STAR-IDAZ
International Research
Consortium on Animal Health

Roadmap Lead Summaries

Disease/pathogen	Bovine tuberculosis					
Roadmap type	Development of Control Strategies					
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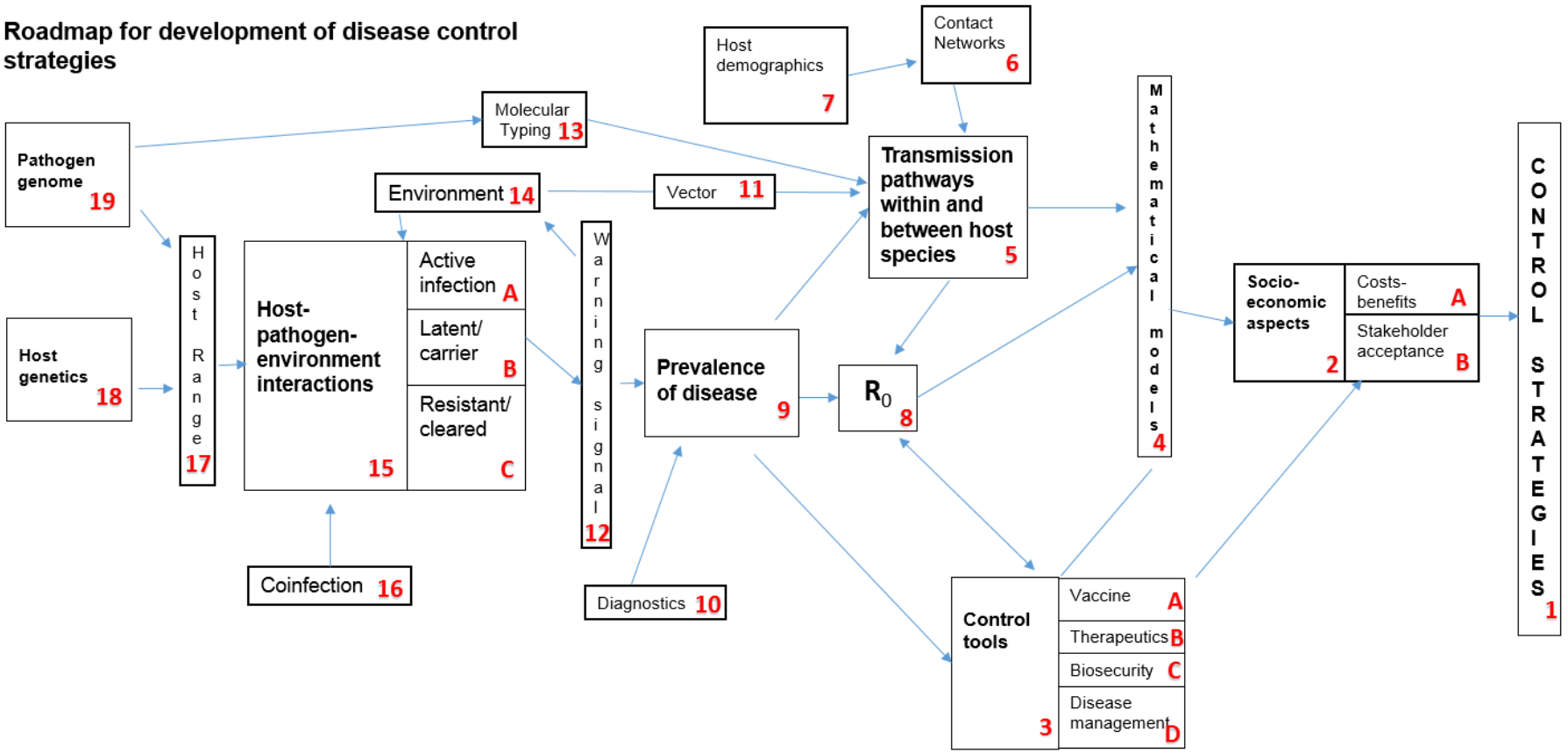
Roadmap for development of disease control strategies
Pathogen genome 19
Host genetics 18
Host Range 17
Molecular Typing 13
Environment 14
Vector 11
Host demographics 7
Contact Networks 6
Transmission pathways within and between host species 5
Host-pathogen-environment interactions 15
Active infection A
Latent/ carrier B
Resistant/ cleared C
Coinfection 16
Warning signal 12
Diagnostics 10
Prevalence of disease 9
R0 8
Mathematical models 4
Socio-economic aspects 2
Costs-benefits A
Stakeholder acceptance B
Control tools 3
Vaccine A
Therapeutics B
Biosecurity C
Disease management D
CONTROL STRATEGIES 1

Lead Summary [1]

Title:	The control of bovine TB progressively leading to disease eradication

Research Question

What are we trying to achieve and why? What is the problem we are trying to solve?

The control and ultimate elimination of TB infection at a herd, regional and national level (in the EU to below threshold).
Prevention of transmission to humans.
Preventing spread of pathogen resulting
from the poor implementation of control measures.
Manage and limit the within- and between-country trade implications of having TB.
Limit the impact of TB on affected wildlife.
Limit massive cattle herd culling

Challenge(s)

What are the scientific and technological challenges (knowledge gaps needing to be addressed)?

Sensitive detection and elimination of infected and pathogen-shedding animals; current tests lack sensitivity; current knowledge of different TB disease status in cattle is limited
Prevention of spread through immunisation, elimination of Mb shedders culling at risk to transmit and improved biosecurity.
Knowledge outreach – evidence of misinformation.
Spillover/spillback involving other livestock, wildlife, and on occasion humans.
Environmental survival to at least some extent.

Evidence supporting both direct and indirect transmission routes but context dependent.
Challenging to obtain compliance with biosecurity measures – difficult and expensive to undertake research to provide evidence of value.

Prevention of infection requires very strong international collaboration and alignment of approaches – should it be reinforced?
Diversity of local contexts where control needs to be implemented.
Engagement of all stakeholders who determine control strategy inputs (regulators, cattle industry) and are affected by outcomes.
Disease control tends to be managed under statute – creates challenges regarding cost and responsibility sharing.
Consideration of varied restraints/concerns: breeds, value, environment, social concerns, food security, cost, supplies.
Outcome of exposure/infection determined by host factors (including genetic predisposition, inflammatory response etc.), pathogen factors (including dose and route) and “environmental” risks, including concurrent infection(s), malnutrition, pregnancy, stress, reservoirs for Mb survival (water, amoebae) etc.
Current immunological tests index prior “exposure”, not necessarily infection and infectivity.

