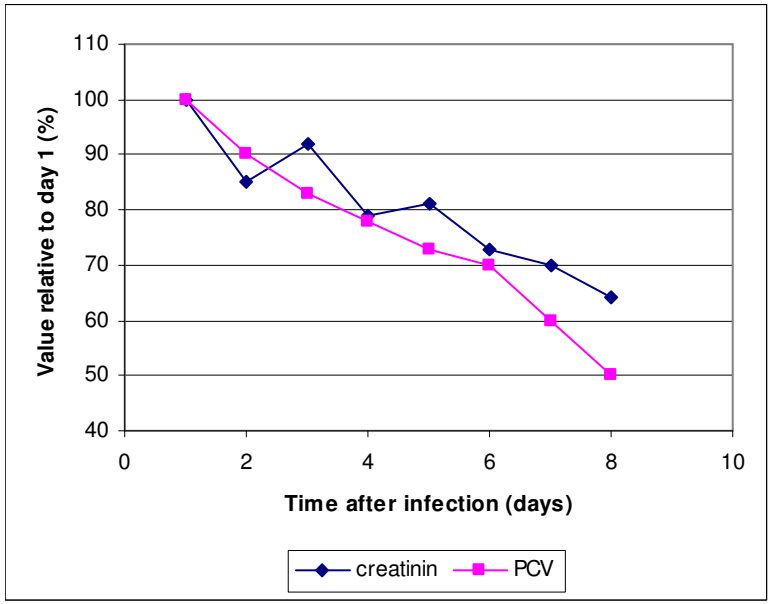
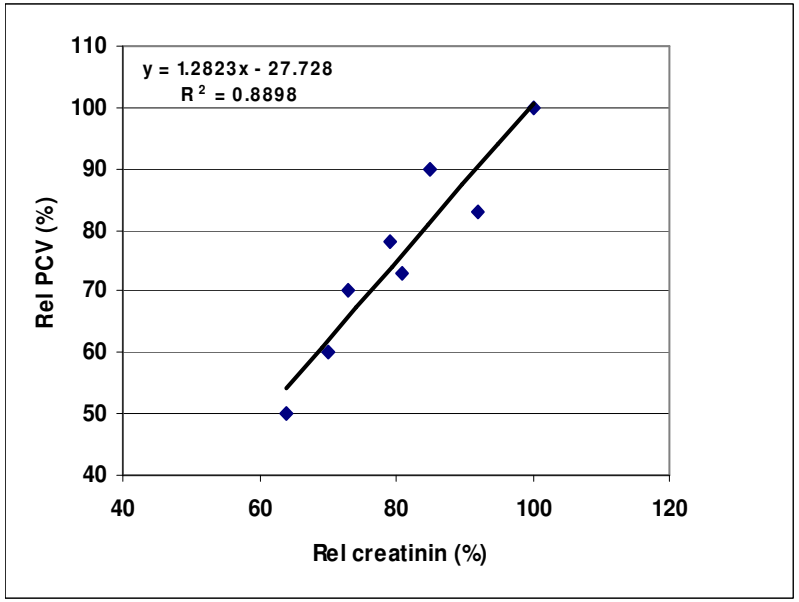
COMPENSATED HYPOTENSION-BABESIA



Dynamics of creatinin and red blood cell concentrations in B. canis infected dogs (n=5)



Correlation between concentrations of creatinin and red blood cells in B. canis infected dogs (n=5)

During hypotension water is retained, reflected in dilution of blood components -dilution of creatinin is similar to that of the red blood cells-

Schetters et al. 1997 Vet. Parasitol. 73, 35-41

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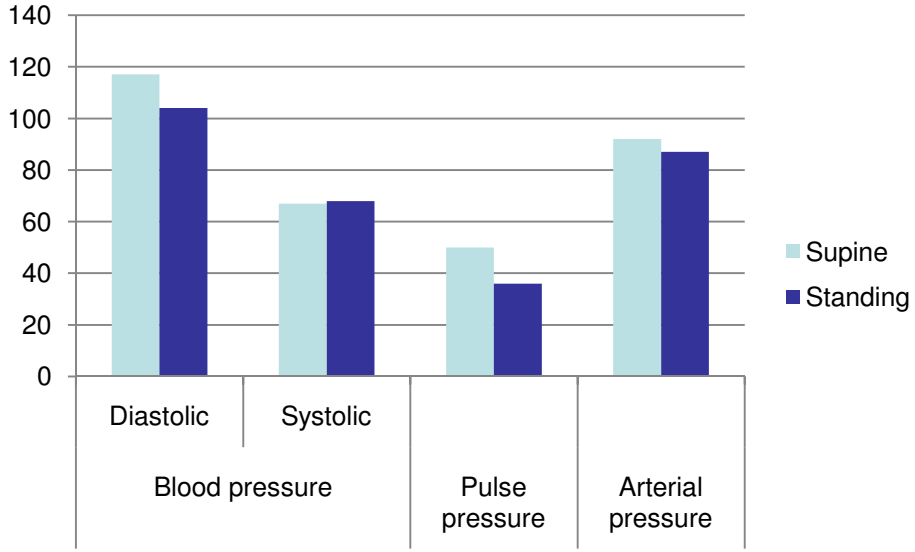
COMPENSATED HYPOTENSION-MALARIA

Orthostatic hypotension



Due to decreased capillary resistance orthostatic hypotension leads to dizziness and syncope (fainting)

