Construction of generic roadmaps for the strategic coordination of global research into infectious diseases of animals and zoonoses

Citation for published version:
Entrican, G, Charlier, J, Dalton, L, Messori, S, Sharma, S, Taylor, R & Morrow, A 2020, 'Construction of generic roadmaps for the strategic coordination of global research into infectious diseases of animals and zoonoses', Transboundary and Emerging Diseases. https://doi.org/10.1111/tbed.13821

Digital Object Identifier (DOI):
10.1111/tbed.13821

Link:
Link to publication record in Edinburgh Research Explorer

Document Version:
Publisher's PDF, also known as Version of record

Published In:
Transboundary and Emerging Diseases

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INTRODUCTION

Global livestock systems are experiencing profound changes as a result of anthropogenic pressures including the growing human population, consumption patterns and environmental issues (Herrero & Thornton, 2013). Healthy animals are critical for sustainable livestock farming, and, as systems evolve, there is a growing need for veterinary services, improved disease surveillance and control tools to understand and manage animal and zoonotic disease dynamics (Perry, Grace, & Sones, 2013).

Livestock health is an integral component of the challenges facing global human communities in the 21st century. Approximately 60% of all human infectious diseases and 75% of emerging human infections are caused by pathogens of (wild) animal origin. Hence,
the wildlife–livestock–human interfaces are important drivers for emergence and transmission of zoonotic diseases (Taylor, Latham, & Woolhouse, 2001). Control of animal diseases can therefore have wide-ranging health and socio-economic impacts on humans such as cost-effective provision of food, reductions in water-borne diseases and financial survival of rural populations. The handling and consumption of uncooked contaminated livestock products compromise food safety and pose potential risks of zoonotic disease transmission (van den Brom, de Jong, van Engelen, Heuvelink, & Vellema, 2020). Antimicrobial resistance (AMR) in humans is inter-linked with AMR in farm animals and in the wider environment (Woolhouse, Ward, van Bunnik, & Farrar, 2015). Finally, control of infectious diseases in ruminant livestock can reduce methane emissions by as much as 33% thereby mitigating against climate change (Fox, Smith, Houdijk, Athanasiadou, & Hutchings, 2018). These grand challenges call for solutions requiring co-ordinated, cross-disciplinary approaches involving multiple stakeholders, that needs to cooperate for the collective good (http://www.onehealthglobal.net/). The global Strategic Alliance for Research into Infectious Diseases of Animals and Zoonoses (STAR-IDAZ) International Research Consortium (IRC) aims to coordinate global research for the development of new and improved animal health strategies for priority diseases/infections/issues. STAR-IDAZ IRC currently has 28 partners from 19 countries and is linked to the wider STAR-IDAZ network of over 40 countries. It is governed by an Executive Committee, advised by a Scientific Committee, and is supported by the Secretariat for the International Research Consortium on Animal Health (SIRCAH) which coordinates STAR-IDAZ IRC activities. It also has a number of Working Groups assigned to priority diseases or topics. Details of the structure, aim and objectives of STAR-IDAZ IRC can be found on the website (https://www.star-idaz.net/).

Here, we describe the construction of four generic STAR-IDAZ IRC roadmaps for the development of candidate vaccines, diagnostic tests, therapeutics and disease control strategies. We explain how these generic roadmaps can be applied to develop disease-specific roadmaps that can be ultimately translated into the development of novel tools and strategies for disease control.

## 2 | CONSTRUCTION OF THE GENERIC STAR-IDAZ IRC ROADMAPS

The four generic roadmaps were constructed by considering the desired endpoint, which could be a target product profile (TPP) or a control strategy, and working back through the steps that are essential for reaching that endpoint. This creates a continuous pipeline that encompasses basic and translational scientific research to deliver the goal. Each step on the roadmaps is shown as a distinct node. Each node defines a criterion/theme that is essential for progressing towards the final goal. The generic roadmaps have been designed to be broadly applicable to the STAR-IDAZ IRC priority diseases to be fit for purpose. There are two exceptions to this which are described below.

