Institution: University of Birmingham

Unit of Assessment: A1

Title of case study: Providing an evidence base for the FDA ban of fluoroquinolone antibiotic use in animals

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

Research by Professor Laura Piddock at the University of Birmingham has shown that the use of fluoroquinolone antibiotics in veterinary medicine can select for antibiotic resistance in certain strains of bacteria which then present a potential risk to human health. Fluoroquinolone antibiotics are widely used in human medicine to treat bacterial infections. For those patients with chronic bacterial gastroenteritis and/or an invasive infection, fluoroquinolone antibiotics are the empiric treatment of choice by GPs; resistance to these agents represents a large public health risk. The outcomes of the research have been used by policy makers to define the human risks of food borne infection from antibiotic resistant strains and have led to the review and amendment of international policy on the use of antibiotics in food producing animals, in particular the World Health Organisation (published outside of the review period) and US Food and Drug Administration (FDA). The research described has had a direct impact on international policy and the ban on the use of certain antibiotics has had an impact on the levels of fluoroquinolone resistance in bacteria isolated from food producing animals, reducing the transmission of resistant strains to humans.

2. Underpinning research (indicative maximum 500 words)

Non-typhoidal Salmonella and Campylobacter are the top two causes of human bacterial gastroenteritis, generally arising from the consumption of infected meat and poultry. Chronic and invasive infections by these species in people are usually treated with antibiotics, therefore antibiotic resistance arising from the use of antibiotics in food producing animals is a valid concern. The research led by Professor Laura Piddock (at the University of Birmingham since 1987), over a period from 1987 to 2009, investigated how exposure of these bacterial species to fluoroquinolone antibiotics resulted in the emergence of antibiotic resistant strains. Resistance was demonstrated in laboratory studies (1,2) and then in the large scale sampling of commercial flocks of chickens and pigs pre, during and post therapeutic application of fluoroquinolone antibiotics. The work documented a rapid emergence of resistant strains in the animals, which were then passed on through the food chain (3-6).

The research described above provided a scientific and mechanistic insight into the consequence of use of fluoroquinolone antibiotics in animals reared for food production, particularly poultry, and selection of fluoroquinolone resistant mutants. The work provided quantitative data as to how likely resistance was to emerge, the conditions under which resistance can be selected and the genetic mechanisms of this resistance as well as demonstration for both Salmonella and Campylobacter that the same mechanisms seen in animal isolates are common in human isolates. These seminal studies provided unequivocal evidence of the selection of antibiotic resistant bacteria in animals reared for food production and which were present at slaughter and entry to the food chain.

The project team published over 25 manuscripts (cited over 250 times, average journal impact factor of 7.4) describing the selection, mechanisms of resistance, occurrence and evidence of entry into the human food chain of fluoroquinolone resistant non-typhoidal Salmonella and

Campylobacter.

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

1. Gaunt PN, Piddock LJ. Ciprofloxacin resistant *Campylobacter* spp. in humans: an epidemiological and laboratory study. J Antimicrob Chemother. 1996; 37:747–57. *PMID: 8722540*
2. Piddock, L.J.V., Ricci, V., Pumbwe, L, Everett, M.J. & Griggs, D.J. (2003) Fluoroquinolone Resistance in *Campylobacter* species from Man and Animals: detection of mutations in Topoisomerase Genes *Journal of Antimicrobial Chemotherapy* 51: 19-26. *PMID: 12493783*
3. Delsol AA, Sunderland J, Woodward MJ, Pumbwe L, Piddock LJ, Roe JM. Emergence of fluoroquinolone resistance in the native Campylobacter coli population of pigs exposed to enrofloxacin. J Antimicrob Chemother. 2004 May;53(5):872-4. Epub 2004 Mar 17. *PMID: 15028665.*
4. Humphrey TJ, Jørgensen F, Frost JA, Wadda H, Domingue G, Elviss NC, Griggs DJ, Piddock LJ. Prevalence and subtypes of ciprofloxacin-resistant Campylobacter spp. in commercial poultry flocks before, during, and after treatment with fluoroquinolones. Antimicrob Agents Chemother. 2005 Feb;49(2):690-8. *PubMed PMID: 15673753; PMID: 547194.*
5. Griggs, D.J., Johnson, M.M., Frost, J.A., Humphrey, T.J, Jorgensen, F., Piddock, L.J.V. (2005). The incidence and mechanism of ciprofloxacin resistance in *Campylobacter* spp. isolated from commercial poultry flocks in the United Kingdom before, during and after fluoroquinolone treatment. *Antimicrobial Agents and Chemotherapy* 49: 699-707 *PMID: 15673754*
6. Randall LP, Eaves DJ, Cooles SW, Ricci V, Buckley A, Woodward MJ, Piddock LJ. Fluoroquinolone treatment of experimental Salmonella enterica serovar Typhimurium DT104 infections in chickens selects for both gyrA mutations and changes in efflux pump gene expression. J Antimicrob Chemother. 2005 Aug;56(2):297-306. Epub 2005 Jun 14. *PMID: 15956100.*

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

The outcomes of this research have supported policy makers and opinion leaders to formulate opinions as to the safe use of antibiotics in food producing animals and have been used extensively by the FDA in their proposal to ban the fluoroquinolone antibiotics enrofloxacin and sarafloxacin use in food producing animals, which became law in the USA in September 2005 (1, 2) and which has, therefore, **impacted substantially on the use of antibiotics in food producing animals and the presence of antibiotic resistant strains in the food chain since this date and throughout the impact period.**