Solution Routes

What approaches could/should be taken to address the research question?

Probably no single "magic bullet" for TB control; requires "marginal gains" and a package of control measures across all relevant sources.
Routine, sensitive testing to pick up infected animals before transmission occurs. Prevention is better than cure – important to keep TB out of herd – difficult to remove.
Reduction of spread through reduced susceptibility (immunisation and/or genetic selection refer).
Reduction of spread through improved biosecurity.
Owner cooperation through establishing cost and benefits of control.
Risk factor studies in sporadic, recurrent, and persistent TB herds
Identification of shedders to go towards bTB control at the level of the individual and not the herd (limit massive herd culling)
Knowledge outreach – communicate evidence from modelling and transmission dynamics studies.
Consider Cattle Health Certification Standards (or equivalent) certification/accreditation, if available.
Develop robust, repeatable methods to speed up generation of pathogen genomic data for epidemiological inference and source tracing.

Dependencies

What else needs to be done before we can solve this need?

That control strategies are communicated and accepted, cost effective and don't cripple producers.
That the strategy is acceptable to key stakeholders, especially producers.
The availability of sensitive diagnostic tests.
The availability and market authorisation of acceptable, effective DIVA vaccines to prevent infection, progression, and/or the onward transmission of infection.
Encourage stakeholder uptake of genetic/genomic selection to reduce TB susceptibility where available; reassure stakeholders of lack of antagonisms with other desirable breeding goals.
Detailed knowledge of the source of infection and transmission pathways.
Animal-level database recording location, tests, and movements.
Animal level of clinical status and Mb shedding risk
Detailed maps of farm locations and fragmentation, rented grazing etc.

State of the Art

Existing knowledge including successes and failures

Projects

What activities are planned or underway?

Lead Summary [2]

Title:	Socio-economics

Research Question

What are we trying to achieve and why? What is the problem we are trying to solve?

How can effective guidelines and control measures be designed that are practical and accepted by the farmer in different local contexts?

Challenge(s)

What are the scientific and technological challenges (knowledge gaps needing to be addressed)?

Understand the risk factors associated with sporadic, recurrent, and persistent TB herds.
Communicate evidence from modelling and transmission dynamics studies.
Counter misinformation and confirmation bias from full spectrum of stakeholders.
Understanding drivers and reasons for cattle movement patterns.
Understanding farmer attitudes to control measures i.e., biosecurity, cattle vaccination, wildlife vaccination, genetics etc. including vaccination.

Solution Routes

What approaches could/should be taken to address the research question?

Social (behavioural) sciences studies to understand human behaviours and produce applicable guidelines that could reduce bTB spread and to describe level of acceptance/compliance of various measures. Monitor impact of interventions.
Human-animal interface studies at critical sites, including social and behavioural sciences

Dependencies

What else needs to be done before we can solve this need?

State of the Art

Existing knowledge including successes and failures

Projects

What activities are planned or underway?

Lead Summary [2A]

Title:	Cost and benefit

Research Question

What are we trying to achieve and why? What is the problem we are trying to solve?

To establish the extent and where the burden of cost lies and who would benefit in any control strategy at a farm, regional or national level.

Challenge(s)

What are the scientific and technological challenges (knowledge gaps needing to be addressed)?

Establishing the full cost of disease to farmers.
Establishing the full cost of disease to government and tax payers.
Establishing the full cost of the various control strategies, including interventions in wildlife; model and cost control options.
Establishing the cost resulting from human infections with *M. bovis* and who are most at risk.
Establish the real or potential impact on local, national, and international trade.

Solution Routes

What approaches could/should be taken to address the research question?

Cost of diagnostic surveillance compared to stamping out.
Compare (model) cost and outcome scenarios with and without wildlife control (selective culling, non-selective culling, vaccination), cattle vaccination, genetic selection etc.

Dependencies

What else needs to be done before we can solve this need?

Properly list and describe all options and make sure to have the right methodology to assess the costs

State of the Art

Existing knowledge including successes and failures

Projects

What activities are planned or underway?

Lead Summary [2B]

Title:	Stakeholder acceptability

Research Question

What are we trying to achieve and why? What is the problem we are trying to solve?

Management interventions often require changing human behaviours in stakeholders and regulators. Despite progress in epidemiological science, desirable disease management outcomes often remain unachieved; barriers to disease control or elimination are often social and political, as opposed to scientific.
Successful implementation of a control strategy depends on the cooperation of livestock producers.
Acceptance by the general public towards infection control measures in cattle and potentially wildlife, and cattle vaccination policy etc.

What methods prevent stigmatization and have ease of adoption?
Knowledge outreach from trusted experts; challenge misinformation and confirmation bias.
Stakeholders can understand the evidence and logic for behaviour change but tend to resist changing traditional behaviours (eg. risk-based trading, informed purchase etc.)
What are the barriers to uptake of “no regrets” biosecurity interventions etc.?

Challenge(s)

What are the scientific and technological challenges (knowledge gaps needing to be addressed)?

Lack of communication between various stakeholders on the best ways to move forward.
Knowledge outreach required from trusted and impartial experts.
Evidence of misinformation and confirmation bias at both extremes of the stakeholder spectrum.
Local suitability/acceptability of the standard solution in different geographical areas; context dependent solutions.
Safe management of contaminated herds/farms.
Challenging and costly to undertake studies that might provide evidence that, for example, enhanced biosecurity would reduce risk.

Solution Routes

What approaches could/should be taken to address the research question?

“Spend to save?” – more severe control now (more sensitive testing) may reduce costs/impacts later – requires modelling.
Strategic use of stamping out.

Bring in local knowledge and acceptable practices to aid acceptance. Establish compensation levels for farmers. Establish and evaluate “focus farms” where best/better practice implemented.

Dependencies

What else needs to be done before we can solve this need?

Knowledge outreach required from trusted and impartial experts. Evidence of misinformation and confirmation bias at both extremes of the spectrum.

State of the Art

Existing knowledge including successes and failures

Projects

What activities are planned or underway?