To avoid the roadmaps becoming overly complicated, criteria/themes were only assigned to nodes if they constituted a major barrier to progression to the final goal. Certain nodes have sub-themes but only where these are inter-related to each other and the overarching theme. Each node is populated with five ‘Lead’ areas that highlight the knowns and unknowns for the issue in question. These are as follows: (1) research question; (2) challenge; (3) solution routes; (4) dependency notes; and (5) state of the art. Each Lead has an over-arching question and/or statement of intent with supporting information that is designed to focus research efforts (Figure 1).

The STAR-IDAZ IRC generic roadmaps can be accessed here: https://roadmaps-public.star-idaz.net/#/home. The roadmaps are interactive and by placing the cursor above a given node, the direction of travel of nodes that feed into that node will appear. The four generic roadmaps are described in the subsections below.

### 2.1 | Roadmap for the development of candidate vaccines

Vaccination is a well-established and sustainable strategy for the prevention and control of infectious diseases and the enormous contribution that vaccines have made to societal health cannot be underestimated. Indeed, they have been described as ‘an achievement of civilization, a human right, our health for the future’ (Rappuoli, [Table 1](#table1)

| Lead Area | Description |
|-----------|-------------|
| 1. Research question: | What are we trying to achieve and why? What is the problem we are trying to solve? |
| 2. Challenge: | What are the scientific and technological challenges (knowledge gaps needing to be addressed)? |
| 3. Solution routes: | What approaches could/should be taken to address the research question? |
| 4. Dependency notes: | What else need to be done before we can solve this need? |
| 5. State-of-the-art: | Existing knowledge including successes and failures |

FIGURE 1 The five Lead areas listed under each node on the generic roadmaps. Each Lead has an overarching question and/or contains information on the current state of knowledge with the collective aim of focusing research efforts towards the desired goal.
Santoni, & Mantovani, 2019). Early vaccines were developed 'empirically' rather than 'rationally', relying on growth of the organism to produce the vaccine antigen (De Gregorio & Rappuoli, 2014). In learning from past success, we must adapt, develop, exploit and apply technological advances to new approaches to vaccinology to deal with evolving threats to global health (Andreano, D’Oro, Rappuoli, & Finco, 2019). There are many criteria that a successful vaccine must meet. While safety and efficacy are foremost, vaccines need to be stable, cost-effective and easy to deliver to the target population. These criteria need to be considered in the TPP and the earlier in the research pipeline that these criteria are identified, the greater the likelihood of developing a vaccine that meets the targeted stakeholder needs.

While there are different types of vaccines (attenuated organisms, inactivated organisms, genetic, subunit and vectored), there are a number of common criteria that need to be considered for all. These are safety, delivery route, delivery platform and efficacy in a challenge model (Figure 2). These four criteria are examples of inter-related sub-themes within a common theme as described above. The choice of vaccine type depends on a number of factors that are not common to all. Thus, the attenuated vaccine nodes are linked to identification of virulence factors node but are not to adjuvants whereas the opposite is true for subunit vaccines. This reflects the relative co-dependencies of these nodes. Likewise, knowledge of protective antigens has different dependencies for different vaccine types. A notable advantage of veterinary vaccine research compared to human is the experimental challenge model to evaluate efficacy. In veterinary species, this is usually conducted in the target species which avoids the translational step from a biomedical model into the target species. This provides opportunities to study immune responses to both vaccination and challenge in the natural host (Entrican, Wattegedera, & Griffiths, 2015).

2.2 | Roadmap for the development of diagnostic tests

The reliable identification of infected animals is a fundamental component of effective disease control strategies. It also underpins many government policies for the movement and trade of animals and animal products (Holm, Hill, Farsang, & Jungback, 2019). Sensitive and specific diagnostic tests not only underpin the generation of reliable epidemiological data and the development of targeted control approaches, they are also a major driver for investment in the development of new vaccines and therapeutics. Effective diagnostic tests need to be accurate and internationally standardized to ensure consistent results in different settings, and there is a recognized need for international harmonization of diagnostic testing for livestock diseases (Holm et al., 2019). The OIE Manual of Diagnostic Tests and Vaccines for Terrestrial Animals (OIE, 2019a) and Manual

![FIGURE 2 Roadmap for the development of candidate vaccines. The interactive vaccine development roadmap can be found at https://roadmaps-public.star-idaz.net/#/34wCF](https://roadmaps-public.star-idaz.net/#/34wCF)
of Diagnostic Tests for Aquatic Animals (OIE, 2019b) provide international standards for diagnostics methods, which are essential for ensuring the control of animal diseases, and the safe trade of animals and their products, at a global level.

