

Hablemos de tuberculosis animal



SABIO

Sanidad y Biotecnología
Health and Biotechnology



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Instituto de Investigación
en Recursos Cinegéticos
CSIC - UCLM - JCCM



It is a nasty and selfish bug that slowly invades and destroys every tissue. Without intervention, it will spread to contaminate and corrupt in-contact organisms.

DISPATCHES

Tuberculosis-Associated Death among Adult Wild Boars, Spain, 2009–2014

Jose A. Barasona, Pelayo Acevedo, Iratxe Diez-Delgado, Joao Queiros, Ricardo Carrasco-García, Christian Gortazar, Joaquín Vicente

juveniles (12–24 months of age). In adults (>2 years of age), the observed proportion of wild boars with generalized tuberculosis was 6.8%, suggesting some degree of TB-driven death among juveniles (6.8). TB is a sporadic cause of death among

Health & Biotechnology
(SaBio)



SaBio research: Disease control – Reproductive biotechnology – Vector-borne infections – Wildlife management (...)

IREC

Wildlife Research Institute



Ciudad Real - Spain





Reunión Ciencia & Txuletón 2024



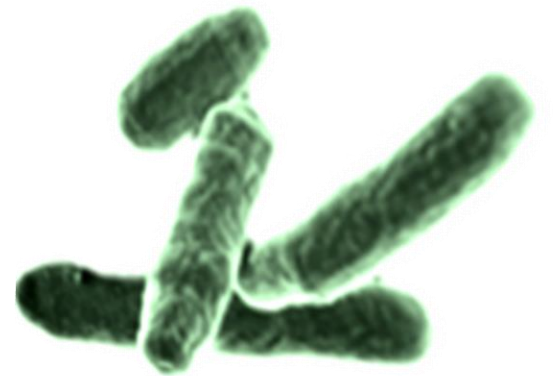
Ramon A. Juste (Externo)



lucas (No comprobado)

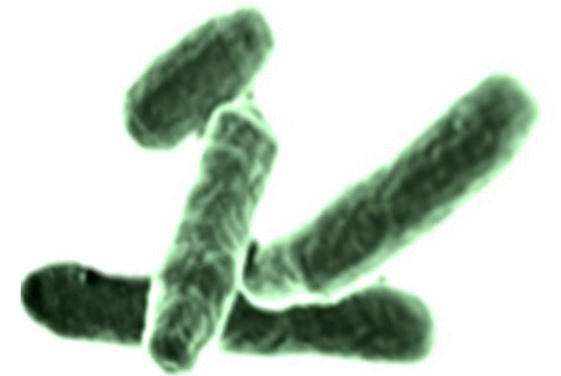
Estructura de la presentación

- Situación actual de la TB animal
- Epidemiología: hospedadores y transmisión
- Análisis de riesgos y diagnóstico epidemiológico
- Herramientas de control
 - Pruebas y matadero en bovinos
 - Control de hospedadores no bovinos
 - Bioseguridad
 - Vacunación
- Cuatro mensajes clave



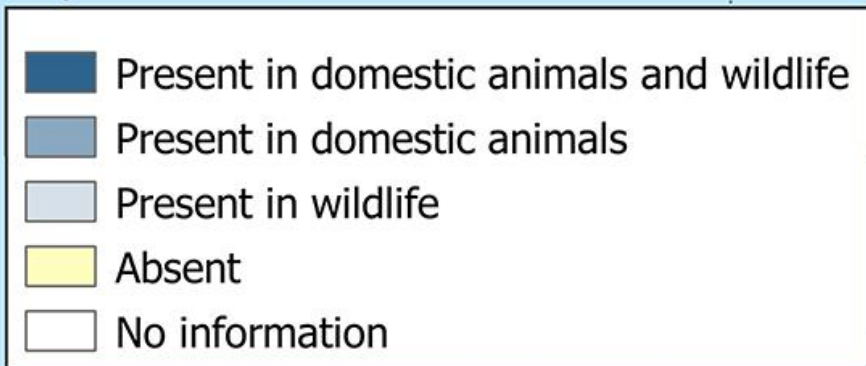
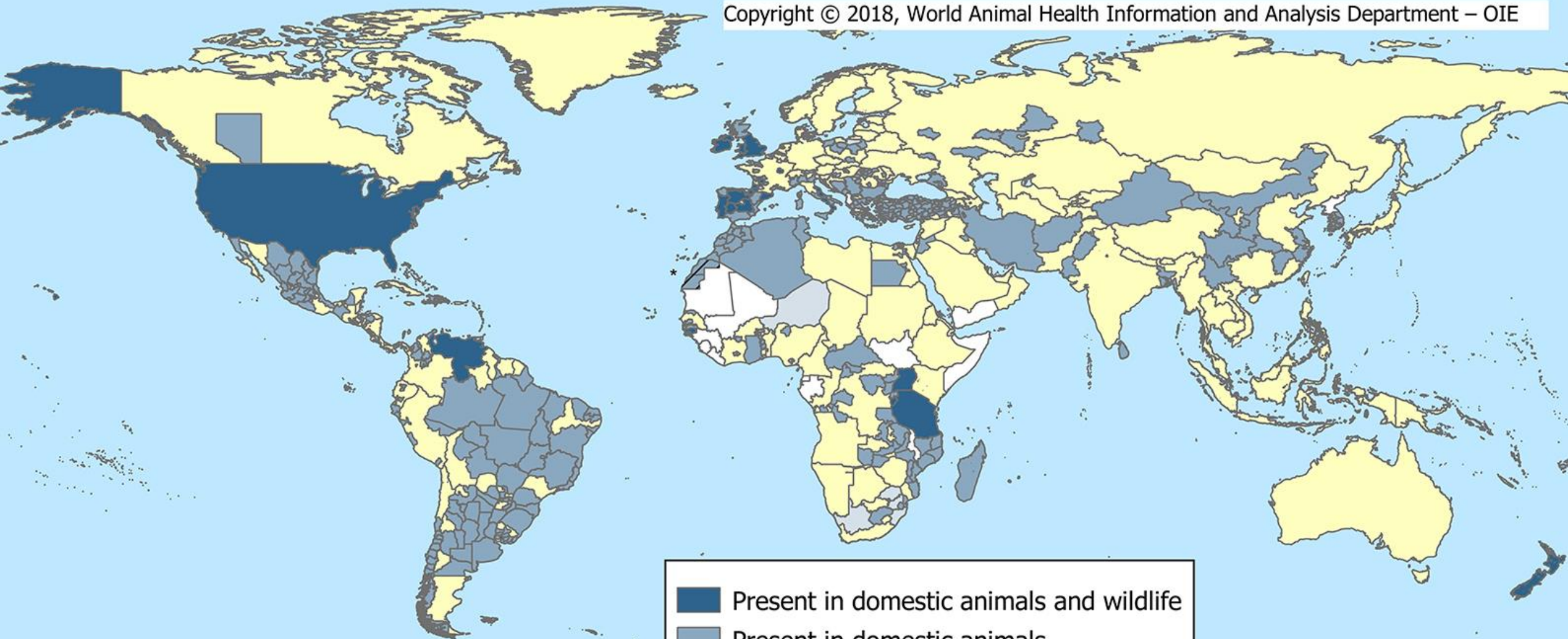
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Situación epidemiológica mundial

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* Data provided by Morocco

Age culling

- Rationale: remove older animals to slaughter to decrease the risk of TB breakdown, removing a source of infection for the younger animals
- Successfully used in Australia during TB eradication
- Applied to animals ≥ 8 years - where disease prevalence was high (3%), animals ≥ 5 years were removed



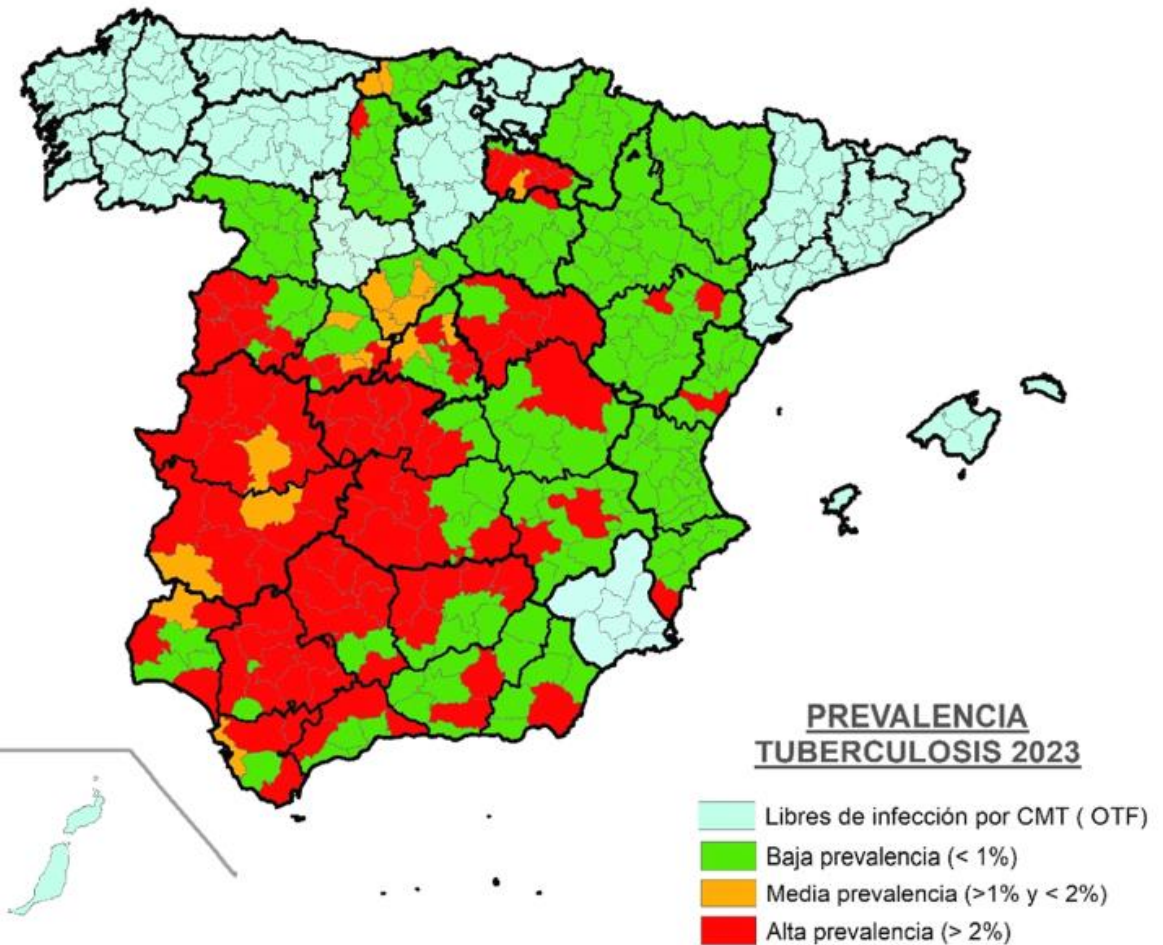
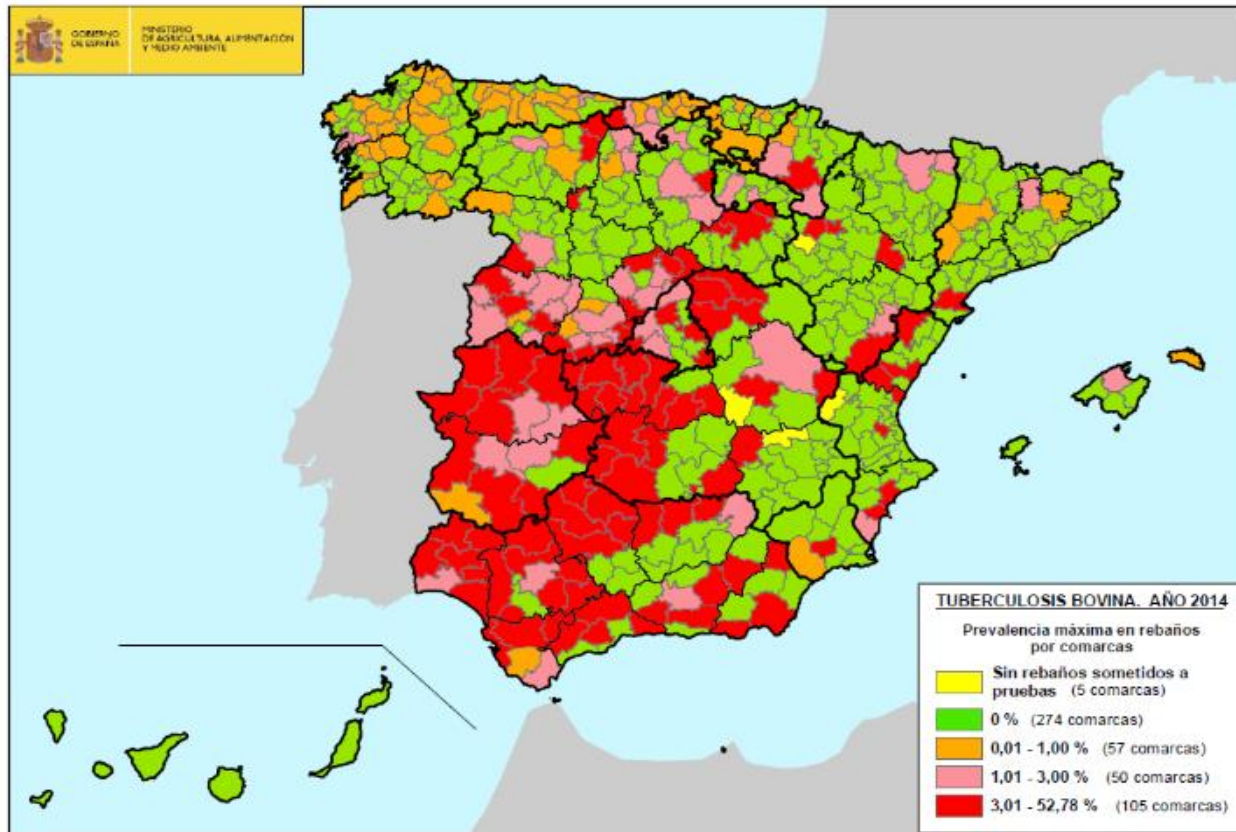




