Institution:	**Heriot-Watt University**
Unit of Assessment:	**7: Earth Systems and Environmental Sciences**
Title of case study:	**Commercialised fish vaccines essential to sustaining fish health in European aquaculture**

1. Summary of the impact (indicative maximum 100 words)

Heriot-Watt University (HWU) does essential research to underpin testing for market release of over 0.5 billion vaccine doses per annum to fish-farms across Europe. These vaccines prevent established and emerging fish diseases in some 25% of trout and 70% of sea bream and bass production in Europe. These diseases would otherwise compromise security and future expansion of important human food supplies. Vaccines are tested for the UK arm of Merck (USA), representing half the company's fish vaccine product range, four of which are in Merck's top 250 products worldwide. Furthermore, research at HWU on MSD Animal Health (MSDAH) Relera™ vaccine efficacy against novel emerging strains of enteric red mouth (ERM) disease opened-up new markets in Eastern and Central Europe.

2. Underpinning research (indicative maximum 500 words)

Pioneering research on vaccine development was undertaken at HWU from the mid-1990s (McIntosh & Austin 1993 [1]; Durbin et al. 1999 [2]) based on characterisation of key fish-pathogenic bacteria including *Aeromonas salmonicida* (causing furunculosis), *Vibrio (Listonella) anguillarum, V. ordalii* (both agents causing vibriosis) and *Yersinia ruckeri* (causing ERM). This research was initiated by **Austin** (whose has left HWU for career advancement) who provided a basis for effective diagnosis and development of appropriate control measures, including vaccines, probiotics and dietary additives.

The research programme continues under the direction of **Lyndon** (Pieters et al. 2008 [3]; Tinsley et al. 2011a [4], 2011b [5]) and Morris (returned in UoA 6). The work of **Lyndon** and Morris in collaboration with Austin and a leading industrial partner (initially Aquaculture Vaccines Ltd, Saffron Waldon, which was subsequently bought by Intervet-Schering-Plough, and then MSD Animal Health (MSDAH; the UK arm of Merck USA) led to the development of new vaccines. The vaccines developed are based on inactivated cultures of pathogen and several have subsequently been developed commercially by the company as the AquaVac™ series of vaccines.

Under **Lyndon's** current direction, HWU is responsible for the market release testing of safety and efficacy of these vaccines. Further research at HWU has involved identification of novel disease strains, characterisation of vaccine performance in relation to emerging infections (Tinsley et al. 2011b), development of novel vaccine antigens (Scott et al. 2013), and immune modulating feed additives. The facilities at HWU have been audited to Good Laboratory Practice (GLP) standards by the Veterinary Medicines Directorate (VMD; 2009), and have subsequently been re-accredited to Good Manufacturing Practice (GMP) standards by the VMD.

3. References to the research (indicative maximum of six references)

The references identified with * are the ones which best indicate the quality of the underpinning research.

[1]* McIntosh D, Austin B (1993) Potential use of vaccines based on cell-wall-defective or -deficient (L-form) Aeromonas salmonicida for the control of furunculosis. Journal of Aquatic Animal Health 5: 254-258. DOI:10.1577/1548-8667(1993)005<0254:PUOVBO>2.3.CO;2

[2]* Durbin M, McIntosh D, Smith PD, Wardle R, Austin B (1999) Immunization against furunculosis in rainbow trout with iron-regulated outer membrane protein vaccines: Relative efficacy of immersion, oral and injection delivery. Journal of Aquatic Animal Health 11: 68-75 DOI:10.1577/1548-8667(1999)011<0068:IAFIRT>2.0.CO;2

[3]* Pieters N, Brunt J, Austin B & Lyndon AR (2008) Efficacy of in-feed probiotics against *Aeromonas bestiarum* and *Ichthyophthirius multifiliis* skin infections in rainbow trout (*Oncorhynchus mykiss*, Walbaum). Journal of Applied Microbiology 105:723-732. DOI:10.1111/j.1365-2672.2008.03817.x

[4] Tinsley JW, Austin DA, Lyndon AR, Austin B (2011a) Novel non-motile phenotypes of Yersinia ruckeri suggests expansion of the current clonal complex theory. *Journal of Fish Diseases* 34:311-317. DOI:10.1111/j.1365-2761.2011.01237.x

[5] Tinsley JW, Lyndon AR, Austin B (2011b) 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 111: 8-16. DOI:10.1111/j.1365-2672.2011.05020.x

[6] Scott, C., Austin, B., Austin, D., Morris, P. (2013). Non-adjuvanted flagellin elicits a non-specific protective immune response in rainbow trout (*Oncorhynchus mykiss*, Walbaum) towards bacterial infections. Vaccine 31: 3262–3267 DOI:10.1016/j.vaccine.2013.05.025

4. Details of the impact (indicative maximum 750 words)

Fish vaccines are essential for maintaining aquaculture production in the face of widespread bacterial diseases, which would otherwise constrain production of an essential human food source. Around 205000 tonnes of rainbow trout and 150000 tonnes of sea bass and bream are produced in the EU annually, worth some 1 billion Euros in total (see EC and FAO reports, in Section 5 below).