Brooks et al. 1967 Am. J. Med. 43, 735-744

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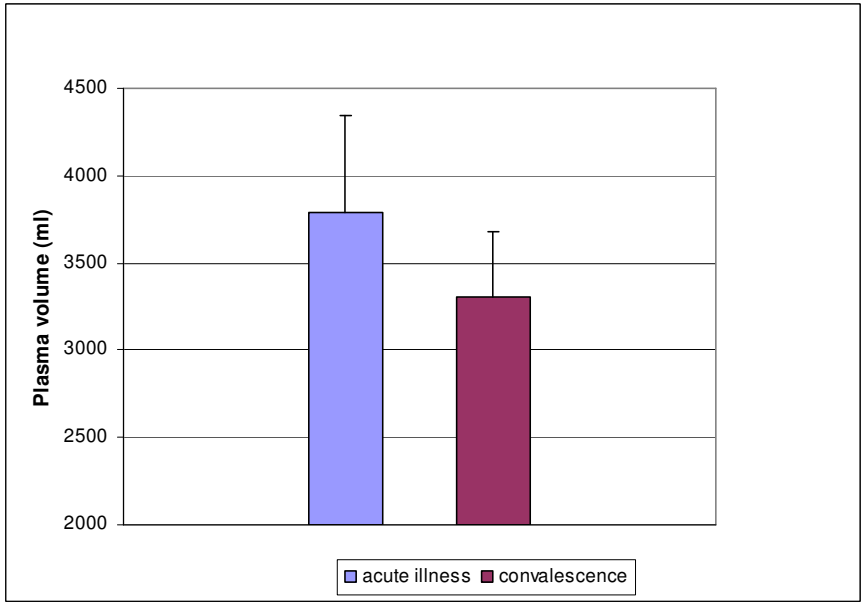
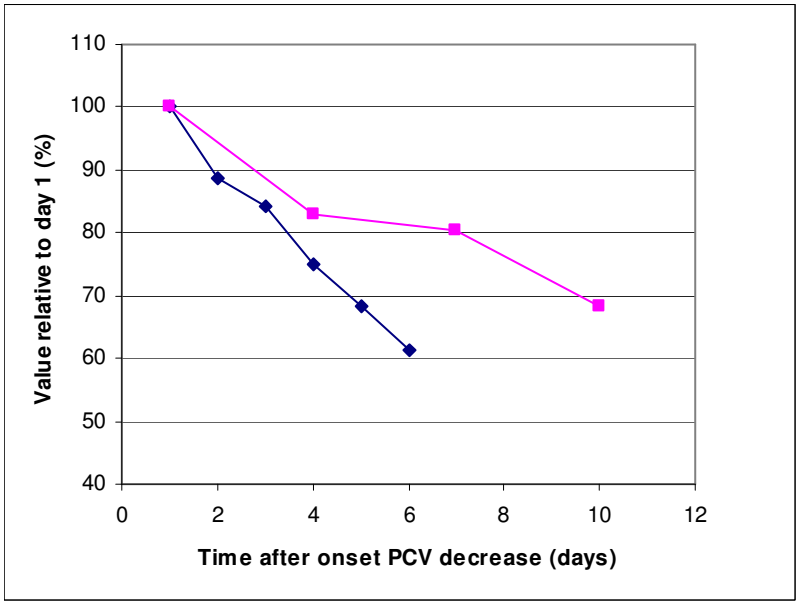
COMPENSATED HYPOTENSION-MALARIA



Plasma volume changes in P. falciparum patients receiving therapeutic treatment (n=23). Average change is 485 ml, 12.5% (p<0.001)



Dynamics of red blood cell concentrations in patients receiving therapeutic P. falciparum infection

During hypotension water is retained, reflected in dilution of blood components

Malloy et al. 1967 Am. J. Med. 43, 745-750

Feldman and Murphy 1945 J. Clin. Invest. 24, 780-792

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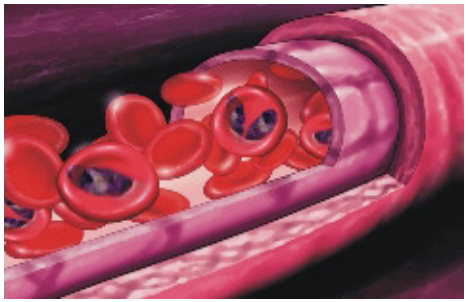
BLOCKED CAPILLARIES-BABESIA

CONCLUSIONS

- Early in Babesia infection dogs develop ***hypotension***
- Hypotension is ***compensated*** by increase of blood volume in 2-3 days
- Haematocrit decreases are largely the result of ***haemodilution***
- ***Capillary resistance*** remains low which reduces blood flow through capillaries
- Reduced blood flow facilitates ***adherence*** of infected red blood cells
- Similar processes occur in ***malaria***
- These aspects are largely neglected



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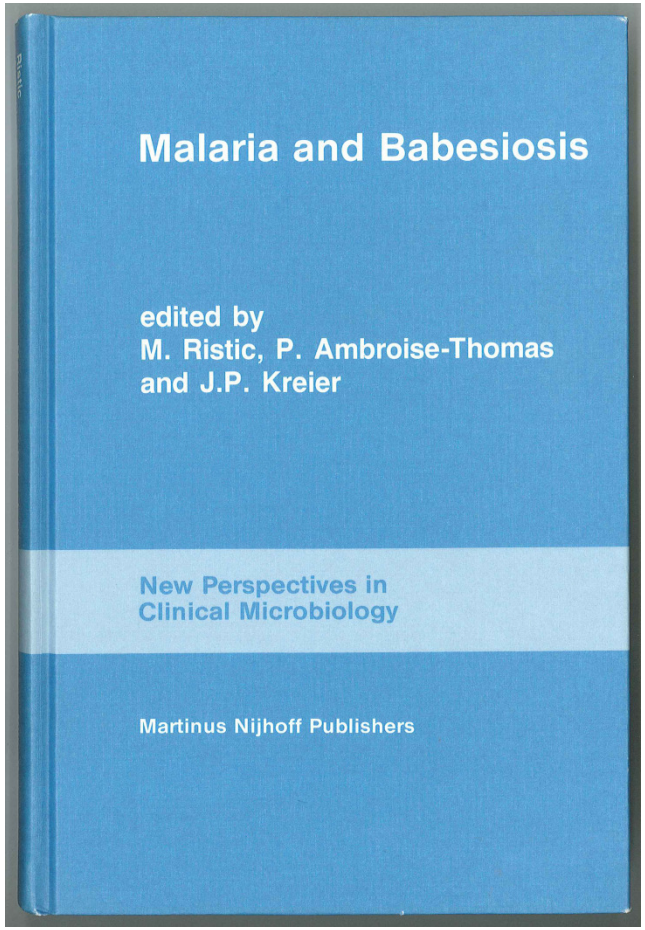
VACCINATION-BABESIA



Supernatants of in vitro cultures of the parasite can be used as vaccines

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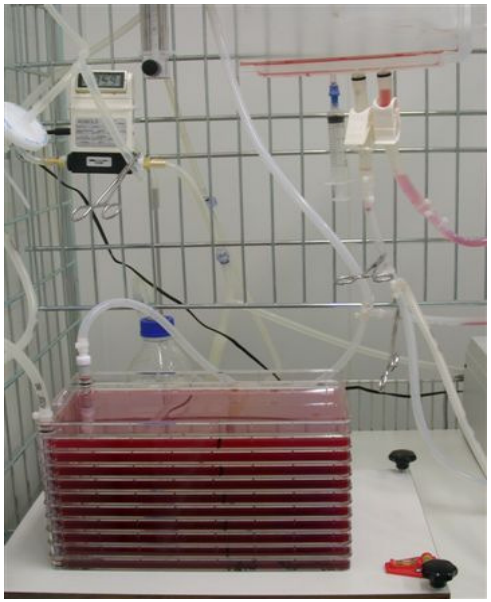
VACCINATION-BABESIA

Antigen production (SPA)



Adjuvant production (saponin)

A single dose is supernatant antigen (SPA) produced by 1 x 10e8 infected erythrocytes. Quil A (250 ug/ml) is used as adjuvant. A single dose volume is 1ml. Two subcutaneous injections with 3-week interval

