Institution: Heriot-Watt University

Unit of Assessment: UoA B07 - Earth Systems and Environmental Sciences

Title of case study: Vaccines for finfish aquaculture

Period when the underpinning research was undertaken: Jan 2003 – Apr 2020

Details of staff conducting the underpinning research from the submitting unit:

Name(s):	Role(s) (e.g. job title):	Period(s) employed by submitting HEI:
Alistair Lyndon	Associate Professor	Sep 1995 – present
Brian Austin	Professor	Oct 1984 – Jun 2009
Austin Dawn	Research Associate	Sep 1996 – Jul 2020

Period when the claimed impact occurred: 2014 – 2020

Is this case study continued from a case study submitted in 2014? Yes

1. Summary of the impact

Research undertaken by the Fish Pathology Unit (FPU), Institute of Life & Earth Sciences, Heriot-Watt University demonstrated the utility of an existing MSD Animal Health bivalent fish vaccine in conferring immunity to a wide range of novel variants of the targeted disease. This led to increased uptake of this vaccine in the face of growing prevalence of these new disease strains across Europe. This has resulted, since 2014, in protection of almost one third of EU rainbow trout production (approximately 142,000,000 fish p.a., valued at over EUR167,000,000 p.a.) against these diseases.

2. Underpinning research

Novel variant strains of *Yersinia ruckeri,* the pathogenic bacterium causing Enteric Redmouth (ERM) disease in rainbow trout (*Oncorhynchus mykiss*), have been arising across Europe since around 2008, resulting in increasing failures of monovalent vaccines against the original Hagerman strain. Research at the Heriot-Watt University Fish Pathology Unit (HWU FPU) by Dr Dawn Austin, identified and characterised field samples sent by Intervet (predecessor of MSD Animal Health), creating an important culture collection of these new *Y. ruckeri* variant strains [3.1, 3.2]. Intervet-funded research directed by Dr Alistair Lyndon and Prof. Brian Austin led to the description of a range of novel phenotypes within these variants [3.1]. Importantly this research analysed the efficacy of the recently developed bivalent vaccine (AquaVac Relera™) towards these new variants [3.3].

The AquaVac Relera™ vaccine was originally developed to commercialisation by Intervet following earlier research undertaken at HWU FPU [3.4] that identified a novel non-motile biotype of *Y. ruckeri*, designated EX5, which was used as the second antigen in this bivalent vaccine. By 2012, the AquaVac Relera™ vaccine was protecting just over 16% of European rainbow trout production (this estimate was based on 2012 European trout production of 184 500 tonnes (FEAP, 2017), comprising 49 300 tonnes of large trout (assumed 1.5 kg at harvest = 32,800,000 fish) and 135 200 tonnes of portion size trout (300 g (FAO, 2013) = 451,000,000

fish), giving a total of 483,800,000 fish; 78,000,000 priming doses of the AquaVac Relera™ vaccine were supplied to the EU market p.a. [i.e. (78/483.8)*100 = 16.1% of fish were protected]). The novel variant strains of *Y. ruckeri* more closely resembled EX5 than Hagerman strain, thus giving justification for assessment of AquaVac Relera™ as possibly providing cross-protection against them [3.3].

Our research on the new variants successfully demonstrated that the AquaVac Relera™ bivalent vaccine was also effective against the novel emerging strains (Tinsley, 2010) [3.3]. Further work with international collaborators is developing complementary methods to support and enhance vaccine efficacy against *Y. ruckeri* by investigating plant extract feed additives [3.5, 3.6] and novel delivery methods [3.6] a means of augmenting the immune response, with the goal of improving vaccine efficacy and hence enhancing aquatic disease control.

3. References to the research

[3.1] Tinsley, JW, Austin, DA, Lyndon, AR & Austin, B 2011, 'Novel non-motile phenotypes of Yersinia ruckeri suggest expansion of the current clonal complex theory', *Journal of Fish Diseases*, vol. 34, no. 4, pp. 311-317. https://doi.org/10.1111/j.1365-2761.2011.01237.x

[3.2] Austin, B, Austin DA 2016, 'Yersinia ruckeri', in Austin, B, Austin, DA (eds.) *Bacterial fish pathogens: disease of farmed and wild fish*, 6th edn. pp. 368 – 379, Switzerland, Springer. https://doi.org/10.1007/978-3-319-32674-0

[3.3] Tinsley, JW, Lyndon, AR & Austin, B 2011, 'Antigenic and cross-protection studies of biotype 1 and biotype 2 isolates of Yersinia ruckeri in rainbow trout, Oncorhynchus mykiss (Walbaum)', *Journal of Applied Microbiology*, vol. 111, no. 1, pp. 8-16. https://doi.org/10.1111/j.1365-2672.2011.05020.x

