
# Bovine tuberculosis - exploiting host and pathogen genetics

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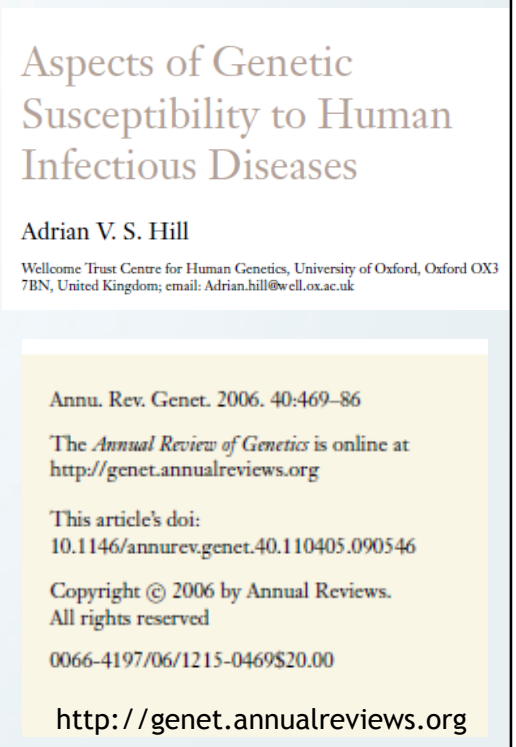
# Bovine TB host genetics:

## A genetic basis for resistance?

# TB host genetics

- "*Infectious diseases are hereditary*"
  - Louis Pasteur (1830s)
- When individuals are exposed to infection, some contract the disease and others do not
  - A spectrum of susceptibility
  - Exploitable genetic variation
- Primary immuno-deficiences (PIDs)
  - Susceptible to certain infections and not others
- **Could host genes determine whether infection occurs in the first place?**

- The genetic basis of complex diseases
- Most are the sum of many minor susceptibility alleles and a very small number of alleles of larger effect
- TB resistance - likely a highly polygenic trait



Aspects of Genetic Susceptibility to Human Infectious Diseases

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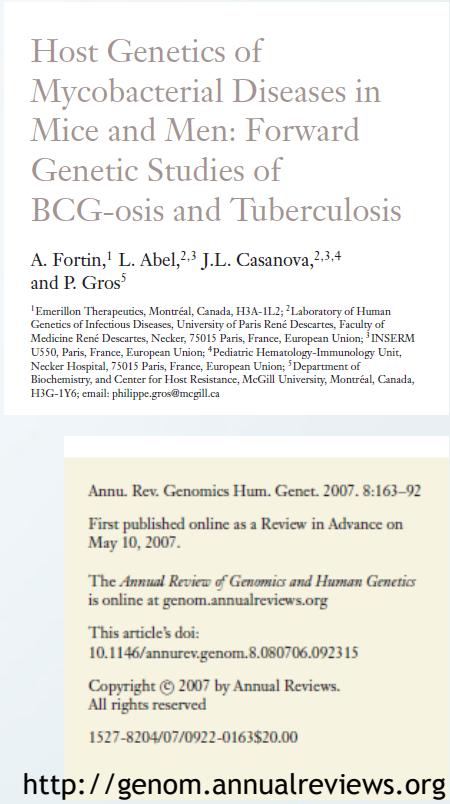
0066-4197/06/1215-0469$20.00

http://genet.annualreviews.org

- ‘Simple’ Mendelian Susceptibility to Mycobacterial Disease (MSMD)
- Genetic factors have long been suspected to contribute to onset and outcome
  - Different inter-individual clinical outcomes
  - Different progression from infection
  - Familial clustering of cases
  - Higher concordance of TB in identical v non-identical twins (exposure?)
- Complex inheritance – confounded by environment
  - Includes pathogen phenotype



Host Genetics of Mycobacterial Diseases in Mice and Men: Forward Genetic Studies of BCG-osis and Tuberculosis

A. Fortin,[1] L. Abel,[2,3] J.L. Casanova,[2,3,4] and P. Gros[5]

[1]Emerillon Therapeutics, Montréal, Canada, H3A-1L2; [2]Laboratory of Human Genetics of Infectious Diseases, University of Paris René Descartes, Faculty of Medicine René Descartes, Necker, 75015 Paris, France, European Union; [3]INSERM U550, Paris, France, European Union; [4]Pediatric Hematology-Immunology Unit, Necker Hospital, 75015 Paris, France, European Union; [5]Department of Biochemistry, and Center for Host Resistance, McGill University, Montréal, Canada, H3G-1Y6; email: philippe.gros@mcgill.ca