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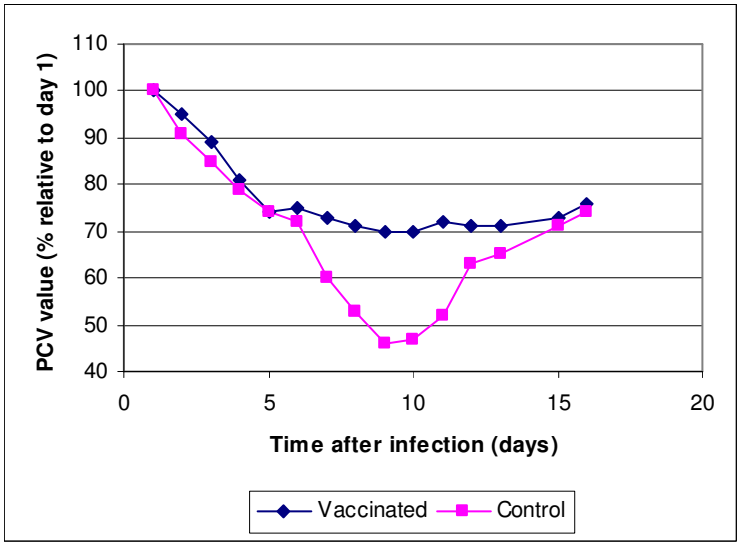
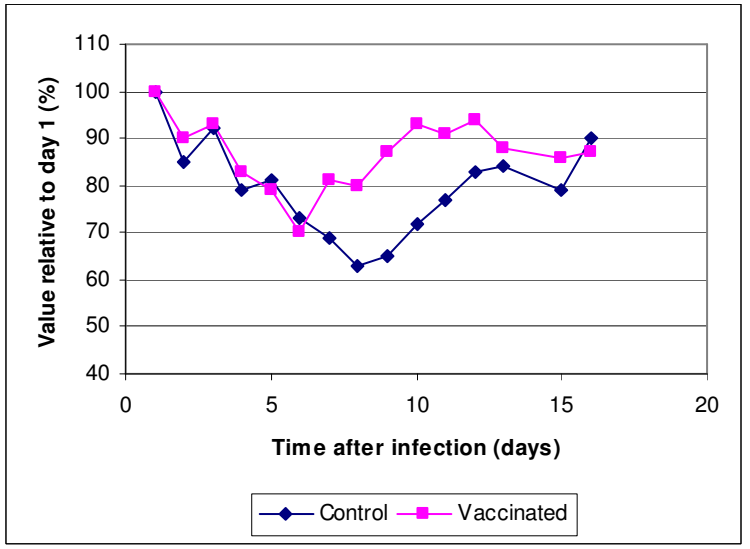
VACCINATION-BABESIA



Effect of vaccination of dogs with SPA on the red blood cell concentration (PCV) in blood. Data represent the average values from vaccinated and controls dogs (n=5)



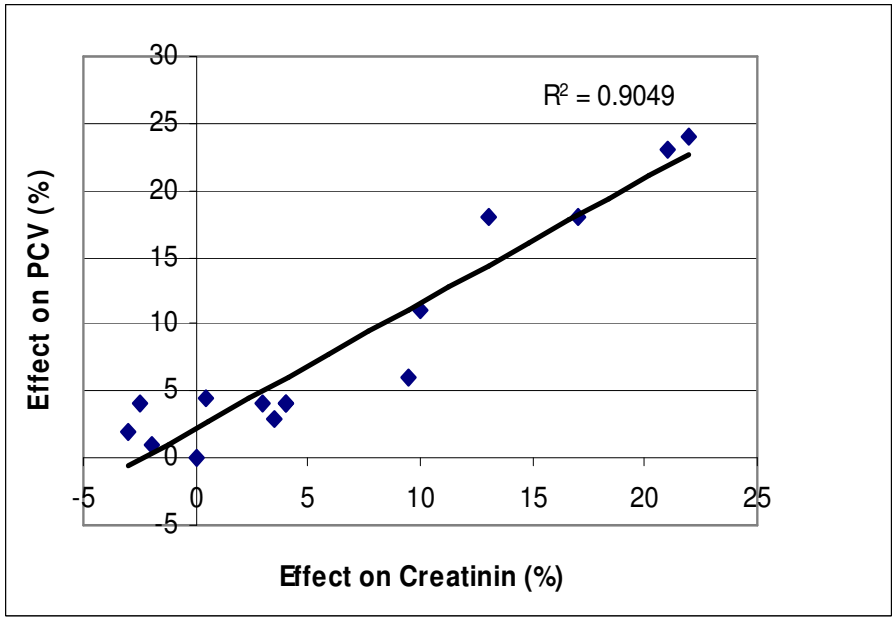
Effect of vaccination of dogs with SPA on the creatinin concentration in blood. Data represent the average values from vaccinated and controls dogs (n=5)

Vaccination with SPA controls excessive PCV and creatinin decreases

Schetters et al. 1997 Vet. Parasitol. 73, 35-41

MSD Be well

VACCINATION-BABESIA



Effect of vaccination of dogs with SPA on the red blood cell concentration (PCV) and creatinin concentration in blood. Data represent the difference between values from vaccinated dogs and controls dogs (n=5)

Protected dog

Because both parameters are affected to the same extent it is concluded that vaccination with SPA limits haemodilution

Schetters et al. 1997 Vet. Parasitol. 73, 35-41

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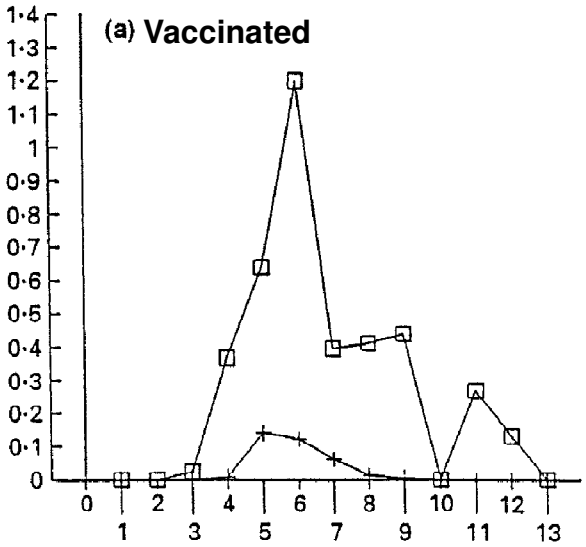
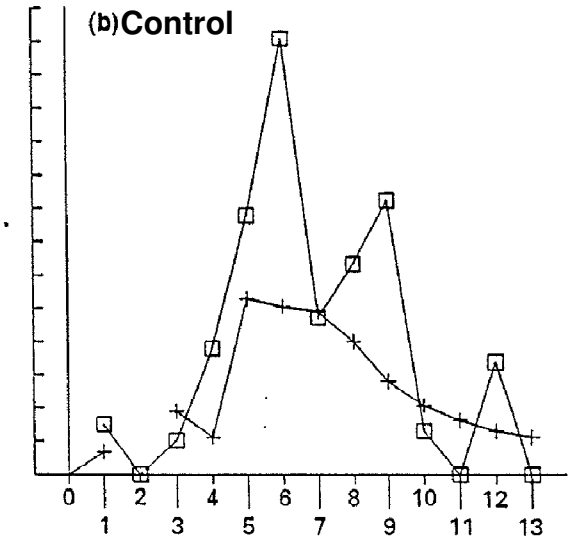
VACCINATION-BABESIA



Dynamics of parasitaemia (squares) and SPA concentrations (crosses) in vaccinated dogs (n=5)



