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The association between Tendon Ruptures and Use of Fluoroquinolone, and other oral antibiotics in 1.1 million U.S. senior Medicare beneficiaries

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4 **The association between Tendon Ruptures and Use of Fluoroquinolone, and other oral**
5 **antibiotics in 1.1 million U.S. senior Medicare beneficiaries**
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44 **3609 Words (4000 MAX;)**
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3 **Abstract (Max 300 words, 294 now)**
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5 **Objectives:** To assess the association of fluoroquinolone use with tendon ruptures
6 compared to no fluoroquinolone and that of the four most commonly prescribed non-
7 fluoroquinolone antibiotics in the US.
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14 **Design:** Prospective observational study.
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16 **Setting:** U.S. senior enrolled in the federal old-age, survivors insurance program.
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18 **Participants:** 1,186,013 Medicare fee-for-service beneficiaries and their inpatient,
19 outpatient, prescription drug records were used.
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23 **Interventions:** Seven oral antibiotics, fluoroquinolones (ciprofloxacin, levofloxacin,
24 moxifloxacin) and amoxicillin, amoxicillin-clavulanate, azithromycin and cephalexin.
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28 **Primary and Secondary Outcome measures:** All tendon ruptures combined, and three
29 types of tendon ruptures by anatomic site, Achilles tendon rupture, rupture of rotator cuff
30 and tendon ruptures on other anatomic sites.
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34 **Results:** Of three fluoroquinolones, only levofloxacin exhibited a significant increased
35 risk of tendon ruptures - 16%, and 112% for rotator cuff and Achilles tendon rupture
36 respectively in the ≤ 30 day window. Ciprofloxacin and moxifloxacin exhibited little to no
37 increased risk of tendon ruptures. Notably, the risk of levofloxacin never exceeded the
38 risk of the non-fluoroquinolone, cephalexin in any comparison.
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47 Among the non-fluoroquinolone antibiotics, amoxicillin, amoxicillin-clavulanate, and
48 azithromycin exhibited none to benign risk of tendon rupture. Cephalexin exhibited
49 modest to large *increased* risk of tendon rupture at ≤ 30 day window across all sites and
50 its risk exceeded the risk for levofloxacin.
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9 **Conclusions:** In our study, fluoroquinolones as a class were not associated with the
10 increased risk of tendon ruptures. Neither ciprofloxacin nor moxifloxacin exhibited any
11 risk for tendon ruptures. Levofloxacin did exhibit significant increased risk. Cephalexin
12 with no reported effect on metalloprotease activity had an equal or greater risk than
13 levofloxacin; so we question whether metalloprotease activity has any relevance to
14 observed associations with tendon rupture. Confounding by indication bias may be more
15 relevant and should be given more consideration as explanation for significant
16 associations in observational studies of tendon rupture.
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Strengths and limitations of this study

- We conducted a large (more than 1 million US senior subjects) prospective study of outpatient prescription drug records to assess the association between the use of fluoroquinolones and the occurrence of tendon ruptures compared to the most commonly used non-fluoroquinolone oral antibiotics.
- Our study included all oral fluoroquinolones (ciprofloxacin, levofloxacin, moxifloxacin) prescribed in the US and the four most commonly prescribed non-fluoroquinolone antibiotics: amoxicillin, amoxicillin-clavulanate, azithromycin and cephalexin as controls.
- In addition to reporting the risk of any tendon rupture, we also reported the risk of three types of tendon ruptures by anatomic site 1) Achilles tendon rupture, 2) rupture of rotator cuff and 3) tendon ruptures on other anatomic sites as separate outcomes.
- This study is possibly only applicable to U.S. senior, aged 65 or more, Medicare fee-for-service beneficiaries.
- We had no options to verify claims diagnoses via chart review.

Introduction

Fluoroquinolones (FQ) are among the most widely prescribed antibiotics in the outpatient setting[1,2] due to their broad spectrum treatment of bacteria found in respiratory, urinary, joint, and skin infections. Several observational studies have reported the association between the use of FQs and tendinitis and tendon rupture (TR), especially of the Achilles tendon[3–12] and the FDA issued black box warnings to FQ antibiotics beginning in 2008.[13] The warning was updated in 2016 to recommend using alternative antibiotics when possible.[14,15] The fact that FQs upregulate the production of metalloproteinase (MMP) enzymes with collagenase activity that could weaken tendons is taken as a mechanism to explain this reported risk.[16–18]

Studies that reported association between FQ use and TR used one or more other antibiotics as controls. One study compared the FQ rupture rates with patients using azithromycin, the most frequently used oral antibiotic in the US. Only two focused principally on TR risk among the elderly. None compared TR rates of *FQs* with those of cephalexin -- the 3rd most commonly prescribed oral antibiotic in the US.

The Virtual Research Data Center (VRDC) of Center for Medicare and Medicaid Services (CMS)[19] carries more than 10 years of Medicare claims, which include information about the usage of prescription drugs and encounter diagnoses (including tendon ruptures). It also carries information about 42 major chronic diseases, demographic characteristic and vital status. We conducted a large observational study using the VRDC to assess the association of FQ antibiotics with TR compared to that of

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3 the four most commonly prescribed non-FQ antibiotics in the US. Here we report the
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5 results of that analysis.
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10 **Methods**

11 *Patient and public involvement*

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14 Patients or the public were not involved in the design of the study.
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19 *Study population*

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21 We derived our study population from a 20% random sample of Medicare prescription
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23 drug coverage (Part D) fee-for-service enrollees who first enrolled in the Medicare under
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25 old age and survivors insurance within a month of age 65 (779-781 month-old) and on or
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27 after 1/1/2007 - the first full year of Part D prescriptions availability. We included claim
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29 data through 12/31/2016, the end of VRDC claim data available to us. All of the VRDC
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31 data is de-identified and researchers must perform all of their analysis within the VRDC
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33 computer systems, and can only pull statistical results from it.[19] We obtained approvals
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35 for these studies from the CMS privacy board and NIH OHSRP as not human subject
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37 studies.
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44 We required subjects to be continuously enrolled in hospital insurance (Part A) and
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46 medical insurance (Part B) to assure we had full outpatient and inpatient claims data,
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48 which are not available for nearly 20% of patients with Part D only.[20] To obtain an
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50 incident cohort of TR patients, we excluded (washed out) individuals with TRs recorded
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3 in the first year of their Medicare entitlement.[21] In order to assure sufficient follow-up,
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5 we excluded patients with less than 1-year follow-up (See Figure 1 Consort Diagram).
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10 Primary Outcome

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12 We identified patients with TR based upon International Classification of Diseases
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14 (ICD)-9-CM codes of 726.13, 727.60-727.69, and ICD-10-CM codes of M66.2, M66.3,
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16 M66.8, M66.9, and M75.1. We combined all TRs and reported them as one outcome, and
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18 report three types of TRs by anatomic site 1) Achilles tendon rupture, 2) rupture of
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20 rotator cuff and 3) TRs on other anatomic sites as separate outcomes. We focused on
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22 Achilles TR because it was the sole focus of many prior studies and on rotator cuff TR
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24 because it is the predominant TR of the elderly. We lumped the remaining as “other
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26 TRs”.
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33 Study antibiotics

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35 As a study antibiotic, we included all three oral FQs prescribed in the US -- moxifloxacin
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37 (MXF), ciprofloxacin (CIP), levofloxacin (LVX), which is the active stereoisomer of
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39 ofloxacin. As controls, we also included the four most frequently prescribed non-FQ oral
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41 antibiotics - amoxicillin (AMX), amoxicillin clavulanate (AMC), azithromycin (AZT)
42
43 and cephalixin (LEX). Five of our study antibiotics, AZT, AMX, AMC, CIP and LEX,
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45 were the top five U.S. antibiotic agents in 2011.
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51 Statistical Analysis

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3 We analyzed each of the four TR outcomes in separate Fine-Gray competing risk
4 regression analyses with death as the competing risk.[22,23] Patients became eligible for
5 “the study” at their Medicare enrollment but prescription data did not become available
6 until their Part D enrollment. We followed them from their entry in Part D (while
7 accounting for left truncation[24]) until their death, switch to a capitated plan,
8 disenrollment from Medicare or 12/31/2016 – whichever came first. We adjusted hazard
9 ratio (HR) of each study antibiotic for concurrent use of other study antibiotics and
10 adjusted for calendar year of subject’s Part D entry, to account for secular trends. We also
11 adjusted each HR for patient’s characteristics, income, gender, race, rural residency
12 (Yes/No) and also for 42 chronic conditions from the Medicare Master Beneficiary
13 Summary File (MBSF)[25] with >1% prevalence, as a measure of overall health. Based
14 upon monthly indicators of dual-eligibility and Low Income Subsidy (LIS) status, we
15 separated study individuals into three groups: 1) dual whose income is <135% Federal
16 Poverty Line (FPL); 2) non-dual LIS whose income is between 135 and 150% FPL; and
17 non-dual no LIS whose income is >150% FPL. We used this variable in the analysis as a
18 surrogate for economic status.[26]

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21 We assumed that patients were on a given kind of study drug from the prescription
22 dispensing date to the end of days of supply. We did not distinguish between different
23 brands of a study drugs. Following the approach of prior studies,[3–5] we separated
24 subjects by temporal exposure within each study drug, including groups for never
25 exposed, exposed within 30 days, 31-60 days, and >60 days. Thus, by this approach we
26 could detect the presumed short term action of the FQ’s on tendons and avoid the risk of

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3 non-differential misclassification that can occur with too simple (yes/no) drug exposure
4 measures.[27] In order to minimize the immortal time bias, we treated all drug usage
5 measures and all patients characteristics, except gender and race, as time-varying
6 covariates.[28,29] In order to mitigate selection bias toward use of any study antibiotics,
7 we employed a propensity score (PS) approach.[30,31] We first derived a PS of taking
8 any of study antibiotics as a function of patient's characteristics at the date of the first
9 antibiotic use after Part D entry from a multiple logistic regression. We used the median
10 days to the first study antibiotic use in patients taking study antibiotics as the cutoff time
11 for subjects taking no study antibiotics. We performed our analyses with an inverse
12 propensity score weight (IPSW) excluding individuals with the PS below 0.1 and above
13 0.9, to mitigate poorer performance in the presence of a strong treatment-selection
14 process.[32] In post-hoc analyses, we also compared the risk of TR of each study
15 antibiotics to that of every other study antibiotic on a pairwise basis.
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35 **Results**

36 *Study population and Secular trend*

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38 From our 20% sample of Part D enrollees, 1,186,013 patients satisfied all our selection
39 criteria including the washout of individuals with TR in their first year of Medicare
40 (Figure 1 Consort Diagram). Follow-up began with an individual's enrollment in Part D
41 program (median (IQR) 0 (0-122) days from the Medicare entitlement). We followed
42 them for a median of 3.7 years (total 4,736,653 patient-years) until the their first
43 diagnosis of TR (3.7%), death (5.0%), switch from fee-for-service to health maintenance
44 organization (HMO) plans (12.5%), disenrollment from Medicare (<1%) or study end on
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3 12/31/2016 (78.8%), whichever came first. Patients had their first post enrollment claim
4 with a diagnosis of TR at a median age of 68.5 (IQR 67.2-70.4). The proportions of non-
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6 Hispanic White, female and rural residents were 81.2%, 57.9%, and 22.7% respectively.
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8 About a fifth of patients received federal/state subsidies, i.e. Medicaid coverage on top of
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10 Medicare (dual 16.1%) or assistance in paying their Part D premium and
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12 coinsurance/copayment (non-dual LIS 2.6%). Among the 42 Medicare chronic disease
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14 covariates, hypertension (68.5%), hyperlipidemia (69.5%), cataract (47.2%), rheumatoid
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16 arthritis/osteoarthritis (38.6%), anemia (32.0%), ischemic heart disease (27.5%), and
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18 chronic kidney disease (18.7%) were the seven most prevalent (Table 1).
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26 Of the 438,387 (37.0%) study patients who took a FQ prescription, 71.8%, 49.5% and
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28 5.3% ever took CIP, LVX and MXF respectively. Of 737,446 (62.2%) of patients who
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30 took a non-FQ antibiotic, the figures were 55.9%, 46.2%, 35.2% and 33.0% for AZM,
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32 AMX, LEX, and AMC, respectively. Patients who took one or more study antibiotics
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34 took a median (IQR) of 3.0 (1.0-6.0) study antibiotic prescriptions and took a median
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36 (IQR) 2.0 (1.0-3.0) different study antibiotics during the observation period.
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42 Secular trends in study antibiotics usage existed. MXF usage declined precipitously from
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44 5.0% in 2007 to almost zero in 2016 – overweighting the MXF statistics for early entrants
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46 into Medicare and yielding a longer mean follow up time. CIP use hit a peak, and LVX, a
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48 nadir, in 2011. The use of AMX, AMC and LEX trended slowly upward (Supplementary
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50 Figure 1). The mode (median) of supply durations for each antibiotics were 10 (7) for
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52 AMX, 10 (10) for AMC, 5 (5) for AZM, 10 (7) for LEX, 7 (7) for CIP, 10 (7) for LVX,
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3 10 (11) for MXF. About thirty percent of patients were never exposed to any one of the
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5 study antibiotics during the study period.
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10 Unadjusted figures for TR prevalence across each of the seven study antibiotic users and
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12 the no study antibiotic users ranged from a high of 5.6% for MXF to a low of 3.0% for no
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14 antibiotic (Table 1). Except for MXF, the *unadjusted* prevalence of TRs associated with
15
16 each non-FQ antibiotic was *greater than* or equal to that of each FQ antibiotic. The TR
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18 rates per 1000 patient-years followed the same pattern, with the non-FQ antibiotics
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20 topping the rates of all FQs except MXF (which had the highest rate), possibly due to
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22 overweighting of MXF usage in the early years of the study. The study subjects who ever
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24 took an FQ had the highest unadjusted rate of death per 1000 person-years. LVX's death
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26 rate was nearly twice the rate of each non-FQ antibiotics. The size of the associations
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28 with diseases like diabetes, chronic renal failure and heart failure paralleled the
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30 magnitude of the death rates and was generally higher with FQs than non-FQ antibiotics
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32 (Table 1).
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44 Primary Analysis

45 Table 2 presents HRs for all covariates in our Fine-Gray competing risk regression with
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47 IPSW, for all tendon ruptures taken together. Being a female (vs. male), African-
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49 American, Hispanic, and Asian (vs. white), being Dual or non-Dual LIS (vs. non-Dual no
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51 LIS) and living in a rural area were all associated with a *reduced* risk of tendon rupture.
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53 These risk reductions were 24% or more for all but Hispanics and rural residency
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3 covariates, and the reductions were similar across all anatomic sites. In general, life
4 threatening chronic disease, such as COPD, heart failure and colorectal/lung/endometrial
5 cancers were associated with a lower risk of TR in a range of 15-60% below control
6 possibly due to constrained physical activity and/or shortened life span. Notably, diabetes
7 and chronic renal disease, previously reported as risk factors for TR,[33,34] exhibited no
8 increased TR risk. Mobility impairments had reduced risk of TR similar to that of the
9 severe life threatening diseases, likely due to reduced activity. Most diseases with low
10 life threats such as cataract, glaucoma, depression, asthma, hyperlipidemia, hypertension,
11 prostatic hyperplasia, migraine/other chronic headache, and deafness/hearing impairment
12 exhibited risks of 10 to 40% *above* controls probably for reasons related to longer life
13 spans and less inhibited activity. Ischemic heart did not fit the mold of sicker equals
14 lower TR risk. Patients with rheumatoid arthritis/osteoarthritis were a special case and
15 had TR risk of 183% *above* control possibly due to joint and associated tendon
16 inflammation with these disorders. Fibromyalgia/chronic pain and fatigue also exhibited
17 a 40% increased risk of TR possibly also due to an inflammatory component.

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39 The Achilles tendon carries the full force of the extra weight carried by obese patients
40 and obesity was associated with a significant (21%) increase in Achilles TR ruptures
41 while its effect on other TR classes was significant but miniscule (4-6%) (Data not
42 shown).

43 44 45 46 47 48 49 ***Effect of antibiotics***

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52 Table 3 shows the risk associated with each study antibiotic broken down by time lag
53 between the antibiotic use and the claim reported TR, as well as by anatomic sites. Of the
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3 total 44,098 patients with any TR occurrence, complete rupture of rotator cuff
4 represented the major share (80.7%), followed by other TRs (16.8%) and Achilles TR
5 (2.5%). In the survival analysis we followed patients until the first occurrence of TR; so,
6 these figures count only the first TR occurrence independent of anatomic site.
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13 Of the non-FQ antibiotics, AMX exhibited a reduced risk of TR compared to no AMX in
14 every tendon class and time window, similar to its low risk in previous studies. It
15 exhibited a significantly lower risk in the 30, and 60-day window except for the Achilles
16 tendon. AZM and AMC exhibited a similar benign risk in all time windows except for
17 TR of rotator cuff in >60 days window
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26 LEX was the surprise non-FQ antibiotic. It exhibited modest to large *increased* TR risk at
27 ≤ 30 days across all sites ranging from a low of 16% increase for complete rupture of
28 rotator cuff to a high 114% increase for Achilles TR. Its risk was also significantly
29 higher at each time window for all TRs taken together.
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36 Of the FQs, CIP, the most frequently prescribed FQ, and MXF, the least frequently
37 prescribed FQ, exhibited little to no increased risk of TR within each anatomic site and
38 each time frame (Table 3). LVX is the only FQ to exhibit a significant *increase* in TR
39 risk - of 16%, and 112% for rupture of rotator cuff and Achilles TR respectively in the
40 ≤ 30 day window. Notably, the risk of LVX never exceeded the risk of the non-FQ, LEX
41 in any comparison.
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51 In a post-hoc analysis (Table 4), we compared the TR risk of each antibiotic with every
52 other antibiotic (pairwise comparisons of FQ vs. FQ and FQ vs. non-FQ), for ≤ 30 day
53 window. These results paralleled the above-mentioned risk for each study antibiotic.
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3 Again, TR risk for LVX was greater than that of CIP, MXF, AMC, AMX, and AZM in a
4 ≤ 30 day window. However, LVX risk was comparable to that of LEX for Achilles TR
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6 and rupture of rotator cuff and significantly lower than LEX for the other TR class. When
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8 comparing the risk of FQs as a class against that of non-FQ antibiotics, most of the non-
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10 FQ antibiotics had significantly greater risk than the FQ class as a whole across all TR
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12 sites.
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20 **Discussion**

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22 Our results conflict with the common assertion that the Achilles tendon rupture is the
23 most common, up to 90% of tendon ruptures.[35] In our elderly cohort, Achilles TRs
24 were a tiny proportion (2.9 %) of all ruptures. Some of this difference may be explained
25 by the differences in demographics. Reports of high prevalence of Achilles TR came
26 from studies of young military populations.[36,37] In contrast, our data came from an
27 elderly Medicare population. Some of the difference could also be due to less ability to
28 diagnose non-Achilles tendon ruptures without 3D joint imaging.
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41 Many authorities describe the relationship between FQs and TRs as a class “effect”.
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43 However, FQs as a class had no significant risk of TR compared with each of the three
44 non-FQ antibiotics in any time window. Further, neither MXF (n= 23,207 subjects) nor
45 CIP (n=314,864 subjects), the oral FQ with the greatest use and with a greater effect on
46 metalloproteases than other FQs,[38–40] had any TR risk at any anatomic site in any time
47 window. CIP’s lack of risk is consistent with two studies[5,9] in which CIP exhibited
48 zero risk or small risks compared to ofloxacin, a racemic mixture whose active ingredient
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3 is the levo-isomer, LVX. We do see a strong association between LVX and TRs whether
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5 we used no LVX or three of the non-FQ antibiotics as controls. However, with LEX, the
6
7 one cephalosporin as comparator, this association disappears.
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12 One previous study described the effect of FQs on TR risk as small and unimportant.[10]
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14 Two studies reported no effect of FQs on TR risk.[9,11] At least 7 previous observational
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16 studies reported increased risks of TR after the use of FQ.[3–8,12] However, in all but
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18 one study, the TR event rates were very low (between 5 and 111) among patients taking
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20 an FQ. In comparison, our study included 17,949 (4.1%) such patients. One previous
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22 study did report a large number of events, 23,000 (3.5%) patients with TRs while on FQs
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24 and, like our study, it also focused exclusively on elderly patients.[3] However, it did not
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26 compare FQ use against no FQ use (but against times when FQ's were used and not used
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28 in one patient population so they could not adjust for the different levels of clinical
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30 attention at visits requiring a systemic antibiotic vs visits that did not). Furthermore, they
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32 assessed the association between AMX and TRs in separate analysis and used the risk of
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34 TRs in that analysis as the comparator for the risk observed in the FQ analysis. But AMX
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36 treated patients are likely at much lower acuity level (per our data) introducing large
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38 possible differential biases into that comparison. Furthermore, their analysis did not
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40 include death as a competing risk as is recommend when death rates exceed event
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42 rates.[23] They reported no death rates, but death rates in their study likely exceeded their
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44 event rates given the similarity of their population with ours.
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3 According to our data, the AMX treated patients had fewer comorbidities (as was also
4 true in Daneman's study), almost 14% fewer hospitalizations and half of death rate per
5 1000 patient-years, compared to patients taking LVX. So the two populations are not
6 comparable. LVX appears to be reserved for more severe infections or more fragile
7 patients and thus subject to differential biases.
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17 The reported activation of metalloprotease activity by FQs has underpinned the idea of a
18 causal link between FQs and TRs. The argument goes as follows: FQs stimulate
19 metalloproteases, which can break down collagen; the tendon is made of collagen; so FQs
20 may cause TRs. However, our data disrupts this argument. CIP which strongly *stimulates*
21 MMP activity,[17,18] exhibited *no* risk of TRs in our study, and LEX which *inhibits*
22 MMP activity[41,42] exhibited a *large* risk. So we have to question whether
23 metalloprotease activity has any relevance to TR risk, and consider other explanations for
24 the observed associations.
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38 The indication for an antibiotic is a presumed bacterial infection. The reported
39 associations between antibiotics and TR could be consequence of the indication rather
40 than the antibiotic itself and be an example of the confounding by indication bias.[43]
41 Such a bias could explain many reported associations between drugs and TR risk
42 including associations with non-antibiotic drugs reported by Nyysönen.[8]
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51 This bias could manifest in two ways. First, that the bacterial infection might directly
52 increase the risk of TR via stimulation of general immune or cytokine responses, or by
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3 bacterial invasion. A recent study found gram-positive bacteria in a major share of
4 ruptured tendons but not in “control” tendons removed surgically for grafting,[44] giving
5 some plausibility to this hypothesis.
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12 Secondly, the greater clinical attention likely focused on patients needing systemic
13 antibiotics, especially those with severe infections, could increase the chance of noticing
14 and documenting a pre-existing TR. Furthermore, a reservoir of such cases is likely to
15 exist, because patients do not necessarily correctly identify joint and extremity symptoms
16 as TRs and seek immediate care for them. Tendon ruptures of the shoulder capsule, for
17 example, are notorious for developing symptoms slowly over 2-3 years[45] before being
18 correctly diagnosed. Even Achilles tendon ruptures, can be missed (in 30% of cases) at
19 the first presentation.[46] Seeger et al. reviewed the medical records of patients with an
20 insurance claim reporting TRs following antibiotic use and found that nearly half of the
21 TRs recorded in the claims were either something else (e.g., Bursa inflammation
22 miscoded as a TR) or the chart had occurred before the antibiotic use but only seen in a
23 claim after antibiotic use.[11]
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42 We cannot conclude that confounding by indication fully explains the observed TR
43 associations with LEX and LVX, but they are candidates that should be considered before
44 we rush to causal judgements about such associations.
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51 **Limitation**

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3 This study faces all of the limitations of observational studies. Furthermore, it applies
4 only to fee-for-service Medicare populations. In addition, we had no options to verify
5 claims diagnoses via chart review.
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54 critical review of study content; manuscript drafting; approval of the final manuscript. JL:
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3 study concept and interpretation; manuscript drafting; approval of the final manuscript.
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5 VH: study conception and interpretation; manuscript drafting; approval of the final
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7 manuscript. CJM: study conception, design and interpretation; critical review of study
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9 content; manuscript drafting; approval of the final manuscript.
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14 **Patient Consent for publication:** Not required.
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19 **Data availability:** Available upon reasonable request.
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Figure 1. Consort Diagram

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Table 1. Outcome, Medical/Medication Use, Diseases and Patient Characteristics by Type of Antibiotics

VARIABLE	Overall	FLQ	CIP	LVX	MXF	AMX	AZM	LEX	AMC	None
N	1,186,013	438,387	314,864	216,796	23,207	340,814	412,465	259,720	243,470	358,966
Any Tendon rupture	44,098(3.7)	17,949(4.1)	12,715(4.0)	8,774(4.0)	1,308(5.6)	13,666(4.0)	17,813(4.3)	11,397(4.4)	9,665(4.0)	10,665(3.0)
Death	58,947(5.0)	32,523(7.4)	21,093(6.7)	21,057(9.7)	3,458(14.9)	13,801(4.0)	21,130(5.1)	16,262(6.3)	14,315(5.9)	14,524(4.0)
Censored at HMO entry	148,155(12.5)	38,486(8.8)	27,619(8.8)	16,383(7.6)	2,525(10.9)	29,169(8.6)	36,628(8.9)	20,758(8.0)	18,087(7.4)	67,111(18.7)
Censored at disenrollment	163(0.0)	30(0.0)	16(0.0)	16(0.0)	2(0.0)	26(0.0)	32(0.0)	26(0.0)	24(0.0)	86(0.0)
Censored at DEC 31 2016	934,650(78.8)	349,399(79.7)	253,421(80.5)	170,566(78.7)	15,914(68.6)	284,152(83.4)	336,862(81.7)	211,277(81.3)	201,379(82.7)	266,580(74.3)
Years of follow-up, median(total)	3.7(4,736,653)	4.4(2,108,848)	4.6(1,558,932)	4.6(1,071,395)	5.8(134,098)	4.3(1,642,127)	4.4(1,993,833)	4.7(1,301,503)	4.4(1,180,082)	2.4(1,068,045)
Tendon ruptures in 1000 person-year	9.31	8.51	8.16	8.19	9.75	8.32	8.93	8.76	8.19	9.99
Death in 1000 person-years	12.44	15.42	13.53	19.65	25.79	8.40	10.60	12.49	12.13	13.60
Female	686,191(57.9)	268,614(61.3)	199,875(63.5)	127,986(59.0)	14,203(61.2)	202,687(59.5)	262,764(63.7)	153,714(59.2)	145,039(59.6)	192,297(53.6)
White	962,892(81.2)	368,022(83.9)	263,797(83.8)	184,123(84.9)	19,830(85.4)	284,057(83.3)	347,625(84.3)	223,266(86.0)	208,962(85.8)	273,667(76.2)
Black	86,160(7.3)	25,870(5.9)	18,496(5.9)	11,820(5.5)	1,395(6.0)	20,007(5.9)	22,779(5.5)	12,447(4.8)	12,188(5.0)	35,414(9.9)
Hispanic	65,120(5.5)	22,403(5.1)	16,681(5.3)	10,800(5.0)	960(4.1)	16,221(4.8)	19,561(4.7)	11,884(4.6)	10,514(4.3)	24,719(6.9)
Asian	30,361(2.6)	9,596(2.2)	7,040(2.2)	4,264(2.0)	542(2.3)	9,856(2.9)	10,391(2.5)	4,679(1.8)	4,574(1.9)	10,506(2.9)
Other	41,480(3.5)	12,496(2.9)	8,850(2.8)	5,789(2.7)	480(2.1)	10,673(3.1)	12,109(2.9)	7,444(2.9)	7,232(3.0)	14,660(4.1)
Dual	190,474(16.1)	72,592(16.6)	51,951(16.5)	39,324(18.1)	4,613(19.9)	47,213(13.9)	60,955(14.8)	42,048(16.2)	34,847(14.3)	67,807(18.9)
Non-dual LIS	30,839(2.6)	10,048(2.3)	7,233(2.3)	5,077(2.3)	589(2.5)	6,865(2.0)	8,985(2.2)	5,564(2.1)	5,122(2.1)	12,821(3.6)
Non-dual no LIS	964,700(81.3)	355,747(81.1)	255,680(81.2)	172,395(79.5)	18,005(77.6)	286,736(84.1)	342,525(83.0)	212,108(81.7)	203,501(83.6)	278,338(77.5)
Living in rural area	269,718(22.7)	105,600(24.1)	76,431(24.3)	54,376(25.1)	4,632(20.0)	78,183(22.9)	97,183(23.6)	66,881(25.8)	57,690(23.7)	77,621(21.6)
Days on RX, median(IQR)	N/A	N/A	10.0(7.0-20.0)	10.0(7.0-20.0)	10.0(7.0-14.0)	10.0(7.0-20.0)	6.0(5.0-15.0)	10.0(7.0-17.0)	10.0(10.0-20.0)	N/A
Hospitalization	349,959(29.5)	198,846(45.4)	142,538(45.3)	113,829(52.5)	14,002(60.3)	132,304(38.8)	156,185(37.9)	119,209(45.9)	103,515(42.5)	51,525(14.4)
Outpatient visits per year, median(IQR)	19.6(11.1-33.0)	27.1(17.2-42.7)	27.3(17.5-42.9)	30.1(19.0-47.8)	34.0(21.7-53.7)	23.6(14.5-37.5)	24.6(15.5-38.8)	27.5(17.2-43.2)	26.6(16.7-42.2)	12.3(6.0-21.8)
AMI	25,822(2.2)	13,365(3.0)	9,219(2.9)	8,126(3.7)	1,075(4.6)	8,592(2.5)	10,974(2.7)	8,329(3.2)	7,242(3.0)	5,103(1.4)
Atrial Fibrillation	88,563(7.5)	43,513(9.9)	30,171(9.6)	25,198(11.6)	3,187(13.7)	32,510(9.5)	36,148(8.8)	29,866(11.5)	26,056(10.7)	16,536(4.6)
Cataract	559,583(47.2)	244,465(55.8)	179,419(57.0)	122,945(56.7)	14,520(62.6)	189,761(55.7)	232,931(56.5)	148,677(57.2)	136,980(56.3)	125,610(35.0)
Chronic Kidney Disease	221,890(18.7)	116,699(26.6)	85,372(27.1)	65,142(30.0)	7,467(32.2)	73,023(21.4)	90,452(21.9)	68,947(26.5)	60,172(24.7)	43,467(12.1)
COPD	172,328(14.5)	103,941(23.7)	65,202(20.7)	71,669(33.1)	10,259(44.2)	58,641(17.2)	96,369(23.4)	54,994(21.2)	55,940(23.0)	23,222(6.5)
Heart Failure	129,993(11.0)	72,127(16.5)	49,366(15.7)	45,112(20.8)	6,216(26.8)	45,517(13.4)	58,766(14.2)	44,275(17.0)	38,781(15.9)	22,301(6.2)
Diabetes	344,557(29.1)	154,018(35.1)	111,041(35.3)	81,644(37.7)	9,558(41.2)	109,157(32.0)	134,201(32.5)	91,923(35.4)	83,309(34.2)	82,220(22.9)
Glaucoma	179,324(15.1)	75,509(17.2)	55,889(17.8)	36,817(17.0)	4,624(19.9)	59,916(17.6)	72,717(17.6)	45,015(17.3)	41,873(17.2)	42,576(11.9)
Hip/Pelvic Fracture	9,969(0.8)	5,630(1.3)	4,169(1.3)	3,273(1.5)	458(2.0)	3,656(1.1)	4,196(1.0)	3,494(1.3)	2,734(1.1)	1,733(0.5)
Ischemic Heart Disease	326,305(27.5)	160,828(36.7)	113,815(36.1)	90,604(41.8)	11,221(48.4)	113,981(33.4)	140,977(34.2)	96,904(37.3)	88,665(36.4)	64,072(17.8)
Depression	263,154(22.2)	131,795(30.1)	96,524(30.7)	71,887(33.2)	8,813(38.0)	91,018(26.7)	116,614(28.3)	79,419(30.6)	73,001(30.0)	49,814(13.9)
Alzheimer's Disease Or Senile Dementia	47,984(4.0)	26,582(6.1)	19,523(6.2)	15,387(7.1)	1,937(8.3)	15,125(4.4)	19,170(4.6)	16,083(6.2)	12,919(5.3)	9,593(2.7)
Osteoporosis	131,554(11.1)	64,596(14.7)	48,633(15.4)	33,271(15.3)	4,594(19.8)	46,862(13.8)	60,466(14.7)	37,260(14.3)	34,276(14.1)	25,391(7.1)
Rheumatoid Arthritis/Osteoarthritis	457,256(38.6)	219,767(50.1)	161,736(51.4)	114,796(53.0)	13,468(58.0)	171,692(50.4)	204,700(49.6)	138,911(53.5)	123,436(50.7)	82,578(23.0)
Stroke/Transient Ischemic Attack	72,098(6.1)	37,348(8.5)	27,127(8.6)	21,120(9.7)	2,665(11.5)	24,161(7.1)	30,139(7.3)	22,711(8.7)	19,678(8.1)	14,528(4.0)
Breast Cancer	55,748(4.7)	26,507(6.0)	19,726(6.3)	13,536(6.2)	1,548(6.7)	18,343(5.4)	24,234(5.9)	17,211(6.6)	14,315(5.9)	11,119(3.1)

Colorectal Cancer	19,288(1.6)	9,912(2.3)	7,248(2.3)	5,509(2.5)	592(2.6)	5,739(1.7)	7,054(1.7)	5,494(2.1)	4,875(2.0)	4,186(1.2)
Prostate Cancer	44,960(3.8)	25,817(5.9)	20,459(6.5)	12,558(5.8)	972(4.2)	14,604(4.3)	15,726(3.8)	12,260(4.7)	10,969(4.5)	8,424(2.3)
Lung Cancer	19,307(1.6)	12,412(2.8)	7,302(2.3)	8,971(4.1)	1,415(6.1)	5,539(1.6)	9,454(2.3)	5,617(2.2)	6,079(2.5)	2,900(0.8)
Endometrial Cancer	9,025(0.8)	4,636(1.1)	3,594(1.1)	2,299(1.1)	267(1.2)	2,860(0.8)	3,605(0.9)	2,653(1.0)	2,191(0.9)	1,872(0.5)
Anemia	379,500(32.0)	192,157(43.8)	139,042(44.2)	105,622(48.7)	12,941(55.8)	134,693(39.5)	163,370(39.6)	112,491(43.3)	101,770(41.8)	72,066(20.1)
Asthma	116,515(9.8)	69,444(15.8)	44,946(14.3)	46,600(21.5)	7,161(30.9)	41,571(12.2)	69,541(16.9)	37,221(14.3)	39,249(16.1)	13,935(3.9)
Hyperlipidemia	824,020(69.5)	343,365(78.3)	248,590(79.0)	172,542(79.6)	19,239(82.9)	263,142(77.2)	320,295(77.7)	203,560(78.4)	190,838(78.4)	202,679(56.5)
Hyperplasia	147,478(12.4)	78,374(17.9)	59,791(19.0)	39,048(18.0)	3,968(17.1)	51,492(15.1)	56,331(13.7)	41,857(16.1)	38,373(15.8)	27,598(7.7)
Hypertension	812,062(68.5)	340,354(77.6)	244,672(77.7)	174,349(80.4)	19,336(83.3)	255,879(75.1)	310,348(75.2)	202,254(77.9)	186,560(76.6)	203,427(56.7)
Hypothyroidism	241,371(20.4)	111,526(25.4)	81,897(26.0)	57,796(26.7)	6,854(29.5)	81,135(23.8)	104,685(25.4)	65,755(25.3)	61,689(25.3)	50,607(14.1)
Anxiety Disorders	188,338(15.9)	99,450(22.7)	72,980(23.2)	55,437(25.6)	6,837(29.5)	68,299(20.0)	88,527(21.5)	58,896(22.7)	54,366(22.3)	32,009(8.9)
Bipolar Disorder	22,352(1.9)	11,667(2.7)	8,668(2.8)	6,596(3.0)	816(3.5)	7,570(2.2)	9,470(2.3)	7,267(2.8)	6,113(2.5)	4,295(1.2)
Major Depressive Affective Disorder	192,927(16.3)	100,587(22.9)	73,797(23.4)	55,907(25.8)	7,005(30.2)	68,188(20.0)	87,366(21.2)	61,097(23.5)	55,544(22.8)	34,020(9.5)
Schizophrenia and Other Psychotic Disorders	20,889(1.8)	11,859(2.7)	8,718(2.8)	7,097(3.3)	911(3.9)	6,173(1.8)	7,989(1.9)	7,130(2.7)	5,496(2.3)	4,390(1.2)
Epilepsy	19,882(1.7)	10,315(2.4)	7,476(2.4)	6,039(2.8)	700(3.0)	5,922(1.7)	7,690(1.9)	6,218(2.4)	5,063(2.1)	4,263(1.2)
Cystic Fibrosis and Metabolic Disorders	12,209(1.0)	6,270(1.4)	4,671(1.5)	3,448(1.6)	445(1.9)	4,394(1.3)	5,473(1.3)	3,738(1.4)	3,370(1.4)	2,196(0.6)
Fibromyalgia, Chronic Pain and Fatigue	210,878(17.8)	111,190(25.4)	81,838(26.0)	61,637(28.4)	7,420(32.0)	78,553(23.0)	99,990(24.2)	68,291(26.3)	62,553(25.7)	34,163(9.5)
Viral Hepatitis (general)	14,494(1.2)	6,408(1.5)	4,462(1.4)	3,602(1.7)	443(1.9)	4,281(1.3)	5,155(1.2)	3,715(1.4)	3,326(1.4)	3,780(1.1)
Liver Disease Cirrhosis and other liver conditions	78,506(6.6)	43,855(10.0)	32,340(10.3)	24,720(11.4)	3,136(13.5)	27,186(8.0)	34,311(8.3)	24,344(9.4)	22,635(9.3)	13,593(3.8)
Leukemias and Lymphomas	17,825(1.5)	10,263(2.3)	6,948(2.2)	6,633(3.1)	882(3.8)	6,154(1.8)	8,393(2.0)	5,665(2.2)	5,745(2.4)	2,799(0.8)
Migraine and other chronic headache	40,625(3.4)	21,449(4.9)	16,251(5.2)	11,461(5.3)	1,485(6.4)	15,458(4.5)	20,000(4.8)	12,746(4.9)	12,337(5.1)	6,453(1.8)
Mobility Impairments	25,125(2.1)	13,568(3.1)	9,989(3.2)	7,900(3.6)	926(4.0)	7,313(2.1)	9,063(2.2)	8,158(3.1)	6,350(2.6)	5,596(1.6)
Obesity	227,801(19.2)	108,503(24.8)	78,347(24.9)	58,906(27.2)	6,536(28.2)	79,851(23.4)	96,219(23.3)	68,680(26.4)	61,392(25.2)	45,069(12.6)
Peripheral Vascular Disease	112,814(9.5)	62,250(14.2)	44,377(14.1)	37,004(17.1)	4,875(21.0)	39,571(11.6)	50,623(12.3)	39,277(15.1)	33,794(13.9)	18,709(5.2)
Tobacco Use Disorders	124,413(10.5)	61,579(14.0)	39,941(12.7)	38,193(17.6)	4,862(21.0)	37,089(10.9)	52,063(12.6)	34,177(13.2)	32,020(13.2)	27,318(7.6)
Pressure Ulcers and Chronic Ulcers	39,536(3.3)	24,923(5.7)	18,268(5.8)	15,406(7.1)	1,988(8.6)	12,855(3.8)	15,975(3.9)	18,878(7.3)	14,319(5.9)	5,172(1.4)
Deafness and Hearing Impairment	73,788(6.2)	37,425(8.5)	27,525(8.7)	20,022(9.2)	2,633(11.3)	28,696(8.4)	34,931(8.5)	22,986(8.9)	23,349(9.6)	11,975(3.3)

Note. Data are presented as No. (%) of patients unless otherwise noted.

