Human-Relevant Non-Animal Methodologies (NAMs)
Specialised Models Series: **Immune & Infectious Disease**
Infectious Disease Models
Reference 2.2 in Full Scope Roadmap

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Legal & Scientific Imperative for Universities

Section 2A of the Animals (Scientific Procedures) Act 1986 imposes a statutory duty on the Secretary of State to ensure compliance with the principles of replacement, reduction and refinement. The principle of replacement requires that, wherever possible, a scientifically satisfactory method or testing strategy not entailing the use of protected animals must be used instead of a regulated procedure.

Traditional animal models in infectious disease research—particularly rodent models of viral, bacterial, and fungal infections—have significant limitations due to species differences in immune responses, pathogen tropism, disease progression, and host-pathogen interactions. These limitations are evident in the following critical disparities:

- **Host-Pathogen Interaction Mismatch:** Pathogens often exhibit high specificity for human-only receptors or cellular entry mechanisms. Rodent models frequently fail to recapitulate the human-specific tropism required to study the true pathogenesis of emerging viruses (e.g., SARS-CoV-2, Ebola).
- **Immune Response and Cytokine Dysregulation:** Human immune responses to infection, particularly the "cytokine storm" dynamics, are highly distinct from the responses observed in standard rodent models. This mismatch often leads to failure in predicting clinical safety and efficacy during vaccine or therapeutic development.
- **Physiological Pathogen Progression:** The lack of human-like cellular architecture in rodent tissues means that disease progression, viral replication cycles, and bacterial colonisation patterns do not reliably reflect the clinical manifestation of the disease in human patients.
- **High-Severity Experimental Procedures:** Modelling severe human infectious diseases in animals often requires high-containment protocols and procedures that result in significant suffering, providing a major ethical and regulatory impetus to prioritise replacement.

Accelerating the adoption of human-relevant Non-Animal Methodologies (NAMs)—such as organoid infection models, host-pathogen MPS, advanced immune-competent infection platforms, and patient-derived iPSC infection models—is therefore both a scientific imperative and a legal imperative for UK universities.

Landmark Regulatory & Scientific Momentum

Significant progress has been made in the development and application of human infectious disease NAMs:

- **Organoid infection models (gut, lung, brain, kidney, etc.)** have been successfully used to model SARS-CoV-2, influenza, norovirus, rotavirus, and other pathogens. They enable study of viral entry, replication, host responses, and antiviral drug testing in human tissue.

- **Host-pathogen interaction MPS and infection-on-chip platforms** integrate epithelial cells, immune cells, and vascular components to model infection dynamics, immune responses, and pathogen dissemination under controlled conditions.

- **Advanced immune-competent infection models (including lymph node-on-chip and multi-cellular immune–pathogen assembloids)** enable more physiologically relevant testing of vaccines, antivirals, and immunomodulatory therapies.

- **Patient-derived iPSC infection models** allow precision study of genetic susceptibility to infections and patient-specific responses to pathogens and treatments.

- **Multi-organ infection MPS** are being developed to model systemic spread of pathogens and the effects of infection on multiple organ systems.

- **Growing regulatory and industry interest** in these platforms for improving translational success in infectious disease drug and vaccine development, particularly highlighted during the COVID-19 pandemic.

These advancements position organoid and MPS infection models as powerful, increasingly accepted alternatives for infectious disease research.