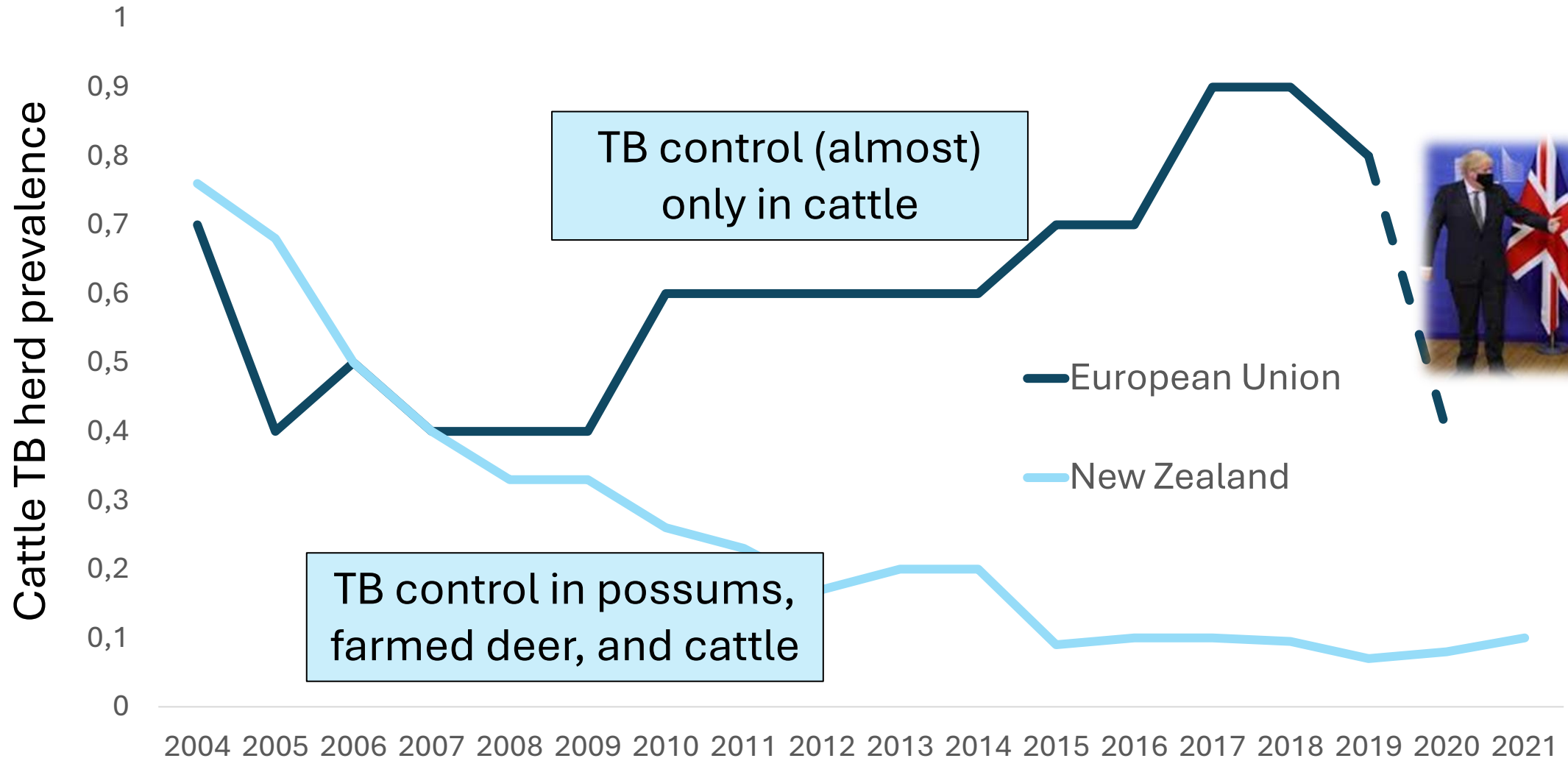
TB bovina en España

2014 – prev. rebaño 1.7%

2023 – prev. rebaño 1.6%

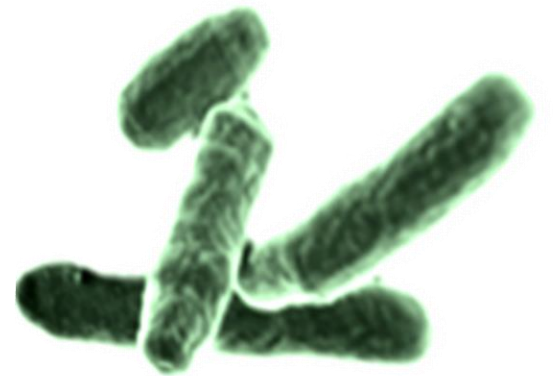


EU vs NZ

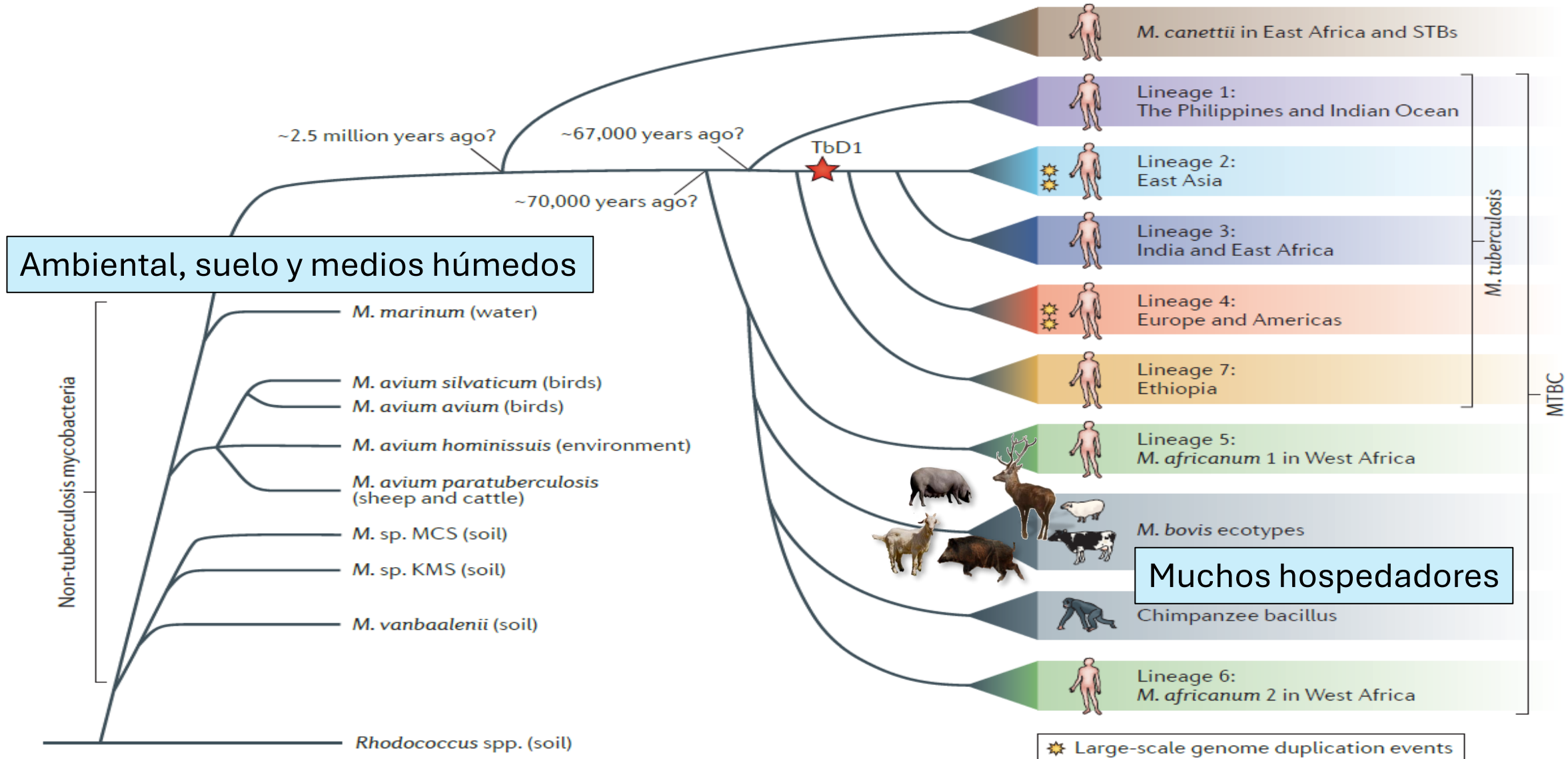


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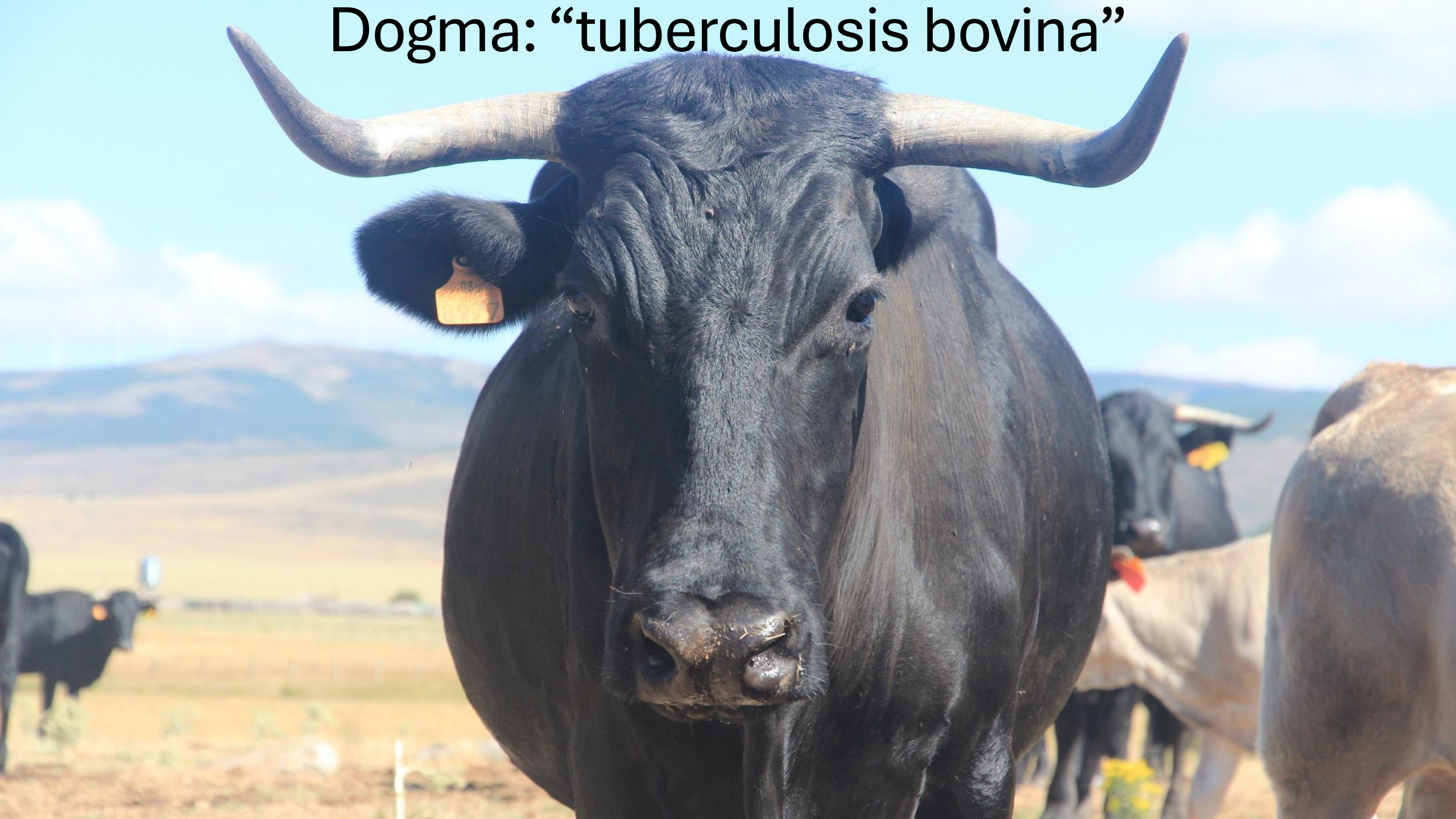
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Intro: *Mycobacterium tuberculosis* complex



Dogma: “tuberculosis bovina”



Hospedadores domésticos no bovinos



2013

Short Communications *Veterinary Record* doi:10.1136/vr.101347

Short Communications

Evidence of goats acting as domestic reservoirs of bovine tuberculosis

S. Napp, A. Allepuz, I. Mercader, M. Nofrarías, S. López-Soria, M. Domingo, B. Romero, J. Bezos, B. Pérez de Val

Hernández and others 1996). In 2000, in Asturias (Northern Spain), a 12 per cent (73 out of 600) of goats and a 92 per cent (23 out of 25) of goat herds were found positive to the gamma interferon test, while the prevalence on bovines and bovine herds was 0.1 per cent and 0.4 per cent, respectively (Balseiro and others 2001). However, in Spain, the testing of goat herds is only compulsory in mixed (cattle and goats) farms, or when they share pastures with cattle (Anonymous 2012a). Yet, some autonomous communities (Andalusia, Castile and Leon, Murcia, and the Canary Islands) have started implementing regional control and eradication programmes in goat herds.

Even though a possible role of goats in bTB epidemiology in Spain has been proposed (Alvarez and others 2008, Bezos and others 2010, Rodríguez and others 2011), there are no published evidences of the spread of the bacteria from goats to cattle. The aim of the present

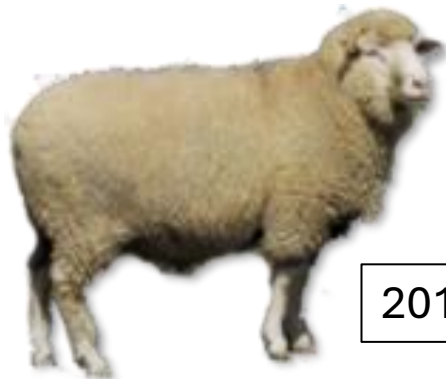


2012

JCM
Journals.ASM.org

Epidemiological Significance of the Domestic Black Pig (*Sus scrofa*) in Maintenance of Bovine Tuberculosis in Sicily

Vincenzo Di Marco,^a Piera Mazzone,^b Maria Teresa Capucchio,^c Maria Beatrice Boniotti,^d Vincenzo Aronica,^a Miriam Russo,^a Michele Fiasconaro,^a Noemi Cifani,^{e,f} Sara Corneli,^b Elena Biasibetti,^c Massimo Biagetti,^b Maria Lodovica Pacciarini,^d Monica Cagiola,^b Paolo Pasquali,^f and Cinzia Marianelli^f



2016

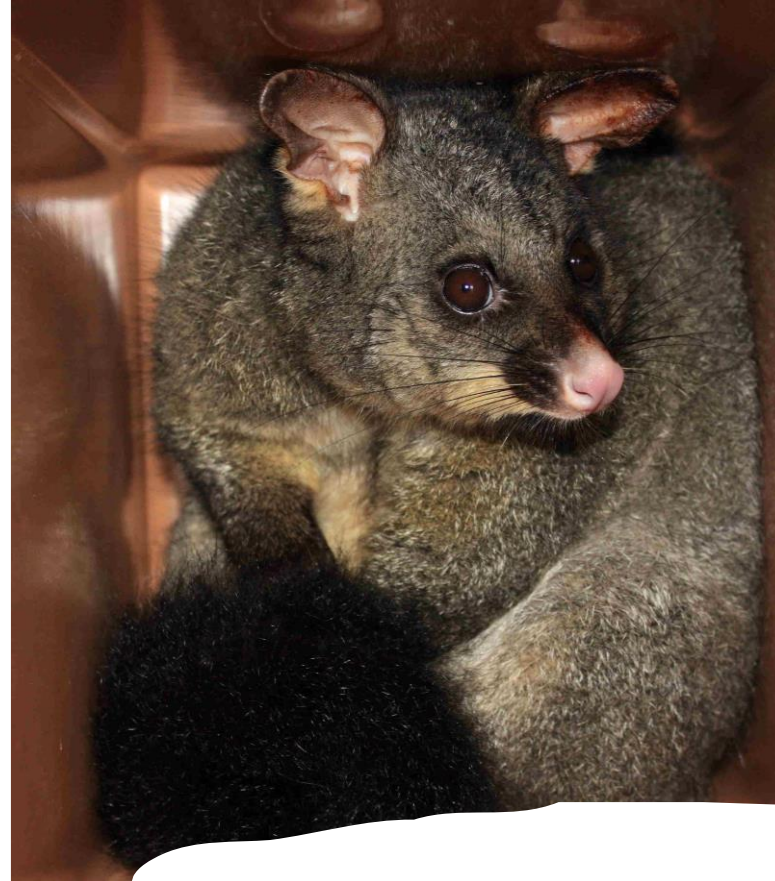
Transboundary and Emerging Diseases

Transboundary and Emerging Diseases

ORIGINAL ARTICLE

Sheep as a Potential Source of Bovine TB: Epidemiology, Pathology and Evaluation of Diagnostic Techniques

M. Muñoz-Mendoza¹, B. Romero², A. del Cerro³, C. Gortázar⁴, J. F. García-Marín⁵, S. Menéndez⁶, J. Mourelo¹, L. de Juan², J. L. Sáez⁷, R. J. Delahay⁸ and A. Balseiro³



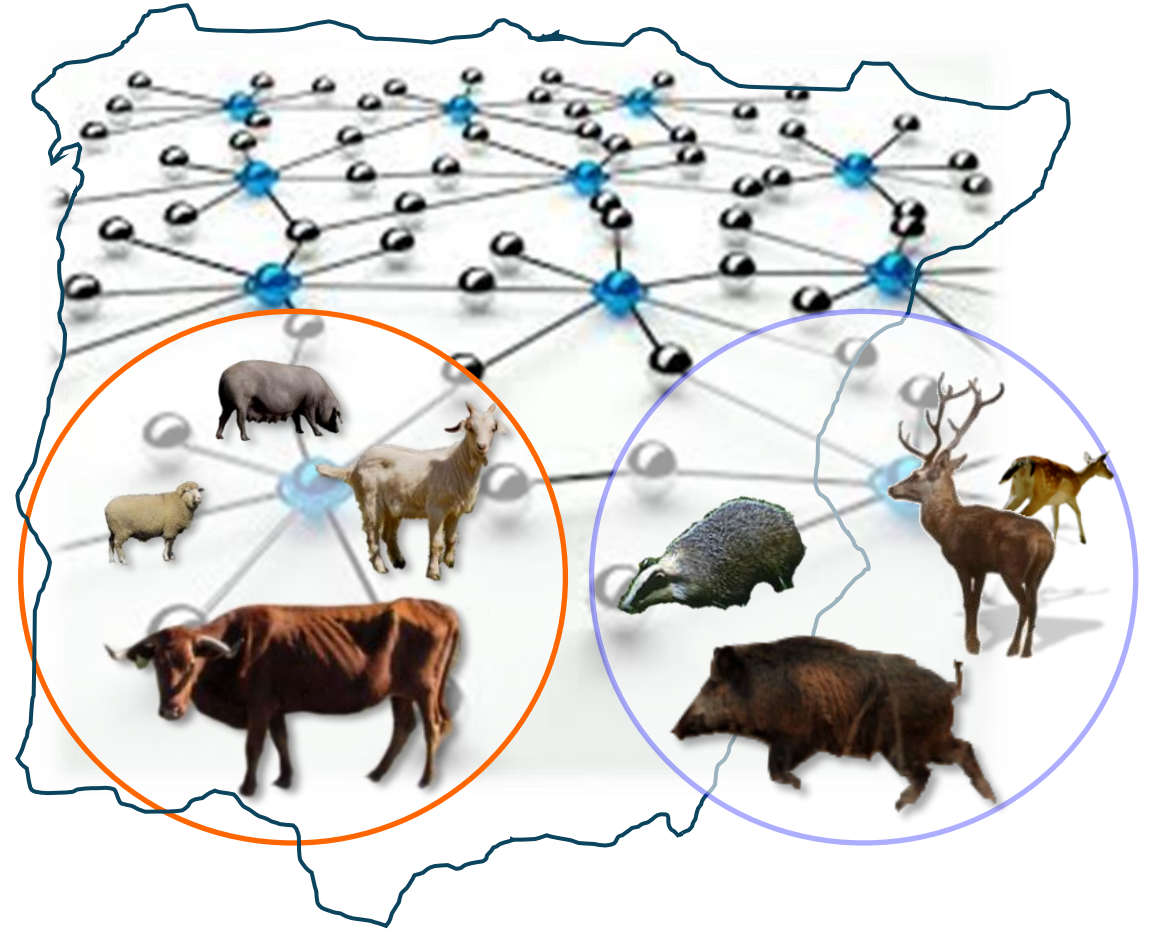
Acorn ⓘ 059F 015C 09/09/2016 07:1



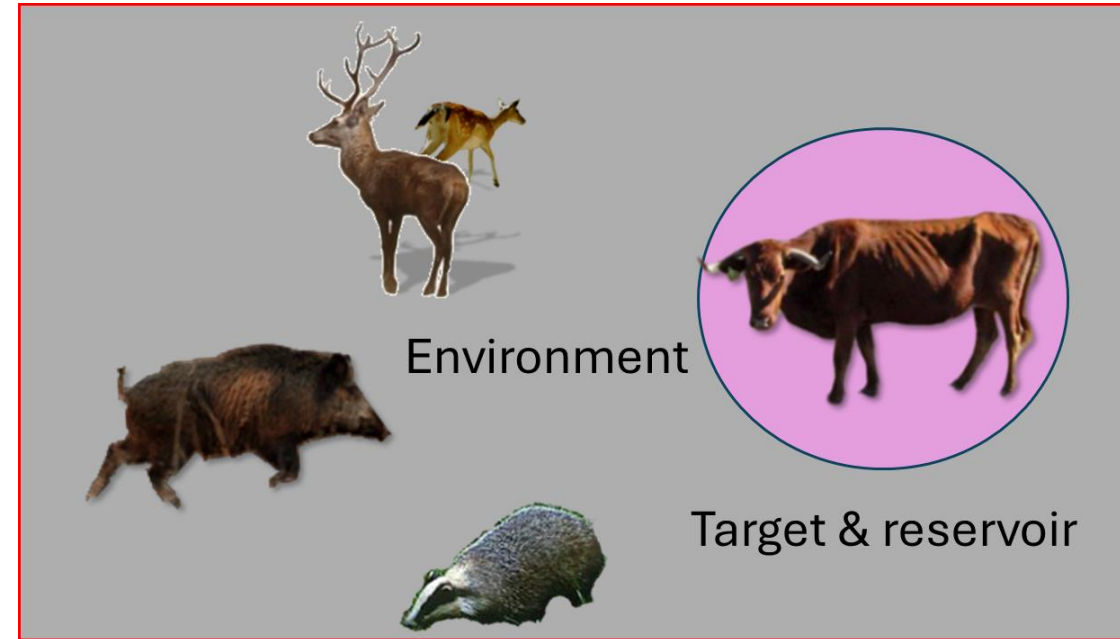
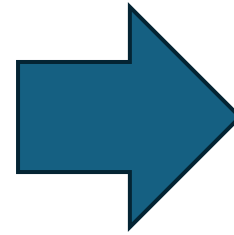
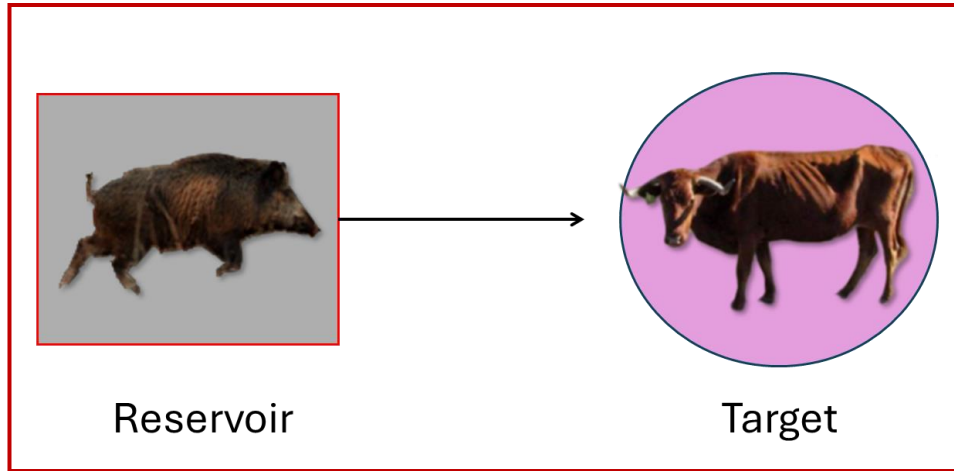
Wildlife hosts

