Fluoroquinolone use in poultry and antibiotic resistance in people

A briefing paper from the Alliance to Save Our Antibiotics

Fluoroquinolones use in poultry

Fluoroquinolones are synthetic antibiotics developed in the 1970s and introduced into human medicine in the 1980s [1]. They are used for treating many foodborne infections such as *Campylobacter*, invasive *Salmonella*, *E. coli* and *Shigella*.

The World Health Organization (WHO) has classified these drugs as 'critically important in human medicine' and said that efforts to reduce antibiotic use in farm animals should prioritise the fluoroquinolones and another antibiotic class known as the modern cephalosporins. The reason for the WHO's concern is that there is clear evidence that most antibiotic resistance in *Campylobacter* and *Salmonella* infections in humans comes from farm antibiotic use. The WHO also says that resistant *E. coli* can spread from farm animals to humans through the food chain [2].

The most widely used fluoroquinolone antibiotic in poultry production is enrofloxacin, sold under the trade name Baytril and also marketed in the UK in various generic versions [3]. Enrofloxacin is closely related to ciprofloxacin, a fluoroquinolone used in human medicine.

Under current legislation, if a small number of chickens show signs of ill-health, enrofloxacin can be added to the drinking water of the whole flock for up to 10 days at a time, even when most of the birds are not ill. Fluoroquinolones can also be used in breeding birds, and any resistant bacteria which subsequently develop resistance may be transmitted to chicks.

A recent report from The European Medicines Agency [4] sets out statistics (p 24) which show that in the UK just under half of all fluoroquinolone use is as oral solutions, while across the EU as a whole, over three-quarters of all veterinary fluoroquinolone antibiotics are used in this way. The report also links oral use with herd or flock therapy, rather than the treatment of individual animals[1].

In 1998, a House of Lords' Committee called for the poultry industry to reduce its use of fluoroquinolones and warned of 'a return to the pre-antibiotic era' if we failed to stem the rising tide of antibiotic-resistant infections [5]. Following this call to action, the veterinary use of fluoroquinolones fell sharply in 2000 to 1.23 tonnes. However, no Parliamentary or independent scientific committee has kept this issue under review and fluoroquinolone use has been allowed to

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[1] The report states (p10) that across the EU as a whole, 'The proportion of fluoroquinolones sold as oral solution was 78.5% and injections accounted for 20.8%'. It also states (p9) that approximately 90% of sales of all antibiotics were for herd [or flock] treatment rather than individual treatment. The report also states (p12), 'Since the proportions of sales of oral powders and oral solutions for individual treatment are relatively low compared to those for herd treatment, the reported sales of oral powders and oral solutions are considered to be mainly used for herd treatment of food-producing animals.'

increase again, by 70% to 2.09 tonnes in 2011 [6]. Table 1 shows how the use of fluoroquinolones in veterinary medicine in the UK, after having fallen sharply in 1999, has increased steadily over the past decade.

Table 1 Use of fluoroquinolones in UK veterinary medicine (kgs of active ingredient).

1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011
2290	1230	1320	1370	1360	1410	1460	1620	1951	1928	1849	2232	2085

According to the Veterinary Medicines Directorate (VMD), in terms of weight of active ingredient, fluoroquinolones account for just 0.6% of antibiotic use in animals in the UK. Compared with tetracyclines, the most widely used antibiotics in UK farming, the disparity seems large: in 2010-11 approximately 155 tonnes of tetracylines were used in veterinary medicine in the UK, accounting for about 40% of total antibiotic use.

However, fluoroquinolones are highly potent antibiotics and the European Medicines Agency has estimated that one dose of fluoroquinolones weighs 30 to 70 times less than one dose of tetracycline antibiotics [7]. The French Agency for Food, Environmental and Occupational Health and Safety published statistics on veterinary antibiotic use in both weight of active ingredient and weight of animal treated (which is essentially a measure of the frequency of treatments), the latter taking into account the differences in the weight of each dosage. These figures show that, although fluoroquinolones only account for 0.5% of antibiotic use in terms of weight of active ingredient, in terms of weight of animal treated, they account for 3.7% of total use [8]. It is therefore, likely that in the UK fluoroquinolones similarly account for about 4% of the weight of animals treated.