Core Specialised Human-Relevant Models for Infectious Research

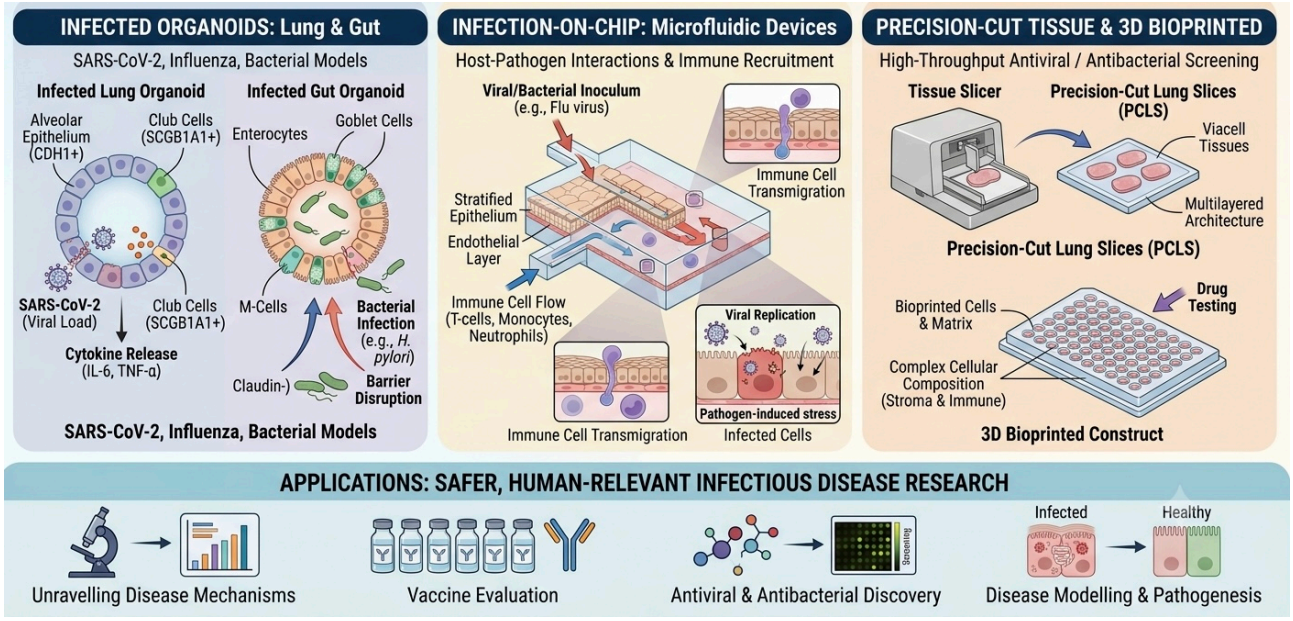

Figure 1: Core Specialised Infectious Disease Models — Infected lung or gut organoids modelling SARS-CoV-2, influenza, or bacterial infections (left), infection-on-chip with immune cells for host-pathogen interaction studies (centre), and precision-cut tissue slices or 3D bioprinted constructs for high-throughput antiviral/antibacterial screening (right) for safer, human-relevant infectious disease research.

Table 1: Advanced Human-Relevant Non-Animal Models (NAMs) for Infection and Host-Pathogen Research

Platform / Model	Description	Key Applications	Benefits for Universities & 3Rs
Organoid Infection Models	3D self-organising structures from human stem/primary cells	Viral/bacterial/fungal replication, host response, tropism	Human-relevant alternative; excellent for training
Host-Pathogen Infection-on-Chip	Microfluidic platforms integrating epithelial/ immune/vascular cells	Modelling infection, immune recruitment, dissemination	Enables dynamic human infection study; strong translation
Advanced Immune-Competent Models	Complex 3D models combining infected cells with immune components	Vaccine development, immunotherapy, immune evasion	Addresses immunodeficient animal model limitations
Patient-Derived iPSC Infection Models	iPSC lines from patients with genetic susceptibilities	Precision mechanistic studies, patient-specific responses	Mutation-specific replacement for transgenic models
Multi-Organ Infection MPS	Interconnected MPS modelling primary and secondary sites	Systemic spread, sepsis modelling, inflammatory response	Enables holistic study of systemic infection
Precision-Cut Tissue Slices	Viable thin sections of human tissues infected ex vivo	Short-term replication studies, host responses, drug efficacy	Preserves native tissue; fast route to human data

Cross-Cutting & Enabling Platforms for Infectious Disease Research

These platforms support multiple infectious disease research areas and are widely applicable across virology, microbiology, vaccine development, host–pathogen interactions, and antimicrobial resistance studies. While specialised models focus on specific pathogens or disease states, these enabling platforms are essential for validating high-maturity NAMs and ensuring they meet the high standards required for regulatory-accepted, “fit-for-purpose” research.
Table 2: Cross-Cutting & Enabling Platforms in Infectious Diseases