Dynamics of parasitaemia (squares) and SPA concentrations (crosses) in control dogs (n=5)

Not peripheral parasitaemia but the level of SPA in plasma correlates with protection

Schetters et al. 1996 Parasite Immunol. 18, 1-6

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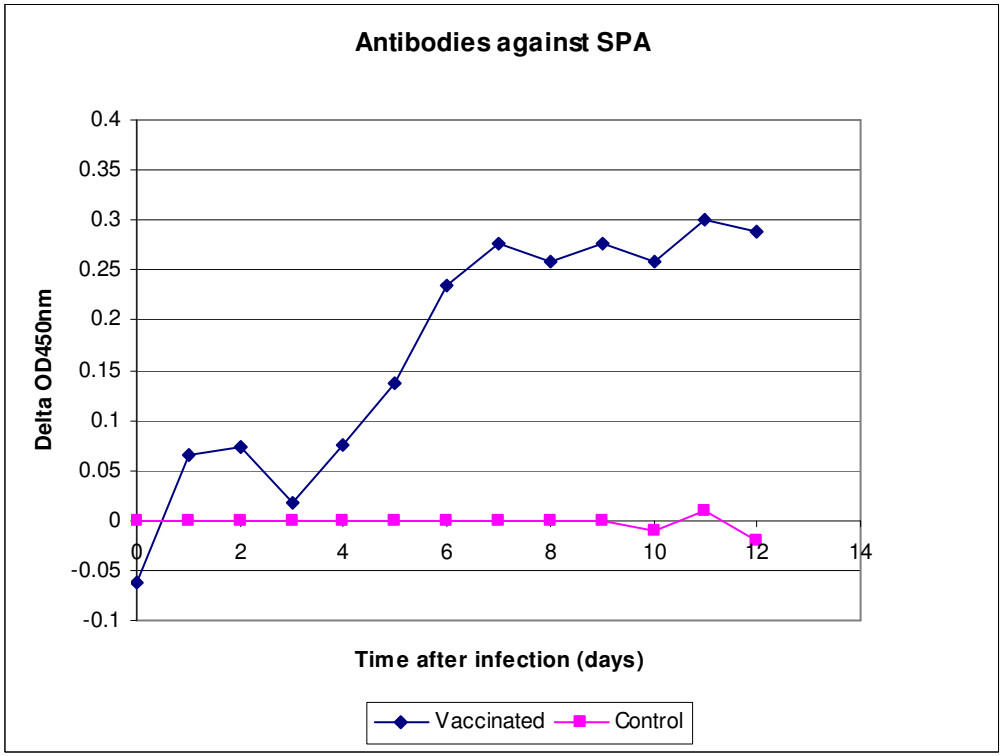
VACCINATION-BABESIA



The antibody response against SPA correlates with protection

Schetters et al. 1996 Parasite Immunol. 18, 1-6

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VACCINATION-BABESIA

CONCLUSIONS

- SPA of Babesia canis parasites cause disease
- Vaccination with SPA induces protection
- Protection is reflected in decreased SPA in plasma
- Protection is associated with an **antibody response against SPA**
- In experimental infections anti-SPA response is absent
- Vaccine-induced protection is essentially different from infection-induced protection

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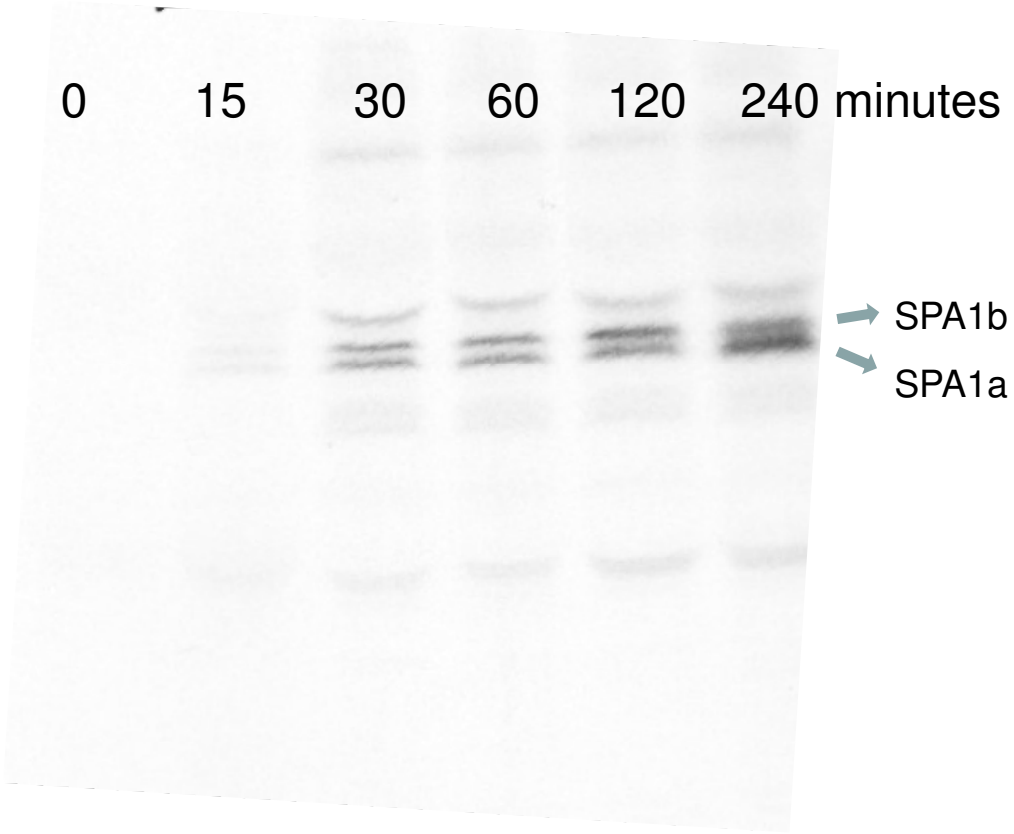
ANALYSIS SUPERNATANT ANTIGENS



A doublet at Mr 38-40kDa is produced by B. canis after 15 minutes pulse and chased at different time points