Infección multi-hospedador

A más especies
afectadas – mayor
estabilidad del
sistema

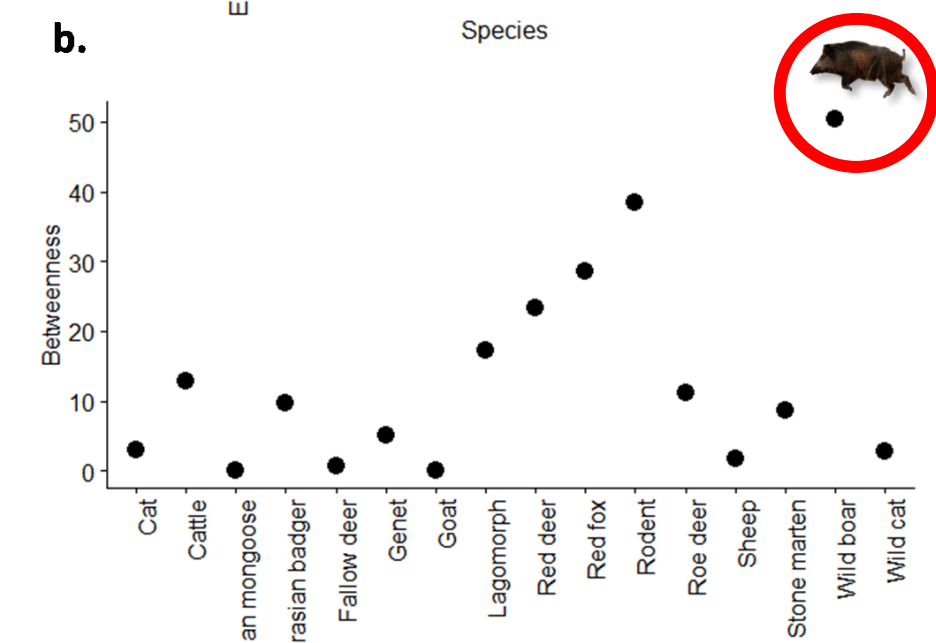
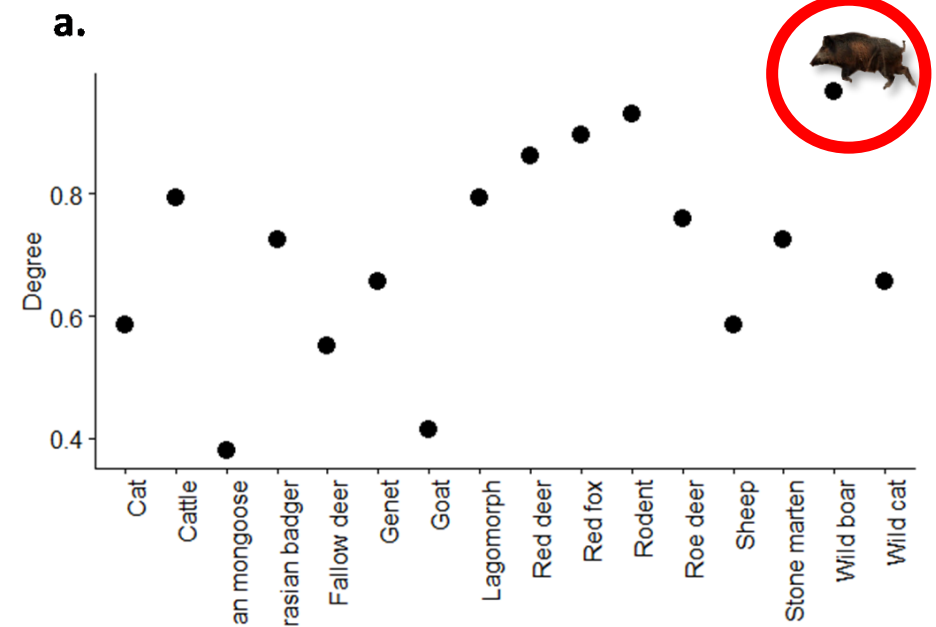
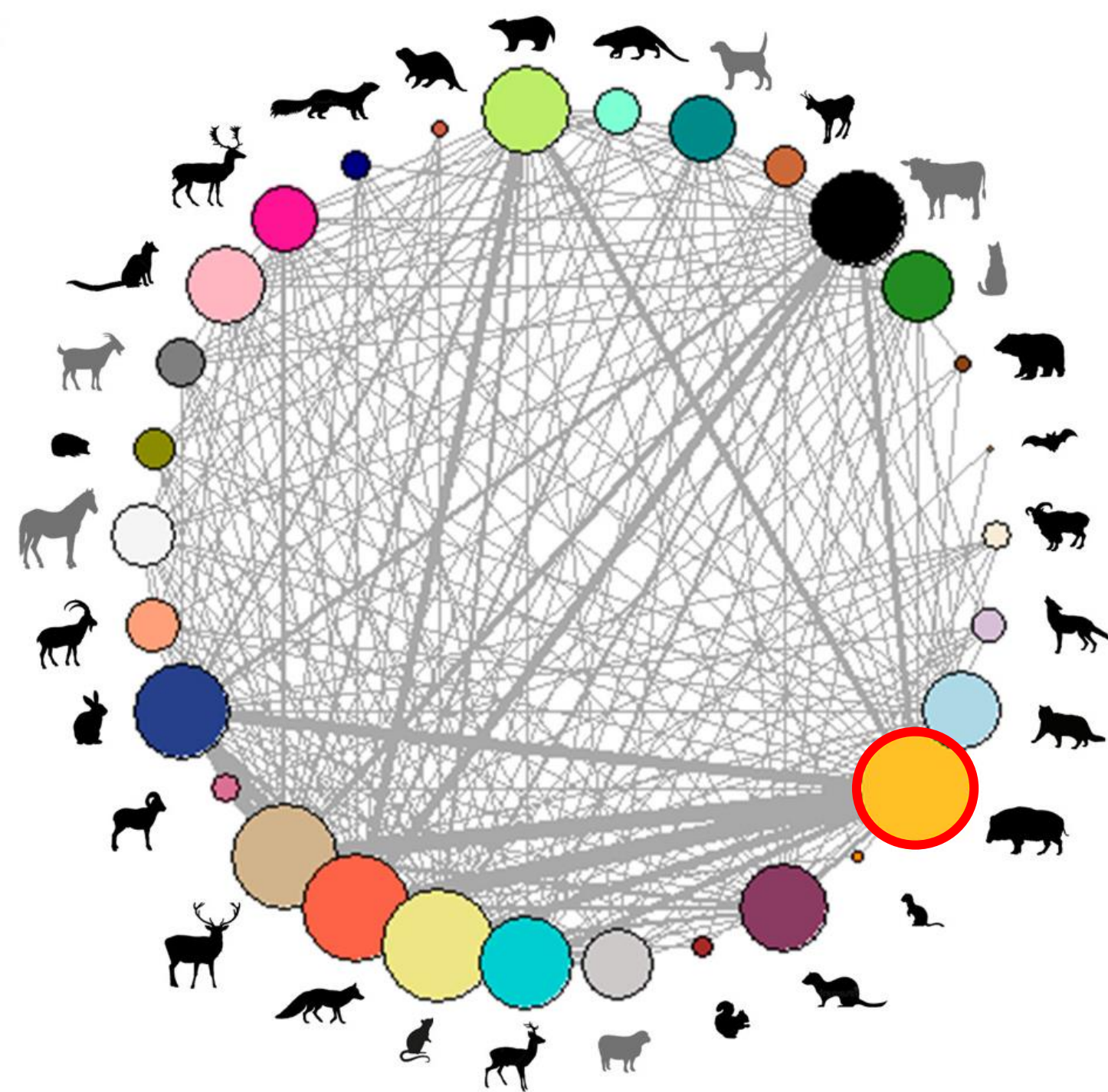


Episystems

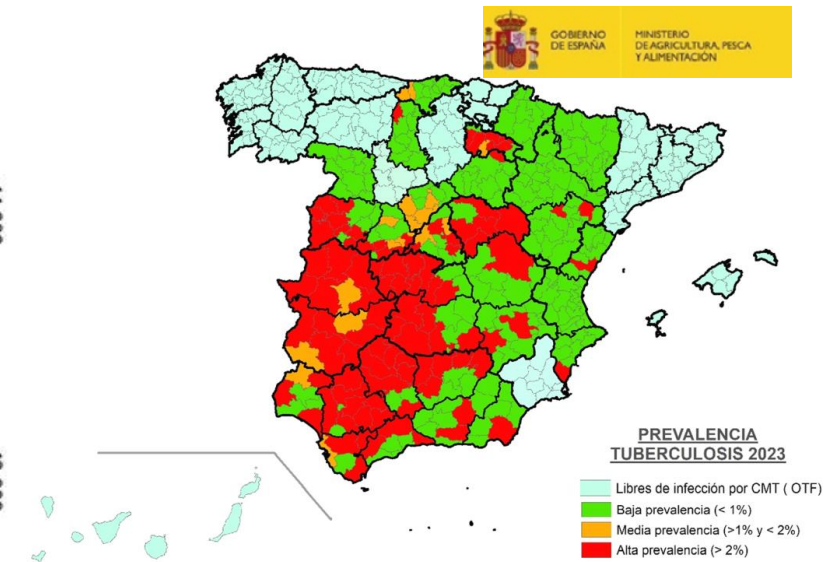
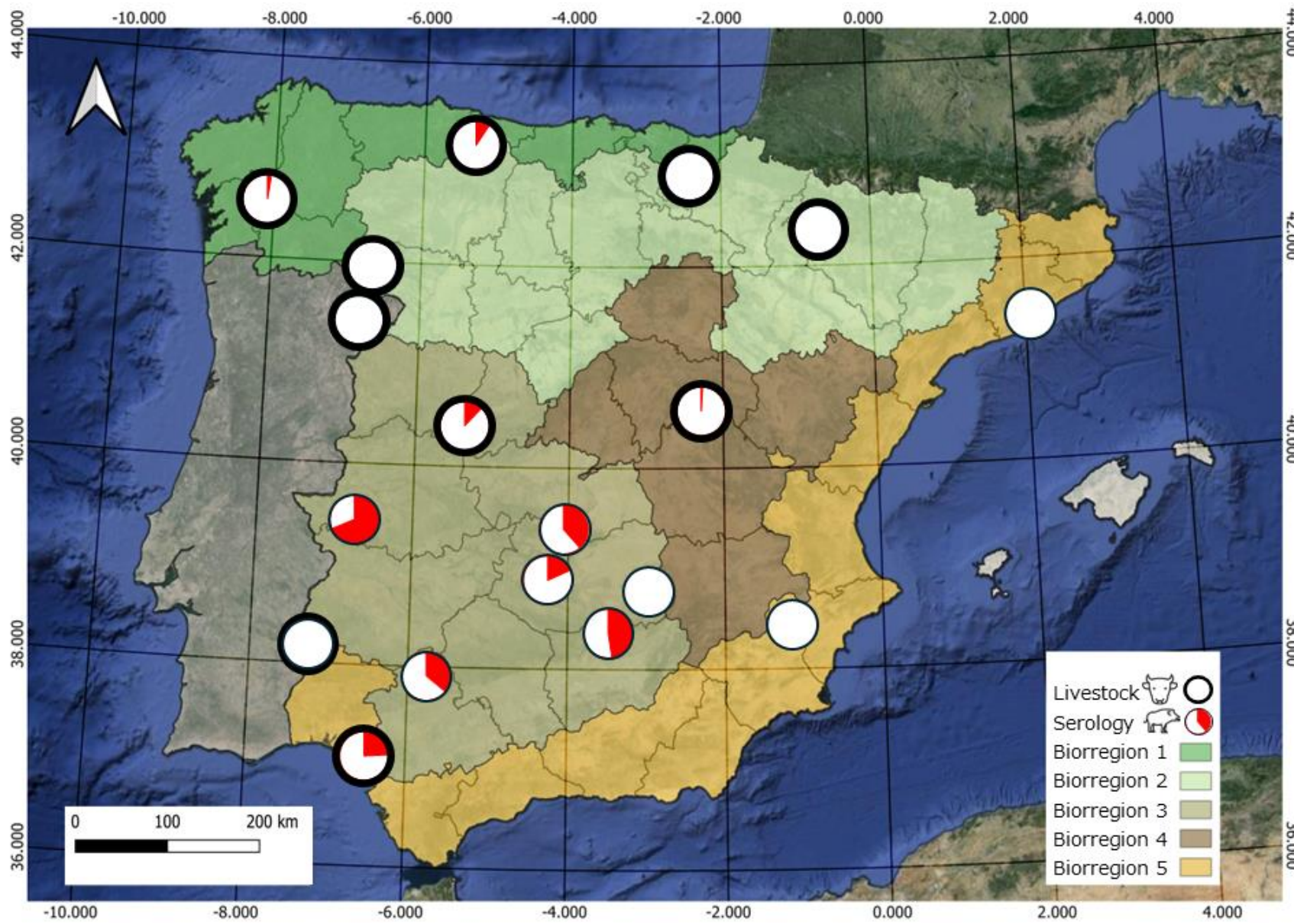


“The set of biological, environmental, and epidemiological elements of an infection in defined geographic and temporal scales”



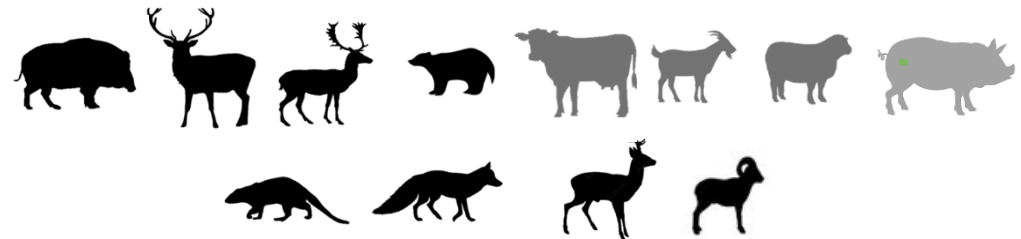
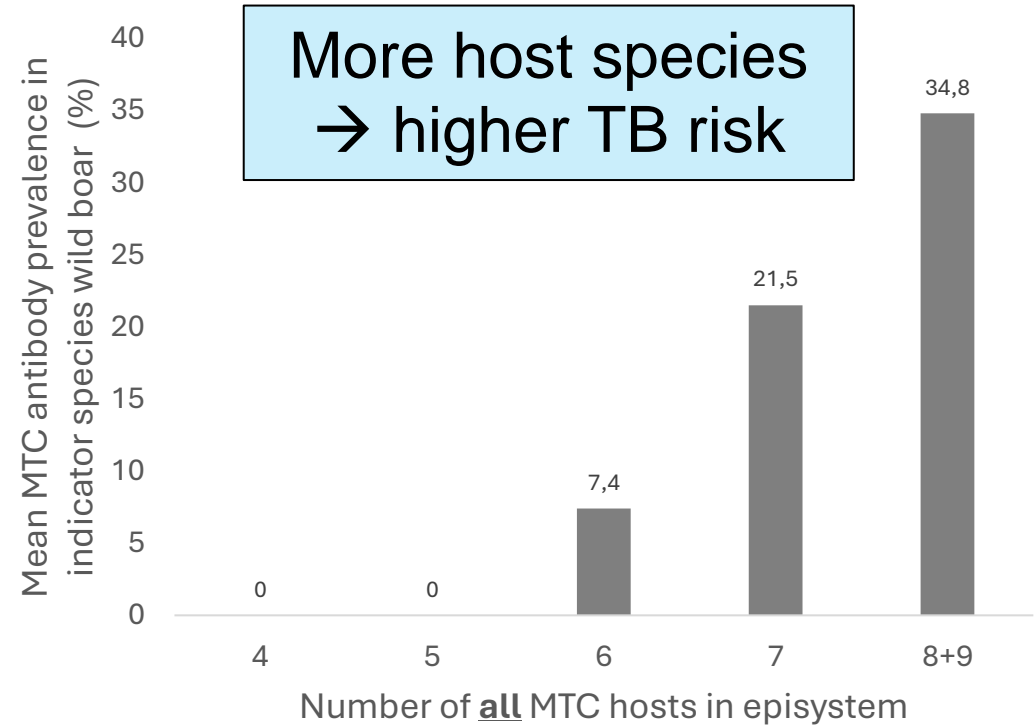
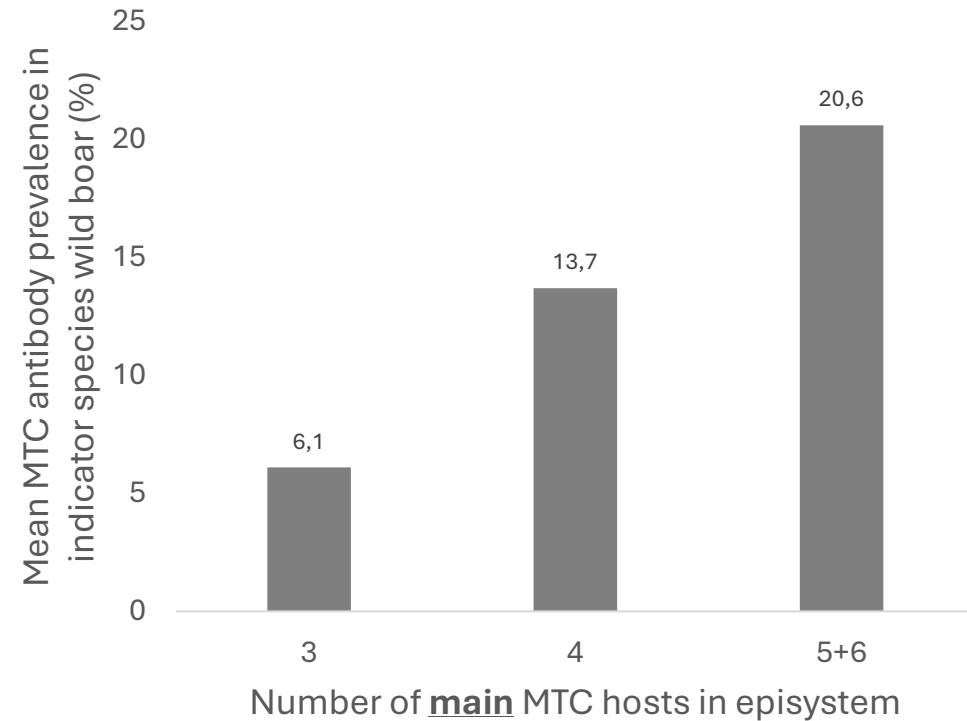