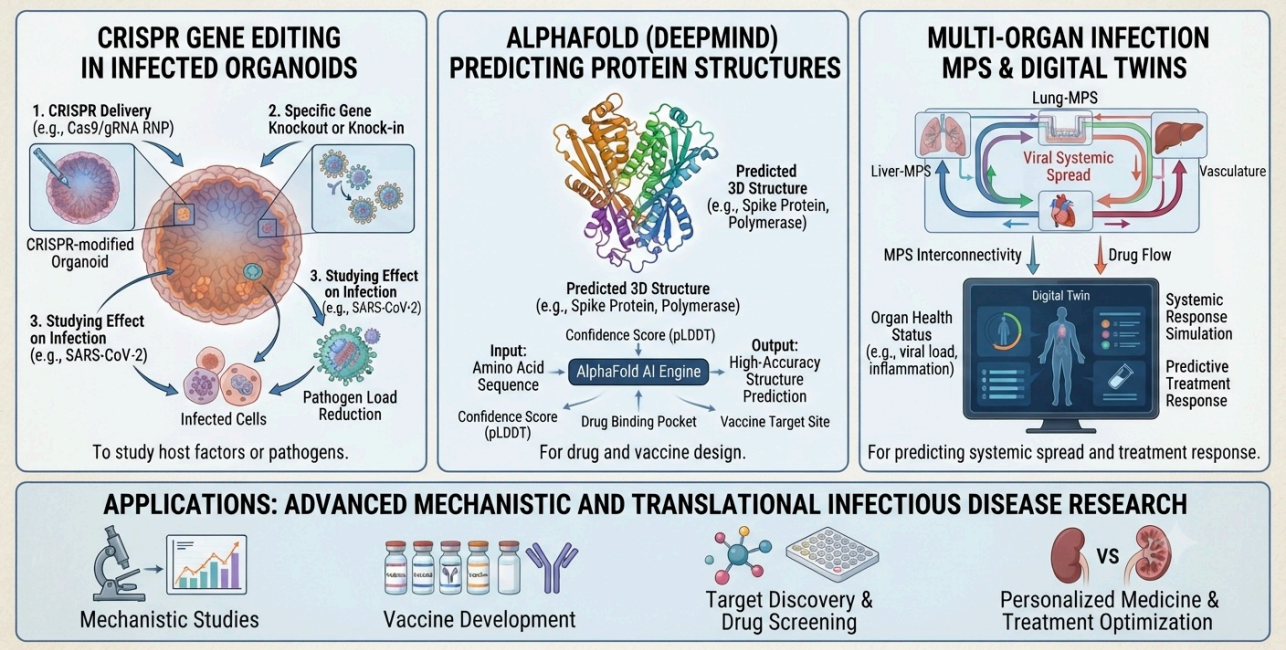

Figure 2: Cross-Cutting & Enabling Platforms for Infectious Disease Research — CRISPR gene editing in infected organoids to study host factors or pathogens (left), AlphaFold (DeepMind) predicting structures of viral or bacterial proteins for drug and vaccine design (centre), and multi-organ infection MPS or digital twins for predicting systemic spread and treatment response (right) for advanced mechanistic and translational infectious disease research.

Table 2: Cross-Cutting & Enabling Platforms in Infectious Disease Research

Enabling Platfor	Description	Strategic Value for 3Rs
CRISPR Functiona Genomics	High-throughput gene editing to identify pathogen dependency factors.	Reduces need for initial animal screen studies.
Computational Structural Biology	AI-driven (e.g., AlphaFold) protein-ligan viral-host interface mapping.	Speeds target discovery, bypassing ea stage animal testing.
Digital Twin Modelling	Virtualised representation of human infe progression and treatment response.	Enables precision dosing and reduces trial sample sizes.
Multi-Omic Integration	Systems-level data aggregation (transcriptomics, proteomics, metabolor from NAMs.	Provides robust Weight-of-Evidence (V regulatory submissions.

Regulatory Software & Strategy Frameworks

Regulatory acceptance of NAMs—referred to as "fit-for-purpose qualification"—is not a one-size-fits-all process. Researchers should utilise the following frameworks to ensure their computational and biological strategies align with the *Animals (Scientific Procedures) Act 1986* and industry best practices:

- **Context of Use (COU) Documentation:** Before deploying models, clearly define the specific scientific question the model is intended to address. This is critical for demonstrating that the NAM is reliable and suitable for its intended regulatory purpose.
- **Technical Characterisation:** Maintain comprehensive Standard Operating Procedures (SOPs) and study plans for both the biological NAM and any software used to analyse its output. This transparency is vital for successful project licence applications.
- **Early Regulatory Engagement:** Leverage institutional or external regulatory support to track "fit-for-purpose" milestones. Early engagement with the Home Office/ASRU is strongly encouraged to test the acceptability of a computational or NAM-based approach before full project submission.
- **Weight-of-Evidence (WoE) Frameworks:** Use integrated digital dashboards to aggregate data from both *in vitro* (NAM) and *in silico* (computational) sources. Building a strong "weight-of evidence" argument is the most effective way to strengthen Replacement justifications when moving away from traditional animal models.