Lead Summary [3a]

Title:	Vaccine

Research Question

What are we trying to achieve and why? What is the problem we are trying to solve?

The development of a safe, effective vaccine against bTB, reducing R_0 to <1 and allowing vaccinated to be differentiated from infected and doesn't interfere with current diagnostic surveillance.
Development of an effective and safe (including food safety) vaccine for cattle and wildlife.

Challenge(s)

What are the scientific and technological challenges (knowledge gaps needing to be addressed)?

The availability of a safe, effective vaccine, acceptable internationally to Regulators, that doesn't interfere with current cattle statutory diagnostic tests.
Challenge to obtain Market Authorisation and regulatory approval.
Challenge to undertake and interpret sufficiently powered safety and efficacy research field trials.
Challenge to secure ongoing supply of quality-assured vaccine, should field trials support roll out.
Understanding the immune correlates of vaccine protection, vaccine dose, and timing of booster and testing protocols.

Solution Routes

What approaches could/should be taken to address the research question?

See vaccine development roadmap

Dependencies

What else needs to be done before we can solve this need?

Agree and source vaccine candidate, adjuvant and vaccination/booster protocol.
Specify, fund and undertake sufficiently powered, controlled and replicated field studies to establish the safety and efficacy of, for example, BCG vaccine.

State of the Art

Existing knowledge including successes and failures

Projects

What activities are planned or underway?

Lead Summary [3b]

Title:	Therapeutics

Research Question

What are we trying to achieve and why? What is the problem we are trying to solve?

No antibiotic treatment will be allowed in cattle since resistant strains may develop with considerable risk of transmission to humans.

Challenge(s)

What are the scientific and technological challenges (knowledge gaps needing to be addressed)?

Possibilities of developing tools to harness the cattle immune system and achieve pathogen clearance

Solution Routes

What approaches could/should be taken to address the research question?

Dependencies

What else needs to be done before we can solve this need?

State of the Art

Existing knowledge including successes and failures

Projects

What activities are planned or underway?

Lead Summary [3c]

Title:	Biosecurity

Research Question

What are we trying to achieve and why? What is the problem we are trying to solve?

Prevention of disease transmission through improved biosecurity measures.
Prevent introduction of TB into a herd, within-herd amplification and onward transmission to other herds and possibly local wildlife, establishing a local cycle of spillover/spillback.
Accepting that infectious local wildlife represent a well-documented risk, limit potential for introduction by adopting biosecurity measures to minimise exposure.
Accepting that other cattle, including those testing false-negative, pose a risk, take reasonable precautions to limit exposure to that potential source.

Challenge(s)

What are the scientific and technological challenges (knowledge gaps needing to be addressed)?

Identifying cost-effective tools and strategies to improve on farm biosecurity.
Challenging to communicate and "prove" that "common sense" biosecurity measures, such as informed purchase, risk-based trading, wildlife exclusion etc. will reduce risk on a specific farm.
Contextualize and adapt standard biosecurity measures in local settings? Needs likely to be context-dependent and likely to require veterinary input.
Some evidence of misinformation and confirmation bias in stakeholder spectrum.
Education of small-holder farmers (e.g., training on better practices to be used). Consider herd certification or accreditation schemes, if available.
Consider herd-level veterinary risk and management plan approach (VRAMP).
Aging and variable cattle housing systems.
Getting producer and worker engagement to do biosecurity every day.
Showing that there is value in everyday biosecurity.
Biosecurity likely equally relevant to other infectious diseases that transmit on the network of cattle farms, i.e., BVD, Johne's, IBR etc.
Evidence that biosecurity measures can limit the direct/indirect exposure of cattle to wildlife; lacking published evidence that such measures associated with reduced risk.

Solution Routes

What approaches could/should be taken to address the research question?

Establish the effectiveness of a) strict testing and quarantine procedures when animals are introduced into a herd, b) separation of livestock from wildlife – zero grazing, c) control of wildlife reservoirs.
Recognised difficulty in "proving" that biosecurity measures work.
Consider herd certification or accreditation schemes, if available.
Consider adopting and evaluating herd-level veterinary risk and management plan approach (VRAMP).
Might be possible to associate enhanced biosecurity measures with reduced incidence if sufficiently powered, controlled and replicated case-control risk factor epidemiological studies can be undertaken.

Dependencies

What else needs to be done before we can solve this need?

Knowledge of the locally relevant sources of infection and transmission pathways; for example, a small number of published, context-dependent, transmission dynamics studies illustrate the importance of within-herd cattle-cattle spread amplifying the initial introduction of TB.
Establishing the local importance of wildlife reservoirs should inform intervention decisions.

Establishing the survival of the pathogen in the local farmed environment and farm slurry/silage, digestate etc.
Establish the importance of disinfection procedures.

State of the Art

Existing knowledge including successes and failures

Published evidence suggests that the risk from slurry appears relatively low.

Projects

What activities are planned or underway?

Lead Summary [3d]

Title:	Disease management: identification of signatures of clinical status at the individual level

Research Question

What are we trying to achieve and why? What is the problem we are trying to solve?

To develop biosignatures (combination of biomarkers) that could inform on the latent/carrier status of an animal and evaluate the risk of Mb shedding and transmission .
Development of tools to identify animals at risk to transmit for targeted elimination to end massive herd culling

Challenge(s)

What are the scientific and technological challenges (knowledge gaps needing to be addressed)?

We need to understand the different clinical states of TB in cattle akin to what is now established for human TB
We need to develop easy and affordable tools to identify biosignatures
We need to identify a biosignature in circulating blood (the easiest and less invasive procedures for sampling large numbers of animals)

Solution Routes

What approaches could/should be taken to address the research question?

We need to embrace the One Health approach and work together with human TB specialists

Dependencies

What else needs to be done before we can solve this need?

We need to establish robust pipelines with all stakeholders- including bTB surveillance programs- to ensure rigorous and longitudinal follow-up of animals in the field

State of the Art

Existing knowledge including successes and failures

Projects

What activities are planned or underway?

Lead Summary [3]

Title:	

Research Question

What are we trying to achieve and why? What is the problem we are trying to solve?

Challenge(s)

What are the scientific and technological challenges (knowledge gaps needing to be addressed)?

Solution Routes

What approaches could/should be taken to address the research question?

Dependencies

What else needs to be done before we can solve this need?

