Why the use of fluoroquinolone antibiotics in poultry should be banned

Summary

Fluoroquinolones are antibiotics classified by the World Health Organization as 'critically important in human medicine' due to their importance for treating infections such as Campylobacter, Salmonella and E. coli.

There have long been concerns that their introduction to veterinary medicine (in 1993 in the UK, and earlier in some EU countries) might undermine their effectiveness in human medicine. As a result, in 1998, a report on antimicrobial resistance published by the House of Lords Science and Technology Committee recommended that fluoroquinolones no longer be permitted for mass medication in farm animals, and be restricted to individual treatments only. Such a ban would effectively have meant the antibiotics could not have been used in poultry, since they are only used for mass medication in that species.

However, in 2016, mass medication of poultry with fluoroquinolones is still permitted in the UK and most of the EU, although it was banned in the US in 2005. Fluoroquinolones are also not used in poultry in any Nordic country or in Australia.

Furthermore, the latest data on resistance rates in human infections, which are at record levels for Campylobacter in the UK and the EU, shows that concerns that resistance would be transmitted from farm animals have been realised.

International regulatory and advisory bodies are clear that most fluoroquinolone resistance in human Campylobacter and Salmonella infections is coming from farm-animal antibiotic use. Evidence for resistance transmission from farm animals to humans is particularly strong in the case of Campylobacter and the use of the antibiotics in poultry.

The European Food Safety Authority and the European Centre for Disease Prevention and Control recently reported that resistance rates in EU countries was either "high", "very high" or "extremely high", and said that it was their assessment that "a large proportion of human campylobacteriosis infections comes from handling, preparation and consumption of broiler meat". They said "this is a compelling example of how antimicrobial resistance in food and animals may impact the availability of effective antimicrobial agents for treating severe human Campylobacter infections".

However, in the UK, industry bodies representing the pharmaceutical industry, farmers and veterinarians have frequently challenged these scientific conclusions and have lobbied against proposals for a ban on the use of fluoroquinolones in poultry. They have claimed that the bans on the use of fluoroquinolones in countries like the United States and Denmark have failed because they have not reduced resistance rates in humans.

This report will show that these claims are based on an incorrect and incomplete analysis of the available data. We will show that the US ban on fluoroquinolones in poultry has in fact been a major public-health success story, as the rate of resistance in human Campylobacter infections (22%) is now much lower than the average for the EU (60%). This is despite much higher levels of use of quinolone antibiotics in human medicine in the US compared with most EU countries.

In contrast, the UK is the lowest user of fluoroquinolone antibiotics in human medicine in Europe, and per person uses less than a third of the quantity used in the US, yet it has a fluoroquinolone resistance rate in human Campylobacter which is far higher than the US (48% in England).

Data collected and published voluntarily by the British Poultry Council suggests that poultry consumption of fluoroquinolones was significantly reduced in 2015 compared with 2014, which is a welcome development. The UK's consistently below-average resistance rate, when compared with other EU countries, is likely to be due to its below-average consumption of the antibiotics in farm animals, and in particular in poultry. The UK's resistance rate is nevertheless increasing, and is at record levels, due to ongoing use of fluoroquinolones in poultry.

Industry advocates have claimed that increases in fluoroquinolone resistance in human Campylobacter infections in Denmark in recent years (to 35%), despite no use of the antibiotics in Danish poultry, show that it is human fluoroquinolone use which is to blame. We will, however, show that large increases in recent years in the importation of poultry meat into Denmark from countries that use fluoroquinolones in poultry are by far the most likely explanation for the trend.

The Danish experience shows that international action to ban fluoroquinolone use in poultry is required if the antibiotics are to remain available for treating future Campylobacter infections.

This report will also present data showing that countries which no longer use fluoroquinolones in poultry (Australia, Denmark, Finland, Iceland, Norway, Sweden and the US) all have much lower levels of resistance in human Campylobacter infections than every EU country that uses the antibiotics in poultry and which provide data on resistance to the EU.

Nearly 20 years after the House of Lords recommendation, and with such clear evidence that fluorouqinolone use in poultry is undermining the effectiveness of a critically important antibiotic in human medicine, the UK government and the EU must finally act to ban the use of these antibiotics in poultry and for all mass medication.

April 2016

Table of Contents

1. Usefulness of fluoroquinolones is being undermined by resistance

Fluoroquinolones are one of the few classes of antimicrobials which have activity against the full range of pathogens which cause bacterial gastroenteritis (most commonly Campylobacter, Salmonella, Shigella or E. coli). This means that they have often been used for empiric treatment in human medicine, when the pathogen is not yet known, before laboratory tests are carried out [1]. Their importance for treating Campylobacter, Salmonella and E. coli infections has led the the World Health Organization classifying them as 'critically important in human medicine'.

Unfortunately, in some countries, fluoroquinolone resistance in Campylobacter has risen to very high or extremely high levels, which means that the antibiotics are being abandoned for empiric treatment.

A recent study by scientists from the Royal Liverpool University Hospital said that the record level of resistance found in 2014 (49.9%) had led to a change from using fluoroquinolones to using a macrolide antibiotic for empiric therapy[2].

Macrolides, however, are not as well tolerated as fluoroquinolones and do not have as wide a range of activity [1].

According to a 2009 document jointly published by the European Centre for Disease Prevention and Control (ECDC) and advisory committees from the European Food Safety Authority (EFSA), the European Medicine Agency (EMA) and the European Commission:
"The health impact of infection with quinolone-resistant Campylobacter is of concern, because these infections are associated with longer duration of illness, and a greater risk of invasive disease or death. Adverse clinical events are increased 6-fold within 30 days of infection and 3-fold within 90 days, when patients were infected with quinolone-resistant compared to quinolone-susceptible strains" [3].

In a report published in 2016, EFSA and the ECDC said "Resistance to fluoroquinolones in some Member States was extremely high; in such settings, the effective treatment options for human enteric Campylobacter infection may be significantly reduced" [4].

2. Resistance in human infections is linked to farm use

Increasing fluoroquinolone resistance in human Campylobacter infections is generally attributed to the use of these antibiotics in farm animals, and in particular poultry.

One reason for this, as explained by the European Medicines Agency's (EMA) Committee for Medicinal Products for Veterinary Use (CVMP), is that "food-producing animals, especially poultry, very commonly have campylobacters in high numbers as commensals in their gastro-intestinal flora" whereas "it needs to be emphasised that in humans campylobacters are only present in the patients gut during an infection with the organism" [5]. According to the CVMP, this means that, in food animals, "During treatment of infectious diseases like colibacillosis, resistant mutants [of Campylobacter] are readily selected", but on the other hand "In humans fluoroquinolone-resistant mutants will be selected only during treatment of campylobacteriosis with fluoroquinolones. Since in human therapy fluoroquinolones are predominantly used for other infectious diseases, its relative contribution to the resistance levels of Campylobacter jejuni will be less significant."

There are two other main reasons why it is generally accepted that most antibiotic resistance, including fluoroquinolone, in human campylobacter infections comes from farm-animal use, and in particular poultry use of the antibiotics:

- Most human campylobacter infections are of food-animal origin. According to the Food Safety Authority, about 80% of campylobacter infections in the UK are acquired from contaminated poultry [6]. Some other estimates put poultry's contribution to human infections at lower levels, at between 38% and 77%, and link cattle to about 20% of human cases [7][8]. The European Food Safety Authority estimates the chicken reservoir as a whole (including transfer to humans on food, via environmental pathways and via direct contact) may account for 50% to 80% of human campylobacterosis [9]. Many of the studies linking human Campylobacter infections with poultry have studied the genetics of the Campylobacter found in human infections, and compared it with the bacteria found in poultry, other farm animals and other sources. They have used different methods such as "Multi-locus sequencing typing", "Pulsed-field gel electrophoresis" and *fla*-typing, and these consistently show that poultry is the main source of human infections, particularly in urban areas [8].
- According to the FAO, WHO and OIE, "Even in countries without surveillance on antimicrobial use in food animals, temporal associations have been demonstrated between the first approved use of an antimicrobial agent in food animals and an increase in antimicrobial resistance. In the United States, for example, there was a marked increase in the proportion of domestically-acquired Campylobacter infections that were fluoroquinolone-resistant following the first approved use of fluoroquinolones in food animals in 1995. Similar temporal associations were observed in several European countries including the United Kingdom and the Netherlands. Similar associations between resistance development in Salmonella and approval of use of antimicrobial agents in food-producing animals have been described" [10].

Very similar arguments and evidence also points to a farm-animal origin for most fluoroquinolone resistance in human Salmonella infections.