Results: TB distribution & prevalence

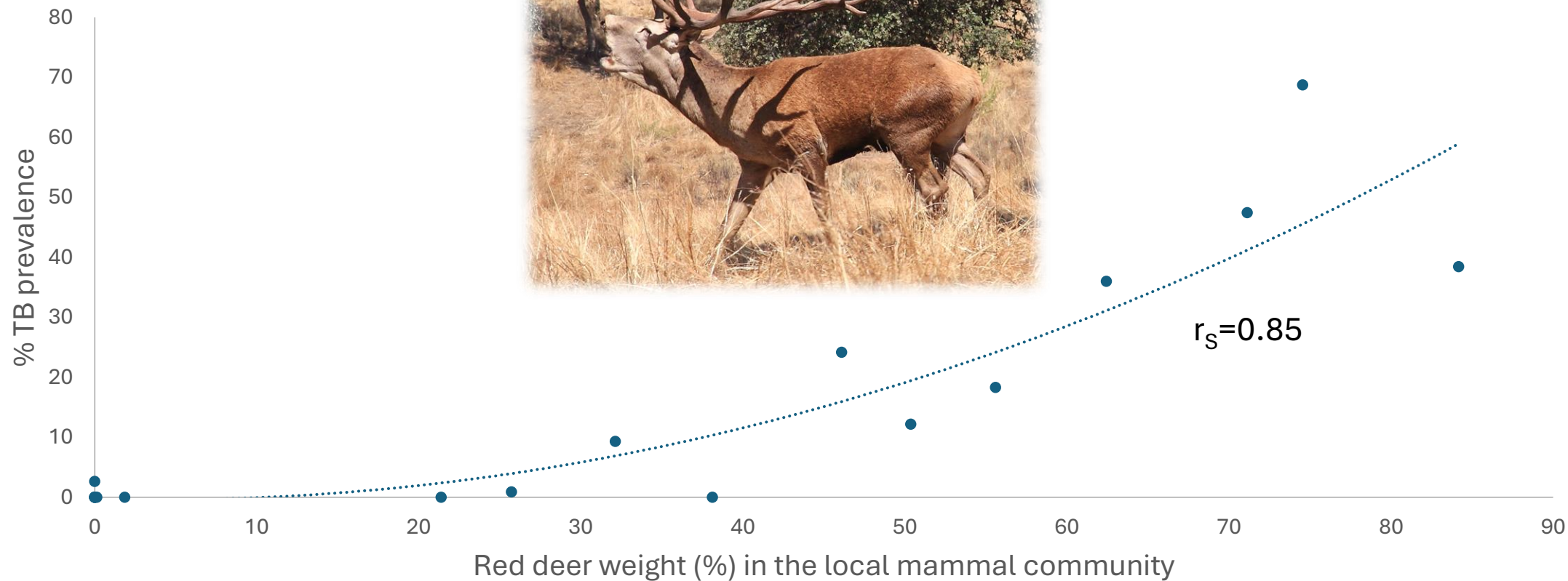


- TB detected in 4/5 bioregions (BRs)
- Mean prevalence 14% (range 0-68%)
- Highest prevalence in BR 3 (“Dehesa” region)

Results: more MTC host species → more TB

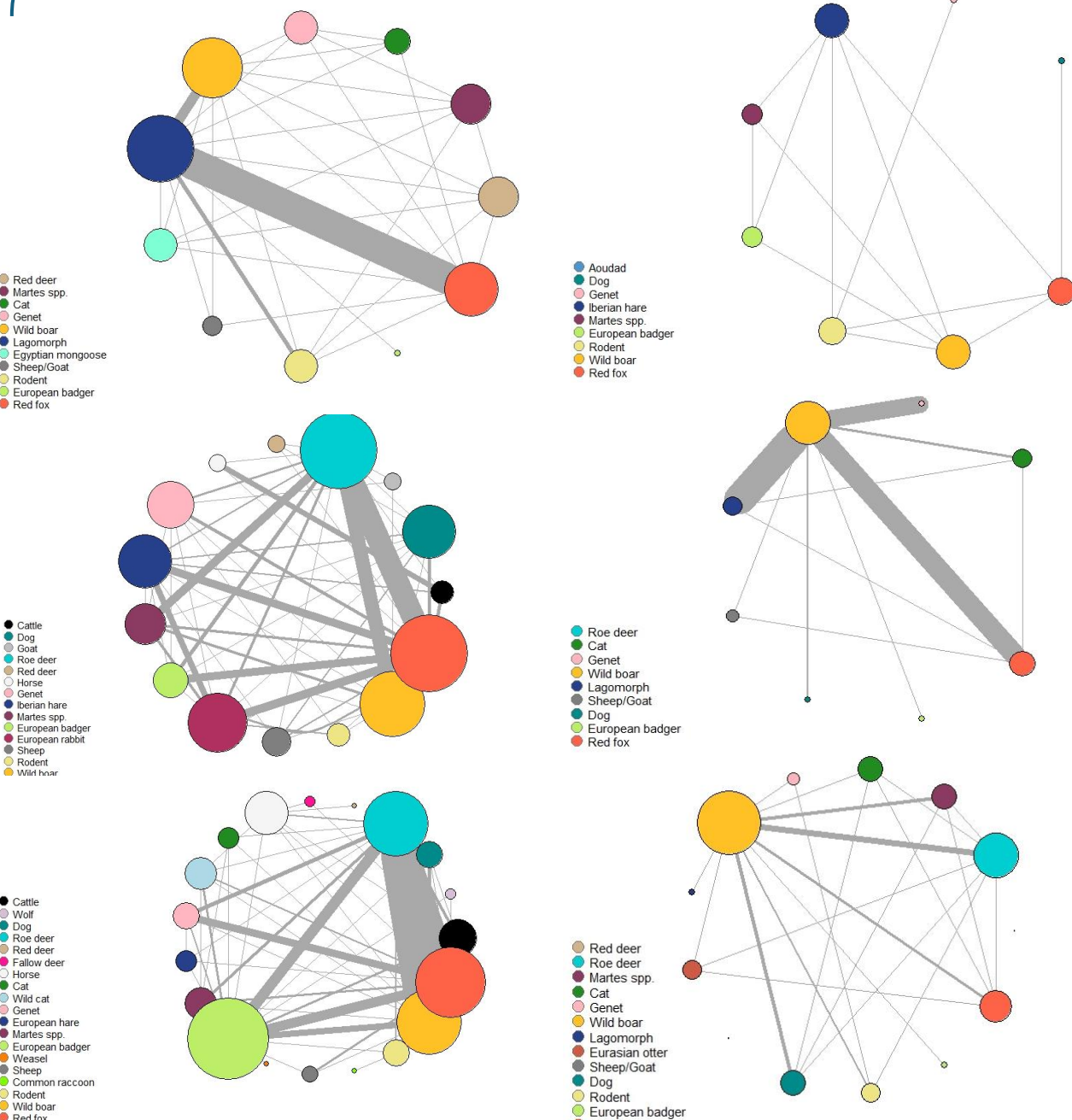
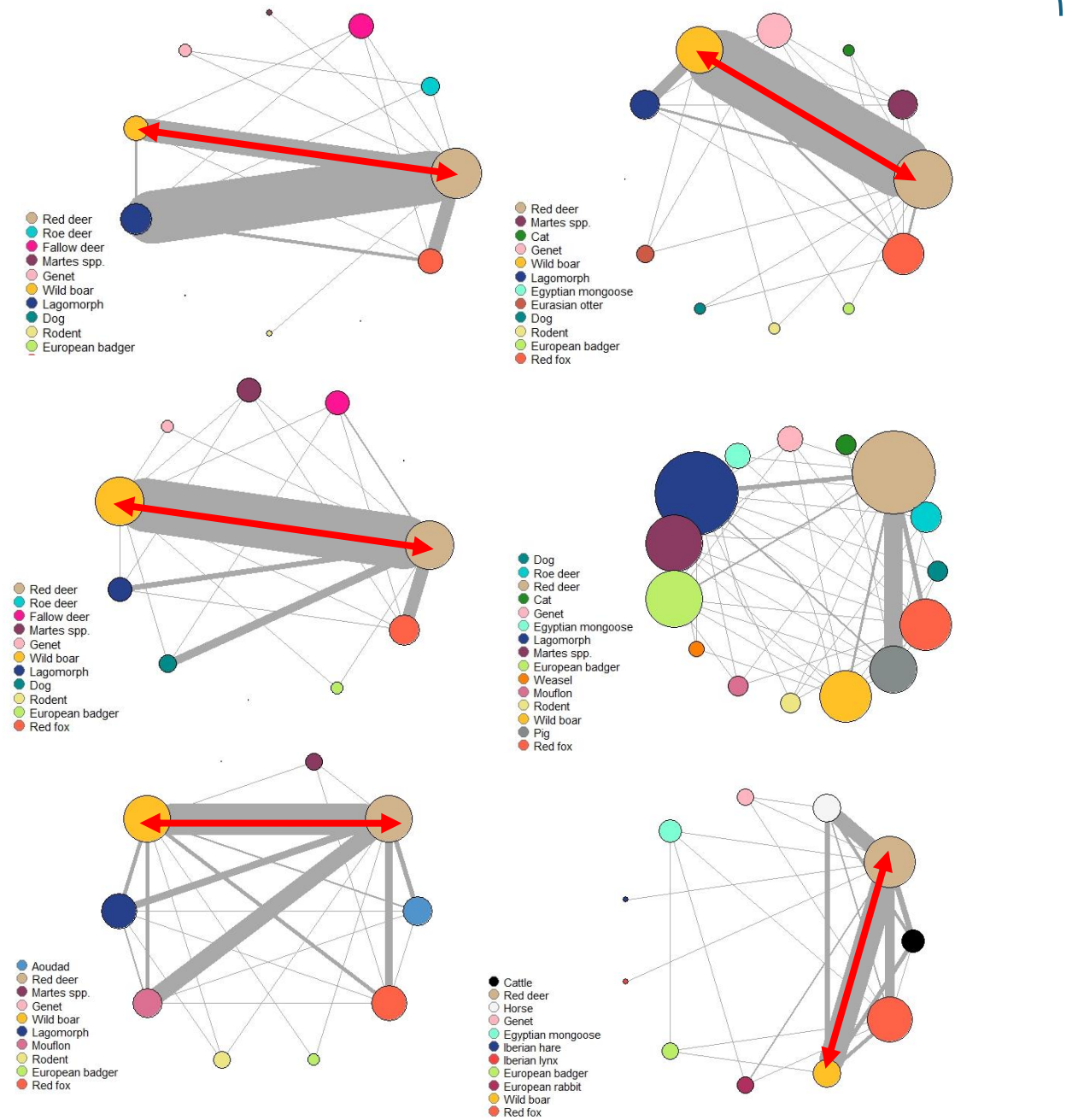


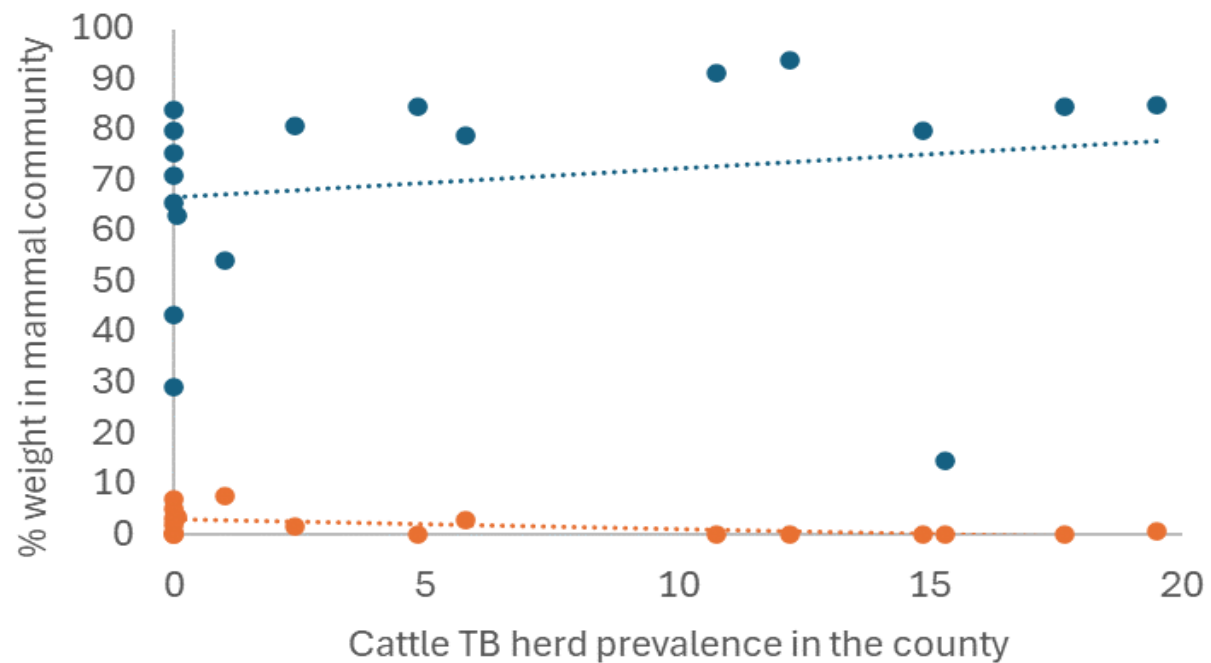
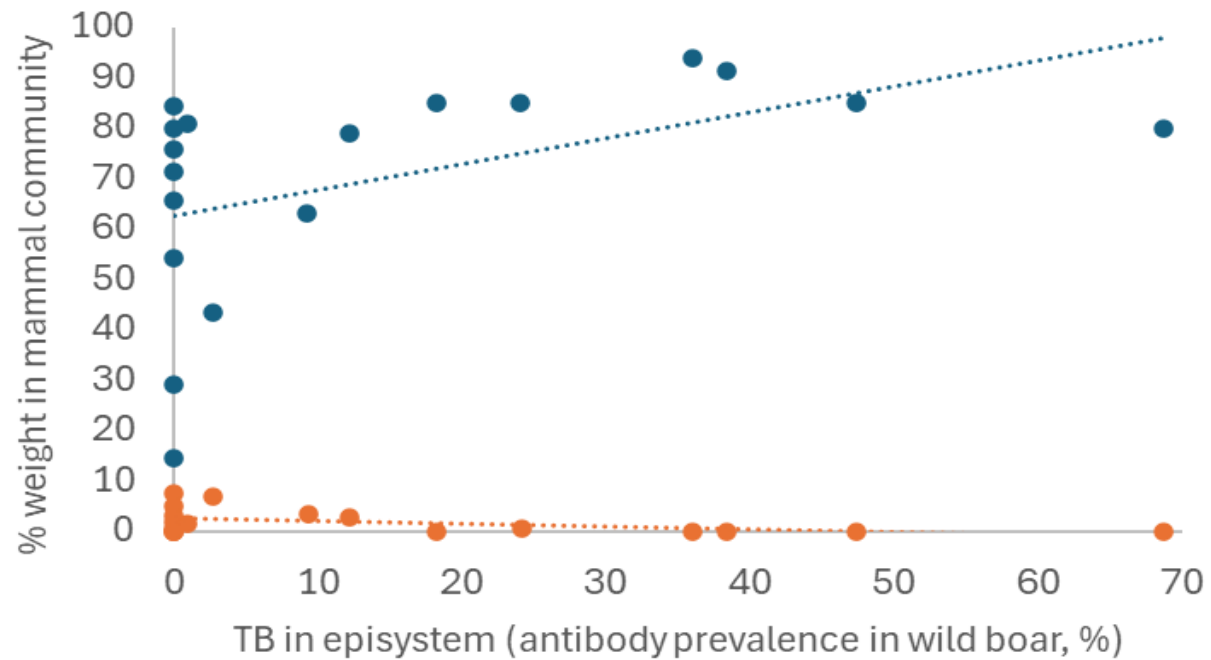
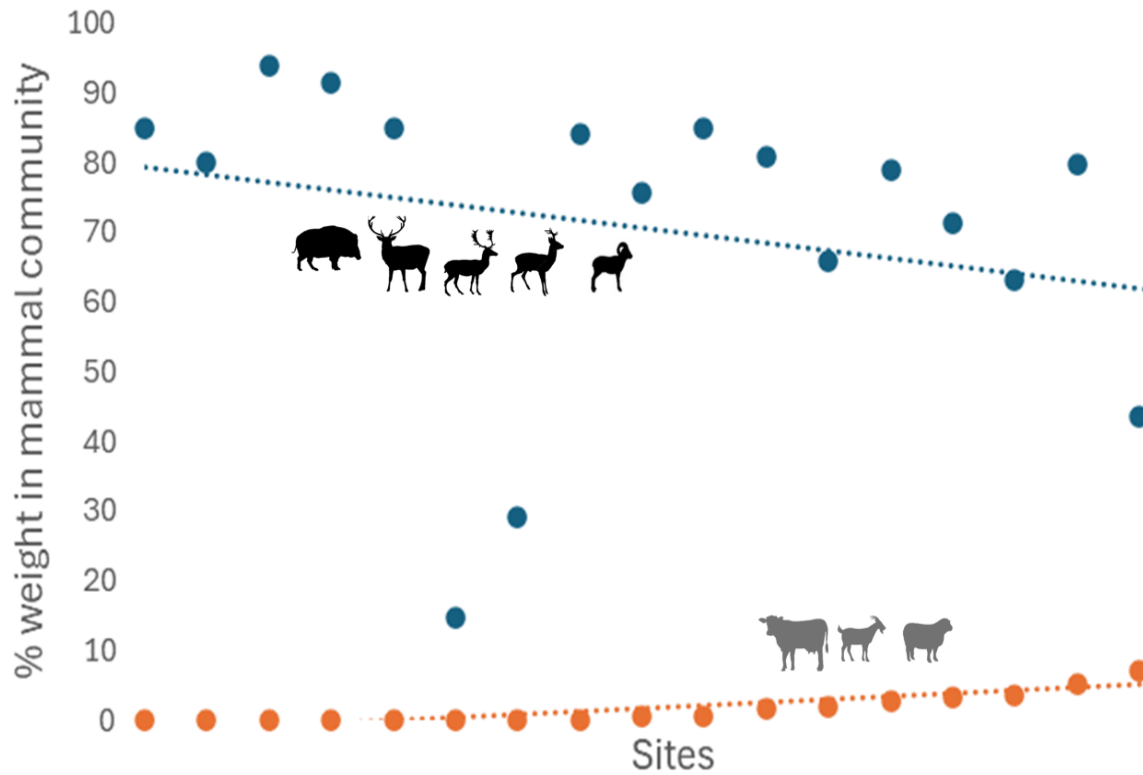
Results: Red deer weight correlates strongly with TB