Skills • Training, and Capacity Building

Successful adoption of high-maturity Non-Animal Methodologies (NAMs) requires a strategic shift in workforce development. To ensure the long-term success of the platforms outlined in this series, universities should prioritise the following training initiatives to build institutional capacity:

- **Integrated Infectious Disease Research & Data Science:** Training programmes should bridge the gap between bench-top laboratory biology and computational analysis. Researchers require dual proficiency in 3D culture techniques (such as organoids and infection-on-chip models) and the digital pipelines used to interpret complex imaging, host–pathogen interaction data, and high-throughput antiviral/antimicrobial screening results.
- **Regulatory Competency:** Staff should receive formal training on "Fit-for-Purpose" qualification and the specific regulatory expectations of the Home Office/ASRU. This includes understanding how to document evidence for the 3Rs within formal project licence applications to ensure they meet legal standards.
- **Technological Literacy:** Skills in CRISPR gene editing, organoid infection models, infection-on-chip / microphysiological systems (MPS), immune-competent assembloids, multi-organ infection MPS, and digital twin modelling are increasingly critical for modern infectious disease research. Universities should facilitate internal workshops or establish external partnerships to provide PhD students and postdoctoral fellows with hands-on experience in these specialised tools.
- **Ethics & Translation:** Education should focus on the scientific imperative of human-relevant research, emphasising why NAMs provide more predictive insights for clinical outcomes than traditional rodent models. This fosters a culture of excellence and ethical research design that is fully aligned with modern international standards.

Table 3: Skills • Training and Capacity Building

Capability Domain	Focus Area	Impact on 3Rs/Replacement
Technical	Anaerobic/BSL-2+ Organoid & Chip culture	Direct Replacement of restrictive animal models
Bioinformatics	Host-pathogen transcriptomic integration	Bypasses animal-based tissue sampling
Regulatory	ASPA 1986 Compliance & AWERB	Facilitates faster ASRU approvals
Computational	Infection progression & kinetic modelling	Eliminates invasive animal viral/bacterial load tests

Strategic Note: This investment in human expertise is a key component of a robust, future-proof institutional roadmap, demonstrating to regulators that the institution is committed to the safe and effective operation of high-maturity NAMs.

Clinical Translation Case Studies

Case Study 1: CRISPR-Edited Models in Infection Research Accelerating Antiviral and Vaccine Development

- **Background:** Traditional preclinical testing for infectious diseases often depends on animal models that frequently fail to accurately predict human host–pathogen interactions, immune responses, and drug efficacy.

- **The Paradigm Shift:** CRISPR gene editing combined with infection organoids and immune-competent microphysiological systems has significantly accelerated development. CRISPR-edited organoids and cell models have supported multiple antiviral and vaccine candidates now in clinical trials for viruses such as SARS-CoV-2, influenza, and emerging pathogens.

- **The Methodology:** Researchers use CRISPR to introduce or correct genetic variants in human iPSCs or primary cells, then differentiate them into infection organoids (gut, lung, brain, etc.) or test them in lymph node-on-chip and multi-organ infection MPS. These human-relevant platforms model viral entry, replication, immune evasion, and therapeutic responses, generating robust data for IND submissions and candidate prioritisation.

- **University & Legal Takeaway:** These approaches deliver compelling non-animal evidence for Project Licence applications, demonstrating strong Replacement potential under the 3Rs and Section 2A of the Animals (Scientific Procedures) Act 1986.

Case Study 2: AlphaFold-Enabled Design of Antiviral Proteins and Vaccine Candidates

AI-driven protein structure prediction tools such as AlphaFold are now playing a key role in infectious disease pipelines. AlphaFold has been used to model viral proteins (e.g., SARS-CoV-2 spike variants, NSPs) and host–pathogen interfaces, enabling rapid design of antiviral molecules and improved vaccine immunogens that have advanced into early-phase clinical trials.