Biosecurity
Diagnostics
vaccines

State of the Art

Existing knowledge including successes and failures

Projects

What activities are planned or underway?

Lead Summary [4]

Title:	Mathematical models

Research Question

What are we trying to achieve and why? What is the problem we are trying to solve?

Develop mathematical models to simulate the local TB epidemic, to better understand risk factors, longitudinal disease trends and predictions.
Can models be developed to test and cost various interventions?

Challenge(s)

What are the scientific and technological challenges (knowledge gaps needing to be addressed)?

To investigate risk factors that models are sensitive to.
To investigate cattle-only, wildlife-only, and integrated epi-systems.
To understand the distribution of TB cases by herd – often over-dispersed in surveillance data.
To understand the connectivity of cattle herds and the animal networks over which TB spreads.
To estimate the relative role of cattle movements and local wildlife in spillover/spillback events.
To model the implementation of various interventions
To model the cost-benefit of various interventions.
Accessing national databases of animal-level identification, pedigree, test history and movement data.
Integrating such data with geographical information in compliance with GDPR.
Access to data specialists: data analytics, network analysts, veterinary epidemiology, quantitative genetics etc.
Challenge to obtain accurate parameter estimates from experimental models or field data.

Solution Routes

What approaches could/should be taken to address the research question?

Different models required for different analyses, to investigate different questions; for example, agent-based models may be used to simulate transmission of virtual epidemics from estimated variable parameters.
Depending on the reliability of input variables, models are potentially a very powerful means to investigate aspects of TB epidemiology and control intervention options/costs.

Dependencies

What else needs to be done before we can solve this need?

Curate and integrate national animal-level identification, location, pedigree, test history and movement data.

State of the Art *Existing knowledge including successes and failures*

Projects

What activities are planned or underway?

Lead Summary [5]

Title:	Transmission pathways

Research Question

What are we trying to achieve and why? What is the problem we are trying to solve?

To identify the transmission pathway(s) whereby the pathogen gets from infected to susceptible animals – within- and between-species.

Challenge(s)

What are the scientific and technological challenges (knowledge gaps needing to be addressed)?

Establishing how infection spreads between species – domestic animals, wildlife, and humans.
To deploy mathematical model(s) to investigate TB transmission pathways from routinely captured surveillance data.
Under ascertainment of infected host status due to test sensitivity issues; need more sensitive detection of exposure/infection, especially when attempting molecular/genomic epidemiology, including phylodynamics (evolutionary theory plus genome epidemiology).
Molecular and genome epidemiology currently require specialist positive cultures from affected hosts and environmental sampling.
Conventional molecular epidemiology lacks resolution for estimating transmission pathways, other than at a large scale.
Require temporal signal in whole-genome sequencing data i.e., require structured longitudinal sampling and biobank over time.
Model systems or non-invasive ways to study intraspecies transmission

Solution Routes

What approaches could/should be taken to address the research question?

Much has been gleaned about transmission pathways and TB epidemiology from mathematical modelling and molecular epidemiology based on TB test, location, and movement data.
Define specific case studies and ensure maximal sampling of affected hosts etc.
Establishing excretion levels from infected animal of various species including *M. tuberculosis* by people in contact with livestock.
Simulation modelling supported by molecular epidemiology

Dependencies

What else needs to be done before we can solve this need?

Possible to simulate (agent-based) and model transmission from estimated transmission parameters.
Structured, longitudinal pathogen sampling required for investigating transmission pathways using genome epidemiology.

Establishing the infectious dose; mathematical and phylodynamic models can help estimate disease parameters.
Establishing the sources of infection including wildlife reservoirs and humans.
Establishing the contact networks allowing spread within and between herds.

State of the Art

Existing knowledge including successes and failures

Projects

What activities are planned or underway?

Lead Summary [6]

Title:	Contact networks

Research Question

What are we trying to achieve and why? What is the problem we are trying to solve?

Establishing how animals interact with others that might facilitate disease spread.

Challenge(s)

What are the scientific and technological challenges (knowledge gaps needing to be addressed)?

Challenge to compute the cattle movement network from animal-level relational databases.
Several territories have established the ecological home range, population size, and disease status of key wildlife hosts.

Solution Routes

What approaches could/should be taken to address the research question?

Establishing the structure of the dairy and beef industries and movements within components.
Establish stability of movement networks and key nodes; identify the most connected herds and premises.
Simulate TB transmission on established network models; compare model fit to field data.
Establish the movement patterns of wildlife (bait marking, collars, cameras etc.) and their contact with livestock.
Simulation modelling supported by molecular epidemiology.

Dependencies

What else needs to be done before we can solve this need?

Host demographics, both wildlife and livestock, and structure of the livestock industry.

State of the Art

Existing knowledge including successes and failures

Most competent authorities are required to curate animal-level cattle location, identification, pedigree, test, and movement histories, integrated with land parcel mapping.

Projects

What activities are planned or underway?

Lead Summary [7]

Title:	Host demographics – including wildlife hosts

Research Question

What are we trying to achieve and why? What is the problem we are trying to solve?

Obtaining accurate animal-level cattle location, test and movement and farming practice data.
Obtaining accurate wildlife population data, population density, disease prevalence etc. over time and at appropriate scales.
Farm size and size of susceptible wildlife populations will affect pathogen transmission.

Challenge(s)

What are the scientific and technological challenges (knowledge gaps needing to be addressed)?

Cattle data tend to be exceptionally well recorded and can be integrated.
Wildlife population and disease prevalence data are notoriously difficult to estimate over time.

Solution Routes

What approaches could/should be taken to address the research question?

Establishing the structure of the livestock industry and contact network.
Consider wildlife roadkill disease surveillance at broad geographic scales and targeted surveillance in hotspots.
Wildlife population dynamics.
Establish the carrying capacity of an area for a particular wildlife species that acts as a reservoir.

Dependencies

What else needs to be done before we can solve this need?

Establish cattle identification, registration, and movement database; integrate active and passive TB surveillance.
Establish periodic wildlife population estimation and ongoing TB surveillance via, for example, roadkill surveillance.

State of the Art

Existing knowledge including successes and failures

Projects

What activities are planned or underway?

Lead Summary [8]

Title:	R_0 (Reproduction Index)

Research Question

What are we trying to achieve and why? What is the problem we are trying to solve?