The development of new diagnostic tests should take into account their application to ensure that they are fit for purpose with a defined TPP. As for the vaccine roadmap, this is the starting point of the STAR-IDAZ IRC diagnostic tests roadmap and can be derived from the five Lead areas (Figure 3). Diagnostic tests can indicate current and past infection through a combination of pathogen detection and measurement of host immune responses (antigen-specific humoral or cellular immunity). The relative importance of these tests depends on the disease in question and their development relies on different research approaches. Consequently, within the roadmap, ‘organism detection’ and ‘host-pathogen interactions’ are two distinct nodes that link back to the original diagnostic sample. Both nodes have sub-themes to encapsulate different inter-related elements. Although distinct, these themes are not absolutely mutually exclusive; hence, they both link to the node on identification of biomarkers. The importance of this comes to the fore when considering the many endemic diseases of livestock that are subclinical in nature. Infection with such pathogens can result in ‘carrier status’ animals that do not have overt disease but can still transmit infection to other animals and also potentially to humans depending on the pathogen in question and cause production losses in livestock (Tomley & Shirley, 2009).

Knowledge of the host immune response and of biomarkers is also important for development of concerted disease control strategies involving diagnosis and vaccination. The specification of the diagnostic test and the vaccine can influence vaccine deployment in situations where disease surveillance and management policies rely on the ability of diagnostic tests to discriminate between infected and vaccinated animals (DIVA). In such cases, the information in the ‘dependencies’ tab needs to be taken into consideration.

2.3 | Roadmap for the development of therapeutics

While ‘prevention is better than cure’ is a highly desirable goal in disease control, it is not always easy to achieve. Depending on the policies for different livestock diseases, this can mean culling or treatment. Antibiotics and antiparasitics are common therapeutics for control of livestock diseases, and both are used extensively in animal production systems. However, their deployment needs to be carefully managed to maximize impact while minimizing potential adverse effects in animals, humans and on the environment (Vercruysse et al., 2018; Woolhouse et al., 2015). Despite the emergence of AMR and the development of new vaccines that can help to reduce the use of antibiotics (Hoelzer et al., 2018), new therapeutic options (e.g. antimicrobial peptides, phages and immunostimulants) will be needed to preserve animal health and welfare (Seal, Lillehoj, Donovan, & Gay, 2013). The control of parasitic helminths is heavily reliant on therapeutics due to the difficulties in developing effective prophylactic vaccines. However, anthelmintic resistance is making parasite control increasingly more difficult, hence the need to develop new treatments and control strategies (Vercruysse et al., 2018). The STAR-IDAZ IRC roadmap for developing new therapeutics is shown in Figure 4.

Once again, the starting point for development of a novel therapeutic is the TPP and it is identified within the five Leads under the ‘therapeutic’ node. Practical steps in the process involve chemistry, risk assessment methodologies and clinical testing. In turn, these are dependent on more basic knowledge of host-pathogen interactions and mode of action that allow screening of compound libraries for identification of potential target compounds for evaluation in animal models for pharmacokinetics and efficacy (Figure 4).

2.4 | Roadmap for the development of disease control strategies

The roadmaps for candidate vaccines, diagnostics and therapeutics have all been designed with a TPP in mind (Figures 2-4). However, the roadmap for development of disease control strategies has been constructed to provide an over-arching framework that integrates the multiple components of successful disease control strategies. This includes vaccines, diagnostic tests and therapeutics that all feed into the ‘control tools’ node either directly or indirectly. Thus, the
three other generic roadmaps can be directly accessed via the disease control roadmap by clicking on their ascribed nodes (Figure 5).