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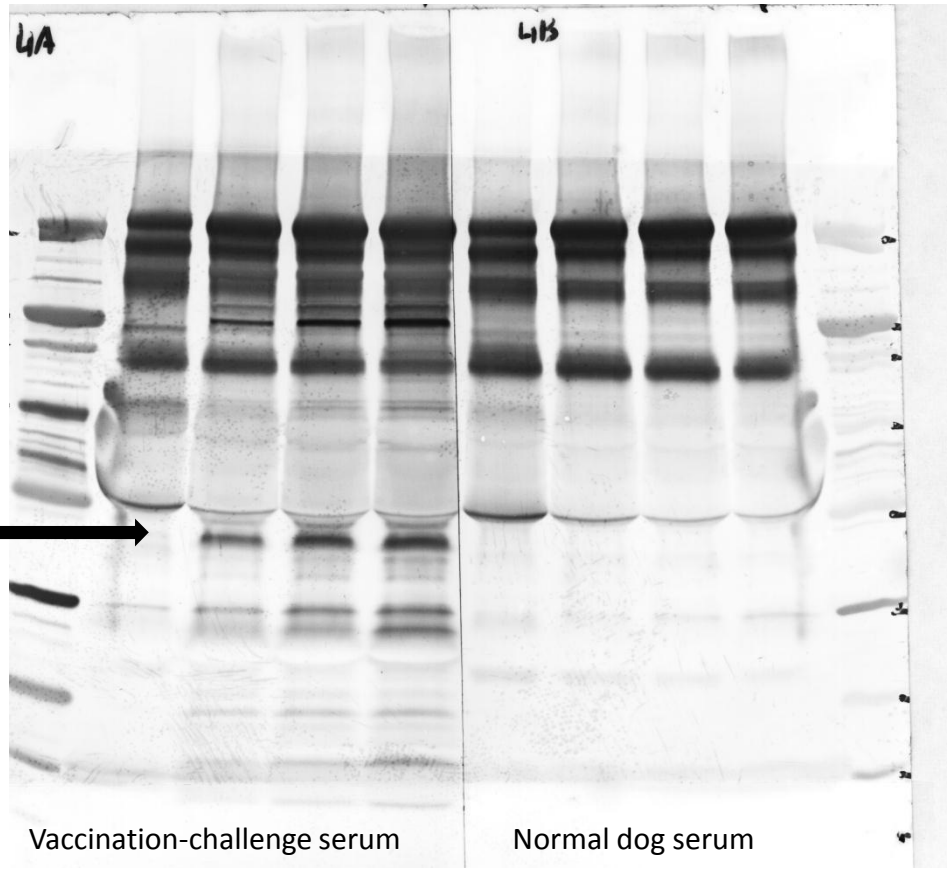
ANALYSIS SUPERNATANT ANTIGENS

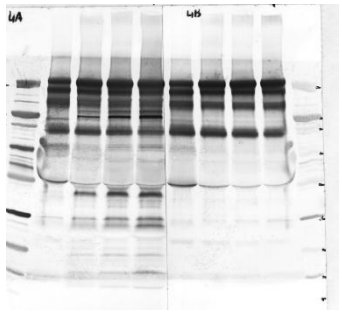


Vaccination-challenge serum recognizes SPA (mainly Mr 38kDa molecule)
-western blot analysis-

VACCINATION REC. SPA 1 ANTIGEN

DISCOVERY OF THE SPA1 GENE OF BABESIA CANIS

- The major antigens from SPA of B. canis were purified
- Partial amino acid sequences were revealed
- The genome of B. canis was sequenced
- The gene encoding for SPA1 was identified



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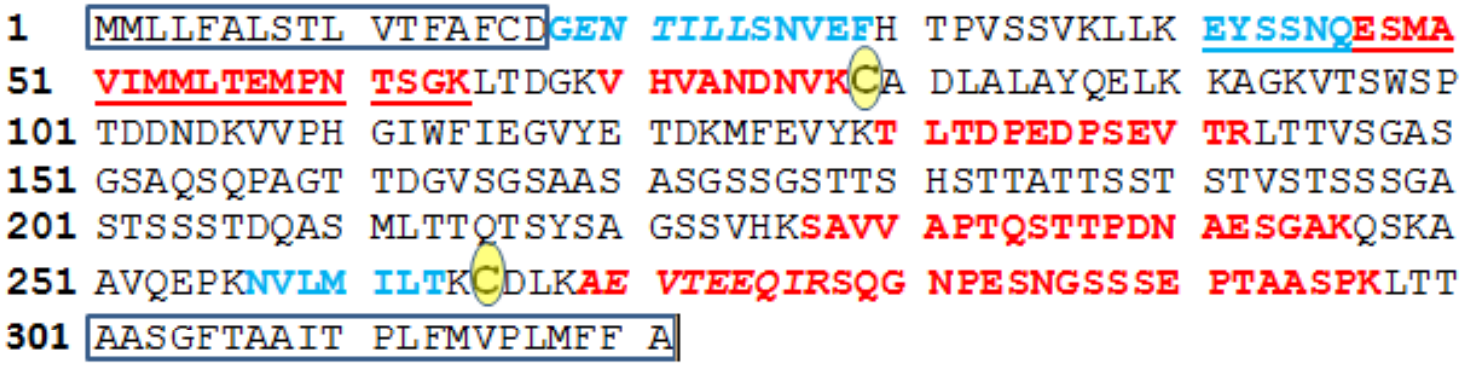
RECOMBINANT SPA 1 ANTIGEN

SPA1 GENE OF BABESIA CANIS



Signal sequences are boxed (GPI-anchored!)
In **blue,** peptides from purified SPA1b Mr40kDa (technique 1)
In ***blue/italics,*** peptide from purified SPA1a Mr 38kDa (technique 1)
In **red,** peptides from SPA1b (technique 2)
In **yellow** circles, cysteines that can lead to intramolecular di-sulphide bond

The SPA doublet is encoded by a single gene

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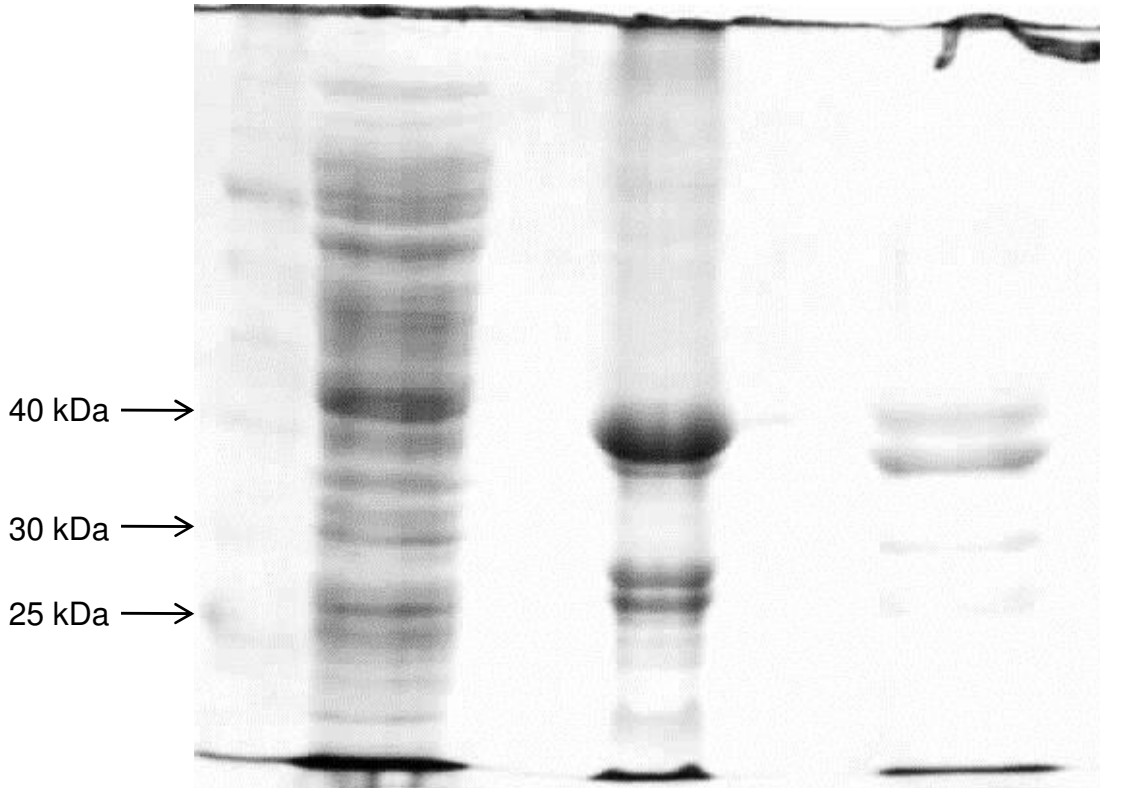
RECOMBINANT SPA 1 ANTIGEN