Abbreviations: FLQ, fluoroquinolone; CIP, ciprofloxacin; LVX, levofloxacin; MXF, moxifloxacin; AMX, Amoxicillin; AMC, Amoxicillin Clavulanate; AZT, Azithromycin; LEX, Cephalexin; IQR, interquartile range.

Table 2. Hazard Ratios of Tendon Rupture for Each Covariate

VARIABLE	REFERENCE	HR(95% CI)
Female	Male	0.71(0.70,0.72)
Black		0.76(0.74,0.78)
Hispanic	White	0.91(0.88,0.94)
Asian		0.68(0.64,0.72)
Other		1.03(0.99,1.07)
Dual ever	Non-dual non-LIS	0.67(0.65,0.69)
Non-dual LIS		0.69(0.66,0.72)
Living in rural area	No	0.93(0.92,0.95)
Medicare part d since 2008		1.04(1.00,1.07)
Medicare part d since 2009		1.13(1.09,1.17)
Medicare part d since 2010		1.19(1.15,1.23)
Medicare part d since 2011		1.23(1.19,1.27)
Medicare part d since 2012	Medicare part D since 2007	1.19(1.15,1.23)
Medicare part d since 2013		1.13(1.09,1.17)
Medicare part d since 2013		1.17(1.13,1.22)
Medicare part d since 2015		1.08(1.03,1.12)
Medicare part d since 2016		1.29(0.47,3.55)
AMI	No	0.76(0.71,0.81)
Atrial Fibrillation	No	0.93(0.91,0.96)
Cataract	No	1.24(1.22,1.25)
Chronic Kidney Disease	No	0.91(0.89,0.93)
COPD	No	0.86(0.83,0.88)
Heart Failure	No	0.78(0.76,0.81)
Diabetes	No	0.98(0.96,0.99)
Glaucoma	No	1.11(1.09,1.13)
Hip/Pelvic Fracture	No	0.76(0.69,0.85)
Ischemic Heart Disease	No	1.11(1.09,1.12)
Depression	No	1.17(1.14,1.21)
Alzheimer's Disease or Senile Dementia	No	0.69(0.65,0.72)
Osteoporosis	No	1.04(1.02,1.06)
Rheumatoid Arthritis/Osteoarthritis	No	2.83(2.79,2.88)
Stroke/Transient Ischemic Attack	No	0.96(0.93,1.00)
Breast Cancer	No	0.94(0.91,0.97)
Colorectal Cancer	No	0.77(0.72,0.83)
Prostate Cancer	No	1.01(0.97,1.04)
Lung Cancer	No	0.39(0.35,0.44)
Endometrial Cancer	No	0.85(0.77,0.94)
Anemia	No	1.01(0.99,1.03)

1	Asthma	No	1.24(1.21,1.27)
2	Hyperlipidemia	No	1.36(1.34,1.38)
3	Hyperplasia	No	1.14(1.11,1.16)
4	Hypertension	No	1.10(1.09,1.12)
5	Hypothyroidism	No	1.08(1.06,1.10)
6	Anxiety Disorders	No	0.98(0.96,1.00)
7	Bipolar Disorder	No	1.02(0.96,1.08)
8	Major Depressive Affective Disorder	No	1.03(1.00,1.07)
9	Schizophrenia and Other Psychotic Disorders	No	0.66(0.61,0.72)
10	Epilepsy	No	0.85(0.80,0.91)
11	Fibromyalgia, Chronic Pain and Fatigue	No	1.39(1.36,1.41)
12	Viral hepatitis (general)	No	1.02(0.94,1.10)
13	Liver Disease Cirrhosis and other liver conditions	No	0.94(0.91,0.97)
14	Leukemias and Lymphomas	No	0.94(0.88,1.00)
15	Migraine and other chronic headache	No	1.26(1.21,1.30)
16	Mobility Impairments	No	0.69(0.64,0.74)
17	Obesity	No	1.06(1.04,1.08)
18	Peripheral Vascular Disease	No	1.00(0.97,1.03)
19	Tobacco Use Disorders	No	0.81(0.79,0.84)
20	Pressure Ulcers and Chronic Ulcers	No	0.81(0.77,0.85)
21	Deafness And Hearing Impairment	No	1.19(1.16,1.23)

Abbreviations: HR, hazard ratio, CI, confidence interval; FLQ, fluoroquinolone; CIP, ciprofloxacin; LVX, levofloxacin; MXF, moxifloxacin; AMX, Amoxicillin; AMC, Amoxicillin Clavulanate; AZT, Azithromycin; LEX, Cephalexin.

Table 3. Hazard Ratios of Each Antibiotic by Anatomic Sites and Temporal Order of Drug Exposure

VARIABLE	REFERENCE	Any Tendon Rupture	Achilles Tendon Rupture	Complete Rupture of Rotator Cuff	Other Tendon Ruptures
		HR(95% CI)	HR(95% CI)	HR(95% CI)	HR(95% CI)
Use AMX ≤ 30 days		0.87(0.82,0.92)	0.92(0.66,1.29)	0.88(0.83,0.94)	0.83(0.73,0.94)
Use AMX 31 - 60 days	No AMX	0.92(0.86,0.98)	0.79(0.52,1.20)	0.92(0.86,0.99)	0.96(0.83,1.10)
Use AMX ≥ 61 days		1.00(0.99,1.02)	0.94(0.84,1.05)	1.02(1.00,1.04)	0.97(0.93,1.01)
Use AMC 0 - 30 days		0.97(0.90,1.04)	1.28(0.88,1.85)	0.93(0.86,1.01)	1.11(0.95,1.29)
Use AMC 31 - 60 days	No AMC	1.04(0.96,1.14)	1.44(0.95,2.19)	1.03(0.94,1.13)	1.01(0.84,1.22)
Use AMC ≥ 61 days		1.06(1.04,1.08)	0.90(0.79,1.03)	1.07(1.04,1.09)	1.02(0.97,1.07)
Use AZM ≤ 30 days		1.02(0.97,1.08)	1.03(0.76,1.41)	1.03(0.97,1.09)	1.01(0.89,1.13)
Use AZM 31 - 60 days	No AZM	0.94(0.88,1.00)	0.91(0.63,1.31)	0.94(0.88,1.01)	0.97(0.85,1.11)
Use AZM ≥ 61 days		1.07(1.06,1.09)	1.05(0.95,1.16)	1.09(1.07,1.11)	1.01(0.98,1.05)
Use LEX ≤ 30 days		1.26(1.18,1.34)	2.14(1.61,2.85)	1.16(1.08,1.25)	1.67(1.48,1.88)
Use LEX 31 - 60 days	No LEX	1.09(1.01,1.18)	1.09(0.68,1.76)	1.09(1.00,1.19)	1.09(0.92,1.30)
Use LEX ≥ 61 days		1.09(1.07,1.12)	1.07(0.94,1.21)	1.09(1.07,1.11)	1.15(1.10,1.20)
Use LVX ≤ 30 days		1.15(1.07,1.23)	2.12(1.54,2.91)	1.16(1.07,1.26)	1.02(0.87,1.21)
Use LVX 31 - 60 days	No LVX	1.06(0.97,1.16)	2.12(1.46,3.09)	1.07(0.97,1.17)	0.97(0.80,1.19)
Use LVX ≥ 61 days		1.00(0.97,1.02)	1.11(0.97,1.27)	1.01(0.99,1.04)	0.95(0.90,1.00)
Use CIP ≤ 30 days		0.94(0.88,1.00)	0.88(0.61,1.28)	0.95(0.89,1.01)	0.83(0.72,0.95)
Use CIP 31 - 60 days	No CIP	0.95(0.89,1.02)	0.92(0.60,1.41)	0.95(0.88,1.03)	0.93(0.79,1.08)
Use CIP ≥ 61 days		0.96(0.94,0.98)	1.08(0.96,1.20)	0.97(0.95,0.99)	0.90(0.87,0.94)
Use MXF ≤ 30 days		0.69(0.49,0.97)	0.61(0.10,3.90)	0.55(0.36,0.85)	1.07(0.61,1.86)
Use MXF 31 - 60 days	No MXF	0.69(0.46,1.02)	0.00(0.00,0.00)	0.74(0.48,1.14)	0.44(0.16,1.21)
Use MXF ≥ 61 days		1.00(0.95,1.05)	1.18(0.89,1.56)	0.99(0.93,1.05)	1.12(1.00,1.24)

Abbreviations: HR, hazard ratio, CI, confidence interval; FLQ, fluoroquinolone; CIP, ciprofloxacin; LVX, levofloxacin; MXF, moxifloxacin; AMX, Amoxicillin; AMC, Amoxicillin Clavulanate; AZT, Azithromycin; LEX, Cephalexin.

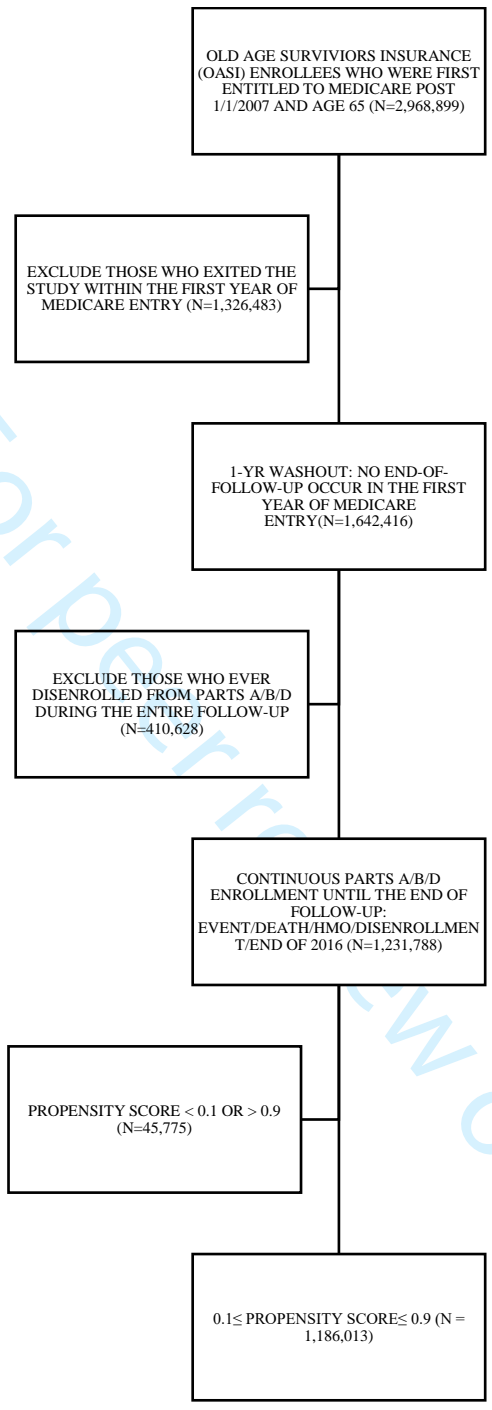
Table 4. Pairwise Comparisons

COMPARISON	LEVEL	Any Tendon Rupture HR(95% CI)	Achilles Tendon Rupture HR(95% CI)	Complete Rupture Of Rotator Cuff HR(95% CI)	Other Tendon Rupture HR(95% CI)
CIP VS. LVX	≤ 30	0.82(0.74,0.90)	0.42(0.25,0.69)	0.81(0.73,0.90)	0.81(0.65,1.01)
CIP VS. MXF	≤ 30	1.36(0.96,1.92)	1.45(0.22,9.66)	1.71(1.11,2.64)	0.78(0.44,1.38)
LVX VS. MXF	≤ 30	1.66(1.18,2.35)	3.48(0.53,22.97)	2.10(1.36,3.24)	0.96(0.53,1.71)
CIP VS. AMX	≤ 30	1.08(0.99,1.17)	0.96(0.58,1.59)	1.08(0.98,1.18)	1.00(0.82,1.21)
CIP VS. AZM	≤ 30	0.92(0.85,1.00)	0.86(0.53,1.37)	0.92(0.84,1.01)	0.82(0.68,0.99)
CIP VS. LEX	≤ 30	0.74(0.68,0.81)	0.41(0.26,0.66)	0.82(0.74,0.90)	0.50(0.41,0.60)
CIP VS. AMC	≤ 30	0.97(0.88,1.07)	0.69(0.41,1.17)	1.02(0.91,1.13)	0.75(0.61,0.92)
LVX VS. AMX	≤ 30	1.32(1.20,1.45)	2.29(1.44,3.64)	1.32(1.19,1.46)	1.23(0.99,1.52)
LVX VS. AZM	≤ 30	1.13(1.03,1.23)	2.05(1.32,3.19)	1.13(1.02,1.25)	1.01(0.82,1.25)
LVX VS. LEX	≤ 30	0.91(0.83,1.00)	0.99(0.64,1.53)	1.00(0.90,1.12)	0.61(0.50,0.75)
LVX VS. AMC	≤ 30	1.19(1.07,1.32)	1.66(1.02,2.69)	1.25(1.11,1.40)	0.92(0.74,1.15)
MXF VS. AMX	≤ 30	0.79(0.56,1.12)	0.66(0.10,4.35)	0.63(0.41,0.97)	1.29(0.73,2.28)
MXF VS. AZM	≤ 30	0.68(0.48,0.95)	0.59(0.09,3.90)	0.54(0.35,0.83)	1.06(0.60,1.87)
MXF VS. LEX	≤ 30	0.55(0.39,0.77)	0.28(0.04,1.86)	0.48(0.31,0.73)	0.64(0.36,1.13)
MXF VS. AMC	≤ 30	0.71(0.51,1.01)	0.48(0.07,3.19)	0.59(0.38,0.92)	0.96(0.54,1.72)
FLQ VS. AMX	≤ 30	1.04(0.91,1.18)	1.13(0.55,2.33)	0.96(0.82,1.13)	1.16(0.92,1.48)
FLQ VS. AZM	≤ 30	0.89(0.78,1.01)	1.01(0.50,2.06)	0.83(0.70,0.97)	0.96(0.76,1.21)
FLQ VS. LEX	≤ 30	0.72(0.63,0.82)	0.49(0.24,0.98)	0.73(0.62,0.86)	0.58(0.46,0.73)
FLQ VS. AMC	≤ 30	0.94(0.82,1.08)	0.82(0.39,1.72)	0.91(0.77,1.08)	0.87(0.68,1.12)

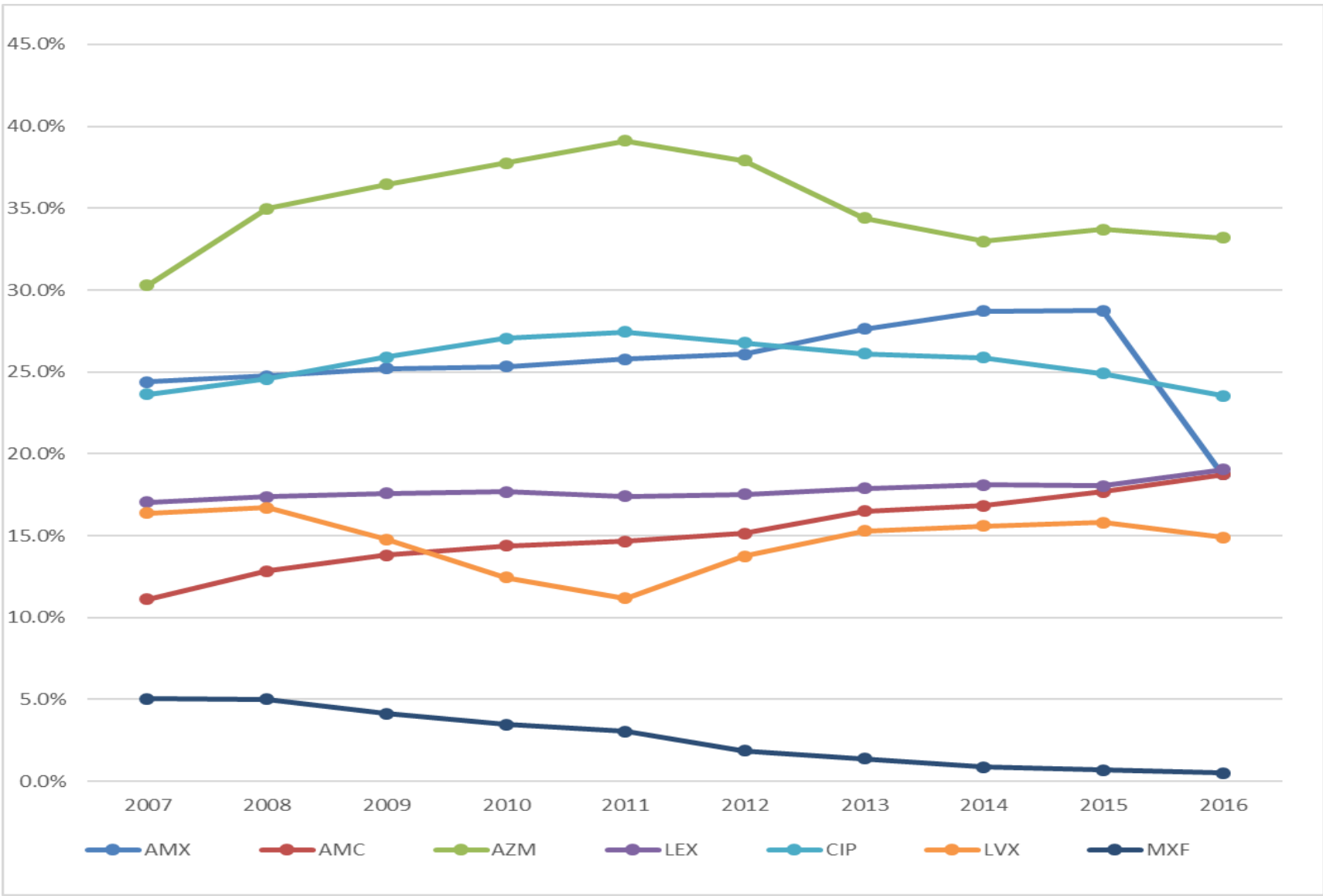
Abbreviations: HR, hazard ratio, CI, confidence interval; FLQ, fluoroquinolone; CIP, ciprofloxacin; LVX, levofloxacin; MXF, moxifloxacin; AMX, Amoxicillin; AMC, Amoxicillin Clavulanate; AZT, Azithromycin; LEX, Cephalexin.

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For peer review only



Supplementary Figure. Trend in Study Antibiotic Use



STROBE Statement—Checklist of items that should be included in reports of *case-control studies*

	Item No	Recommendation	Page No
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	1
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(a) Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls	6
		(b) For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7
Bias	9	Describe any efforts to address potential sources of bias	8-9
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	7-9
		(b) Describe any methods used to examine subgroups and interactions	n/a
		(c) Explain how missing data were addressed	n/a
		(d) If applicable, explain how matching of cases and controls was addressed	n/a
		(e) Describe any sensitivity analyses	n/a
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	9
		(b) Give reasons for non-participation at each stage	9
		(c) Consider use of a flow diagram	9
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9-10
		(b) Indicate number of participants with missing data for each variable of interest	n/a
Outcome data	15*	Report numbers in each exposure category, or summary measures of exposure	10

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3	Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
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12	Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
13			
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15			
16	Discussion		
17	Key results	18	Summarise key results with reference to study objectives
18			14
19	Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
20			14-17
21	Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
22			14-17
23	Generalisability	21	Discuss the generalisability (external validity) of the study results
24			16
25	Other information		
26	Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based
27			18
28			

*Give information separately for cases and controls.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at <http://www.strobe-statement.org>.

BMJ Open

The association between Tendon Ruptures and Use of Fluoroquinolone, and other oral antibiotics: A 10-year Prospective Study of 1 million U.S. senior Medicare beneficiaries

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4 **The association between Tendon Ruptures and Use of Fluoroquinolone, and other oral**
5 **antibiotics: A 10-year Prospective Study of 1 million U.S. senior Medicare beneficiaries**
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46 **3609 Words (4000 MAX)**
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3 **Abstract (Max 300 words, 286 now)**
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5 **Objectives:** To assess the association of fluoroquinolone use with tendon ruptures
6 compared to no fluoroquinolone and that of the four most commonly prescribed non-
7 fluoroquinolone antibiotics in the US.
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14 **Design:** Prospective observational study.
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16 **Setting:** U.S. senior enrolled in the federal old-age, survivor's insurance program.
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18 **Participants:** 1,009,925 Medicare fee-for-service beneficiaries and their inpatient,
19 outpatient, prescription drug records were used.
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23 **Interventions:** Seven oral antibiotics, fluoroquinolones (ciprofloxacin, levofloxacin,
24 moxifloxacin) and amoxicillin, amoxicillin-clavulanate, azithromycin and cephalexin.
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28 **Primary and Secondary Outcome measures:** All tendon ruptures combined, and three
29 types of tendon ruptures by anatomic site, Achilles tendon rupture, rupture of rotator cuff
30 and tendon ruptures on other anatomic sites.
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34 **Results:** Of three fluoroquinolones, only levofloxacin exhibited a significant increased
35 risk of tendon ruptures - 16%, and 120% for rotator cuff and Achilles tendon rupture
36 respectively in the ≤ 30 day window. Ciprofloxacin and moxifloxacin exhibited little to no
37 increased risk of tendon ruptures. Notably, the risk of levofloxacin never exceeded the
38 risk of the non-fluoroquinolone, cephalexin in any comparison.
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47 Among the non-fluoroquinolone antibiotics, amoxicillin, amoxicillin-clavulanate, and
48 azithromycin exhibited none to benign risk of tendon rupture. Cephalexin exhibited
49 modest to large *increased* risk of tendon rupture at ≤ 30 day window across all anatomic
50 rupture sites.
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9 **Conclusions:** In our study, fluoroquinolones as a class were not associated with the
10 increased risk of tendon ruptures. Neither ciprofloxacin nor moxifloxacin exhibited any
11 risk for tendon ruptures. Levofloxacin did exhibit significant increased risk. Cephalexin
12 with no reported effect on metalloprotease activity had an equal or greater risk than
13 levofloxacin; so we question whether metalloprotease activity has any relevance to
14 observed associations with tendon rupture. Confounding by indication bias may be more
15 relevant and should be given more consideration as explanation for significant
16 associations in observational studies of tendon rupture.
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Strengths and limitations of this study

- We conducted a large (more than 1 million US senior subjects) prospective study of outpatient prescription drug records to assess the association between the use of fluoroquinolones and the occurrence of tendon ruptures compared to the most commonly used non-fluoroquinolone oral antibiotics.
- Our study included all oral fluoroquinolones (ciprofloxacin, levofloxacin, moxifloxacin) prescribed in the US and the four most commonly prescribed non-fluoroquinolone antibiotics: amoxicillin, amoxicillin-clavulanate, azithromycin and cephalexin as controls.
- In addition to reporting the risk of any tendon rupture, we also reported the risk of three types of tendon ruptures by anatomic site 1) Achilles tendon rupture, 2) rupture of rotator cuff and 3) tendon ruptures on other anatomic sites as separate outcomes.
- This study is possibly only applicable to U.S. senior, aged 65 or more, Medicare fee-for-service beneficiaries.
- We had no options to verify claims diagnoses via chart review.

Introduction

Fluoroquinolones (FQ) are among the most widely prescribed antibiotics in the outpatient setting[1,2] due to their broad spectrum treatment of bacteria found in respiratory, urinary, joint, and skin infections. Several observational studies have reported the association between the use of FQs and tendinitis and tendon rupture (TR), especially of the Achilles tendon[3–12] and the U.S. Food and Drug Administration (FDA) issued black box warnings to FQ antibiotics beginning in 2008.[13] The warning was updated in 2016 to recommend using alternative antibiotics when possible.[14,15] The fact that FQs upregulate the production of metalloproteinase (MMP) enzymes with collagenase activity that could weaken tendons is taken as a mechanism to explain this reported risk.[16–18]

Studies that reported association between FQ use and TR used one or more other antibiotics as controls. One study compared the FQ rupture rates with patients using azithromycin, the most frequently used oral antibiotic in the US. Only two focused principally on TR risk among the elderly. None compared TR rates of *FQs* with those of cephalexin -- the 3rd most commonly prescribed oral antibiotic in the US.

The Virtual Research Data Center (VRDC) of Center for Medicare and Medicaid Services (CMS)[19] carries more than 10 years of Medicare claims, which include information about the usage of prescription drugs and encounter diagnoses (including tendon ruptures). It also carries information about 42 major chronic diseases, demographic characteristic and vital status. We conducted a large observational study using the VRDC to assess the association of FQ antibiotics with TR compared to that of

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3 the four most commonly prescribed non-FQ antibiotics in the US. Here we report the
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5 results of that analysis.
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10 **Methods**

11 *Patient and public involvement*

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14 Neither patients nor the public were not involved in the design of the study.
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19 *Study population*

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21 We derived our study population from a 20% random sample of Medicare prescription
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23 drug coverage (Part D) fee-for-service enrollees who first enrolled in the Medicare under
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25 old age and survivors insurance within a month of age 65 (779-781 month-old) and on or
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27 after 1/1/2007 - the first full year of Part D prescriptions availability. We included claim
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29 data through 12/31/2016, the end of VRDC claim data available to us. All of the VRDC
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31 data is de-identified and researchers must perform all of their analysis within the VRDC
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33 computer systems, and can only pull statistical results from it.[19] We obtained approvals
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35 for these studies from the CMS privacy board and NIH OHSRP as not human subject
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37 studies.
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44 We required subjects to be continuously enrolled in hospital insurance (Part A) and
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46 medical insurance (Part B) to assure we had full outpatient and inpatient claims data,
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48 which are not available for nearly 20% of patients with Part D only.[20] To obtain a
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50 cohort of new TR patients, we excluded (washed out) individuals with TRs recorded in
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52 the first year of their Medicare entitlement.[21] In order to assure sufficient follow-up,
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3 we excluded patients with less than 1-year follow-up. Moreover, to obtain incident (or
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5 new) drug user cohort, we excluded individuals who were prescribed any study
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7 antibiotics during their first 3-month after Part D enrollment, while ignoring the data
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9 during the same time window for patients not taking study antibiotics. By doing so, we
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11 minimize survivor bias from a prevalent users (See Figure 1 Consort Diagram).
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16 17 Primary Outcome

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19 We identified patients with TR based upon International Classification of Diseases
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21 (ICD)-9-CM codes of 726.13, 727.60-727.69, and ICD-10-CM codes of M66.2, M66.3,
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23 M66.8, M66.9, and M75.1. We combined all TRs and reported them as one outcome, and
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25 report three types of TRs by anatomic site 1) Achilles tendon rupture, 2) rupture of
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27 rotator cuff and 3) TRs on other anatomic sites as separate outcomes. We focused on
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29 Achilles TR because it was the sole focus of many prior studies and on rotator cuff TR
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31 because it is the predominant TR of the elderly. We lumped the remaining as “other
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33 TRs”.
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40 Study antibiotics

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42 As a study antibiotic, we included all three oral FQs prescribed in the US -- moxifloxacin
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44 (MXF), ciprofloxacin (CIP), levofloxacin (LVX), which is the active stereoisomer of
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46 ofloxacin. As controls, we also included the four most frequently prescribed non-FQ oral
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48 antibiotics - amoxicillin (AMX), amoxicillin clavulanate (AMC), azithromycin (AZT)
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50 and cephalexin (LEX). One of the FQs, and all four of the non-FQ, study antibiotics
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52 constituted the five most frequently used U.S. oral antibiotics in 2011.
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Statistical Analysis

We analyzed each of the four TR outcomes in separate Fine-Gray competing risk regression analyses with death as the competing risk.[22,23] Patients became eligible for “the study” at their Medicare enrollment but prescription data did not become available until their Part D enrollment. We followed them from their entry in Part D (while accounting for left truncation[24]) until their death, switch to a capitated plan, disenrollment from Medicare or 12/31/2016 – whichever came first. We adjusted hazard ratio (HR) of each study antibiotic for concurrent use of other study antibiotics and adjusted for calendar year of subject’s Part D entry, to account for secular trends. We also adjusted each HR for patient’s characteristics, income, gender, race, rural residency (Yes/No) and also for 42 chronic conditions from the Medicare Master Beneficiary Summary File (MBSF)[25] with >1% prevalence, as a measure of overall health. Based upon monthly indicators of dual-eligibility and Low Income Subsidy (LIS) status, we separated study individuals into three groups: 1) dual whose income is <135% Federal Poverty Line (FPL); 2) non-dual LIS whose income is between 135 and 150% FPL; and non-dual no LIS whose income is >150% FPL. We used this variable in the analysis as a surrogate for economic status.[26]

We assumed that patients were on a given kind of study drug from the prescription dispensing date to the end of days of supply. We did not distinguish between different brands of a study drugs. Following the approach of prior studies,[3–5] we separated subjects by temporal exposure within each study drug, including groups for never

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3 exposed, exposed within 30 days, 31-60 days, and >60 days of the index (or TR event)
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5 time. Thus, by this approach we could detect the presumed short term action of the FQ's
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7 on tendons and avoid the risk of non-differential misclassification that can occur with too
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9 simple (yes/no) drug exposure measures.[27] In order to minimize the immortal time
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11 bias, we treated all drug usage measures and all patients characteristics, except gender,
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13 race and rural residency, as time-varying covariates.[28,29] In order to mitigate selection
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15 bias toward use of any study antibiotics, we employed a propensity score (PS)
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17 approach.[30,31] We first derived a PS of taking any of study antibiotics as a function of
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19 patient's characteristics at the date of the first antibiotic use after Part D entry from a
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21 multiple logistic regression. We used the median days to the first study antibiotic use in
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23 patients taking study antibiotics as the cutoff time for subjects not taking study
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25 antibiotics. We performed our analyses with an inverse propensity score weight (IPSW)
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27 excluding individuals with the PS below 0.1 and above 0.9, to mitigate poorer
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29 performance in the presence of a strong treatment-selection process.[32] In post-hoc
30
31 analyses, we also compared the risk of TR of each study antibiotics to that of every other
32
33 study antibiotic on a pairwise basis.
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42 **Results**

43 44 *Study population and Secular trend*

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46 From our 20% sample of Part D enrollees, 1,009,925 patients satisfied all our selection
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48 criteria including the washout of individuals with any antibiotic use in their first 3-month
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50 of Part D enrollment (Figure 1 Consort Diagram). Follow-up began with an individual's
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52 enrollment in Part D program (median (IQR) 0 (0-122) days from the Medicare
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entitlement). We followed them for a median of 3.6 years (total 4,030,897 patient-years) until their first diagnosis of TR (3.5%), death (4.6%), switch from fee-for-service to health maintenance organization (HMO) plans (12.6%), disenrollment from Medicare (<1%) or study end on 12/31/2016 (79.3%), whichever came first. Patients had their first post enrollment claim with a diagnosis of TR at a median age of 68.5 (IQR 67.2-70.4). The proportions of non-Hispanic White, female and rural residents were 80.7%, 57.0%, and 22.6% respectively. About a fifth of patients received federal/state subsidies, i.e. Medicaid coverage on top of Medicare (dual 16.1%) or assistance in paying their Part D premium and coinsurance/copayment (non-dual LIS 2.7%). Among the 42 Medicare chronic disease covariates, hypertension (67.3%), hyperlipidemia (68.4%), cataract (46.4%), rheumatoid arthritis/osteoarthritis (36.6%), anemia (30.4%), ischemic heart disease (26.2%), and chronic kidney disease (17.9%) were the seven most prevalent (Table 1).

Of the 328,654 (33.0%) study patients who took a FQ prescription, 71.5%, 47.5% and 4.5% ever took CIP, LVX and MXF respectively. Of 576,885 (57.1%) of patients who took a non-FQ antibiotic, the figures were 53.6%, 44.9%, 33.9% and 31.1% for AZM, AMX, LEX, and AMC, respectively. Patients who took one or more study antibiotics took a median (IQR) of 3.0 (1.0-6.0) study antibiotic prescriptions and took a median (IQR) 2.0 (1.0-3.0) different study antibiotics during the observation period. About 2.5% patients who took one or more study antibiotics took more than one antibiotics at the same time.

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3 Secular trends in study antibiotics usage existed. MXF usage declined precipitously from
4 5.0% in 2007 to almost zero in 2016 – overweighting the MXF statistics for early entrants
5 into Medicare and yielding a longer mean follow up time. CIP use hit a peak, and LVX, a
6 nadir, in 2011. The use of AMX, AMC and LEX trended slowly upward (Supplementary
7 Figure 1). The mode (median) of supply durations for each antibiotics were 10 (7) for
8 AMX, 10 (10) for AMC, 5 (5) for AZM, 10 (7) for LEX, 7 (7) for CIP, 10 (7) for LVX,
9 10 (11) for MXF. About thirty five percent of patients were never exposed to any one of
10 the study antibiotics during the study period.
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24 Unadjusted figures for TR prevalence across each of the seven study antibiotic users and
25 the no study antibiotic users ranged from a high of 5.2% for MXF to a low of 2.9% for no
26 antibiotic (Table 1). Except for MXF, the *unadjusted* prevalence of TRs associated with
27 each non-FQ antibiotic was *greater than* or equal to that of each FQ antibiotic. The TR
28 rates per 1000 patient-years followed the same pattern, with the non-FQ antibiotics
29 topping the rates of all FQs except MXF (which had the highest rate), possibly due to
30 overweighting of MXF usage in the early years of the study. The study subjects who ever
31 took an FQ had the highest unadjusted rate of death per 1000 person-years. LVX's death
32 rate was nearly twice the rate of each non-FQ antibiotics. The size of the associations
33 with diseases like diabetes, chronic renal failure and heart failure paralleled the
34 magnitude of the death rates and was generally higher with FQs than non-FQ antibiotics
35 (Table 1).
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Primary Analysis

Table 2 presents HRs for all covariates in our Fine-Gray competing risk regression with IPSW, for all anatomic types of tendon ruptures taken together. Being a female (vs. male), African-American, Hispanic, and Asian (vs. white), being Dual or non-Dual LIS (vs. non-Dual no LIS) and living in a rural area were all associated with a *reduced* risk of tendon rupture. These risk reductions were 24% or more for all but Hispanics and rural residency covariates, and the reductions were similar across all anatomic sites. In general, life threatening chronic disease, such as AMI, COPD, heart failure and colorectal/lung/endometrial cancers were associated with a lower risk of TR in a range of 15-60% below control possibly due to constrained physical activity and/or shortened life span. Notably, diabetes and chronic renal disease, previously reported as risk factors for TR,[33,34] exhibited no increased TR risk. Mobility impairments had reduced risk of TR similar to that of the severe life threatening diseases, likely due to reduced activity. Most diseases with low life threats such as cataract, glaucoma, depression, asthma, hyperlipidemia, hypertension, prostatic hyperplasia, migraine/other chronic headache, and deafness/hearing impairment exhibited risks of 8 to 34% *above* controls probably for reasons related to longer life spans and less inhibited activity. Ischemic heart did not fit the mold of sicker equals lower TR risk. Patients with rheumatoid arthritis/osteoarthritis were a special case and had TR risk of 184% *above* control possibly due to joint and associated tendon inflammation with these disorders. Fibromyalgia/chronic pain and fatigue also exhibited a 39% increased risk of TR possibly also due to an inflammatory component.

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3 The Achilles tendon carries the full force of the extra weight carried by obese patients
4 and obesity was associated with a significant (13%) increase in Achilles TR ruptures
5 while its effect on other TR classes was significant but miniscule (2-3%) (Data not
6 shown).
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12 13 ***Effect of antibiotics*** 14

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16 Table 3 shows the risk associated with each study antibiotic broken down by time lag
17 between the antibiotic use and the TR reported in a claim as well as by anatomic sites. Of
18 the total 34,880 patients with any TR occurrence, complete rupture of rotator cuff
19 represented the major share (80.5%), followed by other TRs (16.9%) and Achilles TR
20 (2.6%). In the survival analysis, we followed patients until the first occurrence of TR; so,
21 these figures count only the first TR occurrence independent of anatomic site.
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31 Of the non-FQ antibiotics, AMX exhibited a reduced risk of TR compared to no AMX in
32 every tendon class and time window, similar to its low risk in previous studies. It
33 exhibited a significantly lower risk in the ≤ 30 -day window except for the Achilles
34 tendon. AZM and AMC exhibited a similar benign risk in all time windows except for
35 TR of rotator cuff in >60 -day window
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44 LEX was the surprise non-FQ antibiotic. It exhibited modest to large *increased* TR risk at
45 ≤ 30 -day window across all sites ranging from a low of 19% increase for complete rupture
46 of rotator cuff to a high 93% increase for Achilles TR. Its risk was also significantly
47 higher at ≤ 30 -day window for all TRs taken together.
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3 Of the FQs, CIP, the most frequently prescribed FQ, and MXF, the least frequently
4 prescribed FQ, exhibited little to no increased risk of TR within each anatomic site and
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6 prescribed FQ, exhibited little to no increased risk of TR within each anatomic site and
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8 each time frame. LVX is the only FQ to exhibit a significant *increase* in TR risk - of
9
10 16%, and 120% for rupture of rotator cuff and Achilles TR respectively in the ≤ 30 -day
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12 window. Notably, the risk of LVX never exceeded the risk of the non-FQ, LEX in any
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14 comparison.
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18 In a post-hoc analysis (Table 4), we compared the TR risk of each antibiotic with every
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20 other antibiotic (pairwise comparisons of FQ vs. FQ and FQ vs. non-FQ), for ≤ 30 day
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22 window and FQs as a class vs. each non-FQ after combining the data from the three time
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24 windows. These results paralleled the above-mentioned risk for each study antibiotic in
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26 Table 3. Again, TR risk for LVX was greater than that of CIP, MXF, AMC, AMX, and
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28 AZM in a ≤ 30 day window. However, LVX risk was comparable to that of LEX for
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30 Achilles TR, and rupture of rotator cuff and significantly lower than LEX for the other
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32 TR class. When comparing the risk of FQs as a class against that of non-FQ antibiotics,
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34 most of the non-FQ antibiotics had significantly greater risk than the FQ class as a whole
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36 across all TR sites (See last 5 rows of Table 4).
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44 **Discussion**

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46 Our results conflict with the common assertion that the Achilles tendon rupture is the
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48 most common tendon rupture (up to 90% in one report[35]). In our elderly cohort,
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50 Achilles TRs were a tiny, 2.6%, proportion of all TRs. Some of this difference may be
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52 explained by the differences in demographics. Reports of high prevalence of Achilles TR
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54 came from studies of young military populations.[36,37] In contrast, our data came from
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3 an elderly Medicare population. Some of the difference could also be due to less ability to
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5 diagnose non-Achilles tendon ruptures until MRI joint imaging became widely available,
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7 because such TRs are less amenable to diagnosis by physical exam.
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12 Many authorities describe the relationship between FQs and TRs as a class “effect”.