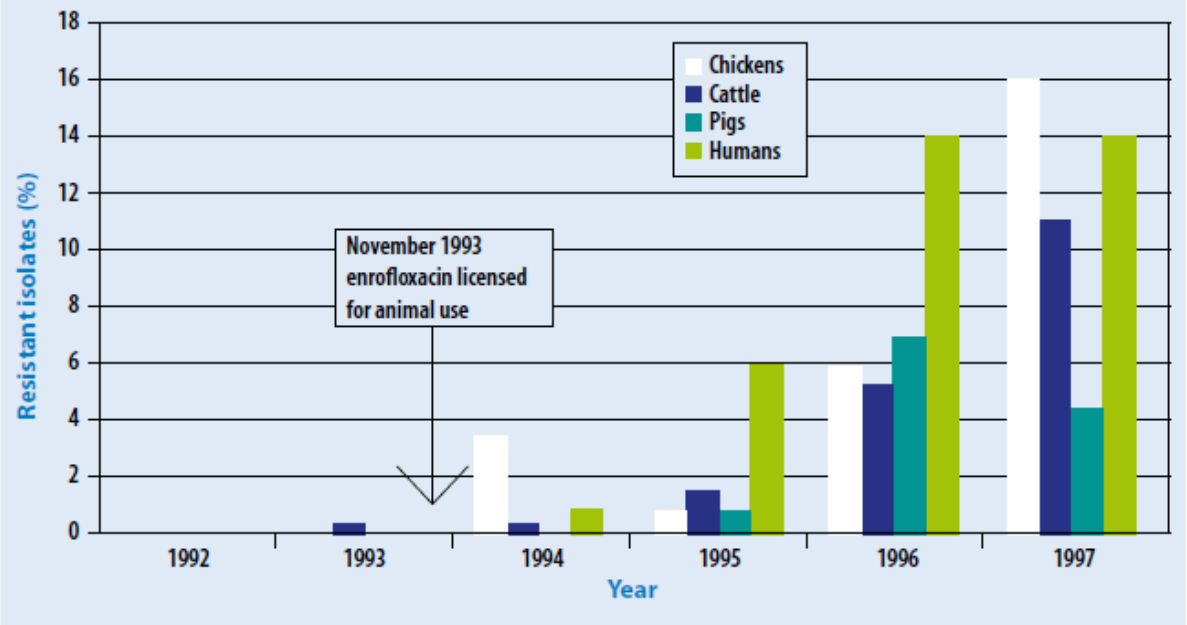
This report will not attempt to produce a review of the scientific evidence linking fluoroquinolone use in poultry with resistance in human infections. A large number of scientific papers have been published on the topic over many years, and reviews of the evidence by bodies such as EFSA and the WHO are already available [11][12]. Instead this report will focus on the validity or otherwise of industry statements claiming that there is little or no link between poultry antibiotic use and resistance in human infections.

3. The view of national and international authorities

Because a large proportion of human Campylobacter and Salmonella are of food origin, scientists have long suspected that the introduction of fluoroquinolones into might lead to resistance to the antibiotics in these infections.

In the UK, a few years after the introduction of fluoroquinolones to farming in November 1993, evidence began to appear that resistance was transferring to human Salmonella infections. Graph 1 was produced by Public Health Laboratory Scientists (PHLS) and has been widely reproduced by the WHO and others as evidence of the impact of fluoroquinolones in farming [3][12].

Graph 1 Fluoroquinolone resistance in Salmonella typhimurium DT104 in farm animals and humans following licensing of fluoroquinolones in farming in 1993



Based on this and other evidence, as early as 1998 a report by the House of Lords was recommending that fluoroquinolones no longer be permitted for mass medication (which would effectively mean that they couldn't be used in poultry, since the antibiotics are only used for mass medication in poultry). The House of Lords report said:

""Potent agents important to human medicine, such as the fluoroquinolones, deserve extreme economy of use in veterinary practice. **It is right for large animals and companion animals to receive such agents on an individual basis for short-term therapy; but mass-treatment of herds of pigs and flocks of poultry with such agents cannot be best practice from the point of view of human public health**" [emphasis added] [13].

In 2000, a report published by the Advisory Committee on the Microbiological Safety of Food said:
"The trend data we have seen appear to indicate a contribution of veterinary usage of quinolones to resistance in human isolates of Campylobacter. The picture we see with respect to fluoroquinolone resistance in salmonellas also points to a veterinary contribution to this resistance, as illustrated by the trends in the data for DT104. Campylobacter and S. Typhimurium DT104 both occur in poultry, and these pathogens are likely to have been exposed to similar antibiotics. Given the propensity for Campylobacter and certain salmonellas to develop quinolone resistance, it seems reasonable to conclude that veterinary usage of fluoroquinolones will have made a significant contribution to quinolone resistance in isolates of Campylobacter and Salmonella from humans. Given the levels of resistance being seen in some other countries, particularly for Campylobacter, it is important that fluoroquinolones retain efficacy in the treatment of human and animal infections" [14].

According the House of Lords report, the PHLS data relating to fluoroquinolone resistance in Salmonella Typhiumurium DT104 was passed on to the FDA in the US, which took it seriously. The House of Lords report said: "in 1997, a telephone call from the PHLS Laboratory of Enteric Pathogens alerted FDA to the emergence of ciprofloxacin resistance in S. typhimurium DT104 in the United Kingdom. Since then, FDA has issued no more approvals for fluoroquinolones for animals; meanwhile, resistance to fluoroquinolones has been found

in Campylobacter, though none as yet in Salmonella. FDA are using DNA fingerprinting to see whether resistance in Campylobacter can be traced to poultry and sarafloxacin. In discussion at FDA, during our visit to the USA (see Appendix 6), we were taken aback to be asked why the United Kingdom continues to approve fluoroquinolones for animal use, when the USA has stopped doing so on information from the PHLS" [13].

A rapid increase in fluoroquinolone resistance in human Campylobacter infections in the 1990s in the US, and several epidemiological and microbiological studies linking human Campylobacter infections with poultry led the FDA to propose in October 2000 to withdraw the approval of fluoroquinolones in poultry [15].

One pharmaceutical company producing fluoroquinolones for poultry, Abbott Laboratories, accepted the FDA's position and withdrew their product. The other, Bayer Corporation, opposed the FDA and requested a hearing. The Animal Health Institute, the trade association representing pharmaceutical companies selling veterinary medicines in the US, also supported Bayer in challenging the FDA. Eventually, in July 2005, the FDA's Commissioner final decision was announced, and from September 2005 all fluorouquinolones were withdrawn from use in poultry in the US [15].

The FDA said in its final decision:
"The FDA's Center for Veterinary Medicine (CVM) began proceedings to withdraw use of this animal drug in poultry because of scientific data that showed that the use of enrofloxacin in poultry caused resistance to emerge in Campylobacter, a bacterium that causes foodborne illness. Chickens and turkeys normally harbor Campylobacter in their digestive tracts without causing poultry to become ill. Enrofloxacin does not completely eliminate Campylobacter from the birds' intestinal tracts, and those Campylobacter bacteria that survive are resistant to fluoroquinolone drugs. These resistant bacteria multiply in the digestive tracts of poultry and persist and spread through transportation and slaughter, and are found on chicken carcasses in slaughter plants and retail poultry meats" [16].

The WHO has long been clear that the use of fluoroquinolones in food animals was contributing to resistance in human infections. In 1997 a WHO report stated:
"Following the introduction of fluoroquinolones for use in poultry there has been a dramatic rise in the prevalence of fluoroquinolone-resistant Campylobacter jejuni isolated in live poultry, poultry meat and from infected humans. Moreover, prior to any use in poultry, no resistant strains were reported in individuals with no previous exposure to quinolones. Fluoroquinolone-resistant C. jejuni has been associated with therapeutic failures in humans" [17].

In a 2011 report, the WHO said:
"Resistance in the foodborne zoonotic bacteria Salmonella and Campylobacter is clearly linked to antibiotic use in food animals, and foodborne diseases caused by such resistant bacteria are well documented in people. Of special concern is resistance to so-called critically important antibiotics for human medicine. For example, the use of fluoroquinolones in food animals has led to a corresponding antibiotic resistance in Salmonella and Campylobacter species, thus causing infections in people. Also, antibiotic resistance in Salmonella has been 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. Treatment failures, increased hospitalization and a higher risk of death have been reported for multiresistant Salmonella Typhimurium definitive phage type (DT)104 that exhibits quinolone resistance" [12].

Although the European Union has not banned the use of fluoroquinolones in poultry (individual member states such as Denmark, Finland or Sweden do not use the drugs in poultry), various EU bodies have also drawn the conclusion that use in poultry results in resistance in human Campylobacter and Salmonella. In 2008, a European Food Safety Authority (EFSA) report said:
"Resistant Salmonella and Campylobacter involved in human disease are mostly spread through foods. With regards to Salmonella, contaminated poultry meat, eggs, pork and beef are prominent in this regard. For Campylobacter, contaminated poultry meat is prominent."

EFSA also said "A major source of human exposure to fluoroquinolone resistance *via* food appears to be poultry" [1].

In 2016, a joint report by EFSA and the European Centre for Disease Prevention and Control said:
"Very high to extremely high resistance levels to ciprofloxacin were reported in human Campylobacter isolates from all reporting Member States (although lower in Norway). Five of 13 MSs reported ciprofloxacin resistance in > 80% of isolates and one country in 97.7%; in such settings, effective treatment options for human enteric Campylobacter infection are significantly reduced. **Given the high levels of resistance to fluoroquinolones in broilers and the assessment that a large proportion of human campylobacteriosis infections comes from handling, preparation and consumption of broiler meat (EFSA BIOHAZ Panel, 2010a), this is a compelling example of how AMR in food and animals may impact the availability of effective antimicrobial agents for treating severe human Campylobacter infections**. High levels of tetracycline resistance were also observed (46.4% for C. jejuni and 53.8% for C. coli)" [18]. [emphasis added]

4. Industry opposition to banning fluoroquinolone use in poultry and claims that bans have not worked

Despite the widely held consensus view that fluoroquinolone use in poultry is contributing to resistance in human Campylobacter and Salmonella infections, only a small number of countries do not use the antibiotics in poultry (this includes at least the United States, Australia, Denmark, Finland, Iceland, Norway and Sweden). Campaigners have long called for fluoroquinolone use to be banned in poultry [19][20], but the failure of most countries to act has likely been influenced by industry lobbying on the issue.

