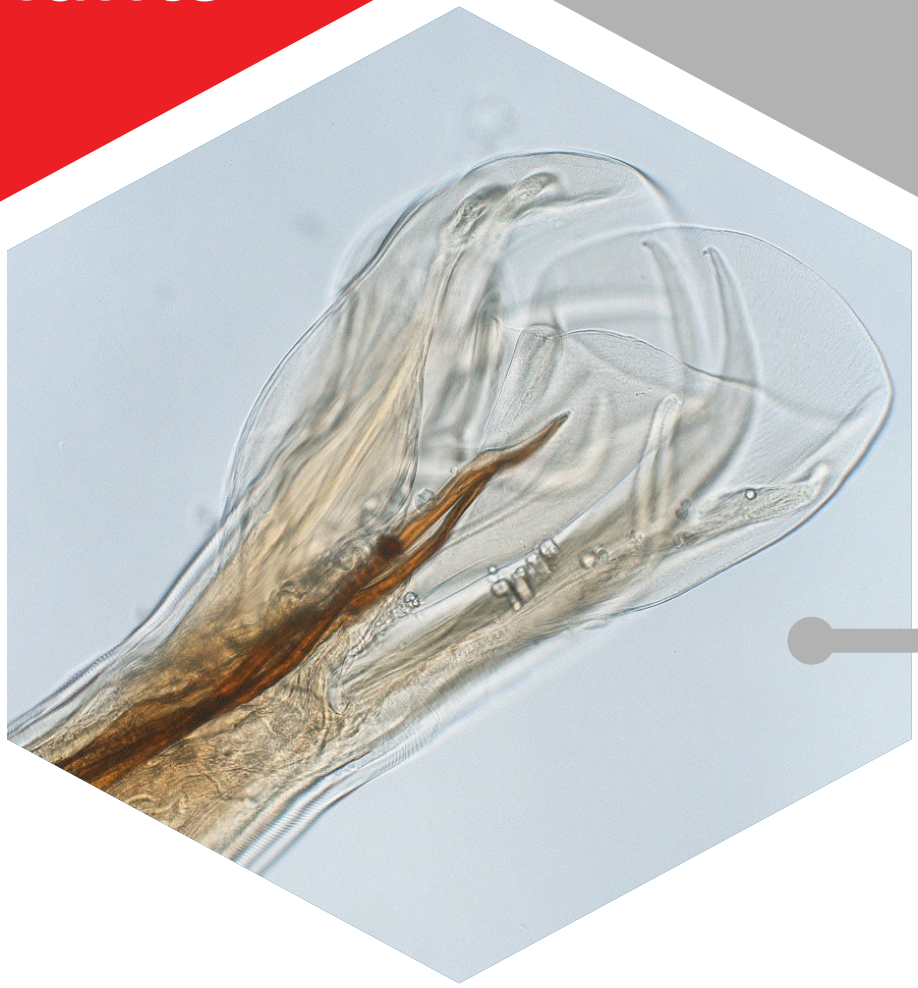
COMBAR
combatting anthelmintic resistance in ruminants

Helminth infection control in farmed ruminants

Key priority research needs

August 2020



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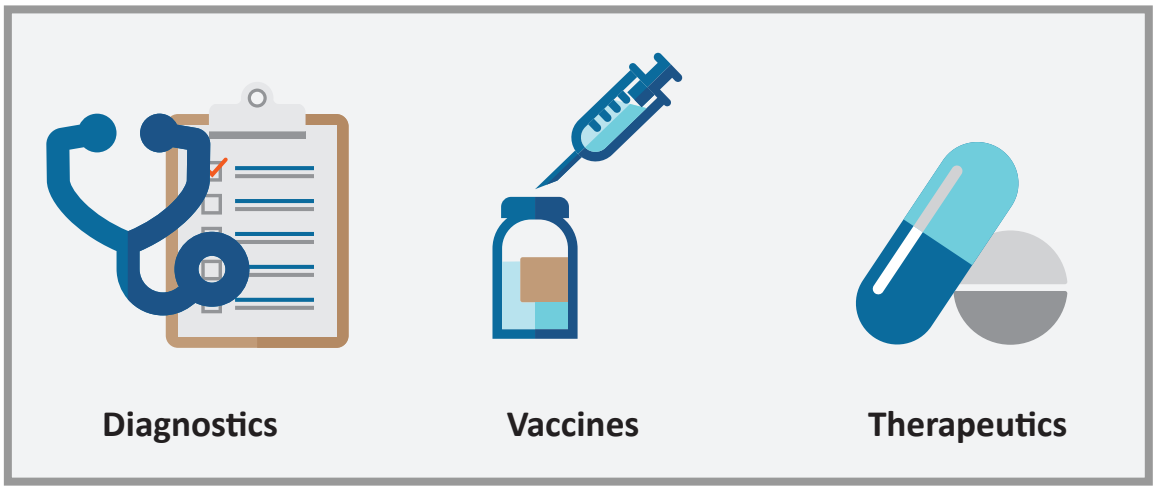
EUROPEAN COOPERATION IN SCIENCE & TECHNOLOGY

LiHRA
Livestock Helminth Research Alliance

STAR-IDAZ
International Research Consortium on Animal Health

Funded by the Horizon 2020 Framework Programme of the European Union

For a better CONTROL of helminth infections we need



Integrated parasite control.

