Institution: Queen's University Belfast		
Unit of Assessment: UoA 6		
Title of case study: Porcine Circovirus 2 Vaccine – An essential component of a sustainable global pig industry		
Period when the underpinning research was undertaken: 2000-2016		
Details of staff conducting the underpinning research from the submitting unit:		
Name(s): Gordon Allan	**Role(s) (e.g. job title):** Professor	**Period(s) employed by submitting HEI:** 2008-current.
Period when the claimed impact occurred: 2013 – 2020		
Is this case study continued from a case study submitted in 2014? Y		

1. Summary of the impact

Economic significance: Porcine circovirus 2 (PCV2) causes porcine-circovirus-associated-diseases (PCVADs), resulting in approx. 40% pig mortality. This impact has been negated by PCV2 vaccines, developed by Professor Allan and team. The PCV2 vaccines are used globally, with **>1 pig vaccinated/8 seconds** and sales **increasing by 28% to GBP2,300,000,000 in total between 2013-2017**.

Industrial/Societal significance: Alongside increases in vaccine sales a study commissioned by Prof. Allan has also revealed that not only have PCV2 vaccinated pigs increased finishing weights and reproductive capacity, they have **reduced Greenhouse gas (GHG) and ammonia emissions**. Independent research also shows that **antimicrobial use in pigs has reduced** from 263.5mg/kg in 2015 to 104mg/kg in 2020, aided by the PCV2 vaccine.

2. Underpinning research

Professor Allan and his team confirmed that PVC2 was the primary aetiological agent of Porcine postweaning multisystemic wasting syndrome (PMWS) **[3.1]**. Prof Allan's team, including international collaborators, subsequently also demonstrated **for the first time** the involvement of PCV2 in reproductive disorders, porcine dermatitis and nephropathy syndrome (PDNS), thus expanding the pathogenic profile of PCVDs beyond post-weaning multisystemic wasting syndrome (PMWS) **[3.2]**. This initial research resulted in Professor Allan and his team **developing the first PCV2 vaccine,** which was commercialised by Merial in 2006/7 (acquired by Boehringer Ingelheim (BI) in 2017), with sublicenses to develop further PCV2 vaccines granted by Merial to Intervet, Pfizer, and BI. All of the PCV2 vaccines commercialised to date (4) are dependent on the initial IPR filed by Professor Allan and his collaborators **[4 patent families and 38 granted patents** to date**]**. Professor Allan and his team have worked extensively with these commercial companies, national and international bodies to further develop control strategies, epidemiological understanding and diagnostics for PCV2.

Professor Allan's extensive research portfolio also includes the first recognition, isolation and characterisation of a second genotype of PCV2 in Swedish pigs, the prototype virus that now differentiates PCV2 into genotypes a and b **[3.3],** which are now incorporated into a new PCV2 dual genotype vaccine. Additionally, within this REF cycle Professor Allan's team, in conjunction with vaccine company Merial, developed the first reliable and repeatable experimental model of PCVAD and applied this to the initial testing and evaluation of candidate PCV2 vaccines **[3.4].**

In addition, Allan's team worked with colleagues in Merial (France), Spain, Switzerland and North America to elucidate the host immune system-PCV2 interactions and pathogenic process i.e. immunosuppression. In 2003 they reported that PCV2 did not infect porcine T-cells but did infect monocytes, pulmonary macrophages (PMs) and monocyte-derived macrophages **[3.5]**. Importantly, PCV2 antigen remained in these antigen-presenting cells, without replication or degradation. It was later confirmed by Prof Allan and his team that the virus did persist in dendritic cells (DCs) without loss of infectivity nor the induction of cell death. However, there was no modulation of DC surface major histocompatibility complex class I and class II, CD80/86, CD25, CD16, or CD14. Furthermore, infected DC did not transmit virus to syngeneic T lymphocytes, even when the latter were activated. The results demonstrated **for the first time** that PCV2 can persist in DCs in the absence of virus replication or degradation and that this silent virus infection presents a **novel mechanism** of immune evasion and DC degradation.

This impact case builds upon this seminal research and the previous REF 2014 impact case through demonstrating: **1.** increased sales of the vaccine; **2.** that the PCV2 vaccine results in global reductions in GHG and ammonia emissions from pigs; **3.** that the vaccine has reduced the reliance on antimicrobials, therefore minimising the risk of antimicrobial resistance development and transmission to humans. The evidence for these statements are shown in depth in section 4.