Annu. Rev. Genomics Hum. Genet. 2007. 8:163–92

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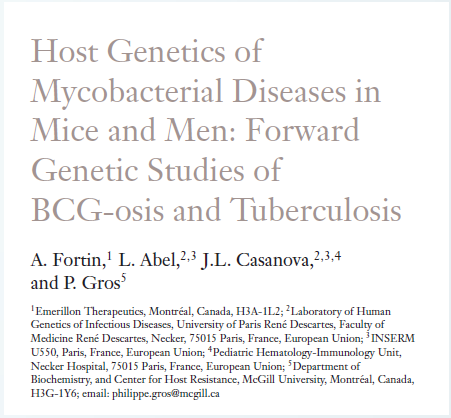
- Inbred mouse strains with different TB susceptibilities
  - KOs, KDs
- Genes involved - positional cloning
  - Nramp1, IFNgR etc
- Candidates for human genetic epidemiology studies
  - Some associations in some populations
- *Detected a major locus controlling binary skin test response (T-cell independent)
- *Detected a second major locus controlling skin test QTL or intensity of DTH (T-cell dependent)
  - *Cobat and others (2009). Two loci control tuberculin skin test reactivity in an area hyper-endemic for tuberculosis. JEM doi:10.1084/jem.20090892



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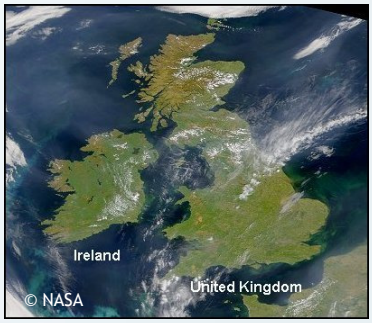
# Context: bovine TB incidence

- $3 billion worldwide (2003)
- Initial control for public health
- Now includes trade-based considerations
- *"One of the most complex and difficult multi-species endemic diseases currently facing government, the veterinary profession and the farming industry in the United Kingdom and Ireland"*

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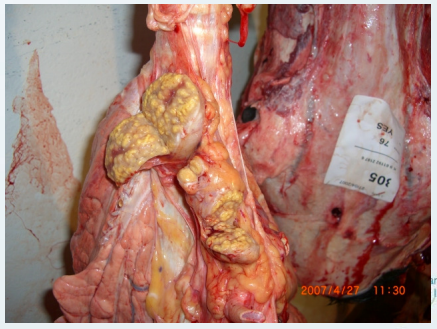
# Context: bovine TB incidence

- GB: largely unexplained increase year-on-year?
  - £1,000M by 2011
- NI: ***down*** ~50% 2002-2008
  - Levelled off – stable endemic
    - 5.57% herd incidence
    - 0.57% animal incidence
  - NIAO/PAC Report £200M in 10 years
    - Compensation and testing

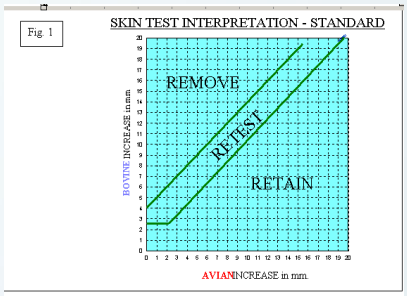
# Bovine TB - control

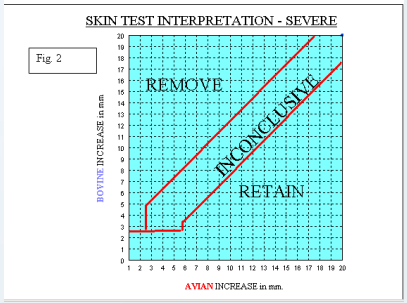
- Directive 64/432 EEC
- Computer database
- Test-and-slaughter protocol
  - Field diagnosis
    - Annual TB skin test (SICTT)
    - Abattoir
      - Reactors - *post-mortem* examination
      - Non-reactors - targeted surveillance
  - Lab confirmation
- Abattoir and lab confirmation - low sensitivity
- Remove reactors
- Consequences
  - Movement restrictions
  - Short interval retests

# Phenotype data – bTB skin test

- Interpretation
  - Standard
  - Severe
- **Performance***
  - **Sensitivity = 80.0% (52-100%)**
    - **93.5% severe**
  - **Specificity = 99.5% (78.8-100%)**
  - **GB Sensitivity = 75.0-95.5%**
  - **GB Specificity = 99.99%**

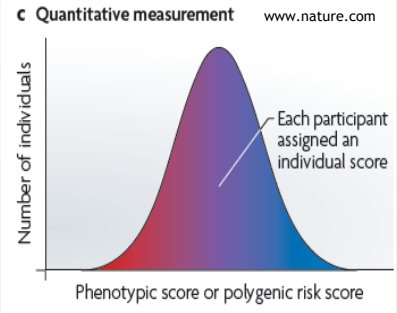



*Ricardo de la Rua Domenech and others (2006). *Res Vet Sci* **81**: 190-210

# Phenotype data – bTB skin test

- Disease geneticists are looking for measurable ***variation*** in outcome (population level) as evidence for genetic component
- Variation is found at population scale