Considering local epidemiology, anthelmintic resistance, climate change and farm management

The future of helminth control

Helminth infections in ruminants are the cause of commonly witnessed, and economically very important, diseases around the world. Essentially, all livestock with outdoor access are exposed to these parasites. Even though in some cases mortality can be high, most often helminth infections are chronic and **affect general health and welfare**, causing, often hidden production losses such as reduced weight gain, milk yield and wool growth. In today's context, helminth control in ruminants has an important role to play in improving sustainable livestock production to meet the increasing human demand for dietary protein and to help reduce greenhouse gas emissions from the livestock sector.

The control of helminths relies on **pasture management practices combined with the efficient use of chemotherapeutics**. However, by way of their inherent genetic diversity, helminths have consistently found ways to circumvent existing control measures. As a consequence, we are currently faced with an escalating spread of parasites that are resistant to available drugs (anthelmintic resistance, AR) and infection patterns that are being altered by changes in climate, land-use and associated farm husbandry practices. The sustainability of grass-based livestock farming, therefore, depends on integrating scientific advances, developed through research, into the adoption of efficient, robust and sustainable parasite control methods.

Working together

The COST Action COMBAR (Combatting Anthelmintic Resistance in Ruminants) is a network of 196 researchers from 31 countries that have agreed to share resources and work together to combat AR in ruminants. It recognizes that an integrated approach to parasite control is the most effective strategy, and, therefore, have engaged with LiHRA and the STAR-IDAZ IRC to develop research roadmaps for improved control tools.

The LiHRA (Livestock Helminth Research Alliance) is a European network of research institutions and SMEs that unites partners with expertise in different disciplines within helminth research. It initiates and coordinates helminth research activities at the international and national levels and identifies areas for future research. LiHRA engages with international experts and partner organisations around the globe.

STAR-IDAZ IRC is an International Research Consortium (IRC) of research funders and programme owners, aiming to maximise funding for coordinated animal health research. 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 priority diseases, infections, and animal health issues. STAR-IDAZ IRC have developed generic research roadmaps, that can be applied to a variety of infectious animal diseases, including helminth infections, for vaccines, diagnostics, therapeutics and disease control strategies.

Economic burden of helminth infections and anthelmintic resistance

COMBAR has conducted a European-wide assessment of the economic burden of gastrointestinal nematodes, the common liver fluke, and bovine lungworm infections to the ruminant livestock industry (Charlier *et al*., in press). The combined annual cost [low estimate-high estimate] of the three helminth infections in 18 participating countries was estimated at **€ 1.8 billion** [€ 1.0 - 2.7 billion]. Eighty-one percent of this cost was due to lost production and 19% was attributed to treatment costs. The cost of gastrointestinal nematode infections with resistance against macrocyclic lactones was estimated to be **€ 38 million** [€ 11 – 87 million] annually. The costs were largest in the dairy cattle sector, followed by the beef cattle, dairy sheep, meat sheep and dairy goat sectors. The current known investment into research on helminth control, by the public sector within Europe, is 0.16 % of the estimated annual costs for the parasitic diseases considered. Our data suggests that the costs of enzootic helminth

infections in ruminants, that occur at high prevalence annually, are similar to or higher than those of severe epizootic disease outbreaks. This initial assessment can be used to inform decision making in research and policy to mitigate the negative impacts of helminth infections and anthelmintic resistance in Europe, and provide a baseline against which future changes can be measured.

Research roadmaps

The three organisations united forces to construct six research roadmaps for the control of gastrointestinal nematode (GIN) and liver fluke infections in ruminants. The roadmaps show the steps and dependencies that need to be addressed by research to develop solutions, and help to show gaps in the knowledge. The six full documents can be accessed via the STAR-IDAZ IRC website:


Helminths: Development of diagnostic tests


Helminths: Development of therapeutics


Nematodes: Development of candidate vaccines


Liverfluke: Development of candidate vaccines


Nematodes: Development of control strategies


Liver fluke: Development of control strategies

The key priorities that we have deducted from the roadmaps are:

Improving diagnostic tools

The methods used for diagnosing and monitoring nematode infections, including assessing drug efficacy, have changed little over the past decades. Current diagnostics typically involve performing faecal egg counts to measure infection intensity, occasionally followed by faecal culture with species identification confirmed by larval morphology/morphometric analysis or by conventional/real-time PCR/sequencing. These approaches are time-consuming, expensive and typically 'low-throughput' in nature, and so are not routinely used in veterinary practice.

