Addendum to: Relative and Absolute Risk of Tendon Rupture with Fluoroquinolone and Concomitant Fluoroquinolone/Corticosteroid Therapy: Population-Based Nested Case–Control Study

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Dear Editor,

The European Medicines Agency (EMA) recently concluded a safety review of fluoroquinolone antibiotics, which are commonly prescribed in Europe [1]. The EMA recommended that the marketing authorization of medicines containing cinoxacin, flumequine, nalidixic acid, and piperidic acid should be suspended and that the use of the remaining fluoroquinolone antibiotics should be restricted due to the risk of disabling and potentially long-term side effects [2]. This led to a restriction in indication following a harmonization procedure as part of the referral. We recently published a nested case–control study characterizing the risk of tendon rupture with fluoroquinolone therapy demonstrating that the relative incidence associated with fluoroquinolone exposure varied by timing, type of tendon rupture and concomitant exposure to systemic corticosteroids [3]. Whilst an absolute measure of risk was calculated, the number needed to harm (NNH) may be easier to interpret for policy makers, clinicians and patients. In this regard, the larger the NNH the more patients can on average be treated with fluoroquinolones before one person is harmed. We have therefore calculated the NNH for tendon rupture associated with different durations of fluoroquinolone therapy, overall and stratified by age and gender.

The NNH was calculated using the reciprocal of the adjusted rate difference for tendon rupture per 10,000 person-years of fluoroquinolone exposure and was calculated for different durations of fluoroquinolone therapy (5-, 7-, 10-, 14-, 21- and 28-day courses). These durations were chosen to reflect the variation in clinical practice according to the condition being treated [4]. NNH for different durations of fluoroquinolone therapy varied by age, gender and duration of fluoroquinolone therapy (Table 1). For any tendon rupture: the overall NNH ranged from 44,951 patients (28-day course) to 251,724 patients (5-day course); NNH was lower in women and in those aged ≥ 60 years. A similar distribution was seen with concomitant exposure to fluoroquinolone and systemic corticosteroid therapy but NNH were lower in this case (Table 1). For any tendon rupture associated with concomitant fluoroquinolone and corticosteroid exposure: the overall NNH ranged from 11,959 patients (28-day course) to 66,972 patients (5-day course); NNH was lower in women and in those aged ≥ 60 years. For Achilles tendon rupture, the most common type of tendon rupture associated with the largest increased relative incidence, estimates for NNH followed a similar distribution as for any tendon rupture apart for a lower NNH in men and the NNH being marginally greater (Table 2).

Absolute risk estimates are informative for public health and there are limited data on absolute risk of tendon rupture associated with fluoroquinolone therapy. A recently published nested case–control study reported incidence rate differences (IRD) in line with those from our original study but with less precision (IRD 3.73, 95% CI 2.08–5.39 per 10,000 person-years of current exposure for all patients) giving further confidence in the validity of our original findings [5]. Our results show the frequency of tendon rupture events varies across the population depending on several factors: namely duration of therapy, age, gender and concomitant exposure to systemic corticosteroids. The Summary of Product Characteristics (SmPC) is

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Table 1 Number needed to treat to cause one additional tendon rupture with different durations of fluoroquinolone and fluoroquinolone/corticosteroid exposure

Duration of therapy	Fluoroquinolone NNH (95% CI)	Fluoroquinolone/corticosteroid NNH (95% CI)
Overall		
5 days	251,724 (197,297–331,818)	66,972 (52,143–87,952)
7 days	179,803 (140,927–237,013)	47,837 (37,245–62,823)
10 days	125,862 (98,649–165,909)	33,486 (26,071–43,976)
14 days	89,901 (70,463–118,506)	23,919 (18,622–31,411)
21 days	59,934 (46,976–79,004)	15,946 (12,415–20,941)
28 days	44,951 (35,232–59,253)	11,959 (9311–15,706)
Men		
5 days	317,391 (243,333–405,556)	50,000 (38,830–65,179)
7 days	226,708 (173,810–289,683)	35,714 (27,736–46,556)
10 days	158,696 (121,667–202,778)	25,000 (19,415–32,589)
14 days	113,354 (86,905–144,841)	17,857 (13,868–23,278)
21 days	75,569 (57,937–96,561)	11,905 (9245–15,519)
28 days	56,677 (43,452–72,421)	8929 (6934–11,639)
Women		
5 days	235,484 (182,500–304,167)	92,405 (72,277–121,667)
7 days	168,203 (130,357–217,262)	66,004 (51,627–86,905)
10 days	117,742 (91,250–152,083)	46,203 (36,139–60,833)
14 days	84,101 (65,179–108,631)	33,002 (25,813–43,452)
21 days	56,068 (43,452–72,421)	22,001 (17,209–28,968)
28 days	42,051 (32,589–54,315)	16,501 (12,907–21,726)
Age ≥ 60 years		
5 days	130,357 (101,389–169,767)	37,245 (28,968–48,667)
7 days	93,112 (72,421–121,262)	26,603 (20,692–34,762)
10 days	65,179 (50,694–84,884)	18,622 (14,484–24,333)
14 days	46,556 (36,210–60,631)	13,302 (10,346–17,381)
21 days	31,037 (24,140–40,421)	8868 (6897–11,587)
28 days	23,278 (18,105–30,316)	6651 (5173–8690)
Age < 60 years		
5 days	521,429 (405,556–730,000)	121,667 (94,805–158,696)
7 days	372,449 (289,683–521,429)	86,905 (67,718–113,354)
10 days	260,714 (202,778–365,000)	60,833 (47,403–79,348)
14 days	186,224 (144,841–260,714)	43,452 (33,859–56,677)
21 days	124,150 (96,561–173,810)	28,968 (22,573–37,785)
28 days	93,112 (72,421–130,357)	21,726 (16,929–28,339)