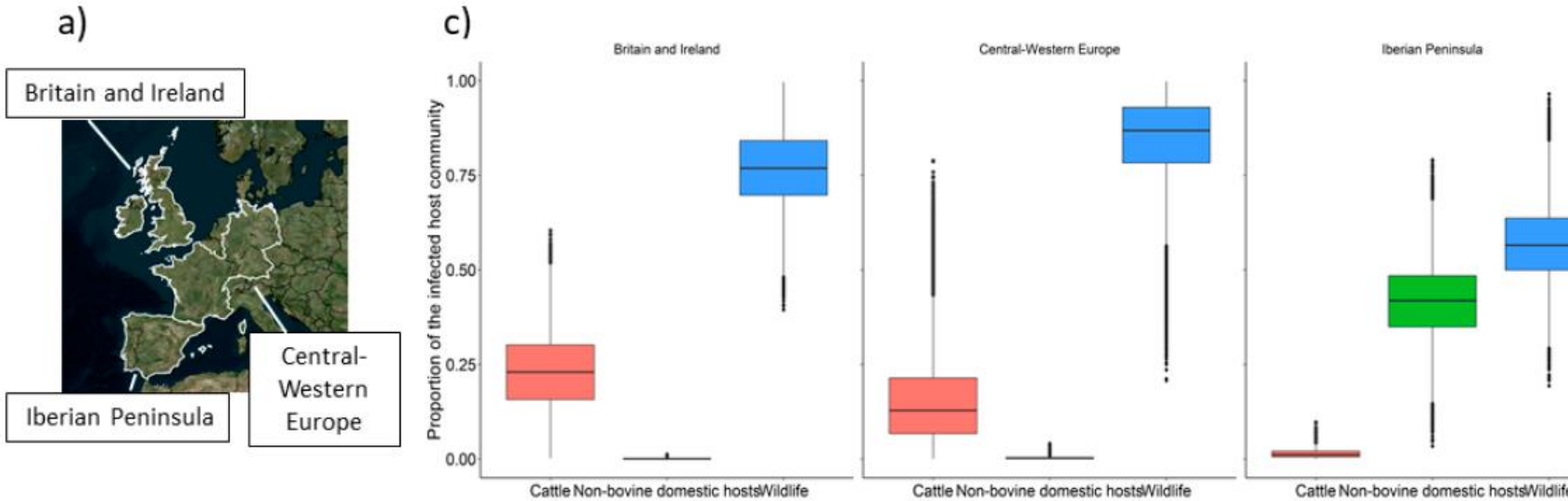
High TB prevalence host communities

TB-free host communities

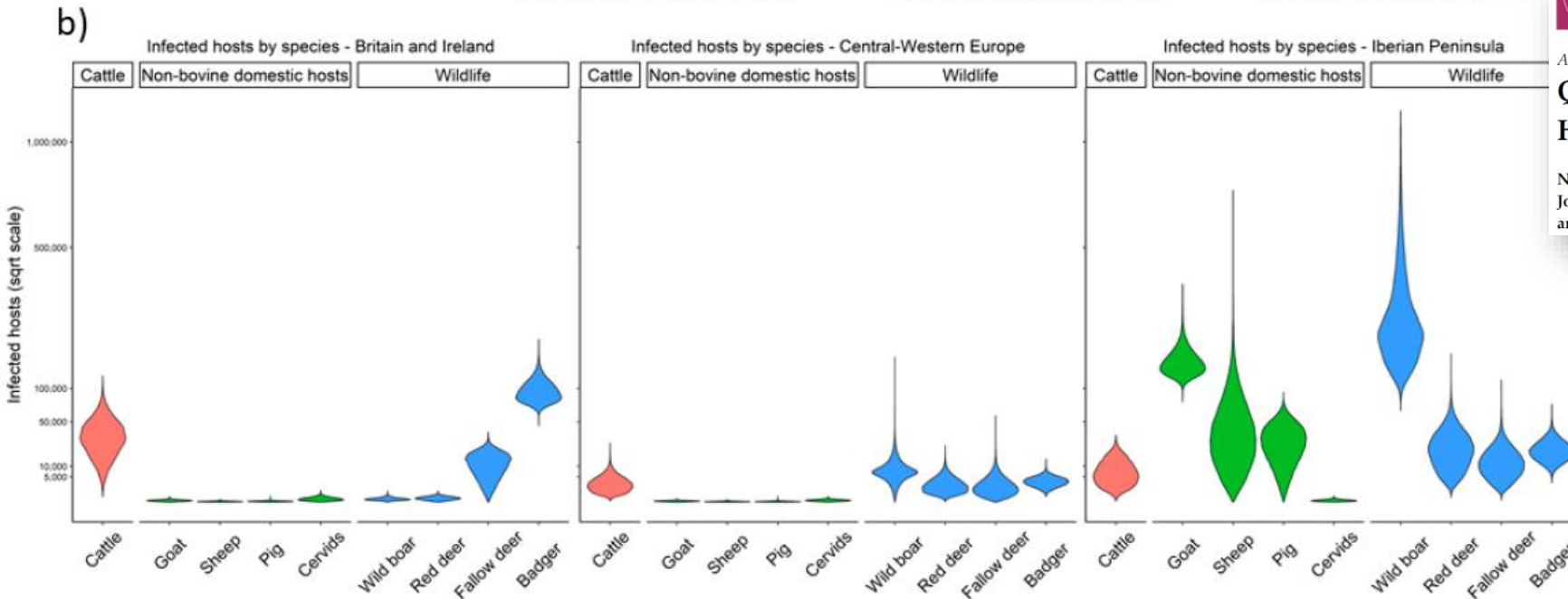




Are we targeting the right hosts?



Non-cattle >> Cattle



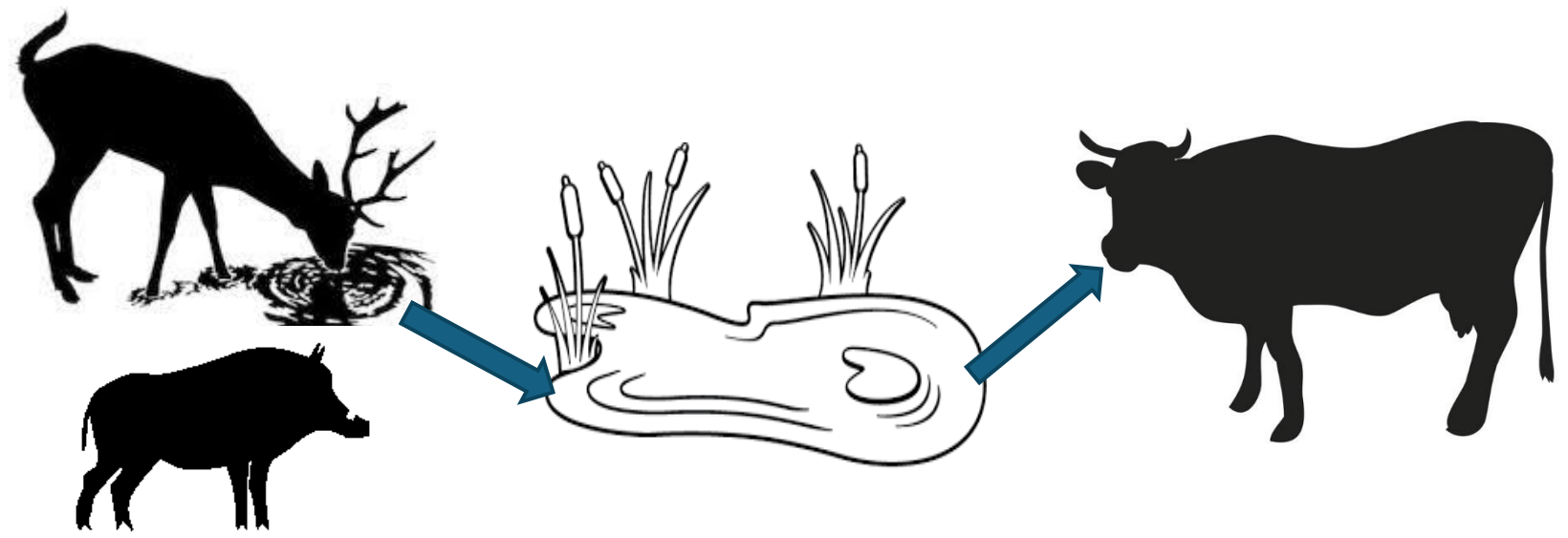
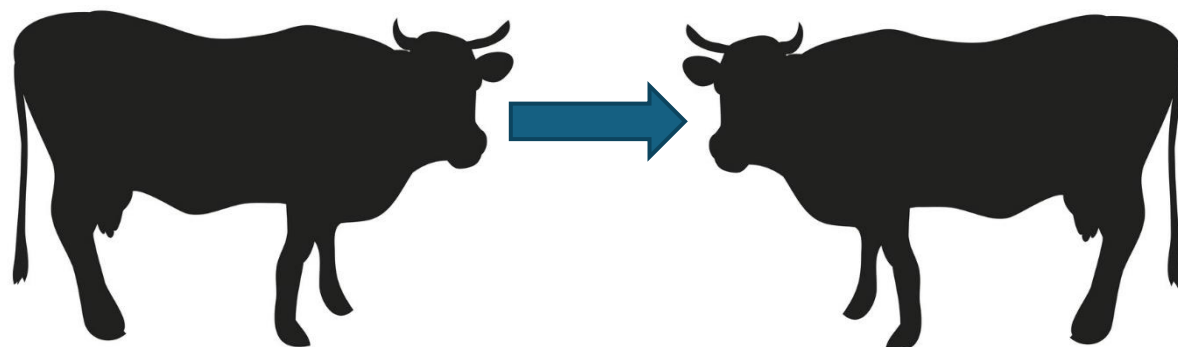
Article

Quantification of the Animal Tuberculosis Multi-Host Community Offers Insights for Control

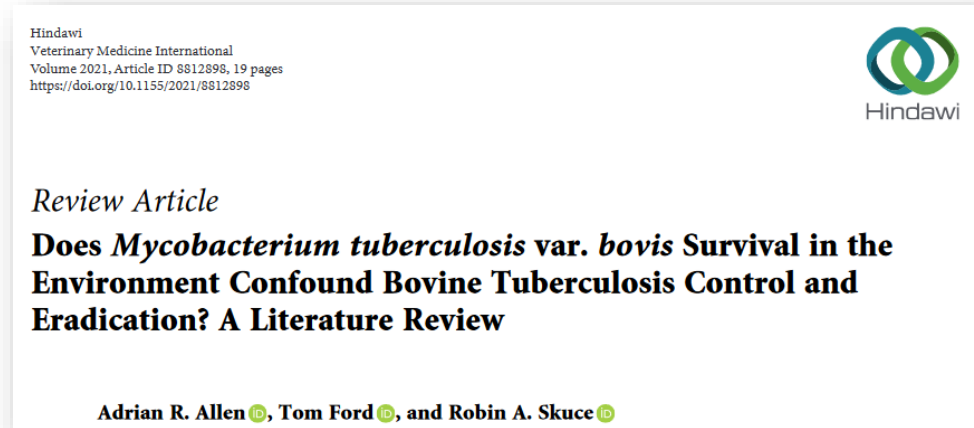
Nuno Santos ^{1*}, Céline Richomme ², Telmo Nunes ³, Joaquín Vicente ⁴, Paulo C. Alves ^{1,5,6}, José de la Fuente ^{4,7}, Margarida Correia-Neves ^{8,9}, Maria-Laura Boschioli ¹⁰, Richard Delahay and Christian Gortázar ⁴

Dogma: “contagio respiratorio”

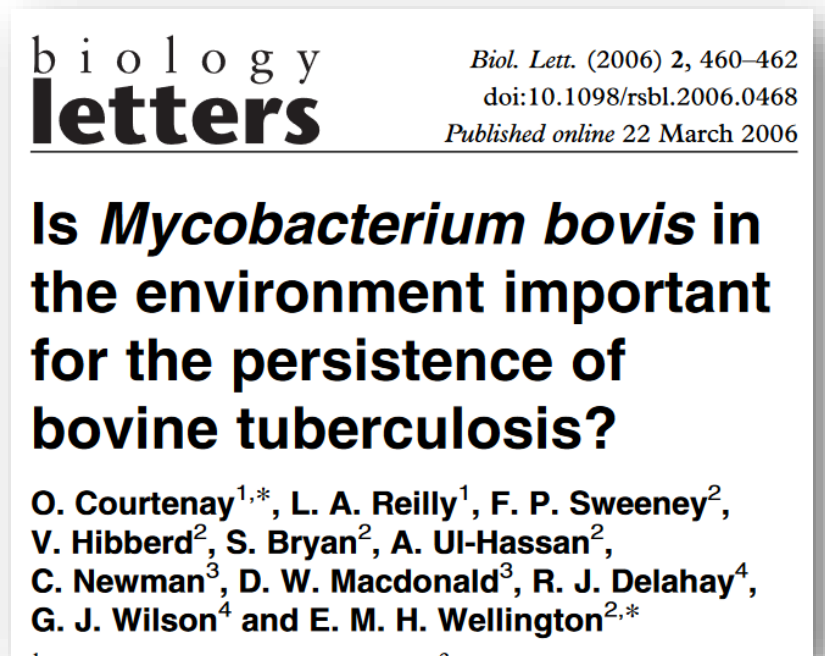




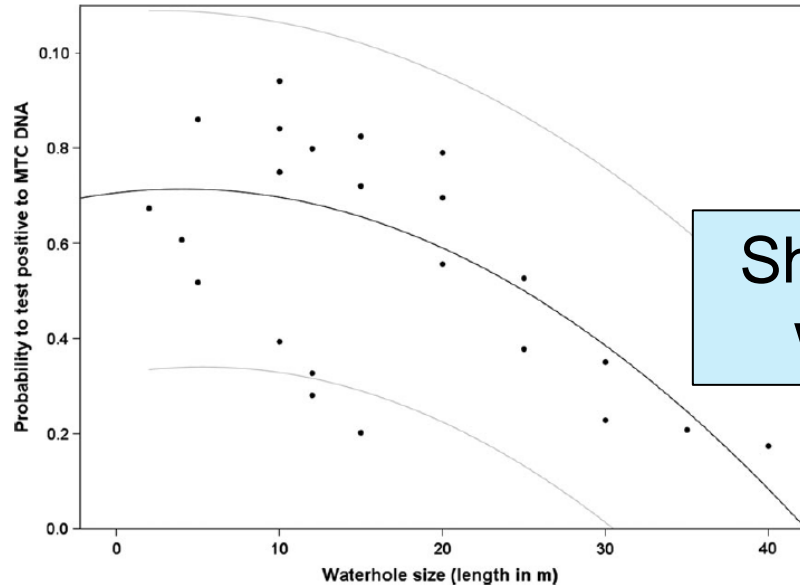
Indirect transmission



- *M. bovis* might be deposited by excretion and contaminate the environment
- *M. bovis* is relatively resilient in the environment, where it can infect a range of vertebrate and invertebrate hosts

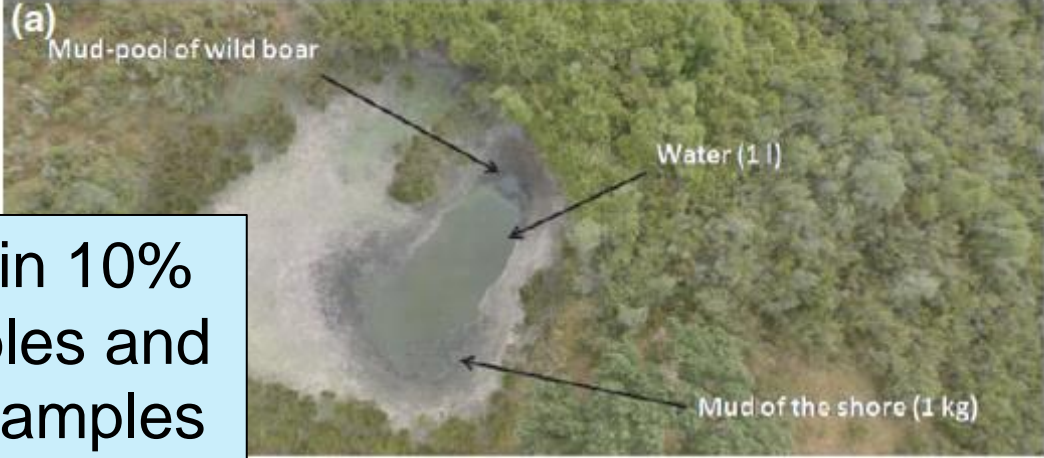


eDNA targeting MTC



Shallow and small waterholes (+)

MTC DNA in 10% water samples and 50% mud samples



Visibly sick animals at (+) waterholes



ORIGINAL ARTICLE

Environmental Presence of *Mycobacterium tuberculosis* Complex in Aggregation Points at the Wildlife/Livestock Interface

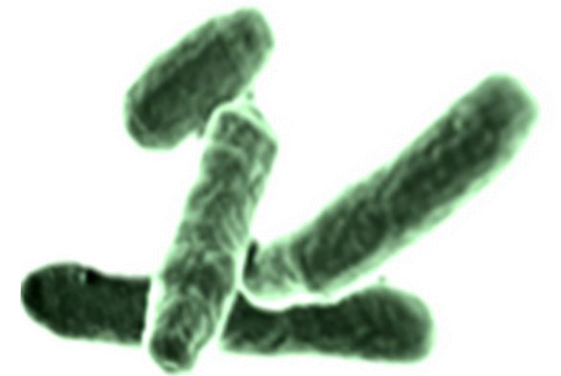
J. A. Barasona¹, J. Vicente¹, I. Díez-Delgado^{1,2}, J. Aznar^{3,4}, C. Gortázar¹ and M. J. Torres³

Transmisión entre especies es indirecta



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Gestión purines



Proximidad a bosque o matorral



Contacto rebaños bovinos

Contacto ciervo, gamo

Contacto jabalí



Saneamientos

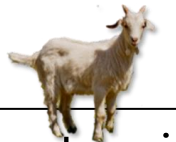
Proximidad a maizal o afines

Almacenes de alimento

Densidad rebaños bovinos

Contacto gatos, perros

Contacto caprinos, ovinos, porcino extensivo...



Distancia rebaños próximos

Desinfección

Contacto tejón

Proximidad a río

Tamaño del rebaño

Comederos

Puntos de agua

Movimientos



Cerramiento exterior


Proximidad a coto de caza mayor



Movimientos

Sanearamientos

Tamaño del rebaño



Contacto rebaños bovinos

Densidad rebaños bovinos

Distancia rebaños próximos

Puntos de agua

Almacenes de alimento

Comederos




Cerramiento exterior

Cerramiento zona novillas

Gestión purines

Contacto caprinos, ovinos, porcino...