Just as Bayer Corporation and the Animal Health Institute opposed the ban in the United States, industry organisations in the UK have opposed banning fluoroquinolone use in poultry and repeatedly sought to question the scientific validity of the view that the use of the antibiotics in poultry leads to resistance in human infections.

UK bodies representing the farming and pharmaceutical industries and veterinarians, such as RUMA, NOAH and the BVA have generally focused on highlighting the apparent lack of effect on resistance in human Campylobacter infections of the bans on fluoroquinolones in poultry in countries like the US and Denmark.

In 2012, the BVA President Peter Jones said:
"We know from the USA and Denmark that banning or restricting the use of certain antimicrobials in certain species has not reduced the incidence of resistance to certain organisms in humans" [18].

In its 2013 submission to the House of Commons Science and Technology Committee, the BVA said:
"In Denmark, severe restrictions on the use of fluoroquinolones in animals were put in place in the mid-1990s. However, although Campylobacter jejuni resistance to these fluoroquinolones in domestic human

cases declined somewhat in the early 2000s, this was followed by a marked increase towards the end of the decade" [21].

The BVA also said in the same document:
"In the USA, the fluoroquinolone enrofloxacin was banned in poultry in 2005. However, data shows that resistance in man has continued to rise."

Similarly, in RUMA's submission to the same committee it said:
"Actions have been taken in some member states to limit antibiotic use in animals to reduce resistance in humans. Latest reports from Denmark confirm the trends over the past few years and show that Campylobacter resistance to fluoroquinolones in man acquired domestically continues to rise despite severe restrictions on the use of this antimicrobial in veterinary medicine" [22].

NOAH said in a 2010 briefing on the fluoroquinolones:
"In the United States, the Food and Drug Administration (FDA) have withdrawn the use of fluoroquinolones in poultry. The scientific basis for this action has been challenged by various institutions representing the poultry veterinarians and the manufacturer. They are convinced, as are many scientists and officials, that the responsible use of fluoroquinolones for the therapy of life-threatening animal diseases does not result in a danger to public health" [23].

In his 2013 oral evidence to the Science and Technology Select Committee, John Fitzgerald, RUMA Secretary General, said:
"My colleague has just given me information about the USA, where they banned enrofloxacin in poultry in 2005. They are looking at the issues as well, because there were problems about fluoroquinolone resistance in Campylobacter in man. The evidence – the data – shows that since they introduced the ban, resistance in man has continued to rise. Again, science would suggest that you have done one thing, but are not necessarily getting the result that you hoped you were going to get.[…] There may be issues in the way that fluoroquinolones are used in man in the United States that may have led to the increase" [24].

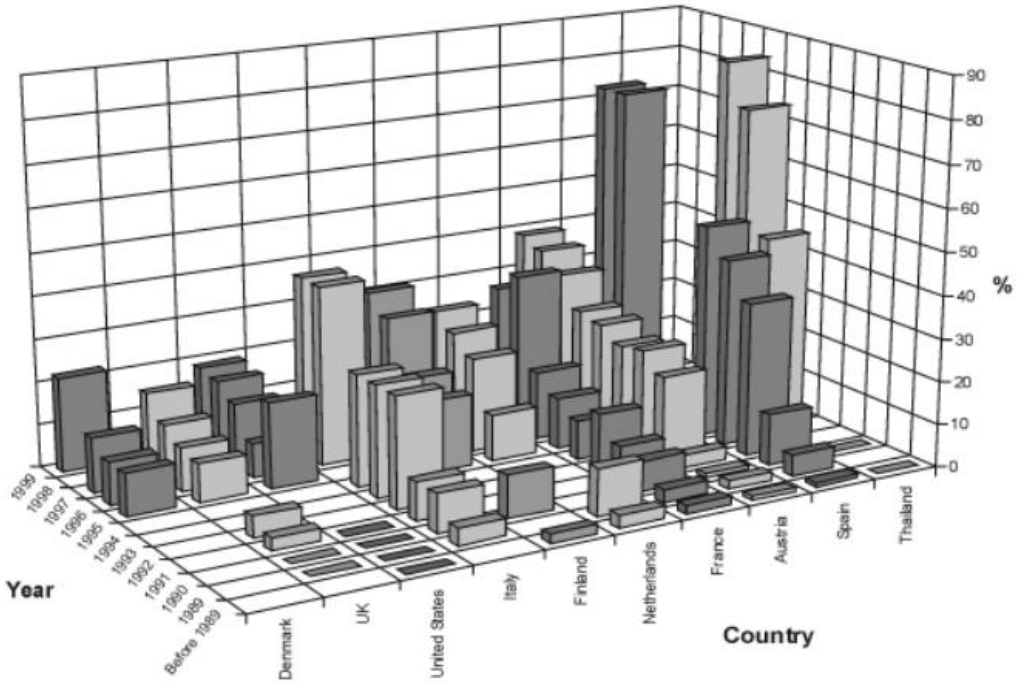
Referring to the increase in fluoroquinolone resistance in human Campylobacter infections in Denmark, Phil Sketchley of NOAH said during the same oral hearing:
"We have to address the facts. I am sure that the initiatives in Denmark were done with good intention – to reduce, hopefully, the incidence of resistance – but sadly that has not proven to be the case. The facts are now showing the opposite."

5. The US ban has been a clear success

Industry claims that the US ban on fluoroquinolones in poultry in September 2005 has not had the desired effect on the levels of resistance in human Campylobacter are based on a poor reading of the data.

The US had no fluoroquinolone resistance in human Campylobacter prior to the introduction of fluoroquinolones into US farming in 1995 [25]. Graph 2 shows that resistance in human infections quickly emerged thereafter (and similar increases in resistance were seen in other countries after they introduced fluoroquinolones to farming).

Graph 2 Emergence of fluoroquinolone resistance (%) in human Campylobacter in the US after fluoroquinones introduced to US farming in 1995 [25]



It is also interesting to note the large increase in fluoroquinolone resistance in the UK after the licensing of fluoroquinolones for use in farming in 1993. Some cases of resistant Campylobacter did occur prior to 1993, but British scientists, including government scientists, believed these cases to be mainly due to foreign travel and the importation of poultry meat into the UK from EU countries, such as the Netherlands, which had already licensed fluoroquinolones for use in poultry (in 1987 in the case of the Netherlands) [26].

Since the US ban on fluoroquinolones in poultry in 2005, there has been no significant further increase in resistance rates. Table 1 shows the rates of resistance found in human Campylobacter jejuni in the US since 2005.

Table 1 Resistance (%) to ciprofloxacin in human Campylobacter jejuni in the US 2005 to 2013 [27]

2005	2006	2007	2008	2009	2010	2011	2012	2013
21.6	19.6	26	22.6	23.1	22	24.1	25.3	22.3

As Table 1 shows, there has been little change in resistance in humans since 2005 and resistance in 2013 was still about 22%, as it was in 2005[1].

In contrast, in the UK and in most European countries, resistance in humans is still increasing and is at much higher levels than in the US. Table 2 summarises the average rate of resistance in reporting EU Member States, according to annual reports published by EFSA and ECDC[2].

[1] The exact figure each year should not be given too much importance, given that only about 150 to 300 isolates are tested per year, whereas it is estimated that about 2 million cases of Campylobacter infection occur in the US each year [28].

Table 2 Average resistance (%) to ciprofloxacin in human Campylobacter jejuni in EU reporting countries 2009 to 2014, with number of reporting countries in brackets [27]

2005	2006	2009	2010	2011	2012	2013	2014
37	44.2	53.3 (10)	51.6 (11)	52.5 (12)	54.1 (14)	54.6 (13)	60.2 (13)

So while it is true that banning fluoroquinolone use in poultry has not reduced resistance in human Campylobacter in the US, it certainly appears to have ensured that there has not been the large increase seen in Europe, where most countries still use fluoroquinolones in poultry.

Furthermore, the lack of a fall in resistance in humans in the US may simply be due to the fact that fluoroquinolone-resistant Campylobacter can be more biologically 'fit' than fluoroquinolone-sensitive Campylobacter (that is it competes well with fluoroquinolone-sensitive Campylobacter in the absence of fluoroquinolones, and its growth rate is not reduced as happens with some resistant bacteria), which means that removal of the antibiotic will not necessarily be followed by a reduction in resistance [30] .

In more recent years, however, the level of resistance in US retail poultry has fallen begun to fall (in 2013, resistance fell to an all-time low of just 11% [27], compared with an EU average of 65% in 2014 [4]), and this may result in falls in resistance in humans in years to come.