[3.4] Austin, DA, Robertson, PAW & Austin, B 2003, 'Recovery of a new biogroup of Yersinia ruckeri from diseased rainbow trout (Oncorhynchus mykiss, Walbaum)', *Systematic and Applied Microbiology*, vol. 26, no. 1, pp. 127-131. https://doi.org/10.1078/072320203322337416

[3.5] Awad, E, Austin, D, Lyndon, A & Awaad, A 2019, 'Possible effect of hala extract (*Pandanus tectorius*) on immune status, anti-tumour and resistance to *Yersinia ruckeri* infection in rainbow trout (*Oncorhynchus mykiss*)', *Fish and Shellfish Immunology*, vol. 87, pp. 620-626. https://doi.org/10.1016/j.fsi.2019.02.012

[3.6] Awad, E, El-Fiqi, A, Austin, D & Lyndon, A 2020, 'Possible effect of lesser galangal (Alpinia officinarum) extracts encapsulated into mesoporous silica nanoparticles on the immune status of rainbow trout (Oncorhynchusn)', *Aquaculture Research*, vol. 51, no. 9, pp. 3674-3684. https://doi.org/10.1111/are.14717

4. Details of the impact

Prior to the present impact, the development of the novel bivalent AquaVac Relera™ vaccine, based on the original research at HWU FPU, protected ~16% of EU trout production (MSDAH, 2017; see section 2).

The subsequent research into cross-protection of the AquaVac Relera™ vaccine against newly emergent disease strains provided clinical efficacy evidence that directly resulted in increased demand for this vaccine in the market, amounting to an average of 142,500,000 doses p.a. between 2014 and 2020 (approximate doubling of supply from the previous period). This represented protection of some 29.3% of European trout in 2016 (most recent available data), despite European trout production numbers remaining stable over the same period [our estimate of 2016 EU trout production = 196,593 tonnes (FEAP, 2017; http://feap.info/wp-content/uploads/2018/05/production-report-2017_web.pdf), comprising 63 239 tonnes of 1.5 kg fish = 42,200,000 fish and 133,354 tonnes of 0.3 kg fish = 444,500,000 fish; total = 486,700,000 fish, cf. 2012 calculation above; % protected = (142.5/486.7)*100 = 29.3%).

Thus, the proportion of European trout protected by this vaccine effectively doubled during the present Case Study period (2014-2020) in response to increasing emergence of variant *Y. ruckeri* strains during the same period (Calvez et al., 2014; Hjeltnes et al., 2019).

The AquaVac Relera™ bivalent vaccine is not only a result of HWU FPU research, but the HWU FPU is also responsible for the batch-release regulatory testing of all batches of the AquaVac Relera™ bivalent vaccine to GMP standards (overseen by the UK Veterinary Medicines Directorate as the releasing authority). This makes HWU FPU directly responsible for the supply of all doses of AquaVac Relera™ vaccine to market.

Beneficiaries of this work include the vaccine production company MSD Animal Health, subsidiary of Merck & Co, Inc, USA (one of the top 3 global pharmaceutical companies). FPU research led to the development of the (MSDAH) Relera™ vaccine against enteric red-mouth (ERM) disease of farmed trout. In particular, a study of cross protection undertaken by FPU examining the efficacy of this vaccine against novel emerging strains of the disease opened up new market opportunities for the company, across Europe between 2014 and 2020 [5.1]. Other beneficiaries also include European trout producers (representing 23.5% of global production in 2016, worth EUR700,000,000; FAO, 2020; European Commission, 2020), European trout processors (reliant on steady fish supply), retailers and consumers (security of food supply).

The farmed fish also gain benefit in terms of their welfare and wellbeing in not being subject to disease and mortality, as do neighbouring wild fish populations resulting from reduced exposure to *Y. ruckeri* originating from farms. There is also a human and environmental benefit from the use of this effective preventative vaccine due to the reduction of antibiotic use to control infections, since in many areas there is limited resistance of *Y. ruckeri* to antibiotics (Calvez et al., 2014), which, in the absence of effective vaccine like AquaVac Relera™, could encourage their increased use with the observed increase in novel variant infections. However, greater recourse to antibiotics in turn increases the risk of antibiotic resistance arising in natural bacterial populations and subsequent horizontal transfer of such resistance to medically relevant microbes (Cabello, 2006). Previous evidence shows that effective vaccination can practically eliminate the use of antibiotics in finfish aquaculture (WHO, 2015; RUMA, 2017).

5. Sources to corroborate the impact

[5.1] Letter from Aquaculture Testing Coordinator, MSD Animal Health (a subsidiary of Merck & Co).

[5.2] Letter from Head of QA, MSD Animal Health (a subsidiary of Merck & Co).

The importance of Oncorhynchus mykiss in aquaculture and the international market:

- European Commission (2020) Fisheries: fish and shellfish species. https://ec.europa.eu/fisheries/marine_species/
- European Commission (2020) EU Fish Market report (p98). https://ec.europa.eu/fisheries/press/eu-fish-market-2020-edition-now-online_en