The increase in the use of fluoroquinolones can probably be explained by several factors. Firstly, they are broad spectrum antibiotics[2], so can be used to treat a wide variety of diseases on intensive farms. Secondly, the EU ban on the use of antibiotics as growth promoters, which was phased in between 1999 and 2006, contributed to an increase in the use of many other medically important antibiotics used in feed or water. Although this ban was scientifically justified, the lack of restrictions on antibiotics still available for group treatment under veterinary prescription allowed use to increase. This was predicted as long ago as 1999 in the case of fluoroquinolones [9]. Even today, at least one industry website presents data purporting to show that the use of enrofloxacin increases the growth rate of infected chickens compared with untreated infected chickens [10]. Finally, the introduction of generic versions of enrofloxacin has contributed to price reductions.

There are very large differences in the use of fluoroquinolones in farming in different EU countries. Per weight of livestock treated, Denmark uses the least, 80 times less than the UK, whereas Hungary and Spain use over 20 times more than the UK [4]. Some countries, such as Finland and Denmark do not use fluoroquinolones in poultry at all, although they are used in other farm animals.

Use of fluoroquinolones in farming has led to large increases in resistance

When enrofloxacin is added to the drinking water of chickens and turkeys, bacteria in the animals' intestines such as *Campylobacter*, *Salmonella* and *E. coli* can become resistant to fluoroquinolone

[2] All bacteria are classified as either 'Gram-positive' or 'Gram-negative'. Broad-spectrum antibiotics are antibiotics which kill both Gram-positive and Gram-negative bacteria.

antibiotics. Resistance can also pass to meat birds 'vertically' from the use of fluoroquinolones in breeding flocks. Resistant bacteria can then contaminate chicken meat during the slaughtering process and pass to people on food or in other ways causing infections which can no longer be treated successfully by ciprofloxacin or other fluoroquinolones.

Cooking meat thoroughly will kill off any bacteria present on the meat, and good kitchen hygiene will also reduce the risks of the bacteria being passed to humans. However, despite this, hundreds of thousands of cases of food poisoning occur in the UK each year, and the bacteria can also be passed to humans through the environment or by direct contact with farm animals [11].

Campylobacter

Campylobacter is the most common cause of food poisoning in the UK, causing an estimated 371,000 infections a year in England and Wales [12]. Fluoroquinolones are one of two families of antibiotics used to treat campylobacter infections in humans. According to the WHO, the use of fluoroquinolones in farm animals has led to an increase in resistance in *Campylobacter* infecting humans [2].

Before fluoroquinolones were introduced to farming, no humans without prior exposure to the drugs were known to carry fluoroquinolone-resistant *Campylobacter* [13], and in 1993 when fluoroquinolones were first approved for use in poultry in the UK, just 1% of British birds carried fluoroquinolone-resistant *Campylobacter* [14].

In contrast, in the Netherlands fluoroquinolones were licensed for used in poultry in 1987, and between 1982 and 1989, resistance to ciprofloxacin from Dutch poultry and Dutch people rose from 0% to 14% and 11% respectively. An advisory committee to the UK's Department of Health commented that the increase in resistance in poultry and man 'followed the extensive use of enrofloxacin, a ciprofloxacin analogue, by the poultry industry' [15].

The introduction of fluoroquinolones into British poultry in 1993 was similarly followed by large increases in resistance: by 1997, 12% of human cases had become resistant to ciprofloxacin. Government scientists from the then Public Health Laboratory Service (PHLS) warned of the 'possible clinical consequences of the continuing use of fluoroquinolone antibiotics in food animals' [16].