Can we estimate and monitor R_0 for infection within the cattle population and different wildlife populations, badgers, wild boar, deer etc.?
What is the R_0 value of intraspecies and interspecies transmission in the various TB epi-systems?
Can we investigate whether control measures impact system R_0?

If the R_0 value is less than 1 then infection will die out within a population. For wildlife populations this will indicate if they are potentially long-term maintenance hosts.
Herd management procedure will impact on transmission within a herd or population.

Challenge(s)

What are the scientific and technological challenges (knowledge gaps needing to be addressed)?

Challenge to obtain animal- or herd-level cattle data and samples if required.
Challenge to obtain animal-level wildlife data or samples if required.
Challenging to undertake sufficiently powered, well controlled and replicated studies.
Expensive transmission experiments to obtain data. Establishing if signal of super-shedder herd and/or animals within livestock and/or wildlife hosts; what is the impact of their removal?

Solution Routes

What approaches could/should be taken to address the research question?

Require detailed herd- or animal-level cattle data and samples over time in sufficiently powered, controlled, and replicated field studies.
Require animal- or group-level wildlife data and samples over time in study areas.
Mathematical/epidemiological modelling, including transmission dynamics (phylodynamics) studies.
Large scale longitudinal studies monitoring natural infection in various species and contexts.

Dependencies

What else needs to be done before we can solve this need?

State of the Art

Existing knowledge including successes and failures

Projects

What activities are planned or underway?

Lead Summary [9]

Title:	Prevalence of disease/infection

Research Question

What are we trying to achieve and why? What is the problem we are trying to solve?

Establish how much infection is in a herd, area or territory (country) as this will influence the level of transmission; what are the trends?
How well are TB control measures and interventions working?
Active and/or passive surveillance in cattle is required at national level depending on prevalence to support trade and ensure food safety.
Establishing the prevalence of TB in wildlife via surveillance.
Establishing the level of *M. bovis* infection in humans.
Establishing the level of *M. tuberculosis* in cattle.
Development of key performance indicators of testers.

Challenge(s)

What are the scientific and technological challenges (knowledge gaps needing to be addressed)?

Performance characteristics of current tests.
Active and passive cattle surveillance tests and lab confirmation, while specific, have well documented variable (moderate) sensitivity and give a measure of apparent prevalence, which underestimates true prevalence.
Challenge to maximise yield of test positives within herds using test combinations.
Wildlife surveillance tests have relatively limited sensitivity.
Testing can be confounded by factors, such as coinfections, non-communicable disease, nutrition, stress etc.
Knowing when best to apply the GIFN test.
Importance of anergic animals.

Solution Routes

What approaches could/should be taken to address the research question?

Regular testing of cattle using diagnostic algorithm i.e., combination of tests based on estimated performance characteristics.
Routine testing of livestock
Capture and testing of wildlife populations or roadkill surveillance.

Dependencies

What else needs to be done before we can solve this need?

The development, evaluation, and validation of more rapid, sensitive, and specific diagnostics.
Understanding and monitoring test performance characteristics (epidemiology) and configuring testing algorithms.

State of the Art *Existing knowledge including successes and failures*

Projects

What activities are planned or underway?

Lead Summary [10]

Title:	Diagnostics

Research Question

What are we trying to achieve and why? What is the problem we are trying to solve?

More sensitive, specific, rapid, easy to use, pen side test(s).
Optimal strategies for early detection.

Challenge(s)

What are the scientific and technological challenges (knowledge gaps needing to be addressed)?

To develop, evaluate and validate more sensitive tests for cattle and wildlife.
Understand performance characteristics of various tests and develop testing algorithms.
Early detection.

Solution Routes

What approaches could/should be taken to address the research question?

See diagnostic test development.

Dependencies

What else needs to be done before we can solve this need?

Engagement of public and private sectors.
Availability of well documented sample biobanks and study farms/areas.
Impartial evaluation and validation of candidate tests.
Modelling potential impacts based on test performance characteristics.

State of the Art

Existing knowledge including successes and failures

Projects

What activities are planned or underway?

Lead Summary [11]

Title:	Vector

Research Question
What are we trying to achieve and why? What is the problem we are trying to solve?

Challenge(s)
What are the scientific and technological challenges (knowledge gaps needing to be addressed)?

Solution Routes
What approaches could/should be taken to address the research question?

Dependencies
What else needs to be done before we can solve this need?

State of the Art
Existing knowledge including successes and failures

Projects
What activities are planned or underway?

Lead Summary [Number]

Title:	

Research Question
What are we trying to achieve and why? What is the problem we are trying to solve?

Challenge(s)
What are the scientific and technological challenges (knowledge gaps needing to be addressed)?

Solution Routes
What approaches could/should be taken to address the research question?

Dependencies
What else needs to be done before we can solve this need?

State of the Art
Existing knowledge including successes and failures

Projects
What activities are planned or underway?

Lead Summary [13]

Title:	Molecular typing

Research Question

What are we trying to achieve and why? What is the problem we are trying to solve?

To understand the evolution and epidemiology of *M. bovis*, surveillance, methods, and data have essentially two applications:

1. To investigate important aspects of bovine TB epidemiology – transmission dynamics, phenotypes using descriptive, analytical and disease modelling studies
2. To inform outbreak investigations, case studies and contact tracings (test, track-and-trace - risk pathway assessment)

Challenge(s)

What are the scientific and technological challenges (knowledge gaps needing to be addressed)?

Due to test and lab confirmation sensitivity issues, not all TB cases yield an isolate for molecular typing.

Challenge to undertake structured surveillance over time, at herd- or animal-level.

Transmission dynamics (phylodynamic) modelling is challenging with such a slowly evolving pathogen.

Wildlife likely to be significantly under sampled compared to cattle.

Currently expensive – SNP-based testing might provide a "triage" and sequencing directly from tissue samples would be desirable.

Solution Routes

What approaches could/should be taken to address the research question?

Whole-genome sequencing provides significantly improved information content, functionality, and resolution.

Much has been learned about TB epidemiology from previous molecular epidemiology tests and studies; need to understand the extent of correlation between tests.

Dependencies

What else needs to be done before we can solve this need?

Most reference labs are proficient in these techniques.