The **major impact of this work** within the period of review relates to the continuing impact of the ban of fluoroquinolone antibiotic use in animals and the consequent impact on human health. The ban on the use of these types of antibiotics has resulted in a reduction in the presence of antibiotic resistant strains in the human food chain. Following the ban on the use of fluoroquinolone antibiotics in food producing animals, studies have been conducted by a variety of groups including US Food Safety Research Organisations (3), the FDA (4) and Academics Food Science Departments (5) to examine the impact of the ban on fluoroquinolone resistance levels in pathogens isolated from food producing animals. These studies have shown varied patterns of resistance for different bacterial strains, with decreases in the proportion of resistant strains of *E.*

coli and *Enterococcus* being identified in isolates from food producing animals (3-5). In contrast for Campylobacter, no change in the levels of resistant strains were identified in samples taken immediately after the ban, however in more recent studies decreases in the level of resistant strains have been detected (3-5). These data suggest that the ban of fluoroquinolone use has impacted on different species in different ways, but overall there has been a reduction in fluoroquinolone resistance rates of pathogenic species in animal isolates present in the food chain. Latest data from the USA where the fluoroquinolone ban in veterinary medicine was enforced shows very low levels of fluoroquinolone resistance in *Salmonella* isolated from people, whilst rates of resistant isolates of *Campylobacter* have remained steady (6).

The work was disseminated by publication in international peer reviewed journals, conference presentations and informal discussion with government agencies including the Department for the Environment, Food and Rural Affairs (DEFRA), Veterinary Medicines Directive (VMD) and Advisory Committee on the Microbiological Safety of Food (ACMSF) and continues to this day. In the UK, the VMD reviewed the licences of fluoroquinolone antibiotics but did not withdraw the products from market. Instead they increased awareness of the impact of the use of fluoroquinolone antibiotics in animals, through the publication of advisory material (7) and this has led to a reduction of the amount used by veterinarians. The European Medicines Agency is again reviewing the EU policy on antibiotics used veterinary medicine on a case by case basis and the use of fluoroquinolone antibiotics in animals reared for food production has once again come under close scrutiny (8). Data arising from research carried out by the Piddock team is part of the portfolio of evidence being re-examined.

Professor Laura Piddock has also used her international profile in the field of antimicrobial resistance to launch the 'Antibiotic Action' campaign – a global initiative designed to inform and educate all about the need for discovery, research and development of new antibiotics as well as appropriate use (http://antibiotic-action.com/). Professor Piddock has also been awarded a Chair from the British Society in Antimicrobial Chemotherapy in Public Engagement. These activities have resulted in significant recent interactions with politicians, policy makers, industry, the media and general public and allowed her to engage with broad audiences and explain issues including the use of antibiotics in animals (9-10). This activity can be quantified by the number of articles, radio and television programmes and interviews on antibiotics an antibiotic resistance pre November 2011 (when Antibiotic Action was launched) and 2013: using the unique combination of search term words 'Professor LJV Piddock, Director of Antibiotic Action' has been quoted in print, broadcast and digital media to the lay and specialist press over 7000 times.

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

1. http://www.fda.gov/AnimalVeterinary/NewsEvents/CVMUpdates/ucm048444.htm
2. http://www.fda.gov/AnimalVeterinary/SafetyHealth/RecallsWithdrawals/ucm042004.htm
3. Ciprofloxacin-resistant Campylobacter persists in raw retail chicken after the fluoroquinolone ban. Nannapaneni R, Hanning I, Wiggins KC, Story RP, Ricke SC, Johnson MG. Food Addit Contam Part A Chem Anal Control Expo Risk Assess. 2009 Oct;26(10):1348-53.PMID: 21462579
4. Antimicrobial resistance of Campylobacter isolates from retail meat in the United States between 2002 and 2007. Zhao S, Young SR, Tong E, Abbott JW, Womack N, Friedman SL, McDermott PF. Appl Environ Microbiol. 2010 Dec;76(24):7949-56. Epub 2010 Oct 22. PMID:20971875

5. Prevalence and antimicrobial resistance among Campylobacter spp. in Louisiana retail chickens after the enrofloxacin ban. Han F, Lestari SI, Pu S, Ge B. Foodborne Pathog Dis. 2009 Mar;6(2):163-71. doi: 10.1089/fpd.2008.0171.
6. Annual report of the National Antimicrobial Resistance Monitoring System 2011. http://www.cdc.gov/narms/pdf/2011-annual-report-narms-508c.pdf
7. VMD guidance material published on the use of fluroquinolone antibiotics – updated June 2011.
8. http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2013/04/news_detail_001764.jsp&mid=WC0b01ac058004d5c1
9. The world poultry science association and British society for animal science annual conference, Nottingham April 2013. Talk title: Effects of antibiotic resistance in food borne bacteria on human health. http://www.wpsa-uk.com/newSite/meetings/2013_AnnualMeeting.html
10. Drug information association conference, Amsterdam, March 2013. Largest European conference in pharmaceutical sciences and which is attended by all major Pharma and SMEs, and pharmacists in industry, academia and the Healthcare sectors. Talk title: Getting the message across - using antibiotics appropriately. http://www.diahome.org/en-GB/Flagship-Meetings/13101-EuroMeeting.aspx