CI confidence interval, NNH number needed to harm

a document that includes information such as how to use a medicine, its method of administration, special warnings and adverse effects. In many fluoroquinolone SmPCs the frequency of tendon rupture is listed as *very rare* (<1/10,000) but in others it is listed as *rare* ($\geq 1/10,000$ to < 1/1000) [6] or *frequency unknown* [7]. Our results also highlight that absolute risk may vary markedly due to different baseline risk among subpopulations. Further work on understanding how this affects extrapolation of

benefit–risk to stratified populations or those commonly excluded from clinical trials, could be valuable.

A strength of this study is that we provide confidence intervals for each NNH. However, other potential subgroups of patients may exist in which the NNH may vary that have not been studied. This may be important if linear relationships between exposure and risk do not exist. Although it is completely appropriate that different indications may require different durations of antibiotic therapy, evidence underpinning the minimum effective duration to successfully treat

Table 2 Number needed to treat to cause one additional Achilles tendon rupture with different durations of fluoroquinolone and fluoroquinolone/corticosteroid exposure

Duration of therapy	Fluoroquinolone NNH (95% CI)	Fluoroquinolone/corticosteroid NNH (95% CI)
Overall		
5 days	347,619 (270,370–456,250)	148,980 (117,742–197,297)
7 days	248,299 (193,122–325,893)	106,414 (84,101–140,927)
10 days	173,810 (135,185–228,125)	74,490 (58,871–98,649)
14 days	124,150 (96,561–162,946)	53,207 (42,051–70,463)
21 days	82,766 (64,374–108,631)	35,471 (28,034–469,760)
28 days	62,075 (48,280–81,473)	26,603 (21,025–35,232)
Men		
5 days	456,250 (347,619–561,538)	132,727 (102,817–173,810)
7 days	325,893 (248,299–401,099)	94,805 (73,441–124,150)
10 days	228,125 (173,810–280,769)	66,364 (51,408–86,905)
14 days	162,946 (124,150–200,549)	47,403 (36,720–62,075)
21 days	108,631 (82,766–133,700)	31,602 (24,480–41,383)
28 days	81,473 (62,075–100,275)	23,701 (18,360–31,037)
Women		
5 days	347,619 (270,370–456,250)	187,179 (146,000–243,333)
7 days	248,299 (193,122–325,893)	133,700 (104,286–173,810)
10 days	173,810 (135,185–228,125)	93,590 (73,000–121,667)
14 days	124,150 (96,561–162,946)	66,850 (52,143–86,905)
21 days	82,766 (64,374–108,631)	44,567 (34,762–57,937)
28 days	62,075 (48,280–81,473)	33,425 (26,071–43,452)
Age ≥ 60 years		
5 days	243,333 (187,179–317,391)	110,606 (86,905–146,000)
7 days	173,810 (133,700–226,708)	79,004 (62,075–104,286)
10 days	121,667 (93,590–158,696)	55,303 (43,452–73,000)
14 days	86,905 (66,850–113,354)	39,502 (31,037–52,143)
21 days	57,937 (44,567–75,569)	26,335 (20,692–34,762)
28 days	43,452 (33,425–56,677)	19,751 (15,519–26,071)
Age < 60 years		
5 days	608,333 (456,250–811,111)	347,619 (270,370–456,250)
7 days	434,524 (325,893–579,365)	248,299 (193,122–325,893)
10 days	304,167 (228,125–405,556)	173,810 (135,185–228,125)
14 days	217,262 (162,946–289,683)	124,150 (96,561–162,946)
21 days	144,841 (108,631–193,122)	82,766 (64,374–108,631)
28 days	108,631 (81,473–144,841)	62,075 (48,280–81,473)

CI confidence interval, NNH number needed to harm

infections can be limited. From a safety perspective, a medicine should be used for the shortest possible duration at the lowest effective dose. Shortening the duration of antibiotic therapy could therefore reduce the risk of fluoroquinolone-associated adverse effects, a potential area for further evidence generation with antibiotic stewardship interventions [8, 9]. This may also affect other potential adverse reactions associated with fluoroquinolones including antibiotic resistance, peripheral neuropathy and potentially aortic aneurysm [10–14]. The NNH in the highest risk group that we

evaluated, those aged ≥ 60 years and prescribed fluoroquinolone therapy for 28 days with concomitant corticosteroid therapy, was 6651 patients that would equate to a frequency of *rare* in an SmPC [15]. The number of fluoroquinolone products listed across Europe is extensive and the extent of variation in the frequency of tendon ruptures listed in all SmPCs across Europe is uncertain. Despite this, a range of frequencies presented in the SmPC of fluoroquinolone products may better reflect differences in risk compared to a single figure.

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Compliance with Ethical Standards

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Ethical approval No approval was required to conduct this study as it uses published data.

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