State of the Art

Existing knowledge including successes and failures

Molecular typing provides “Information for action” - tools to help understand bovine TB spread and persistence, to rule TB herds and/or animals in or out of clusters, and evidence to help identify where transmission can be interrupted.
Due to low rates of molecular evolution, outbreak settings can be very genetically homogeneous. So source tracing with molecular data needs to be supported by animal and herd level data on movements, test histories etc.

Projects
What activities are planned or underway?

Lead Summary [14]

Title:	Environment

Research Question

What are we trying to achieve and why? What is the problem we are trying to solve?

Role of environmental and ecological variables in pathogen transmission patterns.

Challenge(s)

What are the scientific and technological challenges (knowledge gaps needing to be addressed)?

Establishing if manure and fomites are a risk.
Investigate whether viable M. bovis detectable in the farmed environment; investigate whether a transmission risk to cattle and/or wildlife.
Challenging to undertake and interpret environmental sampling tests and studies.
Importance of wildlife reservoirs; direct and/or indirect transmission?

Solution Routes

What approaches could/should be taken to address the research question?

Investigate whether (culture, molecular, genomic tests) *M. bovis* survives in manure, slurry, dust, and other samples from the farmed environment.
Identification of farm/environment risk factors by VRAMP on affected farms.
Identify matched case-control study farms.
Include parameter estimates in disease modelling.

Dependencies

What else needs to be done before we can solve this need?

Understand performance characteristics of tests deployed.
Data transparency across regions.
Data collection harmonization so that there is consistency.
Shared data and protocols across countries.
Monitor wildlife at strategic points.

State of the Art

Existing knowledge including successes and failures

Projects

What activities are planned or underway?

Lead Summary [15]

Title:	Host pathogen interaction

Research Question

What are we trying to achieve and why? What is the problem we are trying to solve?

What are the fundamental pathways for host pathogen interaction and disease progression?

Challenge(s)

What are the scientific and technological challenges (knowledge gaps needing to be addressed)?

How does the host handle pathogen exposure?
Are there informative diagnostic biomarkers?
What is the distribution of host responses?
What are the stages of infection post-exposure?
What is the natural history of infection?
What are the correlates of protection (vaccines and diagnostics)?
Is it possible to distinguish immune clearance from infection?
Establishing the relationship between exposure dose and the number of exposure occurrences and risk of infection.
Establishing the relationship between host factors (stress) and infection.
The identity of the factors that determine disease progression rates.
Could certain pathogen lineages be associated with worse disease outcomes – intersection between this and susceptibility could constitute a type of superspreader phenotype?

Solution Routes

What approaches could/should be taken to address the research question?

Omics studies to understand fundamental mechanisms of host-pathogen interaction.
Establishing the infectious dose for various animal species/breeds.
Establishing the differences in susceptibility of different breeds/lines and the rate of progression to active infection/lesion development.
Investigation of disease progression rates in different animal species, breeds and individuals.
Establishing the consequences of multiple exposure.
Modelling pathogenesis and epidemiology in different infections.
Assessing impact of pathogen lineage on disease outcomes like pathology etc through *in vivo* and *in vitro* experimentation.

Dependencies

What else needs to be done before we can solve this need?

Improved understanding of the role of Coinfection

State of the Art *Existing knowledge including successes and failures*

Projects

What activities are planned or underway?'

Lead Summary [15a]

Title:	HPI – Active infection

Research Question

What are we trying to achieve and why? What is the problem we are trying to solve?

What are the fundamental pathways for host pathogen interaction and disease progression?
Excretion levels – when do animals become infectious and do super-shedders exist

Challenge(s)

What are the scientific and technological challenges (knowledge gaps needing to be addressed)?

How does the host handle pathogen exposure?
Are there informative diagnostic biomarkers?
What is the distribution of host responses?
What are the stages of infection post-exposure?
What is the natural history of infection?
What are the correlates of protection (vaccines and diagnostics)?
Is it possible to distinguish immune clearance from infection?

Solution Routes

What approaches could/should be taken to address the research question?

Monitor excretion levels in different infection situations.
Consider experimental infection challenge models, in vitro macrophage, granuloma or organoid models or in vivo models.
Consider investigating time course in experimental infection studies and read outs.
Consider disease epidemiological modelling, including parameters estimated from experimental work.

Dependencies

What else needs to be done before we can solve this need?

State of the Art

Existing knowledge including successes and failures

Projects

What activities are planned or underway?

Lead Summary [15b]

Title:	HPI – latent/carrier: identification of signatures of clinical status at the individual level

Research Question

What are we trying to achieve and why? What is the problem we are trying to solve?

Due to limited test sensitivity and pathogenesis, a proportion of infected animals fail to react to current tests; can we quantify this, and what are the implications of the undiagnosed cases?
Excretion levels – when do animals become infectious?.

To develop biosignatures (combination of biomarkers) that could inform on the latent/carrier status of an animal and evaluate the risk of Mb shedding and transmission .
Development of tools to identify animals at risk to transmit for targeted elimination to end massive herd culling

Challenge(s)

What are the scientific and technological challenges (knowledge gaps needing to be addressed)?

Challenging to distinguish exposure from infection and infectivity.
Immunoreactivity indexes past exposure.
No validated live test to confirm infection in cases testing negative.
Whether *M. bovis* establishes long-term infection and reactivation remains to be demonstrated/quantified.

We need to understand the different clinical states of TB in cattle akin to what is now establish for human TB
We need to develop easy and affordable tools to identify biosignatures
We need to identify a biosignature in circulating blood (the easiest and less invasive procedures for sampling large numbers of animals)

Solution Routes

What approaches could/should be taken to address the research question?

Epidemiological analysis of herds with confirmed TB cases, unconfirmed immunoreactive cases and cases found lesioned at slaughter; investigate secondary attack rate etc.
Molecular epidemiology data suggestive of long-term undisclosed infection in cohort of moved animals.
Monitor excretion levels in different infection situations,
Embrace the One Health approach and work together with human TB specialists

Dependencies

What else needs to be done before we can solve this need?

Comprehensive cattle identification, registration, movement, and test data.

We need to establish robust pipelines with all stakeholders- including bTB surveillance programs- to ensure rigorous and longitudinal follow-up of animals in the field

State of the Art

Existing knowledge including successes and failures

Projects

What activities are planned or underway?