Molecular tests for detecting anthelmintic resistance against all major drug classes in the helminth species of importance are urgently needed to inform sustainable control approaches. This requires improving reference genomes for the major helminth species, applying population and functional genomics approaches to identify and validate resistance mutations as diagnostic markers and developing appropriate molecular diagnostic platforms to allow flexible and affordable molecular based diagnostic tests.

A second cross-cutting priority for diagnostic tools is the development of **pen- side tests and associated decision support tools that rapidly inform on the levels of infection and morbidity**. This includes development of scalable, parasite detection using artificial intelligence for automated counting of parasitic elements and research towards establishing biomarkers and their link with parasite infection and health outcomes.

Improved therapeutic responses

Since the 1960's the control of helminth infections in livestock has relied on anthelmintics. Despite progress in the development of parasite vaccines and other novel control methods, anthelmintics will remain vital for the control of nematode and trematode infections in the foreseeable future, either alone or in combination with other control methods.

To counteract anthelmintic resistance, research on **improved therapeutic response for existing anthelmintics** in livestock animals is needed. Improved therapeutic response can be achieved based on enhanced drug exposure, drug combinations and the use of bioactive natural products.

Novel active pharmaceutical and/or phytochemical ingredients (API) with alternative mode of action and/or expanded therapeutic response against helminth parasites resistant to other available anthelmintic drugs need to be identified. This can be achieved by genomic-assisted drug discovery or other screening-based technologies. The elaboration of a target product profile (TPP) for new API with anthelmintic activity should guide the assessment of the clinical efficacy and safety in the process of development of any potentially new compound. Further epidemiological, genetic and pharmaco-parasitological based research to understand the mechanisms of resistance in different helminth parasites of economic relevance in livestock animals will be critical to define a rational use for any novel API introduced into future helminth control programmes.

Developing vaccines for nematodes and liver fluke

Vaccines against gastrointestinal nematodes and liver fluke have the potential to overcome some of the limitations of control through anthelmintics. However, the only helminth vaccines currently on the market are a live vaccine against *Dictyocaulus viviparus* in cattle and a subunit vaccine for *Haemonchus contortus* in sheep. Experimental vaccines show considerable variability in the induced immune responses between individual animals. Moreover, highest efficacies are achieved with native antigens and there has been little success so far with single recombinant vaccine antigens, expressed in conventional expression systems.