Contacto gatos, perros

Proximidad a río

Proximidad a maizal o afines

Proximidad a bosque o matorral



Proximidad a coto de caza mayor

Contacto tejón

Contacto jabalí

Contacto ciervo, gamo

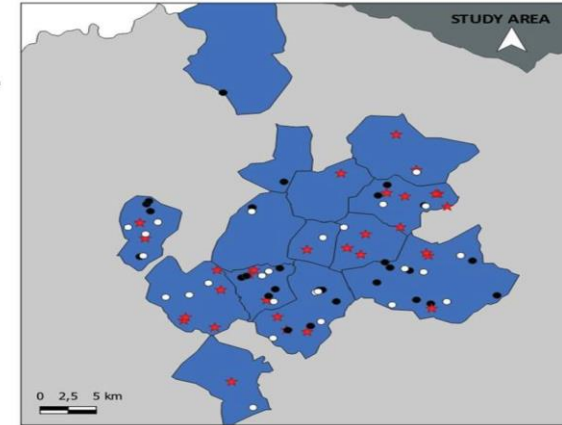
Ejemplo en ganaderías de carne: Salamanca, España

European Journal of Wildlife Research (2024) 70:81
<https://doi.org/10.1007/s10344-024-01833-z>

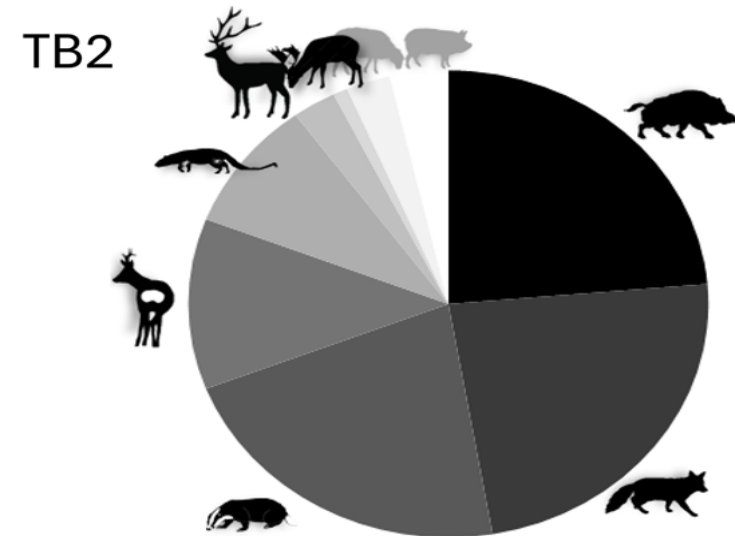
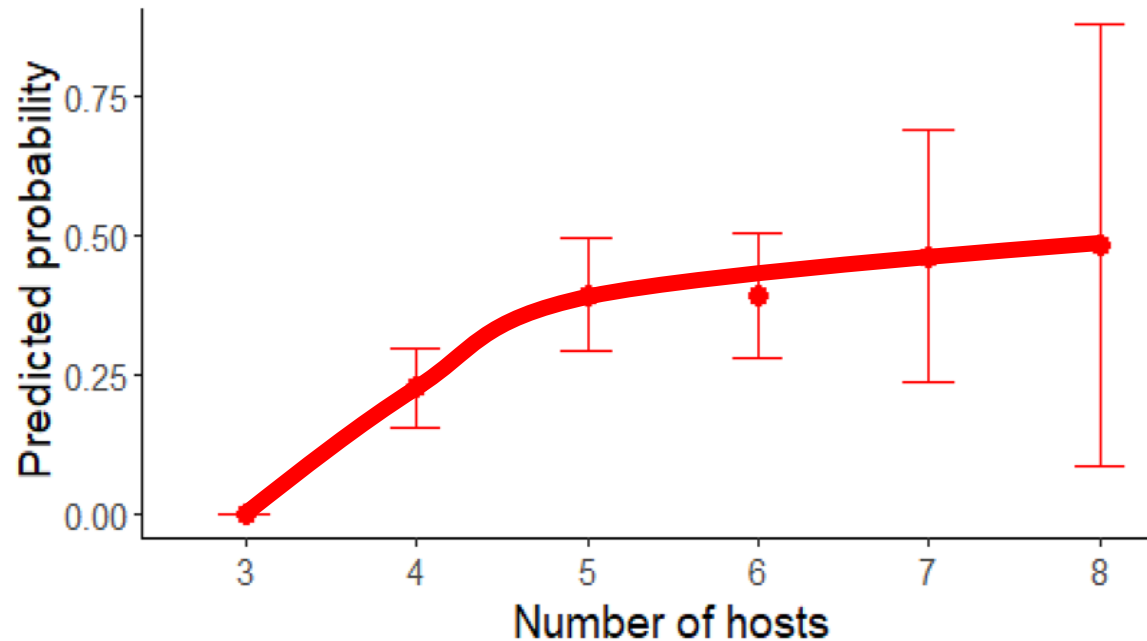
RESEARCH

Farm management practices and host species richness associated with higher likelihood of tuberculosis positive farms in Western Spain

Gloria Herrero-García¹ · Rita Vaz-Rodrigues² · Pilar Pozo^{2,3} · Patricia Barroso¹ · David Relimpio² · Jesús Nácar⁴ · Anna Grau⁴ · Olga Mínguez⁵ · Alberto García-Rodríguez¹ · Ana Balseiro^{1,6} · Christian Gortázar²



Gloria Herrero-García



Ejemplo en ganaderías de leche: Navarra, España



Animal

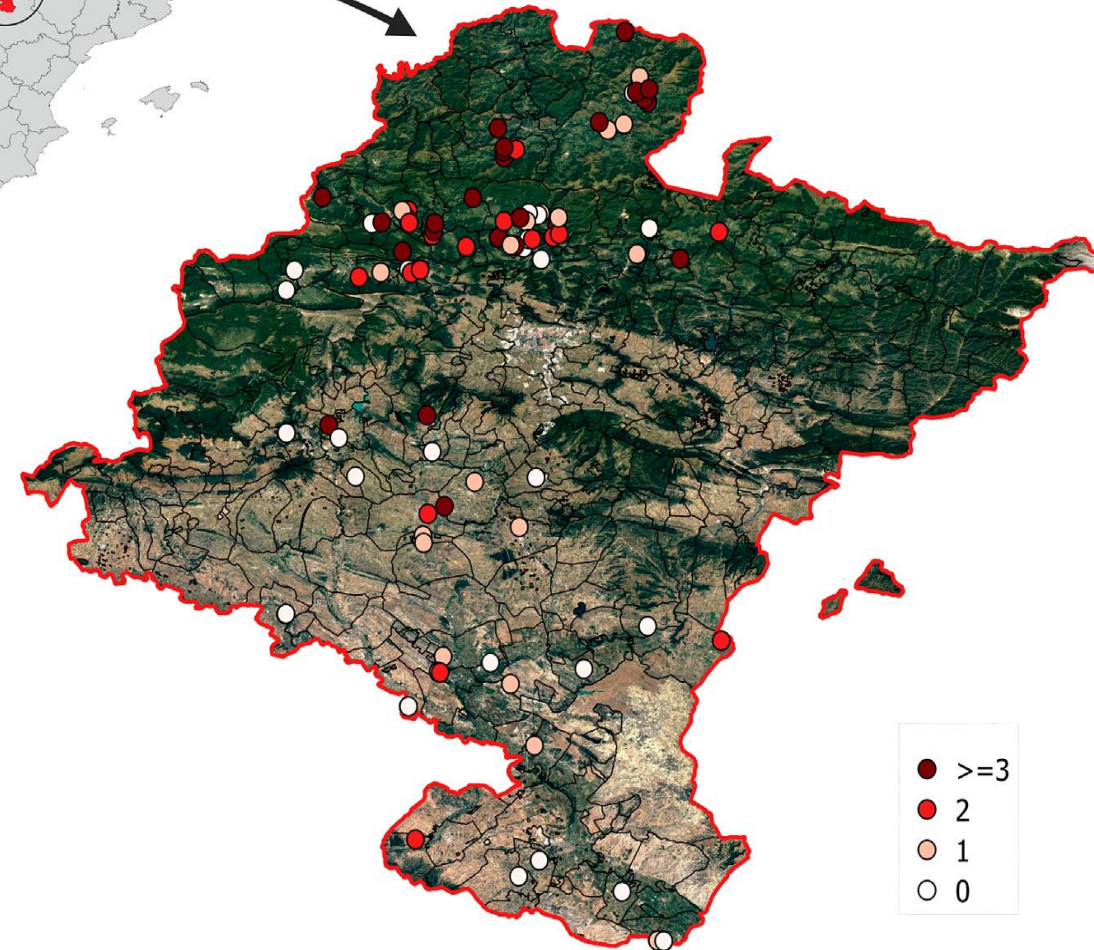
The international journal of animal biosciences

Contribution of herd management, biosecurity, and environmental factors to the risk of bovine tuberculosis in a historically low prevalence region

P. Pozo ^{a,1,*}, J. Isla ^{b,1}, A. Asiain ^c, D. Navarro ^d, C. Gortázar ^a



Julio Isla
(Sabiotec)



Ejemplo en ganaderías de leche: Navarra, España



Animal

The international journal of animal biosciences

Contribution of herd management, biosecurity, and environmental factors to the risk of bovine tuberculosis in a historically low prevalence region

P. Pozo^{a,1,*}, J. Isla^{b,1}, A. Asiain^c, D. Navarro^d, C. Gortázar^a

Principales factores de riesgo:

- Contacto con **ovinos**
- Presencia de **fauna** (tejón, jabalí)
- Ausencia **vallado** completo
- **Movimientos**

Variable	Level	Prevalence index					%	OR	95% Confidence interval		P-value ^a	P-value ^b
		0	1	2	≥3	Total			2.5%	97.5%		
Leasing pastures for sheep flocks during Winter	No	25	15	16	11	67	71.3	NA	NA	NA	NA	0.05
	Yes	3	6	4	14	27	28.7	3.09	1.02	9.99	0.05	
Use of pastures	No	17	9	7	3	36	38.3	NA	NA	NA	NA	0.34
	Yes	11	12	13	22	58	61.7	1.99	0.48	8.47	0.34	
Frequency of badger sightings	0 (never)	21	10	9	6	46	48.9	NA	NA	NA	NA	0.03
	1 (sporadically)	6	9	8	13	36	38.3	3.03	1.12	8.51	0.03	
	>1 (monthly to daily)	1	2	3	6	12	12.8	4.34	1.13	17.48	0.03	
Solid fencing around farmyard	No	15	15	16	22	68	72.3	NA	NA	NA	NA	0.06
	Yes	13	6	4	3	26	27.7	0.42	0.16	1.04	0.06	
Movement to pastures	On foot	4	3	7	18	32	34.0	NA	NA	NA	NA	0.001
	None	17	9	9	4	39	41.5	0.57	0.12	2.74	0.48	
	Transport	1	2	2	1	6	6.4	0.49	0.08	2.89	0.42	
	Vehicle	6	7	2	2	17	18.1	0.09	0.02	0.31	0.001	
0 1	Intercept						0.43	NA	NA	0.33		
1 2	Intercept						1.56	NA	NA	0.61		
2 ≥3	Intercept						6.09	NA	NA	0.04		



Esponjas para detectar TB



Esponja impregnada con líquido que destruye patógenos pero conserva su ADN y ARN



La esponja recoge ADN y ARN ambiental sobre superficies como comederos, bebederos o piel



La muestra se traslada al laboratorio para extraer ADN y ARN ambiental





RT PCR a tiempo real siguiendo protocolos en laboratorio acreditado

ORIGINAL ARTICLE

Transboundary and Emerging Diseases | WILEY

Detection of environmental SARS-CoV-2 RNA in a high prevalence setting in Spain

Isabel G. Fernández-de-Mera¹  | Francisco J. Rodríguez del-Río² | José de la Fuente^{1,3} | Marta Pérez-Sancho⁴ | Dolores Hervás² | Inmaculada Moreno⁵ | Mercedes Domínguez⁵ | Lucas Domínguez⁴ | Christian Gortázar¹ 



Proyecto ONE HEALTH FARMING

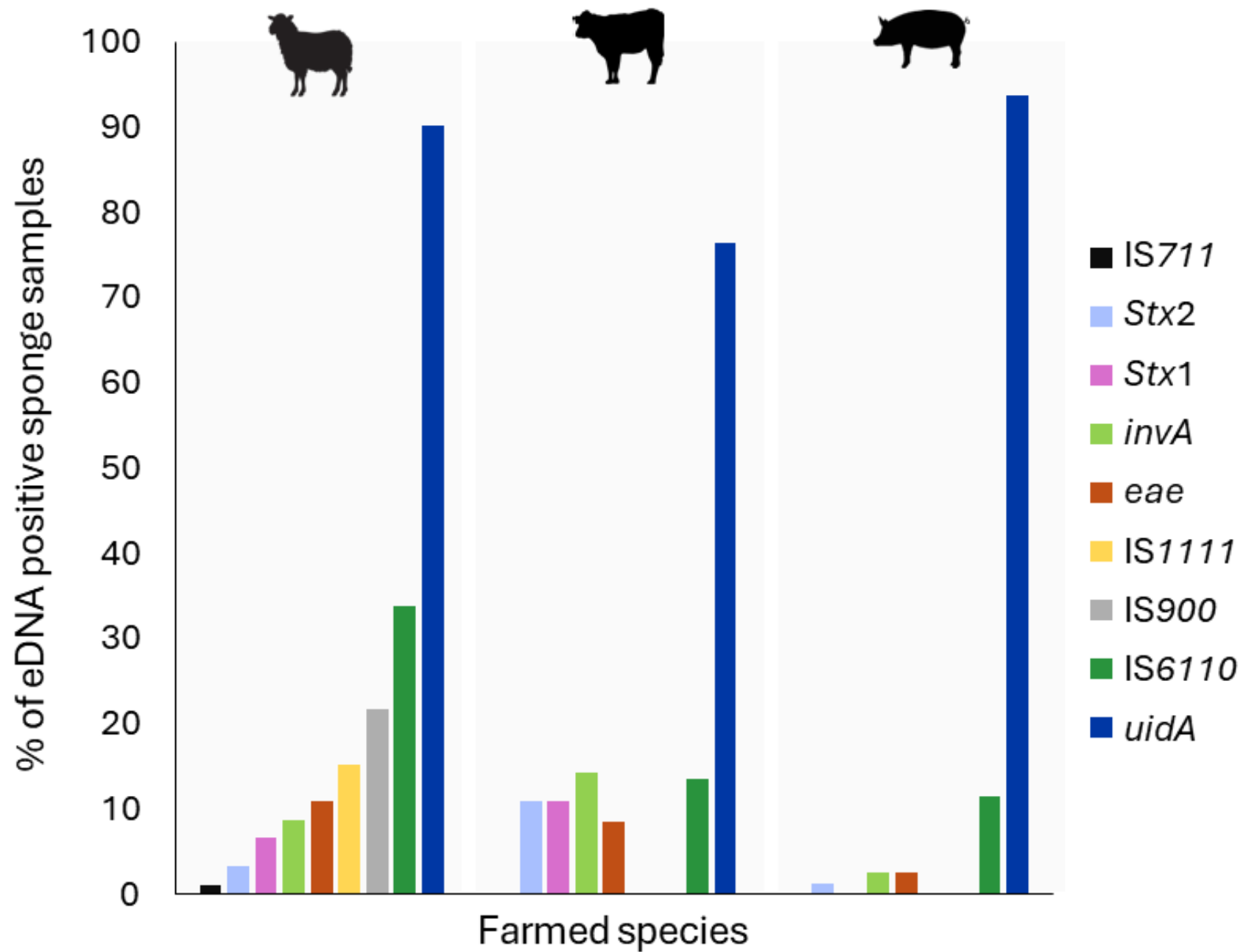
Vigilancia medioambiental y mitigación de riesgos para una producción alimentaria ganadera segura y sostenible y la conservación de la biodiversidad

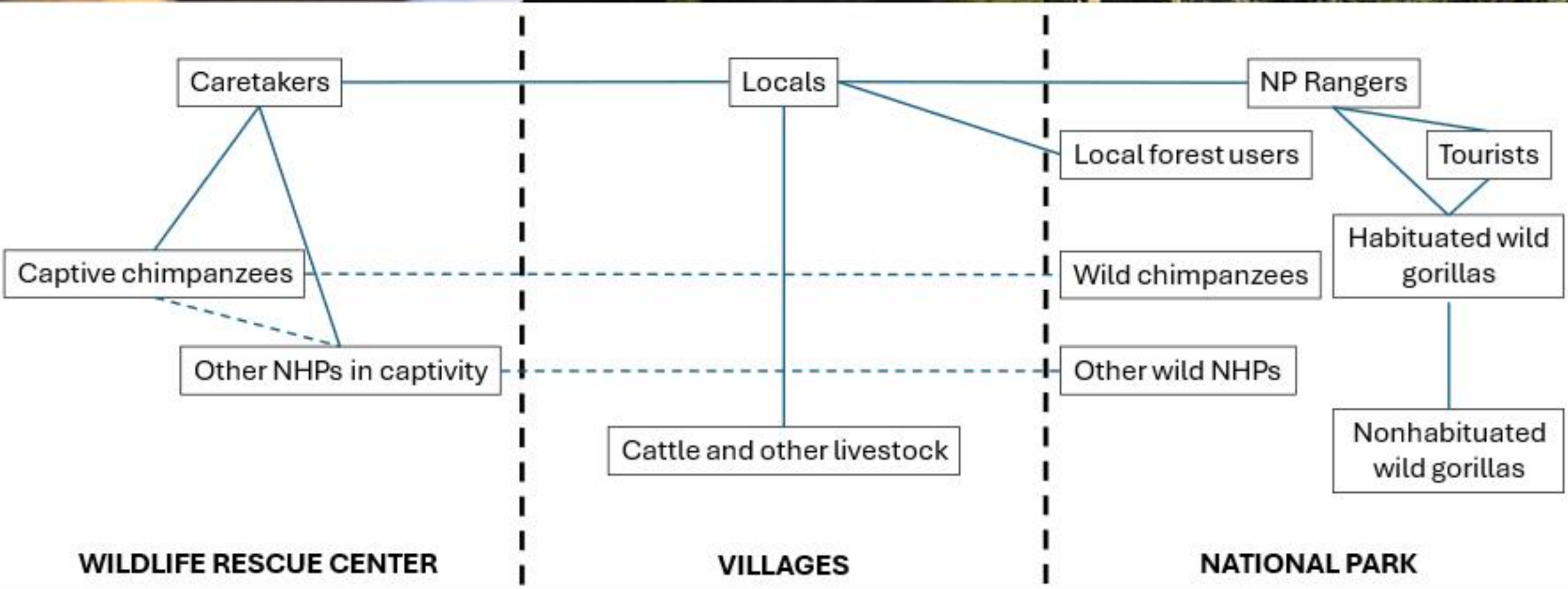


Objetivo: mejorar la **bioseguridad** de las explotaciones extensivas para hacerlas más resistentes a las enfermedades emergentes, más competitivas y más sostenibles.