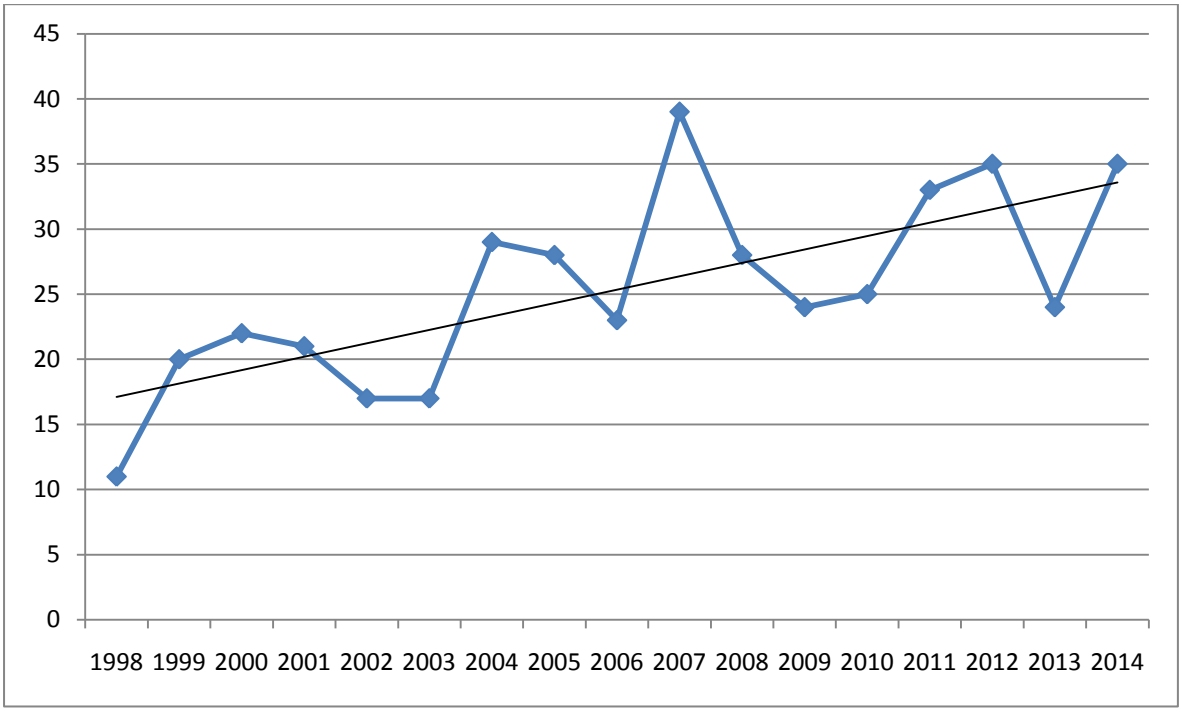
6. Increasing fluoroquinolone resistance in human Campylobacter in Denmark is due to increases in importation of retail poultry meat

Fluoroquinolones have not been used in chickens in Denmark since 2010, and only extremely small quantities were used in 2008 and 2009 [31], and low amounts in earlier years. Despite this, fluoroquinolone resistance in human Campylobacter infections in Denmark has continued on an upwards trend[3]. See Graph 3.

[2] The Member States reporting each year are not always the same, so the average is not exactly comparable from year to year. On the other hand, between 2009 and 2014 between 6,000 and 12,000 isolates are tested each year, so the resistance rates found are statistically significant.

[3] Only a relatively small number of isolates are tested each year (circa 100), so some of the changes from year to year is due to random variation, but the increasing trend seems clear.

Graph 3 Fluoroquinolone resistance (%) in human Campylobacter jejuni infections in Denmark [32], with trendline added



As section 3 shows, the BVA, RUMA and NOAH have suggested that this means the removal of fluoroquinolones from Danish poultry production has not benefited resistance rates in humans. The BVA blames "overprescribing of these compounds in humans" in Denmark [22].

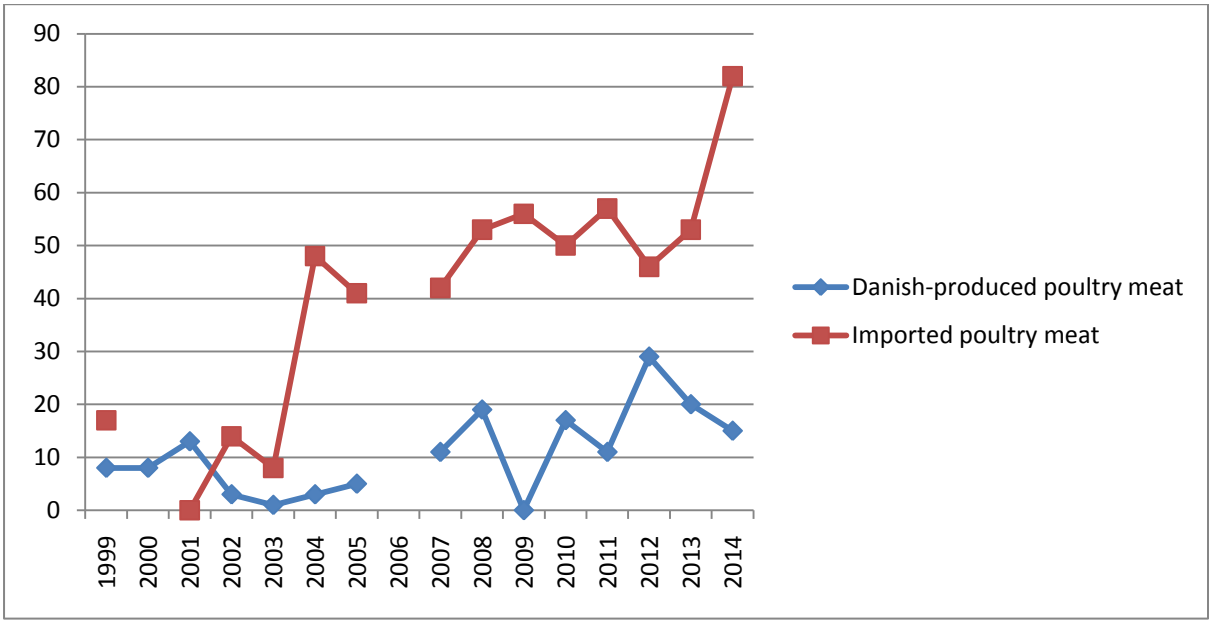
However, there are several reasons why imported poultry is likely to be the main cause of the increasing resistance in humans.

Firstly, as the annual Danish government DANMAP reports make clear, there is much more campylobacter in imported poultry meat than in Danish-produced poultry meat: only about 10-20% of Danish poultry meat is contaminated by campylobacter [33], whereas the contamination rate in the UK, for example, is about 59% [34], meaning that imported poultry will contribute disproportionately to the number of human Campylobacter infections.

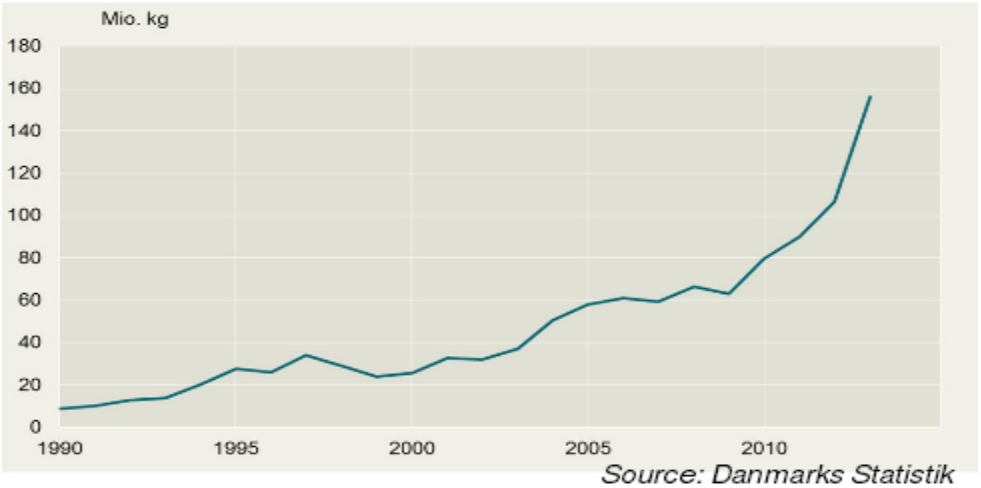
Secondly, as Graph 4 shows, fluoroquinolone resistance is much higher in imported retail poultry meat in Denmark than Danish-produced poultry meat[4], and is also increasing. And finally, as shown by Graphs 5 and 6, imported poultry meat has increased very significantly in recent years and now makes up a large proportion of total Danish consumption.

[4] It is worth noting that fluoroquinolone resistance in Danish poultry meat continued to increase until 2012, even after an end to the use of the antibiotics in Danish poultry. This is most likely because Denmark imports significant numbers of grandparent birds from the UK, either directly or via Sweden, and that these birds were often been treated with fluoroquinolones. It has been shown that fluoroquinolone resistance can be passed on to the parent birds and broilers from the grandparent birds for E. coli [35], and it is possible that this might have been happening for Campylobacter as well.

Graph 4 Resistance to fluoroquinolones (%) in Campylobacter jejuni in Danish-produced and imported poultry meat in Denmark [32]

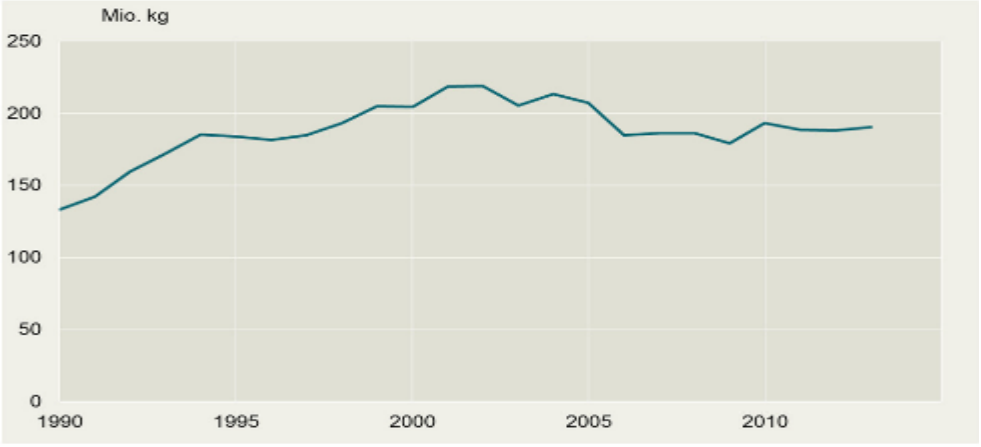


Graph 5 Imports of poultry meat to Denmark [36]



Source: Danmarks Statistik

Graph 6 Production of poultry meat in Denmark [36]



Source: Danmarks Statistik

Given the large increases in the importation of poultry meat into Denmark in recent years, and the fact that the Campylobacter on imported poultry is much more fluoroquinolone resistant than that on Danish-produced poultry meat, it is entirely to be expected that the rate of fluoroquinolone resistance in human Campylobacter infections in Denmark would go up, in spite of the lack of fluoroquinolone use in Danish poultry.