Production of recombinant SPA1 antigen in E. coli

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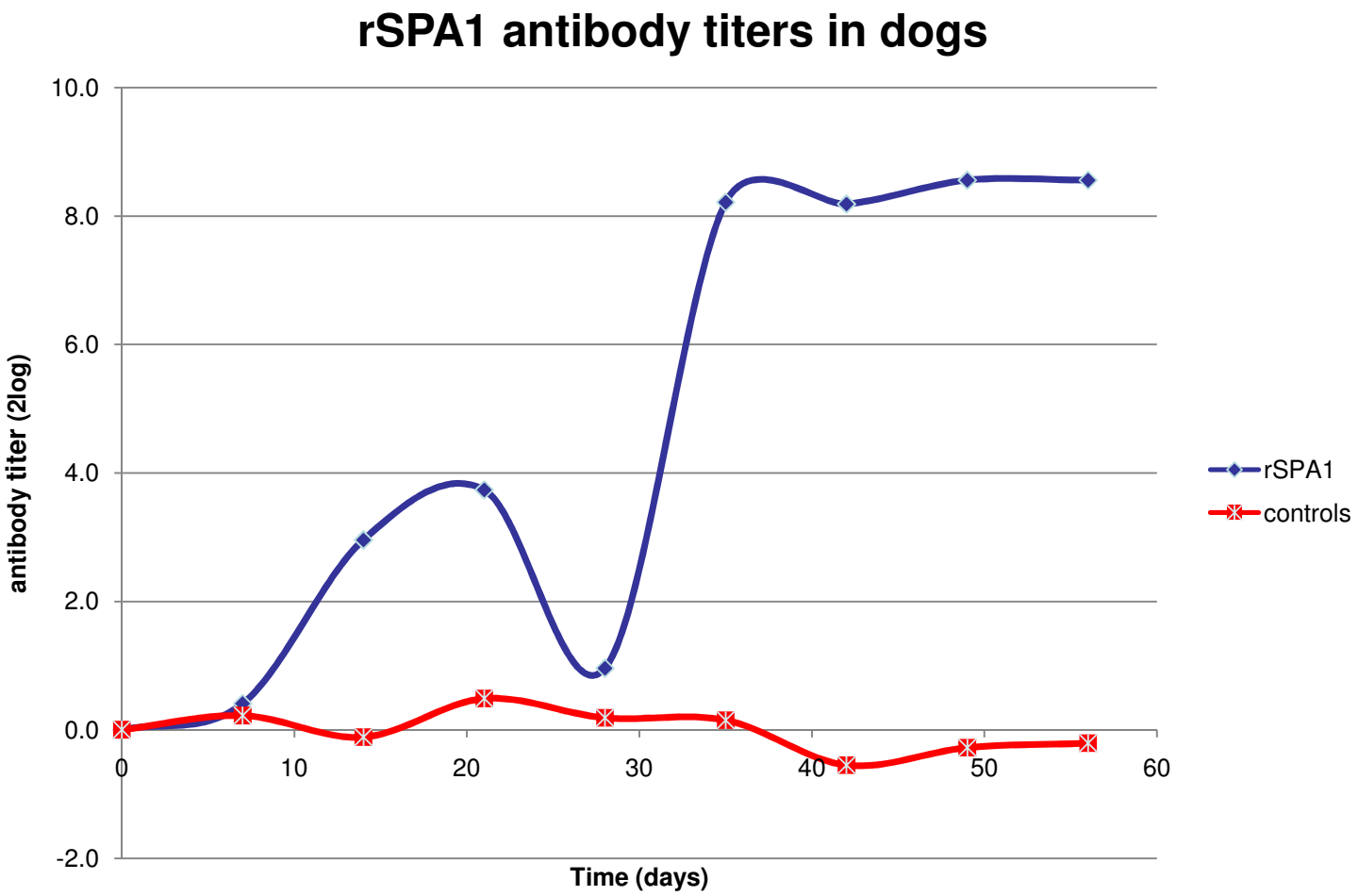
SEROCONVERSION RECOMBINANT SPA 1



Vaccination (day 0, 21 and 42) with Quil A adjuvant. Challenge day 56.

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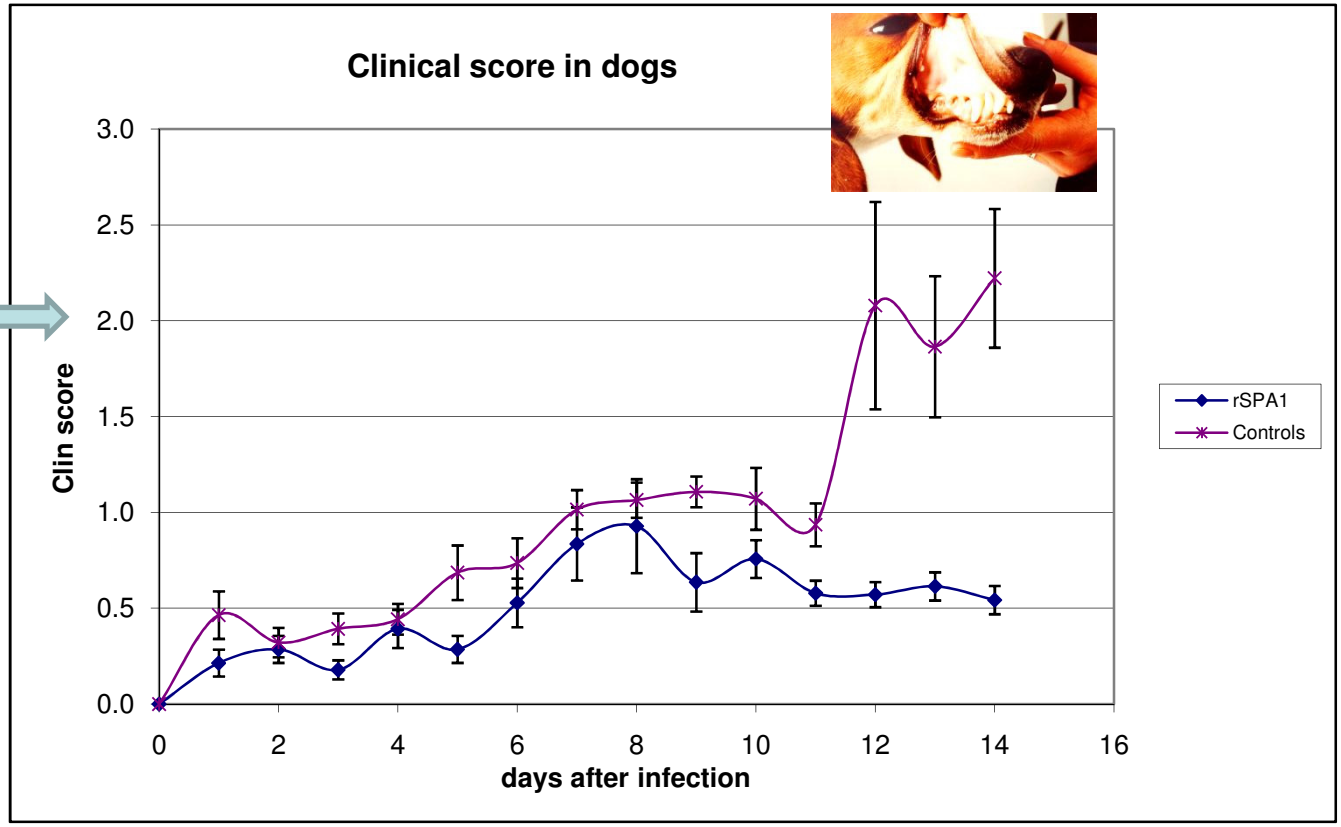
CLINICAL SIGNS