# Phenotype data – bTB confirmation

- TB reactors
  - Visible lesions (VL) 40% confirmed 99%
  - No Visible lesions (NVL) 60% 02%
- Passive surveillance
  - Lesions at routine slaughter (LRS) 75%
    - 20% breakdowns
- Lab confirmation
  - Histology
    - H&E, ZN
  - Bacteriology
    - Presumptive
    - Molecular confirmed
    - Molecular type

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# Review

- Much current effort
  - Deployment of control programmes
  - Improving diagnosis
  - Vaccines and adjuvants – cattle and wildlife
  - Badger culling trials
- *Failure of Ireland, the UK and other EU member states to reach TB-free bovine herd status plus the high cost of existing eradication programmes…
- Other measures still required

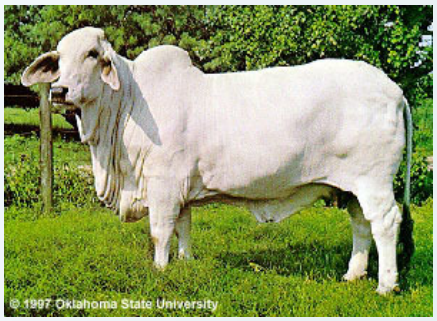
- *Bermingham and others (2009). J Dairy Sci 92: 3447-3456

# Review

- The contribution that both ***host*** and ***pathogen*** genetic variation makes to disease outcome - largely overlooked
- Both the ***host*** and ***pathogen*** are sources of genetic variation which may influence the outcome of exposure to bTB
- **Genetic selection for improved resistance to bTB in cattle?**

# bTB resistance in livestock

- Evidence* that *Bos indicus* is more resistant than *Bos taurus*
- Anecdotal evidence of resistance/susceptibility differences within some families




*Ameni and others (2007). *Clin Vaccine Immunol* **14**: 1356-1361

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# bTB resistance in livestock

- bTB in farmed deer (NZ)
- Differential susceptibility in outbreaks and transmission rates
- Continuous normal distribution response to disease
- From experimental infection studies identified highly R and highly S sires*
- Strong genetic basis to R phenotype
- $h^2 = 0.48$!

*Mackintosh and others (2000) *Infect Immun* 68: 1620-1625

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# Genetic epidemiology - resources

- Large epi-field phenotype datasets
  - Abattoir and lab confirmation
- Large pedigree and performance datasets
- Mathematical models
- Experimental models
- Genomics
  - The bovine genome
    - The Bovine Genome Sequencing and Analysis Consortium (2009). *Science* **324**: 522-528
  - The Bovine HapMap (~2.4M SNPs)
    - The Bovine HapMap Consortium (2009). *Science* **324**: 528-532


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# Genetic epidemiology - concepts

- **Heritability:** the relative contributions of differences in genetic and non-genetic factors to the total phenotypic variance in a population (0-1)
  - Human height $h^2 = 0.80$
  - Milk yield $h^2 = 0.50$
  - Mastitis $h^2 = 0.09$
- Population stratification
- Phenotype (P) = Genotype (G) + Environment (E)
- Definition of ***phenotype***?
  - Exposure
  - Infection
  - Disease
- **Infectious disease genetics - concerns?**
  - **Incomplete exposure**
  - **Imperfect diagnosis (*Se*/*Sp*)**

OPEN ACCESS Freely available online

PLoS one

# On the Genetic Interpretation of Disease Data

**Stephen C. Bishop*, John A. Woolliams**

The Roslin Institute and Royal (Dick) School of Veterinary Studies, University of Edinburgh, Roslin, Midlothian, United Kingdom

**Citation:** Bishop SC, Woolliams JA (2010) On the Genetic Interpretation of Disease Data. PLoS ONE 5(1): e8940. doi:10.1371/journal.pone.0008940

- Genetic variation in host resistance to infectious diseases ubiquitous
- Derived models to predict impact on heritability of
  - Incomplete exposure
  - Imperfect diagnosis (*Se*/*Sp*)
- All tend to ***underestimate*** true heritability
- Not fatal in demonstrating host genetic differences in resistance – just reduces power
- Finding detectable genetic variation in field data implies that the true heritability is likely to be much higher
- Helps explain low apparent disease heritability under field conditions

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J. Dairy Sci. 92:3447–3456
doi:10.3168/jds.2008-1848


## Genetics of tuberculosis in Irish Holstein-Friesian dairy herds

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*Moorepark Production Research Centre, Fermoy, Co. Cork, Ireland
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§The Irish Cattle Breeding Federation, Bandon, Co. Cork, Ireland
#Institute of Evolutionary Biology, University of Edinburgh, West Mains Road, Edinburgh EH9 3JT, United Kingdom