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14 However, FQs as a class had no significant risk of TR compared with each of the three
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16 non-FQ antibiotics in any time window. Further, neither MXF (n= 14,728 subjects) nor
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18 CIP (n=234,994 subjects), the oral FQ with the greatest use and with a greater effect on
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20 metalloproteases than other FQs,[38–40] had any TR risk at any anatomic site in any time
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22 window. CIP’s lack of risk is consistent with two studies[5,9] in which CIP exhibited
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24 zero risk or small risks compared to ofloxacin, a racemic mixture whose active ingredient
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26 is the levo-isomer, LVX. We do see a strong association between LVX and TRs whether
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28 we used no LVX or three of the non-FQ antibiotics as controls. However, with LEX, the
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30 one cephalosporin, as comparator, this association disappears.
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38 One previous study described the effect of FQs on TR risk as small and unimportant.[10]
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40 Two studies reported no effect of FQs on TR risk.[9,11] At least 7 previous observational
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42 studies reported increased risks of TR after the use of FQ.[3–8,12] However, in all but
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44 one study, the TR event rates were very low (between 5 and 111) among patients taking
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46 an FQ. In comparison, our study included 12,517 (3.8%) such patients. One previous
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48 study did report a large number of events, 23,000 (3.5%) patients with TRs while on FQs
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50 and, like our study, it also focused exclusively on elderly patients.[3] However, it did not
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52 compare FQ use against no FQ use (but against times when FQ’s were used and not used
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3 in one patient population so they could not adjust for the different levels of clinical
4 attention at visits requiring a systemic antibiotic vs visits that did not). Furthermore, they
5 assessed the association between AMX and TRs in separate analysis and used the risk of
6 TRs in that analysis as the comparator for the risk observed in the FQ analysis. But AMX
7 treated patients are likely at much lower acuity level (per our data) introducing large
8 possible differential biases into that comparison. Furthermore, their analysis did not
9 include death as a competing risk as is recommend when death rates exceed event
10 rates.[23] They reported no death rates, but death rates in their study likely exceeded their
11 event rates given the similarity of their population with ours.
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26 According to our data, the AMX treated patients had fewer comorbidities (as was also
27 true in Daneman's study), almost 14% fewer hospitalizations and half of death rate per
28 1000 patient-years, compared to patients taking LVX. So the two populations are not
29 comparable. LVX appears to be reserved for more severe infections or more fragile
30 patients and thus subject to differential biases.
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40 The reported activation of metalloprotease activity by FQs has underpinned the idea of a
41 causal link between FQs and TRs. The argument goes as follows: FQs stimulate
42 metalloproteases, which can break down collagen; the tendon is made of collagen; so FQs
43 may cause TRs. However, our data disrupts this argument. CIP which strongly *stimulates*
44 MMP activity,[17,18] exhibited *no* risk of TRs in our study, and LEX which *inhibits*
45 MMP activity[41,42] exhibited a *large* risk. So we have to question whether
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3 metalloprotease activity has any relevance to TR risk, and consider other explanations for
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5 the observed associations.
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10 The indication for an antibiotic is a presumed bacterial infection. The reported
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12 associations between antibiotics and TR could be a consequence of the indication rather
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14 than the antibiotic itself and be an example of the confounding by indication bias.[43]
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16 Such a bias could explain many reported associations between drugs and TR risk
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18 including associations with non-antibiotic drugs reported by Nyysönen.[8]
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24 This bias could manifest in two ways. First, that the bacterial infection might directly
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26 increase the risk of TR via stimulation of general immune or cytokine responses, or by
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28 bacterial invasion. A recent study found gram-positive bacteria in a major share of
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30 ruptured tendons but not in “control” tendons removed surgically for grafting,[44] giving
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32 some plausibility to a hypothesis that bacterial invasion associated with the infection
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34 treated by the antibiotic could be the culprit.
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40 Secondly, the greater clinical attention likely focused on patients needing systemic
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42 antibiotics, especially those with severe infections, could increase the chance of noticing
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44 and documenting a pre-existing TR. Furthermore, a reservoir of not-yet-diagnosed such
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46 cases is likely to exist, because patients do not necessarily correctly identify joint and
47
48 extremity symptoms as TRs and seek immediate care for them. Tendon ruptures of the
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50 shoulder capsule, for example, are notorious for developing symptoms slowly over 2-3
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52 years[45] before being correctly diagnosed. Even Achilles tendon ruptures, can be missed
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3 (in 30% of cases) at the first presentation.[46] Seeger et al. reviewed the medical records
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5 of patients with an insurance claim reporting TRs following antibiotic use and found that
6
7 nearly half of the TRs recorded in the claims were either something else (e.g., Bursa
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9 inflammation miscoded as a TR) or had occurred pre antibiotic use but only seen in a
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11 claim post antibiotic use.[11]
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17 We cannot conclude that confounding by indication fully explains the observed TR
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19 associations with LEX and LVX, but they are candidates that should be considered before
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21 we rush to causal judgements about such associations.
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26 **Limitation**

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28 This study faces all of the limitations of observational studies. Furthermore, it applies
29
30 only to fee-for-service Medicare populations. In addition, we had no options to verify
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32 claims diagnoses via chart review.
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48 **Competing interests Statement**

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51 All authors have no competing interest to declare.
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56 **Contributorship Statement**

1
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3 SB: study conception, design, analysis and interpretation; critical review of study content;
4 manuscript drafting; approval of the final manuscript. JL: study concept and
5 interpretation; manuscript drafting; approval of the final manuscript. VH: study
6 conception and interpretation; manuscript drafting; approval of the final manuscript.
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8 CJM: study conception, design and interpretation; critical review of study content;
9 manuscript drafting; approval of the final manuscript.
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12 **Data availability**

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15 The authors confirm that the data supporting the findings of this study are available
16 within the article [and/or] its supplementary materials.
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3 **Figure 1. Consort Diagram**
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For peer review only

Table 1. Outcome, Medical/Medication Use, Diseases and Patient Characteristics by Type of Antibiotics

Variable	Overall	FLQ	CIP	LVX	MXF	AMX	AZM	LEX	AMC	None
N	1,009,925	328,654	234,994	155,991	14,728	259,125	308,985	195,731	179,616	356,364
Tendon Rupture	34,880(3.5)	12,517(3.8)	8,811(3.7)	5,904(3.8)	770(5.2)	9,636(3.7)	12,448(4.0)	8,019(4.1)	6,622(3.7)	10,169(2.9)
Death	46,468(4.6)	23,249(7.1)	14,821(6.3)	14,610(9.4)	2,136(14.5)	9,632(3.7)	14,608(4.7)	11,394(5.8)	9,951(5.5)	13,645(3.8)
Censored at HMO entry	127,162(12.6)	27,573(8.4)	19,847(8.4)	11,142(7.1)	1,571(10.7)	21,215(8.2)	26,140(8.5)	14,887(7.6)	12,674(7.1)	65,886(18.5)
Censored at disenrollment	145(0.0)	25(0.0)	13(0.0)	13(0.0)	2(0.0)	19(0.0)	27(0.0)	23(0.0)	16(0.0)	85(0.0)
Censored at Dec 31 2016	801,270(79.3)	265,290(80.7)	191,502(81.5)	124,322(79.7)	10,249(69.6)	218,623(84.4)	255,762(82.8)	161,408(82.5)	150,353(83.7)	266,579(74.8)
Years of follow-up, median(total)	3.6(4,030,897)	4.6(1,620,894)	4.8(1,190,308)	4.8(789,849)	6.0(87,397)	4.5(1,274,357)	4.6(1,529,370)	4.8(1,000,459)	4.6(890,340)	2.5(1,067,731)
Tendon rupture, 1000 person-years	8.65	7.72	7.40	7.47	8.81	7.56	8.14	8.02	7.44	9.52
Death, 1000 person-years	11.53	14.34	12.45	18.50	24.44	7.56	9.55	11.39	11.18	12.78
Female	575,885(57.0)	197,915(60.2)	146,745(62.4)	89,682(57.5)	8,747(59.4)	151,383(58.4)	194,101(62.8)	113,308(57.9)	104,749(58.3)	191,069(53.6)
White	814,933(80.7)	274,785(83.6)	196,048(83.4)	131,725(84.4)	12,464(84.6)	215,101(83.0)	259,657(84.0)	167,825(85.7)	153,723(85.6)	271,906(76.3)
Black	75,930(7.5)	20,017(6.1)	14,286(6.1)	8,893(5.7)	956(6.5)	15,622(6.0)	17,296(5.6)	9,625(4.9)	9,199(5.1)	35,023(9.8)
Hispanic	56,582(5.6)	17,044(5.2)	12,607(5.4)	7,943(5.1)	628(4.3)	12,494(4.8)	14,805(4.8)	8,976(4.6)	7,802(4.3)	24,391(6.8)
Asian	26,336(2.6)	7,316(2.2)	5,362(2.3)	3,144(2.0)	356(2.4)	7,624(2.9)	7,945(2.6)	3,539(1.8)	3,440(1.9)	10,437(2.9)
Other	36,144(3.6)	9,492(2.9)	6,691(2.8)	4,286(2.7)	324(2.2)	8,284(3.2)	9,282(3.0)	5,766(2.9)	5,452(3.0)	14,607(4.1)
Ever Dual	162,988(16.1)	54,055(16.4)	38,277(16.3)	28,156(18.0)	2,908(19.7)	35,305(13.6)	44,940(14.5)	30,962(15.8)	25,255(14.1)	66,986(18.8)
Non-Dual LIS	26,955(2.7)	7,648(2.3)	5,459(2.3)	3,746(2.4)	385(2.6)	5,224(2.0)	6,828(2.2)	4,191(2.1)	3,818(2.1)	12,595(3.5)
Non-Dual No LIS	819,982(81.2)	266,951(81.2)	191,258(81.4)	124,089(79.5)	11,435(77.6)	218,596(84.4)	257,217(83.2)	160,578(82.0)	150,543(83.8)	276,783(77.7)
Living in rural area	228,199(22.6)	78,581(23.9)	56,385(24.0)	38,847(24.9)	2,801(19.0)	58,805(22.7)	72,282(23.4)	49,977(25.5)	42,288(23.5)	77,087(21.6)
Days on Rx, median (IQR)	N/A	N/A	10.0(7.0-20.0)	10.0(7.0-17.0)	10.0(7.0-12.0)	10.0(7.0-20.0)	5.0(5.0-11.0)	10.0(7.0-16.0)	10.0(10.0-20.0)	N/A
Hospitalization	349,959(29.5)	198,846(45.4)	142,538(45.3)	113,829(52.5)	14,002(60.3)	132,304(38.8)	156,185(37.9)	119,209(45.9)	103,515(42.5)	51,525(14.4)
Outpatient visits per year, median (IQR)	19.6(11.1-33.0)	27.1(17.2-42.7)	27.3(17.5-42.9)	30.1(19.0-47.8)	34.0(21.7-53.7)	23.6(14.5-37.5)	24.6(15.5-38.8)	27.5(17.2-43.2)	26.6(16.7-42.2)	12.3(6.0-21.8)
AMI	21,222(2.1)	9,999(3.0)	6,810(2.9)	5,862(3.8)	698(4.7)	6,474(2.5)	8,079(2.6)	6,215(3.2)	5,292(2.9)	5,012(1.4)
Atrial Fibrillation	71,635(7.1)	31,752(9.7)	21,757(9.3)	17,731(11.4)	2,028(13.8)	23,974(9.3)	26,182(8.5)	21,935(11.2)	18,764(10.4)	16,314(4.6)
Cataract	468,608(46.4)	183,870(55.9)	134,196(57.1)	88,574(56.8)	9,216(62.6)	144,455(55.7)	174,897(56.6)	112,020(57.2)	101,079(56.3)	124,931(35.1)
Chronic Kidney Disease	180,441(17.9)	86,021(26.2)	62,323(26.5)	46,121(29.6)	4,651(31.6)	53,713(20.7)	65,577(21.2)	50,361(25.7)	43,182(24.0)	42,916(12.0)
COPD	130,840(13.0)	71,913(21.9)	43,961(18.7)	48,430(31.0)	6,106(41.5)	40,109(15.5)	66,536(21.5)	37,413(19.1)	37,579(20.9)	22,739(6.4)
Heart Failure	103,010(10.2)	51,814(15.8)	34,870(14.8)	31,377(20.1)	3,776(25.6)	32,792(12.7)	41,647(13.5)	31,585(16.1)	27,223(15.2)	21,907(6.1)
Diabetes	284,919(28.2)	113,424(34.5)	81,175(34.5)	57,697(37.0)	5,942(40.3)	81,155(31.3)	98,176(31.8)	67,548(34.5)	59,984(33.4)	81,448(22.9)
Glaucoma	150,839(14.9)	56,990(17.3)	41,984(17.9)	26,603(17.1)	2,930(19.9)	45,597(17.6)	54,726(17.7)	33,936(17.3)	31,065(17.3)	42,355(11.9)
Hip/Pelvic Fracture	7,982(0.8)	4,086(1.2)	3,000(1.3)	2,289(1.5)	274(1.9)	2,673(1.0)	3,005(1.0)	2,515(1.3)	1,914(1.1)	1,689(0.5)
Ischemic Heart Disease	264,648(26.2)	117,416(35.7)	82,182(35.0)	63,659(40.8)	6,956(47.2)	83,682(32.3)	101,999(33.0)	70,612(36.1)	63,363(35.3)	63,372(17.8)
Depression	210,714(20.9)	94,554(28.8)	68,625(29.2)	49,277(31.6)	5,298(36.0)	65,642(25.3)	83,253(26.9)	56,747(29.0)	51,150(28.5)	49,320(13.8)
Alzheimer's Disease or Senile Dementia	39,132(3.9)	19,796(6.0)	14,309(6.1)	11,030(7.1)	1,206(8.2)	11,140(4.3)	13,809(4.5)	11,846(6.1)	9,309(5.2)	9,400(2.6)
Osteoporosis	106,966(10.6)	47,033(14.3)	35,217(15.0)	22,918(14.7)	2,738(18.6)	34,610(13.4)	44,016(14.2)	26,996(13.8)	24,393(13.6)	25,216(7.1)

Rheumatoid Arthritis/Osteoarthritis	369,584(36.6)	160,091(48.7)	117,018(49.8)	80,115(51.4)	8,259(56.1)	126,702(48.9)	148,653(48.1)	101,310(51.8)	88,017(49.0)	81,855(23.0)
1 Stroke/Transient Ischemic Attack	58,886(5.8)	27,702(8.4)	19,843(8.4)	15,051(9.6)	1,670(11.3)	17,829(6.9)	22,038(7.1)	16,684(8.5)	14,245(7.9)	14,262(4.0)
2 Breast Cancer	45,316(4.5)	19,362(5.9)	14,344(6.1)	9,442(6.1)	984(6.7)	13,451(5.2)	17,676(5.7)	12,543(6.4)	10,156(5.7)	11,042(3.1)
3 Colorectal Cancer	15,905(1.6)	7,487(2.3)	5,421(2.3)	4,048(2.6)	390(2.6)	4,304(1.7)	5,170(1.7)	4,085(2.1)	3,605(2.0)	4,104(1.2)
4 Prostate Cancer	37,038(3.7)	19,705(6.0)	15,577(6.6)	9,232(5.9)	643(4.4)	10,967(4.2)	11,733(3.8)	9,252(4.7)	8,070(4.5)	8,333(2.3)
5 Lung Cancer	14,946(1.5)	8,965(2.7)	5,144(2.2)	6,356(4.1)	905(6.1)	3,859(1.5)	6,633(2.1)	3,977(2.0)	4,267(2.4)	2,733(0.8)
6 Endometrial Cancer	7,396(0.7)	3,447(1.0)	2,670(1.1)	1,635(1.0)	160(1.1)	2,095(0.8)	2,637(0.9)	1,957(1.0)	1,604(0.9)	1,847(0.5)
8 Anemia	307,310(30.4)	140,606(42.8)	100,819(42.9)	74,308(47.6)	7,980(54.2)	99,190(38.3)	118,327(38.3)	81,967(41.9)	72,587(40.4)	71,098(20.0)
9 Asthma	86,120(8.5)	46,350(14.1)	29,327(12.5)	30,152(19.3)	4,091(27.8)	27,632(10.7)	46,823(15.2)	24,426(12.5)	25,465(14.2)	13,802(3.9)
10 Hyperlipidemia	691,148(68.4)	257,086(78.2)	185,199(78.8)	123,828(79.4)	12,162(82.6)	199,236(76.9)	239,414(77.5)	152,879(78.1)	140,364(78.1)	201,258(56.5)
11 Hyperplasia	122,010(12.1)	59,809(18.2)	45,517(19.4)	28,616(18.3)	2,587(17.6)	39,031(15.1)	42,070(13.6)	31,606(16.1)	28,398(15.8)	27,336(7.7)
11 Hypertension	679,287(67.3)	253,601(77.2)	181,231(77.1)	124,646(79.9)	12,218(83.0)	192,686(74.4)	230,409(74.6)	150,995(77.1)	136,292(75.9)	201,777(56.6)
13 Hypothyroidism	197,447(19.6)	81,468(24.8)	59,450(25.3)	40,372(25.9)	4,198(28.5)	59,893(23.1)	76,582(24.8)	47,973(24.5)	44,249(24.6)	50,280(14.1)
14 Anxiety Disorders	148,983(14.8)	70,688(21.5)	51,377(21.9)	37,563(24.1)	4,032(27.4)	48,859(18.9)	62,418(20.2)	41,655(21.3)	37,588(20.9)	31,709(8.9)
15 Bipolar Disorder	17,882(1.8)	8,368(2.5)	6,104(2.6)	4,533(2.9)	468(3.2)	5,442(2.1)	6,658(2.2)	5,147(2.6)	4,227(2.4)	4,242(1.2)
16 Major Depressive Affective Disorder	153,182(15.2)	71,732(21.8)	52,101(22.2)	38,055(24.4)	4,148(28.2)	48,846(18.9)	61,872(20.0)	43,416(22.2)	38,642(21.5)	33,660(9.4)
17 Schizophrenia and other Psychotic Disorders	16,764(1.7)	8,591(2.6)	6,176(2.6)	4,934(3.2)	548(3.7)	4,421(1.7)	5,597(1.8)	5,101(2.6)	3,811(2.1)	4,300(1.2)
18 Epilepsy	16,155(1.6)	7,543(2.3)	5,383(2.3)	4,269(2.7)	415(2.8)	4,310(1.7)	5,488(1.8)	4,510(2.3)	3,621(2.0)	4,191(1.2)
19 Fibromyalgia, Chronic Pain and Fatigue	166,279(16.5)	78,877(24.0)	57,494(24.5)	41,843(26.8)	4,410(29.9)	56,152(21.7)	70,667(22.9)	48,422(24.7)	43,379(24.2)	33,843(9.5)
20 Viral Hepatitis (General)	11,969(1.2)	4,659(1.4)	3,188(1.4)	2,523(1.6)	287(1.9)	3,156(1.2)	3,732(1.2)	2,712(1.4)	2,348(1.3)	3,735(1.0)
21 Liver Disease Cirrhosis and other Liver Conditions	62,675(6.2)	31,930(9.7)	23,284(9.9)	17,386(11.1)	1,919(13.0)	19,624(7.6)	24,544(7.9)	17,393(8.9)	15,958(8.9)	13,350(3.7)
22 Leukemias and Lymphomas	13,906(1.4)	7,228(2.2)	4,822(2.1)	4,536(2.9)	551(3.7)	4,385(1.7)	5,905(1.9)	4,025(2.1)	3,969(2.2)	2,758(0.8)
24 Migraine and other Chronic Headache	31,628(3.1)	14,936(4.5)	11,282(4.8)	7,520(4.8)	873(5.9)	10,841(4.2)	13,893(4.5)	8,763(4.5)	8,403(4.7)	6,419(1.8)
25 Mobility Impairments	20,600(2.0)	10,182(3.1)	7,356(3.1)	5,767(3.7)	577(3.9)	5,372(2.1)	6,629(2.1)	5,995(3.1)	4,610(2.6)	5,439(1.5)
26 Obesity	185,101(18.3)	79,130(24.1)	56,609(24.1)	41,226(26.4)	3,997(27.1)	58,654(22.6)	69,611(22.5)	49,984(25.5)	43,740(24.4)	44,772(12.6)
27 Peripheral Vascular Disease	90,132(8.9)	45,276(13.8)	31,866(13.6)	25,977(16.7)	3,001(20.4)	28,747(11.1)	36,241(11.7)	28,343(14.5)	23,977(13.3)	18,446(5.2)
28 Tobacco Use Disorders	101,890(10.1)	45,304(13.8)	28,907(12.3)	27,202(17.4)	3,042(20.7)	27,261(10.5)	37,860(12.3)	25,002(12.8)	22,975(12.8)	26,896(7.5)
29 Pressure Ulcers and Chronic Ulcers	30,345(3.0)	17,688(5.4)	12,800(5.4)	10,603(6.8)	1,196(8.1)	9,006(3.5)	10,926(3.5)	13,404(6.8)	9,960(5.5)	4,992(1.4)
30 Deafness and Hearing Impairment	59,576(5.9)	27,383(8.3)	19,976(8.5)	14,014(9.0)	1,609(10.9)	21,213(8.2)	25,498(8.3)	16,849(8.6)	16,787(9.3)	11,900(3.3)

Note. Data are presented as No. (%) of patients unless otherwise noted.

Abbreviations: FLQ, fluoroquinolone; CIP, ciprofloxacin; LVX, levofloxacin; MXF, moxifloxacin; AMX, Amoxicillin; AMC, Amoxicillin Clavulanate; AZT, Azithromycin; LEX, Cephalexin; IQR, interquartile range.

Table 2. Hazard Ratios of Tendon Rupture for Each Covariate

Variables	Reference	HR(95% CI)
Female	Male	0.70(0.69,0.72)‡
Black	White	0.76(0.73,0.78)‡
Hispanic		0.91(0.87,0.94)‡
Asian		0.67(0.63,0.71)‡
Other		1.05(1.01,1.09)†
Dual Ever		Non-Dual Non-LIS
Non-Dual Lis		0.66(0.63,0.70)‡
Living In Rural Area	No	0.94(0.92,0.95)‡
Medicare Part D Since 2008	Medicare Part D Since 2007	1.03(1.00,1.07)
Medicare Part D Since 2009		1.11(1.07,1.15)‡
Medicare Part D Since 2010		1.16(1.12,1.21)‡
Medicare Part D Since 2011		1.17(1.13,1.22)‡
Medicare Part D Since 2012		1.12(1.08,1.16)‡
Medicare Part D Since 2013		1.03(1.00,1.07)
Medicare Part D Since 2013		1.05(1.01,1.09)†
Medicare Part D Since 2015		0.91(0.87,0.96)‡
Medicare Part D Since 2016		0.93(0.19,4.55)
AMI		No
Atrial Fibrillation	No	0.94(0.91,0.97)‡
Cataract	No	1.23(1.21,1.25)‡
Chronic Kidney Disease	No	0.92(0.89,0.94)‡
COPD	No	0.83(0.81,0.86)‡
Heart Failure	No	0.79(0.77,0.82)‡
Diabetes	No	0.98(0.96,0.99)†
Glaucoma	No	1.10(1.08,1.12)‡
Hip/Pelvic Fracture	No	0.68(0.60,0.77)‡
Ischemic Heart Disease	No	1.10(1.08,1.12)‡
Depression	No	1.17(1.13,1.21)
Alzheimer's Disease or Senile Dementia	No	0.67(0.63,0.71)‡
Osteoporosis	No	1.03(1.01,1.06)†
Rheumatoid Arthritis/Osteoarthritis	No	2.84(2.80,2.89)‡
Stroke/Transient Ischemic Attack	No	0.97(0.94,1.01)
Breast Cancer	No	0.94(0.91,0.98)†
Colorectal Cancer	No	0.79(0.74,0.85)‡

1	Prostate Cancer	No	1.03(0.99,1.07)
2	Lung Cancer	No	0.39(0.34,0.45)‡
3	Endometrial Cancer	No	0.85(0.77,0.94)†
4	Anemia	No	1.01(0.99,1.03)
5	Asthma	No	1.27(1.24,1.31)‡
6	Hyperlipidemia	No	1.34(1.31,1.36)‡
7	Hyperplasia	No	1.13(1.10,1.16)‡
8	Hypertension	No	1.09(1.07,1.11)‡
9	Hypothyroidism	No	1.08(1.06,1.10)‡
10	Anxiety Disorders	No	0.98(0.96,1.01)
11	Bipolar Disorder	No	1.02(0.95,1.08)
12	Major Depressive Affective Disorder	No	1.06(1.02,1.10)†
13	Schizophrenia and Other Psychotic Disorders	No	0.67(0.61,0.74)‡
14	Epilepsy	No	0.83(0.77,0.90)‡
15	Fibromyalgia, Chronic Pain and Fatigue	No	1.39(1.36,1.42)‡
16	Viral Hepatitis (General)	No	1.04(0.96,1.13)
17	Liver Disease Cirrhosis And Other Liver Conditions	No	0.95(0.92,0.99)†
18	Leukemias and Lymphomas	No	0.94(0.88,1.01)
19	Migraine and Other Chronic Headache	No	1.28(1.23,1.33)‡
20	Mobility Impairments	No	0.70(0.65,0.76)‡
21	Obesity	No	1.04(1.02,1.06)†
22	Peripheral Vascular Disease	No	1.00(0.97,1.04)
23	Tobacco Use Disorders	No	0.82(0.80,0.85)‡
24	Pressure Ulcers and Chronic Ulcers	No	0.82(0.77,0.87)‡
25	Deafness and Hearing Impairment	No	1.21(1.17,1.25)‡

Abbreviations: HR, hazard ratio, CI, confidence interval; FLQ, fluoroquinolone; CIP, ciprofloxacin; LVX, levofloxacin; MXF, moxifloxacin; AMX, Amoxicillin; AMC, Amoxicillin Clavulanate; AZT, Azithromycin; LEX, Cephalexin.

‡ = P-value < 0.001

† = 0.001 ≤ P-value < 0.05

Table 3. Hazard Ratios of Each Antibiotic by Anatomic Sites and Temporal Order of Drug Exposure

		Any Tendon Rupture	Achilles Tendon Rupture	Complete Rupture of Rotator Cuff	Other Tendon Rupture
	Temporal Exposure	HR(95% CI)	HR(95% CI)	HR(95% CI)	HR(95% CI)
AMX VS. NO AMX	≤ 30 days	0.86(0.80,0.92)‡	0.88(0.59,1.33)	0.88(0.82,0.95)†	0.79(0.67,0.93)†
	31 – 60 days	0.94(0.87,1.01)	0.80(0.49,1.31)	0.91(0.84,0.99)†	1.08(0.93,1.27)
	≥ 61 days	1.00(0.98,1.02)	0.99(0.86,1.13)	1.01(0.99,1.04)	0.97(0.92,1.01)
AMC VS. NO AMC	≤ 30 days	0.93(0.85,1.02)	1.25(0.79,1.97)	0.87(0.79,0.97)†	1.17(0.98,1.41)
	31 – 60 days	0.95(0.85,1.05)	1.37(0.82,2.29)	0.95(0.84,1.06)	0.81(0.63,1.04)
	≥ 61 days	1.07(1.04,1.09)‡	0.95(0.81,1.12)	1.07(1.04,1.10)‡	1.02(0.96,1.08)
AZM VS. NO AZM	≤ 30 days	0.99(0.93,1.06)	1.15(0.82,1.63)	1.00(0.93,1.08)	0.87(0.75,1.01)
	31 – 60 days	0.90(0.84,0.98)†	0.99(0.65,1.49)	0.91(0.84,0.99)†	0.95(0.81,1.11)
	≥ 61 days	1.07(1.05,1.09)‡	1.02(0.91,1.15)	1.09(1.07,1.12)‡	0.99(0.95,1.04)
LEX VS. NO LEX	≤ 30 days	1.31(1.22,1.41)‡	1.93(1.35,2.75)‡	1.19(1.09,1.29)‡	1.79(1.56,2.06)‡
	31 – 60 days	1.05(0.95,1.15)	1.14(0.66,1.96)	1.06(0.96,1.18)	1.02(0.82,1.26)
	≥ 61 days	1.08(1.05,1.11)‡	1.00(0.85,1.16)	1.07(1.05,1.10)‡	1.15(1.09,1.21)‡
LVX VS. NO LVX	≤ 30 days	1.14(1.05,1.25)†	2.20(1.50,3.24)‡	1.16(1.06,1.28)†	0.96(0.78,1.19)
	31 – 60 days	1.09(0.98,1.21)	1.91(1.17,3.10)†	1.09(0.97,1.22)	1.14(0.90,1.43)
	≥ 61 days	1.02(1.00,1.05)	1.22(1.03,1.43)†	1.03(1.00,1.07)†	0.97(0.91,1.03)
CIP VS. NO CIP	≤ 30 days	0.96(0.89,1.03)	1.06(0.70,1.60)	0.96(0.88,1.04)	0.84(0.71,1.00)†
	31 – 60 days	0.92(0.85,1.01)	1.02(0.63,1.67)	0.91(0.82,1.00)†	0.95(0.78,1.14)
	≥ 61 days	0.96(0.94,0.98)‡	1.16(1.02,1.32)†	0.96(0.94,0.99)†	0.92(0.88,0.97)†
MXF VS. NO MXF	≤ 30 days	0.59(0.37,0.93)	0.97(0.15,6.24)	0.52(0.30,0.91)†	0.76(0.33,1.77)
	31 – 60 days	0.71(0.43,1.15)	0.00(0.00,0.00)	0.63(0.35,1.13)	0.93(0.39,2.25)
	≥ 61 days	0.99(0.93,1.06)	1.02(0.69,1.51)	0.99(0.92,1.06)	1.10(0.95,1.27)
FLQ VS. AMX	≤ 30 days	1.00(0.84,1.19)	1.49(0.69,3.19)	0.94(0.77,1.16)	1.08(0.77,1.50)
	31 – 60 days	0.95(0.79,1.15)	0.07(0.04,0.12)‡	0.94(0.75,1.17)	0.92(0.65,1.31)
	≥ 61 days	0.99(0.96,1.02)	1.14(0.94,1.40)	0.98(0.95,1.02)	1.03(0.96,1.11)
FLQ VS. AZM	≤ 30 days	0.87(0.73,1.03)	1.14(0.54,2.39)	0.83(0.68,1.02)	0.98(0.70,1.37)
	31 – 60 days	0.99(0.82,1.19)	0.06(0.04,0.09)‡	0.93(0.75,1.16)	1.06(0.75,1.49)
	≥ 61 days	0.93(0.90,0.96)‡	1.10(0.91,1.34)	0.91(0.88,0.94)‡	1.00(0.93,1.08)
FLQ VS. LEX	≤ 30 days	0.66(0.55,0.78)‡	0.68(0.32,1.42)	0.70(0.57,0.87)†	0.47(0.34,0.66)‡
	31 – 60 days	0.85(0.70,1.04)	0.05(0.03,0.09)‡	0.80(0.64,1.01)	0.99(0.68,1.44)
	≥ 61 days	0.92(0.89,0.95)‡	1.13(0.92,1.40)	0.92(0.89,0.96)‡	0.86(0.80,0.93)‡
FLQ VS. AMC	≤ 30 days	0.93(0.77,1.11)	1.05(0.48,2.32)	0.96(0.77,1.19)	0.72(0.51,1.02)
	31 – 60 days	0.94(0.77,1.15)	0.04(0.02,0.07)‡	0.90(0.72,1.14)	1.24(0.83,1.86)

≥ 61 days

0.93(0.90,0.97)‡

1.19(0.95,1.49)

0.93(0.89,0.96)‡

0.98(0.90,1.06)

Abbreviations: HR, hazard ratio; CI, confidence interval; FLQ, fluoroquinolone; CIP, ciprofloxacin; LVX, levofloxacin; MXF, moxifloxacin; AMX, Amoxicillin; AMC, Amoxicillin Clavulanate; AZT, Azithromycin; LEX, Cephalexin.

‡ = P-value < 0.001

† = 0.001 ≤ P-value < 0.05

For peer review only

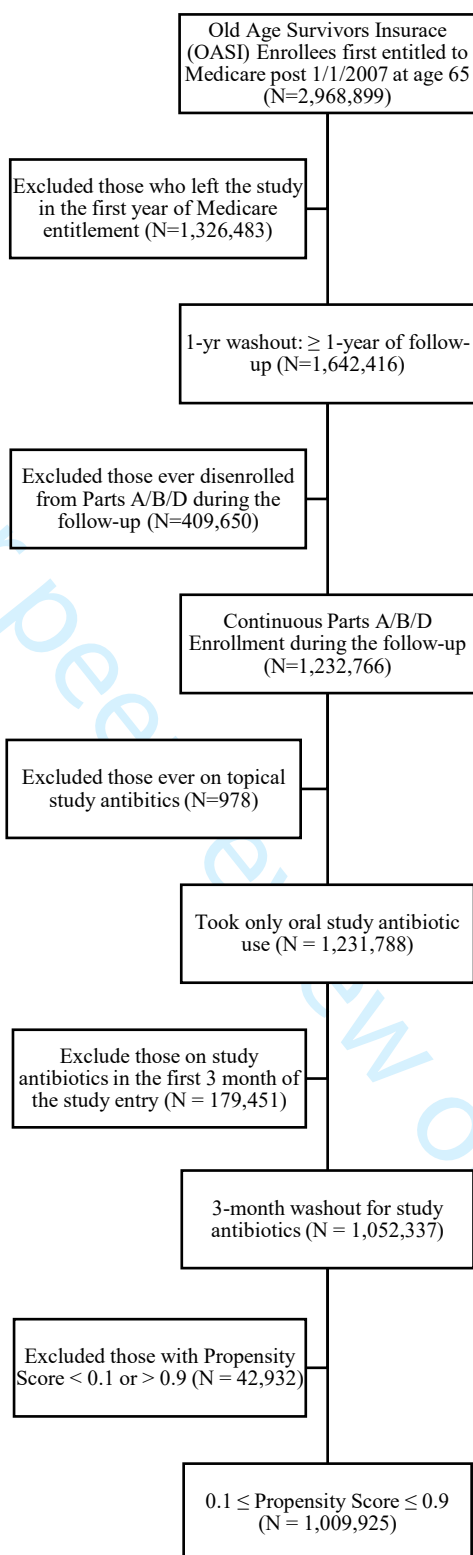
Table 4. Pairwise Comparisons

Comparison	Temporal Exposure	Any Tendon Rupture	Achilles Tendon Rupture	Complete Rupture of Rotator Cuff	Other Tendon Rupture
		HR(95% CI)	HR(95% CI)	HR(95% CI)	HR(95% CI)
CIP VS. LVX	≤ 30 days	0.84(0.75,0.94)†	0.48(0.27,0.86)†	0.82(0.73,0.94)†	0.87(0.67,1.15)
CIP VS. MXF	≤ 30 days	1.63(1.02,2.61)†	1.08(0.16,7.29)	1.84(1.05,3.24)†	1.10(0.47,2.60)
LVX VS. MXF	≤ 30 days	1.95(1.21,3.13)†	2.26(0.34,15.17)	2.24(1.27,3.94)†	1.26(0.53,3.01)
CIP VS. AMX	≤ 30 days	1.11(1.01,1.23)†	1.20(0.66,2.16)	1.09(0.97,1.21)	1.06(0.84,1.34)
CIP VS. AZM	≤ 30 days	0.97(0.87,1.06)	0.91(0.53,1.57)	0.96(0.86,1.07)	0.96(0.77,1.21)
CIP VS. LEX	≤ 30 days	0.73(0.66,0.81)‡	0.55(0.31,0.95)†	0.81(0.72,0.91)‡	0.47(0.37,0.59)‡
CIP VS. AMC	≤ 30 days	1.03(0.91,1.16)	0.84(0.46,1.56)	1.10(0.96,1.25)	0.71(0.56,0.92)†
LVX VS. AMX	≤ 30 days	1.33(1.19,1.49)‡	2.50(1.45,4.29)†	1.32(1.16,1.49)‡	1.22(0.93,1.59)
LVX VS. AZM	≤ 30 days	1.15(1.03,1.29)†	1.91(1.13,3.23)†	1.16(1.03,1.31)†	1.10(0.84,1.44)
LVX VS. LEX	≤ 30 days	0.87(0.78,0.98)†	1.14(0.68,1.92)	0.98(0.86,1.12)	0.54(0.41,0.69)‡
LVX VS. AMC	≤ 30 days	1.23(1.08,1.40)†	1.76(0.98,3.15)	1.33(1.15,1.54)‡	0.82(0.62,1.08)
MXF VS. AMX	≤ 30 days	0.68(0.43,1.09)	1.10(0.16,7.41)	0.59(0.34,1.03)	0.96(0.41,2.27)
MXF VS. AZM	≤ 30 days	0.59(0.37,0.94)†	0.84(0.13,5.65)	0.52(0.30,0.91)†	0.88(0.37,2.07)
MXF VS. LEX	≤ 30 days	0.45(0.28,0.72)†	0.50(0.08,3.35)	0.44(0.25,0.77)†	0.43(0.18,1.00)
MXF VS. AMC	≤ 30 days	0.63(0.39,1.01)	0.78(0.11,5.33)	0.60(0.34,1.05)	0.65(0.28,1.53)
FLQ VS. AMX	Overall	0.98(0.90,1.07)	0.49(0.36,0.68)‡	0.95(0.86,1.06)	1.01(0.86,1.19)
FLQ VS. AZM	Overall	0.93(0.85,1.01)	0.42(0.30,0.57)‡	0.89(0.80,0.98)†	1.01(0.86,1.19)
FLQ VS. LEX	Overall	0.80(0.73,0.88)‡	0.34(0.24,0.47)‡	0.80(0.72,0.89)‡	0.74(0.62,0.88)‡
FLQ VS. AMC	Overall	0.93(0.85,1.02)	0.37(0.26,0.52)‡	0.93(0.83,1.03)	0.96(0.80,1.15)

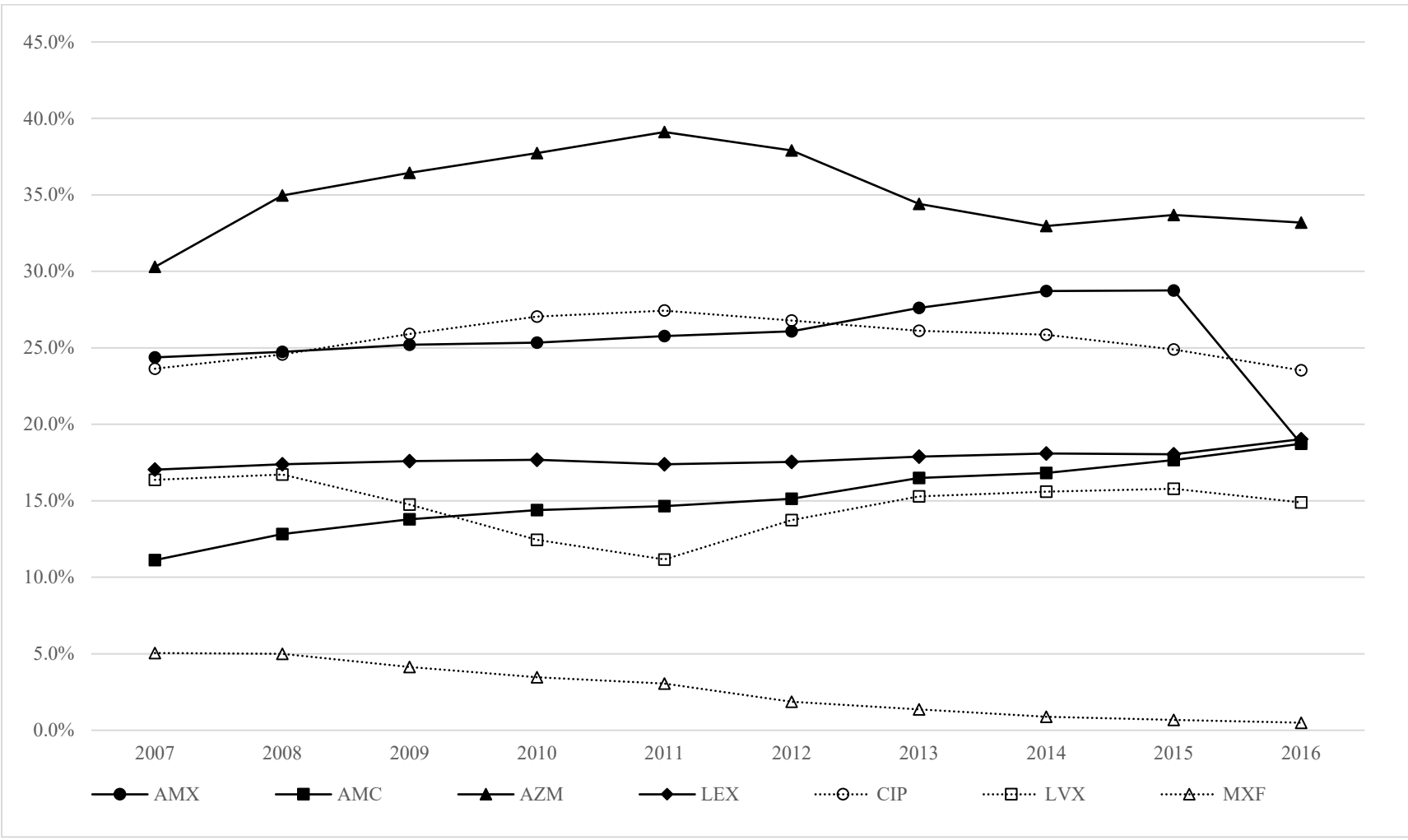
Abbreviations: HR, hazard ratio, CI, confidence interval; FLQ, fluoroquinolone; CIP, ciprofloxacin; LVX, levofloxacin; MXF, moxifloxacin; AMX, Amoxicillin; AMC, Amoxicillin Clavulanate; AZT, Azithromycin; LEX, Cephalexin.