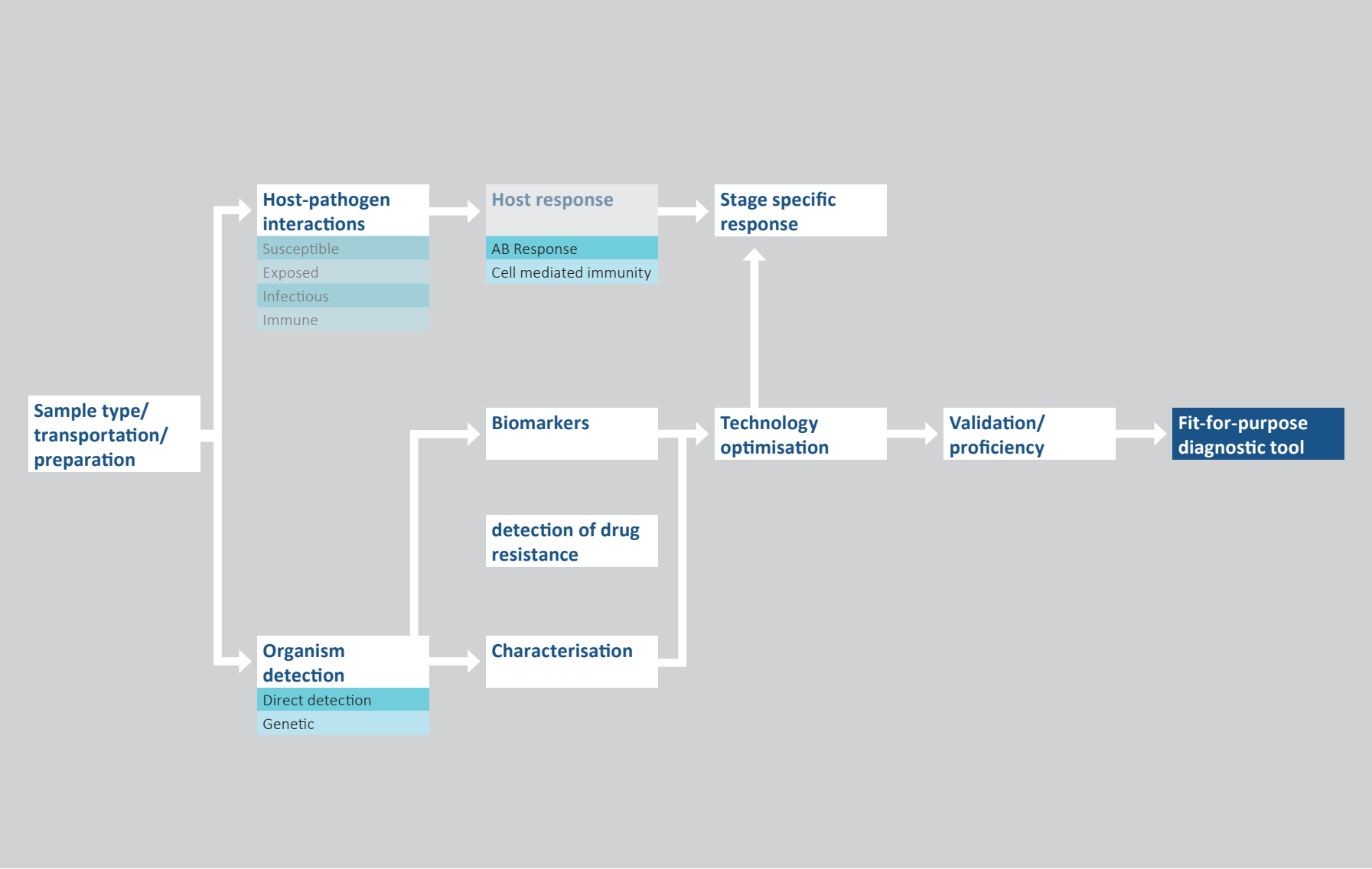
There is need **for improved knowledge of the immune mechanisms associated with natural and vaccine-induced protection**. Both for nematodes and trematodes studies of host transcriptomic responses to infection and identification of protective immune responses (from antigen recognition up to effector responses), including why some animals respond well and others do not, are needed to inform strategies for antigen delivery and adjuvant selection.

Further support is needed to develop **flexible, modifiable expression systems for various antigen's conformations and secondary modifications** (e.g. glycosylation). Synthetic biology studies can help us to understand glycosylation pathways in parasitic helminths, and the resultant glycoproteins expressed.

Rational integration of future control practices

The development of future control practices for helminth infections in livestock may require the **establishment of regional/national/international reference laboratories**. These would carry out the identification, production and preservation of anthelmintic susceptible and resistant isolates, facilitate experimental studies on different control approaches and help in the development of standardised guidelines to test and evaluate complementary control approaches. The future control of helminths will be based on anthelmintics complemented with other control options including pasture management, vaccines, bio-active forages and breeding for resistance approaches. This will require **improved risk assessments and decision support tools** including spatial modelling, big data and sensor approaches for the locally adapted, targeted and integrated use of different control methods. Socio-economic studies are needed to define optimum control methods under different scales, geographies and production systems to ensure acceptable and sustainable novel anthelmintic control approaches.