- ICBF pedigree and performance data
- DAFF AHC bTB test and movement data
- Data extracts and edits – episodes
- Phenotype = skin test and *M. bovis* infection
- Significant genetic variation for PPD response
- Significant genetic variation for confirmed infection - genetic improvement possible
- **Heritability = 0.18** (underestimated)
- Strong correlation between susceptibility to confirmed bTB and bTB skin test responsiveness
- Skin test can be used as indirect bTB susceptibility measure
- Select for increased resistance to PPD response will reduce susceptibility to infection in the national herd – complement and benefit existing measures

J. Dairy Sci. 93:1234–1242
doi:10.3168/jds.2009-2609


## Evidence of genetic resistance of cattle to infection with *Mycobacterium bovis*

**S. Brotherstone,*[1] I. M. S. White,* M. Coffey,† S. H. Downs,‡ A. P. Mitchell,‡ R. S. Clifton-Hadley,‡ S. J. More,§ M. Good,# and J. A. Woolliams||**
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||The Roslin Institute, Roslin Biocentre, Roslin, Midlothian EH25 9PS, United Kingdom

- Different farming practices ROI and GB
- Defra VetNet data
- NMR-CDI-HUK pedigree and performance data
- Data extracts and edits – episodes
- Heritable variation in bTB risk for culled and confirmed cattle
- $h^2 = 0.18$ (underestimated), $P<0.001$
- Selection for milk yield unlikely to have contributed to current epidemic and *vice versa*
- Select breeding stock to produce offspring with enhanced resistance
- Genetics could play an important role in controlling bTB
- Reduce incidence and severity of herd breakdowns

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Preventive Veterinary Medicine 93 (2010) 153–161

Contents lists available at ScienceDirect

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journal homepage: www.elsevier.com/locate/prevetmed

# Bovine tuberculosis and milk production in infected dairy herds in Ireland

F. Boland [a,*], G.E. Kelly [a], M. Good [b], S.J. More [c]

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[b] Department of Agriculture, Fisheries and Food, Kildare St, Dublin 2, Ireland
[c] Centre for Veterinary Epidemiology and Risk Analysis, UCD School of Agriculture, Food Science and Veterinary Medicine, University College Dublin, Belfield, Dublin 4, Ireland

- Are high producing cows more or less likely to be detected as bTB reactors?
- ICBF and DAFF data extracts and edits - for all lactations and years – milk yield ***lower*** for bTB reactor cows
- This study:
  - Low milk yield is a risk factor for being a bTB reactor in Irish dairy herds
  - Low milk yield tends to precede infection
- **Consistent with ROI and GB data – genetic basis to bTB susceptibility**
  - Genetic selection for bTB resistance should not have negative impact on herd productivity – maybe the opposite
  - No evidence that bTB reactors are on average the most productive cows in a herd
  - National bTB programme should not be leading to loss of highest producing cows
  - Other work ongoing – association with other traits (MB)

# The ‘on/off’ relationship

- Quantitative geneticists
  - Exploitable variation in risk
  - Estimated breeding values (EBVs)
  - Artificial selection
  - Genomic selection
  - Less concerned with identifying ‘genes’!

# The ‘on/off’ relationship

- Molecular geneticists
  - Genes (variants), pathways, networks – the molecular basis of the phenotype – how?
  - Host mechanisms of protection
  - Dissecting the host/pathogen interaction
    - Gene expression profiling
      - HD microarrays, RNAseq
  - Rational targets
  - Vaccines
  - Diagnostics
  - Marker-assisted selection
- Dialogue important!

# Genetic epidemiology analysis

- Look for genetic variants associated with phenotype
- Study design
  - Genotype cases and controls
  - Genotype extremes of sire risk ranking
- Definition of phenotype
- Based on Holstein-Friesian dairy cattle
  - Population stratification
- Logistics - sampling cases and controls
- Molecular genetics analysis
  - High-density SNP arrays
    - Illumina SNP800K
  - Power to detect associations