OVERT CLINICAL DISEASE



Vaccinated dogs are protected from clinical disease
-circulatory problems in control dogs from day 11 onwards-

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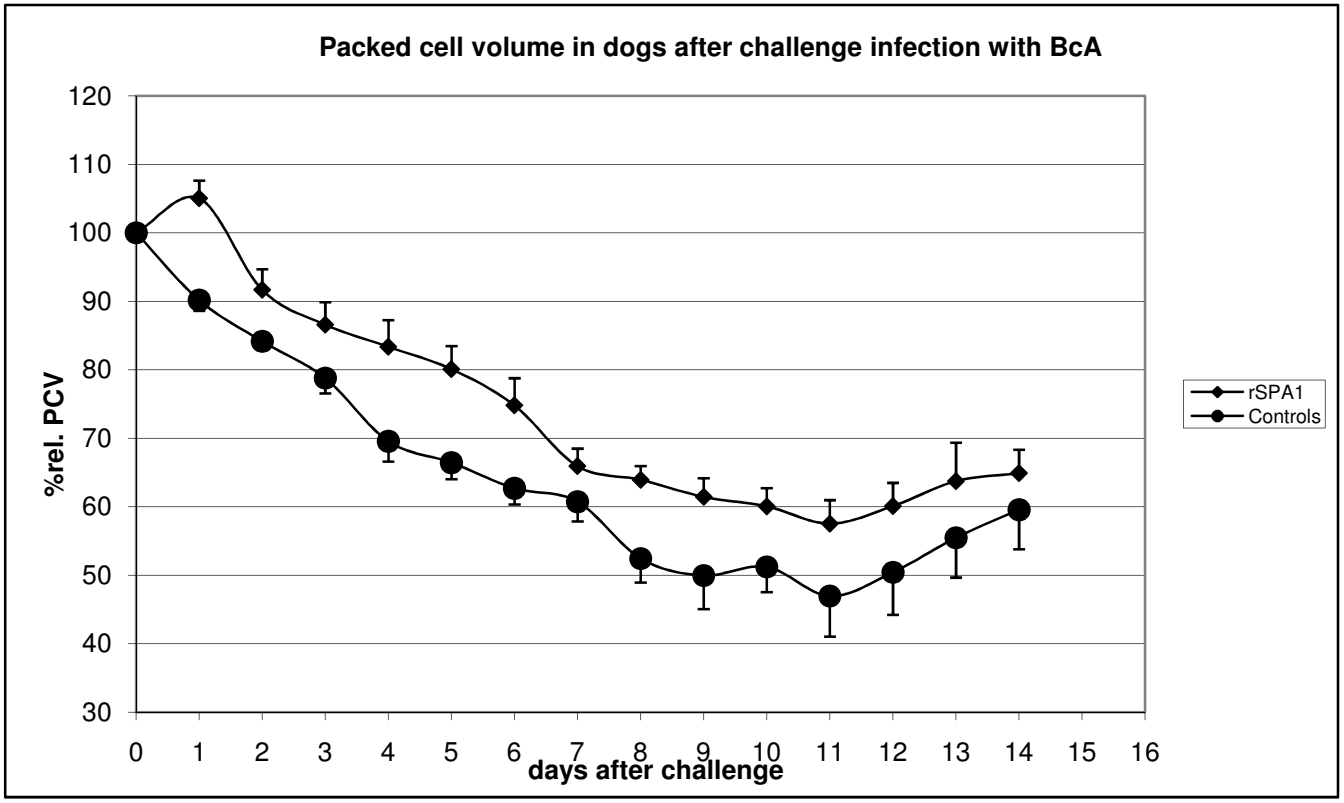
PACKED CELL VOLUME



Vaccinated dogs showed limited decreases in packed cell volume

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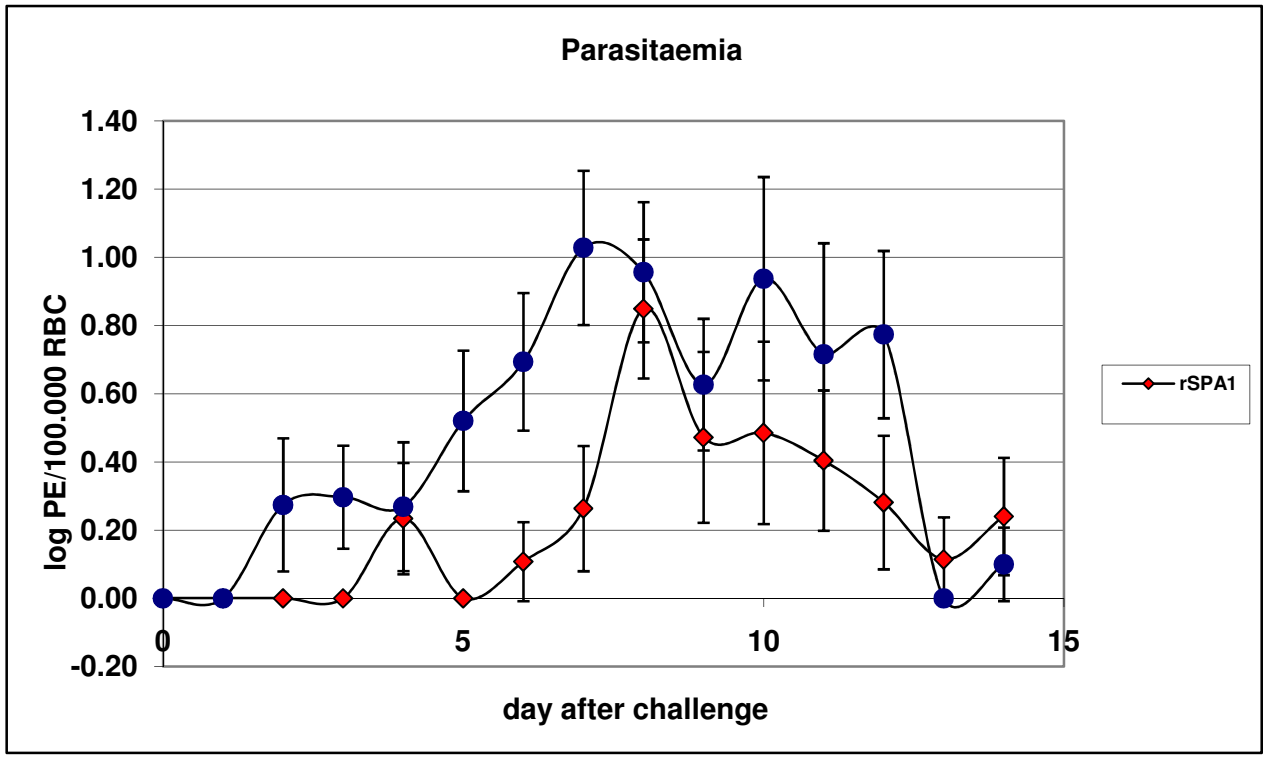
PARASITAEMIA