Helminths: Development of diagnostic tests



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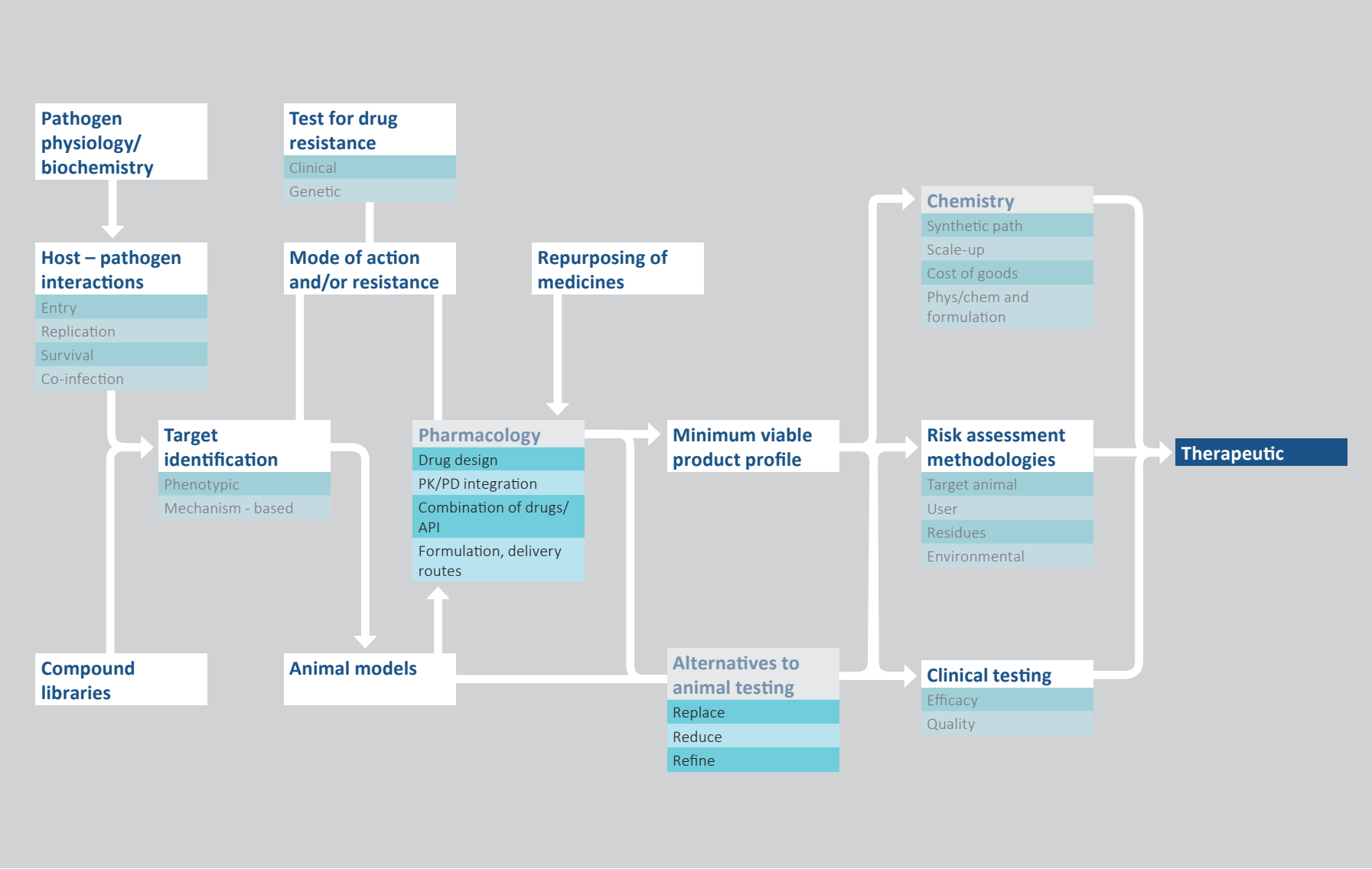
Helminths: Development of therapeutics



