Institution: University of Edinburgh and SRUC, Scotland's Rural College

Unit of Assessment: 6

Title of case study: Bovine Neonatal Pancytopenia (BNP), a newly recognised disease of calves, is caused by colostral transfer of cross-reactive alloantibodies induced in dams by PregSure Bovine Viral Diarrhoea (BVD) vaccine.

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

Impact: Animal Health and Welfare, Economics: The BVD vaccine associated with emergence of BNP was withdrawn from sale.

Significance: BNP cases have been reported worldwide. On affected farms, the case fatality rate is very high, with losses of up to 5% of calves in a herd being reported. Despite the vaccine being withdrawn, cases continue to be found in some calves born to dams that have been historically vaccinated. In addition, reporting has increased due to increased awareness and Zoetis subsidising post-mortem examinations. However, as an indirect measure, the number of cases being diagnosed at post-mortem at SRUC fell by 42% between 2012 and 2013.

Beneficiaries: Livestock Industry, Animal Health Company, Farmers.

Attribution: Work performed by University of Edinburgh (Penny, Morrison, Sargison, Bell) and SRUC (Hosie, Howie, Kerr, Caldow) identified BNP as a new disease entity, elucidated the cause, and developed strategies to reduce the incidence. This also involved a collaboration with the Moredun Research Institute (Willoughby)

Reach: BNP is recognised world-wide (a peak of 4500 cases in 2011) including France, Germany, United Kingdom, Ireland, Netherlands, Belgium, Luxembourg, Italy, and Spain. The disease is unknown in countries which do not vaccinate against BVD (Denmark, Austria, and Switzerland)

2. Underpinning research (indicative maximum 500 words)

In 2009, the University of Edinburgh and SRUC (UoE employment dates: Penny (Senior Lecturer employed 1990-2010), Morrison (Professor of Immunology and Group leader employed 2002-onwards), Sargison (Professor of Farm Animal Medicine, employed 1999-onwards), Bell (Postgraduate 2007-2013)) (SRUC employment dates: Hosie (Group Manager - Veterinary Services employed 1983-onwards), Howie (Veterinary Investigation Officer employed 1993-onwards), Kerr (Veterinary Investigation Officer employed 2006-onwards), Caldow (Veterinary Centre Manager employed 1987-onwards) were the first to describe an unexplained haemorrhagic disease of calves, characterised by profound depletion of blood leukocytes and platelets and named Bovine Neonatal Pancytopenia (BNP) [3.1]. To date BNP has been reported across Europe and in New Zealand, and between March 2009 and February 2011 more than 4,500 confirmed cases of BNP had been reported in Europe. Our subsequent research enabled recognition of this disease as truly novel and characterised the clinical, haematological and pathological findings [3.2]. We contributed to a symposium on the condition held at the European Buiatrics Forum in Marseille in 2009, where it was agreed with European colleagues that the disease was truly novel and that the presentation appeared the same in all countries reporting cases.

Early observations suggested a role for colostrum in the pathogenesis of BNP, and our research at Edinburgh demonstrated that the disease could be prevented by colostrum substitution [3.3]. These findings were subsequently confirmed by an experimental feeding trial conducted in collaboration with the Moredun Research Institute [3.4]. Recent research has demonstrated that serum from cows that have produced BNP calves contains alloreactive antibodies, including high titres against MHC proteins [3.5].

Our demonstration of a link between BNP and administration of a bovine viral diarrhoea vaccine, PregSure, led to withdrawal of this product from the European market in June 2010, on a precautionary basis, and subsequent retraction of marketing authorisation by the European Medicines Authority. An association between BNP and the vaccine was subsequently confirmed by a Defra (SRUC and AHVLA) epidemiological study with input from the University of Edinburgh

[3.6]. Our on-going work has demonstrated that colostral alloantibodies in serum of vaccinated cows that have produced BNP cases react with the cell line used to grow virus for production of this vaccine.

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

3.1 Penny, C.D., Bell, C., Morrison, L., Howie, F. & Willoughby, K. (2009). Pancytopenia and haemorrhage in young beef calves. The Veterinary Record 164, 762. http://dx.doi.org/10.1136/vr.164.24.762

3.2 Bell, C.R., Scott, P.R., Sargison, N.D., Wilson, D.J., Morrison, L., Howie, F., Willoughby, K., Penny, C.D., (2010a). Idiopathic bovine neonatal pancytopenia in a Scottish beef herd. Veterinary Record, 167, 938-940. http://dx.doi.org/10.1136/vr.c4004

3.3 Bell, C.R., Scott, P.R, Kerr, M.G, Willoughby, K., (2010b). Possible preventive strategy for bovine neonatal pancytopenia. Veterinary Record, 167, 758. http://dx.doi.org/10.1136/vr.c6209