The work at HWU directly results in excess of half-a-billion doses of fish vaccines being released to market in Europe each year. This equates to treatment of more than 25% of trout and 70% of sea bass and sea bream produced across Europe each year. The vaccines tested include AquaVac™ ERM, AquaVac™ ERM oral and AquaVac™ Relera (vaccines against ERM of which there were 195 million doses in 2012); AquaVac™ Furovac and AquaVac™ FNMplus (vaccines against furunculosis); AquaVac™ Vibrio injection/immersion, AquaVac™ Vibrio oral (vaccines against vibriosis of which there were 250 million doses in 2012), and AquaVac™ Pastuerella (vaccine against photobacteriosis, of which there were 110 million doses in 2012).

The original research at HWU led directly to the production and subsequent development of commercialised vaccines which are currently in use. For example, in relation to ERM, caused by *Yersinia ruckeri* bacteria, approximately 158 million trout are treated annually with either Relera™ or ERM vaccines released to market as a result of quality assurance undertaken by HWU. New strains of the ERM pathogen were originally identified at HWU, resulting in the development of the improved Relera™ vaccine, and research at HWU showed that this vaccine was effective against a range of emerging strains. This observation has in turn opened-up new markets for the vaccine in eastern and central Europe over the last two years. A senior manager at MSD Animal Health confirmed that HWU studies "*of cross-protection undertaken at HWU examining the efficacy of this vaccine against novel emerging strains of the disease opened-up new market opportunities in Eastern and Central Europe*" [**S1**].

The figure of 25% of European trout being treated with these two vaccines is based on the following data: the European trout production is 205000 tonnes (2007) (European Commission 2012a) worth 580 million Euros, at an average production weight of 300 g (FAO, 2013) representing 600 million trout per aunnum. Trout vaccines (ERM) supplied = 157.5 million fish (60 million priming doses Relera; 97.5 million priming doses ERM vaccine) = approx. 26% of European trout production treated using Relera and ERM vaccines released to market on the basis of testing at HWU.

Others vaccines developed are used in the protection of marine species (sea bass and sea bream) in the Mediterranean against vibriosis and photobacteriosis. A senior co-ordinator from the Schering Plough Animal health confirmed "*the key role which research … at Heriot-Watt University has played in the testing and marketing of several fish vaccines produced by MSDAH, including Relera™, ERM vaccine and several of the Aquavac range of vaccines against vibriosis*" [**S2**]. Sea bream production (85 000 tonnes p.a., mean fish size = 500 g in 2007 (European Commission 2012a)) represents 170 million fish, whilst sea bass production (58000 tonnes per annum, mean fish size = 400g (ibid.)) represents 145 million fish, giving a combined total of 315 million fish per annum worth some 470 million Euros (European Commission 2012a). Thus, up to 231 million of these two species (over 70%) are treated with vaccines derived from research at HWU and made available through market release quality control tests required by regulators also undertaken at

HWU. One of MSD Animal Health's Directors [**S3**] can confirm the importance of HWU research to their global business, especially in relation to salmonids.

The beneficiaries of the vaccine release work conducted at HWU include the vaccine production company (MSDAH) which has derived and developed significant commercial products; European fish farm companies which experience substantially reduced losses to disease; European fish processors the supply stream for which is assured in the absence of disease induced losses; European fish retailers for which the supply chain is more predictable for the same reasons; European fish consumers for whom access to a healthy and popular food is maintained and improved; the fish in terms of improved welfare (reduced suffering from debilitating and fatal disease); and the environment because of reduced use of harmful chemical treatments and antibiotics. The nature of the benefits to humans are in terms of improved food security from trout, sea bream and sea bass; safeguarding of profitability and thus sustainability of the industries producing these fish; reduction of disease reservoirs in aquaculture leading to protection of wild fish populations; and reduction of antibiotic use in fish farms and consequently reduced potential for induction of antibiotic resistance in environmental bacteria.

5. Sources to corroborate the impact (indicative maximum of 10 references)

Contacts for Corroboration

[S1] Senior manager, MSD Animal Health, Milton Keynes, UK
Can corroborate many elements of the Case Study especially the use made of particular HWU studies, particularly those on cross-protection.

[S2] Senior co-ordinator, Schering-Plough Animal Health, Middlesex UK
Can corroborate many elements of the Case Study especially the role of HWU research in underpinning decisions on taking a range of vaccines to market.

[S3] A director, MSD Animal Health, Milton Keynes, UK
Can corroborate many elements of the Case Study especially the role of HWU research in their global business particularly their salmonid vaccines.

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

- European Commission (2012a) Fisheries: fish and shellfish species. http://ec.europa.eu/fisheries/marine_species/index_en.htm
- European Commission (2012b) Trout Oncorhynchus mykiss. Fisheries and aquaculture in Europe 57: 2 pp. http://ec.europa.eu/fisheries/documentation/publications/factsheets-aquaculture-species/trout_en.pdf
- FAO (Food and Agriculture Organisation) (2013) Oncorhynchus mykiss (Walbaum, 1792). Cultured aquatic species information series. www.fao.org/fishery/culturedspecies/Oncorhynchus_mykiss/en