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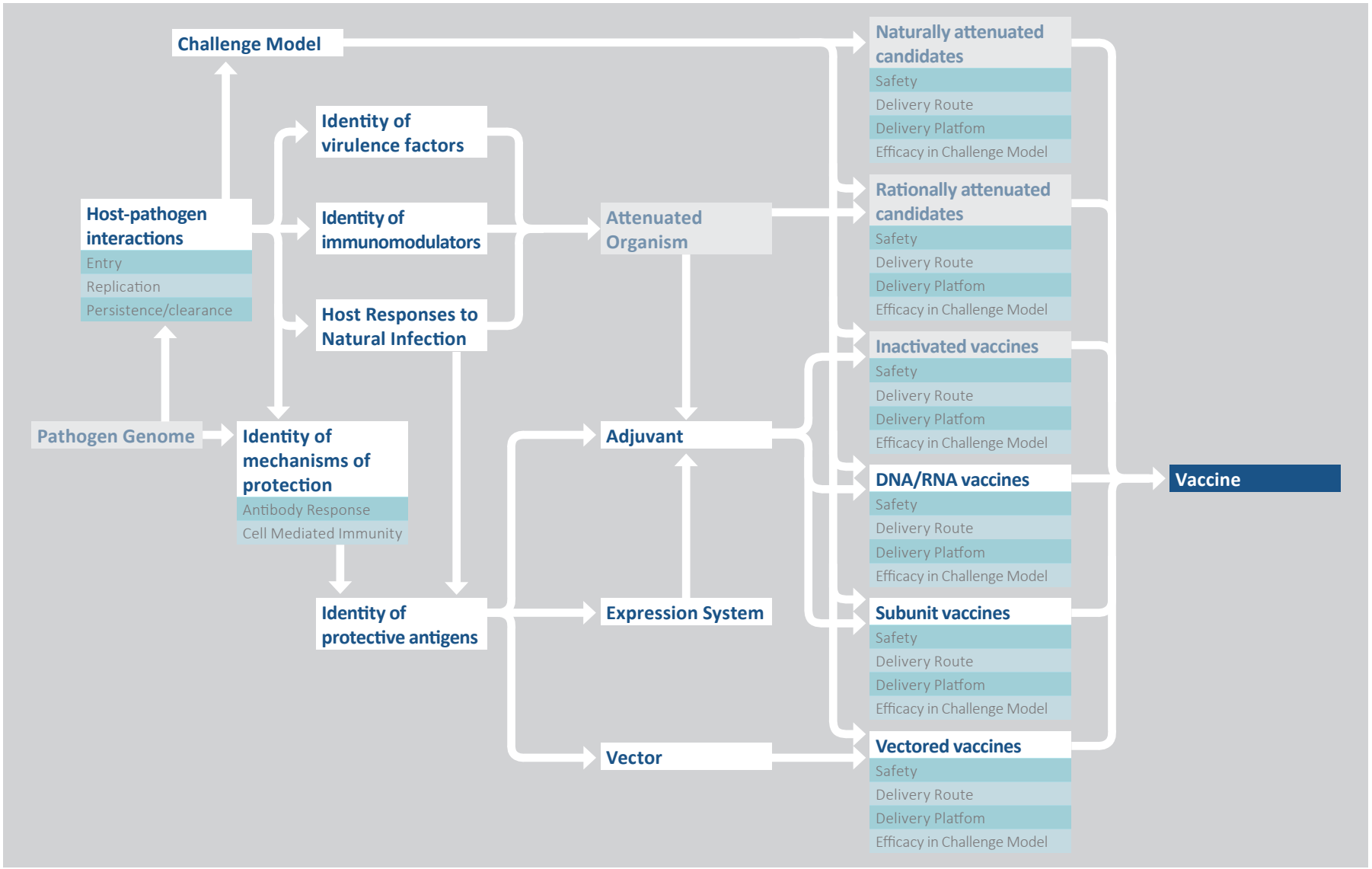
Nematodes: Development of candidate vaccines



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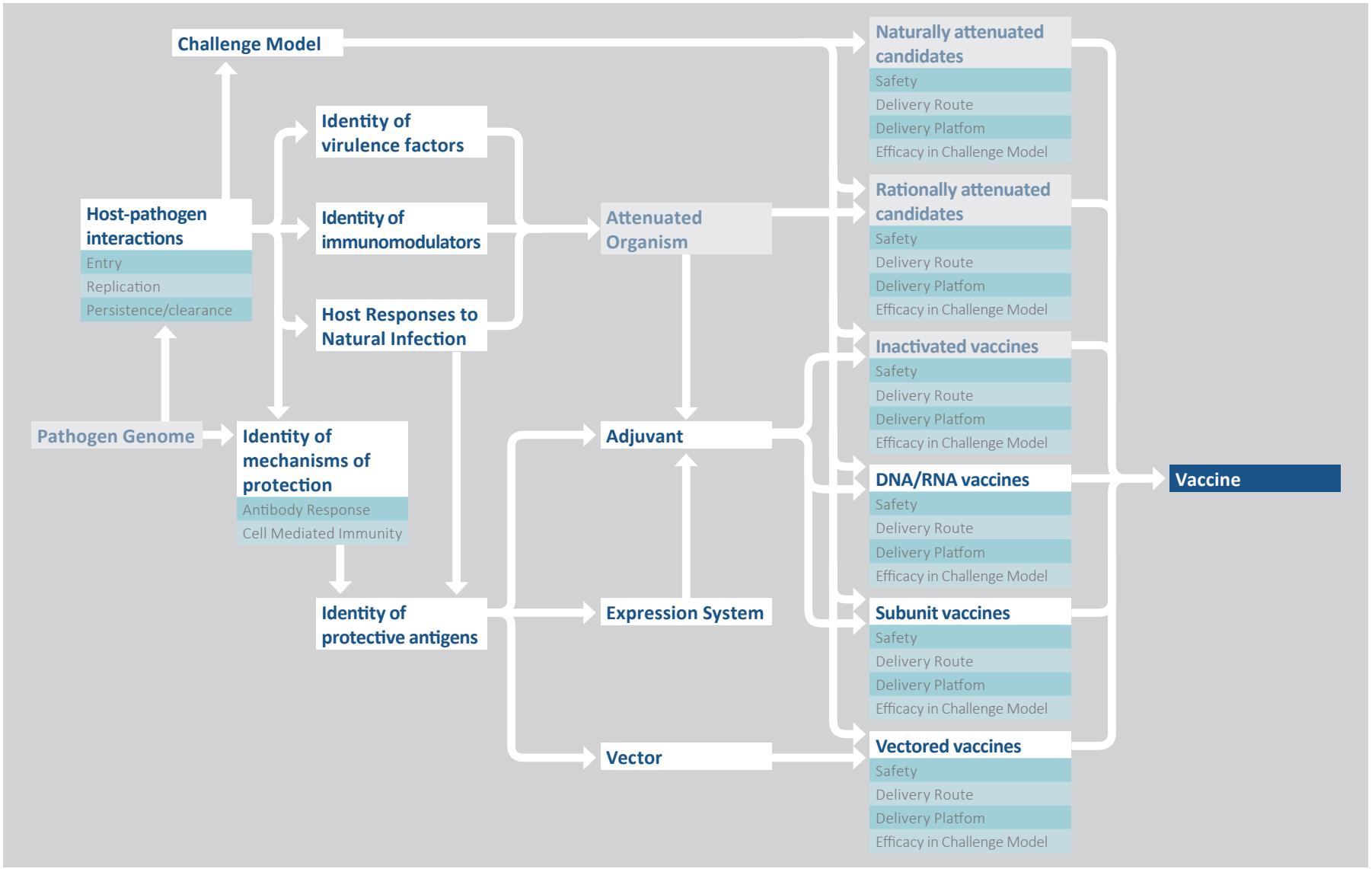
Liver Fluke: Control strategies