3. References to the research

3.1 Krakowka S, Ellis JA, Meehan B, Kennedy S, McNeilly F, Allan G. (2000). Viral wasting syndrome of swine: experimental reproduction of postweaning multisystemic wasting syndrome in gnotobiotic swine by coinfection with porcine circovirus 2 and porcine parvovirus. Veterinary Pathology. 37(3):254-63.

3.2 Meehan BM, McNeilly F, McNair I, Walker IW, Ellis JA, Krakowka S, Allan GM. 2001. Isolation and characterisation of porcine circovirus 2 from cases of sow abortion and porcine dermatitis and nephropathy syndrome. Archives of Virology, 146, 1-8.

3.3 Segales J, Olvera A, Grau-Roma L, Charreyre C, Nauwynck H, Larsen L, Dupont K, McCullough K, Ellis J, Krakowka S, Mankertz A, Fredholm M, Fossum C, Timmusk S, Stockhofe-Zurwieden N, Beattie V, Armstrong D, Grassland B, Baekbo P, Allan G. 2008. PCV-2 genotype definition and nomenclature. Veterinary Record. 162, 867-868.

3.4 McKillen J, McNair I, Lagan P, McKay K, McClintock J, Casement V, Charreyre C, Allan G. 2016. Reproduction of post-weaning multi-systemic wasting syndrome in an animal disease model as a tool for vaccine testing under controlled conditions. Research in Veterinary Science. 105, 143-52.

3.5 Gilpin DF, McCullough K, Meehan BM, McNeilly F, McNair I, Stevenson LS, Foster JC, Ellis JA, Krakowka S, Adair BM, Allan GM. 2003. In-vitro studies on the infection and replication of porcine circovirus 2 in cells of the porcine immune system. Veterinary Immunology and Immunopathology. 94, 149-161.

4. Details of the impact

Economic Impact: The vaccine continues to benefit the veterinary pharmaceutical industry with **global sales** from 2013-2017 **increasing by 28% to approximately GBP2,300,000,000** in total **[5.1; 5.2]** and Boehringer Ingelheim estimated that in 2016 **>1 pig vaccinated/8 seconds [5.3]**.

Industrial impact: According to numerous sources, including the USDA, global pig meat production has increased substantially between 1993-2019, from approx. 2 to 11 million metric tons. This growth has made us globally more food secure and was enabled by the development of the PCV2 vaccine, which allows pig producers to achieve better finishing weights **[5.1]**. For example, a meta-analysis compared finishing weights in vaccinated and unvaccinated animals and found that the average weight in finished pigs that received the PCV2 vaccine was 41.5g pounds heavier than unvaccinated animals **[5.4].** Consequently, vaccinated pigs produce a better potential profit for the farmer. Testimonials from industrial partners **[5.5 & 5.6]** also confirmed increases in production in vaccinated pigs:

Testimonial for Corporate Swine Technical manager, CEVA, the main distributor for Circovac [**5.1]**, April 2019 **[5.5]**:

'On the farm with the history of PCVD the vaccination reduces significantly the mortality and weight gain losses especially in the fattening period and reduces the use of antibiotics. A meta-analysis study of 66 published field trials performed in clinically affected farms found a positive effect of PCV2 vaccination on productivity measured as an increase of ADWG (10–40 g/day in vaccinated pigs compared with non-vaccinated controls) and reduction in mortality rates'.

Testimonial from a Senior Consultant, SEGES, one of the largest Danish Pig Producers, April 2019 **[5.6]**:

'PMWS/PCVDs were eventually controlled in Denmark (and around the world) using PCV2 vaccines, which Prof Allan, in collaboration with Merial, was initially involved in developing and evaluating. All PCV2 vaccines used around the world are based on the PCV2 virus originally isolated and characterised by Prof Allan's group. These vaccines continue, to this day, to add

significant benefits to pig health and welfare and contribute to sustainable pig farming in Denmark and around the world'.

