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Fluoroquinolone Use and Associated Adverse Drug Events in England

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Dear Editor,

We read with great interest the article published in this journal that addressed the complex interactions of antimicrobial stewardship, bacterial drug resistance, sepsis and the resultant lay press coverage of these topics in the United Kingdom (UK) currently.[1] Oral fluoroquinolones have been extensively used to treat a wide range of bacterial infections for many years, some of which have been complicated by sepsis, and have been predominately used in the primary care setting. Concerns for overuse of these drugs with resultant worsening bacterial resistance, more adverse drug reactions (ADR), and the increased risk of *Clostridium difficile* infection have been a focus of educational interventions for clinicians, the public, and policymakers.[1,2]

Earlier trend studies[3-7] involving segments of the population in the UK have been reported and provide a profile of fluoroquinolone use, but have inconsistent results with no detailed information on types of fluoroquinolone-related ADR. Therefore, the aim of the current investigation was to better define contemporary trends in fluoroquinolone use and provide a characterization of reported ADR in a large, population-based investigation from England.

Data for all oral antibiotics prescribed in the community setting (outside hospitals) in England between 2010 and 2017 were extracted from the Prescription Cost Analysis data held by NHS Digital (https://digital.nhs.uk/data-and-information/publications/statistical/prescription-cost-analysis). Clinicians who issued the prescriptions included physicians, nurse practitioners, and other health care providers, including dentists. For this investigation, a focus on fluoroquinolones was conducted with data for each oral fluoroquinolone included.

National Yellow Card Interactive Drug Analysis Profile data from the Medicines and Healthcare Products Regulatory Agency (MHRA) (http://yellowcard.mhra.gov.uk/iDAP/) were interrogated and data extracted for all reported ADR to fluoroquinolones that were administered orally, or where the route of administration was not stated (reactions to drugs administered parenterally, topically or by other routes were excluded), between 2010 and 2017, to define the rate of ADR with the ADR rate/million prescriptions calculated. In addition, an investigation of the different organ systems involved in an ADR was done for comparative purposes among the different oral fluoroquinolones that had been prescribed during the study period.

Overall, there were over six million prescriptions for oral fluoroquinolones issued in the community setting for the eight years of the study period and ciprofloxacin accounted for 91.6% of prescriptions. Remarkably, there was a 29.8% decline (880,970 for 2010 to 618,229 for 2017) in ciprofloxacin prescriptions over this period with a decline noted in each of the study years (Figure 1). Prescriptions issued for the other oral fluoroquinolones also declined over the study period, except for levofloxacin and ofloxacin where prescriptions increased the last two years of the study.

For every million prescriptions issued over the study period, 250 resulted in an ADR of which 39, 205, and 6 were designated as non-serious, serious, or fatal, respectively. For ciprofloxacin, musculoskeletal reactions were the most frequently reported serious reactions (n=889) (Table 1), with tendon disorders being the most common of these (n=248). Nervous system disorders were the next most frequently reported serious reactions (n=602) of which paresthesia/dysesthesia/peripheral neuropathy was most common (n=196) followed by headaches (n=55) and seizures (n=43). Of the 25 fatal ciprofloxacin-related reactions reported, 5 were reported as “sudden death”, 6 as infections,

of which 3 were attributed to *C. difficile* infection, and 4 as psychiatric disorders resulting in suicide.

Previous surveys from England have yielded varied results and are likely due, in part, to the variability in healthcare settings of patient cohorts included in databases previously used for investigation. [3-7] For example, in one large investigation of 98% (n=158) of acute hospitals in the National Health Service that included data from IMS Health, a data warehouse, between 2009 and 2013, fluoroquinolone use increased 1.6%.[3] Notably, there were large variations in data comparisons between individual hospitals and use included all routes of fluoroquinolone administration. In contrast, data retrieved from the UK THIN database for 2000-2015, which included six percent of the UK's General Practice patient population, demonstrated a reduction in fluoroquinolone use in recent years.[7] By inclusion of all community-prescribed oral fluoroquinolone use in England in the current work, the trend analysis is likely to be more accurate than that of prior reports.

In response to largely post-approval ADR,[2] serial warnings have been released to inform clinicians and patients of potential risks of fluoroquinolone use, which could have impacted fluoroquinolone use in the current investigation, along with educational and institutional interventions. Although uncommon, some of these ADR can be chronic and result in disabling effects on patients who suffer a diminished quality of life.