Far from providing evidence that fluoroquinolone resistance does not pass from poultry to humans, as suggested by industry groups, the Danish data provides further evidence that the resistance does transfer. Furthermore, it should be noted that at 35%, fluoroquinolone resistance in humans in Denmark is much lower than the EU average of 60%.

7. Countries with no fluoroquinolone use in poultry have much lower levels of resistance in human Campylobacter

Industry groups have tried to downplay the positive effect on resistance in humans from removing fluoroquinolones in poultry. However, in reality those countries which have banned or have never used fluoroquinolones in poultry have much lower levels of resistance in human Campylobacter infections than those countries which continue to use the drugs in poultry.

We know of seven countries which do not use fluoroquinonlones in poultry: Australia, Denmark, Finland, Iceland, Norway, Sweden and the United States. All of these countries have, by international standards, low levels of fluoroquinolone resistance in human Campylobacter infections. See Table 3.

Table 3 Fluoroquinolone (ciprofloxacin) resistance in human Campylobacter in countries that do not use fluoroquinolones in poultry [37][38][39][40][4][41][27]

Australia	**2%** (isolates collected in 2001-2002)
Denmark	**35%** (isolates collected in 2014)
Finland	**11.6%** (isolates collected in 2012)
Iceland	**6%** (isolates collected in 2013)
Norway	**29.7%** (isolates collected in 2014)
Sweden	**14%** (isolates collected in 2014)
United States	**22.3 %** (isolates collected in 2013)

On the other hand, data from a recent EFSA/ECDC report provides resistance rates in humans in 13 EU countries which use fluoroquinolones in poultry. See Table 2. On average, resistance was 60.2%, and all countries had resistance rates above 50%, with five countries having a rate above 80%.

Table 4 Fluoroquinolone (ciprofloxacin) resistance in human Campylobacter jejuni in 13 European countries that use fluoroquinolones in poultry in 2014 [4]

	N	% Res
Austria[(a)]	357	69.7
Estonia[(a)]	31	80.6
France	4,627	55.4
Italy[(a)]	69	81.2
Lithuania	198	87.4
Luxembourg[(a)]	761	64.5
Malta	182	69.8
Netherlands	3,033	59.8
Portugal[(a)]	96	97.9
Romania[(a)]	16	50.0
Slovakia	1,211	50.6
Slovenia[(a)]	1,028	69.5
Spain	246	87.4
Total (MSs 13	**11,855**	**60.2**

It is worth noting that the three countries with the highest reported resistance rate in humans in Table 4, Lithuania (87.4%), Spain (87.4%) and Portugal (97.9%) all have particularly high usage of fluoroquinolones in farming, using per Population Correction Unit (an EMA measure of the size of the total livestock population) respectively 3.5, 4.8 and 7.3 times more than the UK does [44].

The UK did not provide data for this recent report, but in the report published in 2015, the British resistance rate in human Campylobacter jejuni infections was reported at 46.9% [42] and recently obtained data from Public Health England shows that resistance in England was 48% in 2015 [43]. This below-average resistance rate is consistent with the UK's below-average use of fluoroquinolones and other quinolone antibiotics in farming compared with other EU countries (see [44]).

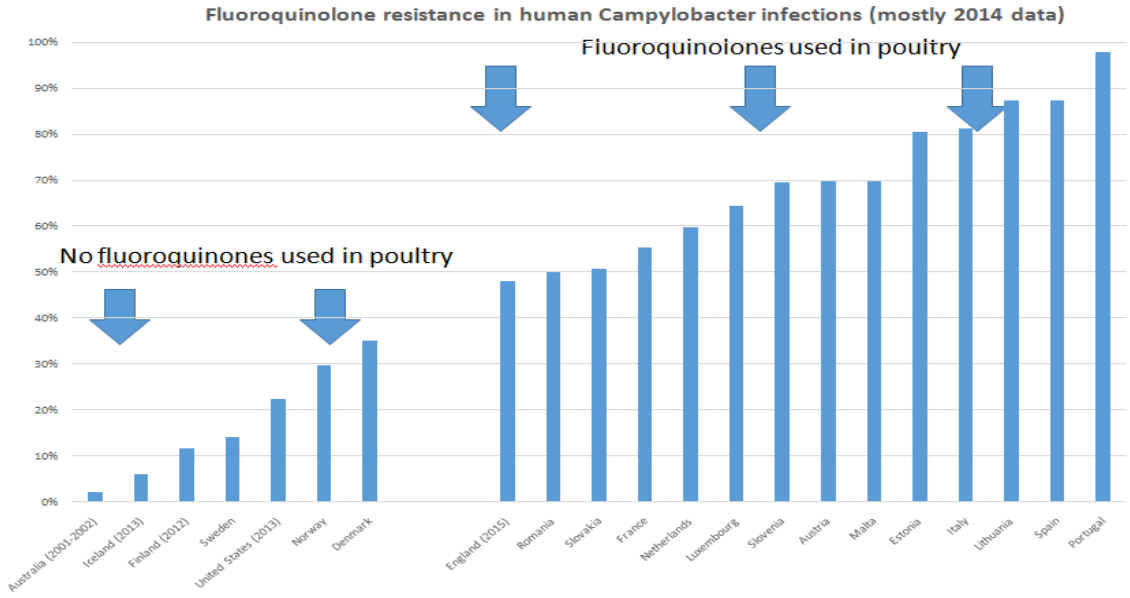
Unfortunately, data on fluoroquinolone use in poultry is not available in most countries (as data is not broken down by species).

However, in 2012, the British Poultry Council (BPC) committed to voluntarily ceasing all preventative use of fluoroquinolones in day-old chicks [45]. Furthermore, usage data voluntarily collected by the BPC since 2012 suggests that fluoroquinolone use in British chickens by BPC members has been cut to just 20kg in 2015, and that total usage by BPC members, including usage in turkeys, ducks and geese, was half a tonne [46] (BPC membership includes approximately 90% of poultry meat produced in the UK from chickens, turkeys, ducks and geese, but does not cover the other 10% or egg producers or game birds).

This usage level, particularly in chickens, is likely to be significantly lower than in most EU countries, which is consistent with the UK having one of the lowest, and perhaps the lowest resistance rate in human Campylobacter infections of all countries which use the antibiotics in poultry.

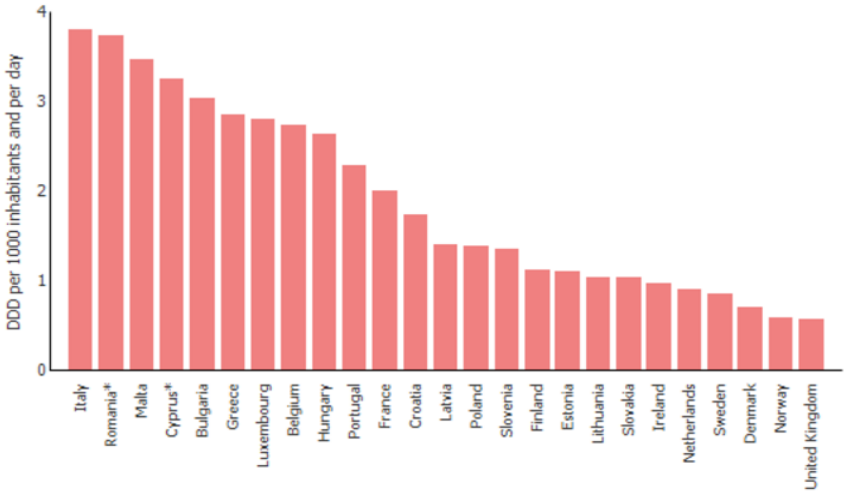
However, the resistance rate in the UK is still significantly higher than in countries that do not use fluoroquinolones in poultry [47]. See Graph 7.

Graph 7 Fluoroquinolone resistance in human Campylobacter jejuni infections (%)



It is worth noting that the UK is the lowest user of fluoroquinolone antibiotics in human medicine in Europe, see Graph 8. Even countries like Finland and Sweden consume significantly more fluoroquinolones in human medicine than the UK does (94% and 49% more respectively in 2014), and yet have much lower levels of fluoroquinolone resistance in Campylobacter infections in humans than the UK (12% for Finland, 14% for Sweden), because they do not use the antibiotics in poultry.