Environmental Impact: Climate change, as a result of rising GHG emissions, is threatening planetary health and livestock production contributes to around 14% of anthropogenic methane released into the environment. Another key environmental challenge in pig production is the release of ammonia, which although not a GHG, can lead to nitrous oxide (23 x more potent than methane as a GHG) formation through deposition and denitrification in soils. In 2015, Devenish Nutrition and Professor Allan commissioned a study in conjunction with the Scottish Agricultural College (SAC Consulting), using published, peer-reviewed data from 147 UK pig farms, to determine the theoretical values of the GHG and ammonia reductions associated with PCV2 vaccination **[5.7]**. The figures were generated using SAC's Agricultural Resource Efficiency Calculator; AgRE Calc©, which is certified to PAS 2050:2011 standards, and follows the GHG emissions Tier 2 methodology published by the Intergovernmental Panel on Climate Change (IPCC). A modified version of AgRE Calc© was used to calculate ammonia emissions. The three scenarios modelled using AgRE Calc© were based on clinical infection, sub-clinical infection and no disease. The study showed that global use of PCV2 vaccine (90% vaccinated) to control both clinical and subclinical pig infections results in significant reductions in GHG and ammonia emissions **[5.7; Table 1]**. Specifically, the results indicate that the pigs with no disease had the lowest GHG and ammonia emissions, whereas the **clinically infected animals had 13% higher GHG emissions,** and the sub-clinically infected animals had 6% higher emissions owing to inefficiencies in production due to infection **[5.7; Table 1]**. Consequently, based on current global pig meat production of approx. 11 million tons, there is potential to **save up to 88,242,000 tons of CO_2 equivalents,** which is **comparable to GHG emissions from around 35,296,800 cars/annum.** In terms of ammonia emissions, the **clinically infected animals had up 92% higher ammonia emissions** compared with pigs with no disease. Sub-clinically infected pigs had 69% higher ammonia emissions in the finishing phase, as a result of more feed being consumed/head, combined with a lower growth rate, resulting in more nitrogen excreted/unit feed **[5.7; Table 1]**.

Table 1. Greenhouse gas and ammonia emissions from healthy, sub-clinically infected and pigs showing signs of clinical diseases associated with PCV2 infection

	Scenario 1 Clinical	**Scenario 2 Sub-Clinical**	**Scenario 3 No Disease**
GHG Emissions *(kg CO_2e/kg lwt)*	5.59	5.24	**4.95**
Ammonia Emissions *(kg NH_3 /animal/ year)*	4.25	3.73	**2.22**

Societal Health Impact. The introduction of the PCV2 vaccines has also facilitated reductions in the use of antibiotics in swine production globally **[5.8, 5,9, 5.10]**. In 2015, antimicrobial use in the swine industry was estimated at 263.5mg/kg, by 2017 this figure was estimated to have halved to 131mg/kg, with recent figures from AHDB suggesting that 2020 usage was even lower at 104mg/kg **[5.9]**. Given that antibiotic usage is linked to the development of multi-drug resistant bacteria, it is likely that the vaccine has an indirect positive effect on animal and human health as a consequence of the need for less antimicrobial usage in vaccinated pigs.

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

5.1 Details of Circovac vaccine sold by Ceva https://www.swine.ceva.com/PRODUCTS/Vaccines/PCV2/CIRCOVAC-R
Brochure also attached (PDF).

5.2 QUB commercialisation team can be contacted for sales figures

5.3 Article in Pig Progress referencing 2 billion pig vaccinated in 2016 https://www.pigprogress.net/Health/Articles/2016/10/PCV2-vaccine-reaches-2-billion-pigs-protected-2906160W/ (PDF)

5.4 Kristensen CS, Baadsgaard NP, Toft N. 2011. A meta-analysis comparing the effect of PCV2 vaccines on average daily weight gain and mortality rate in pigs from weaning to slaughter. Preventative Veterinary Medicine. 1;98(4):250-8. doi: 10.1016/j.prevetmed.2010.11.015.

5.5 Testimonial from CEVA

5.6 Testimonial from a major Danish Pig Producer (SEGES)

5.7 SAC Carbon calculation report https://www.agrecalc.com/#casestudies
Full report also attached (p.12 shows the data).

5.8 Article in Pig Progress outlining reduction in antimicrobial use due to the PCV2 vaccines – https://www.pigprogress.net/Special-Focus/Alternative-Growth-Promotion/Boehringer/ (PDF)

5.9 AHDB article showing decline in antibiotic use in pigs between 2015-2020. https://ahdb.org.uk/news/pig-sector-continues-to-reduce-antibiotic-use (PDF)

5.10 Raith J, Trauffler M, Firth CL, Lebl K, Schleicher C, Köfer J. 2016. Influence of porcine circovirus type 2 vaccination on the level of antimicrobial consumption on 65 Austrian pig farms. *Veterinary Record.* 78:504.