Fluoroquinolone use has been associated with an increased risk of development of *C. difficile* infection, which can be recurrent and severe complications can occur, including sepsis and death, the latter of which was seen in the current investigation. This has been the subject of national campaigns in the UK to reduce the use of fluoroquinolones and have likely impacted the trend data of fluoroquinolone use described in our study.[4,8,9]

The development of fluoroquinolone resistance among aerobic gram-negative bacilli has reduced use of this drug class and could have contributed to the trend data displayed in the current investigation. Interestingly, with the reduction in fluoroquinolone "burden" on bacteria seen in clinical practice, improvement in *in vitro* susceptibility of some organisms has been described.[10]

A major limitation of this work is that information is lacking so that we are unable to identify causal factors responsible for the declining use of oral fluoroquinolones in the community-based practice in England. As cited previously, use of the Yellow Card system to identify ADR is dependent on passive reporting and is biased by the likelihood that non-severe reactions are less often reported, as evidenced by the data presented in the current survey.

Based on findings presented herein, there has been a marked reduction in oral fluoroquinolone use in the ambulatory care setting in England. Ciprofloxacin has accounted for the bulk of this use; reports of serious ADR coupled with antimicrobial stewardship programs that have advocated for diminished use of oral fluoroquinolones have likely been responsible for the decline, although cause-and-effect was not evaluated.

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Transparency declarations

All authors have no declarations of conflicts of interest.

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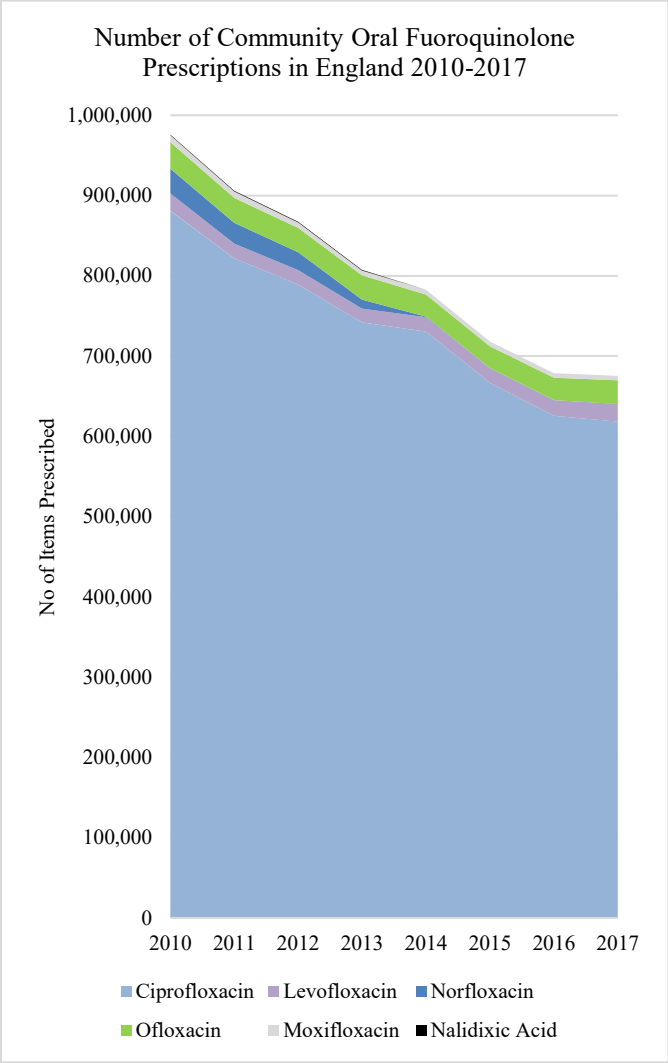
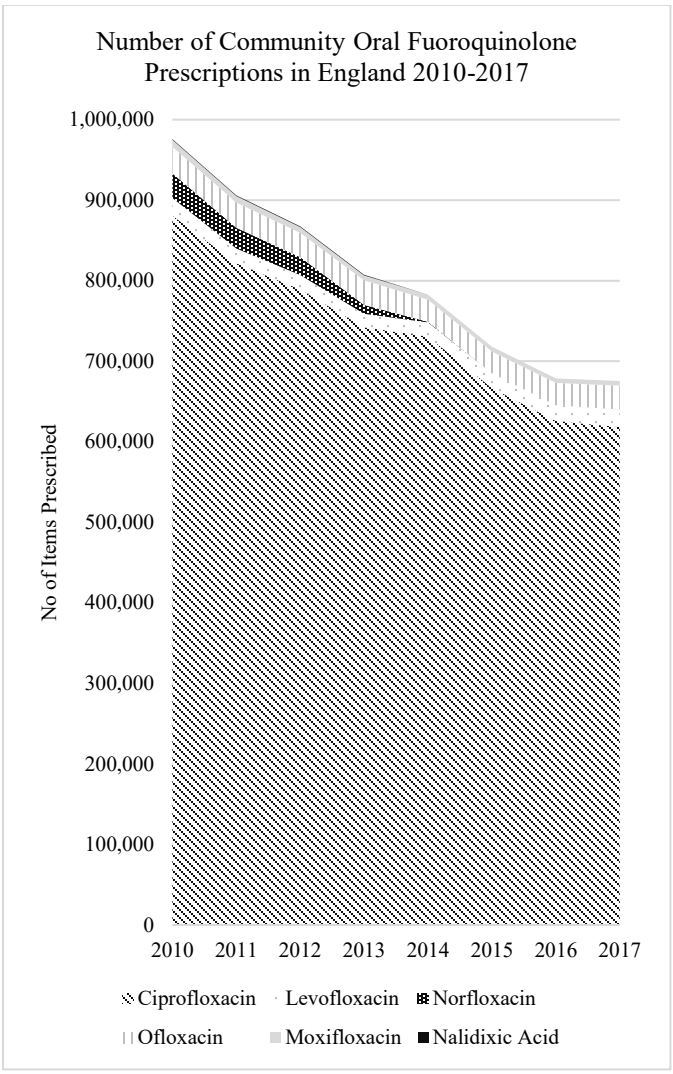
Table 1 Different types of serious and fatal adverse reactions reported for oral fluoroquinolones between 2010-2017