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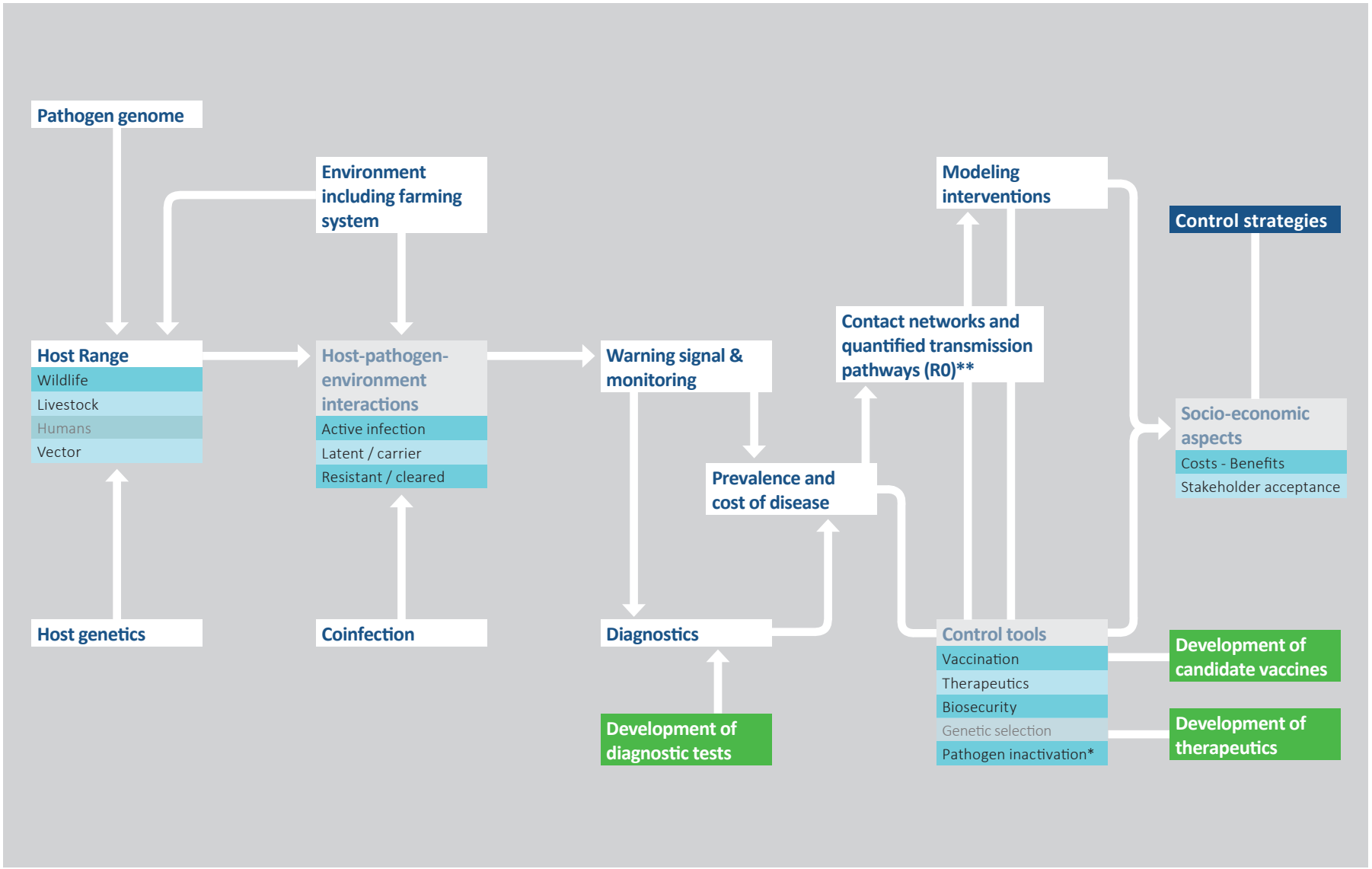
Nematodes: Development of control strategies