3.4 Bell, C.R., Rocchi, M.S., Dagleish, M.P., Melzi, E., Ballingall, K.T., Connelly, M., Kerr, M.G., Scholes, S.F.E., Willoughby, K., (2013). Reproduction of bovine neonatal pancytopenia (BNP) by feeding of pooled colostrum reveals variable alloantibody damage to different haematopoietic lineages. Veterinary Immunology and Immunopathology 151(3-4), 303-14. http://dx.doi.org/10.1016/j.vetimm.2012.12.002

3.5. Bell, C.R., MacHugh, N.D, Connelley, T.K, Degnan, K., and Morrison W.I. The specificity of alloantibody in Bovine Neonatal Pancytopaenia (BNP). Accepted abstract at British Society of Immunology Congress (2nd-5th Dec 2013) (Document available on request.)

3.6 Lambton, S. L., Colloff, A. D., Smith, R. P., Caldow, G.L., Scholes, S. F. E., Willoughby K., Howie, F., Ellis-Iversen, J., David, G., Cook, A. J., Holliman, A., (2012). Factors associated with bovine neonatal pancytopenia (BNP) in calves: a case-control study. PLoS One 7(5):e34183. http://dx.doi.org/10.1371/journal.pone.0034183

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

The immediate impact of the research was the acknowledgment by Pfizer Animal Health (now Zoetis) of the connection of BNP to the use of the PregSure BVD vaccine in the dam, which led to the **withdrawal of the vaccine from sale in Europe and elsewhere in the world** (5.1). Despite the vaccine being withdrawn, cases of bleeding calf syndrome continue to be found in some calves born to dams that have been historically vaccinated. In addition, reporting has increased due to increased awareness of disease and Zoetis subsidising post-mortem examinations. However, as an indirect measure the number of cases being diagnosed at post-mortem at SRUC fell by 42% between 2012 and 2013 (SRUC post mortem figures).

The Recognition of BNP as a truly novel disease and characterisation of the disease was translated into impact through the following means:

- Dissemination of our findings through publication in the veterinary press (5.2,5.3,5.4), delivery of talks (Association for Veterinary Teaching and Research Work Congress 2010, British Cattle Veterinary Association Congress 2011, Vet Trust Conference 2013) and widespread press coverage (5.5, 5.6) allowed rapid transfer of information to the veterinary profession and farming community allowing prompt recognition of cases.
- Findings contributed to the Defra BNP working group. That group generated a case definition for the disease which was used in further large-scale epidemiological studies (5.7, 5.8)
- Findings contributed to recognition and characterisation of the disease at a European level (5.9)
- Cases of BNP were reported by the veterinary profession through the pharmacovigilance system.

The demonstration that cases of BNP can be prevented by colostrum substitution allowed dissemination of practical advice through the veterinary press that enabled farmers to prevent many further cases of the disease (5.10)

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

5.1. European Medicines Agency, (2010). Pregsure BVD – Article 78 referal – Annexes I, II. http://tinyurl.com/nv6usqk

5.2. Bell, C.R. (2011). Bovine Neonatal Pancytopaenia or bleeding calf syndrome. UK Vet: Livestock, 16(1), 24-28. http://dx.doi.org/10.1111/j.2044-3870.2010.00004.x

5.3. SAC Emerging Diseases Reports. Vigilance urged for 'bleeding calf syndrome'. Veterinary Record 2009;165:515 http://dx.doi.org/10.1136/vr.165.18.515-a

5.4. Bell, C.R. (2011). Bleeding disorders in cattle. BVA In Practice, 33(3), 106-115. http://dx.doi.org/10.1136/inp.d1194

5.5. BBC news report, 21st September 2009. Calves dying from mystery disease. http://tinyurl.com/p2bdr2k

5.6. Farmers Weekly report 21st September 2009, Bleeding calf syndrome on the rise. http://tinyurl.com/nsesh6g

5.7. Defra Scanning Surveillance Report: Investigation of the emergence of a novel bleeding disorder of calves (bovine neonatal pancytopenia) in Great Britain. 2010. http://tinyurl.com/p4v63dz

5.8. Defra (Department for Environment, Food and Rural Affairs, UK) (2011). Investigation of an emerging syndrome of bovine neonatal pancytopenia in calves http://tinyurl.com/on9abg7

5.9. Proceedings of the European Buiatrics forum satellite symposium on haemorrhagic diathesis in calves, Marseilles, France, 1-3 Dec 2009. http://tinyurl.com/prcu3t6

5.10. Bell, C.R., Scott, P.R, Kerr, M.G, Willoughby, K., (2010b). Possible preventive strategy for bovine neonatal pancytopenia. Vet.Rec.167, 758. http://dx.doi.org/10.1136/vr.c6209