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Quantitative Genetic Analysis of the bTB Diagnostic Single Intradermal Comparative Cervical Test (SICCT)

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Bovine Tuberculosis (bTB) control – a major challenge

- **Impact**
  - **Economics**
    total cost of £100m per annum
  - **Animal health and welfare**
  - **Public health**
    developing world (10-15% of human TB cases)

Genetic selection for bTB resistance so far…

» Disease control through selection of individuals genetically more resistant to bTB

- **Heritable genetic variation in bTB resistance**
  (Woolliams et al. 2008; Bermingham et al. 2009; Brotherstone et al. 2010)
- **Initial estimates of the prediction accuracy for marker-based genomic selection** (Tsairidou et al. 2014)
- **Published bTB genetic evaluations for cattle in the UK (TB advantage)**

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SICCT-based identification of bTB cases

» The **hierarchical**, **comparative** structure of SICCT

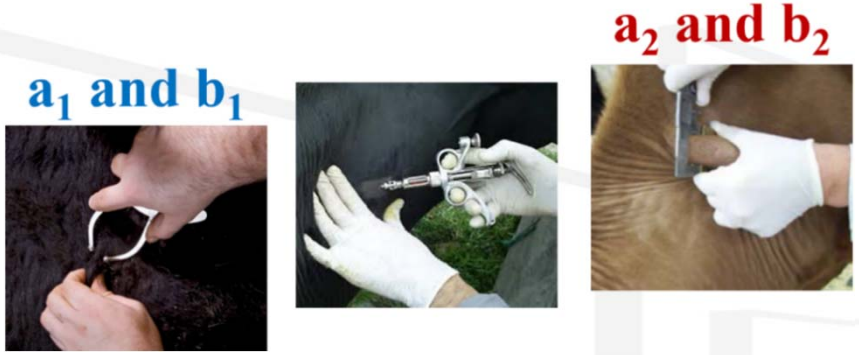
dc = (b_2 - b_1) - (a_2 - a_1) = db - da

Skin thickness measurements (mm)

a_1: site of avian tuberculin pre-inoculation
a_2: 3 days post-inoculation
b_1: site of bovine tuberculin pre-inoculation
b_2: 3 days post-inoculation

SICCT Reactor / Inconclusive R / Non-Reactor

standard or severe interpretation
pre-determined thresholds



Specificity > 99%
Sensitivity = 55-91%

Selection for bTB resistance partially informed by SICCT

- **Central role in bTB diagnosis and control in the UK**
  ~93% of bTB cases have involved SICCT in the diagnostic process

- **Criterion index to inform genetic selection**
  implicit role in defining phenotypes

Aims of study

— **What would be the impact of selection for bTB resistance on the epidemiological properties of SICCT at the genetic level?**

- Understand the possible correlated responses in SICCT and its components
- Would the Specificity and/or Sensitivity of SICCT change?

➢ Conduct a quantitative genetic analysis of the continuous responses in SICCT using the available field data collected during bTB herd testing

Materials & Methods

- **Data:** 88,932 SICCT measurements analysed after removing repeated records and retaining only the first test within each breakdown
- **Sire model:** Variance component analyses in ASReml and genetic regressions between SICCT components

$$\mathbf{y} = \mathrm{m}\mathbf{1} + \mathbf{X}\beta + \mathbf{f}(\mathbf{age}) + \mathbf{Z}\mathbf{u} + \mathbf{e}$$

y: the test components **a_1, b_1, da, db,** and **dc=db-da**
β: breakdown fixed effect, each breakdown in each herd is a new mini epidemic
f (age): age at test fitted as a smoothing cubic spline
u: vector of random sire effects with **u** ~ MVN (0, **A**σ_S^2)
relationships between sires accounted for through **pedigree**

$$h^2 = \sigma_A^2 / \sigma_P^2, \text{ where } \sigma_A^2 = 4\sigma_S^2$$

Results – genetic basis of the hierarchy of SICCT

	σ_A^2 (SE)	h^2 (SE)
a_1	0.540 (0.026)	0.489 (0.021)
b_1	0.557 (0.027)	0.493 (0.021)
da	0.155 (0.020)	0.056 (0.007)
db	0.257 (0.035)	0.059 (0.008)
dc	0.038 (0.012)	0.010 (0.003)

- Skin thickness is substantially heritable
- Very low heritability for da and db
- dc has lower heritability than its components

Results – after removing standard Reactors

	σ_A^2 (SE)	h^2 (SE)
a_1	0.544 (0.026)	0.493 (0.021)
b_1	0.562 (0.027)	0.498 (0.022)
da	0.132 (0.018)	0.050 (0.007)
db	0.060 (0.009)	0.043 (0.006)
dc	0.029 (0.006)	0.020 (0.004)

- Variation in the healthy animals, after removing variance due to cases
- dc has very low heritability

Results – correlations between the components of SICCT and regression analyses

- **The hierarchical, comparative design of SICCT makes it a robust test at the genetic level**