The roadmap incorporates socio-economic and environmental (including farming system) aspects of disease control. The uptake and...
implementation of control strategies are dependent on the socio-economic factors; hence, these are closely linked on the roadmap and need to be considered at an early stage of development (Charlier & Barkema, 2018). The roadmap takes into account disease surveillance, epidemiology and modelling that are linked back to the basic science that generates knowledge on infection status, host range, pathogen genome and also host genetics. Depending on the disease in question and the tools available (or under development), control strategies also include contact tracing of animals, segregation of infected animals and culling. As for the previous roadmaps, the basic scientific research will be driven by an awareness of the ultimate translational goal, which in this case is a practical and effective disease control strategy.

3 | APPLICATION OF THE GENERIC ROADMAPS TO THE STAR-IDAZ IRC PRIORITY DISEASES

In addition to the generic roadmaps described above, the STAR-IDAZ IRC has been developing roadmaps for its priority diseases. These are at different stages of development, reflected by their relative current representation within the generic roadmaps. The most fully developed disease roadmaps today are those for foot-and-mouth disease (FMD), African swine fever (ASF), porcine reproductive and respiratory syndrome (PRRS), bovine tuberculosis (bTB), helminth infections and brucellosis (https://roadmaps-public.star-idaz.net/#/home). The construction of the disease roadmaps is informed by the gap analyses that are conducted by the various STAR-IDAZ IRC WGs (https://www.star-idaz.net/reports/gap-analysis). Several of these diseases are already a focus of co-ordinated international research alliances such as FMD (Global Foot-and-Mouth Research Alliance [GARA]), ASF (Global African Swine Fever Research Alliance [GARA]), bTB (Global Research Alliance for Bovine Tuberculosis [GrabTB]) and helminths (Livestock Helminth Research Alliance [LiHRA]). These alliances have been heavily involved in the STAR-IDAZ IRC disease-specific roadmaps. Building on the success of this approach, STAR-IDAZ IRC envisages to support the creation of new alliances to perform gaps analyses for the other priority diseases as listed on the consortium website (https://www.star-idaz.net/priority-topic/).

The gap analyses inform on the research priorities for the different diseases. For example, improved detection/identification tools are required for FMD, ASF and helminths; hence, these can be found within the generic diagnostic tests roadmap whereas new/improved vaccines are required for FMD, bTB, ASF, PRRS, helminths and brucellosis and these can all be found within the generic vaccine roadmap. However, FMD, ASF and helminths (but not the others) appear in the generic diagnostic roadmap since improved detection/identification tools are specifically required for these diseases. Only helminths appear under the therapeutic roadmap as novel therapeutics are not desired control options for the other diseases. These differences are encapsulated with the generic control strategies roadmap where the relative importance of the various control tools for a specific disease can be evaluated together.

4 | DISCUSSION

The overall objective of the STAR-IDAZ IRC is to coordinate research at the international level to contribute to new and improved animal health strategies for a number of priority diseases/infections/issues and deliver candidate vaccines, diagnostic tests and therapeutics. The four generic roadmaps described here are designed to focus research efforts on the key gaps in knowledge and capability that need to be addressed to deliver control tools or strategies for any given disease in an animal host. Gap analysis in animal disease control is regularly performed by various organizations or initiatives such as the DISCONTOOLS database where the availability of animal disease control tools and the associated gaps and research needs are mapped and updated for over 50 infectious animal diseases (O’Brien, Scudamore, Charlier, & Delavergne, 2017).

The generic roadmaps described here have evolved as a process of STAR-IDAZ activities. Through global coordination, STAR-IDAZ IRC decided to build further on existing gap analyses by structuring them into research roadmaps. The STAR-IDAZ IRC research roadmaps originated from the idea that by structuring gap analyses of disease control in a logical order, similar to critical path analysis, the key research bottlenecks can be better identified. Moreover, during the construction of the roadmaps and discussions with various disease experts, it became clear that the development of a vaccine/diagnostic/therapeutic/control strategy often requires similar research approaches, independent of the infectious disease considered. This allowed for the generic roadmap concept. The generic roadmaps are used as the backbone to collect and structure disease-specific research needs. Disease-specificity can also be encapsulated by leaving non-relevant nodes in the roadmap blank, which will remain shaded in the interactive webtool. At the core of STAR-IDAZ IRC research roadmaps is the concept that by mapping ongoing research efforts over the roadmaps, unfunded but needed areas of research may become easily identifiable.