# Phenotype: case-control study

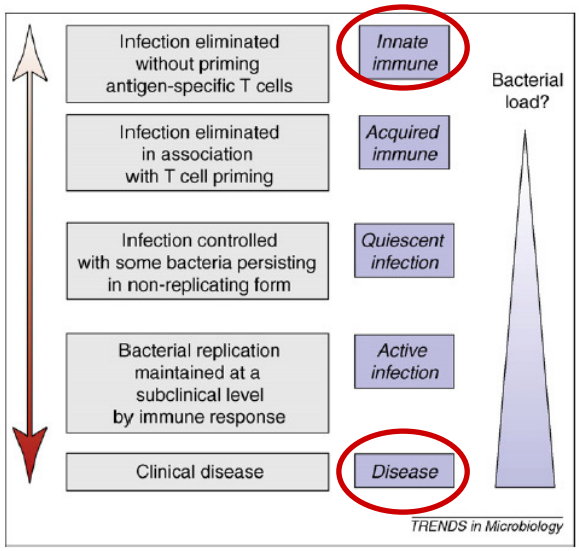


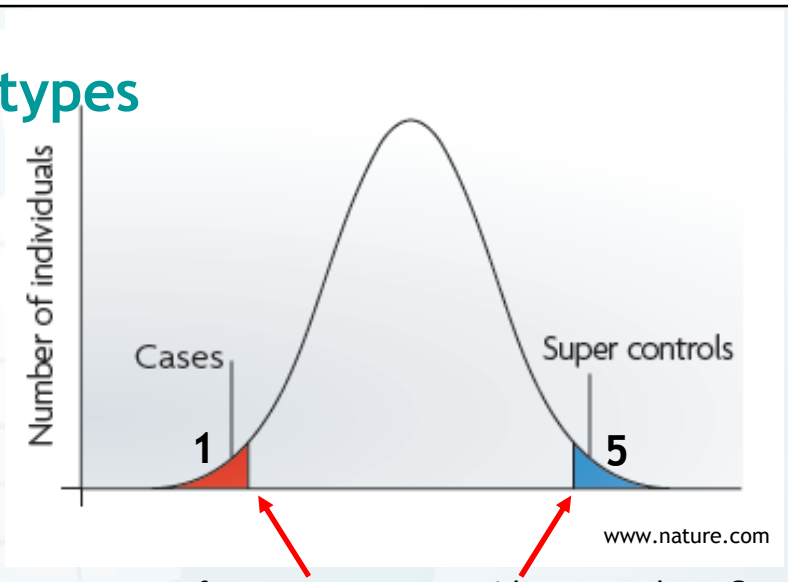

**Figure 2.** A spectrum of responses to tuberculosis infection. **Infection with *M. tuberculosis*** is usually viewed in terms of a binary outcome: **as active disease or** latent infection. We propose that a model that includes a **spectrum of responses** provides a better representation of the biology of infection **and might assist in** formulation of appropriate research questions.

DB Young *TRENDS in Microbiology* 2009

**TB control**

**TB case**

# Phenotypes



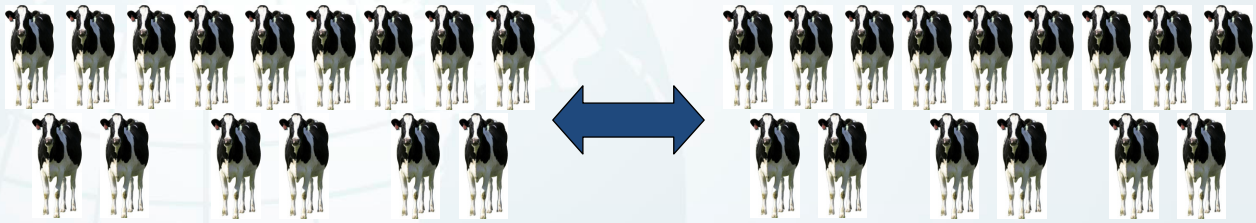

Phenotypes at extremes of spectrum may provide most robust Case & Control definitions.

Also – occupying extremes of distribution is likely to maximise detection of any underlying genetic difference.

**Phenotype 1 – Cases: skin test positive, macroscopic lesions & bacterial culture.**

**Phenotype 5 – Controls: exposed but skin test negative on multiple occasions**

# Case-control study



700
DISEASED ANIMALS
SAMPLED > 3,000

700
CONTROL ANIMALS
SAMPLE >1,000

# Whole genome SNP scan


Next steps:

- Select 'case' and 'control' samples for **whole-genome scan** (WGS) genotyping
- New genetic tools from the bovine genome sequence (2009)
  - Illumina SNP800 chip
  - Denser arrays, re-sequencing, CNVs
- **Analyse for genetic variation statistically-associated with cases or controls**
  - SNPs will direct towards causative variation
  - Map and clone genes (pathways) which predispose to disease
    - Diagnosis
    - Vaccinology
    - Genetic tests

# Beneficiaries

- Advance our understanding of bovine TB
  - Host and pathogen genetics
  - Pathogenesis
  - Epidemiology
- **The prospect of breeding cattle for increased TB resistance**
  - Sire selection
  - Marker-assisted genetic selection
- Potential engagement with cattle industry
  - Rapid genetic turnover in UK dairy herd
  - May obtain benefits quickly