During the past decade, resistance levels have continued to increase. In 2008, 18% of *C. jejuni* and 25% of *C. coli* from taken from chickens during an abattoir survey were ciprofloxacin resistant [17]. Surveys of retail chicken meat have also shown rising levels of resistance: a 2001 FSA survey found that 13% of *Campylobacter jejuni* and 15% of *Campylobacter coli*[3] from the meat were resistant to ciprofloxacin [18]. A similar FSA survey of retail chicken carried out in 2007-8 found that resistance in *C. jejuni* had increased to 21% and in *C. coli* to 35%. This survey also found that 41.5% of retail chicken were contaminated with campylobacter [19].

Resistance in human *Campylobacter* has also increased sharply: data published in 2006 for England and Wales showed that 24% of human *C. jejuni* and 29% of *C. coli* were ciprofloxacin resistant [20], whereas data published in 2010 for 2007 showed that this had increased to 46% and 35% respectively [21].

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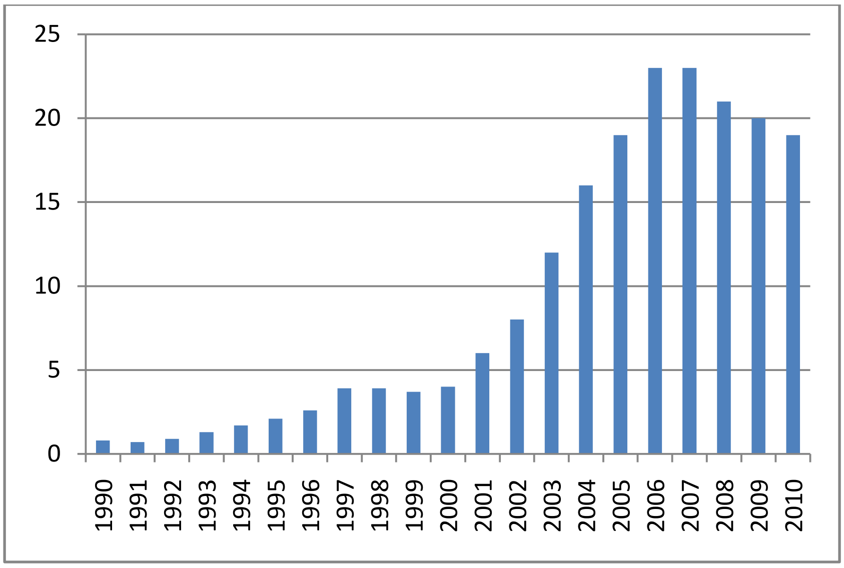
[3] *Campylobacter coli* is the second most common type found in poultry. It also accounts for 5-10% of human cases.

As a result of the different levels of use of fluoroquinolones in EU member states, there are now large differences in resistance in poultry: in Finland, where fluoroquinolones are not used in poultry, just 1% of *C. jejuni* from poultry are ciprofloxacin resistant, whereas in Hungary and Spain where fluoroquinolones are very heavily used in the poultry industry, 89% and 92% of *C. jejuni* from poultry respectively are resistant [22].

E. coli

As Graph 1 shows, after fluoroquinolones were licensed for use in poultry, resistance in human *E. coli* blood infections increased from less than 1% in 1992 to over 20% in 2006. Since then, resistance rates have fallen slightly as fluoroquinolone use in hospitals has been reduced.

Graph 1 Fluoroquinolone resistance in human *E. coli* blood infections in England, Wales and Northern Ireland (HPA data)



Statistics on fluoroquinolone resistance in *E. coli* from poultry are no longer published in the UK, but in 2007, 6% from chicken and 11% from turkey were resistant [21].

In Spain, where fluoroquinolones are used much more heavily in poultry than in the UK, the situation is significantly worse: in 2009, 87% of *E. coli* from poultry were fluoroquinolone resistant [23], and in 2010, 33% of human *E. coli* causing blood poisoning were fluoroquinolone resistant [24]. In contrast, in Australia where fluoroquinolones have never been licensed for use in farm animals, just 4-5% of human *E. coli* are fluoroquinolone resistant [25].