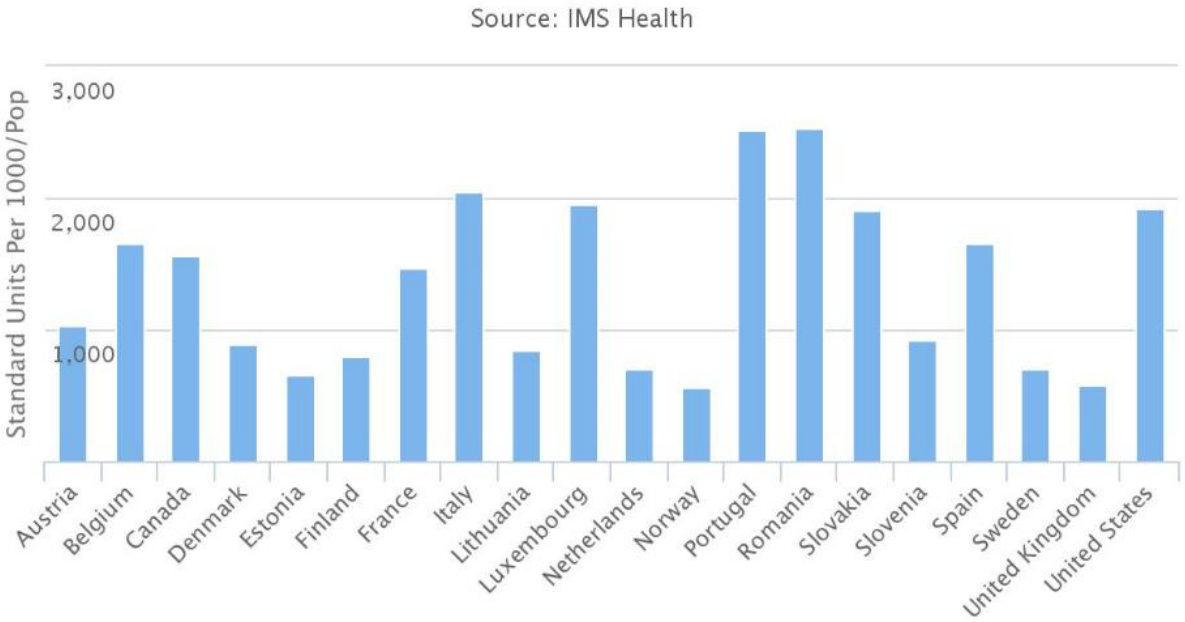
Graph 8 Consumption of fluoroquinolones in human medicine in European countries in 2014 [48]



The comparison is particularly striking when we compare human antibiotic consumption in the US with consumption in the UK. The only data we have available for the US is for all quinolone consumption (fluoroquinolones are quinolones, but not all quinolones are fluoroquinolones) for 2010. There is a large amount of cross-resistance between fluoroquinolones and other quinolones, large differences in quinolone consumption in human medicine should be having an impact on fluoroquinolone resistance if it is primarily human antibiotic use which influences resistance levels. Graph 9 includes as many countries as possible that we have resistance data for (see Graph 7). We can see that the US is a very high consumer of quinolones in

human medicine, and consumes more than three times per person what the UK consumes, yet it has much lower resistance levels in human Campylobacter infections.

Graph 9 Consumption of quinolone antibiotics in human medicine in 2010 with US data compared with European countries [49]



8. Increase fluoroquinolone resistance in human Campylobacter in England as fluoroquinolone use in humans is cut

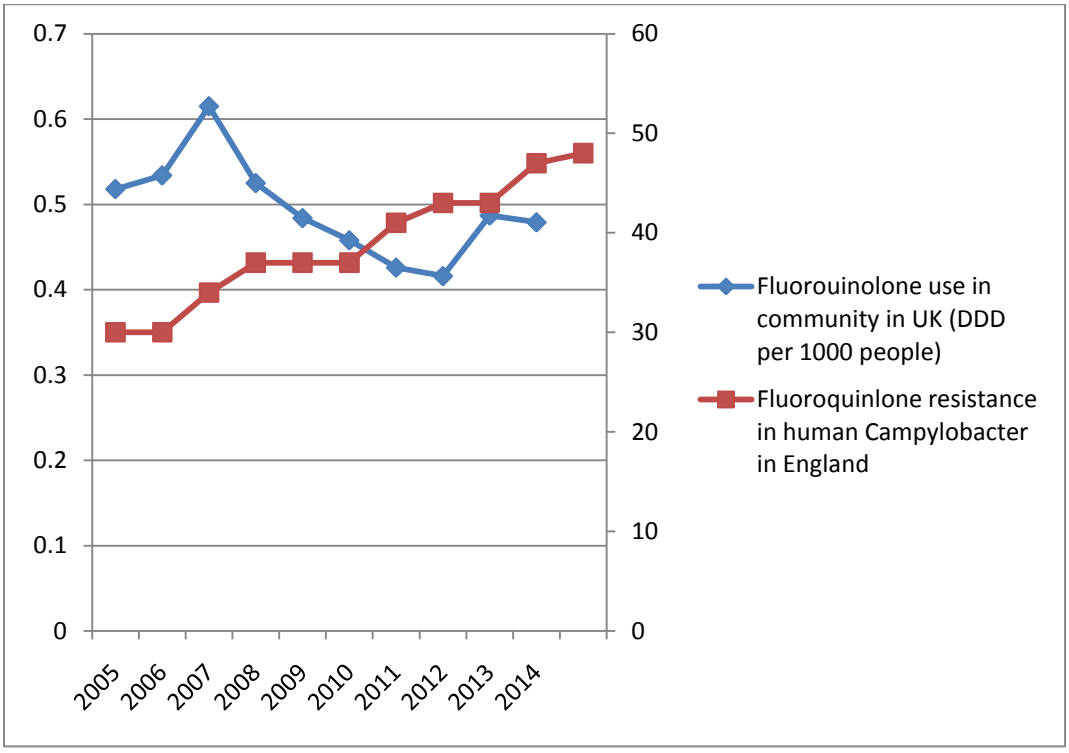
Data obtained by the Bureau of Investigative Jouralism from Public Health England, via a Freedom of Information request, shows increasing fluoroquinolone resistance in human Campylobacter infections in England since 2005. See Table 5.

Table 3 Fluoroquinolone resistance in human Campylobacter, England, 2005-2015 (%) [50]

2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015
30	30	34	37	37	37	41	43	43	47	48

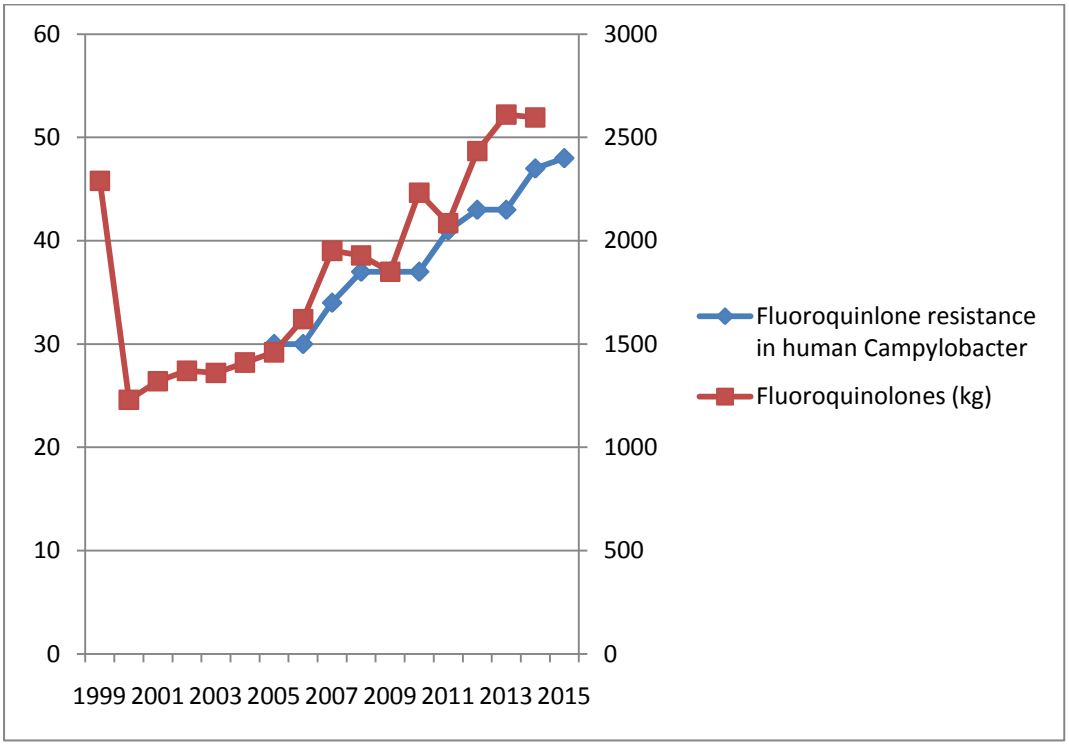
This trend of increasing fluoroquinolone resistance in human Campylobacter infections has been occurring despite cuts in the use of fluoroquinolone use in recent years. As mentioned in the previous section, the UK is now the lowest user of fluoroquinolones in Europe, and Graph 10 shows that cuts in the use of fluoroquinolones in the community (ie. outside of hospitals, which is where most fluoroquinolones use occurs in human medicine) has not had a discernable impact on resistance.