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# Policy relevance

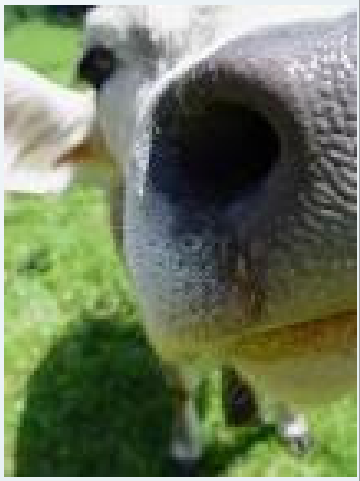
- Reduced susceptibility would support other control measures
- May inadvertently improve resistance to other pathogens
- Powerful demonstration of exploiting Government and industry databases
- No negative impact on wildlife populations
- **Genetics can play an important complementary role in control strategies**
  - Not the sole strategy (assuming R not absolute)
- A more sustainable approach to disease control

# Bovine TB pathogen genetics:

## Getting to know the enemy

# Bovine TB

- Infectious respiratory disease caused by infection with *Mycobacterium bovis*
- Complex epidemiology
  - An epidemic involving multiple species
  - Transmission within and between populations of cattle and wildlife
  - Wildlife reservoir in badgers
  - Relatively low transmissibility
- Disease ***source*** and ***spread*** not clearly understood
- Difficulties in identifying epidemiologically-linked cases



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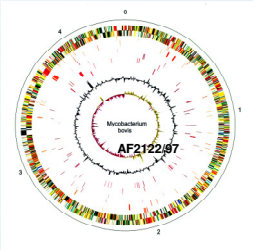
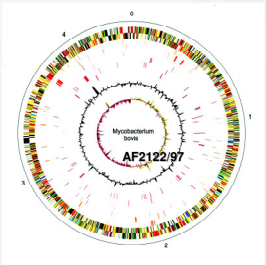
# Genomes

- Circular chromosome (5 million bp) coding ~4,000 genes
- Human-adapted (*M. tuberculosis*) and bovine-adapted (*M. bovis*) >**99.95% identical!!**
  - ***M. tuberculosis* H37Rv (1998)**
  - ***M. tuberculosis* CDC1551 and others**
  - ***M. bovis* AF2122/97 (2003)**
  - ***M. bovis* BCG**
- Exploiting the genome sequence
  - Comparative genomics, physiology and pathogenesis
  - Understanding attenuation
  - Diagnostics and vaccine candidates
- Mutations: powerful markers of genome evolution



# Molecular sub-typing

- Molecular sub-typing and epidemiology:
  - Research tool
    - Epidemiology questions
    - Population structure
    - Genotype:phenotype
  - Decision-support tool
    - Source of infection
    - Route of transmission




- Require a fundamental understanding of selective and neutral forces that shape bacterial populations
  - Influence on current TB epidemic?

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# Biogeography of human TB lineages

- Important phenotypic consequences
  - Differences in virulence
  - Differences in immunogenicity
- Might impact new diagnostics, drugs and vaccines
  - Gagneux and Small (2007) Lancet Inf Dis 7: 328-337
  - Hirsh and others (2004) PNAS 101: 4871-4876
  - Hershberg and others (2008) PLoS Biology: 6 e311
- Biogeography has important consequences for geographical distribution of relevant lineage-specific phenotypic traits
  - A large proportion of variation in BCG efficacy linked to geography

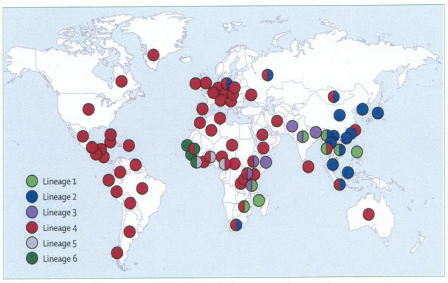


*Figure 2:* **Global phylogeography of *M tuberculosis***
Dots indicate the dominant lineage in country as sampled in Gagneux et al[86] with additional data from Filliol et al.[58]
Adapted with permission from Gagneux et al,[86] copyright (2006) National Academy of Sciences USA.

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# TB bacteria – molecular epidemiology

- Until recently assumed that all bTB isolates were the same
- Post genomics - different tools (markers) inform on different evolutionary scales

- Evolution and phylogenetics
  - **lineages = LSPs, RDs, SNPs**
- Population structure
  - **clones = spoligotype**
- Outbreak investigation
  - **strains = VNTRs**