Lead Summary [15c]

Title:	HPI – Resistant/cleared : the role of innate immunity

Research Question

What are we trying to achieve and why? What is the problem we are trying to solve?

As indicated by epidemiological studies of human TB, there must exist animals that are exposed to *M bovis* in herds but do resist/clear infection without signs of exposition (TST neg) . We need to understand the innate immune system of these individuals

We are trying to better define immune resistance (strong link with action 18 Host Genetics)

Challenge(s)

What are the scientific and technological challenges (knowledge gaps needing to be addressed)?

To define the roles of different cells of the immune system in cattle (alveolar macrophages, neutrophils and others) in uptake and clearance of the pathogen)

Solution Routes

What approaches could/should be taken to address the research question?

Embrace the One Health approach and work together with human TB specialists

Dependencies

What else needs to be done before we can solve this need?

Comprehensive cattle identification, registration, movement, and test data.

To establish robust pipelines with all stakeholders-including bTB surveillance programs- to ensure rigorous and longitudinal follow-up of animals in the field

State of the Art

Existing knowledge including successes and failures

Projects

What activities are planned or underway?

Lead Summary [16]

Title:	Coinfection

Research Question

What are we trying to achieve and why? What is the problem we are trying to solve?

Establish the impact of coinfection with other pathogens and its consequence for disease development and pathogen excretion (pathogenesis) and consequences for diagnosis and implementing/interpreting control interventions.

Challenge(s)

What are the scientific and technological challenges (knowledge gaps needing to be addressed)?

Challenging to define pathological or immunological read outs required to test for interactions with coinfections.
Coinfection data may not be as well recorded or extensive as TB data.
Epidemiological study design to test for interactions on coinfections is challenging.
Challenge in having relevant immunology toolbox for various host species.

Solution Routes

What approaches could/should be taken to address the research question?

Establishing the role of co-infections in disease progression.
Classical epidemiological analyses from field data; investigating the impact of coinfection on, for example, diagnosis, response to vaccination etc.
Consider experimental coinfection challenge models, in vitro or in vivo.
Consider investigating timing and order of experimental coinfection studies and read outs.
Consider disease epidemiological modelling, including parameters estimated from experimental work.
Coinfections might drive pathogenesis and immune responses in opposing directions and may contribute to unintended consequences.

Dependencies

What else needs to be done before we can solve this need?

Structured surveillance for coinfecting agents.
Immunological toolbox for hosts species.

State of the Art *Existing knowledge including successes and failures*

Projects

What activities are planned or underway?

Lead Summary [17]

Title:	Host range

Research Question

What are we trying to achieve and why? What is the problem we are trying to solve?

Establish the various hosts that can be infected and act as a source infection for livestock and humans. Determine the molecular underpinning of true host adaptation which determine if an animal can be infected and if it can then disseminate infection.

Challenge(s)

What are the scientific and technological challenges (knowledge gaps needing to be addressed)?

Challenging to establish whether natural or spillover host.
Challenging to undertake structured and sufficiently powered surveillance; diagnostic tools may lack sensitivity.
Challenge to distinguish associated from causal.
Challenge to establish directionality in multi-host and environmental systems.
Likely to find some positives during wildlife surveillance; challenging to determine role and risk posed.

Solution Routes

What approaches could/should be taken to address the research question?

Establish the range of wildlife species that can develop active infections in an area.
Maximise surveillance through targeted sampling, post-mortem and histopathology and consider transmission dynamics studies; likely to be under powered to detect effects in under sampled hosts.

Dependencies

What else needs to be done before we can solve this need?

Literature review.
Consider wildlife surveillance needs and context dependent plausibility as infectious hosts.

State of the Art

Existing knowledge including successes and failures

Good work done over the years showing that *M. bovis* and *M. tuberculosis* exhibit distinct tropisms. *In vivo* infections of cattle with both pathogens have demonstrated different pathologies. *Ex vivo* / *in vitro* infections have demonstrated divergent transcriptomics, methylation patterns and transcriptional regulation of *M. bovis* vs *M. tuberculosis*. Similarly, microscopic pathology differs considerably between both pathogens.

Across *M. bovis* lineages could we expect to see similar heterogeneity in outcomes that might affect epidemiology?

Projects

What activities are planned or underway?

Lead Summary [18]

Title:	Genetic selection

Research Question

What are we trying to achieve and why? What is the problem we are trying to solve?

Is there exploitable (by selective breeding) genetic variation in the risk of TB following exposure?
Can we breed cattle with reduced TB susceptibility that won't interfere with current testing protocols?
Can we breed cattle for lower TB infectivity?
If so, can industry-led genetic indices be developed?

Challenge(s)

What are the scientific and technological challenges (knowledge gaps needing to be addressed)?

Challenging to curate and link cattle pedigree data with cattle TB data at population levels.
Challenging to communicate and encourage adoption of TB genetic indices by industry.
Suspect some misinformation and confirmation bias exists; initial concerns about using TB skin test results as metric investigated and allayed.

Solution Routes

What approaches could/should be taken to address the research question?

Exploitable heritability of TB susceptibility trait has been estimated, initially in Holsteins, followed by other dairy and beef breeds.
Industry-led TB resistance indices are increasingly available and increasingly accurate.
Research continues to investigate "TB infectivity" as a further trait.
Interest in the mechanism(s) by which some cattle resist TB; relevant for diagnostics and vaccines.
Knowledge outreach from trusted and impartial experts.

Establish the importance of early detection and rapid removal of infected animals.

Dependencies

What else needs to be done before we can solve this need?

Ensure ongoing availability and integration of animal-level pedigree and TB data to refresh genetic indices.
Knowledge outreach from trusted and impartial experts.

State of the Art

Existing knowledge including successes and failures

Evidence that taurine cattle (*Bos taurus*) are more susceptible to TB than indicine cattle (*Bos indicus*).
Substantial quantitative genetics evidence that there is heritable and exploitable genetic variation in risk following exposure i.e., there are relatively high risk and low risk sires, depending on the TB status that follows in their daughters.
This facilitated the development of industry-led genetic selection indexes, initially for Holstein cattle but extended to other dairy and beef breeds, allowing cattle to be bred with cumulative reducing TB susceptibility. Further genetic gain is achievable via genomic prediction and no significant "antagonisms" with other desirable traits are evident.
Research is progressing to evaluate "relative infectivity" as a further TB trait.