Graph 10 Fluoroquinolone resistance in human Campylobacter in England (%) and fluoroquinolone use in human medicine in the community in the UK [51]



On the other hand, Graph 11 shows that fluoroquinolone sales for use in veterinary me

Graph 11 Fluoroquinolone resistance in human Campylobacter in England (%) and fluoroquinolone sales in veterinary medicine in the UK



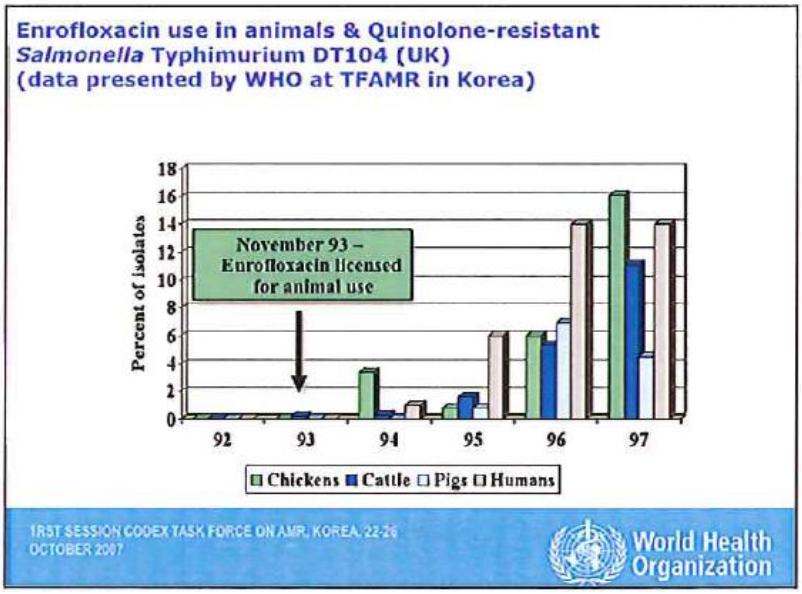
8. NFU's invalid criticism of graph showing that fluoroquinolone resistance in human Salmonella infections is linked to farm antibiotic use

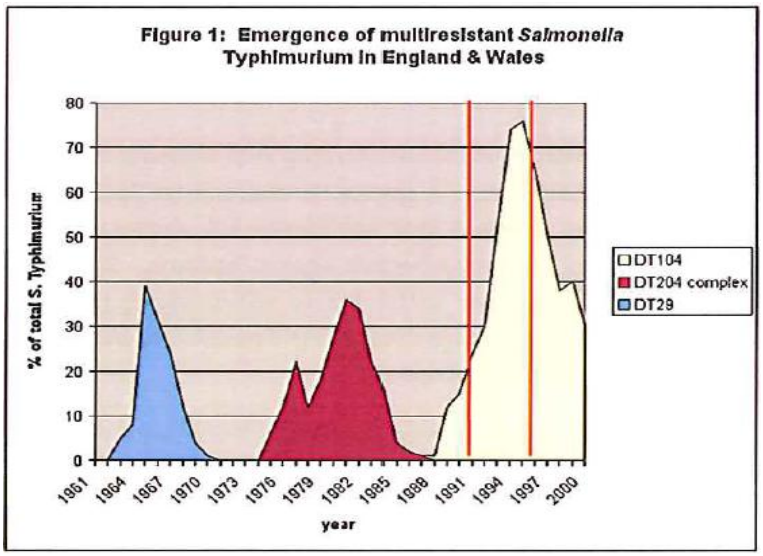
As mentioned above in Section 2, the introduction of fluoroquinolones to farming in 1993 in the UK led to a subsequent emergence of fluoroquinolone resistance in Salmonella Typhimurium DT104 in humans and farm animals. Salmonella typhiumurium DT104 was a widespread strain of Salmonella, which was frequently multi-resistant (meaning resistant to three or more families of antibiotics), but which had been fluoroquinolone sensitive in both humans and farm animals prior to 1993.

This data was collected by the PHLS and widely quoted, including by the WHO and the ECDC [12][3][12], as evidence that the use of fluoroquinolones in farming was likely to be having an impact on resistance levels in human medicine and, as mentioned in Section 2, it even motivated the FDA to put an end to licensing new fluoroquinolone products for poultry and to investigate the situation further.

However, in 2012, the NFU published a document which claimed that the graph was essentially misleading because it did not include earlier years [53]. According to the NFU, had earlier years been included, it would have shown that Salmonella typhimurium DT104 was increasing before fluoroquinolones were licensed in 1993, and that resistant strains occurred before DT104. The NFU published the two graphs below (see Graph 12) and said that the WHO graph only covered the period between the two red lines in the second graph.

Graph 12 NFU graph purporting to show that WHO graph was misleading





The reason the NFU's objection is wrong is that it is confusing fluoroquinolone-resistant Salmonella with multi-resistant Salmonella. Multi-resistant Salmonella are Salmonella which are resistant to at least three or four antibiotics from different antibiotic families (e.g. tetracyclines, ampicillin, streptomycin, trimethoprim), but multi-resistant does not necessarily mean resistant to any fluoroquinolones. It is true that the Salmonella typhimurium DT104 epidemic began before the introduction of fluoroquinolones to farming, and it is also true that there had previously been epidemics of other multi-resistant strains of Salmonella, but these Salmonellae were not fluoroquinolone resistant.

The NFUs second graph simply shows the rise and fall of several strains of multi-resistant Salmonella, but is not a depiction of fluoroquinolone resistance. The first WHO graph shows that fluoroquinolone resistance in the then widespread strain DT104 only began after fluoroquinolones were introduced to farming.

9. Recommendations

Fluoroquinolones are critically important antibiotics in human medicine which are used for treating severe and invasive infections. Their use in all farm animals, not just poultry, should therefore be kept to an absolute minimum.

In addition to their current use for mass medication in poultry, fluoroquinolones can be commonly used in cattle and pigs for controlling diseases like diarrhoea [54] which are frequently caused by inappropriately early weaning or stressful husbandry conditions. Overuse in other farm-animal species can also contribute to higher levels of resistance in human Salmonella, E. coli, and Campylobacter infections [11][12].

Fluoroquinolones should not be used as a production tool, but only as life-saving antibiotics for treating individual animals. Fluoroquinolones should therefore:

- be banned for all mass medication
- be restricted to use in individual sick animals. Fluoroquinolones should not be used preventatively, even in individual animals.
- be restricted to use in situations where sensitivity testing, or knowledge of recent sensitivity testing results, indicates that non-critically important antibiotics are unlikely to work
- be restricted to on-label use, ie. only used in species where the antibiotics are licensed.

References

All links were accessed in March or April of 2016.

[1] WHO, 1998. Use of Quinolones in Food Animals and Potential Impact on Human Health, http://apps.who.int/iris/bitstream/10665/65514/1/WHO_EMC_ZDI_98.10.pdf

[2] Stockdale et al. 2015, Emergence of extensive fluoroquinolone resistance in Campylobacter gastroenteritis in Liverpool, UK, *Journal of Infection*, http://www.journalofinfection.com/article/S0163-4453(15)00392-8/abstract

[3] ECDC and others, 2009. Joint Opinion on antimicrobial resistance (AMR) focused on zoonotic infections, http://www.efsa.europa.eu/sites/default/files/scientific_output/files/main_documents/1372.pdf

[4] EFSA and ECDC, 2016. The European Union summary report on antimicrobial resistance in zoonotic and indicator bacteria from humans, animals and food in 2014, http://ecdc.europa.eu/en/publications/Publications/antimicrobial-resistance-zoonotic-bacteria-humans-animals-food-EU-summary-report-2014.pdf

[5] CVMP, 2007. Public Statement on the Use of (Fluoro)Quinolones in Food-Producing Animals in the European Union: Developmet of Resistance and Impact on Human and Animal Health, http://www.ema.europa.eu/docs/en_GB/document_library/Public_statement/2009/10/WC500005152.pdf

[6] FSA, Campylobacter – what it is and how does it affect you?, https://www.food.gov.uk/sites/default/files/campylobacter-what-is-it.pdf

[7] Gras et al. 2012, Risk Factors for Campylobacteriosis of Chicken, Ruminant, and Environmental Origin: A Combined Case-Control and Source Attribution Analysis, *PLoS One*, http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3411806/pdf/pone.0042599.pdf

[8] Skarp et al. 2016, Camylobacterosis: the role of poultry meat, *Clinical Microbiology and Infection*, http://www.clinicalmicrobiologyandinfection.com/article/S1198-743X(15)01025-3/pdf

[9] EFSA, 2010. Scientific Opinion on the Quantification of the risk posed by broiler meat to human campylobacterosis in the EU, http://www.efsa.europa.eu/sites/default/files/scientific_output/files/main_documents/1437.pdf

[10] FAO, WHO and OIE, 2003. Joint FAO/OIE/WHO Expert Workshop on Non-Human Antimicrobial Usage and Antimicrobial Resistance: Scientific assessment, http://www.oie.int/doc/ged/D454.PDF

[11] EFSA, 2008. Foodborne antimicrobial resistance as a biological hazard, http://www.efsa.europa.eu/sites/default/files/scientific_output/files/main_documents/biohaz_op_ej765_antimicrobial_resistance_en%2C3.pdf

[12] WHO, 2011. Tackling antibiotic resistance from a food safety perspective in Europe, http://www.euro.who.int/__data/assets/pdf_file/0005/136454/e94889.pdf

[13] House of Lords, 1998, Science and Technology, Seventh Report, http://www.parliament.the-stationery-office.co.uk/pa/ld199798/ldselect/ldsctech/081vii/st0701.htm and https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/250978/4172.pdf

[14] ACMSF, 2000. Microbial Antibiotic Resistance in Relation to Food Safety, http://www.poultry-health.com/library/antimicrobials/acmsf996.htm