**Discrimination**

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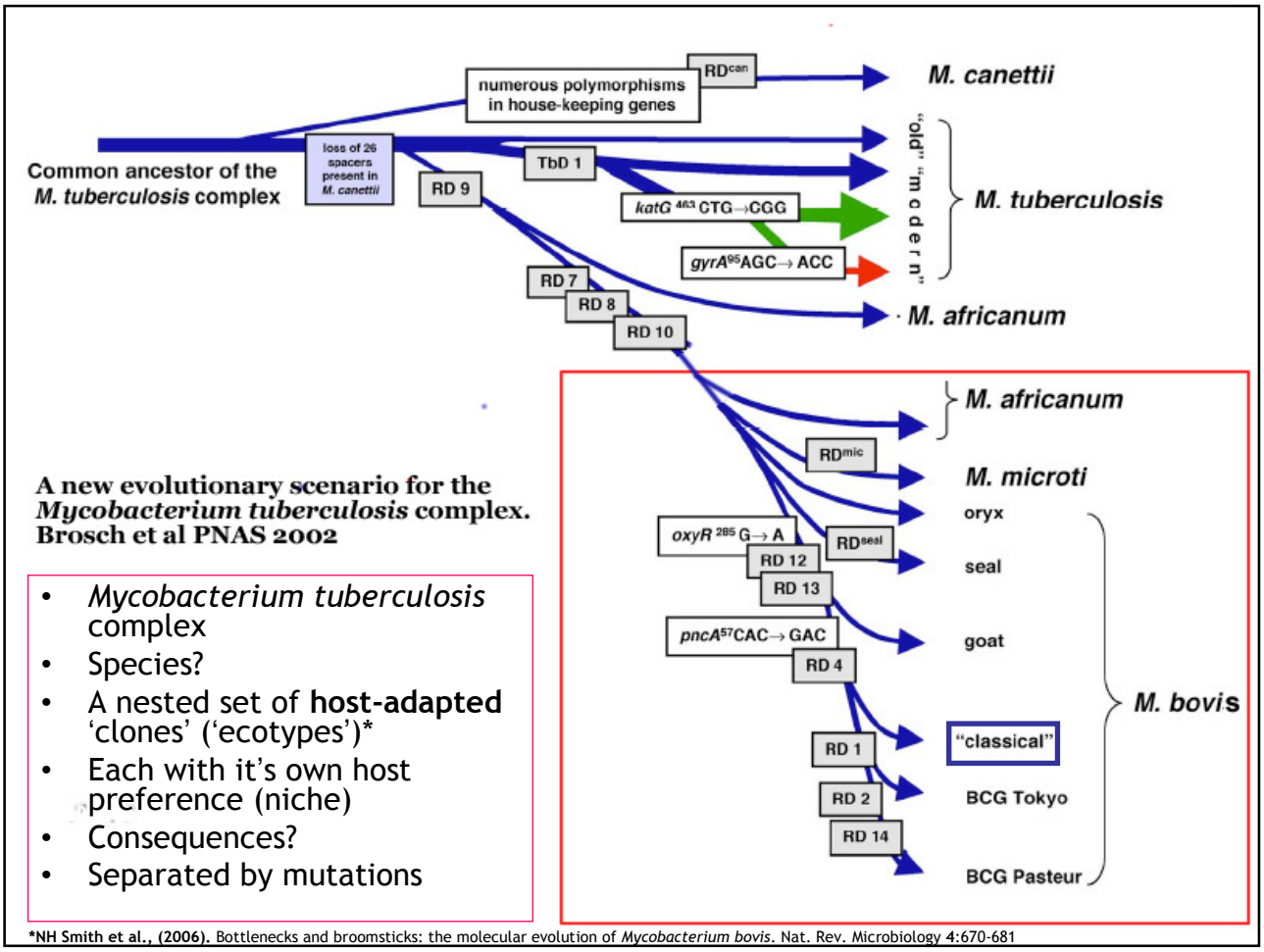
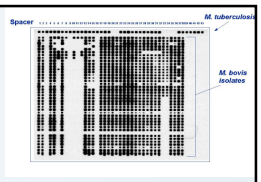



**A new evolutionary scenario for the *Mycobacterium tuberculosis* complex. Brosch et al PNAS 2002**

- *Mycobacterium tuberculosis* complex
- Species?
- A nested set of **host-adapted** 'clones' ('ecotypes')*
- Each with it's own host preference (niche)
- Consequences?
- Separated by mutations

*NH Smith et al., (2006). Bottlenecks and broomsticks: the molecular evolution of *Mycobacterium bovis*. Nat. Rev. Microbiology 4:670-681




# *M. bovis* spoligotypes: geographical localisation by country (%)

| Spoligotype | GB | NI | ROI | FR |
|---|---|---|---|---|
| SB0140 | 36 | 66 | 52 | 1 |
| SB0142 | 1 | 19 | 13 | 0 |
| SB0263 | 24 | 7 | 0 | 0 |
| SB0130 | 1 | 1 | 15 | 1 |
| SB0274 | 13 | 0 | 0 | 1 |
| SB0120 (BCG-like) | 0 | 0 | 0 | 26 |
| SB0121 | 1 | 0 | 0 | 12 |

NH Smith et al (2006) Nature Reviews Microbiology 4: 670-681

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# British Isles TB epidemic

- Now relatively limited diversity*
  - Population 'bottleneck'?
    - 'Test and slaughter' policy?
- Clonal expansion...series of local epidemics

*NH Smith (2003) PNAS 100(25): 15271-15275

# British Isles TB epidemic

- UK and Ireland dominated by *M. bovis* of a particular lineage
  - Spoligotype SB0140 'clonal complex'
    - From which most other UK spoligotypes readily derived
  - Genetic distance?