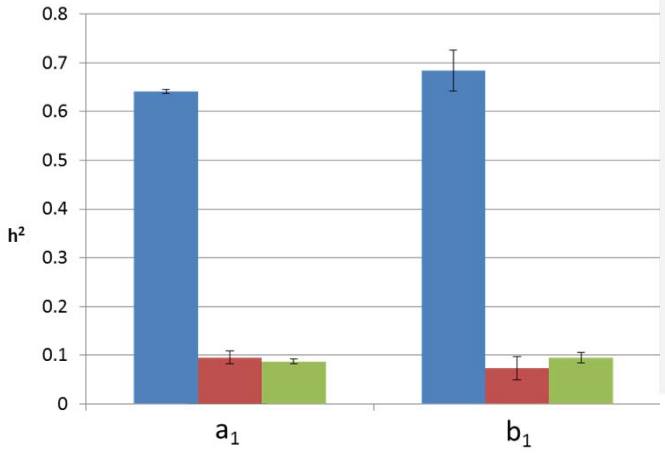
  - » Controls for initial skin thickness
  - » Corrects for responsiveness to mycobacteria and protects from changes in individual test components **dc = db – 1.da**

Trait A	Trait B	Cor_G (SE)	Reg_G (SE)
a_1	b_1	0.999 (0.001)	1.009 (0.005)
a_1	a_2	0.910 (0.012)	1.149 (0.033)
b_1	b_2	0.871 (0.018)	1.168 (0.042)
da	db	0.901 (0.029)	1.040 (0.071)

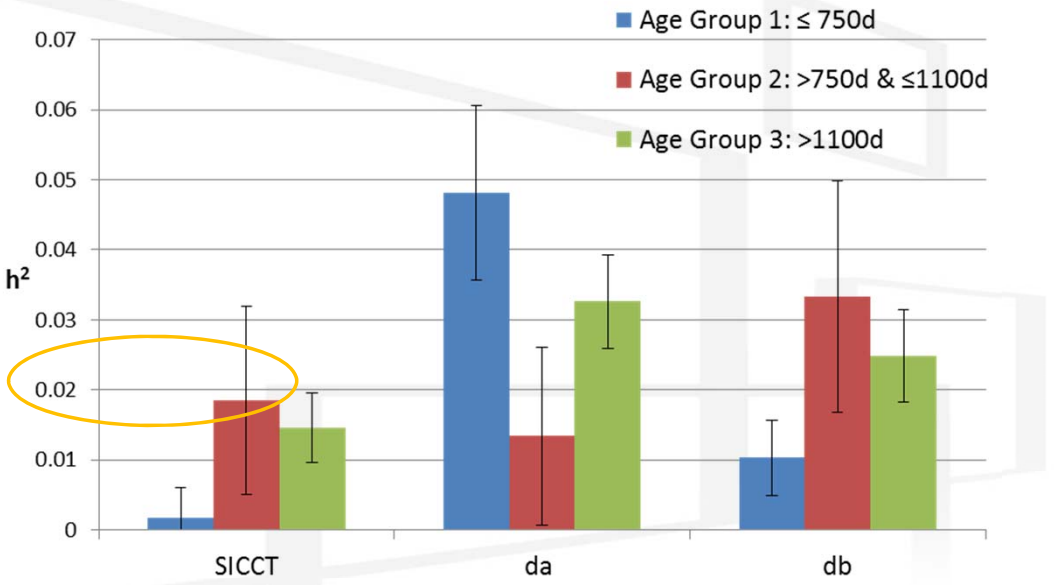
a_1: site of avian tuberculin pre-inoculation
a_2: 3 days post-inoculation
b_1: site of bovine tuberculin pre-inoculation
b_2: 3 days post-inoculation

Results – impact of age on the genetics of SICCT components

- The hierarchical, comparative design of SICCT controls for age-dependent differences



$Reg_G \approx 1$



Genetic basis of variation in SICCT response conditional on bTB infection status

- **Investigate possible correlated responses to selection for bTB resistance that may change the probability that an uninfected animal goes above the threshold**
  - » Probability of correctly identifying non-infected animals **i.e. the individual test Specificity**

	SICCT positivity	
	0	1
Healthy	$(1-p_i)\,Sp_i$	$(1-p_i)\,(1-Sp_i)$
Diseased	$p_i\,(1-Se)$	$p_i\,Se$

Genetic basis of variation in SICCT response conditional on bTB infection status

- Bivariate analysis between the dc measurement and SICCT positivity, in the healthy animals (standard IRs and NRs)
  - » Genetic correlation between individual Sp on the liability scale and bTB susceptibility on the 0/1 scale

$$Cor_G = -0.01 \text{ (s.e. } 0.14)$$

- Individual test Specificity is unlikely to change
  - » Any response is expected to be weak and slow, and negligible over a small number of generations

Genetic basis of variation in SICCT response conditional on bTB infection status

- Changes in the individual Sensitivity need further **monitoring**
  - Would require observing cases among those that are not detected by SICCT
- Selection is on genetic **variation in true resistance**
  - Not just the animals that respond more but those that are more likely to get the pathogen
  - Selection will reduce the size of the epidemic – fewer false –ves

Conclusions – Genetic selection for bTB resistance informed by the SICCT

- A complementary control strategy to reduce within-herd bTB incidence, likelihood and duration of breakdowns
  - » Using existing genetic variation in resistance

- Protection against genetic changes arising from correlated responses among SICCT components and from random genetic drift, due to either natural or artificial selection
  - » Any adverse correlated responses in individual Specificity are expected to be weak and slow

Future challenges

- Improving quality of measurements and consistency across tests
- Continued monitoring of key population data
  e.g. SICCT measurements, case confirmation
- Expanding the training sets for genomic prediction for bTB resistance
- Using genetic epidemiology approaches to capture the total genetic risk for bTB by exploiting variation in host infectivity

Thank you

Implications: The results of this project have contributed to the decision to publish bTB genetic evaluations for cattle in the UK from January 2016 onwards

(Tsairidou et al. 2016 manuscript submitted)

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A. Doeschl-Wilson