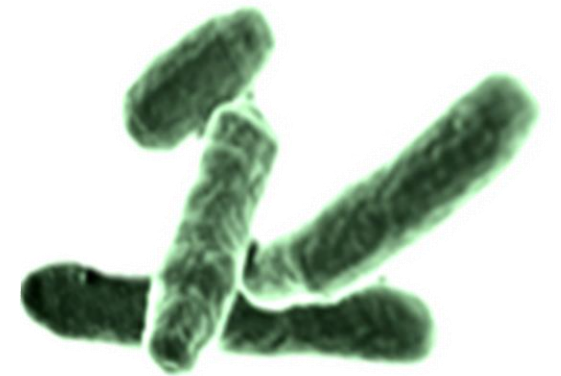
Cattle farm in Vitigudino (Salamanca)



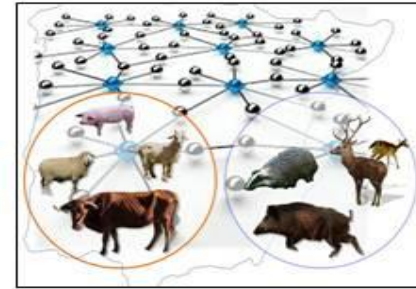


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 - **Bioseguridad**
 - **Vacunación**
- Cuatro mensajes clave



Control de TB



A.- No actuar ni desarrollar vigilancia sanitaria (desaconsejado)

B.- No actuar (coste > beneficio), pero realizar vigilancia sanitaria

C.- Actuar (coste < beneficio), siempre realizando vigilancia sanitaria

Vigilancia poblacional y sanitaria

Prevención y bioseguridad

Control de poblaciones

Vacunación

1. Diagnóstico epidemiológico

2. Decisión entre tres opciones

3. Intervención (control integrado)

4. Valorar el efecto de la intervención y nueva decisión

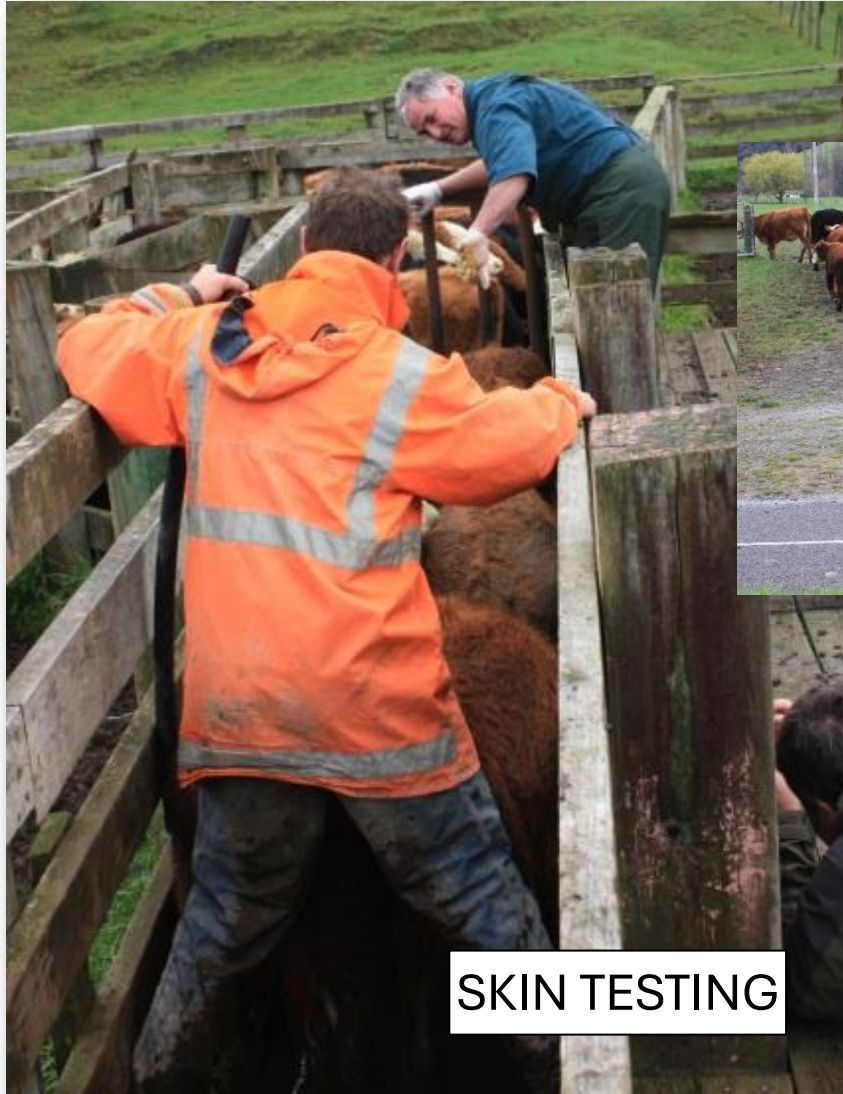


MINISTERIO DE AGRICULTURA Y PESCA, ALIMENTACIÓN Y MEDIO AMBIENTE

PATUBES

Plan de Actuación sobre TUBerculosis en Especies Silvestres

Standard TB control in cattle



These tools work

–

**but are
expensive**

–

**& limited to
cattle**



(C) TOMI MARJO

Farm biosafety; Michigan (USA)



66% less bovine TB



Kurt VerCauteren,
USDA

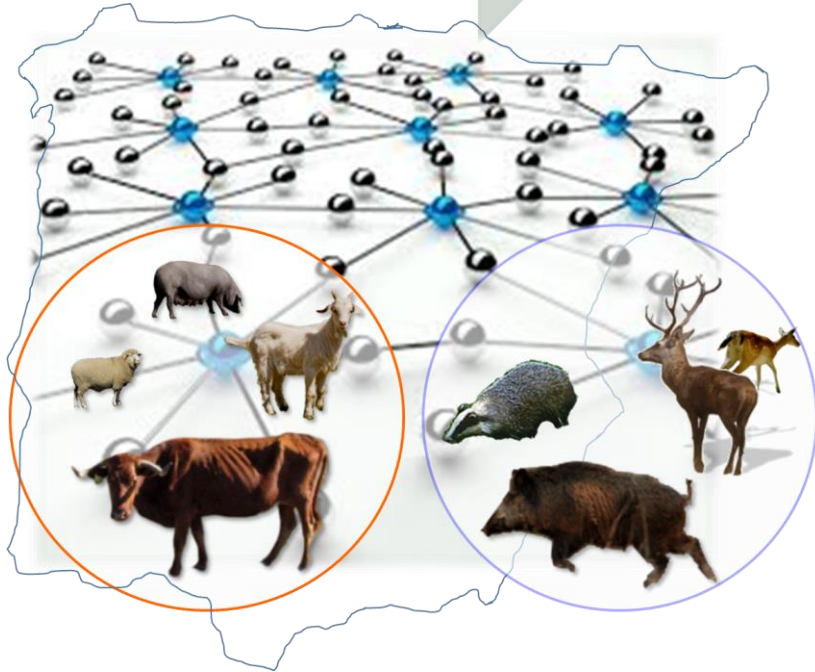
RESEARCH ARTICLE

Environmental DNA: A promising factor for tuberculosis risk assessment in multi-host settings

Jordi Martínez-Guijosa^{1,2,3,4}, Beatriz Romero^{2,6}, José Antonio Infantes-Lorenzo^{2,3}, Elena Díez⁴, Mariana Boadella⁴, Ana Balseiro⁵, Miguel Veiga², David Navarro⁴, Inmaculada Moreno¹, Javier Ferreres¹, Mercedes Domínguez¹, Cesar Fernández⁴, Lucas Domínguez^{2,3}, Christian Gortázar¹

Diagnóstico epidemiológico

- Poblaciones
- *fauna
- *ganado
- Situación TB



Spatially explicit modeling of animal tuberculosis at the wildlife-livestock interface in Ciudad Real province, Spain

Nathaniel P. LaHue^{1,2,3}, Joaquín Vicente Baños¹, Pelayo Acevedo¹, Christian Gortázar¹, Beatriz Martínez-López¹

Análisis de riesgos

- Explotación
- Zona



Description and implementation of an On-farm Wildlife Risk Mitigation Protocol at the wildlife-livestock interface: Tuberculosis in Mediterranean environments

Jordi Martínez-Guijosa^{1,2,3,4}, Jose Francisco Lima-Barbero¹, Pelayo Acevedo¹, David Cano-Terriza¹, Saúl Jiménez-Ruiz^{1,5}, Jose Ángel Barasona¹, Mariana Boadella¹, Ignacio García-Bocanegra¹, Christian Gortázar¹, Joaquín Vicente¹

Intervención

- Infraestructuras
- Manejo
- Animales

MANUAL PARA LA ACTUACIÓN FRENTE A LA TUBERCULOSIS EN FAUNA SILVESTRE



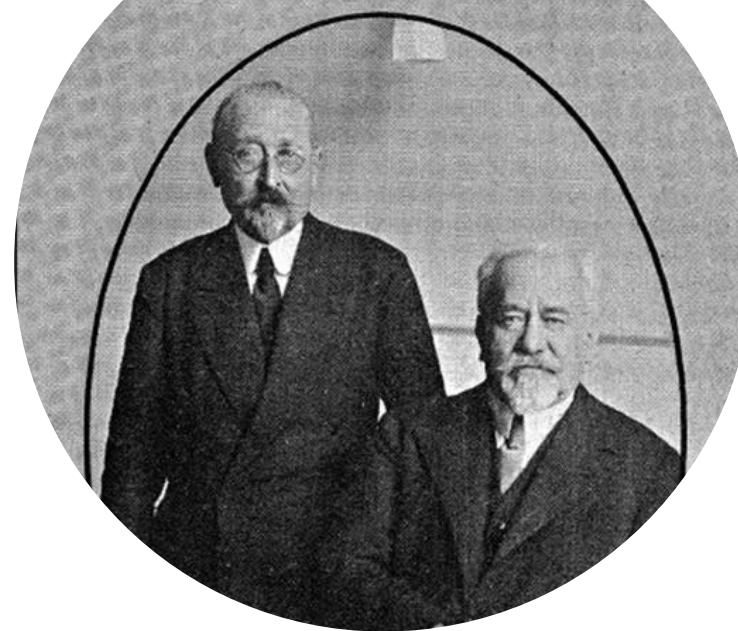
Medidas de bioseguridad
en explotaciones extensivas de ganado bovino

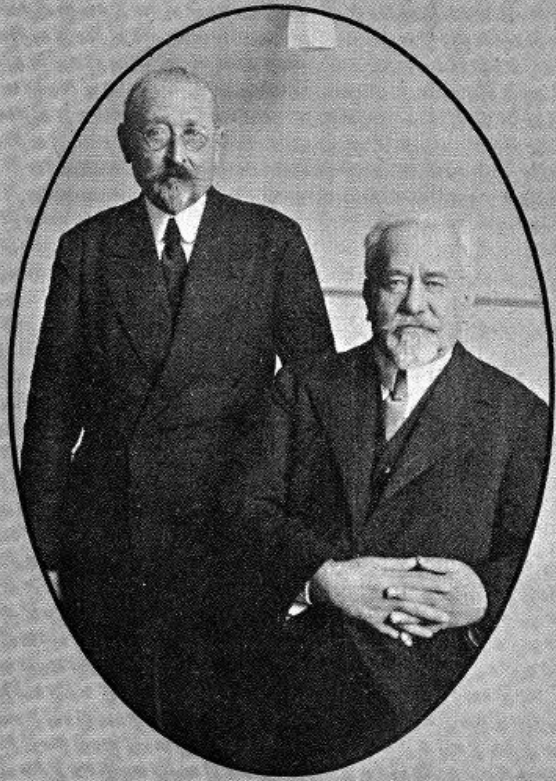
TB vaccines

- **Bacillus Calmette Guerin (BCG)**
 - 1920's Institut Pasteur
 - Live, natural deletion mutant
 - *Mycobacterium bovis*
 - Causes cross-reaction with CMI tests
 - Survives in vaccinated – safety concerns

- **MtbVac (UNIZAR-Zendal)**
 - 2000's Carlos Martín, Zaragoza
 - Live, targeted deletion mutant
 - *Mycobacterium tuberculosis*
 - Causes cross-reactions
 - Human TB – safety concerns in animals

- **HIMB (NEIKER-Sabiotec + Consortium)**
 - 2010's Ramón Juste, NEIKER
 - Heat-killed field strain
 - *Mycobacterium bovis*
 - No cross-reaction by oral route
 - Heat-killed – no safety concerns





1930. Le D^r Guérin en compagnie du D^r Calmette

Wellcome Images

A. CALMETTE
Sous-Directeur de l'Institut Pasteur

LA VACCINATION
PRÉVENTIVE
CONTRE
LA TUBERCULOSE
PAR LE "BCG"

AVEC LA COLLABORATION DE
C. GUÉRIN, A. BOQUET et L. NÈGRE

- Attenuated *M. bovis* mutant obtained after several re-cultures by Albert Calmette & Camille Guérin at Inst. Pasteur (Calmette 1927)
- BCG is still the most used TB vaccine (Franco-Paredes et al. 2006)




A Meta-Analysis of the Effect of Bacillus Calmette-Guérin Vaccination Against Bovine Tuberculosis: Is Perfect the Enemy of Good?

Sreenidhi Srinivasan^{1,2}, Andrew J. K. Conlan³, Laurel A. Easterling⁴, Christian Herrera^{1,2}, Premanshu Dandapat⁵, Maroudam Veerasami⁶, Gobena Ameni⁷, Naresh Jindal⁸, Gopal Dhinakar Raj⁹, James Wood³, Nick Juleff¹⁰, Douwe Bakker¹¹, Martin Vordermeier^{12,13} and Vivek Kapur^{1,2*}

BCG in cattle

- Meta-analysis: 25% efficacy against infection
- Field studies only: 28-85% efficacy
- At low to moderate TB prevalence (<15%), BCG use can lead to OTF in 10 years

Database #	Authors	Location	BCG source	BCG route	BCG dose	Controls_n	Vaccinates_n	Reported efficacy
579	Ameni et al. (35)	Ethiopia	BCG Danish 1331	Subcutaneous	1–4 × 10 ⁶ CFU	26	23	30%
1266	Ameni et al. (23)	Ethiopia	BCG Danish 1331	Subcutaneous	1 × 10 ⁶ CFU	14	13	60%
1358	Nugent et al. (34)	New Zealand	BCG Danish 1331	Oral and Subcutaneous	1 × 10 ⁸ CFU	531	644	67%
1373	Lopez-Valencia et al. (25)	Mexico	BCG Tokyo	Subcutaneous	1 × 10 ⁶ CFU	66	65	60%
1410	Nugent et al. (36)	New Zealand	BCG Danish 1331	Subcutaneous	3 × 10 ⁵ CFU	297	520	85%
	Batissa et al. (2021)	Ethiopia	BCG Russia	Subcutaneous	1x10 ⁶	18	22	28%
	Retamal et al. (2021)	Chile	BCG Russia	Subcutaneous	2-8x10 ⁵	60	62	66%

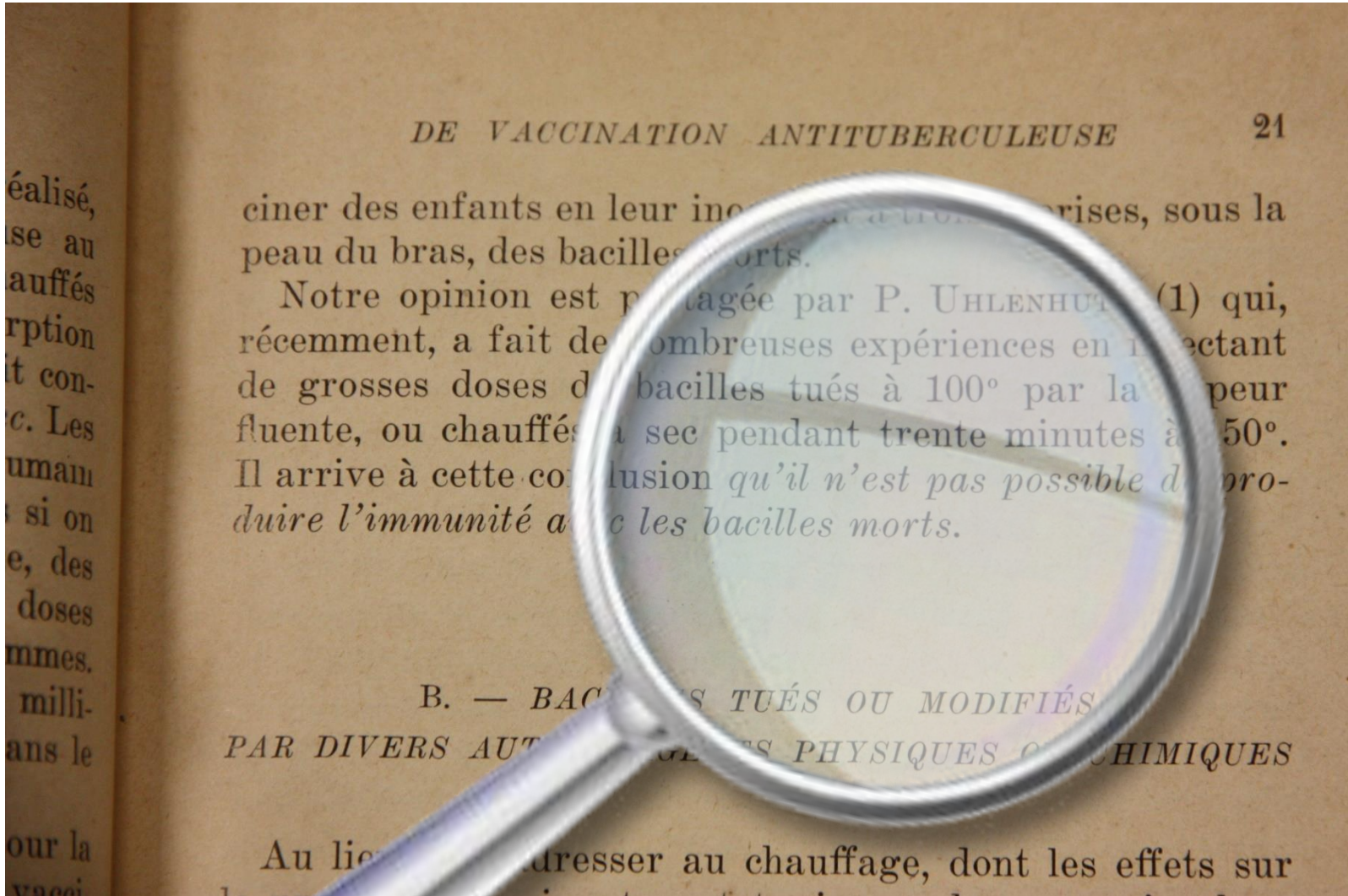


Development of a deployable tuberculosis vaccine for cattle

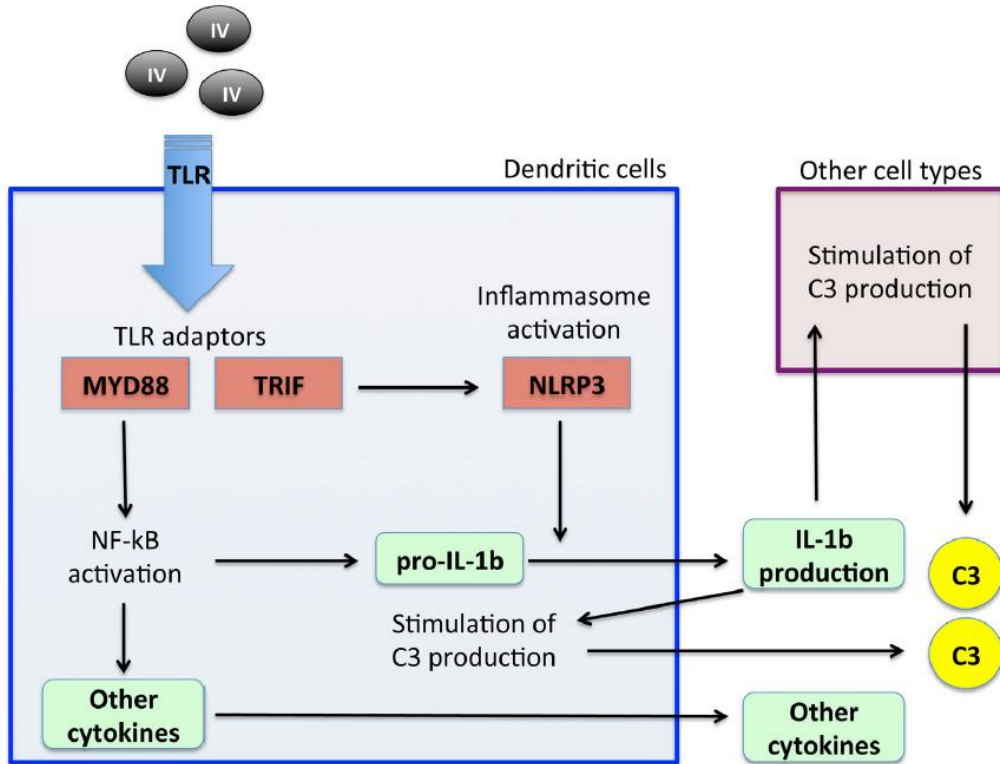
Field Trial update – March 2024

The on-farm aspect of the latest phase (Phase 2) of the TB vaccine field trials has been completed. This phase of the trial enabled government to collect safety data for inclusion in upcoming marketing authorisation applications. All GB administrations have taken the decision to move to a further phase (Phase 3) to gather additional data on the DIVA test specificity and explore options to optimise the performance of the new test. Phase 3 will assess BCG vaccination and the companion DIVA skin test on a broader cohort of herds to further inform our collective planning for delivery. We are continuing to work at pace but will only deploy the vaccine and companion DIVA skin test when we have all the right steps in place. Our aim is to deliver an effective cattle TB vaccination strategy within the next few years to accelerate our continued progress towards achieving OTF status for England and Wales.