‡ = P-value < 0.001

† = 0.001 ≤ P-value < 0.05



Supplementary Figure. Secular Trend of Study Antibiotic Use



X-axis: Calendar year.

Y-axis: % of patients on each drug class.

STROBE Statement—Checklist of items that should be included in reports of *case-control studies*

	Item No	Recommendation	Page No
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	1
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(a) Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls	6
		(b) For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7
Bias	9	Describe any efforts to address potential sources of bias	8-9
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	7-9
		(b) Describe any methods used to examine subgroups and interactions	n/a
		(c) Explain how missing data were addressed	n/a
		(d) If applicable, explain how matching of cases and controls was addressed	n/a
		(e) Describe any sensitivity analyses	n/a
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	9
		(b) Give reasons for non-participation at each stage	9
		(c) Consider use of a flow diagram	9
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9-10
		(b) Indicate number of participants with missing data for each variable of interest	n/a
Outcome data	15*	Report numbers in each exposure category, or summary measures of exposure	10

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3	Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
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	Discussion		
	Key results	18	Summarise key results with reference to study objectives
	Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
	Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
	Generalisability	21	Discuss the generalisability (external validity) of the study results
	Other information		
	Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based
			18

*Give information separately for cases and controls.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at <http://www.strobe-statement.org>.

BMJ Open

The association between Tendon Ruptures and Use of Fluoroquinolone, and other oral antibiotics: A 10-year Retrospective Study of 1 million U.S. senior Medicare beneficiaries

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Secondary Subject Heading:	General practice / Family practice, Pharmacology and therapeutics
Keywords:	CLINICAL PHARMACOLOGY, EPIDEMIOLOGY, ORAL MEDICINE, Musculoskeletal disorders < ORTHOPAEDIC & TRAUMA SURGERY, ACCIDENT & EMERGENCY MEDICINE

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4 **The association between Tendon Ruptures and Use of Fluoroquinolone, and other oral**
5 **antibiotics: A 10-year Retrospective Study of 1 million U.S. senior Medicare beneficiaries**
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46 **3957 Words (4000 MAX)**
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3 **Abstract (Max 300 words, 286 now)**
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5 **Objectives:** To assess the association of fluoroquinolone use with tendon ruptures
6 compared to no fluoroquinolone and that of the four most commonly prescribed non-
7 fluoroquinolone antibiotics in the US.
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14 **Design:** Retrospective observational study.
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16 **Setting:** U.S. senior enrolled in the federal old-age, survivor's insurance program.
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18 **Participants:** 1,009,925 Medicare fee-for-service beneficiaries and their inpatient,
19 outpatient, prescription drug records were used.
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23 **Interventions:** Seven oral antibiotics, fluoroquinolones (ciprofloxacin, levofloxacin,
24 moxifloxacin) and amoxicillin, amoxicillin-clavulanate, azithromycin and cephalexin.
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28 **Primary and Secondary Outcome measures:** All tendon ruptures combined, and three
29 types of tendon ruptures by anatomic site, Achilles tendon rupture, rupture of rotator cuff
30 and tendon ruptures on other anatomic sites.
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34 **Results:** Of three fluoroquinolones, only levofloxacin exhibited a significant increased
35 risk of tendon ruptures - 16%, and 120% for rotator cuff and Achilles tendon rupture
36 respectively in the ≤ 30 day window. Ciprofloxacin and moxifloxacin exhibited little to no
37 increased risk of tendon ruptures. Notably, the risk of levofloxacin never exceeded the
38 risk of the non-fluoroquinolone, cephalexin in any comparison.
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47 Among the non-fluoroquinolone antibiotics, amoxicillin, amoxicillin-clavulanate, and
48 azithromycin exhibited none to benign risk of tendon rupture. Cephalexin exhibited
49 modest to large *increased* risk of tendon rupture at ≤ 30 day window across all anatomic
50 rupture sites.
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3 **Conclusions:** In our study, fluoroquinolones as a class were not associated with the
4 increased risk of tendon ruptures. Neither ciprofloxacin nor moxifloxacin exhibited any
5 risk for tendon ruptures. Levofloxacin did exhibit significant increased risk. Cephalexin
6 with no reported effect on metalloprotease activity had an equal or greater risk than
7 levofloxacin; so we question whether metalloprotease activity has any relevance to
8 observed associations with tendon rupture. Confounding by indication bias may be more
9 relevant and should be given more consideration as explanation for significant
10 associations in observational studies of tendon rupture.
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Strengths and limitations of this study

- We conducted a large (more than 1 million US senior subjects) retrospective study of outpatient prescription drug records to assess the association between the use of fluoroquinolones and the occurrence of tendon ruptures compared to the most commonly used non-fluoroquinolone oral antibiotics.
- Our study included all oral fluoroquinolones (ciprofloxacin, levofloxacin, moxifloxacin) prescribed in the US and the four most commonly prescribed non-fluoroquinolone antibiotics: amoxicillin, amoxicillin-clavulanate, azithromycin and cephalexin as controls.
- In addition to reporting the risk of any tendon rupture, we also reported the risk of three types of tendon ruptures by anatomic site 1) Achilles tendon rupture, 2) rupture of rotator cuff and 3) tendon ruptures on other anatomic sites as separate outcomes.
- This study is possibly only applicable to U.S. senior, aged 65 or more, Medicare fee-for-service beneficiaries.
- We had no options to verify claims diagnoses via chart review.

Introduction

Fluoroquinolones (FQ) are among the most widely prescribed antibiotics in the outpatient setting[1,2] due to their broad spectrum treatment of bacteria found in respiratory, urinary, joint, and skin infections. Several observational studies have reported the association between the use of FQs and tendinitis and tendon rupture (TR), especially of the Achilles tendon[3–12] and the U.S. Food and Drug Administration (FDA) issued black box warnings to FQ antibiotics beginning in 2008.[13] The warning was updated in 2016 to recommend using alternative antibiotics when possible.[14,15] The fact that FQs upregulate the production of metalloproteinase enzymes with collagenase activity that could weaken tendons is taken as a mechanism to explain this reported risk.[16–18]

Studies that reported association between FQ use and TR used one or more other antibiotics as controls. One study compared the FQ rupture rates with patients using azithromycin, the most frequently used oral antibiotic in the US. Only two focused principally on TR risk among the elderly. None compared TR rates of *FQs* with those of cephalexin -- the 3rd most commonly prescribed oral antibiotic in the US.

The Virtual Research Data Center (VRDC) of Center for Medicare and Medicaid Services (CMS)[19] carries more than 10 years of Medicare claims, which include information about the usage of prescription drugs and encounter diagnoses (including tendon ruptures). It also carries information about 42 major chronic conditions, demographic characteristic and vital status. We conducted a large observational study using the VRDC to assess the association of FQ antibiotics with TR compared to that of

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3 the four most commonly prescribed non-FQ antibiotics in the US. Here we report the
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5 results of that analysis.
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10 **Methods**

11 *Patient and public involvement*

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14 Neither patients nor the public were not involved in the design of the study.
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18 *Study population*

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20 We derived our study population from a 20% random sample of Medicare prescription
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22 drug coverage (Part D) enrollees who first enrolled in the Medicare under old age and
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24 survivors insurance within a month of age 65 (779-781 month-old) and on or after
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26 1/1/2007 - the first full year of Part D prescriptions availability. We included claim data
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28 through 12/31/2016, the end of VRDC claim data available to us. All of the VRDC data
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30 is de-identified and researchers must perform all of their analysis within the VRDC
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32 computer systems, and can only pull statistical results from it.[19] We obtained approvals
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34 for these studies from the Office of Human Research Protection at the National Institutes
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36 of Health as not human subject studies.
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44 We required subjects to be continuously enrolled in hospital insurance (Part A) and
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46 medical insurance (Part B) to assure we had full outpatient and inpatient claims data,
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48 which are not available for nearly 20% of subjects with Part D only.[20] To obtain a
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50 cohort of new TR patients, we excluded individuals with TRs recorded in the first year of
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52 their Medicare entitlement.[21] In order to assure sufficient follow-up, we excluded
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3 individuals with less than 1-year follow-up. Moreover, to obtain incident (or new) drug
4 user cohort, we excluded individuals who were prescribed any study antibiotics during
5 their first 3-month after Part D enrollment, while ignoring the data during the same time
6 window for individuals not taking study antibiotics. By doing so, we minimize survivor
7 bias from a prevalent users (Figure 1 Consort Diagram).
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14 15 16 17 Primary Outcome

18 We identified patients with TR based upon International Classification of Diseases
19 (ICD)-9-CM codes of 726.13, 727.60-727.69, and ICD-10-CM codes of M66.2, M66.3,
20 M66.8, M66.9, and M75.1. We combined all TRs and reported them as one outcome, and
21 report three types of TRs by anatomic site 1) Achilles tendon rupture, 2) rupture of
22 rotator cuff and 3) TRs on other anatomic sites as separate outcomes. We focused on
23 Achilles TR because it was the sole focus of many prior studies and on rotator cuff TR
24 because it is the predominant TR of the elderly. We lumped the remaining as “other
25 TRs”.
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40 Study antibiotics

41 We included a total of seven study antibiotics prescribed in the US including all three
42 oral FQs (moxifloxacin (MXF), ciprofloxacin (CIP), levofloxacin (LVX), the active
43 stereoisomer of ofloxacin) and the four most frequently prescribed non-FQ oral
44 antibiotics (amoxicillin (AMX), amoxicillin clavulanate (AMC), azithromycin (AZT) and
45 cephalexin (LEX)) as a control. Ciprofloxacin and the four non-FQ, study antibiotics
46 were the five most frequently used U.S. oral antibiotics in 2011.
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Statistical Analysis

We analyzed each of the four TR outcomes in separate Fine-Gray competing risk regression analyses with death as the competing risk.[22,23] Individuals became eligible for “the study” at their Medicare enrollment but prescription data did not become available until their Part D enrollment. We followed them from their entry in Part D (while accounting for left truncation[24]) until their first diagnosis of TR, death, switch to a capitated plan, disenrollment from Medicare or 12/31/2016 – whichever came first. In each regression analysis, we included the seven antibiotics whose effects on TR were our primary interest. We adjusted hazard ratio (HR) of each study antibiotic for concurrent use of the other study antibiotics. We also adjusted for calendar year of individual’s Part D entry, to account for secular trends, and their socio-demographic characteristics of gender, race, rural residency (Yes/No) and income status. We inferred individual’s income level from the monthly indicators of dual-eligibility and Low Income Subsidy (LIS) status, which separate subjects into three groups; 1) dual whose income is below 135% Federal Poverty Line (FPL); 2) non-dual LIS whose income is between 135 and 150% FPL; and 3) non-dual no LIS whose income is above 150% FPL, respectively. We used this variable in the analysis as a surrogate for economic status.[25] We also included the 42 chronic conditions within the Medicare Master Beneficiary Summary File [26] that had >1% prevalence as measures of overall health. We assumed that patients were on a given study drug from the prescription dispensing date to the end of days of supply. We did not distinguish between different brands of a study drugs. Following the approach of prior studies,[3–5] we separated subjects by temporal exposure within each study drug,

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3 including groups for never exposed, exposed within 30 days, 31-60 days, and >60 days of
4 the index (or TR event) time. Thus, by this approach we could detect the presumed short
5 term action of the FQ's on tendons and avoid the risk of non-differential misclassification
6 that can occur with too simple (yes/no) drug exposure measures.[27] In order to minimize
7 the immortal time bias, we treated all drug usage measures and all socio-demographic
8 characteristics, except gender, race and rural residency, as time-varying
9 covariates.[28,29] In order to mitigate selection bias toward use of any study antibiotics,
10 we employed a propensity score (PS) approach.[30,31] We first derived a PS of taking
11 any of study antibiotics as a function of individual's characteristics at the time of the first
12 antibiotic use after Part D entry from a multiple logistic regression. We used the median
13 days to the first study antibiotic use in patients taking study antibiotics as the cutoff time
14 for individuals not taking study antibiotics. We performed our analyses with an inverse
15 propensity score weight (IPSW) excluding individuals with the PS below 0.1 and above
16 0.9, to mitigate poorer performance in the presence of a strong treatment-selection
17 process.[32] In post-hoc analyses, we also compared the risk of TR of each study
18 antibiotics to that of every other study antibiotic on a pairwise basis.

41 42 **Results**

43 Study population and Secular trend

44 From our 20% sample of Part D enrollees, 1,009,925 individuals satisfied all our
45 selection criteria including the washout of individuals with any antibiotic use in their first
46 3-month of Part D enrollment (Figure 1 Consort Diagram). Follow-up began with an
47 individual's enrollment in Part D program (median (IQR) 0 (0-122) days from the
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3 Medicare entitlement). We followed them for a median of 3.6 years (total 4,030,897
4 patient-years) until their first diagnosis of TR (3.5%), death (4.6%), switch to a capitated
5 plan (12.6%), disenrollment from Medicare (<1%) or study end on 12/31/2016 (79.3%),
6 whichever came first. Patients had their first post enrollment claim with a diagnosis of
7 TR at a median age of 68.5 (IQR 67.2-70.4). The proportions of non-Hispanic White,
8 female and rural residents were 80.7%, 57.0%, and 22.6% respectively. About a fifth of
9 individuals received federal/state subsidies, i.e. Medicaid coverage on top of Medicare
10 (dual 16.1%) or assistance in paying their Part D premium and coinsurance/copayment
11 (non-dual LIS 2.7%). Among the 42 Medicare chronic conditions, hypertension (67.3%),
12 hyperlipidemia (68.4%), cataract (46.4%), rheumatoid arthritis/osteoarthritis (36.6%),
13 anemia (30.4%), ischemic heart disease (26.2%), and chronic kidney disease (17.9%)
14 were the seven most prevalent (Table 1).
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33 Of the 328,654 (33.0%) patients who ever took an FQ, 71.5%, 47.5% and 4.5% had taken
34 CIP, LVX and MXF respectively. Of 576,885 (57.1%) of patients who ever took a non-
35 FQ antibiotic, the figures were 53.6%, 44.9%, 33.9% and 31.1% for AZM, AMX, LEX,
36 and AMC, respectively. Patients who took one or more study antibiotics took a median
37 (IQR) of 3.0 (1.0-6.0) study antibiotic prescriptions and took a median (IQR) 2.0 (1.0-
38 3.0) different study antibiotics during the observation period. About 2.5% patients who
39 took one or more study antibiotics took one or more such antibiotics at the same time.
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49 Secular trends in study antibiotics usage existed. MXF usage declined precipitously from
50 5.0% in 2007 to almost zero in 2016 – overweighting the MXF statistics for early entrants
51 into Medicare and yielding a longer mean follow-up time. CIP use hit a peak, and LVX, a
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3 nadir, in 2011. The use of AMX, AMC and LEX trended slowly upward (Supplementary
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5 Figure 1). The mode (median) of supply durations for each antibiotics were short--10 (7)
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7 for AMX, 10 (10) for AMC, 5 (5) for AZM, 10 (7) for LEX, 7 (7) for CIP, 10 (7) for
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9 LVX, 10 (11) for MXF. About 35% of individuals were never exposed to any of the
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11 study antibiotics during the study period.
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17 Unadjusted figures for TR prevalence across each of the seven study antibiotic users and
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19 the no study antibiotic users ranged from a high of 5.2% for MXF to a low of 2.9% for no
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21 antibiotic (Table 1). Except for MXF, the *unadjusted* prevalence of TRs associated with
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23 each non-FQ antibiotic was *greater than* or equal to that of each FQ antibiotic. The TR
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25 rates per 1000 patient-years followed the same pattern, with the non-FQ antibiotics
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27 topping the rates of all FQs except MXF (with the highest rate), possibly due to
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29 overweighting of MXF usage in the early years of the study. Patients who ever took an
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31 FQ had the highest unadjusted rate of death per 1000 person-years. LVX's death rate was
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33 nearly twice the rate of each non-FQ antibiotics. The size of the associations with
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35 conditions like diabetes, chronic renal failure and heart failure paralleled the magnitude
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37 of the death rates and was generally higher with FQs than non-FQ antibiotics (Table 1).
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45 Primary Analysis

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47 Table 2 presents HRs for all non-antibiotic covariates in our Fine-Gray competing risk
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49 regression with IPSW. For simplicity sake, in Table 2, we report the HRs of all anatomic
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51 types of tendon ruptures taken together. Being a female (vs. male), African-American,
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53 Hispanic, and Asian (vs. white), being dual or non-dual LIS (vs. non-dual no LIS) and
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3 living in a rural area were all associated with a *reduced* risk of tendon rupture. These risk
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5 reductions were 24% or more for all but Hispanics and rural residency covariates, and the
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7 reductions were similar across all anatomic sites. In general, life-threatening chronic
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9 conditions, such as AMI, COPD, heart failure and colorectal/lung/endometrial cancers
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11 were associated with a lower risk of TR in a range of 15-60% below control possibly due
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13 to constrained physical activity and/or shortened life span. Notably, diabetes and chronic
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15 renal disease, previously reported as risk factors for TR,[33,34] exhibited no increased
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17 TR risk. Mobility impairments had reduced risk of TR similar to that of the severe life-
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19 threatening conditions, likely due to reduced activity. Most conditions with low life
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21 threatening conditions, likely due to reduced activity. Most conditions with low life
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23 threats such as cataract, glaucoma, depression, asthma, hyperlipidemia, hypertension,
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25 prostatic hyperplasia, migraine/other chronic headache, and deafness/hearing impairment
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27 exhibited risks of 8 to 34% *above* controls probably for reasons related to longer life
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29 spans and less inhibited activity. Ischemic heart did not fit the mold of sicker equals
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31 lower TR risk. Patients with rheumatoid arthritis/osteoarthritis were a special case and
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33 had TR risk of 184% *above* control possibly due to joint and associated tendon
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35 inflammation with these disorders. Fibromyalgia/chronic pain and fatigue also exhibited
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37 a 39% increased risk of TR possibly also due to an inflammatory component.
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43 The Achilles tendon carries the full force of the extra weight carried by obese patients
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45 and obesity was associated with a significant (13%) increase in Achilles TR ruptures
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47 while its effect on other TR classes was significant but miniscule (2-3%) (Data not
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49 shown).
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52 53 ***Effect of antibiotics*** 54 55 56 57

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3 We report HRs from our primary analysis in tables separate from the non-antibiotic
4 covariates. Table 3 shows the risk associated with each study antibiotic broken down by
5 time lag between the antibiotic use and the TRs (separate rows), and by all TRs together
6 and separately by anatomic sites (in columns). We also report HRs of death (competing
7 risk). We used multiplicity corrected p-values to simultaneously test the difference of
8 pairs of antibiotics to minimize the chance of finding statistically significant difference
9 by random chance.[35] Of the total 34,880 patients with any TR occurrence, complete
10 rupture of rotator cuff represented the major share (80.5%), followed by other TRs
11 (16.9%) and Achilles TR (2.6%). In the survival analysis, we followed patients until the
12 first occurrence of TR; so, these figures count only the first TR occurrence independent
13 of anatomic site.
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29 Of the non-FQ antibiotics, AMX exhibited a reduced risk of TR compared to no AMX in
30 every tendon class and time window, similar to its low risk in previous studies. It
31 exhibited a significantly lower risk in the ≤ 30 -day window except for the Achilles
32 tendon. AZM and AMC exhibited a similar benign risk in all time windows except for
33 TR of rotator cuff in >60 -day window. LEX was the surprise non-FQ antibiotic. It
34 exhibited modest to large *increased* TR risk at ≤ 30 -day window across all sites ranging
35 from a low of 19% increase for complete rupture of rotator cuff to a high 93% increase
36 for Achilles TR. Its risk was also significantly higher at ≤ 30 -day window for all TRs
37 taken together.
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51 Of the FQs, CIP and MXF, the most and least frequently prescribed FQ, exhibited little to
52 no increased risk of TR within each anatomic site and each time frame. LVX is the only
53 FQ to exhibit a significant *increase* in TR risk - of 16%, and 120% for rupture of rotator
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3 cuff and Achilles TR respectively in the ≤ 30 -day window. Notably, the risk of LVX
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5 never exceeded the risk of the non-FQ, LEX in any comparison.
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9 In a post-hoc analysis (Table 4), we compared the TR risk of each antibiotic with every
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11 other antibiotic (pairwise comparisons of FQ vs. FQ and FQ vs. non-FQ), for ≤ 30 -day
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13 window and FQs as a class vs. each non-FQ after combining the data from the three time
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15 windows. These results paralleled the above-mentioned risk for each study antibiotic in
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17 Table 3. Again, TR risk for LVX was greater than that of CIP, MXF, AMC, AMX, and
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19 AZM in a ≤ 30 -day window. However, LVX risk was comparable to that of LEX for
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21 Achilles TR, and rupture of rotator cuff and significantly lower than LEX for the other
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23 TR classes. When comparing the risk of FQs as a class against that of non-FQ antibiotics,
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25 most of the non-FQ antibiotics had significantly greater risk than the FQ class as a whole
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27 across all TR sites (See last 4 rows of Table 4).
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33 In another analysis evaluating risk of death for each antibiotics, each FQ antibiotic
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35 exhibited a significant increase in death risk of – 46% (for CIP), 105% (for MXF) and
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37 119% (for LVX) in a ≤ 30 -day window. Among non-FQ antibiotics, only AMC exhibited
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39 37% increased risk of death in a ≤ 30 -day window. Overall, risk of death for FQs as a
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41 class far outweighed that of each non-FQ antibiotics.
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48 **Discussion**

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50 Our results conflict with the common assertion that the Achilles tendon rupture is the
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52 most common tendon rupture (up to 90% in one report[36]). In our elderly cohort,
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54 Achilles TRs were a tiny, 2.6%, of all TRs. Some of this difference may be explained by
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3 the differences in demographics. Reports of high prevalence of Achilles TR came from
4 studies of young military populations.[37,38] In contrast, our data came from an elderly
5 Medicare population. Some of the difference could also be due to less ability to diagnose
6 non-Achilles tendon ruptures until MRI joint imaging became widely available, because
7 such TRs are less amenable to diagnosis by physical exam.
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17 Many authorities describe the relationship between FQs and TRs as a class “effect”.

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19 However, FQs as a class had no significant risk of TR compared with each of the four
20 non-FQ antibiotics in any time window. CIP (n=234,994 subjects) is the oral FQ with the
21 greatest use and with a greater effect on metalloproteases than other FQs.[39–41]
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24 However, neither MXF (n= 14,728 subjects) nor CIP had any TR risk at any anatomic
25 site in any time window. CIP’s lack of risk is consistent with two studies[5,9] in which
26 CIP exhibited zero risk or small risks compared to ofloxacin, a racemic mixture whose
27 active ingredient is the levo-isomer, LVX. We do see a strong association between LVX
28 and TRs whether we used no LVX or three of the non-FQ antibiotics as controls.
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37 However, when we used LEX, a cephalosporin, as the control for LVX’s effect on TRs,
38 we saw no increased risk.
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44 As noted in the introduction, the FDA has added a black box warning about tendon
45 ruptures to the labels of fluoroquinolones. A 2015 paper[42] described the evidence for
46 this decision based on the FDA’s Adverse Event Reporting System (FAERS) database
47 and an empirical Bayes geometric mean (EBGM) score, which is based on the relative
48 frequency of spontaneous report about a given adverse event in one drug versus the
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3 reporting of that adverse event across all drugs. This EBGM score based upon FAERS
4 database has been useful but FAERS database is still limited by a lack of true
5 denominator for population at risk, underreporting due to a voluntary reporting scheme
6 and bias due to limited adjustment variables.[43] Our study was based on a well-defined
7 Medicare population with 80 variable adjustments. The fact that levofloxacin's EBGM
8 score was six times that of ofloxacin[42] though both drugs have the same active
9 ingredient (the levo-isomer of ofloxacin) and the same dose of that ingredient, raises
10 questions about what factors influenced that score.
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24 One previous study described the effect of FQs on TR risk as small and unimportant.[10]
25 Two studies reported no effect of FQs on TR risk.[9,11] At least 7 observational studies
26 reported that the use of FQs increased risks of TR.[3–8,12] However, in all but one study,
27 the number of TRs among patients taking an FQs was small (between 5 and 111). In
28 comparison, our study included 12,517 (3.8%) such patients. One previous study did
29 report a large number of TR events, 23,000 (3.5%) patients while on FQs and, like our
30 study, it focused exclusively on elderly patients.[3] However, it did not compare the
31 population of FQ users against non-users but FQ usage periods against non-usage periods
32 in the same set of patients, which were likely periods without visits and thus could not
33 account for the effect of increased clinical attention provided at visits requiring a strong
34 systemic antibiotic. Furthermore, they assessed the association between AMX and TRs in
35 separate analysis and used the risk of TRs in that analysis as the comparator for the risk
36 observed in the FQ analysis. Finally, their analysis did not include death as a competing
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3 risk as is recommend when death rates exceed event rates[23] which was likely the case
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5 because in the demographics of their study was very similar to ours.
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10 In our study, AMX treated patients had fewer comorbidities (as was also true in
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12 Daneman's study), almost 14% fewer hospitalizations and half of death rate per 1000
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14 patient-years, compared to patients taking LVX. So the two populations are not
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16 comparable. LVX exhibited 119% increased risk of death in a ≤ 30 -day window. They
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18 appears to be reserved for more severe infections or more fragile patients and thus subject
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20 to differential biases.
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26 The reported activation of metalloprotease activity by FQs has underpinned the idea of a
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28 causal link between FQs and TRs. The argument goes as follows: FQs stimulate
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30 metalloproteases, which can break down collagen; the tendon is made of collagen; so FQs
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32 may cause TRs. However, our data disrupts this argument. CIP which strongly *stimulates*
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34 metalloprotease activity,[17,18] exhibited *no* risk of TRs in our study, and LEX which
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36 *inhibits* metalloprotease activity[44,45] exhibited a *large* risk. So we have to question
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38 whether metalloprotease activity has any relevance to TR risk, and consider other
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40 explanations for the observed associations.
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47 The indication for an antibiotic is a presumed bacterial infection. The reported
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49 associations between antibiotics and TR could be a consequence of the indication rather
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51 than the antibiotic use and a perfect example of the confounding by indication.[46] Such
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3 a bias could explain many reported associations between drugs and TR risk including
4 associations with non-antibiotic drugs reported by Nyysönen.[8]
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10 This bias could manifest in different ways. First, that the bacterial infection might
11 directly increase the risk of TR via stimulation of general immune or cytokine responses,
12 or even by direct bacterial invasion. A recent study found gram-positive bacteria in a
13 major share of ruptured tendons but not in “control” tendons removed surgically for
14 grafting,[47] So the possibility of direct invasion of tendons by circulating bacteria with
15 subsequent weakening and rupture is plausible.
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26 Secondly, the greater clinical attention likely focused on patients needing systemic
27 antibiotics, especially those with severe infections, could increase the chance of noticing
28 and documenting a pre-existing TR. A reservoir of not-yet-diagnosed such cases is likely
29 to exist, because patients do not necessarily correctly identify joint and extremity
30 symptoms as TRs and seek immediate care for them. Tendon ruptures of the shoulder
31 capsule, for example, are notorious for developing symptoms slowly over 2-3 years[48]
32 before being correctly diagnosed. Even Achilles tendon ruptures, can be missed (in 30%
33 of cases) at the first presentation.[49] Seeger et al. reviewed the medical records of
34 patients with an insurance claim reporting TRs following antibiotic use and found that
35 nearly half of the TRs recorded in the claims were either something else (e.g., Bursa
36 inflammation miscoded as a TR) or had occurred pre antibiotic use but only seen in a
37 claim post antibiotic use.[11]
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3 Indication bias is a plausible explanations for associations reported in observational
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5 studies and it should be considered before assuming the associations are causal.
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10 **Limitation**

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12 This study faces all of the limitations of observational studies. Furthermore, it applies
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14 only to fee-for-service Medicare populations. In addition, we had no options to verify
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16 claims diagnoses via chart review. From a statistical point of view, our findings may have
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18 some limitations. First, we included 80 covariates in one analysis and concern about
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20 possibly strong intercorrelation affecting the validity could exist. To evaluate the
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22 intercorrelation among covariates, we calculated an 80x80 correlation matrix of estimated
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24 regression coefficients from our competing risk regression analysis considering their
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26 time-varying nature. The correlation matrix can deliver information about the strength of
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28 all pairwise correlation and indicate the existence of a collinear relationship between two
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30 predictors. All correlations (except diagonal elements) were below 0.5, only 1.6% were
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32 between 0.2 and 0.5. The largest of the pairwise correlations was 0.33 indicating minimal
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34 bias due to intercorrelation. We also did not consider interactions among covariates in our
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36 analysis because of the enormous number of two way interactions (as large as 6,400) and
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38 thus the problem of overfitting.
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Competing interests Statement

All authors have no competing interest to declare.

Contributorship Statement

SB: study conception, design, analysis and interpretation; critical review of study content; manuscript drafting; approval of the final manuscript. JL: study concept and interpretation; manuscript drafting; approval of the final manuscript. VH: study interpretation; manuscript drafting; approval of the final manuscript. CJM: study conception, design and interpretation; critical review of study content; manuscript drafting; approval of the final manuscript.

Data availability

The authors confirm that the data supporting the findings of this study are available within the article [and/or] its supplementary materials.