***NH Smith (2003) PNAS 100(25): 15271-15275**

## High-resolution pathogen genotyping - microbial forensics

- Genetic tracking of pathogens
  - Analysis of their *mutagenic drift*
  - Important surveillance data
- Potential to help clarify:
  - **sources of infection**
  - **chains of transmission**
  - **new tools to investigate spread**

# *M. bovis* VNTR typing (Northern Ireland)

- High-performance PCR-based
- Genotype = Haplotype - a string of 'copy number variants'
- Listed in increasing discrimination*

| 2163b - 4052 | 2461 | 1955 | 1895 | 2165 | 2163a - 3232 |
|---|---|---|---|---|---|
| 4 | 4 | 5 | 3 | 4 | 8 | 10 | 8 |

- Can be simplified to surveyed 'prevalence'
  - Database...link animal-level data (APHIS)
  - Map to herd of slaughter (MapInfo)
  - Combination of spoligotyping* and VNTR

* Skuce and others (2005) Vet Record 157: 501-504

## Herd-level surveillance 2003-present

- Population sample - first (disclosing) isolate per confirmed TB breakdown
- Non-random geographical distribution
  - Significant association with region ($p<0.0001$)
  - Significant inter-annual differences and trend for some genotypes ($p<0.0001$)
- Animal-level surveillance 2008
- Animal test and movement history (APHIS)

# NI surveillance 2003 - present

- Striking geographical localisation of molecular type
- Each molecular type…
  - Has its own home range (unless imported)
  - Responsible for its own micro-epidemic
  - Is a separate experiment!
    - Target eradication of specific genotype(s)?

# Geographical localisation

- Severe geographical localisation of *M. bovis* molecular types in UK
  - *Absence of recombination between bovine TB strains
  - *Natural and imposed movement limitation on domestic cattle
  - Natural social structure and movement of wildlife?
  - Populations genuinely separate (compartmentalised)?
  - Environmental contamination?
  - *Local and national efficiency of control and eradication
  - *Hewinson RG et al (2006). Veterinary Microbiology 112: 127-139

# NI surveillance 2003 - present

- Why do bTB strains cluster?
- Translocation - what's moving them about?
- Frequency of most genotypes relatively stable
- Contraction/expansion of some genotypes
- Emergence/transmission/extinction of new variants

# Cattle-badger association

- That TB in badgers and cattle is linked is ***NOT*** debated
- Strain typing indicates ***epidemiological association***
- **Data cannot be used to infer *direction* or to *quantify* the badger or cattle component**

# NI surveillance 2003 - present

- Role (unquantified) for cattle movement in 'translocation'
  - Movement and social networks?
- **Data implies:**
  - **Stable and local sources**
  - **A series of local epidemics**
- Significant diversity within regions
  - Despite appearance of domination by strains which may have reached fixation

# Applications

- Surveillance
  - Is current situation due to rapid expansion of particular TB types?
  - Need surveillance data over years to help interpret current outbreaks
- Outbreak investigation
  - Source, contacts and route
  - Patterns, prevalence and trends of strains Informed picture of epidemiological features of transmission
  - Inform deployment of additional tests

# Pathogen genotype-phenotype

- Co-variable in genetic epidemiology study
- Genetic association studies
  - Only now sufficiently powered to detect significant interactions
  - Does *M. bovis* molecular type influence, for example:
    - Skin test responses?
    - Lesion status?
    - Outbreak size?
    - Persistence?
    - Latency?
    - Transmissibility?
    - Host susceptibility?

# Conclusions - pathogen

- Isolates have a genetic signature characteristic of their geographic origin
- *M. bovis* population structure and performance characteristics of genotyping support its use to monitor current control and future interventions
- Potential to refine modelling and analyses of policy questions
- *M. bovis* genotyping - with cattle movement databases and wildlife surveillance
  - A powerful tool for investigating bovine TB source, maintenance and spread
- Unique and valuable insight into current TB epidemic

# Conclusions - host

- Significant and exploitable genetic variation exists in cattle in response to *M. bovis* infection
- Both the ***host*** and ***pathogen*** are sources of genetic variation which may influence the outcome of exposure to bTB
- Several interesting bTB phenotypes
- Advances in genetics and genomics should allow dissection of the host/pathogen interaction
  - Identification of genes (variants) associated with resistance
  - Impact of pathogen type on outcome
- Breeding for enhanced resistance – benefits may accrue quickly
- Should complement existing and future control measures
- Contribute to bTB control

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