The development of tools that systematically identify knowledge and capability gaps are beneficial to both researchers and funders alike as they support the co-ordinated prioritization of research funding. This approach is exemplified by the United

Avoidance of unnecessary duplication of effort in research is dependent on knowledge of existing projects. To this end, funded projects (where known) are listed within the nodes of the roadmaps. A database of almost 200 European-funded animal health and welfare projects that are currently running or have ended in the past two years can be found here: https://database.scar-cwg-ahw.org/.

Details of these research projects are either supplied by the member organizations in the STAR-IDAZ IRC and are added to the database by SIRCAH, or are provided by researchers who have been approved to enter their project details themselves. Researchers are invited to ‘Sign up’ on the Roadmaps page and can then be approved to begin adding their project data.
Kingdom Department of Health and Social Care (DHSC) Vaccine Network (UKVN) which has adopted a systematic approach to prioritize vaccinology research into animal pathogens with human epidemic potential (Noad et al., 2019). The approach took into account the stage of vaccine development for each pathogen which could then be mapped to a pipeline using an interactive tool that identifies bottlenecks in vaccine development with a focus on the TPP. The underlying principle is that the identification of these rate-limiting bottlenecks allows funders to take corrective action by directing their strategies accordingly (Drury, Jolliffe, & Mukhopadhyay, 2019). The DHSC UKVN funding is primarily (but not exclusively) focussed on human vaccine development as there is also recognition that disease control in the animal host will reduce transmission of infection to humans. Consequently, DHSC UKVN has therefore developed an equivalent pipeline tool for veterinary vaccine development (Francis, 2020). This tool shares conceptual similarities with the STAR-IDAZ IRC vaccine roadmap, but differs by incorporating regulatory processes in the pipeline process. The STAR-IDAZ IRC generic roadmaps address fundamental and translational research priorities for animal diseases and consider not only vaccine development, but also the development of accompanying diagnostics, therapeutics and key scientific information that could lead to more effective control strategies.

In conclusion, the four generic STAR-IDAZ IRC roadmaps described here are designed to highlight gaps in knowledge and capability that then focus research activities that address these gaps and advance the control of infectious diseases of animals and zoonoses. These roadmaps should therefore be used by research funders and donors in the development of research calls, as well as by researchers at an early stage of preparing funding proposals to speed up the delivery of innovative control tools against priority animal diseases.

ACKNOWLEDGEMENTS

We thank all members of the STAR-IDAZ IRC Scientific Committee and numerous experts for commenting on the generic roadmap structure during their development. This roadmap approach was developed with the assistance of the innovation agency Viadyamics Limited and uses its Innovation Lead model: https://www.viadyamics.com/staridaz. The interactive roadmap tool was built on the Innovation Knowledge Integration framework, Hypha, designed to help tackle innovation challenges: https://www.hypha.cc/staridaz. The Secretariat for the STAR-IDAZ IRC (SIRCAH) is funded from the European Union’s Horizon 2020 Research and Innovation Programme under Grant Agreement Number 727494.

CONFLICT OF INTEREST

None identified.

ETHICAL APPROVAL

The authors confirm that the ethical policies of the journal, as noted on the journal’s author guidelines page, have been adhered to. No ethical approval was required as this is an article describing the development of online tools with no original research data.

DATA AVAILABILITY STATEMENT

This article does not contain original scientific research data. All of the online tools described are publicly accessible via the hyperlinks provided within the Figure legends.

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How to cite this article: Entrican G, Charlier J, Dalton L, et al.
Construction of generic roadmaps for the strategic coordination of global research into infectious diseases of animals and zoonoses. Transbound. Emerg. Dis. 2020;00:1–8. https://doi.org/10.1111/tbed.13821