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3 **Figure 1. Consort Diagram**
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Table 1. Outcome, Medical/Medication Use, Diseases and Patient Characteristics by Type of Antibiotics

Variable	Overall	FLQ	CIP	LVX	MXF	AMX	AZM	LEX	AMC	None
N	1,009,925	328,654	234,994	155,991	14,728	259,125	308,985	195,731	179,616	356,364
Tendon Rupture	34,880(3.5)	12,517(3.8)	8,811(3.7)	5,904(3.8)	770(5.2)	9,636(3.7)	12,448(4.0)	8,019(4.1)	6,622(3.7)	10,169(2.9)
Death	46,468(4.6)	23,249(7.1)	14,821(6.3)	14,610(9.4)	2,136(14.5)	9,632(3.7)	14,608(4.7)	11,394(5.8)	9,951(5.5)	13,645(3.8)
Censored at HMO entry	127,162(12.6)	27,573(8.4)	19,847(8.4)	11,142(7.1)	1,571(10.7)	21,215(8.2)	26,140(8.5)	14,887(7.6)	12,674(7.1)	65,886(18.5)
Censored at disenrollment	145(0.0)	25(0.0)	13(0.0)	13(0.0)	2(0.0)	19(0.0)	27(0.0)	23(0.0)	16(0.0)	85(0.0)
Censored at Dec 31 2016	801,270(79.3)	265,290(80.7)	191,502(81.5)	124,322(79.7)	10,249(69.6)	218,623(84.4)	255,762(82.8)	161,408(82.5)	150,353(83.7)	266,579(74.8)
Years of follow-up, median(total)	3.6(4,030,897)	4.6(1,620,894)	4.8(1,190,308)	4.8(789,849)	6.0(87,397)	4.5(1,274,357)	4.6(1,529,370)	4.8(1,000,459)	4.6(890,340)	2.5(1,067,731)
Tendon rupture, 1000 person-years	8.65	7.72	7.40	7.47	8.81	7.56	8.14	8.02	7.44	9.52
Death, 1000 person-years	11.53	14.34	12.45	18.50	24.44	7.56	9.55	11.39	11.18	12.78
Female	575,885(57.0)	197,915(60.2)	146,745(62.4)	89,682(57.5)	8,747(59.4)	151,383(58.4)	194,101(62.8)	113,308(57.9)	104,749(58.3)	191,069(53.6)
White	814,933(80.7)	274,785(83.6)	196,048(83.4)	131,725(84.4)	12,464(84.6)	215,101(83.0)	259,657(84.0)	167,825(85.7)	153,723(85.6)	271,906(76.3)
Black	75,930(7.5)	20,017(6.1)	14,286(6.1)	8,893(5.7)	956(6.5)	15,622(6.0)	17,296(5.6)	9,625(4.9)	9,199(5.1)	35,023(9.8)
Hispanic	56,582(5.6)	17,044(5.2)	12,607(5.4)	7,943(5.1)	628(4.3)	12,494(4.8)	14,805(4.8)	8,976(4.6)	7,802(4.3)	24,391(6.8)
Asian	26,336(2.6)	7,316(2.2)	5,362(2.3)	3,144(2.0)	356(2.4)	7,624(2.9)	7,945(2.6)	3,539(1.8)	3,440(1.9)	10,437(2.9)
Other	36,144(3.6)	9,492(2.9)	6,691(2.8)	4,286(2.7)	324(2.2)	8,284(3.2)	9,282(3.0)	5,766(2.9)	5,452(3.0)	14,607(4.1)
Ever Dual	162,988(16.1)	54,055(16.4)	38,277(16.3)	28,156(18.0)	2,908(19.7)	35,305(13.6)	44,940(14.5)	30,962(15.8)	25,255(14.1)	66,986(18.8)
Non-Dual LIS	26,955(2.7)	7,648(2.3)	5,459(2.3)	3,746(2.4)	385(2.6)	5,224(2.0)	6,828(2.2)	4,191(2.1)	3,818(2.1)	12,595(3.5)
Non-Dual No LIS	819,982(81.2)	266,951(81.2)	191,258(81.4)	124,089(79.5)	11,435(77.6)	218,596(84.4)	257,217(83.2)	160,578(82.0)	150,543(83.8)	276,783(77.7)
Living in rural area	228,199(22.6)	78,581(23.9)	56,385(24.0)	38,847(24.9)	2,801(19.0)	58,805(22.7)	72,282(23.4)	49,977(25.5)	42,288(23.5)	77,087(21.6)
Days on Rx, median (IQR)	N/A	N/A	10.0(7.0-20.0)	10.0(7.0-17.0)	10.0(7.0-12.0)	10.0(7.0-20.0)	5.0(5.0-11.0)	10.0(7.0-16.0)	10.0(10.0-20.0)	N/A
Hospitalization	349,959(29.5)	198,846(45.4)	142,538(45.3)	113,829(52.5)	14,002(60.3)	132,304(38.8)	156,185(37.9)	119,209(45.9)	103,515(42.5)	51,525(14.4)
Outpatient visits per year, median (IQR)	19.6(11.1-33.0)	27.1(17.2-42.7)	27.3(17.5-42.9)	30.1(19.0-47.8)	34.0(21.7-53.7)	23.6(14.5-37.5)	24.6(15.5-38.8)	27.5(17.2-43.2)	26.6(16.7-42.2)	12.3(6.0-21.8)
AMI	21,222(2.1)	9,999(3.0)	6,810(2.9)	5,862(3.8)	698(4.7)	6,474(2.5)	8,079(2.6)	6,215(3.2)	5,292(2.9)	5,012(1.4)
Atrial Fibrillation	71,635(7.1)	31,752(9.7)	21,757(9.3)	17,731(11.4)	2,028(13.8)	23,974(9.3)	26,182(8.5)	21,935(11.2)	18,764(10.4)	16,314(4.6)
Cataract	468,608(46.4)	183,870(55.9)	134,196(57.1)	88,574(56.8)	9,216(62.6)	144,455(55.7)	174,897(56.6)	112,020(57.2)	101,079(56.3)	124,931(35.1)
Chronic Kidney Disease	180,441(17.9)	86,021(26.2)	62,323(26.5)	46,121(29.6)	4,651(31.6)	53,713(20.7)	65,577(21.2)	50,361(25.7)	43,182(24.0)	42,916(12.0)
COPD	130,840(13.0)	71,913(21.9)	43,961(18.7)	48,430(31.0)	6,106(41.5)	40,109(15.5)	66,536(21.5)	37,413(19.1)	37,579(20.9)	22,739(6.4)
Heart Failure	103,010(10.2)	51,814(15.8)	34,870(14.8)	31,377(20.1)	3,776(25.6)	32,792(12.7)	41,647(13.5)	31,585(16.1)	27,223(15.2)	21,907(6.1)
Diabetes	284,919(28.2)	113,424(34.5)	81,175(34.5)	57,697(37.0)	5,942(40.3)	81,155(31.3)	98,176(31.8)	67,548(34.5)	59,984(33.4)	81,448(22.9)
Glaucoma	150,839(14.9)	56,990(17.3)	41,984(17.9)	26,603(17.1)	2,930(19.9)	45,597(17.6)	54,726(17.7)	33,936(17.3)	31,065(17.3)	42,355(11.9)
Hip/Pelvic Fracture	7,982(0.8)	4,086(1.2)	3,000(1.3)	2,289(1.5)	274(1.9)	2,673(1.0)	3,005(1.0)	2,515(1.3)	1,914(1.1)	1,689(0.5)
Ischemic Heart Disease	264,648(26.2)	117,416(35.7)	82,182(35.0)	63,659(40.8)	6,956(47.2)	83,682(32.3)	101,999(33.0)	70,612(36.1)	63,363(35.3)	63,372(17.8)
Depression	210,714(20.9)	94,554(28.8)	68,625(29.2)	49,277(31.6)	5,298(36.0)	65,642(25.3)	83,253(26.9)	56,747(29.0)	51,150(28.5)	49,320(13.8)
Alzheimer's Disease or Senile Dementia	39,132(3.9)	19,796(6.0)	14,309(6.1)	11,030(7.1)	1,206(8.2)	11,140(4.3)	13,809(4.5)	11,846(6.1)	9,309(5.2)	9,400(2.6)
Osteoporosis	106,966(10.6)	47,033(14.3)	35,217(15.0)	22,918(14.7)	2,738(18.6)	34,610(13.4)	44,016(14.2)	26,996(13.8)	24,393(13.6)	25,216(7.1)

Rheumatoid Arthritis/Osteoarthritis	369,584(36.6)	160,091(48.7)	117,018(49.8)	80,115(51.4)	8,259(56.1)	126,702(48.9)	148,653(48.1)	101,310(51.8)	88,017(49.0)	81,855(23.0)
1 Stroke/Transient Ischemic Attack	58,886(5.8)	27,702(8.4)	19,843(8.4)	15,051(9.6)	1,670(11.3)	17,829(6.9)	22,038(7.1)	16,684(8.5)	14,245(7.9)	14,262(4.0)
2 Breast Cancer	45,316(4.5)	19,362(5.9)	14,344(6.1)	9,442(6.1)	984(6.7)	13,451(5.2)	17,676(5.7)	12,543(6.4)	10,156(5.7)	11,042(3.1)
3 Colorectal Cancer	15,905(1.6)	7,487(2.3)	5,421(2.3)	4,048(2.6)	390(2.6)	4,304(1.7)	5,170(1.7)	4,085(2.1)	3,605(2.0)	4,104(1.2)
4 Prostate Cancer	37,038(3.7)	19,705(6.0)	15,577(6.6)	9,232(5.9)	643(4.4)	10,967(4.2)	11,733(3.8)	9,252(4.7)	8,070(4.5)	8,333(2.3)
5 Lung Cancer	14,946(1.5)	8,965(2.7)	5,144(2.2)	6,356(4.1)	905(6.1)	3,859(1.5)	6,633(2.1)	3,977(2.0)	4,267(2.4)	2,733(0.8)
6 Endometrial Cancer	7,396(0.7)	3,447(1.0)	2,670(1.1)	1,635(1.0)	160(1.1)	2,095(0.8)	2,637(0.9)	1,957(1.0)	1,604(0.9)	1,847(0.5)
8 Anemia	307,310(30.4)	140,606(42.8)	100,819(42.9)	74,308(47.6)	7,980(54.2)	99,190(38.3)	118,327(38.3)	81,967(41.9)	72,587(40.4)	71,098(20.0)
9 Asthma	86,120(8.5)	46,350(14.1)	29,327(12.5)	30,152(19.3)	4,091(27.8)	27,632(10.7)	46,823(15.2)	24,426(12.5)	25,465(14.2)	13,802(3.9)
10 Hyperlipidemia	691,148(68.4)	257,086(78.2)	185,199(78.8)	123,828(79.4)	12,162(82.6)	199,236(76.9)	239,414(77.5)	152,879(78.1)	140,364(78.1)	201,258(56.5)
1 Hyperplasia	122,010(12.1)	59,809(18.2)	45,517(19.4)	28,616(18.3)	2,587(17.6)	39,031(15.1)	42,070(13.6)	31,606(16.1)	28,398(15.8)	27,336(7.7)
1 Hypertension	679,287(67.3)	253,601(77.2)	181,231(77.1)	124,646(79.9)	12,218(83.0)	192,686(74.4)	230,409(74.6)	150,995(77.1)	136,292(75.9)	201,777(56.6)
1 Hypothyroidism	197,447(19.6)	81,468(24.8)	59,450(25.3)	40,372(25.9)	4,198(28.5)	59,893(23.1)	76,582(24.8)	47,973(24.5)	44,249(24.6)	50,280(14.1)
1 Anxiety Disorders	148,983(14.8)	70,688(21.5)	51,377(21.9)	37,563(24.1)	4,032(27.4)	48,859(18.9)	62,418(20.2)	41,655(21.3)	37,588(20.9)	31,709(8.9)
1 Bipolar Disorder	17,882(1.8)	8,368(2.5)	6,104(2.6)	4,533(2.9)	468(3.2)	5,442(2.1)	6,658(2.2)	5,147(2.6)	4,227(2.4)	4,242(1.2)
1 Major Depressive Affective Disorder	153,182(15.2)	71,732(21.8)	52,101(22.2)	38,055(24.4)	4,148(28.2)	48,846(18.9)	61,872(20.0)	43,416(22.2)	38,642(21.5)	33,660(9.4)
1 Schizophrenia and other Psychotic Disorders	16,764(1.7)	8,591(2.6)	6,176(2.6)	4,934(3.2)	548(3.7)	4,421(1.7)	5,597(1.8)	5,101(2.6)	3,811(2.1)	4,300(1.2)
18 Epilepsy	16,155(1.6)	7,543(2.3)	5,383(2.3)	4,269(2.7)	415(2.8)	4,310(1.7)	5,488(1.8)	4,510(2.3)	3,621(2.0)	4,191(1.2)
19 Fibromyalgia, Chronic Pain and Fatigue	166,279(16.5)	78,877(24.0)	57,494(24.5)	41,843(26.8)	4,410(29.9)	56,152(21.7)	70,667(22.9)	48,422(24.7)	43,379(24.2)	33,843(9.5)
20 Viral Hepatitis (General)	11,969(1.2)	4,659(1.4)	3,188(1.4)	2,523(1.6)	287(1.9)	3,156(1.2)	3,732(1.2)	2,712(1.4)	2,348(1.3)	3,735(1.0)
21 Liver Disease Cirrhosis and other Liver Conditions	62,675(6.2)	31,930(9.7)	23,284(9.9)	17,386(11.1)	1,919(13.0)	19,624(7.6)	24,544(7.9)	17,393(8.9)	15,958(8.9)	13,350(3.7)
22 Leukemias and Lymphomas	13,906(1.4)	7,228(2.2)	4,822(2.1)	4,536(2.9)	551(3.7)	4,385(1.7)	5,905(1.9)	4,025(2.1)	3,969(2.2)	2,758(0.8)
23 Migraine and other Chronic Headache	31,628(3.1)	14,936(4.5)	11,282(4.8)	7,520(4.8)	873(5.9)	10,841(4.2)	13,893(4.5)	8,763(4.5)	8,403(4.7)	6,419(1.8)
24 Mobility Impairments	20,600(2.0)	10,182(3.1)	7,356(3.1)	5,767(3.7)	577(3.9)	5,372(2.1)	6,629(2.1)	5,995(3.1)	4,610(2.6)	5,439(1.5)
26 Obesity	185,101(18.3)	79,130(24.1)	56,609(24.1)	41,226(26.4)	3,997(27.1)	58,654(22.6)	69,611(22.5)	49,984(25.5)	43,740(24.4)	44,772(12.6)
27 Peripheral Vascular Disease	90,132(8.9)	45,276(13.8)	31,866(13.6)	25,977(16.7)	3,001(20.4)	28,747(11.1)	36,241(11.7)	28,343(14.5)	23,977(13.3)	18,446(5.2)
28 Tobacco Use Disorders	101,890(10.1)	45,304(13.8)	28,907(12.3)	27,202(17.4)	3,042(20.7)	27,261(10.5)	37,860(12.3)	25,002(12.8)	22,975(12.8)	26,896(7.5)
29 Pressure Ulcers and Chronic Ulcers	30,345(3.0)	17,688(5.4)	12,800(5.4)	10,603(6.8)	1,196(8.1)	9,006(3.5)	10,926(3.5)	13,404(6.8)	9,960(5.5)	4,992(1.4)
30 Deafness and Hearing Impairment	59,576(5.9)	27,383(8.3)	19,976(8.5)	14,014(9.0)	1,609(10.9)	21,213(8.2)	25,498(8.3)	16,849(8.6)	16,787(9.3)	11,900(3.3)

Note. Data are presented as No. (%) of patients unless otherwise noted.

Abbreviations: FLQ, fluoroquinolone; CIP, ciprofloxacin; LVX, levofloxacin; MXF, moxifloxacin; AMX, Amoxicillin; AMC, Amoxicillin Clavulanate; AZT, Azithromycin; LEX, Cephalexin; IQR, interquartile range.

Table 2. Hazard Ratios of Tendon Rupture for Each Covariate

Variables	Reference	HR(95% CI)
Female	Male	0.70(0.69,0.72)↓
Black		0.76(0.73,0.78)↓
Hispanic	White	0.91(0.87,0.94)↓
Asian		0.67(0.63,0.71)↓
Other		1.05(1.01,1.09)↑
Dual Ever	Non-Dual Non-LIS	0.66(0.64,0.68)↓
Non-Dual Lis		0.66(0.63,0.70)↓
Living In Rural Area	No	0.94(0.92,0.95)↓
Medicare Part D Since 2008		1.03(1.00,1.07)
Medicare Part D Since 2009		1.11(1.07,1.15)↑
Medicare Part D Since 2010		1.16(1.12,1.21)↑
Medicare Part D Since 2011		1.17(1.13,1.22)↑
Medicare Part D Since 2012	Medicare Part D Since 2007	1.12(1.08,1.16)↑
Medicare Part D Since 2013		1.03(1.00,1.07)
Medicare Part D Since 2013		1.05(1.01,1.09)↑
Medicare Part D Since 2015		0.91(0.87,0.96)↓
Medicare Part D Since 2016		0.93(0.19,4.55)
AMI	No	0.74(0.69,0.79)↓
Atrial Fibrillation	No	0.94(0.91,0.97)↓
Cataract	No	1.23(1.21,1.25)↑
Chronic Kidney Disease	No	0.92(0.89,0.94)↓
COPD	No	0.83(0.81,0.86)↓
Heart Failure	No	0.79(0.77,0.82)↓
Diabetes	No	0.98(0.96,0.99)↓
Glaucoma	No	1.10(1.08,1.12)↑
Hip/Pelvic Fracture	No	0.68(0.60,0.77)↓
Ischemic Heart Disease	No	1.10(1.08,1.12)↑
Depression	No	1.17(1.13,1.21)
Alzheimer's Disease or Senile Dementia	No	0.67(0.63,0.71)↓
Osteoporosis	No	1.03(1.01,1.06)↑
Rheumatoid Arthritis/Osteoarthritis	No	2.84(2.80,2.89)↑
Stroke/Transient Ischemic Attack	No	0.97(0.94,1.01)
Breast Cancer	No	0.94(0.91,0.98)↓
Colorectal Cancer	No	0.79(0.74,0.85)↓

1	Prostate Cancer	No	1.03(0.99,1.07)
2	Lung Cancer	No	0.39(0.34,0.45)↓
3	Endometrial Cancer	No	0.85(0.77,0.94)↓
4	Anemia	No	1.01(0.99,1.03)
5	Asthma	No	1.27(1.24,1.31)†
6	Hyperlipidemia	No	1.34(1.31,1.36)†
7	Hyperplasia	No	1.13(1.10,1.16)†
8	Hypertension	No	1.09(1.07,1.11)†
9	Hypothyroidism	No	1.08(1.06,1.10)†
10	Anxiety Disorders	No	0.98(0.96,1.01)
11	Bipolar Disorder	No	1.02(0.95,1.08)
12	Major Depressive Affective Disorder	No	1.06(1.02,1.10)†
13	Schizophrenia and Other Psychotic Disorders	No	0.67(0.61,0.74)↓
14	Epilepsy	No	0.83(0.77,0.90)↓
15	Fibromyalgia, Chronic Pain and Fatigue	No	1.39(1.36,1.42)†
16	Viral Hepatitis (General)	No	1.04(0.96,1.13)
17	Liver Disease Cirrhosis And Other Liver Conditions	No	0.95(0.92,0.99)↓
18	Leukemias and Lymphomas	No	0.94(0.88,1.01)
19	Migraine and Other Chronic Headache	No	1.28(1.23,1.33)†
20	Mobility Impairments	No	0.70(0.65,0.76)↓
21	Obesity	No	1.04(1.02,1.06)†
22	Peripheral Vascular Disease	No	1.00(0.97,1.04)
23	Tobacco Use Disorders	No	0.82(0.80,0.85)↓
24	Pressure Ulcers and Chronic Ulcers	No	0.82(0.77,0.87)↓
25	Deafness and Hearing Impairment	No	1.21(1.17,1.25)†

Hazard ratios and confidence intervals from the primary analysis for Covariates except for the study antibiotics (which are in Table 3)

Abbreviations: HR, hazard ratio, CI, confidence interval; FLQ, fluoroquinolone; CIP, ciprofloxacin; LVX, levofloxacin; MXF, moxifloxacin; AMX, Amoxicillin; AMC, Amoxicillin Clavulanate; AZT, Azithromycin; LEX, Cephalexin.

†= significantly high with P-value < 0.001, †= significantly high with $0.001 \leq P\text{-value} < 0.05$

↓= significantly low with P-value < 0.001, ↓= significantly high with $0.001 \leq P\text{-value} < 0.05$

Table 3. Hazard Ratios of Each Antibiotic by Anatomic Sites and Temporal Order of Drug Exposure

		Any Tendon Rupture	Achilles Tendon Rupture	Complete Rupture of Rotator Cuff	Other Tendon Rupture	Death (Competing risk)
	Temporal Exposure	HR(95% CI)	HR(95% CI)	HR(95% CI)	HR(95% CI)	HR(95% CI)
HRs comparing study antibiotic use with no use						
AMX VS. NO AMX	≤ 30	0.86(0.80,0.92)↓	0.88(0.59,1.33)	0.88(0.82,0.95)↓	0.79(0.67,0.93)↓	0.66(0.61,0.71)↓
	31 - 60	0.94(0.87,1.01)	0.80(0.49,1.31)	0.91(0.84,0.99)↓	1.08(0.93,1.27)	0.69(0.63,0.75)↓
	≥ 61	1.00(0.98,1.02)	0.99(0.86,1.13)	1.01(0.99,1.04)	0.97(0.92,1.01)	0.77(0.75,0.78)↓
AMC VS. NO AMC	≤ 30	0.93(0.85,1.02)	1.25(0.79,1.97)	0.87(0.79,0.97)↓	1.17(0.98,1.41)	0.80(0.75,0.84)↓
	31 - 60	0.95(0.85,1.05)	1.37(0.82,2.29)	0.95(0.84,1.06)	0.81(0.63,1.04)	0.77(0.73,0.82)↓
	≥ 61	1.07(1.04,1.09)↑	0.95(0.81,1.12)	1.07(1.04,1.10)↑	1.02(0.96,1.08)	0.71(0.70,0.72)↓
AZM VS. NO AZM	≤ 30	0.99(0.93,1.06)	1.15(0.82,1.63)	1.00(0.93,1.08)	0.87(0.75,1.01)	1.04(0.98,1.10)
	31 - 60	0.90(0.84,0.98)↓	0.99(0.65,1.49)	0.91(0.84,0.99)↓	0.95(0.81,1.11)	1.01(0.94,1.08)
	≥ 61	1.07(1.05,1.09)↑	1.02(0.91,1.15)	1.09(1.07,1.12)↑	0.99(0.95,1.04)	0.86(0.84,0.88)↓
LEX VS. NO LEX	≤ 30	1.31(1.22,1.41)↑	1.93(1.35,2.75)↑	1.19(1.09,1.29)↑	1.79(1.56,2.06)↑	1.46(1.40,1.53)↑
	31 - 60	1.05(0.95,1.15)	1.14(0.66,1.96)	1.06(0.96,1.18)	1.02(0.82,1.26)	1.31(1.24,1.38)↑
	≥ 61	1.08(1.05,1.11)↑	1.00(0.85,1.16)	1.07(1.05,1.10)↑	1.15(1.09,1.21)↑	0.86(0.84,0.88)↓
LVX VS. NO LVX	≤ 30	1.14(1.05,1.25)↑	2.20(1.50,3.24)↑	1.16(1.06,1.28)↑	0.96(0.78,1.19)	2.19(2.11,2.28)↑
	31 - 60	1.09(0.98,1.21)	1.91(1.17,3.10)↑	1.09(0.97,1.22)	1.14(0.90,1.43)	1.80(1.71,1.89)↑
	≥ 61	1.02(1.00,1.05)	1.22(1.03,1.43)↑	1.03(1.00,1.07)↑	0.97(0.91,1.03)	0.99(0.97,1.01)
CIP VS. NO CIP	≤ 30	0.96(0.89,1.03)	1.06(0.70,1.60)	0.96(0.88,1.04)	0.84(0.71,1.00)↓	2.05(1.78,2.35)↑
	31 - 60	0.92(0.85,1.01)	1.02(0.63,1.67)	0.91(0.82,1.00)↓	0.95(0.78,1.14)	1.43(1.18,1.72)↑
	≥ 61	0.96(0.94,0.98)↓	1.16(1.02,1.32)↑	0.96(0.94,0.99)↓	0.92(0.88,0.97)↓	0.89(0.86,0.93)↓
MXF VS. NO MXF	≤ 30	0.59(0.37,0.93)	0.97(0.15,6.24)	0.52(0.30,0.91)↓	0.76(0.33,1.77)	1.37(1.30,1.45)↑
	31 - 60	0.71(0.43,1.15)	0.00(0.00,0.00)	0.63(0.35,1.13)	0.93(0.39,2.25)	1.26(1.17,1.35)↑
	≥ 61	0.99(0.93,1.06)	1.02(0.69,1.51)	0.99(0.92,1.06)	1.10(0.95,1.27)	0.86(0.84,0.88)↓
HRs comparing use of FQ as a class with use of each non-FQ antibiotics						
FLQ VS. AMX	≤ 30	1.00(0.84,1.19)	1.49(0.69,3.19)	0.94(0.77,1.16)	1.08(0.77,1.50)	2.86(2.61,3.13)↑
	31 - 60	0.95(0.79,1.15)	0.07(0.04,0.12)↓	0.94(0.75,1.17)	0.92(0.65,1.31)	2.18(1.96,2.44)↑
	≥ 61	0.99(0.96,1.02)	1.14(0.94,1.40)	0.98(0.95,1.02)	1.03(0.96,1.11)	1.19(1.16,1.22)↑
FLQ VS. AZM	≤ 30	0.87(0.73,1.03)	1.14(0.54,2.39)	0.83(0.68,1.02)	0.98(0.70,1.37)	2.35(2.18,2.53)↑
	31 - 60	0.99(0.82,1.19)	0.06(0.04,0.09)↓	0.93(0.75,1.16)	1.06(0.75,1.49)	1.94(1.77,2.13)↑
	≥ 61	0.93(0.90,0.96)↓	1.10(0.91,1.34)	0.91(0.88,0.94)↓	1.00(0.93,1.08)	1.29(1.25,1.32)↑
FLQ VS. LEX	≤ 30	0.66(0.55,0.78)↓	0.68(0.32,1.42)	0.70(0.57,0.87)↓	0.47(0.34,0.66)↓	1.80(1.67,1.95)↑
	31 - 60	0.85(0.70,1.04)	0.05(0.03,0.09)↓	0.80(0.64,1.01)	0.99(0.68,1.44)	1.48(1.34,1.64)↑

1		≥ 61	0.92(0.89,0.95)↓	1.13(0.92,1.40)	0.92(0.89,0.96)↓	0.86(0.80,0.93)↓	1.06(1.03,1.09)↑
2		≤ 30	0.93(0.77,1.11)	1.05(0.48,2.32)	0.96(0.77,1.19)	0.72(0.51,1.02)	1.37(1.27,1.48)↑
3	FLQ VS. AMC	31 - 60	0.94(0.77,1.15)	0.04(0.02,0.07)↓	0.90(0.72,1.14)	1.24(0.83,1.86)	1.19(1.08,1.31)↑
4		≥ 61	0.93(0.90,0.97)↓	1.19(0.95,1.49)	0.93(0.89,0.96)↓	0.98(0.90,1.06)	1.06(1.03,1.09)↑

Abbreviations: HR, hazard ratio, CI, confidence interval; FLQ, fluoroquinolone; CIP, ciprofloxacin; LVX, levofloxacin; MXF, moxifloxacin; AMX, Amoxicillin; AMC, Amoxicillin Clavulanate; AZT, Azithromycin; LEX, Cephalexin.

↑= significantly high with P-value < 0.001, ↑= significantly high with $0.001 \leq P\text{-value} < 0.05$

↓= significantly low with P-value < 0.001, ↓= significantly high with $0.001 \leq P\text{-value} < 0.05$

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Table 4. Pairwise Comparisons

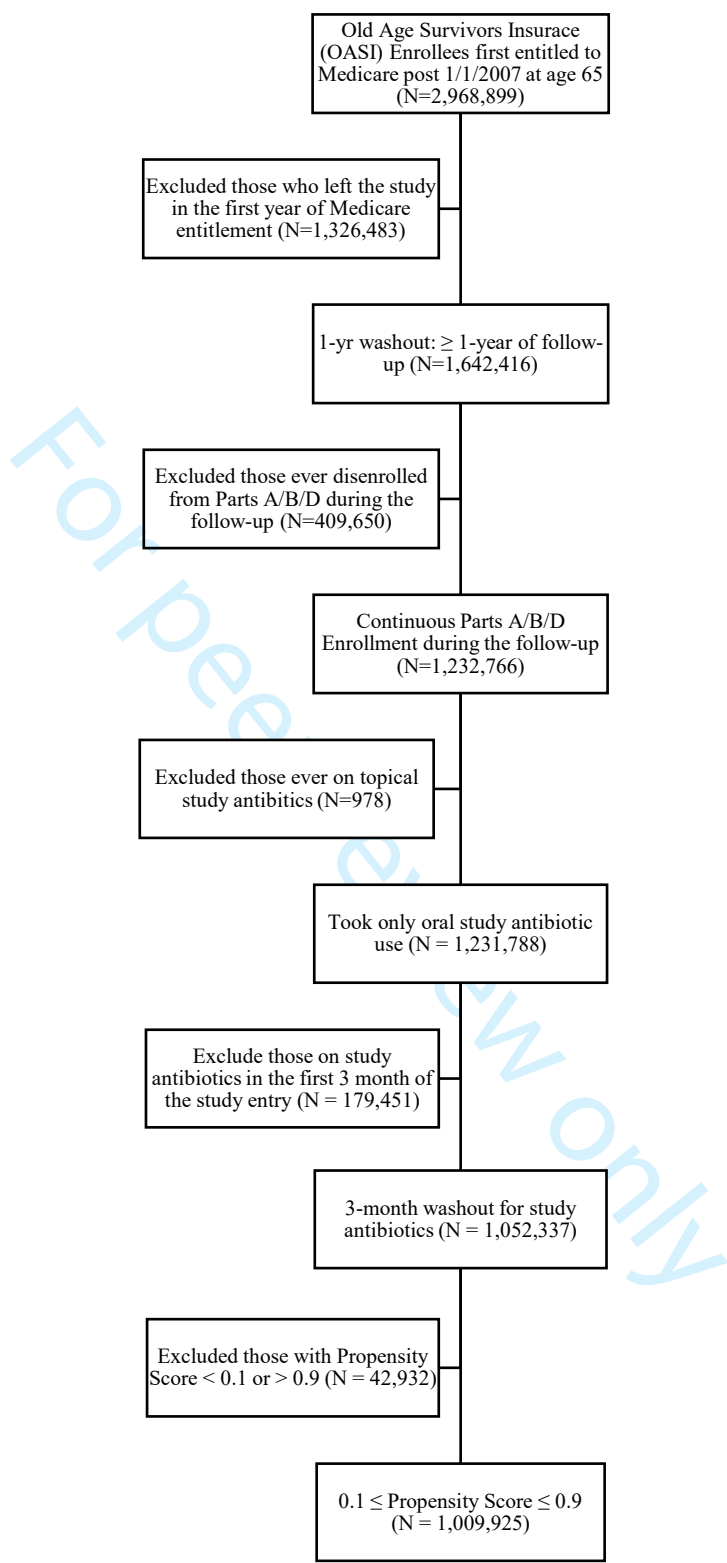
Comparison	Temporal Exposure	Any Tendon Rupture	Achilles Tendon Rupture	Complete Rupture of Rotator Cuff	Other Tendon Rupture	Death (Competing risk)
		HR(95% CI)	HR(95% CI)	HR(95% CI)	HR(95% CI)	HR(95% CI)
HRs comparing use of each FQ with use of each non-FQ antibiotics in a ≤30-day window						
CIP VS. LVX	≤ 30	0.84(0.75,0.94)↓	0.48(0.27,0.86) ↓	0.82(0.73,0.94) ↓	0.87(0.67,1.15)	0.67(0.63,0.71)↓
CIP VS. MXF	≤ 30	1.63(1.02,2.61)↑	1.08(0.16,7.29)	1.84(1.05,3.24)↑	1.10(0.47,2.60)	0.72(0.62,0.83)↓
LVX VS. MXF	≤ 30	1.95(1.21,3.13)↑	2.26(0.34,15.17)	2.24(1.27,3.94)↑	1.26(0.53,3.01)	1.07(0.93,1.24)
CIP VS. AMX	≤ 30	1.11(1.01,1.23)↑	1.20(0.66,2.16)	1.09(0.97,1.21)	1.06(0.84,1.34)	2.23(2.05,2.44)↑
CIP VS. AZM	≤ 30	0.97(0.87,1.06)	0.91(0.53,1.57)	0.96(0.86,1.07)	0.96(0.77,1.21)	1.84(1.71,1.97)↑
CIP VS. LEX	≤ 30	0.73(0.66,0.81)↓	0.55(0.31,0.95) ↓	0.81(0.72,0.91)↓	0.47(0.37,0.59)↑	1.41(1.31,1.52)↑
CIP VS. AMC	≤ 30	1.03(0.91,1.16)	0.84(0.46,1.56)	1.10(0.96,1.25)	0.71(0.56,0.92)↓	1.07(1.00,1.15)
LVX VS. AMX	≤ 30	1.33(1.19,1.49)↑	2.50(1.45,4.29)↑	1.32(1.16,1.49)↑	1.22(0.93,1.59)	3.34(3.07,3.64)↑
LVX VS. AZM	≤ 30	1.15(1.03,1.29)↑	1.91(1.13,3.23)↑	1.16(1.03,1.31)↑	1.10(0.84,1.44)	2.75(2.57,2.95)↑
LVX VS. LEX	≤ 30	0.87(0.78,0.98) ↓	1.14(0.68,1.92)	0.98(0.86,1.12)	0.54(0.41,0.69)↑	2.11(1.97,2.27)↑
LVX VS. AMC	≤ 30	1.23(1.08,1.40)↑	1.76(0.98,3.15)	1.33(1.15,1.54)↑	0.82(0.62,1.08)	1.60(1.49,1.72)↑
MXF VS. AMX	≤ 30	0.68(0.43,1.09)	1.10(0.16,7.41)	0.59(0.34,1.03)	0.96(0.41,2.27)	3.12(2.67,3.65)↑
MXF VS. AZM	≤ 30	0.59(0.37,0.94) ↓	0.84(0.13,5.65)	0.52(0.30,0.91)↓	0.88(0.37,2.07)	2.57(2.21,2.98)↑
MXF VS. LEX	≤ 30	0.45(0.28,0.72) ↓	0.50(0.08,3.35)	0.44(0.25,0.77)↓	0.43(0.18,1.00)	1.97(1.70,2.29)↑
MXF VS. AMC	≤ 30	0.63(0.39,1.01)	0.78(0.11,5.33)	0.60(0.34,1.05)	0.65(0.28,1.53)	1.50(1.29,1.73)↑
HRs comparing use of FQ as a class with use of each non-FQ antibiotics across different time window						
FLQ VS. AMX	Overall	0.98(0.90,1.07)	0.49(0.36,0.68)	0.95(0.86,1.06)	1.01(0.86,1.19)	1.95(1.86,2.05)↑
FLQ VS. AZM	Overall	0.93(0.85,1.01)	0.42(0.30,0.57)	0.89(0.80,0.98)↓	1.01(0.86,1.19)	1.80(1.73,1.88)↑
FLQ VS. LEX	Overall	0.80(0.73,0.88)	0.34(0.24,0.47)	0.80(0.72,0.89)	0.74(0.62,0.88)	1.42(1.35,1.48)↑
FLQ VS. AMC	Overall	0.93(0.85,1.02)	0.37(0.26,0.52)	0.93(0.83,1.03)	0.96(0.80,1.15)	1.20(1.15,1.25)↑

Abbreviations: HR, hazard ratio, CI, confidence interval; FLQ, fluoroquinolone; CIP, ciprofloxacin; LVX, levofloxacin; MXF, moxifloxacin; AMX, Amoxicillin; AMC, Amoxicillin Clavulanate; AZT, Azithromycin; LEX, Cephalexin.

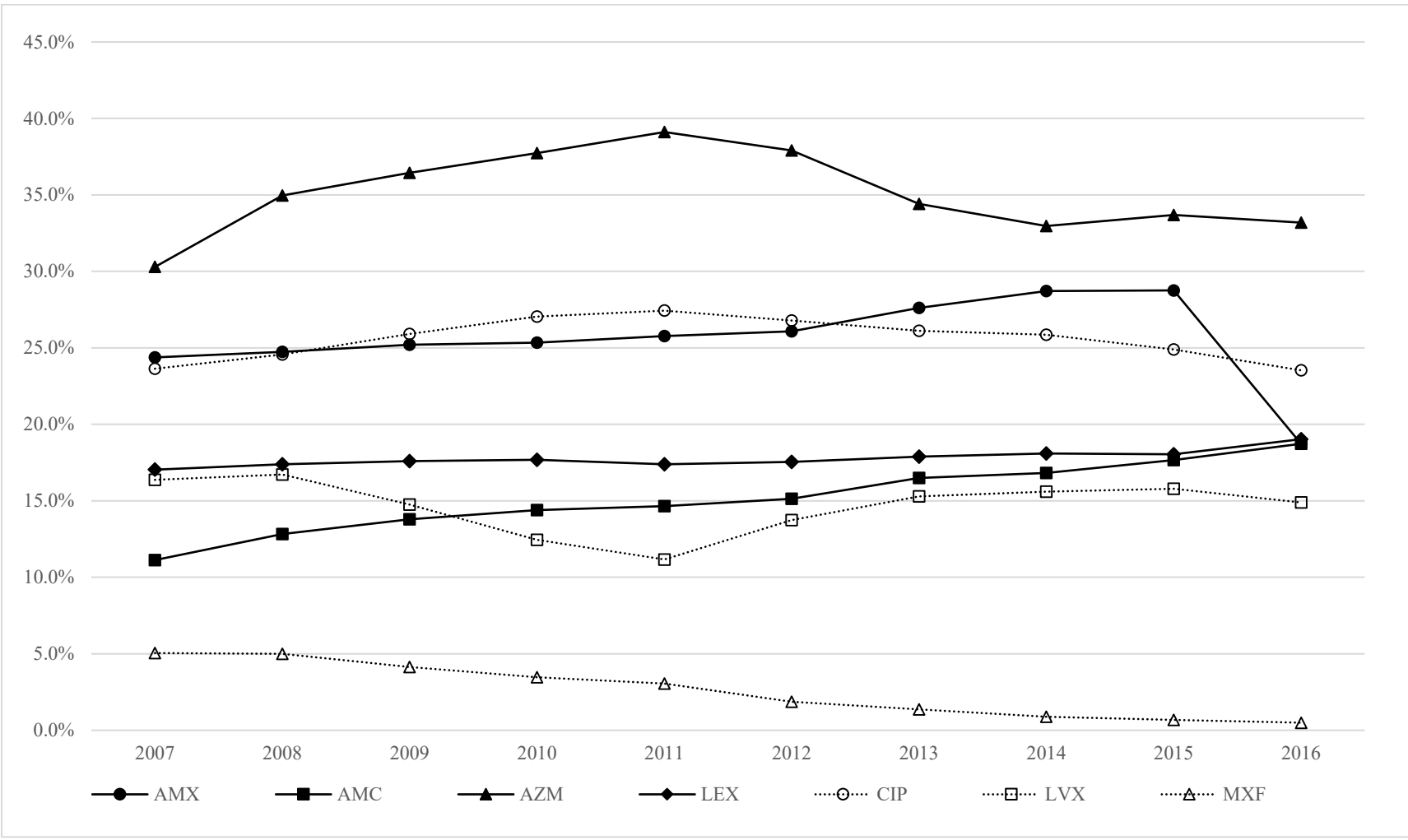
↑= significantly high with P-value < 0.001, ↑= significantly high with 0.001 ≤ P-value < 0.05

↓= significantly low with P-value < 0.001, ↓= significantly high with 0.001 ≤ P-value < 0.05

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Supplementary Figure. Secular Trend of Study Antibiotic Use



X-axis: Calendar year.

Y-axis: % of patients on each drug class.

STROBE Statement—Checklist of items that should be included in reports of *case-control studies*

	Item No	Recommendation	Page No
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	1
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(a) Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls	6
		(b) For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7
Data sources/measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7
Bias	9	Describe any efforts to address potential sources of bias	8-9
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	7-9
		(b) Describe any methods used to examine subgroups and interactions	n/a
		(c) Explain how missing data were addressed	n/a
		(d) If applicable, explain how matching of cases and controls was addressed	n/a
		(e) Describe any sensitivity analyses	n/a
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	9
		(b) Give reasons for non-participation at each stage	9
		(c) Consider use of a flow diagram	9
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9-10
		(b) Indicate number of participants with missing data for each variable of interest	n/a
Outcome data	15*	Report numbers in each exposure category, or summary measures of exposure	10

BMJ Open

The association between Tendon Ruptures and Use of Fluoroquinolone, and other oral antibiotics: A 10-year Retrospective Study of 1 million U.S. senior Medicare beneficiaries

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3 **The association between Tendon Ruptures and Use of Fluoroquinolone, and other oral**
4 **antibiotics: A 10-year Retrospective Study of 1 million U.S. senior Medicare beneficiaries**
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45 **4000 Words (4000 Max)**
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Abstract (298 words; 300 Max)

Objectives: To assess the association of fluoroquinolone use with tendon ruptures compared to no fluoroquinolone and that of the four most commonly prescribed non-fluoroquinolone antibiotics in the US.

Design: Retrospective observational study.

Setting: U.S. seniors enrolled in the federal old-age, survivor's insurance program.

Participants: 1,009,925 Medicare fee-for-service beneficiaries and their inpatient, outpatient, prescription drug records were used.

Interventions: Seven oral antibiotics, fluoroquinolones (ciprofloxacin, levofloxacin, moxifloxacin) and amoxicillin, amoxicillin-clavulanate, azithromycin and cephalexin.

Primary and Secondary Outcome measures: All tendon ruptures combined, and three types of tendon ruptures by anatomic site, Achilles tendon rupture, rupture of rotator cuff and other tendon ruptures occurred in 2007-2016.

Results: Of three fluoroquinolones, only levofloxacin exhibited a significant increased risk of tendon ruptures - 16% (HR=1.16; 95% CI 1.06-1.28), and 120% (HR=2.20; 95% CI 1.50-3.24) for rotator cuff and Achilles tendon rupture respectively in the ≤ 30 -day window. Ciprofloxacin (HR=0.96; 95% CI 0.89-1.03) and moxifloxacin (HR=0.59; 95% CI 0.37-0.93) exhibited no increased risk of tendon ruptures combined.