	Ciprofloxacin		Other Fluoroquinolones		All Fluoroquinolones		No of Events/million Fluoroquinolone Rx	
Type of Adverse Reaction	Serious ADR	Fatal ADR	Serious ADR	Fatal ADR	Serious ADR	Fatal ADR	Serious ADR	Fatal ADR
Blood and lymphatic system disorders	42	1	8	0	**50**	**1**	**7.8**	**0.2**
Cardiac disorders	85	2	25	1	**110**	**3**	**17.2**	**0.5**
Congenital, familial & genetic disorders	4	0	0	0	**4**	**0**	**0.6**	**0.0**
Ear and labyrinth disorders	83	0	22	0	**105**	**0**	**16.4**	**0.0**
Endocrine disorders	1	0	3	0	**4**	**0**	**0.6**	**0.0**
Eye disorders	122	0	29	0	**151**	**0**	**23.6**	**0.0**
Gastrointestinal disorders	347	1	96	0	**443**	**1**	**69.1**	**0.2**
General disorders & administration site conditions	570	7	140	2	**710**	**9**	**110.7**	**1.4**
Hepatobiliary disorders	36	2	9	0	**45**	**2**	**7.0**	**0.3**
Immune system disorders	43	0	11	1	**54**	**1**	**8.4**	**0.2**
Infections and infestations	148	6	42	4	**190**	**10**	**29.6**	**1.6**
Injury, poisoning & procedural complications	177	0	68	0	**245**	**0**	**38.2**	**0.0**
Investigations	153	0	46	0	**199**	**0**	**31.0**	**0.0**
Metabolism & nutrition disorders	63	0	16	0	**79**	**0**	**12.3**	**0.0**
Musculoskeletal & connective tissue disorders	889	0	263	0	**1152**	**0**	**179.7**	**0.0**
Neoplasms benign, malignant & unspecified (incl cysts and polyps)	2	0	0	0	**2**	**0**	**0.3**	**0.0**
Nervous system disorders	602	0	180	3	**782**	**3**	**122.0**	**0.5**
Pregnancy, puerperium & perinatal conditions	0	0	0	0	**0**	**0**	**0.0**	**0.0**
Product issues	3	0	0	0	**3**	**0**	**0.5**	**0.0**
Psychiatric disorders	409	4	149	2	**558**	**6**	**87.0**	**0.9**
Renal and urinary disorders	81	0	13	1	**94**	**1**	**14.7**	**0.2**
Reproductive system & breast disorders	26	0	1	0	**27**	**0**	**4.2**	**0.0**
Respiratory, thoracic & mediastinal disorders	98	0	40	1	**138**	**1**	**21.5**	**0.2**
Skin and subcutaneous tissue disorders	353	2	68	0	**421**	**2**	**65.7**	**0.3**
Social circumstances	10	0	3	0	**13**	**0**	**2.0**	**0.0**
Surgical & medical procedures	4	0	0	0	**4**	**0**	**0.6**	**0.0**
Vascular disorders	48	0	10	0	**58**	**0**	**9.0**	**0.0**
All Reactions	**4399**	**25**	**1242**	**15**	**5641**	**40**	**879.9**	**6.2**

Notes: These data represent the number of different types of adverse event recorded between 2010-2017 for each fluoroquinolone type. Each individual/prescription may be associated with more than one type of adverse event. ADR = Adverse Drug Reaction, Rx = Prescriptions.

Figure 1. Number of community oral fluoroquinolone prescriptions in England, 2010-2017 (both color and B&W versions).




Number of Community Oral Fuoroquinolone Prescriptions in England 2010-2017
No of Items Prescribed
1,000,000
900,000
800,000
700,000
600,000
500,000
400,000
300,000
200,000
100,000
0
2010
2011
2012
2013
2014
2015
2016
2017
Ciprofloxacin
Levofloxacin
Norfloxacin
Ofloxacin
Moxifloxacin
Nalidixic Acid