Development of parasitaemia is limited in vaccinated dogs

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VACCINATION REC. SPA 1 ANTIGEN

CONCLUSIONS -Babesia

- Vaccination of dogs with recombinant SPA1 protects against virulent challenge infection

- Protection is reflected in:
  - Limited decrease in packed cell volume
  - Restricted development of parasitaemia
  - Reduction in clinical signs (circulatory stress)

- It is hypothesized that vaccination interferes with pathological processes that lead to parasite localization which favours parasite proliferation (chronic infection)

- Similar pathological processes have been described in malaria and other systemic diseases

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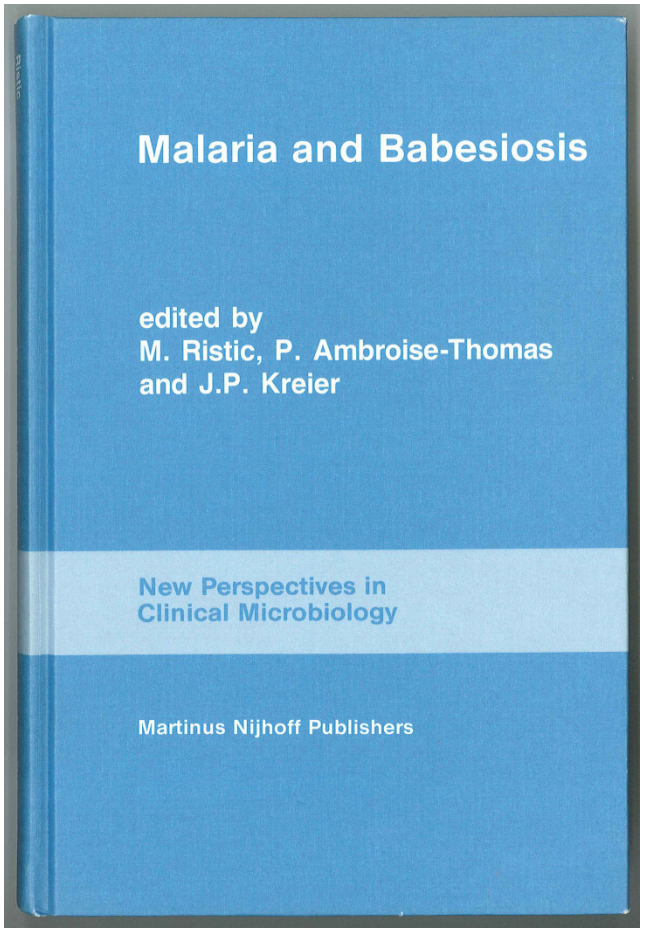
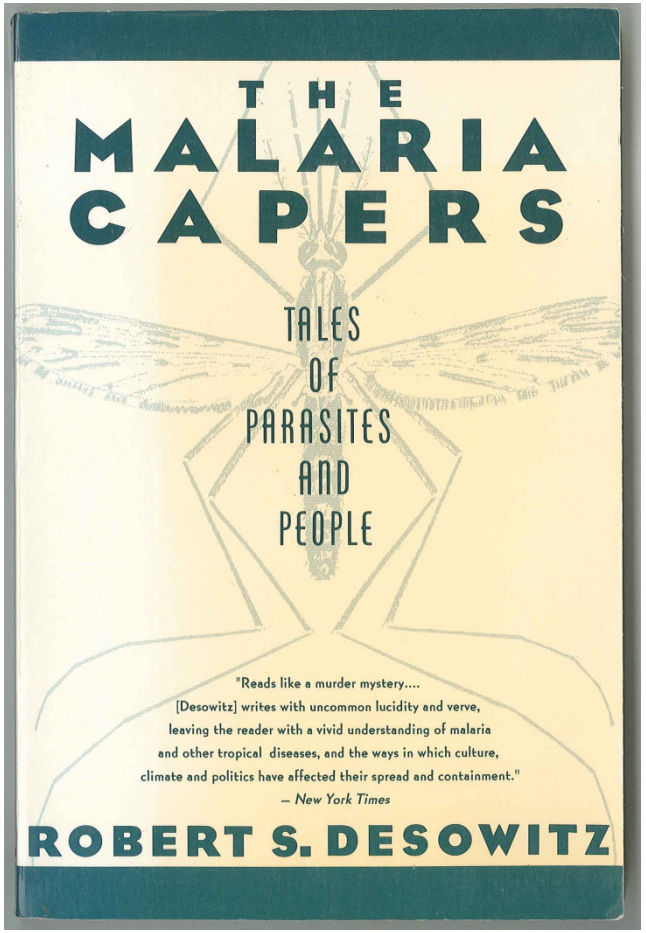
VACCINATION-MALARIA



The vaccine principle was claimed to work in the P. falciparum-squirrel monkey model….



...but the principal investigator was discredited and the research line was abrogated

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ACKNOWLEDGEMENTS

Jos Kleuskens, Nicolette Scholtes, Jos van de Crommert, Elle Krijnen, Karin Kuiper, Leonie Janssen, Liselotte Wolters, Ruud Segers, Mieke Vrijenhoek, Eric van Esch, Karel van Stokkom, Walter Barendts, Evelien van Kempen, Marianne Smit, Danny Goovaerts, Jan Pasman, Gerard de Snayer, Emiel Hendriks, Dominique Clercx, Andre Gorenflot, Eric Precigout, Bernard Carcy, Karina Moubri, Stephane Delbecq, Tom Strydom, Neil Fourie, Tshepo Matjila, Banie Penzhorn, Brian Cooke, David Allred, Bernadette Scholts, and all those who contributed but are not listed here

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