Among the non-fluoroquinolone antibiotics, cephalexin exhibited *increased* risk of combined tendon ruptures (HR=1.31; 95% CI 1.22-1.41) and modest to large risks across all anatomic rupture sites (HRs 1.19-1.93) at ≤ 30 -day window. Notably, the risk of

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3 levofloxacin never exceeded the risk of the non-fluoroquinolone, cephalexin in any
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5 comparison.
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9 **Conclusions:** In our study, fluoroquinolones as a class were not associated with the
10 increased risk of tendon ruptures. Neither ciprofloxacin nor moxifloxacin exhibited any
11 risk for tendon ruptures. Levofloxacin did exhibit significant increased risk. Cephalexin
12 with no reported effect on metalloprotease activity had an equal or greater risk than
13 levofloxacin; so we question whether metalloprotease activity has any relevance to
14 observed associations with tendon rupture. Confounding by indication bias may be more
15 relevant and should be given more consideration as explanation for significant
16 associations in observational studies of tendon rupture.
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Strengths and limitations of this study

- We conducted a large (more than 1 million US senior subjects) retrospective study of outpatient prescription drug records to assess the association between the use of fluoroquinolones and the occurrence of tendon ruptures compared to the most commonly used non-fluoroquinolone oral antibiotics.
- Our study included all oral fluoroquinolones (ciprofloxacin, levofloxacin, moxifloxacin) prescribed in the US and the four most commonly prescribed non-fluoroquinolone antibiotics: amoxicillin, amoxicillin-clavulanate, azithromycin and cephalexin as controls.
- In addition to reporting the risk of any tendon rupture, we also reported the risk of three types of tendon ruptures by anatomic site 1) Achilles tendon rupture, 2) rupture of rotator cuff and 3) tendon ruptures on other anatomic sites as separate outcomes.
- This study is possibly only applicable to U.S. senior, aged 65 or more, Medicare fee-for-service beneficiaries.
- We had no options to verify claims diagnoses via chart review.

Introduction

Fluoroquinolones (FQ) are among the most widely prescribed antibiotics in the outpatient setting[1,2] due to their broad spectrum treatment of bacteria found in respiratory, urinary, joint, and skin infections. Several observational studies have reported the association between the use of FQs and tendinitis and tendon rupture (TR), especially of the Achilles tendon[3–12] and the U.S. Food and Drug Administration (FDA) issued black box warnings to FQ antibiotics beginning in 2008.[13] The warning was updated in 2016 to recommend using alternative antibiotics when possible.[14,15] The fact that FQs upregulate the production of metalloproteinase enzymes with collagenase activity that could weaken tendons is taken as a mechanism to explain this reported risk.[16–18]

Studies that reported association between FQ use and TR used one or more other antibiotics as controls. One study compared the FQ rupture rates with patients using azithromycin, the most frequently used oral antibiotic in the US. Only two focused principally on TR risk among the elderly. None compared TR rates of *FQs* with those of cephalexin -- the 3rd most commonly prescribed oral antibiotic in the US.

The Virtual Research Data Center (VRDC) of Center for Medicare and Medicaid Services (CMS)[19] carries more than 10 years of Medicare claims, which include information about the usage of prescription drugs and encounter diagnoses (including tendon ruptures). It also carries information about 42 major chronic conditions, demographic characteristic and vital status. We conducted a large observational study using the VRDC to assess the association of FQ antibiotics with TR compared to that of

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3 the four most commonly prescribed non-FQ antibiotics in the US. Here we report the
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5 results of that analysis.
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10 **Methods**

11 *Patient and public involvement*

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14 Neither patients nor the public were not involved in the design of the study.
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18 *Study population*

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20 We derived our study population from a 20% random sample of Medicare prescription
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22 drug coverage (Part D) enrollees who first enrolled in the Medicare under old age and
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24 survivors insurance within a month of age 65 (779-781 month-old) and on or after
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26 1/1/2007 - the first full year of Part D prescriptions availability. We included claim data
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28 through 12/31/2016, the end of VRDC claim data available to us. All of the VRDC data
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30 is de-identified and researchers must perform all of their analysis within the VRDC
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32 computer systems, and can only pull statistical results from it.[19] This study was
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34 declared not human subject research by the Office of Human Research Protection at the
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36 National Institutes of Health and by the CMS's Privacy Board.
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44 We required subjects to be continuously enrolled in hospital insurance (Part A) and
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46 medical insurance (Part B) to assure we had full outpatient and inpatient claims data,
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48 which are not available for nearly 20% of subjects with Part D only.[20] To obtain a
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50 cohort of new TR patients, we excluded individuals with TRs recorded in the first year of
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52 their Medicare entitlement.[21] In order to assure sufficient follow-up, we excluded
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3 individuals with less than 1-year follow-up. Moreover, to obtain incident (or new) drug
4 user cohort, we excluded individuals who were prescribed any study antibiotics during
5 their first 3-month after Part D enrollment, while ignoring the data during the same time
6 window for individuals not taking study antibiotics. By doing so, we minimize survivor
7 bias from a prevalent users (Figure 1 Consort Diagram).
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14 15 16 17 Primary Outcome

18 We identified patients with TR based upon International Classification of Diseases
19 (ICD)-9-CM codes of 726.13, 727.60-727.69, and ICD-10-CM codes of M66.2, M66.3,
20 M66.8, M66.9, and M75.1. We combined all TRs and reported them as one outcome, and
21 report three types of TRs by anatomic site 1) Achilles tendon rupture, 2) rupture of
22 rotator cuff and 3) TRs on other anatomic sites as separate outcomes. We focused on
23 Achilles TR because it was the sole focus of many prior studies and on rotator cuff TR
24 because it is the predominant TR of the elderly. We lumped the remaining as “other
25 TRs”.
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40 Study antibiotics

41 We included a total of seven study antibiotics prescribed in the US including all three
42 oral FQs (moxifloxacin (MXF), ciprofloxacin (CIP), levofloxacin (LVX), the active
43 stereoisomer of ofloxacin) and the four most frequently prescribed non-FQ oral
44 antibiotics (amoxicillin (AMX), amoxicillin clavulanate (AMC), azithromycin (AZT) and
45 cephalexin (LEX)) as a control. Ciprofloxacin and the four non-FQ, study antibiotics
46 were the five most frequently used U.S. oral antibiotics in 2011.
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Statistical Analysis

We analyzed each of the four TR outcomes in separate Fine-Gray competing risk regression analyses with death as the competing risk.[22,23] Individuals became eligible for “the study” at their Medicare enrollment but prescription data did not become available until their Part D enrollment. We followed them from their entry in Part D (while accounting for left truncation[24]) until their first diagnosis of TR, death, switch to a capitated plan, disenrollment from Medicare or 12/31/2016 – whichever came first. In each regression analysis, we included the seven antibiotics whose effects on TR were our primary interest. We adjusted hazard ratio (HR) of each study antibiotic for concurrent use of the other study antibiotics. We also adjusted for calendar year of individual’s Part D entry, to account for secular trends, and their socio-demographic characteristics of gender, race, rural residency (Yes/No) and income status. We inferred individual’s income level from the monthly indicators of dual-eligibility and Low Income Subsidy (LIS) status, which separate subjects into three groups; 1) dual whose income is below 135% Federal Poverty Line (FPL); 2) non-dual LIS whose income is between 135 and 150% FPL; and 3) non-dual no LIS whose income is above 150% FPL, respectively. We used this variable in the analysis as a surrogate for economic status.[25] We also included the 42 chronic conditions within the Medicare Master Beneficiary Summary File [26] that had >1% prevalence as measures of overall health. We assumed that patients were on a given study drug from the prescription dispensing date to the end of days of supply. We did not distinguish between different brands of a study drugs. Following the approach of prior studies,[3–5] we separated subjects by temporal exposure within each study drug,

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3 including groups for never exposed, exposed within 30 days, 31-60 days, and >60 days of
4 the index (or TR event) time. Thus, by this approach we could detect the presumed short
5 term action of the FQ's on tendons and avoid the risk of non-differential misclassification
6 that can occur with too simple (yes/no) drug exposure measures.[27] In order to minimize
7 the immortal time bias, we treated all drug usage measures and all socio-demographic
8 characteristics, except gender, race and rural residency, as time-varying
9 covariates.[28,29] In order to mitigate selection bias toward use of any study antibiotics,
10 we employed a propensity score (PS) approach.[30,31] We first derived a PS of taking
11 any of study antibiotics as a function of individual's characteristics at the time of the first
12 antibiotic use after Part D entry from a multiple logistic regression. We used the median
13 days to the first study antibiotic use in patients taking study antibiotics as the cutoff time
14 for individuals not taking study antibiotics. We performed our analyses with an inverse
15 propensity score weight (IPSW) excluding individuals with the PS below 0.1 and above
16 0.9, to mitigate poorer performance in the presence of a strong treatment-selection
17 process.[32] In post-hoc analyses, we also compared the risk of TR of each study
18 antibiotics to that of every other study antibiotic on a pairwise basis.

41 42 **Results**

43 Study population and Secular trend

44 From our 20% sample of Part D enrollees, 1,009,925 individuals satisfied all our
45 selection criteria including the washout of individuals with any antibiotic use in their first
46 3-month of Part D enrollment (Figure 1 Consort Diagram). Follow-up began with an
47 individual's enrollment in Part D program (median (IQR) 0 (0-122) days from the
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3 Medicare entitlement). We followed them for a median of 3.6 years (total 4,030,897
4 patient-years) until their first diagnosis of TR (3.5%), death (4.6%), switch to a capitated
5 plan (12.6%), disenrollment from Medicare (<1%) or study end on 12/31/2016 (79.3%),
6 whichever came first. Patients had their first post enrollment claim with a diagnosis of
7 TR at a median age of 68.5 (IQR 67.2-70.4). The proportions of non-Hispanic White,
8 female and rural residents were 80.7%, 57.0%, and 22.6% respectively. About a fifth of
9 individuals received federal/state subsidies, i.e. Medicaid coverage on top of Medicare
10 (dual 16.1%) or assistance in paying their Part D premium and coinsurance/copayment
11 (non-dual LIS 2.7%). Among the 42 Medicare chronic conditions, hypertension (67.3%),
12 hyperlipidemia (68.4%), cataract (46.4%), rheumatoid arthritis/osteoarthritis (36.6%),
13 anemia (30.4%), ischemic heart disease (26.2%), and chronic kidney disease (17.9%)
14 were the seven most prevalent (Table 1).
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33 Of the 328,654 (33.0%) patients who ever took an FQ, 71.5%, 47.5% and 4.5% had taken
34 CIP, LVX and MXF respectively. Of 576,885 (57.1%) of patients who ever took a non-
35 FQ antibiotic, the figures were 53.6%, 44.9%, 33.9% and 31.1% for AZM, AMX, LEX,
36 and AMC, respectively. Patients who took one or more study antibiotics took a median
37 (IQR) of 3.0 (1.0-6.0) study antibiotic prescriptions and took a median (IQR) 2.0 (1.0-
38 3.0) different study antibiotics during the observation period. About 2.5% patients who
39 took one or more study antibiotics took one or more such antibiotics at the same time.
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49 Secular trends in study antibiotics usage existed (Supplementary Figure 1). MXF usage
50 declined precipitously from 5.0% in 2007 to almost zero in 2016 – overweighting the
51 MXF statistics for early entrants into Medicare and yielding a longer mean follow-up
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3 time. CIP use hit a peak, and LVX, a nadir, in 2011. The use of AMX, AMC and LEX
4 trended slowly upward (Supplementary Figure 1). The mode (median) of supply
5 durations for each antibiotics were short--10 (7) for AMX, 10 (10) for AMC, 5 (5) for
6 AZM, 10 (7) for LEX, 7 (7) for CIP, 10 (7) for LVX, 10 (11) for MXF. About 35% of
7 individuals were never exposed to any of the study antibiotics during the study period.
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17 Unadjusted figures for TR prevalence across each of the seven study antibiotic users and
18 the no study antibiotic users ranged from a high of 5.2% for MXF to a low of 2.9% for no
19 antibiotic (Table 1). Except for MXF, the *unadjusted* prevalence of TRs associated with
20 each non-FQ antibiotic was *greater than* or equal to that of each FQ antibiotic. The TR
21 rates per 1000 patient-years followed the same pattern, with the non-FQ antibiotics
22 topping the rates of all FQs except MXF (with the highest rate), possibly due to
23 overweighting of MXF usage in the early years of the study. Patients who ever took an
24 FQ had the highest unadjusted rate of death per 1000 person-years. LVX's death rate was
25 nearly twice the rate of each non-FQ antibiotics. The size of the associations with
26 conditions like diabetes, chronic renal failure and heart failure paralleled the magnitude
27 of the death rates and was generally higher with FQs than non-FQ antibiotics (Table 1).
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44 Primary Analysis

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47 Table 2 presents HRs for all non-antibiotic covariates in our Fine-Gray competing risk
48 regression with IPSW. For simplicity sake, in Table 2, we report the HRs of all anatomic
49 types of tendon ruptures taken together. Being a female (vs. male), African-American,
50 Hispanic, and Asian (vs. white), being dual or non-dual LIS (vs. non-dual no LIS) and
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3 living in a rural area were all associated with a *reduced* risk of tendon rupture. These risk
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5 reductions were 24% or more for all but Hispanics and rural residency covariates, and the
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7 reductions were similar across all anatomic sites. In general, life-threatening chronic
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9 conditions, such as AMI, COPD, heart failure and colorectal/lung/endometrial cancers
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11 were associated with a lower risk of TR in a range of 15-60% below control possibly due
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13 to constrained physical activity and/or shortened life span. Notably, diabetes and chronic
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15 renal disease, previously reported as risk factors for TR,[33,34] exhibited no increased
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17 TR risk. Mobility impairments had reduced risk of TR similar to that of the severe life-
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19 threatening conditions, likely due to reduced activity. Most conditions with low life
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21 threatening conditions, likely due to reduced activity. Most conditions with low life
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23 threats such as cataract, glaucoma, depression, asthma, hyperlipidemia, hypertension,
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25 prostatic hyperplasia, migraine/other chronic headache, and deafness/hearing impairment
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27 exhibited risks of 8 to 34% *above* controls probably for reasons related to longer life
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29 spans and less inhibited activity. Ischemic heart did not fit the mold of sicker equals
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31 lower TR risk. Patients with rheumatoid arthritis/osteoarthritis were a special case and
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33 had TR risk of 184% *above* control possibly due to joint and associated tendon
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35 inflammation with these disorders. Fibromyalgia/chronic pain and fatigue also exhibited
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37 a 39% increased risk of TR possibly also due to an inflammatory component.
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43 The Achilles tendon carries the full force of the extra weight carried by obese patients
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45 and obesity was associated with a significant (13%) increase in Achilles TR ruptures
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47 while its effect on other TR classes was significant but miniscule (2-3%) (Data not
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49 shown).
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52 53 ***Effect of antibiotics*** 54 55 56 57

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3 We report HRs from our primary analysis in tables separate from the non-antibiotic
4 covariates. Table 3 shows the risk associated with each study antibiotic broken down by
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6 time lag between the antibiotic use and the TRs (separate rows), and by all TRs together
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8 and separately by anatomic sites (in columns). We also report HRs of death (competing
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10 risk). We used multiplicity corrected p-values to simultaneously test the difference of
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12 pairs of antibiotics to minimize the chance of finding statistically significant difference
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14 by random chance.[35] Of the total 34,880 patients with any TR occurrence, complete
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16 rupture of rotator cuff represented the major share (80.5%), followed by other TRs
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18 (16.9%) and Achilles TR (2.6%). In the survival analysis, we followed patients until the
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20 first occurrence of TR; so, these figures count only the first TR occurrence independent
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22 of anatomic site.
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29 Of the non-FQ antibiotics, AMX exhibited a reduced risk of TR compared to no AMX in
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31 every tendon class and time window, similar to its low risk in previous studies. It
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33 exhibited a significantly lower risk in the ≤ 30 -day window except for the Achilles
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35 tendon. AZM and AMC exhibited a similar benign risk in all time windows except for
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37 TR of rotator cuff in >60 -day window. LEX was the surprise non-FQ antibiotic. It
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39 exhibited modest to large *increased* TR risk at ≤ 30 -day window across all sites ranging
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41 from a low of 19% increase for complete rupture of rotator cuff to a high 93% increase
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43 for Achilles TR. Its risk was also significantly higher at ≤ 30 -day window for all TRs
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45 taken together.
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51 Of the FQs, CIP and MXF, the most and least frequently prescribed FQ, exhibited little to
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53 no increased risk of TR within each anatomic site and each time frame. LVX is the only
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55 FQ to exhibit a significant *increase* in TR risk - of 16%, and 120% for rupture of rotator
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3 cuff and Achilles TR respectively in the ≤ 30 -day window. Notably, the risk of LVX
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5 never exceeded the risk of the non-FQ, LEX in any comparison.
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9 In a post-hoc analysis (Table 4), we compared the TR risk of each antibiotic with every
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11 other antibiotic (pairwise comparisons of FQ vs. FQ and FQ vs. non-FQ), for ≤ 30 -day
12
13 window and FQs as a class vs. each non-FQ after combining the data from the three time
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15 windows. These results paralleled the above-mentioned risk for each study antibiotic in
16
17 Table 3. Again, TR risk for LVX was greater than that of CIP, MXF, AMC, AMX, and
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19 AZM in a ≤ 30 -day window. However, LVX risk was comparable to that of LEX for
20
21 Achilles TR, and rupture of rotator cuff and significantly lower than LEX for the other
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23 TR classes. When comparing the risk of FQs as a class against that of non-FQ antibiotics,
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25 most of the non-FQ antibiotics had significantly greater risk than the FQ class as a whole
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27 across all TR sites (See last 4 rows of Table 4).
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33 In another analysis evaluating risk of death for each antibiotics, each FQ antibiotic
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35 exhibited a significant increase in death risk of – 46% (for CIP), 105% (for MXF) and
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37 119% (for LVX) in a ≤ 30 -day window. Among non-FQ antibiotics, only AMC exhibited
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39 37% increased risk of death in a ≤ 30 -day window. Overall, risk of death for FQs as a
40
41 class far outweighed that of each non-FQ antibiotics.
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48 **Discussion**

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50 Our results conflict with the common assertion that the Achilles tendon rupture is the
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52 most common tendon rupture (up to 90% in one report[36]). In our elderly cohort,
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54 Achilles TRs were a tiny, 2.6%, of all TRs. Some of this difference may be explained by
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3 the differences in demographics. Reports of high prevalence of Achilles TR came from
4 studies of young military populations.[37,38] In contrast, our data came from an elderly
5 Medicare population. Some of the difference could also be due to less ability to diagnose
6 non-Achilles tendon ruptures until MRI joint imaging became widely available, because
7 such TRs are less amenable to diagnosis by physical exam.
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17 Many authorities describe the relationship between FQs and TRs as a class “effect”.

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19 However, FQs as a class had no significant risk of TR compared with each of the four
20 non-FQ antibiotics in any time window. CIP (n=234,994 subjects) is the oral FQ with the
21 greatest use and with a greater effect on metalloproteases than other FQs.[39–41]
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25 However, neither MXF (n= 14,728 subjects) nor CIP had any TR risk at any anatomic
26 site in any time window. CIP’s lack of risk is consistent with two studies[5,9] in which
27 CIP exhibited zero risk or small risks compared to ofloxacin, a racemic mixture whose
28 active ingredient is the levo-isomer, LVX. We do see a strong association between LVX
29 and TRs whether we used no LVX or three of the non-FQ antibiotics as controls.
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36 However, when we used LEX, a cephalosporin, as the control for LVX’s effect on TRs,
37 we saw no increased risk.
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45 As noted in the introduction, the FDA has added a black box warning about tendon
46 ruptures to the labels of fluoroquinolones. A 2015 paper[42] described the evidence for
47 this decision based on the FDA’s Adverse Event Reporting System (FAERS) database
48 and an empirical Bayes geometric mean (EBGM) score, which is based on the relative
49 frequency of spontaneous report about a given adverse event in one drug versus the
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3 reporting of that adverse event across all drugs. This EBGM score based upon FAERS
4 database has been useful but FAERS database is still limited by a lack of true
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6 denominator for population at risk, underreporting due to a voluntary reporting scheme
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8 and bias due to limited adjustment variables.[43] Our study was based on a well-defined
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10 Medicare population with 80 variable adjustments. The fact that levofloxacin's EBGM
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12 score was six times that of ofloxacin[42] though both drugs have the same active
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14 ingredient (the levo-isomer of ofloxacin) and the same dose of that ingredient, raises
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16 questions about what factors influenced that score.
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24 One previous study described the effect of FQs on TR risk as small and unimportant.[10]
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26 Two studies reported no effect of FQs on TR risk.[9,11] At least 7 observational studies
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28 reported that the use of FQs increased risks of TR.[3–8,12] However, in all but one study,
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30 the number of TRs among patients taking an FQs was small (between 5 and 111). In
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32 comparison, our study included 12,517 (3.8%) such patients. One previous study did
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34 report a large number of TR events, 23,000 (3.5%) patients while on FQs and, like our
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36 study, it focused exclusively on elderly patients.[3] However, it did not compare the
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38 population of FQ users against non-users but FQ usage periods against non-usage periods
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40 in the same set of patients, which were likely periods without visits and thus could not
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42 account for the effect of increased clinical attention provided at visits requiring a strong
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44 systemic antibiotic. Furthermore, they assessed the association between AMX and TRs in
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46 separate analysis and used the risk of TRs in that analysis as the comparator for the risk
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48 observed in the FQ analysis. Finally, their analysis did not include death as a competing
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3 risk as is recommend when death rates exceed event rates[23] which was likely the case
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5 because in the demographics of their study was very similar to ours.
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10 In our study, AMX treated patients exhibited a similar absolute risk of TR as to LVX
11 treated patients (7.56 vs. 7.47 per 1000 patient-years). However, they had fewer
12 comorbidities (as in Daneman's study), almost 14% fewer hospitalizations and half of
13 death rate, compared to patients taking LVX (7.56 vs. 18.50 per 1000 patient-years). So
14 the two populations are not comparable. LVX exhibited 119% increased risk of death in a
15 ≤ 30 -day window. They appears to be reserved for more severe infections or more fragile
16 patients and thus subject to differential biases.
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28 The reported activation of metalloprotease activity by FQs has underpinned the idea of a
29 causal link between FQs and TRs. The argument goes as follows: FQs stimulate
30 metalloproteases, which can break down collagen; the tendon is made of collagen; so FQs
31 may cause TRs. However, our data disrupts this argument. CIP which strongly *stimulates*
32 metalloprotease activity,[17,18] exhibited *no* risk of TRs in our study, and LEX which
33 *inhibits* metalloprotease activity[44,45] exhibited a *large* risk. So we have to question
34 whether metalloprotease activity has any relevance to TR risk, and consider other
35 explanations for the observed associations.
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49 The indication for an antibiotic is a presumed bacterial infection. The reported
50 associations between antibiotics and TR could be a consequence of the indication
51 (infection) rather than the antibiotic use to treat it. It could be a perfects example of the
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3 confounding by indication.[46] Such a bias could explain many reported associations
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5 between drugs and TR risk including associations with non-antibiotic drugs reported by
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7 Nyyssönen.[8]
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12 This indication (and infection) bias could generate an association between the antibiotic
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14 and TRs in different ways. First, the bacterial infection might directly increase the risk of
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16 TR via stimulation of general immune or cytokine responses, or even by direct bacterial
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18 invasion. A recent study found gram-positive bacteria in a major share of ruptured
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20 tendons but not in “control” tendons removed surgically for grafting,[47] So the
21
22 possibility of direct invasion of tendons by circulating bacteria with subsequent
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24 weakening and rupture is plausible.
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31 Secondly, the greater clinical attention likely focused on patients needing systemic
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33 antibiotics, especially those with more severe infections, could increase the chance of
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35 noticing and documenting a pre-existing TR. A reservoir of not-yet-diagnosed such cases
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37 is likely to exist, because patients do not necessarily correctly identify joint and extremity
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39 symptoms as TRs and seek immediate care for them. Tendon ruptures of the shoulder
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41 capsule, for example, are notorious for developing symptoms slowly over 2-3 years[48]
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43 before being correctly diagnosed. Even Achilles tendon ruptures, can be missed (in 30%
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45 of cases) at the first presentation.[49] Seeger et al. reviewed the medical records of
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47 patients with an insurance claim reporting TRs following antibiotic use and found that
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49 nearly half of the TRs recorded in the claims were either something else (e.g., Bursa
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3 inflammation miscoded as a TR) or had occurred pre antibiotic use but only seen in a
4 claim post antibiotic use.[11]
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10 Indication bias is a plausible explanations for associations reported in observational
11 studies and it should be considered more often before assuming the associations are
12 causal.
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16 17 18 19 **Limitation**

20 This study faces all of the limitations of observational studies. Furthermore, it applies
21 only to fee-for-service Medicare populations. In addition, we had no options to verify
22 claims diagnoses via chart review. From a statistical point of view, our findings may have
23 some limitations. First, we included 80 covariates in one analysis and concern about
24 possibly strong intercorrelation affecting the validity could exist. To evaluate the
25 intercorrelation among covariates, we calculated an 80x80 correlation matrix of estimated
26 regression coefficients from our competing risk regression analysis considering their
27 time-varying nature. The correlation matrix can deliver information about the strength of
28 all pairwise correlation and indicate the existence of a collinear relationship between two
29 predictors. All correlations (except diagonal elements) were below 0.5, only 1.6% were
30 between 0.2 and 0.5. The largest of the pairwise correlations was 0.33 indicating minimal
31 bias due to intercorrelation. We also did not consider interactions among covariates in our
32 analysis because of the enormous number of two way interactions (as large as 6,400) and
33 thus the problem of overfitting.
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Competing interests Statement

All authors have no competing interest to declare.

Contributorship Statement

SB: study conception, design, analysis and interpretation; critical review of study content; manuscript drafting; approval of the final manuscript. JL: study concept and interpretation; manuscript drafting; approval of the final manuscript. VH: study interpretation; manuscript drafting; approval of the final manuscript. CJM: study conception, design and interpretation; critical review of study content; manuscript drafting; approval of the final manuscript.

Data availability

The authors confirm that the data supporting the findings of this study are available within the article [and/or] its supplementary materials.

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Table 1. Outcome, Medical/Medication Use, Diseases and Patient Characteristics by Type of Antibiotics

Variable	Overall	FLQ	CIP	LVX	MXF	AMX	AZM	LEX	AMC	None
N	1,009,925	328,654	234,994	155,991	14,728	259,125	308,985	195,731	179,616	356,364
Tendon Rupture	34,880(3.5)	12,517(3.8)	8,811(3.7)	5,904(3.8)	770(5.2)	9,636(3.7)	12,448(4.0)	8,019(4.1)	6,622(3.7)	10,169(2.9)
Death	46,468(4.6)	23,249(7.1)	14,821(6.3)	14,610(9.4)	2,136(14.5)	9,632(3.7)	14,608(4.7)	11,394(5.8)	9,951(5.5)	13,645(3.8)
Censored at HMO entry	127,162(12.6)	27,573(8.4)	19,847(8.4)	11,142(7.1)	1,571(10.7)	21,215(8.2)	26,140(8.5)	14,887(7.6)	12,674(7.1)	65,886(18.5)
Censored at disenrollment	145(0.0)	25(0.0)	13(0.0)	13(0.0)	2(0.0)	19(0.0)	27(0.0)	23(0.0)	16(0.0)	85(0.0)
Censored at Dec 31 2016	801,270(79.3)	265,290(80.7)	191,502(81.5)	124,322(79.7)	10,249(69.6)	218,623(84.4)	255,762(82.8)	161,408(82.5)	150,353(83.7)	266,579(74.8)
Years of follow-up, median(total)	3.6(4,030,897)	4.6(1,620,894)	4.8(1,190,308)	4.8(789,849)	6.0(87,397)	4.5(1,274,357)	4.6(1,529,370)	4.8(1,000,459)	4.6(890,340)	2.5(1,067,731)
Tendon rupture, 1000 person-years	8.65	7.72	7.40	7.47	8.81	7.56	8.14	8.02	7.44	9.52
Death, 1000 person-years	11.53	14.34	12.45	18.50	24.44	7.56	9.55	11.39	11.18	12.78
Female	575,885(57.0)	197,915(60.2)	146,745(62.4)	89,682(57.5)	8,747(59.4)	151,383(58.4)	194,101(62.8)	113,308(57.9)	104,749(58.3)	191,069(53.6)
White	814,933(80.7)	274,785(83.6)	196,048(83.4)	131,725(84.4)	12,464(84.6)	215,101(83.0)	259,657(84.0)	167,825(85.7)	153,723(85.6)	271,906(76.3)
Black	75,930(7.5)	20,017(6.1)	14,286(6.1)	8,893(5.7)	956(6.5)	15,622(6.0)	17,296(5.6)	9,625(4.9)	9,199(5.1)	35,023(9.8)
Hispanic	56,582(5.6)	17,044(5.2)	12,607(5.4)	7,943(5.1)	628(4.3)	12,494(4.8)	14,805(4.8)	8,976(4.6)	7,802(4.3)	24,391(6.8)
Asian	26,336(2.6)	7,316(2.2)	5,362(2.3)	3,144(2.0)	356(2.4)	7,624(2.9)	7,945(2.6)	3,539(1.8)	3,440(1.9)	10,437(2.9)
Other	36,144(3.6)	9,492(2.9)	6,691(2.8)	4,286(2.7)	324(2.2)	8,284(3.2)	9,282(3.0)	5,766(2.9)	5,452(3.0)	14,607(4.1)
Ever Dual	162,988(16.1)	54,055(16.4)	38,277(16.3)	28,156(18.0)	2,908(19.7)	35,305(13.6)	44,940(14.5)	30,962(15.8)	25,255(14.1)	66,986(18.8)
Non-Dual LIS	26,955(2.7)	7,648(2.3)	5,459(2.3)	3,746(2.4)	385(2.6)	5,224(2.0)	6,828(2.2)	4,191(2.1)	3,818(2.1)	12,595(3.5)
Non-Dual No LIS	819,982(81.2)	266,951(81.2)	191,258(81.4)	124,089(79.5)	11,435(77.6)	218,596(84.4)	257,217(83.2)	160,578(82.0)	150,543(83.8)	276,783(77.7)
Living in rural area	228,199(22.6)	78,581(23.9)	56,385(24.0)	38,847(24.9)	2,801(19.0)	58,805(22.7)	72,282(23.4)	49,977(25.5)	42,288(23.5)	77,087(21.6)
Days on Rx, median (IQR)	N/A	N/A	10.0(7.0-20.0)	10.0(7.0-17.0)	10.0(7.0-12.0)	10.0(7.0-20.0)	5.0(5.0-11.0)	10.0(7.0-16.0)	10.0(10.0-20.0)	N/A
Hospitalization	349,959(29.5)	198,846(45.4)	142,538(45.3)	113,829(52.5)	14,002(60.3)	132,304(38.8)	156,185(37.9)	119,209(45.9)	103,515(42.5)	51,525(14.4)
Outpatient visits per year, median (IQR)	19.6(11.1-33.0)	27.1(17.2-42.7)	27.3(17.5-42.9)	30.1(19.0-47.8)	34.0(21.7-53.7)	23.6(14.5-37.5)	24.6(15.5-38.8)	27.5(17.2-43.2)	26.6(16.7-42.2)	12.3(6.0-21.8)
AMI	21,222(2.1)	9,999(3.0)	6,810(2.9)	5,862(3.8)	698(4.7)	6,474(2.5)	8,079(2.6)	6,215(3.2)	5,292(2.9)	5,012(1.4)
Atrial Fibrillation	71,635(7.1)	31,752(9.7)	21,757(9.3)	17,731(11.4)	2,028(13.8)	23,974(9.3)	26,182(8.5)	21,935(11.2)	18,764(10.4)	16,314(4.6)
Cataract	468,608(46.4)	183,870(55.9)	134,196(57.1)	88,574(56.8)	9,216(62.6)	144,455(55.7)	174,897(56.6)	112,020(57.2)	101,079(56.3)	124,931(35.1)
Chronic Kidney Disease	180,441(17.9)	86,021(26.2)	62,323(26.5)	46,121(29.6)	4,651(31.6)	53,713(20.7)	65,577(21.2)	50,361(25.7)	43,182(24.0)	42,916(12.0)
COPD	130,840(13.0)	71,913(21.9)	43,961(18.7)	48,430(31.0)	6,106(41.5)	40,109(15.5)	66,536(21.5)	37,413(19.1)	37,579(20.9)	22,739(6.4)
Heart Failure	103,010(10.2)	51,814(15.8)	34,870(14.8)	31,377(20.1)	3,776(25.6)	32,792(12.7)	41,647(13.5)	31,585(16.1)	27,223(15.2)	21,907(6.1)
Diabetes	284,919(28.2)	113,424(34.5)	81,175(34.5)	57,697(37.0)	5,942(40.3)	81,155(31.3)	98,176(31.8)	67,548(34.5)	59,984(33.4)	81,448(22.9)
Glaucoma	150,839(14.9)	56,990(17.3)	41,984(17.9)	26,603(17.1)	2,930(19.9)	45,597(17.6)	54,726(17.7)	33,936(17.3)	31,065(17.3)	42,355(11.9)
Hip/Pelvic Fracture	7,982(0.8)	4,086(1.2)	3,000(1.3)	2,289(1.5)	274(1.9)	2,673(1.0)	3,005(1.0)	2,515(1.3)	1,914(1.1)	1,689(0.5)
Ischemic Heart Disease	264,648(26.2)	117,416(35.7)	82,182(35.0)	63,659(40.8)	6,956(47.2)	83,682(32.3)	101,999(33.0)	70,612(36.1)	63,363(35.3)	63,372(17.8)
Depression	210,714(20.9)	94,554(28.8)	68,625(29.2)	49,277(31.6)	5,298(36.0)	65,642(25.3)	83,253(26.9)	56,747(29.0)	51,150(28.5)	49,320(13.8)
Alzheimer's Disease or Senile Dementia	39,132(3.9)	19,796(6.0)	14,309(6.1)	11,030(7.1)	1,206(8.2)	11,140(4.3)	13,809(4.5)	11,846(6.1)	9,309(5.2)	9,400(2.6)
Osteoporosis	106,966(10.6)	47,033(14.3)	35,217(15.0)	22,918(14.7)	2,738(18.6)	34,610(13.4)	44,016(14.2)	26,996(13.8)	24,393(13.6)	25,216(7.1)

Rheumatoid Arthritis/Osteoarthritis	369,584(36.6)	160,091(48.7)	117,018(49.8)	80,115(51.4)	8,259(56.1)	126,702(48.9)	148,653(48.1)	101,310(51.8)	88,017(49.0)	81,855(23.0)
1 Stroke/Transient Ischemic Attack	58,886(5.8)	27,702(8.4)	19,843(8.4)	15,051(9.6)	1,670(11.3)	17,829(6.9)	22,038(7.1)	16,684(8.5)	14,245(7.9)	14,262(4.0)
2 Breast Cancer	45,316(4.5)	19,362(5.9)	14,344(6.1)	9,442(6.1)	984(6.7)	13,451(5.2)	17,676(5.7)	12,543(6.4)	10,156(5.7)	11,042(3.1)
3 Colorectal Cancer	15,905(1.6)	7,487(2.3)	5,421(2.3)	4,048(2.6)	390(2.6)	4,304(1.7)	5,170(1.7)	4,085(2.1)	3,605(2.0)	4,104(1.2)
4 Prostate Cancer	37,038(3.7)	19,705(6.0)	15,577(6.6)	9,232(5.9)	643(4.4)	10,967(4.2)	11,733(3.8)	9,252(4.7)	8,070(4.5)	8,333(2.3)
5 Lung Cancer	14,946(1.5)	8,965(2.7)	5,144(2.2)	6,356(4.1)	905(6.1)	3,859(1.5)	6,633(2.1)	3,977(2.0)	4,267(2.4)	2,733(0.8)
6 Endometrial Cancer	7,396(0.7)	3,447(1.0)	2,670(1.1)	1,635(1.0)	160(1.1)	2,095(0.8)	2,637(0.9)	1,957(1.0)	1,604(0.9)	1,847(0.5)
8 Anemia	307,310(30.4)	140,606(42.8)	100,819(42.9)	74,308(47.6)	7,980(54.2)	99,190(38.3)	118,327(38.3)	81,967(41.9)	72,587(40.4)	71,098(20.0)
9 Asthma	86,120(8.5)	46,350(14.1)	29,327(12.5)	30,152(19.3)	4,091(27.8)	27,632(10.7)	46,823(15.2)	24,426(12.5)	25,465(14.2)	13,802(3.9)
10 Hyperlipidemia	691,148(68.4)	257,086(78.2)	185,199(78.8)	123,828(79.4)	12,162(82.6)	199,236(76.9)	239,414(77.5)	152,879(78.1)	140,364(78.1)	201,258(56.5)
11 Hyperplasia	122,010(12.1)	59,809(18.2)	45,517(19.4)	28,616(18.3)	2,587(17.6)	39,031(15.1)	42,070(13.6)	31,606(16.1)	28,398(15.8)	27,336(7.7)
11 Hypertension	679,287(67.3)	253,601(77.2)	181,231(77.1)	124,646(79.9)	12,218(83.0)	192,686(74.4)	230,409(74.6)	150,995(77.1)	136,292(75.9)	201,777(56.6)
13 Hypothyroidism	197,447(19.6)	81,468(24.8)	59,450(25.3)	40,372(25.9)	4,198(28.5)	59,893(23.1)	76,582(24.8)	47,973(24.5)	44,249(24.6)	50,280(14.1)
14 Anxiety Disorders	148,983(14.8)	70,688(21.5)	51,377(21.9)	37,563(24.1)	4,032(27.4)	48,859(18.9)	62,418(20.2)	41,655(21.3)	37,588(20.9)	31,709(8.9)
15 Bipolar Disorder	17,882(1.8)	8,368(2.5)	6,104(2.6)	4,533(2.9)	468(3.2)	5,442(2.1)	6,658(2.2)	5,147(2.6)	4,227(2.4)	4,242(1.2)
16 Major Depressive Affective Disorder	153,182(15.2)	71,732(21.8)	52,101(22.2)	38,055(24.4)	4,148(28.2)	48,846(18.9)	61,872(20.0)	43,416(22.2)	38,642(21.5)	33,660(9.4)
17 Schizophrenia and other Psychotic Disorders	16,764(1.7)	8,591(2.6)	6,176(2.6)	4,934(3.2)	548(3.7)	4,421(1.7)	5,597(1.8)	5,101(2.6)	3,811(2.1)	4,300(1.2)
18 Epilepsy	16,155(1.6)	7,543(2.3)	5,383(2.3)	4,269(2.7)	415(2.8)	4,310(1.7)	5,488(1.8)	4,510(2.3)	3,621(2.0)	4,191(1.2)
19 Fibromyalgia, Chronic Pain and Fatigue	166,279(16.5)	78,877(24.0)	57,494(24.5)	41,843(26.8)	4,410(29.9)	56,152(21.7)	70,667(22.9)	48,422(24.7)	43,379(24.2)	33,843(9.5)
20 Viral Hepatitis (General)	11,969(1.2)	4,659(1.4)	3,188(1.4)	2,523(1.6)	287(1.9)	3,156(1.2)	3,732(1.2)	2,712(1.4)	2,348(1.3)	3,735(1.0)
21 Liver Disease Cirrhosis and other Liver Conditions	62,675(6.2)	31,930(9.7)	23,284(9.9)	17,386(11.1)	1,919(13.0)	19,624(7.6)	24,544(7.9)	17,393(8.9)	15,958(8.9)	13,350(3.7)
22 Leukemias and Lymphomas	13,906(1.4)	7,228(2.2)	4,822(2.1)	4,536(2.9)	551(3.7)	4,385(1.7)	5,905(1.9)	4,025(2.1)	3,969(2.2)	2,758(0.8)
24 Migraine and other Chronic Headache	31,628(3.1)	14,936(4.5)	11,282(4.8)	7,520(4.8)	873(5.9)	10,841(4.2)	13,893(4.5)	8,763(4.5)	8,403(4.7)	6,419(1.8)
25 Mobility Impairments	20,600(2.0)	10,182(3.1)	7,356(3.1)	5,767(3.7)	577(3.9)	5,372(2.1)	6,629(2.1)	5,995(3.1)	4,610(2.6)	5,439(1.5)
26 Obesity	185,101(18.3)	79,130(24.1)	56,609(24.1)	41,226(26.4)	3,997(27.1)	58,654(22.6)	69,611(22.5)	49,984(25.5)	43,740(24.4)	44,772(12.6)
27 Peripheral Vascular Disease	90,132(8.9)	45,276(13.8)	31,866(13.6)	25,977(16.7)	3,001(20.4)	28,747(11.1)	36,241(11.7)	28,343(14.5)	23,977(13.3)	18,446(5.2)
28 Tobacco Use Disorders	101,890(10.1)	45,304(13.8)	28,907(12.3)	27,202(17.4)	3,042(20.7)	27,261(10.5)	37,860(12.3)	25,002(12.8)	22,975(12.8)	26,896(7.5)
29 Pressure Ulcers and Chronic Ulcers	30,345(3.0)	17,688(5.4)	12,800(5.4)	10,603(6.8)	1,196(8.1)	9,006(3.5)	10,926(3.5)	13,404(6.8)	9,960(5.5)	4,992(1.4)
30 Deafness and Hearing Impairment	59,576(5.9)	27,383(8.3)	19,976(8.5)	14,014(9.0)	1,609(10.9)	21,213(8.2)	25,498(8.3)	16,849(8.6)	16,787(9.3)	11,900(3.3)

Note. Data are presented as No. (%) of patients unless otherwise noted.