[15] Nelson et al., 2007. Fluoroquinolone-Resistant Campylobacter Species and the Withdrawal of Fluoroquinolones from Use in Poultry: A Public Health Success Story, *Clinical Infectious Diseases*, http://www.cdc.gov/narms/pdf/JNelson_FluoroquinoloneRCampy_CID.pdf

[16] FDA, 2005. FDA Announces Final Decision About Veterinary Medicine, http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2005/ucm108467.htm

[17] WHO, 1997. The Medical Impact of Antimicrobial Use in Food Animals. Report of a WHO Meeting. Berlin, Germany, 13-17 October 1997, http://apps.who.int/iris/bitstream/10665/64439/1/WHO_EMC_ZOO_97.4.pdf

[18] Farmers Weekly, 2012. Campaign to ban fluoroquinolones in poultry, http://www.fwi.co.uk/poultry/campaign-to-ban-fluoroquinolones-in-poultry.htm

[19] Young et al., 1999. The Use and Misuse of Antibiotics in UK Agriculture

[20] Alliance to Save Our Antibiotics, 2012. Human risk from farm antibiotics press release, https://www.ciwf.org.uk/includes/documents/cm_docs/2012/p/pr20121116.pdf

[21] BVA, 2014. Written evidence to the House of Commons Science and Technology Committee on Antimicrobial Resistance, http://data.parliament.uk/writtenevidence/committeeevidence.svc/evidencedocument/science-and-technology-committee/antimicrobial-resistance-amr/written/5511.pdf

[22] RUMA, 2014. Written evidence to the House of Commons Science and Technology Committee on Antimicrobial Resistance, http://data.parliament.uk/writtenevidence/committeeevidence.svc/evidencedocument/science-and-technology-committee/antimicrobial-resistance-amr/written/3451.pdf

[23] NOAH, 2010. The Use of Fluoroquinolones in Animal Health, http://www.noah.co.uk/issues/briefingdoc/18-fluoroquinolones.htm

[24] Fizgerald J., 2014. Oral evidence to the House of Commons Science and Technology Committee on Antimicrobial Resistance, 29 January 2014, http://data.parliament.uk/writtenevidence/committeeevidence.svc/evidencedocument/science-and-technology-committee/antimicrobial-resistance-amr/oral/5784.pdf

[25] Enberg et al., 2001, Quinolone and Macrolide Resistance in Campylobacter jejuni and C. coli: Resistance Mechanisms and Trends in Human Isolates, *Emerging Infectious Diseases*, http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2631682/pdf/11266291.pdf

[26] Gaunt and Piddock, 1996. Ciprofloxacin resistant Campylobacter spp. in humans: an epidemiological and laboratory study, *Journal of Antimicrobial Chemotherapy*, https://jac.oxfordjournals.org/content/37/4/747.full.pdf

[27] FDA, 2015. National Antimicrobial Resistance Monitoring Scheme Data Tables, http://www.fda.gov/downloads/AnimalVeterinary/SafetyHealth/AntimicrobialResistance/NationalAntimicrobialResistanceMonitoringSystem/UCM453387.pdf

[28] Palacios, 2007. The Health Burden of Campylobacter Infection and the Impact of Antimicrobial Resistance: Playing Chicken, *Clinical Infections Diseases*, http://cid.oxfordjournals.org/content/44/5/701.full.pdf+html

[29] Various EFSA and ECDC reports,
http://www.efsa.europa.eu/sites/default/files/scientific_output/files/main_documents/1372.pdf
http://www.efsa.europa.eu/sites/default/files/scientific_output/files/main_documents/130r.pdf
http://www.efsa.europa.eu/sites/default/files/scientific_output/files/main_documents/2154.pdf
http://www.efsa.europa.eu/sites/default/files/scientific_output/files/main_documents/2598.pdf
http://www.efsa.europa.eu/sites/default/files/scientific_output/files/main_documents/3196.pdf
http://www.efsa.europa.eu/sites/default/files/scientific_output/files/main_documents/3590.pdf
http://ecdc.europa.eu/en/publications/Publications/antimicrobial-resistance-zoonotic-bacteria-humans-animals-food-EU-summary-report-2013.pdf

http://ecdc.europa.eu/en/publications/Publications/antimicrobial-resistance-zoonotic-bacteria-humans-animals-food-EU-summary-report-2014.pdf

[30] Luo et al., 2005. Enhanced in vivo fitness of fluoroquinolone-resistant Campylobacter jejuni in the absence of antibiotic selection pressure, *Proceedings of the National Academy of Sciences of the United States of America*, http://www.ncbi.nlm.nih.gov/pmc/articles/PMC545549/pdf/pnas-0408966102.pdf

[31] DANMAP, 2014, http://www.danmap.org/~/media/Projekt%20sites/Danmap/DANMAP%20reports/DANMAP%202014/Danmap_2014.ashx
DANMAP 2012, http://www.danmap.org/~/media/Projekt%20sites/Danmap/DANMAP%20reports/DANMAP%202012/Danmap_2012.ashx

[32] Data from annual DANMAP reports, which are available here http://www.danmap.org/Downloads/Reports.aspx

[33] DANMAP 2013, 2014. http://www.danmap.org/~/media/Projekt%20sites/Danmap/DANMAP%20reports/DANMAP%202013/DANMAP%202013.ashx

[34] FSA, 2016. Year 2 of a UK-wide survey of campylobacter contamination on fresh chickens at retail (July 2015 to July 2016), https://www.food.gov.uk/science/microbiology/campylobacterevidenceprogramme/retail-survey-year-2

[35] Börjesson et al., 2015. Introduction of quinolone resistant Escherichia coli to Swedish broiler population by imported breeding animals, *Veterinary Microbiology*, http://www.ncbi.nlm.nih.gov/pubmed/26608722

[36] Danmarks Statistik, http://www.foedevarestyrelsen.dk/SiteCollectionDocuments/25_PDF_word_filer%20til%20download/05kontor/Servicetjek_Fjerkraesektoren/7_%20Introduction-to-the-dansih-broiler-sector-Birthe-Steenberg-Landbrug-og-Foedevarer.pdf

[37] Unicomb L. et al., 2003, Fluoroquinolone Resistance in Campylobacter Absent from Isolates, Australia, *Emerging Infectious Diseases*, http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3035555/pdf/03-0336.pdf

[38] DANMAP 2014, 2015. http://www.danmap.org/~/media/Projekt%20sites/Danmap/DANMAP%20reports/DANMAP%202014/Danmap_2014.ashx

[39] Olkkola S. et al., 2016. Antimicrobial Resistance and Multilocus Sequence Types of Finnish Campylobacter jejuni isolates from Multiple Sources, *Zoonoses and Public Health*, http://onlinelibrary.wiley.com/doi/10.1111/zph.12198/pdf

[40] Sýklalyfjanotkun og sýklalyfjanæmi baktería í mönnum og dýrum á Íslandi 2013, http://www.landlaeknir.is/servlet/file/store93/item24148/Syklalyfjanotkun_og_syklalyfjanaemi_2013.pdf

[41] SVARM/SWEDRES 2014, 2015. http://www.sva.se/globalassets/redesign2011/pdf/om_sva/publikationer/swedres_svarm2014.pdf

[42] EFSA and ECDC, 2015. The European Union summary report on antimicrobial resistance in zoonotic and indicator bacteria from humans, animals and food in 2013, http://www.efsa.europa.eu/sites/default/files/scientific_output/files/main_documents/4036.pdf

[43] Data obtained via a Freedom of Information request submitted by the Bureau of Investigative Journalisem

[44] EMA, 2015. Sales of veterinary antimicrobial agents in 26 EU/EEA countries in 2013, Fifth ESVAC report, http://www.ema.europa.eu/docs/en_GB/document_library/Report/2015/10/WC500195687.pdf

[45] British Poultry Council drive to cut antibiotics, *Farmers Weekly*, http://www.fwi.co.uk/poultry/british-poultry-council-drive-to-cut-antibiotics.htm

[46] British Poultry Council, 2016. Leading the Way in the Responsible Use of Antibiotics, http://www.britishpoultry.org.uk/wp-content/uploads/2016/04/The_BPC_Antibiotic_Stewardship_Scheme_April2016.pdf

[47] Data for 2014 from the ECDC: go to http://ecdc.europa.eu/en/healthtopics/antimicrobial_resistance/esac-net-database/Pages/Antimicrobial-consumption-rates-by-country.aspx, select "fluoroquinolones" and "hospital and community" from drop-down menus

[48] European Centre for Disease Prevention and Control ESAC-Net data, http://ecdc.europa.eu/en/healthtopics/antimicrobial_resistance/esac-net-database/Pages/Antimicrobial-consumption-rates-by-country.aspx

[49] The Center for Disease Dynamics, Economics and Policy, http://resistancemap.cddep.org/resmap/use

[50] Public Health England data obtained via a Freedom of Information request submitted by the Bureau of Investigative Journalism

[51] ECDC, ESAC-Net, http://ecdc.europa.eu/en/healthtopics/antimicrobial_resistance/esac-net-database/Pages/database.aspx

[52] Data on the veterinary sales of fluoroquinolones is from the VMD, from Freedom of Information requests for earlier years, and from sales data reports for later years, https://www.gov.uk/government/publications/veterinary-antimicrobial-resistance-and-sales-surveillance-2014

[53] NFU, 2012. NFU Policy Report, Antibiotics in Agriculture: A review of antibiotic control and usage in England Wales, with reference to other EU Member State systems

[54] De Briyne et al., 2014. Antibiotics used most commonly to treat animals in Europe, *Veterinary Record*, http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4215272/pdf/vetrec-2014-102462.pdf