Case Study 3: Multi-Organ Infection MPS and Digital Twins Supporting Clinical Development

Pharmaceutical companies and research consortia are increasingly using multi-organ infection MPS (e.g., lung–liver–immune or gut–immune systems) and digital twins to model pathogen dissemination, systemic inflammation, sepsis, and personalised treatment responses. These platforms have supported regulatory submissions and are being integrated into clinical trial design for antiviral therapies and vaccine evaluation, improving translational predictions and reducing reliance on animal models.

Executive Summary & Compliance Dashboard

Executive Summary

Traditional animal models in infectious disease research often fail to recapitulate the complex host-pathogen interactions and human-specific immune responses necessary for effective therapeutic development, leading to high translational failure rates. This roadmap outlines a transition to high-fidelity, human-relevant NAMs (organoid infection models, host-pathogen MPS, and patient-derived iPSC platforms), moving toward a research paradigm that is more accurate, ethically sound, and fully aligned with the ASPA 1986 mandate to transition away from regulated animal procedures.

Compliance Dashboard

Focus Area	Primary Animal Model	NAM Replacement Technology	ASPA 1986 Status
Infectious Disease	Rodent models of viral/bacterial infection	Host-Pathogen MPS & Organoid Systems	High

See Appendix: Animal-Free Matrix for the long term strategic implementation roadmap

Maturity Matrix

Phase 1 (Exploratory): Audit current animal use in infectious disease efficacy and pathogen-tropism studies.

Phase 2 (Pilot): Integrate organoid-based infection protocols and microfluidic infection-on-chip platforms into research workflows.

Phase 3 (Integration): Implement multi-organ infection MPS to model systemic pathogen dissemination and inflammatory host response.

Phase 4 (Standardisation): Replace 100% of high-severity infectious disease animal models with qualified human-relevant NAMs.

Final Compliance Statement

All proposed models satisfy the Section 2A statutory duty of ASPA 1986. By adopting these methodologies, the institution positions itself at the forefront of the global transition toward human-centric, cruelty-free medical science.

Integration Context: Roadmap Conclusion

The modules detailed in this roadmap—from the fundamental immunological and lymphoid models (2.1) to the complex host-pathogen infection systems explored in this section (2.2)—demonstrate that replacement is not a siloed scientific exercise but an integrated institutional strategy. By mapping these specialised NAM-based infection models into a unified regulatory framework, the institution moves decisively toward a standardised, human-centric research paradigm. This systemic integration is the essential prerequisite for fulfilling the ASPA 1986 statutory duty, ensuring all research is scientifically accurate, ethically aligned, and regulatory compliant.

Appendix: Animal-Free Maturity Matrix

Strategic Roadmap for NAM Implementation

This matrix outlines the phased progression required to shift from traditional animal-dependent infectious disease research to human-relevant, cruelty-free science, in accordance with the statutory replacement duties under the Animals (Scientific Procedures) Act 1986.

Phase	Maturity Level	Focus Area	Key NAM Integration & Milestone
Phase 1	Exploratory	Baseline Assessment	Audit of current animal-use procedures; calibration of iPSC/primary cell lines against legacy animal data.
Phase 2	Pilot	Technical Validation	Integration of organoids (gut/lung/brain) into antigen screening and host-pathogen interaction studies.
Phase 3	Integration	Operational Capability	Deployment of Multi-Organ MPS (Microphysiological Systems) and Lymphoid-on-Chip platforms.
Phase 4	Standardisation	Full Replacement	100% replacement of high-severity infection protocols with advanced digital twin modeling and systemic immune-kinetic systems.

Implementation Guidance:

Purpose: This matrix is a self-assessment and planning tool for Principal Investigators and AWERB members to identify capability gaps and prioritise investment.

Progression: Stages are iterative. Teams should use this to identify which dimensions of their research (e.g., cell lineage modelling, tissue crosstalk) require the most urgent advancement.

Evidence Base: Progress through these phases should be supported by a "Weight-of-Evidence" (WoE) dossier, aggregating data from *in silico*, *in vitro*, and *ex vivo* human models to justify the move away from regulated procedures.

Strategic Note: This roadmap is a living instrument. Teams should utilise the "Compliance Dashboard" (refer to Page 7) to track real-time progress against these long-term milestones, ensuring that the institution maintains a future-proof, human-relevant research infrastructure.