Abbreviations: FLQ, fluoroquinolone; CIP, ciprofloxacin; LVX, levofloxacin; MXF, moxifloxacin; AMX, Amoxicillin; AMC, Amoxicillin Clavulanate; AZT, Azithromycin; LEX, Cephalexin; IQR, interquartile range.

Table 2. Hazard Ratios of Tendon Rupture for Each Covariate

Variables	Reference	HR(95% CI)
Female	Male	0.70(0.69,0.72)↓
Black		0.76(0.73,0.78)↓
Hispanic	White	0.91(0.87,0.94)↓
Asian		0.67(0.63,0.71)↓
Other		1.05(1.01,1.09)↑
Dual Ever	Non-Dual Non-LIS	0.66(0.64,0.68)↓
Non-Dual Lis		0.66(0.63,0.70)↓
Living In Rural Area	No	0.94(0.92,0.95)↓
Medicare Part D Since 2008		1.03(1.00,1.07)
Medicare Part D Since 2009		1.11(1.07,1.15)↑
Medicare Part D Since 2010		1.16(1.12,1.21)↑
Medicare Part D Since 2011		1.17(1.13,1.22)↑
Medicare Part D Since 2012	Medicare Part D Since 2007	1.12(1.08,1.16)↑
Medicare Part D Since 2013		1.03(1.00,1.07)
Medicare Part D Since 2013		1.05(1.01,1.09)↑
Medicare Part D Since 2015		0.91(0.87,0.96)↓
Medicare Part D Since 2016		0.93(0.19,4.55)
AMI	No	0.74(0.69,0.79)↓
Atrial Fibrillation	No	0.94(0.91,0.97)↓
Cataract	No	1.23(1.21,1.25)↑
Chronic Kidney Disease	No	0.92(0.89,0.94)↓
COPD	No	0.83(0.81,0.86)↓
Heart Failure	No	0.79(0.77,0.82)↓
Diabetes	No	0.98(0.96,0.99)↓
Glaucoma	No	1.10(1.08,1.12)↑
Hip/Pelvic Fracture	No	0.68(0.60,0.77)↓
Ischemic Heart Disease	No	1.10(1.08,1.12)↑
Depression	No	1.17(1.13,1.21)
Alzheimer's Disease or Senile Dementia	No	0.67(0.63,0.71)↓
Osteoporosis	No	1.03(1.01,1.06)↑
Rheumatoid Arthritis/Osteoarthritis	No	2.84(2.80,2.89)↑
Stroke/Transient Ischemic Attack	No	0.97(0.94,1.01)
Breast Cancer	No	0.94(0.91,0.98)↓
Colorectal Cancer	No	0.79(0.74,0.85)↓

1	Prostate Cancer	No	1.03(0.99,1.07)
2	Lung Cancer	No	0.39(0.34,0.45)↓
3	Endometrial Cancer	No	0.85(0.77,0.94)↓
4	Anemia	No	1.01(0.99,1.03)
5	Asthma	No	1.27(1.24,1.31)†
6	Hyperlipidemia	No	1.34(1.31,1.36)†
7	Hyperplasia	No	1.13(1.10,1.16)†
8	Hypertension	No	1.09(1.07,1.11)†
9	Hypothyroidism	No	1.08(1.06,1.10)†
10	Anxiety Disorders	No	0.98(0.96,1.01)
11	Bipolar Disorder	No	1.02(0.95,1.08)
12	Major Depressive Affective Disorder	No	1.06(1.02,1.10)†
13	Schizophrenia and Other Psychotic Disorders	No	0.67(0.61,0.74)↓
14	Epilepsy	No	0.83(0.77,0.90)↓
15	Fibromyalgia, Chronic Pain and Fatigue	No	1.39(1.36,1.42)†
16	Viral Hepatitis (General)	No	1.04(0.96,1.13)
17	Liver Disease Cirrhosis And Other Liver Conditions	No	0.95(0.92,0.99)↓
18	Leukemias and Lymphomas	No	0.94(0.88,1.01)
19	Migraine and Other Chronic Headache	No	1.28(1.23,1.33)†
20	Mobility Impairments	No	0.70(0.65,0.76)↓
21	Obesity	No	1.04(1.02,1.06)†
22	Peripheral Vascular Disease	No	1.00(0.97,1.04)
23	Tobacco Use Disorders	No	0.82(0.80,0.85)↓
24	Pressure Ulcers and Chronic Ulcers	No	0.82(0.77,0.87)↓
25	Deafness and Hearing Impairment	No	1.21(1.17,1.25)†

Hazard ratios and confidence intervals from the primary analysis for Covariates except for the study antibiotics (which are in Table 3)

Abbreviations: HR, hazard ratio, CI, confidence interval; FLQ, fluoroquinolone; CIP, ciprofloxacin; LVX, levofloxacin; MXF, moxifloxacin; AMX, Amoxicillin; AMC, Amoxicillin Clavulanate; AZT, Azithromycin; LEX, Cephalexin.

†= significantly high with P-value < 0.001, †= significantly high with $0.001 \leq P\text{-value} < 0.05$

↓= significantly low with P-value < 0.001, ↓= significantly high with $0.001 \leq P\text{-value} < 0.05$

Table 3. Hazard Ratios of Each Antibiotic by Anatomic Sites and Temporal Order of Drug Exposure

		Any Tendon Rupture	Achilles Tendon Rupture	Complete Rupture of Rotator Cuff	Other Tendon Ruptures	Death (Competing risk)
	Temporal Exposure	HR(95% CI)	HR(95% CI)	HR(95% CI)	HR(95% CI)	HR(95% CI)
AMX VS. NO AMX	≤ 30 days	0.86(0.80,0.92) ↓	0.88(0.59,1.33)	0.88(0.82,0.95) ↓	0.79(0.67,0.93) ↓	0.66(0.61,0.71) ↓
	31 – 60 days	0.94(0.87,1.01)	0.80(0.49,1.31)	0.91(0.84,0.99) ↓	1.08(0.93,1.27)	0.69(0.63,0.75) ↓
	≥ 61 days	1.00(0.98,1.02)	0.99(0.86,1.13)	1.01(0.99,1.04)	0.97(0.92,1.01)	0.77(0.75,0.78) ↓
AMC VS. NO AMC	≤ 30 days	0.93(0.85,1.02)	1.25(0.79,1.97)	0.87(0.79,0.97) ↓	1.17(0.98,1.41)	1.37(1.30,1.45) ↑
	31 – 60 days	0.95(0.85,1.05)	1.37(0.82,2.29)	0.95(0.84,1.06)	0.81(0.63,1.04)	1.26(1.17,1.35) ↑
	≥ 61 days	1.07(1.04,1.09) ↑	0.95(0.81,1.12)	1.07(1.04,1.10) ↑	1.02(0.96,1.08)	0.86(0.84,0.88) ↓
AZM VS. NO AZM	≤ 30 days	0.99(0.93,1.06)	1.15(0.82,1.63)	1.00(0.93,1.08)	0.87(0.75,1.01)	0.80(0.75,0.84) ↓
	31 – 60 days	0.90(0.84,0.98) ↓	0.99(0.65,1.49)	0.91(0.84,0.99) ↓	0.95(0.81,1.11)	0.77(0.73,0.82) ↓
	≥ 61 days	1.07(1.05,1.09) ↑	1.02(0.91,1.15)	1.09(1.07,1.12) ↑	0.99(0.95,1.04)	0.71(0.70,0.72) ↓
LEX VS. NO LEX	≤ 30 days	1.31(1.22,1.41) ↑	1.93(1.35,2.75) ↑	1.19(1.09,1.29) ↑	1.79(1.56,2.06) ↑	1.04(0.98,1.10)
	31 – 60 days	1.05(0.95,1.15)	1.14(0.66,1.96)	1.06(0.96,1.18)	1.02(0.82,1.26)	1.01(0.94,1.08)
	≥ 61 days	1.08(1.05,1.11) ↑	1.00(0.85,1.16)	1.07(1.05,1.10) ↑	1.15(1.09,1.21) ↑	0.86(0.84,0.88) ↓
LVX VS. NO LVX	≤ 30 days	1.14(1.05,1.25) ↑	2.20(1.50,3.24) ↑	1.16(1.06,1.28) ↑	0.96(0.78,1.19)	2.19(2.11,2.28) ↑
	31 – 60 days	1.09(0.98,1.21)	1.91(1.17,3.10) ↑	1.09(0.97,1.22)	1.14(0.90,1.43)	1.80(1.71,1.89) ↑
	≥ 61 days	1.02(1.00,1.05)	1.22(1.03,1.43) ↑	1.03(1.00,1.07) ↑	0.97(0.91,1.03)	0.99(0.97,1.01)
CIP VS. NO CIP	≤ 30 days	0.96(0.89,1.03)	1.06(0.70,1.60)	0.96(0.88,1.04)	0.84(0.71,1.00) ↓	1.46(1.40,1.53) ↑
	31 – 60 days	0.92(0.85,1.01)	1.02(0.63,1.67)	0.91(0.82,1.00) ↓	0.95(0.78,1.14)	1.31(1.24,1.38) ↑
	≥ 61 days	0.96(0.94,0.98) ↓	1.16(1.02,1.32) ↑	0.96(0.94,0.99) ↓	0.92(0.88,0.97) ↓	0.86(0.84,0.88) ↓
MXF VS. NO MXF	≤ 30 days	0.59(0.37,0.93)	0.97(0.15,6.24)	0.52(0.30,0.91) ↓	0.76(0.33,1.77)	2.05(1.78,2.35) ↑
	31 – 60 days	0.71(0.43,1.15)	0.00(0.00,0.00)	0.63(0.35,1.13)	0.93(0.39,2.25)	1.43(1.18,1.72) ↑
	≥ 61 days	0.99(0.93,1.06)	1.02(0.69,1.51)	0.99(0.92,1.06)	1.10(0.95,1.27)	0.89(0.86,0.93) ↓
FLQ VS. AMX	≤ 30 days	1.00(0.84,1.19)	1.49(0.69,3.19)	0.94(0.77,1.16)	1.08(0.77,1.50)	2.86(2.61,3.13) ↑
	31 – 60 days	0.95(0.79,1.15)	0.07(0.04,0.12) ↓	0.94(0.75,1.17)	0.92(0.65,1.31)	2.18(1.96,2.44) ↑
	≥ 61 days	0.99(0.96,1.02)	1.14(0.94,1.40)	0.98(0.95,1.02)	1.03(0.96,1.11)	1.19(1.16,1.22) ↑
FLQ VS. AZM	≤ 30 days	0.87(0.73,1.03)	1.14(0.54,2.39)	0.83(0.68,1.02)	0.98(0.70,1.37)	2.35(2.18,2.53) ↑
	31 – 60 days	0.99(0.82,1.19)	0.06(0.04,0.09) ↓	0.93(0.75,1.16)	1.06(0.75,1.49)	1.94(1.77,2.13) ↑
	≥ 61 days	0.93(0.90,0.96) ↓	1.10(0.91,1.34)	0.91(0.88,0.94) ↓	1.00(0.93,1.08)	1.29(1.25,1.32) ↑
FLQ VS. LEX	≤ 30 days	0.66(0.55,0.78) ↓	0.68(0.32,1.42)	0.70(0.57,0.87) ↓	0.47(0.34,0.66) ↓	1.80(1.67,1.95) ↑
	31 – 60 days	0.85(0.70,1.04)	0.05(0.03,0.09) ↓	0.80(0.64,1.01)	0.99(0.68,1.44)	1.48(1.34,1.64) ↑
	≥ 61 days	0.92(0.89,0.95) ↓	1.13(0.92,1.40)	0.92(0.89,0.96) ↓	0.86(0.80,0.93) ↓	1.06(1.03,1.09) ↑
FLQ VS. AMC	≤ 30 days	0.93(0.77,1.11)	1.05(0.48,2.32)	0.96(0.77,1.19)	0.72(0.51,1.02)	1.37(1.27,1.48) ↑

31 – 60 days	0.94(0.77,1.15)	0.04(0.02,0.07)↓	0.90(0.72,1.14)	1.24(0.83,1.86)	1.19(1.08,1.31)↑
≥ 61 days	0.93(0.90,0.97)↓	1.19(0.95,1.49)	0.93(0.89,0.96)↓	0.98(0.90,1.06)	1.06(1.03,1.09)↑

Abbreviations: HR, hazard ratio, CI, confidence interval; FLQ, fluoroquinolone; CIP, ciprofloxacin; LVX, levofloxacin; MXF, moxifloxacin; AMX, Amoxicillin; AMC, Amoxicillin Clavulanate; AZT, Azithromycin; LEX, Cephalexin.

↑= significantly high with P-value < 0.001, ↑= significantly high with 0.001 ≤ P-value < 0.05

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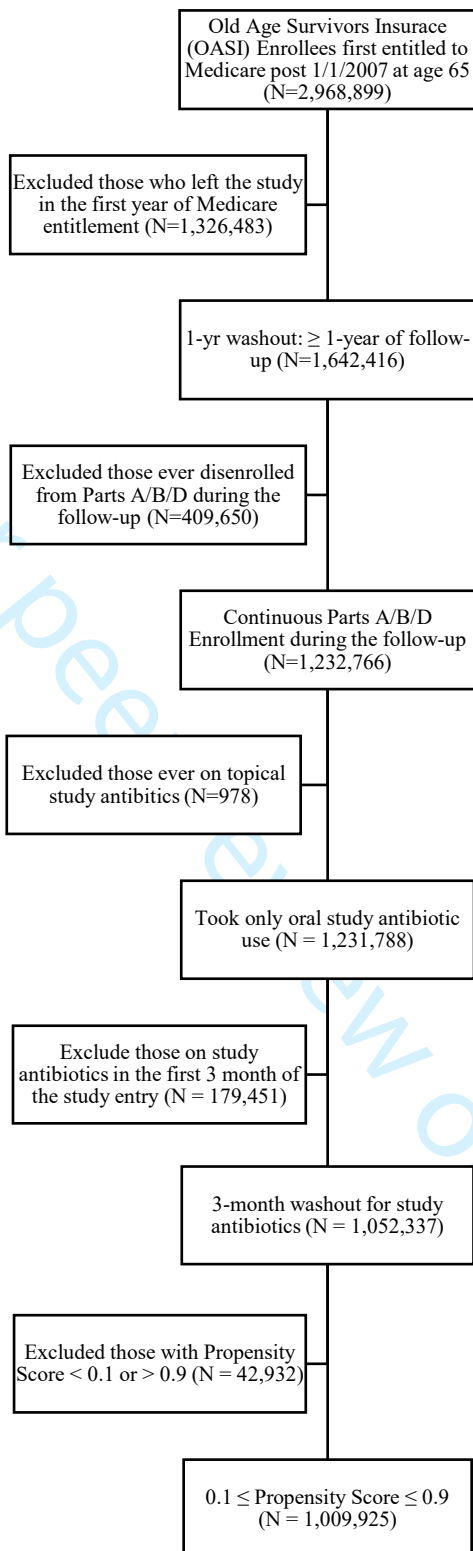
Table 4. Pairwise Comparisons

Comparison	Temporal Exposure	Any Tendon Rupture	Achilles Tendon Rupture	Complete Rupture of Rotator Cuff	Other Tendon Rupture	Death (Competing risk)
		HR(95% CI)	HR(95% CI)	HR(95% CI)	HR(95% CI)	HR(95% CI)
HRs comparing use of each FQ with use of each non-FQ antibiotics in a ≤30-day window						
CIP VS. LVX	≤ 30 days	0.84(0.75,0.94)↓	0.48(0.27,0.86) ↓	0.82(0.73,0.94) ↓	0.87(0.67,1.15)	0.67(0.63,0.71)↓
CIP VS. MXF	≤ 30 days	1.63(1.02,2.61)↑	1.08(0.16,7.29)	1.84(1.05,3.24)↑	1.10(0.47,2.60)	0.72(0.62,0.83)↓
LVX VS. MXF	≤ 30 days	1.95(1.21,3.13)↑	2.26(0.34,15.17)	2.24(1.27,3.94)↑	1.26(0.53,3.01)	1.07(0.93,1.24)
CIP VS. AMX	≤ 30 days	1.11(1.01,1.23)↑	1.20(0.66,2.16)	1.09(0.97,1.21)	1.06(0.84,1.34)	2.23(2.05,2.44)†
CIP VS. AZM	≤ 30 days	0.97(0.87,1.06)	0.91(0.53,1.57)	0.96(0.86,1.07)	0.96(0.77,1.21)	1.84(1.71,1.97)†
CIP VS. LEX	≤ 30 days	0.73(0.66,0.81)↓	0.55(0.31,0.95) ↓	0.81(0.72,0.91)↓	0.47(0.37,0.59)†	1.41(1.31,1.52)†
CIP VS. AMC	≤ 30 days	1.03(0.91,1.16)	0.84(0.46,1.56)	1.10(0.96,1.25)	0.71(0.56,0.92)↓	1.07(1.00,1.15)
LVX VS. AMX	≤ 30 days	1.33(1.19,1.49)†	2.50(1.45,4.29)↑	1.32(1.16,1.49)†	1.22(0.93,1.59)	3.34(3.07,3.64)†
LVX VS. AZM	≤ 30 days	1.15(1.03,1.29)↑	1.91(1.13,3.23)↑	1.16(1.03,1.31)↑	1.10(0.84,1.44)	2.75(2.57,2.95)†
LVX VS. LEX	≤ 30 days	0.87(0.78,0.98) ↓	1.14(0.68,1.92)	0.98(0.86,1.12)	0.54(0.41,0.69)†	2.11(1.97,2.27)†
LVX VS. AMC	≤ 30 days	1.23(1.08,1.40)↑	1.76(0.98,3.15)	1.33(1.15,1.54)†	0.82(0.62,1.08)	1.60(1.49,1.72)†
MXF VS. AMX	≤ 30 days	0.68(0.43,1.09)	1.10(0.16,7.41)	0.59(0.34,1.03)	0.96(0.41,2.27)	3.12(2.67,3.65)†
MXF VS. AZM	≤ 30 days	0.59(0.37,0.94) ↓	0.84(0.13,5.65)	0.52(0.30,0.91)↓	0.88(0.37,2.07)	2.57(2.21,2.98)†
MXF VS. LEX	≤ 30 days	0.45(0.28,0.72) ↓	0.50(0.08,3.35)	0.44(0.25,0.77)↓	0.43(0.18,1.00)	1.97(1.70,2.29)†
MXF VS. AMC	≤ 30 days	0.63(0.39,1.01)	0.78(0.11,5.33)	0.60(0.34,1.05)	0.65(0.28,1.53)	1.50(1.29,1.73)†
HRs comparing use of FQ as a class with use of each non-FQ antibiotics across different time window						
FLQ VS. AMX	Overall	0.98(0.90,1.07)	0.49(0.36,0.68)	0.95(0.86,1.06)	1.01(0.86,1.19)	1.95(1.86,2.05)†
FLQ VS. AZM	Overall	0.93(0.85,1.01)	0.42(0.30,0.57)	0.89(0.80,0.98)↓	1.01(0.86,1.19)	1.80(1.73,1.88)†
FLQ VS. LEX	Overall	0.80(0.73,0.88)	0.34(0.24,0.47)	0.80(0.72,0.89)	0.74(0.62,0.88)	1.42(1.35,1.48)†
FLQ VS. AMC	Overall	0.93(0.85,1.02)	0.37(0.26,0.52)	0.93(0.83,1.03)	0.96(0.80,1.15)	1.20(1.15,1.25)†

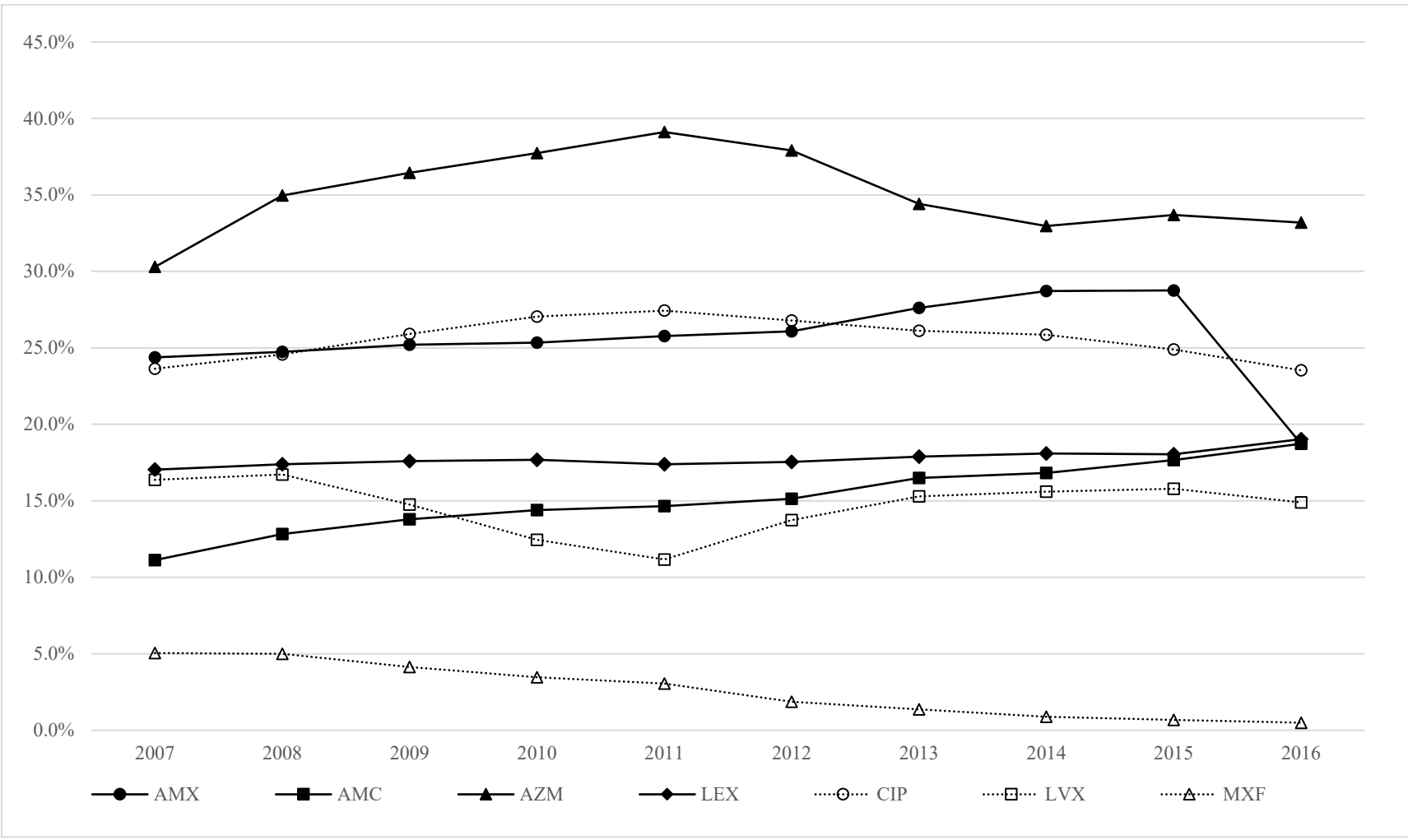
Abbreviations: HR, hazard ratio, CI, confidence interval; FLQ, fluoroquinolone; CIP, ciprofloxacin; LVX, levofloxacin; MXF, moxifloxacin; AMX, Amoxicillin; AMC, Amoxicillin Clavulanate; AZT, Azithromycin; LEX, Cephalexin.

†= significantly high with P-value < 0.001, †= significantly high with 0.001 ≤ P-value < 0.05

‡= significantly low with P-value < 0.001, ‡= significantly high with 0.001 ≤ P-value < 0.05



Supplementary Figure. Secular Trend of Study Antibiotic Use



X-axis: Calendar year.

Y-axis: % of patients on each drug class.

STROBE Statement—Checklist of items that should be included in reports of *case-control studies*

	Item No	Recommendation	Page No
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	1
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(a) Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls	6
		(b) For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7
Bias	9	Describe any efforts to address potential sources of bias	8-9
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	7-9
		(b) Describe any methods used to examine subgroups and interactions	n/a
		(c) Explain how missing data were addressed	n/a
		(d) If applicable, explain how matching of cases and controls was addressed	n/a
		(e) Describe any sensitivity analyses	n/a
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	9
		(b) Give reasons for non-participation at each stage	9
		(c) Consider use of a flow diagram	9
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9-10
		(b) Indicate number of participants with missing data for each variable of interest	n/a
Outcome data	15*	Report numbers in each exposure category, or summary measures of exposure	10

BMJ Open

The association between Tendon Ruptures and Use of Fluoroquinolone, and other oral antibiotics: A 10-year Retrospective Study of 1 million U.S. senior Medicare beneficiaries

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3 **The association between Tendon Ruptures and Use of Fluoroquinolone, and other oral**
4 **antibiotics: A 10-year Retrospective Study of 1 million U.S. senior Medicare beneficiaries**
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Abstract (298 words; 300 Max)

Objectives: To assess the association of fluoroquinolone use with tendon ruptures compared to no fluoroquinolone and that of the four most commonly prescribed non-fluoroquinolone antibiotics in the US.

Design: Retrospective observational study.

Setting: U.S. seniors enrolled in the federal old-age, survivor's insurance program.

Participants: 1,009,925 Medicare fee-for-service beneficiaries and their inpatient, outpatient, prescription drug records were used.

Interventions: Seven oral antibiotics, fluoroquinolones (ciprofloxacin, levofloxacin, moxifloxacin) and amoxicillin, amoxicillin-clavulanate, azithromycin and cephalexin.

Primary and Secondary Outcome measures: All tendon ruptures combined, and three types of tendon ruptures by anatomic site, Achilles tendon rupture, rupture of rotator cuff and other tendon ruptures occurred in 2007-2016.

Results: Of three fluoroquinolones, only levofloxacin exhibited a significant increased risk of tendon ruptures - 16% (HR=1.16; 95% CI 1.06-1.28), and 120% (HR=2.20; 95% CI 1.50-3.24) for rotator cuff and Achilles tendon rupture respectively in the ≤ 30 -day window. Ciprofloxacin (HR=0.96; 95% CI 0.89-1.03) and moxifloxacin (HR=0.59; 95% CI 0.37-0.93) exhibited no increased risk of tendon ruptures combined.

Among the non-fluoroquinolone antibiotics, cephalexin exhibited *increased* risk of combined tendon ruptures (HR=1.31; 95% CI 1.22-1.41) and modest to large risks across all anatomic rupture sites (HRs 1.19-1.93) at ≤ 30 -day window. Notably, the risk of

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3 levofloxacin never exceeded the risk of the non-fluoroquinolone, cephalexin in any
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5 comparison.
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9 **Conclusions:** In our study, fluoroquinolones as a class were not associated with the
10 increased risk of tendon ruptures. Neither ciprofloxacin nor moxifloxacin exhibited any
11 risk for tendon ruptures. Levofloxacin did exhibit significant increased risk. Cephalexin
12 with no reported effect on metalloprotease activity had an equal or greater risk than
13 levofloxacin; so we question whether metalloprotease activity has any relevance to
14 observed associations with tendon rupture. Confounding by indication bias may be more
15 relevant and should be given more consideration as explanation for significant
16 associations in observational studies of tendon rupture.
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Strengths and limitations of this study

- We conducted a large (more than 1 million US senior subjects) retrospective study of outpatient prescription drug records to assess the association between the use of fluoroquinolones and the occurrence of tendon ruptures compared to the most commonly used non-fluoroquinolone oral antibiotics.
- Our study included all oral fluoroquinolones (ciprofloxacin, levofloxacin, moxifloxacin) prescribed in the US and the four most commonly prescribed non-fluoroquinolone antibiotics: amoxicillin, amoxicillin-clavulanate, azithromycin and cephalexin as controls.
- In addition to reporting the risk of any tendon rupture, we also reported the risk of three types of tendon ruptures by anatomic site 1) Achilles tendon rupture, 2) rupture of rotator cuff and 3) tendon ruptures on other anatomic sites as separate outcomes.
- This study is possibly only applicable to U.S. senior, aged 65 or more, Medicare fee-for-service beneficiaries.
- We had no options to verify claims diagnoses via chart review.

Introduction

Fluoroquinolones (FQ) are among the most widely prescribed antibiotics in the outpatient setting[1,2] due to their broad spectrum treatment of bacteria found in respiratory, urinary, joint, and skin infections. Several observational studies have reported the association between the use of FQs and tendinitis and tendon rupture (TR), especially of the Achilles tendon[3–12] and the U.S. Food and Drug Administration (FDA) issued black box warnings to FQ antibiotics beginning in 2008.[13] The warning was updated in 2016 to recommend using alternative antibiotics when possible.[14,15] The fact that FQs upregulate the production of metalloproteinase enzymes with collagenase activity that could weaken tendons is taken as a mechanism to explain this reported risk.[16–18]

Studies that reported association between FQ use and TR used one or more other antibiotics as controls. One study compared the FQ rupture rates with patients using azithromycin, the most frequently used oral antibiotic in the US. Only two focused principally on TR risk among the elderly. None compared TR rates of *FQs* with those of cephalexin -- the 3rd most commonly prescribed oral antibiotic in the US.

The Virtual Research Data Center (VRDC) of Center for Medicare and Medicaid Services (CMS)[19] carries more than 10 years of Medicare claims, which include information about the usage of prescription drugs and encounter diagnoses (including tendon ruptures). It also carries information about 42 major chronic conditions, demographic characteristic and vital status. We conducted a large observational study using the VRDC to assess the association of FQ antibiotics with TR compared to that of

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3 the four most commonly prescribed non-FQ antibiotics in the US. Here we report the
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5 results of that analysis.
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10 **Methods**

11 *Patient and public involvement*

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14 Neither patients nor the public were not involved in the design of the study.
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18 *Study population*

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20 We derived our study population from a 20% random sample of Medicare prescription
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22 drug coverage (Part D) enrollees who first enrolled in the Medicare under old age and
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24 survivors insurance within a month of age 65 (779-781 month-old) and on or after
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26 1/1/2007 - the first full year of Part D prescriptions availability. We included claim data
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28 through 12/31/2016, the end of VRDC claim data available to us. All of the VRDC data
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30 is de-identified and researchers must perform all of their analysis within the VRDC
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32 computer systems, and can only pull statistical results from it.[19] This study was
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34 declared not human subject research by the Office of Human Research Protection at the
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36 National Institutes of Health and by the CMS's Privacy Board.
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44 We required subjects to be continuously enrolled in hospital insurance (Part A) and
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46 medical insurance (Part B) to assure we had full outpatient and inpatient claims data,
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48 which are not available for nearly 20% of subjects with Part D only.[20] To obtain a
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50 cohort of new TR patients, we excluded individuals with TRs recorded in the first year of
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52 their Medicare entitlement.[21] In order to assure sufficient follow-up, we excluded
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3 individuals with less than 1-year follow-up. Moreover, to obtain incident (or new) drug
4 user cohort, we excluded individuals who were prescribed any study antibiotics during
5 their first 3-month after Part D enrollment, while ignoring the data during the same time
6 window for individuals not taking study antibiotics. By doing so, we minimize survivor
7 bias from a prevalent users (Figure 1 Consort Diagram).
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14 15 16 17 Primary Outcome

18 We identified patients with TR based upon International Classification of Diseases
19 (ICD)-9-CM codes of 726.13, 727.60-727.69, and ICD-10-CM codes of M66.2, M66.3,
20 M66.8, M66.9, and M75.1. We combined all TRs and reported them as one outcome, and
21 report three types of TRs by anatomic site 1) Achilles tendon rupture, 2) rupture of
22 rotator cuff and 3) TRs on other anatomic sites as separate outcomes. We focused on
23 Achilles TR because it was the sole focus of many prior studies and on rotator cuff TR
24 because it is the predominant TR of the elderly. We lumped the remaining as “other
25 TRs”.
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40 Study antibiotics

41 We included a total of seven study antibiotics prescribed in the US including all three
42 oral FQs (moxifloxacin (MXF), ciprofloxacin (CIP), levofloxacin (LVX), the active
43 stereoisomer of ofloxacin) and the four most frequently prescribed non-FQ oral
44 antibiotics (amoxicillin (AMX), amoxicillin clavulanate (AMC), azithromycin (AZT) and
45 cephalexin (LEX)) as a control. Ciprofloxacin and the four non-FQ, study antibiotics
46 were the five most frequently used U.S. oral antibiotics in 2011.
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Statistical Analysis

We analyzed each of the four TR outcomes in separate Fine-Gray competing risk regression analyses with death as the competing risk.[22,23] Individuals became eligible for “the study” at their Medicare enrollment but prescription data did not become available until their Part D enrollment. We followed them from their entry in Part D (while accounting for left truncation[24]) until their first diagnosis of TR, death, switch to a capitated plan, disenrollment from Medicare or 12/31/2016 – whichever came first. In each regression analysis, we included the seven antibiotics whose effects on TR were our primary interest. We adjusted hazard ratio (HR) of each study antibiotic for concurrent use of the other study antibiotics. We also adjusted for calendar year of individual’s Part D entry, to account for secular trends, and their socio-demographic characteristics of gender, race, rural residency (Yes/No) and income status. We inferred individual’s income level from the monthly indicators of dual-eligibility and Low Income Subsidy (LIS) status, which separate subjects into three groups; 1) dual whose income is below 135% Federal Poverty Line (FPL); 2) non-dual LIS whose income is between 135 and 150% FPL; and 3) non-dual no LIS whose income is above 150% FPL, respectively. We used this variable in the analysis as a surrogate for economic status.[25] We also included the 42 chronic conditions within the Medicare Master Beneficiary Summary File [26] that had >1% prevalence as measures of overall health. We assumed that patients were on a given study drug from the prescription dispensing date to the end of days of supply. We did not distinguish between different brands of a study drugs. Following the approach of prior studies,[3–5] we separated subjects by temporal exposure within each study drug,

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3 including groups for never exposed, exposed within 30 days, 31-60 days, and >60 days of
4 the index (or TR event) time. Thus, by this approach we could detect the presumed short
5 term action of the FQ's on tendons and avoid the risk of non-differential misclassification
6 that can occur with too simple (yes/no) drug exposure measures.[27] In order to minimize
7 the immortal time bias, we treated all drug usage measures and all socio-demographic
8 characteristics, except gender, race and rural residency, as time-varying
9 covariates.[28,29] In order to mitigate selection bias toward use of any study antibiotics,
10 we employed a propensity score (PS) approach.[30,31] We first derived a PS of taking
11 any of study antibiotics as a function of individual's characteristics at the time of the first
12 antibiotic use after Part D entry from a multiple logistic regression. We used the median
13 days to the first study antibiotic use in patients taking study antibiotics as the cutoff time
14 for individuals not taking study antibiotics. We performed our analyses with an inverse
15 propensity score weight (IPSW) excluding individuals with the PS below 0.1 and above
16 0.9, to mitigate poorer performance in the presence of a strong treatment-selection
17 process.[32] In post-hoc analyses, we also compared the risk of TR of each study
18 antibiotics to that of every other study antibiotic on a pairwise basis.