Projects

What activities are planned or underway?

Lead Summary [19]

Title:	Pathogen genome

Research Question

What are we trying to achieve and why? What is the problem we are trying to solve?

Use genomic information of field isolates to construct phylogenies and answer evolutionary and epidemiological questions.

Unravel transmission dynamics using phylogenetic approaches:tracing of potential sources for outbreaks and determining if an outbreak is 'local' or comes from a more distant source

Alongside these epidemiological uses for genomic data, there is also potential to investigate evolutionary questions. Sequence data can help to infer past population demographics – bottlenecks caused by test and slaughter schemes, expansion of certain lineages etc. Data can also be used to search for signals of selection in the pathogen genomes that might underpin novel phenotypes of epidemiological consequence. The latter is speculative but possible owing to similar findings with *M. tuberculosis.* It is recognised however that searching for signatures of selection in such genetically homogeneous, slowly evolving pathogens as the MTBC is difficult.

Challenge(s)

What are the scientific and technological challenges (knowledge gaps needing to be addressed)?

1 – Collection of representative genomic datasets from multiple affected livestock and wildlife hosts at various geographic scales is necessary to facilitate the transmission dynamics and general disease source tracing applications. This underway in many jurisdictions, but not all. Funding not the same in all countries.

2 – Standardised nomenclature across regions for *M. bovis* as has been achieved for *M. tuberculosis* would facilitate greater utility of datashare between countries.

3 – Standardising wet lab and bioinformatic approaches to ensure comparability between regions would be helpful. There is likely no need to all use the exact same software etc, but some degree of benchmarking through ring trials etc would at least help to ascertain that different labs are producing comparable data.

4 – The low mutation rate of *M. bovis* can make inference of transmission dynamics and disease source tracing difficult – more appreciation of limitations needs to be to the fore. Genomic data needs to be paired with other rich meta-data on animal movement etc to help inform policy makers and vets on the ground.

5 – Reaching a consensus on which methods to use to robustly construct home ranges for phylogeographically localised lineages will aid epidemiological tracing applications.

6 – Similar to above, reaching consensus on SNP cutoffs necessary to define lineages and outbreak clusters should be encouraged.

Solution Routes

What approaches could/should be taken to address the research question?

1 – Efforts to standardise nomenclature should be undertaken across multiple territories. Some efforts in Europe already underway.
2 – Setting up of ring trials for blind sequence comparison to benchmark laboratory and bioinformatic processes.
3 – Mobilise collated data for analyses beyond just epidemiology. Train teams of people to undertake analyses seeking signatures of selection in *M. bovis* genomic data. If candidate loci are identified, design experiments to assess if they have epidemiologically significant phenotypic outcomes. Knowing the latter might have utility in improving eradication schemes.

Dependencies

What else needs to be done before we can solve this need?

Having geographically wide sampling of common *M. bovis* lineages – temporal depth is not such a big concern however.

State of the Art

Existing knowledge including successes and failures

Various updates of the AF2122/97 reference *M. bovis* genome have been completed over the last decade. This reference sequence provides the template against which SNPs are called from raw genome sequence runs of field isolates, enabling the construction of phylogenies which can be used to answer evolutionary and epidemiological questions.

Several studies have used genomic data from outbreaks to inform on transmission dynamics in multi-host systems. Principally the UK and Ireland and French epi-systems involving cattle, badgers, wild boar and deer have been investigated. These phylodynamic approaches are helping to determine which disease transmission routes predominate. They are dependent however on having well sampled epi-systems from multiple hosts over a long period of time. The latter point is crucial to facilitate detection of a temporal signal with which time stamped phylogenies can be produced.

Alongside transmission dynamics, there are more 'everyday' uses for *M. bovis* genomic data - principally in tracing of potential sources for outbreaks and determining if an outbreak is 'local' or comes from a more distant source. The striking phylogeography of *M. bovis* aids this type of work. It is dependent however on having geographically wide sampling of common *M. bovis* lineages – temporal depth is not such a big concern however. It is recognised however that searching for signatures of selection in such genetically homogeneous, slowly evolving pathogens as the MTBC is difficult.

Projects

What activities are planned or underway?

Lead Summary [Number]

Title:	

Research Question

What are we trying to achieve and why? What is the problem we are trying to solve?

Challenge(s)

What are the scientific and technological challenges (knowledge gaps needing to be addressed)?

Solution Routes

What approaches could/should be taken to address the research question?

Dependencies

What else needs to be done before we can solve this need?

State of the Art

Existing knowledge including successes and failures

Projects

What activities are planned or underway?

Lead Summary [Number]

Title:	

Research Question
What are we trying to achieve and why? What is the problem we are trying to solve?

Challenge(s)
What are the scientific and technological challenges (knowledge gaps needing to be addressed)?

Solution Routes
What approaches could/should be taken to address the research question?

Dependencies
What else needs to be done before we can solve this need?

State of the Art
Existing knowledge including successes and failures

Projects
What activities are planned or underway?

Lead Summary [Number]

Title:	

Research Question
What are we trying to achieve and why? What is the problem we are trying to solve?

Challenge(s)
What are the scientific and technological challenges (knowledge gaps needing to be addressed)?

Solution Routes
What approaches could/should be taken to address the research question?

Dependencies
What else needs to be done before we can solve this need?

State of the Art
Existing knowledge including successes and failures

Projects
What activities are planned or underway?

Lead Summary [Number]

Title:	

Research Question
What are we trying to achieve and why? What is the problem we are trying to solve?

Challenge(s)
What are the scientific and technological challenges (knowledge gaps needing to be addressed)?

Solution Routes
What approaches could/should be taken to address the research question?

Dependencies
What else needs to be done before we can solve this need?

State of the Art
Existing knowledge including successes and failures

Projects
What activities are planned or underway?

Lead Summary [Number]

Title:	

Research Question
What are we trying to achieve and why? What is the problem we are trying to solve?

Challenge(s)
What are the scientific and technological challenges (knowledge gaps needing to be addressed)?

Solution Routes
What approaches could/should be taken to address the research question?

Dependencies
What else needs to be done before we can solve this need?

State of the Art
Existing knowledge including successes and failures

Projects
What activities are planned or underway?

Lead Summary [Number]

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State of the Art
Existing knowledge including successes and failures

Projects

What activities are planned or underway?