Heat-inactivated mycobacteria



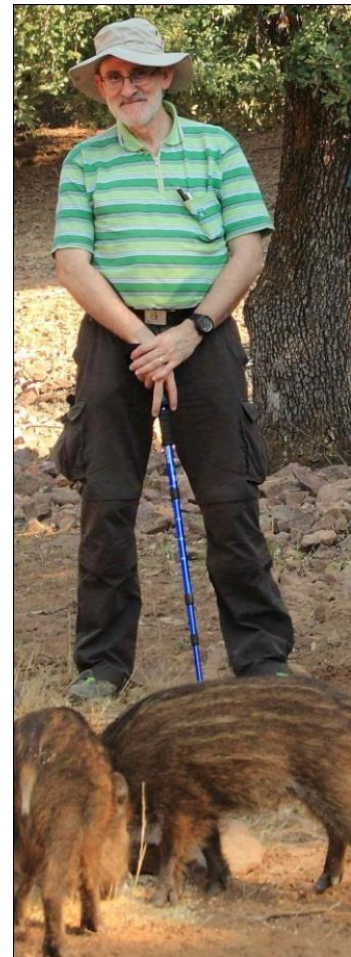
Heat-killed *M. bovis* vaccine HIMB



Dr. Ramón Juste,
NEIKER



Heat inactivated vaccine
(HIMB)
“Machuquillo de Ramón”



OPEN ACCESS Freely available online

PLoS ONE

Protection against Tuberculosis in Eurasian Wild Boar Vaccinated with Heat-Inactivated *Mycobacterium bovis*

Joseba M. Garrido¹, Iker A. Sevilla¹, Beatriz Beltrán-Beck², Esmeralda Minguijón¹, Cristina Ballesteros², Ruth C. Galindo², Mariana Boadella², Konstantin P. Lyashchenko³, Beatriz Romero⁴, Maria Victoria Geijo¹, Francisco Ruiz-Fons², Alicia Aranaz⁴, Ramón A. Juste¹, Joaquín Vicente², José de la Fuente^{2,5}, Christian Gortázar^{2*}

OPEN ACCESS Freely available online

PLoS ONE

Oral Vaccination with Heat Inactivated *Mycobacterium bovis* Activates the Complement System to Protect against Tuberculosis

Beatriz Beltrán-Beck^{1,3}, José de la Fuente^{1,2*}, Joseba M. Garrido³, Alicia Aranaz⁴, Iker Sevilla³, Margarita Villar¹, Mariana Boadella¹, Ruth C. Galindo^{1,2}, José M. Pérez de la Lastra¹, Juan A. Moreno-Cid¹, Isabel G. Fernández de Mera¹, Pilar Alberdi¹, Gracia Santos¹, Cristina Ballesteros¹, Konstantin P. Lyashchenko⁵, Esmeralda Minguijón³, Beatriz Romero⁶, Lucía de Juan⁶, Lucas Domínguez⁶, Ramón Juste³, Christian Gortázar^{1*}



Vaccination (T1)



Revaccination (T2)



Challenge (T3)



Handling (T4)



Necropsy (T5)



n=8 CONTROL

52 days pv



74 days prv

10⁵ cfu
M. bovis

59 days pc



70 days ph

Euthanized



n=4 PARENTERAL INACTIVATED

52 days pv



74 days prv

10⁵ cfu
M. bovis

59 days pc



70 days ph

Euthanized



n=7 ORAL INACTIVATED

52 days pv



74 days prv

10⁵ cfu
M. bovis

59 days pc



70 days ph

Euthanized



n=9 ORAL BCG

52 days pv



74 days prv

10⁵ cfu
M. bovis

59 days pc



70 days ph

Euthanized

Total: n=28



Pathology



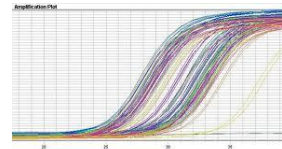
Culture



Serology



Gamma IFN



Gene expression

Pig and wild boar

Red deer

Goat

African buffalo

Cattle

European badger

Zebrafish
(*M. marinum*)

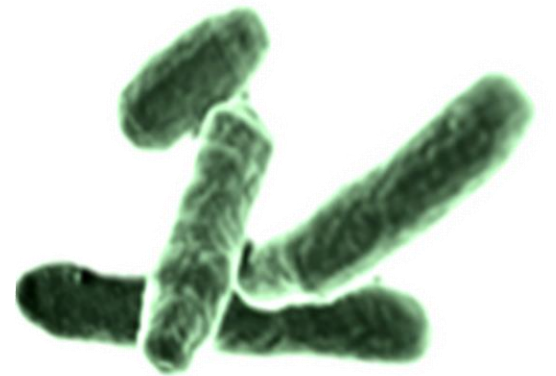


Resultados de 15 años de investigación

- Niveles de protección son equivalentes en BCG y HIMB
- Al igual que BCG, HIMB confiere una protección incompleta, reduciendo las lesiones y la excreción
- Al igual que BCG, HIMB funciona por vía parenteral y por vía oral
- A diferencia de BCG oral, HIMB oral no causa interferencia diagnóstica
- A diferencia de BCG, HIMB no necesita frío
- A diferencia de BCG, HIMB no conlleva riesgos por supervivencia o excreción

Estructura de la presentación

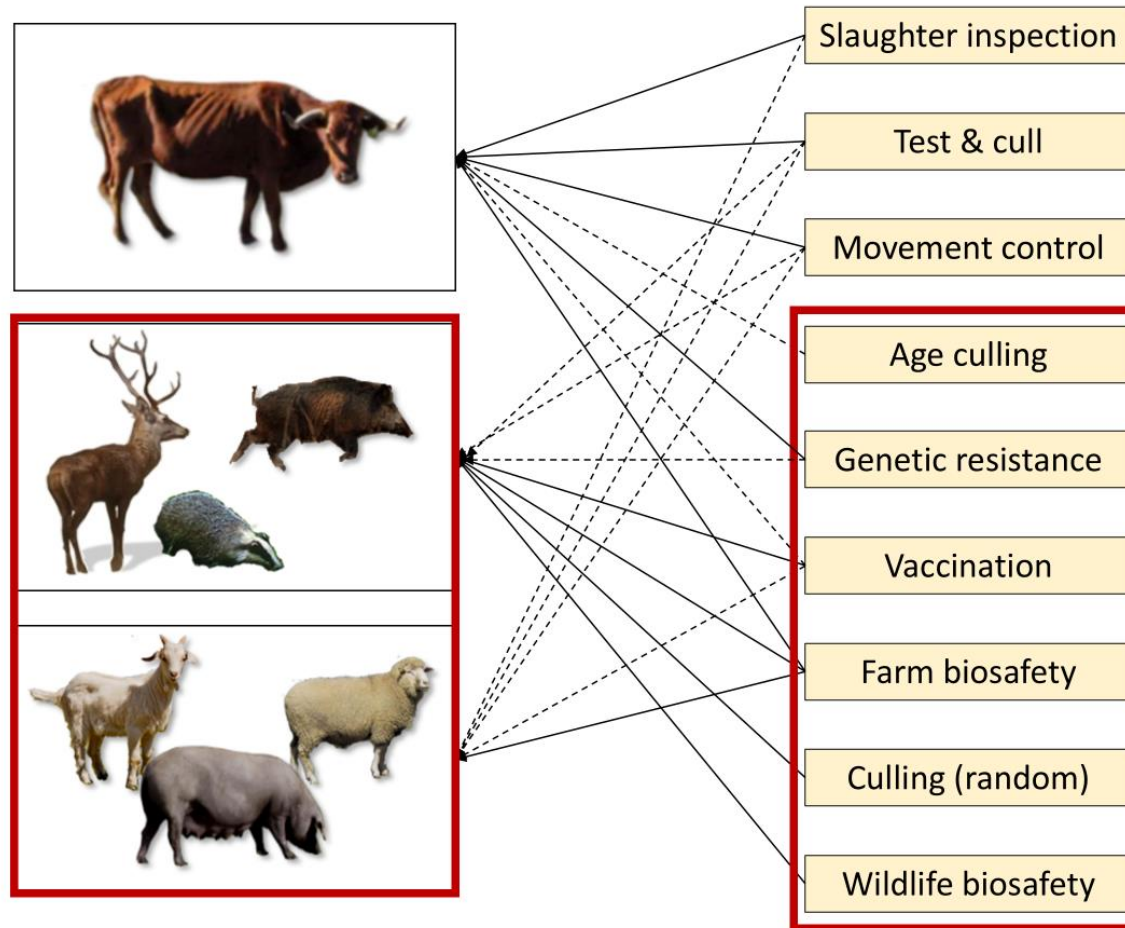
- Situación actual de la TB animal
- Epidemiología: hospedadores y transmisión
- Análisis de riesgos y diagnóstico epidemiológico
- Herramientas de control
 - Pruebas y matadero en bovinos
 - Control de hospedadores no bovinos
 - Bioseguridad
 - Vacunación
- **Cuatro mensajes clave**



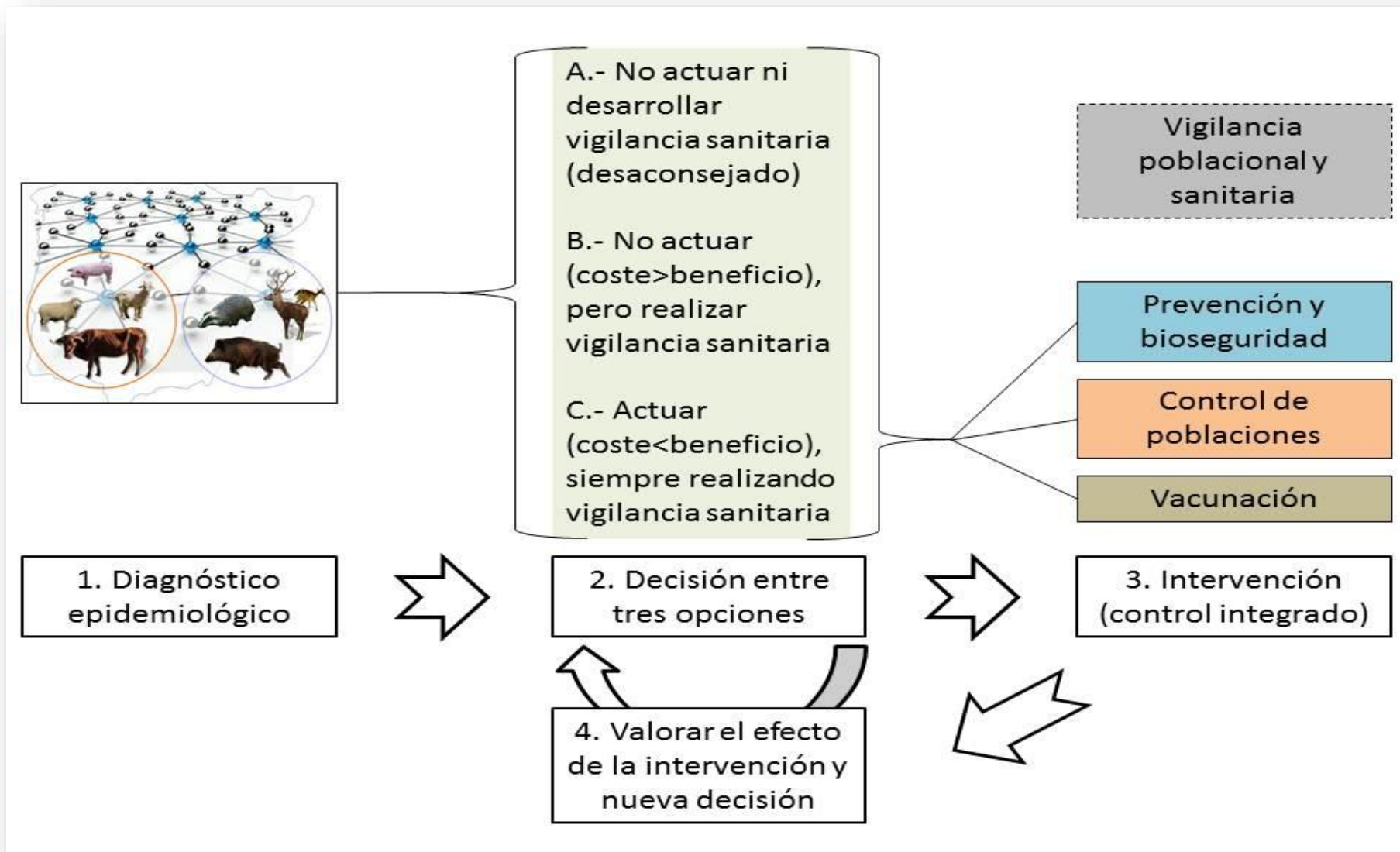
New Zealand's
farmers are
actively involved in
the TB control
scheme

1: Ganaderos





2: Comunidades



4: Control integrado

De la TB animal se puede salir

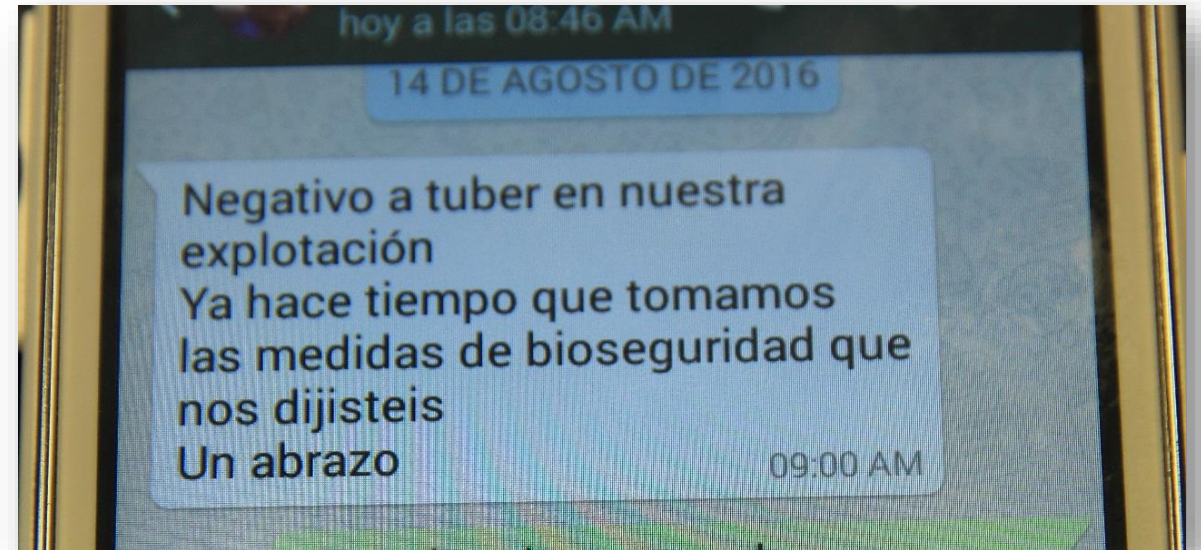
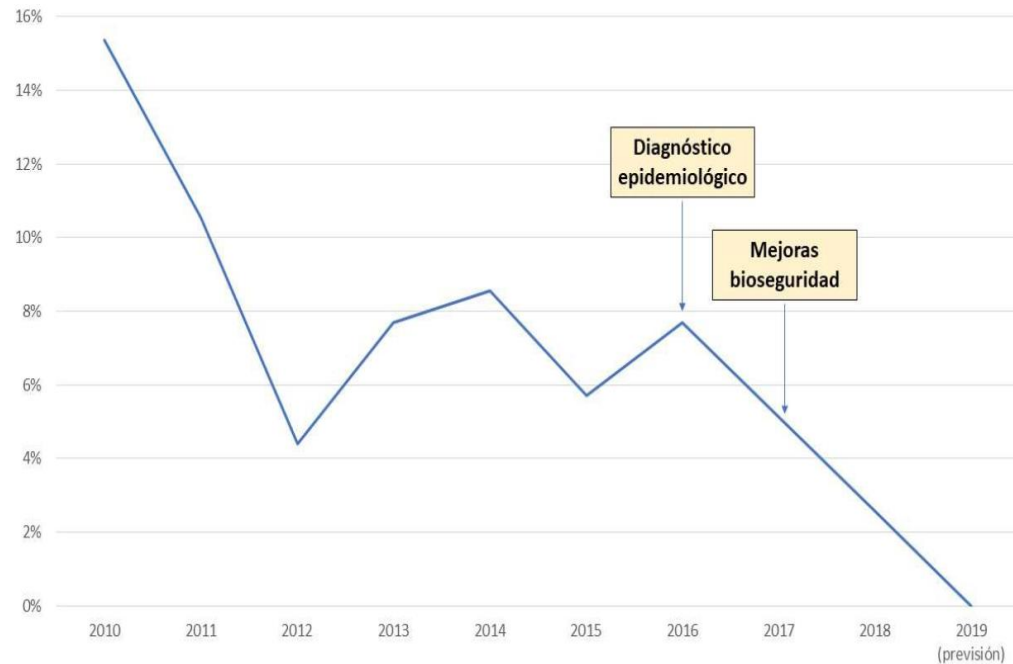


Figura 18.- Mejora de la prevalencia de TB en ganado tras la aplicación de medidas de bioseguridad en charcas y abrevaderos (fuente: Gobierno de Navarra).

Futuro



Campaña de saneamiento



Campaña de saneamiento



Vacunación



Bioseguridad



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 @ChristianGortaz

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¡Gracias!