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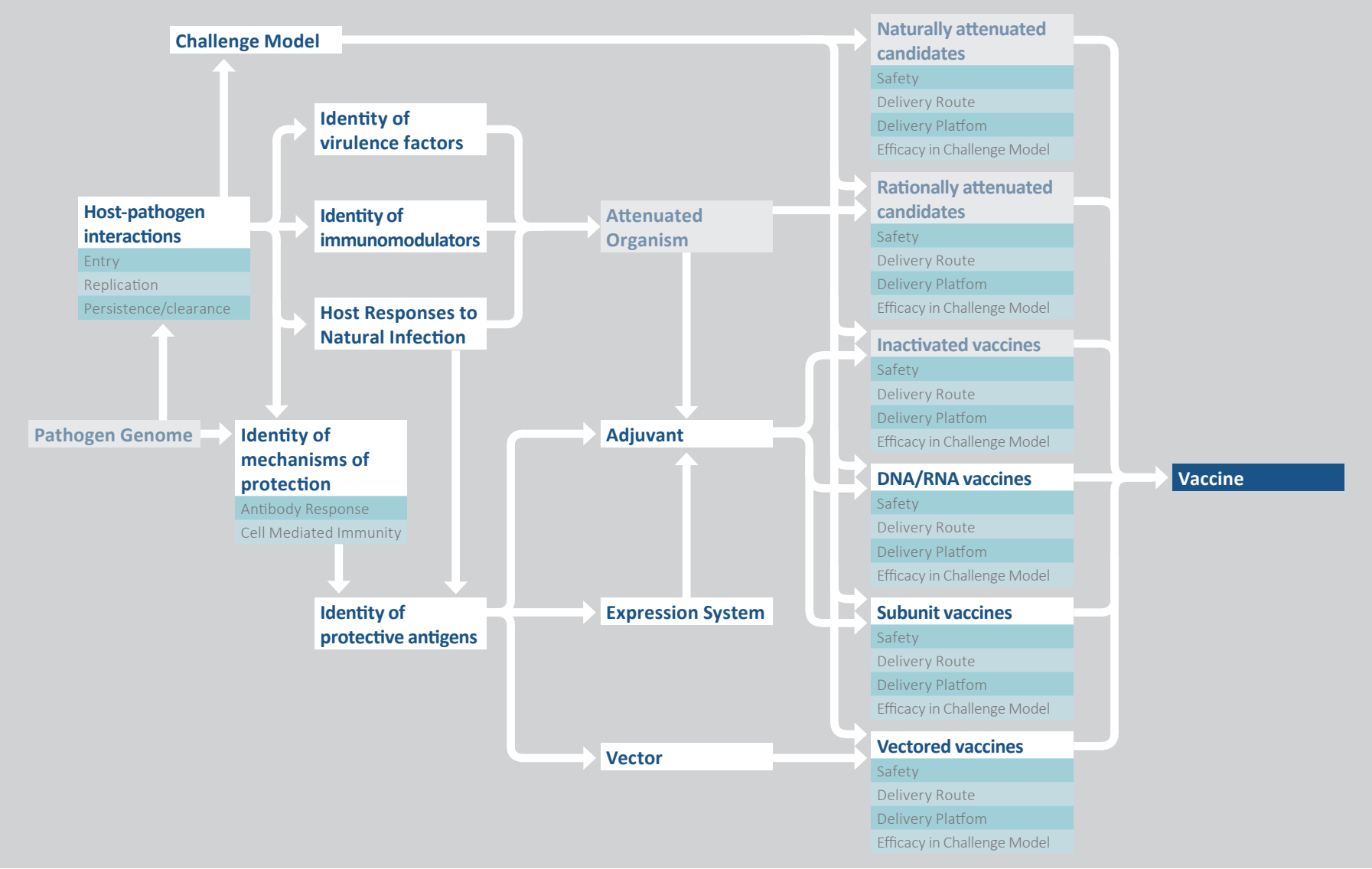
Liver Fluke: Development of candidate vaccines



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