Two studies carried out in Spain and the United States have found that human fluoroquinolone-resistant *E. coli* are genetically distinct from human sensitive *E. coli* but largely genetically indistinguishable from resistant poultry *E. coli*. In contrast, resistant and sensitive poultry *E. coli* are genetically similar. Both groups of scientists drew similar conclusions, the Americans saying that ‘Many drug-resistant human fecal *E. coli* isolates may originate from poultry, whereas drug-resistant poultry-source *E. coli* isolates likely originate from susceptible poultry-source precursors’ [26][27].

Salmonella

The WHO has said that resistance in human *Salmonella* is clearly linked to antibiotic use in farm animals. It also says that resistance is ‘associated with more frequent and longer hospitalization, longer illness, a higher risk of invasive infection and a twofold increase in the risk of death in the two years after infection' [2].

In 2010, 14% of human *Salmonella* infections were fluoroquinolone resistant [28], although resistance in poultry is lower at just 0.6% to 2% [29]. However, a survey of retail poultry carried out by the FSA in 2007 found that 10% of the *Salmonella* was fluoroquinolone resistant. The figure was even higher, at 25%, for *Salmonella enteritidis* the most common *Salmonella* infecting humans [19]. This was an increase over an earlier FSA retail poultry survey, when 7% of *Salmonella* were fluoroquinolone resistant [18].

In some other countries, resistance in *Salmonella* in chickens has reached alarming proportions: in Spain in 2008, 88% of cases were fluoroquinolone resistant [30].

Countries where fluoroquinolones are not used in poultry

Australia has never permitted the use of fluoroquinolones in any farm animals and consequently resistance to fluoroquinolones in *Campylobacter*, *Salmonella* and *E. coli* is rare in farm animals. Resistance in humans is also much lower than in most countries: just 2.6% of *Campylobacter* were resistant in 2006 (and 0% in 2003), and most of these cases were in returning travelers. Resistance in human *E. coli* is also low, at just 4-5% [25].

Finland does not permit the use of fluoroquinolones in poultry. As a result, in 2007 no *Campylobacter* from poultry were fluoroquinolone resistant, whereas in 2008 and 2009 just 1% were resistant [31]. Resistance in *Campylobacter* from Finnish patients who have not recently travelled abroad is just 2-3%, whereas 61% of *Campylobacter* for Finnish patients who have travelled to Spain in the last couple of weeks are fluoroquinolone resistant [32].

In September 2005, the US FDA banned the use of fluoroquinolones in US poultry because of concerns about increasing resistance in *Campylobacter* in poultry and humans [33]. Although the ban had first been proposed by the FDA in 2000, after which one manufacturer of one of the products, Abbott Laboratories, withdrew its drug from market immediately. However, the other, Bayer Corporation, launched a lengthy legal battle that delayed the ban by nearly five years [34].

The effect of the ban on resistance, so far, has been mixed: resistance in human *Campylobacter* in 2010 was 22%, the same as in 2005 [35]. In retail chicken, resistance has fallen sharply in *Campylobacter coli*, the second most common *Campylobacter* in poultry, from 29% in 2005 to 13.5% in 2010, but resistance in *Campylobacter jejuni* has risen from 15% to 22.5% [36].

Some scientists believe that the reason that resistance in US retail poultry hasn't fallen further is because illegal use of fluoroquinolones may be continuing in the US poultry industry. Earlier this year, scientists from the Johns Hopkins Bloomberg School of Public Health and Arizona State University found residues of fluoroquinolones in feather meal [37]. The lead scientist, Dr David Love, said this 'strongly suggests the continued use of these drugs, despite the ban put in place in 2005 by the FDA' [38]. The concentrations of fluoroquinolones found in the feather meal, which is fed to farm animals, including poultry, were high enough to select for resistant bacteria. It is therefore possible that the residues themselves may also be selecting for resistance in the chickens which eat the meal.

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