41 42 **Results**

43 Study population and Secular trend

44 From our 20% sample of Part D enrollees, 1,009,925 individuals satisfied all our
45 selection criteria including the washout of individuals with any antibiotic use in their first
46 3-month of Part D enrollment (Figure 1 Consort Diagram). Follow-up began with an
47 individual's enrollment in Part D program (median (IQR) 0 (0-122) days from the
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3 Medicare entitlement). We followed them for a median of 3.6 years (total 4,030,897
4 patient-years) until their first diagnosis of TR (3.5%), death (4.6%), switch to a capitated
5 plan (12.6%), disenrollment from Medicare (<1%) or study end on 12/31/2016 (79.3%),
6 whichever came first. Patients had their first post enrollment claim with a diagnosis of
7 TR at a median age of 68.5 (IQR 67.2-70.4). The proportions of non-Hispanic White,
8 female and rural residents were 80.7%, 57.0%, and 22.6% respectively. About a fifth of
9 individuals received federal/state subsidies, i.e. Medicaid coverage on top of Medicare
10 (dual 16.1%) or assistance in paying their Part D premium and coinsurance/copayment
11 (non-dual LIS 2.7%). Among the 42 Medicare chronic conditions, hypertension (67.3%),
12 hyperlipidemia (68.4%), cataract (46.4%), rheumatoid arthritis/osteoarthritis (36.6%),
13 anemia (30.4%), ischemic heart disease (26.2%), and chronic kidney disease (17.9%)
14 were the seven most prevalent (Table 1).
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33 Of the 328,654 (33.0%) patients who ever took an FQ, 71.5%, 47.5% and 4.5% had taken
34 CIP, LVX and MXF respectively. Of 576,885 (57.1%) of patients who ever took a non-
35 FQ antibiotic, the figures were 53.6%, 44.9%, 33.9% and 31.1% for AZM, AMX, LEX,
36 and AMC, respectively. Patients who took one or more study antibiotics took a median
37 (IQR) of 3.0 (1.0-6.0) study antibiotic prescriptions and took a median (IQR) 2.0 (1.0-
38 3.0) different study antibiotics during the observation period. About 2.5% patients who
39 took one or more study antibiotics took one or more such antibiotics at the same time.
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49 Secular trends in study antibiotics usage existed (Supplementary Figure 1). MXF usage
50 declined precipitously from 5.0% in 2007 to almost zero in 2016 – overweighting the
51 MXF statistics for early entrants into Medicare and yielding a longer mean follow-up
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3 time. CIP use hit a peak, and LVX, a nadir, in 2011. The use of AMX, AMC and LEX
4 trended slowly upward (Supplementary Figure 1). The mode (median) of supply
5 durations for each antibiotics were short--10 (7) for AMX, 10 (10) for AMC, 5 (5) for
6 AZM, 10 (7) for LEX, 7 (7) for CIP, 10 (7) for LVX, 10 (11) for MXF. About 35% of
7 individuals were never exposed to any of the study antibiotics during the study period.
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17 Unadjusted figures for TR prevalence across each of the seven study antibiotic users and
18 the no study antibiotic users ranged from a high of 5.2% for MXF to a low of 2.9% for no
19 antibiotic (Table 1). Except for MXF, the *unadjusted* prevalence of TRs associated with
20 each non-FQ antibiotic was *greater than* or equal to that of each FQ antibiotic. The TR
21 rates per 1000 patient-years followed the same pattern, with the non-FQ antibiotics
22 topping the rates of all FQs except MXF (with the highest rate), possibly due to
23 overweighting of MXF usage in the early years of the study. Patients who ever took an
24 FQ had the highest unadjusted rate of death per 1000 person-years. LVX's death rate was
25 nearly twice the rate of each non-FQ antibiotics. The size of the associations with
26 conditions like diabetes, chronic renal failure and heart failure paralleled the magnitude
27 of the death rates and was generally higher with FQs than non-FQ antibiotics (Table 1).
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44 Primary Analysis

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47 Table 2 presents HRs for all non-antibiotic covariates in our Fine-Gray competing risk
48 regression with IPSW. For simplicity sake, in Table 2, we report the HRs of all anatomic
49 types of tendon ruptures taken together. Being a female (vs. male), African-American,
50 Hispanic, and Asian (vs. white), being dual or non-dual LIS (vs. non-dual no LIS) and
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3 living in a rural area were all associated with a *reduced* risk of tendon rupture. These risk
4 reductions were 24% or more for all but Hispanics and rural residency covariates, and the
5 reductions were similar across all anatomic sites. In general, life-threatening chronic
6 conditions, such as AMI, COPD, heart failure and colorectal/lung/endometrial cancers
7 were associated with a lower risk of TR in a range of 15-60% below control possibly due
8 to constrained physical activity and/or shortened life span. Notably, diabetes and chronic
9 renal disease, previously reported as risk factors for TR,[33,34] exhibited no increased
10 TR risk. Mobility impairments had reduced risk of TR similar to that of the severe life-
11 threatening conditions, likely due to reduced activity. Most conditions with low life
12 threats such as cataract, glaucoma, depression, asthma, hyperlipidemia, hypertension,
13 prostatic hyperplasia, migraine/other chronic headache, and deafness/hearing impairment
14 exhibited risks of 8 to 34% *above* controls probably for reasons related to longer life
15 spans and less inhibited activity. Ischemic heart did not fit the mold of sicker equals
16 lower TR risk. Patients with rheumatoid arthritis/osteoarthritis were a special case and
17 had TR risk of 184% *above* control possibly due to joint and associated tendon
18 inflammation with these disorders. Fibromyalgia/chronic pain and fatigue also exhibited
19 a 39% increased risk of TR possibly also due to an inflammatory component.

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43 The Achilles tendon carries the full force of the extra weight carried by obese patients
44 and obesity was associated with a significant (13%) increase in Achilles TR ruptures
45 while its effect on other TR classes was significant but miniscule (2-3%) (Data not
46 shown).

47 48 49 50 51 52 53 ***Effect of antibiotics***

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3 We report HRs from our primary analysis in tables separate from the non-antibiotic
4 covariates. Table 3 shows the risk associated with each study antibiotic broken down by
5 time lag between the antibiotic use and the TRs (separate rows), and by all TRs together
6 and separately by anatomic sites (in columns). We also report HRs of death (competing
7 risk). We used multiplicity corrected p-values to simultaneously test the difference of
8 pairs of antibiotics to minimize the chance of finding statistically significant difference
9 by random chance.[35] Of the total 34,880 patients with any TR occurrence, complete
10 rupture of rotator cuff represented the major share (80.5%), followed by other TRs
11 (16.9%) and Achilles TR (2.6%). In the survival analysis, we followed patients until the
12 first occurrence of TR; so, these figures count only the first TR occurrence independent
13 of anatomic site.
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29 Of the non-FQ antibiotics, AMX exhibited a reduced risk of TR compared to no AMX in
30 every tendon class and time window, similar to its low risk in previous studies. It
31 exhibited a significantly lower risk in the ≤ 30 -day window except for the Achilles
32 tendon. AZM and AMC exhibited a similar benign risk in all time windows except for
33 TR of rotator cuff in > 60 -day window. LEX was the surprise non-FQ antibiotic. It
34 exhibited modest to large *increased* TR risk at ≤ 30 -day window across all sites ranging
35 from a low of 19% increase for complete rupture of rotator cuff to a high 93% increase
36 for Achilles TR. Its risk was also significantly higher at ≤ 30 -day window for all TRs
37 taken together.
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51 Of the FQs, CIP and MXF, the most and least frequently prescribed FQ, exhibited little to
52 no increased risk of TR within each anatomic site and each time frame. LVX is the only
53 FQ to exhibit a significant *increase* in TR risk - of 16%, and 120% for rupture of rotator
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3 cuff and Achilles TR respectively in the ≤ 30 -day window. Notably, the risk of LVX
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5 never exceeded the risk of the non-FQ, LEX in any comparison.
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9 In a post-hoc analysis (Table 4), we compared the TR risk of each antibiotic with every
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11 other antibiotic (pairwise comparisons of FQ vs. FQ and FQ vs. non-FQ), for ≤ 30 -day
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13 window and FQs as a class vs. each non-FQ after combining the data from the three time
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15 windows. These results paralleled the above-mentioned risk for each study antibiotic in
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17 Table 3. Again, TR risk for LVX was greater than that of CIP, MXF, AMC, AMX, and
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19 AZM in a ≤ 30 -day window. However, LVX risk was comparable to that of LEX for
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21 Achilles TR, and rupture of rotator cuff and significantly lower than LEX for the other
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23 TR classes. When comparing the risk of FQs as a class against that of non-FQ antibiotics,
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25 most of the non-FQ antibiotics had significantly greater risk than the FQ class as a whole
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27 across all TR sites (See last 4 rows of Table 4).
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33 In another analysis evaluating risk of death for each antibiotics, each FQ antibiotic
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35 exhibited a significant increase in death risk of – 46% (for CIP), 105% (for MXF) and
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37 119% (for LVX) in a ≤ 30 -day window. Among non-FQ antibiotics, only AMC exhibited
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39 37% increased risk of death in a ≤ 30 -day window. Overall, risk of death for FQs as a
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41 class far outweighed that of each non-FQ antibiotics.
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48 **Discussion**

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50 Our results conflict with the common assertion that the Achilles tendon rupture is the
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52 most common tendon rupture (up to 90% in one report[36]). In our elderly cohort,
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54 Achilles TRs were a tiny, 2.6%, of all TRs. Some of this difference may be explained by
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3 the differences in demographics. Reports of high prevalence of Achilles TR came from
4 studies of young military populations.[37,38] In contrast, our data came from an elderly
5 Medicare population. Some of the difference could also be due to less ability to diagnose
6 non-Achilles tendon ruptures until MRI joint imaging became widely available, because
7 such TRs are less amenable to diagnosis by physical exam.
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17 Many authorities describe the relationship between FQs and TRs as a class “effect”.

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19 However, FQs as a class had no significant risk of TR compared with each of the four
20 non-FQ antibiotics in any time window. CIP (n=234,994 subjects) is the oral FQ with the
21 greatest use and with a greater effect on metalloproteases than other FQs.[39–41]
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25 However, neither MXF (n= 14,728 subjects) nor CIP had any TR risk at any anatomic
26 site in any time window. CIP’s lack of risk is consistent with two studies[5,9] in which
27 CIP exhibited zero risk or small risks compared to ofloxacin, a racemic mixture whose
28 active ingredient is the levo-isomer, LVX. We do see a strong association between LVX
29 and TRs whether we used no LVX or three of the non-FQ antibiotics as controls.
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38 However, when we used LEX, a cephalosporin, as the control for LVX’s effect on TRs,
39 we saw no increased risk.
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45 As noted in the introduction, the FDA has added a black box warning about tendon
46 ruptures to the labels of fluoroquinolones. A 2015 paper[42] described the evidence for
47 this decision based on the FDA’s Adverse Event Reporting System (FAERS) database
48 and an empirical Bayes geometric mean (EBGM) score, which is based on the relative
49 frequency of spontaneous report about a given adverse event in one drug versus the
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3 reporting of that adverse event across all drugs. This EBGM score based upon FAERS
4 database has been useful but FAERS database is still limited by a lack of true
5 denominator for population at risk, underreporting due to a voluntary reporting scheme
6 and bias due to limited adjustment variables.[43] Our study was based on a well-defined
7 Medicare population with 80 variable adjustments. The fact that levofloxacin's EBGM
8 score was six times that of ofloxacin[42] though both drugs have the same active
9 ingredient (the levo-isomer of ofloxacin) and the same dose of that ingredient, raises
10 questions about what factors influenced that score.
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24 One previous study described the effect of FQs on TR risk as small and unimportant.[10]
25 Two studies reported no effect of FQs on TR risk.[9,11] At least 7 observational studies
26 reported that the use of FQs increased risks of TR.[3–8,12] However, in all but one study,
27 the number of TRs among patients taking an FQs was small (between 5 and 111). In
28 comparison, our study included 12,517 (3.8%) such patients. One previous study did
29 report a large number of TR events, 23,000 (3.5%) patients while on FQs and, like our
30 study, it focused exclusively on elderly patients.[3] However, it did not compare the
31 population of FQ users against non-users but FQ usage periods against non-usage periods
32 in the same set of patients, which were likely periods without visits and thus could not
33 account for the effect of increased clinical attention provided at visits requiring a strong
34 systemic antibiotic. Furthermore, they assessed the association between AMX and TRs in
35 separate analysis and used the risk of TRs in that analysis as the comparator for the risk
36 observed in the FQ analysis. Finally, their analysis did not include death as a competing
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3 risk as is recommend when death rates exceed event rates[23] which was likely the case
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5 because in the demographics of their study was very similar to ours.
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10 In our study, AMX treated patients exhibited a similar absolute risk of TR as to LVX
11 treated patients (7.56 vs. 7.47 per 1000 patient-years). However, they had fewer
12 comorbidities (as in Daneman's study), almost 14% fewer hospitalizations and half of
13 death rate, compared to patients taking LVX (7.56 vs. 18.50 per 1000 patient-years). So
14 the two populations are not comparable. LVX exhibited 119% increased risk of death in a
15 ≤ 30 -day window. They appears to be reserved for more severe infections or more fragile
16 patients and thus subject to differential biases.
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28 The reported activation of metalloprotease activity by FQs has underpinned the idea of a
29 causal link between FQs and TRs. The argument goes as follows: FQs stimulate
30 metalloproteases, which can break down collagen; the tendon is made of collagen; so FQs
31 may cause TRs. However, our data disrupts this argument. CIP which strongly *stimulates*
32 metalloprotease activity,[17,18] exhibited *no* risk of TRs in our study, and LEX which
33 *inhibits* metalloprotease activity[44,45] exhibited a *large* risk. So we have to question
34 whether metalloprotease activity has any relevance to TR risk, and consider other
35 explanations for the observed associations.
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49 The indication for an antibiotic is a presumed bacterial infection. The reported
50 associations between antibiotics and TR could be a consequence of the indication
51 (infection) rather than the antibiotic use to treat it. It could be a perfects example of the
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3 confounding by indication.[46] Such a bias could explain many reported associations
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5 between drugs and TR risk including associations with non-antibiotic drugs reported by
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7 Nyyssönen.[8]
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12 This indication (and infection) bias could generate an association between the antibiotic
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14 and TRs in different ways. First, the bacterial infection might directly increase the risk of
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16 TR via stimulation of general immune or cytokine responses, or even by direct bacterial
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18 invasion. A recent study found gram-positive bacteria in a major share of ruptured
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20 tendons but not in “control” tendons removed surgically for grafting,[47] So the
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22 possibility of direct invasion of tendons by circulating bacteria with subsequent
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24 weakening and rupture is plausible.
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31 Secondly, the greater clinical attention likely focused on patients needing systemic
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33 antibiotics, especially those with more severe infections, could increase the chance of
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35 noticing and documenting a pre-existing TR. A reservoir of not-yet-diagnosed such cases
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37 is likely to exist, because patients do not necessarily correctly identify joint and extremity
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39 symptoms as TRs and seek immediate care for them. Tendon ruptures of the shoulder
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41 capsule, for example, are notorious for developing symptoms slowly over 2-3 years[48]
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43 before being correctly diagnosed. Even Achilles tendon ruptures, can be missed (in 30%
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45 of cases) at the first presentation.[49] Seeger et al. reviewed the medical records of
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47 patients with an insurance claim reporting TRs following antibiotic use and found that
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49 nearly half of the TRs recorded in the claims were either something else (e.g., Bursa
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3 inflammation miscoded as a TR) or had occurred pre antibiotic use but only seen in a
4 claim post antibiotic use.[11]
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10 Indication bias is a plausible explanations for associations reported in observational
11 studies and it should be considered more often before assuming the associations are
12 causal.
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16 17 18 19 **Limitation**

20 This study faces all of the limitations of observational studies. Furthermore, it applies
21 only to fee-for-service Medicare populations. In addition, we had no options to verify
22 claims diagnoses via chart review. From a statistical point of view, our findings may have
23 some limitations. First, we included 80 covariates in one analysis and concern about
24 intercorrelation affecting the validity could exist. To evaluate the intercorrelation, we
25 calculated an 80x80 correlation matrix of estimated regression which can deliver
26 information about the strength of intercorrelation and indicate the existence of a collinear
27 relationship between two predictors. All pairwise correlations (except diagonal elements)
28 were below 0.5, and the largest was 0.33 indicating minimal bias due to intercorrelation.
29 We also did not consider interactions among covariates in our main analysis because of
30 the problem of overfitting. We ran 4 sensitivity analyses with interaction terms between
31 the study medications and 4 covariates (rheumatoid arthritis/osteoarthritis, obesity,
32 female sex, lung cancer). The inclusion of interactions did not change our conclusion of
33 no TR risk for FQ as a class.
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Competing interests Statement

All authors have no competing interest to declare.

Contributorship Statement

SB: study conception, design, analysis and interpretation; critical review of study content; manuscript drafting; approval of the final manuscript. JL: study concept and interpretation; manuscript drafting; approval of the final manuscript. VH: study interpretation; manuscript drafting; approval of the final manuscript. CJM: study conception, design and interpretation; critical review of study content; manuscript drafting; approval of the final manuscript.

Data availability

The authors confirm that the data supporting the findings of this study are available within the article [and/or] its supplementary materials.

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3 **Figure 1. Consort Diagram**
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Table 1. Outcome, Medical/Medication Use, Diseases and Patient Characteristics by Type of Antibiotics

Variable	Overall	FLQ	CIP	LVX	MXF	AMX	AZM	LEX	AMC	None
N	1,009,925	328,654	234,994	155,991	14,728	259,125	308,985	195,731	179,616	356,364
Tendon Rupture	34,880(3.5)	12,517(3.8)	8,811(3.7)	5,904(3.8)	770(5.2)	9,636(3.7)	12,448(4.0)	8,019(4.1)	6,622(3.7)	10,169(2.9)
Death	46,468(4.6)	23,249(7.1)	14,821(6.3)	14,610(9.4)	2,136(14.5)	9,632(3.7)	14,608(4.7)	11,394(5.8)	9,951(5.5)	13,645(3.8)
Censored at HMO entry	127,162(12.6)	27,573(8.4)	19,847(8.4)	11,142(7.1)	1,571(10.7)	21,215(8.2)	26,140(8.5)	14,887(7.6)	12,674(7.1)	65,886(18.5)
Censored at disenrollment	145(0.0)	25(0.0)	13(0.0)	13(0.0)	2(0.0)	19(0.0)	27(0.0)	23(0.0)	16(0.0)	85(0.0)
Censored at Dec 31 2016	801,270(79.3)	265,290(80.7)	191,502(81.5)	124,322(79.7)	10,249(69.6)	218,623(84.4)	255,762(82.8)	161,408(82.5)	150,353(83.7)	266,579(74.8)
Years of follow-up, median(total)	3.6(4,030,897)	4.6(1,620,894)	4.8(1,190,308)	4.8(789,849)	6.0(87,397)	4.5(1,274,357)	4.6(1,529,370)	4.8(1,000,459)	4.6(890,340)	2.5(1,067,731)
Tendon rupture, 1000 person-years	8.65	7.72	7.40	7.47	8.81	7.56	8.14	8.02	7.44	9.52
Death, 1000 person-years	11.53	14.34	12.45	18.50	24.44	7.56	9.55	11.39	11.18	12.78
Female	575,885(57.0)	197,915(60.2)	146,745(62.4)	89,682(57.5)	8,747(59.4)	151,383(58.4)	194,101(62.8)	113,308(57.9)	104,749(58.3)	191,069(53.6)
White	814,933(80.7)	274,785(83.6)	196,048(83.4)	131,725(84.4)	12,464(84.6)	215,101(83.0)	259,657(84.0)	167,825(85.7)	153,723(85.6)	271,906(76.3)
Black	75,930(7.5)	20,017(6.1)	14,286(6.1)	8,893(5.7)	956(6.5)	15,622(6.0)	17,296(5.6)	9,625(4.9)	9,199(5.1)	35,023(9.8)
Hispanic	56,582(5.6)	17,044(5.2)	12,607(5.4)	7,943(5.1)	628(4.3)	12,494(4.8)	14,805(4.8)	8,976(4.6)	7,802(4.3)	24,391(6.8)
Asian	26,336(2.6)	7,316(2.2)	5,362(2.3)	3,144(2.0)	356(2.4)	7,624(2.9)	7,945(2.6)	3,539(1.8)	3,440(1.9)	10,437(2.9)
Other	36,144(3.6)	9,492(2.9)	6,691(2.8)	4,286(2.7)	324(2.2)	8,284(3.2)	9,282(3.0)	5,766(2.9)	5,452(3.0)	14,607(4.1)
Ever Dual	162,988(16.1)	54,055(16.4)	38,277(16.3)	28,156(18.0)	2,908(19.7)	35,305(13.6)	44,940(14.5)	30,962(15.8)	25,255(14.1)	66,986(18.8)
Non-Dual LIS	26,955(2.7)	7,648(2.3)	5,459(2.3)	3,746(2.4)	385(2.6)	5,224(2.0)	6,828(2.2)	4,191(2.1)	3,818(2.1)	12,595(3.5)
Non-Dual No LIS	819,982(81.2)	266,951(81.2)	191,258(81.4)	124,089(79.5)	11,435(77.6)	218,596(84.4)	257,217(83.2)	160,578(82.0)	150,543(83.8)	276,783(77.7)
Living in rural area	228,199(22.6)	78,581(23.9)	56,385(24.0)	38,847(24.9)	2,801(19.0)	58,805(22.7)	72,282(23.4)	49,977(25.5)	42,288(23.5)	77,087(21.6)
Days on Rx, median (IQR)	N/A	N/A	10.0(7.0-20.0)	10.0(7.0-17.0)	10.0(7.0-12.0)	10.0(7.0-20.0)	5.0(5.0-11.0)	10.0(7.0-16.0)	10.0(10.0-20.0)	N/A
Hospitalization	349,959(29.5)	198,846(45.4)	142,538(45.3)	113,829(52.5)	14,002(60.3)	132,304(38.8)	156,185(37.9)	119,209(45.9)	103,515(42.5)	51,525(14.4)
Outpatient visits per year, median (IQR)	19.6(11.1-33.0)	27.1(17.2-42.7)	27.3(17.5-42.9)	30.1(19.0-47.8)	34.0(21.7-53.7)	23.6(14.5-37.5)	24.6(15.5-38.8)	27.5(17.2-43.2)	26.6(16.7-42.2)	12.3(6.0-21.8)
AMI	21,222(2.1)	9,999(3.0)	6,810(2.9)	5,862(3.8)	698(4.7)	6,474(2.5)	8,079(2.6)	6,215(3.2)	5,292(2.9)	5,012(1.4)
Atrial Fibrillation	71,635(7.1)	31,752(9.7)	21,757(9.3)	17,731(11.4)	2,028(13.8)	23,974(9.3)	26,182(8.5)	21,935(11.2)	18,764(10.4)	16,314(4.6)
Cataract	468,608(46.4)	183,870(55.9)	134,196(57.1)	88,574(56.8)	9,216(62.6)	144,455(55.7)	174,897(56.6)	112,020(57.2)	101,079(56.3)	124,931(35.1)
Chronic Kidney Disease	180,441(17.9)	86,021(26.2)	62,323(26.5)	46,121(29.6)	4,651(31.6)	53,713(20.7)	65,577(21.2)	50,361(25.7)	43,182(24.0)	42,916(12.0)
COPD	130,840(13.0)	71,913(21.9)	43,961(18.7)	48,430(31.0)	6,106(41.5)	40,109(15.5)	66,536(21.5)	37,413(19.1)	37,579(20.9)	22,739(6.4)
Heart Failure	103,010(10.2)	51,814(15.8)	34,870(14.8)	31,377(20.1)	3,776(25.6)	32,792(12.7)	41,647(13.5)	31,585(16.1)	27,223(15.2)	21,907(6.1)
Diabetes	284,919(28.2)	113,424(34.5)	81,175(34.5)	57,697(37.0)	5,942(40.3)	81,155(31.3)	98,176(31.8)	67,548(34.5)	59,984(33.4)	81,448(22.9)
Glaucoma	150,839(14.9)	56,990(17.3)	41,984(17.9)	26,603(17.1)	2,930(19.9)	45,597(17.6)	54,726(17.7)	33,936(17.3)	31,065(17.3)	42,355(11.9)
Hip/Pelvic Fracture	7,982(0.8)	4,086(1.2)	3,000(1.3)	2,289(1.5)	274(1.9)	2,673(1.0)	3,005(1.0)	2,515(1.3)	1,914(1.1)	1,689(0.5)
Ischemic Heart Disease	264,648(26.2)	117,416(35.7)	82,182(35.0)	63,659(40.8)	6,956(47.2)	83,682(32.3)	101,999(33.0)	70,612(36.1)	63,363(35.3)	63,372(17.8)
Depression	210,714(20.9)	94,554(28.8)	68,625(29.2)	49,277(31.6)	5,298(36.0)	65,642(25.3)	83,253(26.9)	56,747(29.0)	51,150(28.5)	49,320(13.8)
Alzheimer's Disease or Senile Dementia	39,132(3.9)	19,796(6.0)	14,309(6.1)	11,030(7.1)	1,206(8.2)	11,140(4.3)	13,809(4.5)	11,846(6.1)	9,309(5.2)	9,400(2.6)
Osteoporosis	106,966(10.6)	47,033(14.3)	35,217(15.0)	22,918(14.7)	2,738(18.6)	34,610(13.4)	44,016(14.2)	26,996(13.8)	24,393(13.6)	25,216(7.1)

Rheumatoid Arthritis/Osteoarthritis	369,584(36.6)	160,091(48.7)	117,018(49.8)	80,115(51.4)	8,259(56.1)	126,702(48.9)	148,653(48.1)	101,310(51.8)	88,017(49.0)	81,855(23.0)
1 Stroke/Transient Ischemic Attack	58,886(5.8)	27,702(8.4)	19,843(8.4)	15,051(9.6)	1,670(11.3)	17,829(6.9)	22,038(7.1)	16,684(8.5)	14,245(7.9)	14,262(4.0)
2 Breast Cancer	45,316(4.5)	19,362(5.9)	14,344(6.1)	9,442(6.1)	984(6.7)	13,451(5.2)	17,676(5.7)	12,543(6.4)	10,156(5.7)	11,042(3.1)
3 Colorectal Cancer	15,905(1.6)	7,487(2.3)	5,421(2.3)	4,048(2.6)	390(2.6)	4,304(1.7)	5,170(1.7)	4,085(2.1)	3,605(2.0)	4,104(1.2)
4 Prostate Cancer	37,038(3.7)	19,705(6.0)	15,577(6.6)	9,232(5.9)	643(4.4)	10,967(4.2)	11,733(3.8)	9,252(4.7)	8,070(4.5)	8,333(2.3)
5 Lung Cancer	14,946(1.5)	8,965(2.7)	5,144(2.2)	6,356(4.1)	905(6.1)	3,859(1.5)	6,633(2.1)	3,977(2.0)	4,267(2.4)	2,733(0.8)
6 Endometrial Cancer	7,396(0.7)	3,447(1.0)	2,670(1.1)	1,635(1.0)	160(1.1)	2,095(0.8)	2,637(0.9)	1,957(1.0)	1,604(0.9)	1,847(0.5)
8 Anemia	307,310(30.4)	140,606(42.8)	100,819(42.9)	74,308(47.6)	7,980(54.2)	99,190(38.3)	118,327(38.3)	81,967(41.9)	72,587(40.4)	71,098(20.0)
9 Asthma	86,120(8.5)	46,350(14.1)	29,327(12.5)	30,152(19.3)	4,091(27.8)	27,632(10.7)	46,823(15.2)	24,426(12.5)	25,465(14.2)	13,802(3.9)
10 Hyperlipidemia	691,148(68.4)	257,086(78.2)	185,199(78.8)	123,828(79.4)	12,162(82.6)	199,236(76.9)	239,414(77.5)	152,879(78.1)	140,364(78.1)	201,258(56.5)
1 Hyperplasia	122,010(12.1)	59,809(18.2)	45,517(19.4)	28,616(18.3)	2,587(17.6)	39,031(15.1)	42,070(13.6)	31,606(16.1)	28,398(15.8)	27,336(7.7)
1 Hypertension	679,287(67.3)	253,601(77.2)	181,231(77.1)	124,646(79.9)	12,218(83.0)	192,686(74.4)	230,409(74.6)	150,995(77.1)	136,292(75.9)	201,777(56.6)
1 Hypothyroidism	197,447(19.6)	81,468(24.8)	59,450(25.3)	40,372(25.9)	4,198(28.5)	59,893(23.1)	76,582(24.8)	47,973(24.5)	44,249(24.6)	50,280(14.1)
1 Anxiety Disorders	148,983(14.8)	70,688(21.5)	51,377(21.9)	37,563(24.1)	4,032(27.4)	48,859(18.9)	62,418(20.2)	41,655(21.3)	37,588(20.9)	31,709(8.9)
1 Bipolar Disorder	17,882(1.8)	8,368(2.5)	6,104(2.6)	4,533(2.9)	468(3.2)	5,442(2.1)	6,658(2.2)	5,147(2.6)	4,227(2.4)	4,242(1.2)
1 Major Depressive Affective Disorder	153,182(15.2)	71,732(21.8)	52,101(22.2)	38,055(24.4)	4,148(28.2)	48,846(18.9)	61,872(20.0)	43,416(22.2)	38,642(21.5)	33,660(9.4)
1 Schizophrenia and other Psychotic Disorders	16,764(1.7)	8,591(2.6)	6,176(2.6)	4,934(3.2)	548(3.7)	4,421(1.7)	5,597(1.8)	5,101(2.6)	3,811(2.1)	4,300(1.2)
18 Epilepsy	16,155(1.6)	7,543(2.3)	5,383(2.3)	4,269(2.7)	415(2.8)	4,310(1.7)	5,488(1.8)	4,510(2.3)	3,621(2.0)	4,191(1.2)
19 Fibromyalgia, Chronic Pain and Fatigue	166,279(16.5)	78,877(24.0)	57,494(24.5)	41,843(26.8)	4,410(29.9)	56,152(21.7)	70,667(22.9)	48,422(24.7)	43,379(24.2)	33,843(9.5)
20 Viral Hepatitis (General)	11,969(1.2)	4,659(1.4)	3,188(1.4)	2,523(1.6)	287(1.9)	3,156(1.2)	3,732(1.2)	2,712(1.4)	2,348(1.3)	3,735(1.0)
21 Liver Disease Cirrhosis and other Liver Conditions	62,675(6.2)	31,930(9.7)	23,284(9.9)	17,386(11.1)	1,919(13.0)	19,624(7.6)	24,544(7.9)	17,393(8.9)	15,958(8.9)	13,350(3.7)
22 Leukemias and Lymphomas	13,906(1.4)	7,228(2.2)	4,822(2.1)	4,536(2.9)	551(3.7)	4,385(1.7)	5,905(1.9)	4,025(2.1)	3,969(2.2)	2,758(0.8)
24 Migraine and other Chronic Headache	31,628(3.1)	14,936(4.5)	11,282(4.8)	7,520(4.8)	873(5.9)	10,841(4.2)	13,893(4.5)	8,763(4.5)	8,403(4.7)	6,419(1.8)
25 Mobility Impairments	20,600(2.0)	10,182(3.1)	7,356(3.1)	5,767(3.7)	577(3.9)	5,372(2.1)	6,629(2.1)	5,995(3.1)	4,610(2.6)	5,439(1.5)
26 Obesity	185,101(18.3)	79,130(24.1)	56,609(24.1)	41,226(26.4)	3,997(27.1)	58,654(22.6)	69,611(22.5)	49,984(25.5)	43,740(24.4)	44,772(12.6)
27 Peripheral Vascular Disease	90,132(8.9)	45,276(13.8)	31,866(13.6)	25,977(16.7)	3,001(20.4)	28,747(11.1)	36,241(11.7)	28,343(14.5)	23,977(13.3)	18,446(5.2)
28 Tobacco Use Disorders	101,890(10.1)	45,304(13.8)	28,907(12.3)	27,202(17.4)	3,042(20.7)	27,261(10.5)	37,860(12.3)	25,002(12.8)	22,975(12.8)	26,896(7.5)
29 Pressure Ulcers and Chronic Ulcers	30,345(3.0)	17,688(5.4)	12,800(5.4)	10,603(6.8)	1,196(8.1)	9,006(3.5)	10,926(3.5)	13,404(6.8)	9,960(5.5)	4,992(1.4)
30 Deafness and Hearing Impairment	59,576(5.9)	27,383(8.3)	19,976(8.5)	14,014(9.0)	1,609(10.9)	21,213(8.2)	25,498(8.3)	16,849(8.6)	16,787(9.3)	11,900(3.3)

Note. Data are presented as No. (%) of patients unless otherwise noted.

Abbreviations: FLQ, fluoroquinolone; CIP, ciprofloxacin; LVX, levofloxacin; MXF, moxifloxacin; AMX, Amoxicillin; AMC, Amoxicillin Clavulanate; AZT, Azithromycin; LEX, Cephalexin; IQR, interquartile range.

Table 2. Hazard Ratios of Tendon Rupture for Each Covariate

Variables	Reference	HR(95% CI)
Female	Male	0.70(0.69,0.72)↓
Black		0.76(0.73,0.78)↓
Hispanic	White	0.91(0.87,0.94)↓
Asian		0.67(0.63,0.71)↓
Other		1.05(1.01,1.09)↑
Dual Ever	Non-Dual Non-LIS	0.66(0.64,0.68)↓
Non-Dual Lis		0.66(0.63,0.70)↓
Living In Rural Area	No	0.94(0.92,0.95)↓
Medicare Part D Since 2008		1.03(1.00,1.07)
Medicare Part D Since 2009		1.11(1.07,1.15)↑
Medicare Part D Since 2010		1.16(1.12,1.21)↑
Medicare Part D Since 2011		1.17(1.13,1.22)↑
Medicare Part D Since 2012	Medicare Part D Since 2007	1.12(1.08,1.16)↑
Medicare Part D Since 2013		1.03(1.00,1.07)
Medicare Part D Since 2013		1.05(1.01,1.09)↑
Medicare Part D Since 2015		0.91(0.87,0.96)↓
Medicare Part D Since 2016		0.93(0.19,4.55)
AMI	No	0.74(0.69,0.79)↓
Atrial Fibrillation	No	0.94(0.91,0.97)↓
Cataract	No	1.23(1.21,1.25)↑
Chronic Kidney Disease	No	0.92(0.89,0.94)↓
COPD	No	0.83(0.81,0.86)↓
Heart Failure	No	0.79(0.77,0.82)↓
Diabetes	No	0.98(0.96,0.99)↓
Glaucoma	No	1.10(1.08,1.12)↑
Hip/Pelvic Fracture	No	0.68(0.60,0.77)↓
Ischemic Heart Disease	No	1.10(1.08,1.12)↑
Depression	No	1.17(1.13,1.21)
Alzheimer's Disease or Senile Dementia	No	0.67(0.63,0.71)↓
Osteoporosis	No	1.03(1.01,1.06)↑
Rheumatoid Arthritis/Osteoarthritis	No	2.84(2.80,2.89)↑
Stroke/Transient Ischemic Attack	No	0.97(0.94,1.01)
Breast Cancer	No	0.94(0.91,0.98)↓
Colorectal Cancer	No	0.79(0.74,0.85)↓

1	Prostate Cancer	No	1.03(0.99,1.07)
2	Lung Cancer	No	0.39(0.34,0.45)↓
3	Endometrial Cancer	No	0.85(0.77,0.94)↓
4	Anemia	No	1.01(0.99,1.03)
5	Asthma	No	1.27(1.24,1.31)†
6	Hyperlipidemia	No	1.34(1.31,1.36)†
7	Hyperplasia	No	1.13(1.10,1.16)†
8	Hypertension	No	1.09(1.07,1.11)†
9	Hypothyroidism	No	1.08(1.06,1.10)†
10	Anxiety Disorders	No	0.98(0.96,1.01)
11	Bipolar Disorder	No	1.02(0.95,1.08)
12	Major Depressive Affective Disorder	No	1.06(1.02,1.10)†
13	Schizophrenia and Other Psychotic Disorders	No	0.67(0.61,0.74)↓
14	Epilepsy	No	0.83(0.77,0.90)↓
15	Fibromyalgia, Chronic Pain and Fatigue	No	1.39(1.36,1.42)†
16	Viral Hepatitis (General)	No	1.04(0.96,1.13)
17	Liver Disease Cirrhosis And Other Liver Conditions	No	0.95(0.92,0.99)↓
18	Leukemias and Lymphomas	No	0.94(0.88,1.01)
19	Migraine and Other Chronic Headache	No	1.28(1.23,1.33)†
20	Mobility Impairments	No	0.70(0.65,0.76)↓
21	Obesity	No	1.04(1.02,1.06)†
22	Peripheral Vascular Disease	No	1.00(0.97,1.04)
23	Tobacco Use Disorders	No	0.82(0.80,0.85)↓
24	Pressure Ulcers and Chronic Ulcers	No	0.82(0.77,0.87)↓
25	Deafness and Hearing Impairment	No	1.21(1.17,1.25)†

Hazard ratios and confidence intervals from the primary analysis for Covariates except for the study antibiotics (which are in Table 3)

Abbreviations: HR, hazard ratio, CI, confidence interval; FLQ, fluoroquinolone; CIP, ciprofloxacin; LVX, levofloxacin; MXF, moxifloxacin; AMX, Amoxicillin; AMC, Amoxicillin Clavulanate; AZT, Azithromycin; LEX, Cephalexin.

†= significantly high with P-value < 0.001, †= significantly high with $0.001 \leq P\text{-value} < 0.05$

↓= significantly low with P-value < 0.001, ↓= significantly high with $0.001 \leq P\text{-value} < 0.05$

Table 3. Hazard Ratios of Each Antibiotic by Anatomic Sites and Temporal Order of Drug Exposure

		Any Tendon Rupture	Achilles Tendon Rupture	Complete Rupture of Rotator Cuff	Other Tendon Ruptures	Death (Competing risk)
	Temporal Exposure	HR(95% CI)	HR(95% CI)	HR(95% CI)	HR(95% CI)	HR(95% CI)
AMX VS. NO AMX	≤ 30 days	0.86(0.80,0.92) ↓	0.88(0.59,1.33)	0.88(0.82,0.95) ↓	0.79(0.67,0.93) ↓	0.66(0.61,0.71) ↓
	31 – 60 days	0.94(0.87,1.01)	0.80(0.49,1.31)	0.91(0.84,0.99) ↓	1.08(0.93,1.27)	0.69(0.63,0.75) ↓
	≥ 61 days	1.00(0.98,1.02)	0.99(0.86,1.13)	1.01(0.99,1.04)	0.97(0.92,1.01)	0.77(0.75,0.78) ↓
AMC VS. NO AMC	≤ 30 days	0.93(0.85,1.02)	1.25(0.79,1.97)	0.87(0.79,0.97) ↓	1.17(0.98,1.41)	1.37(1.30,1.45) ↑
	31 – 60 days	0.95(0.85,1.05)	1.37(0.82,2.29)	0.95(0.84,1.06)	0.81(0.63,1.04)	1.26(1.17,1.35) ↑
	≥ 61 days	1.07(1.04,1.09) ↑	0.95(0.81,1.12)	1.07(1.04,1.10) ↑	1.02(0.96,1.08)	0.86(0.84,0.88) ↓
AZM VS. NO AZM	≤ 30 days	0.99(0.93,1.06)	1.15(0.82,1.63)	1.00(0.93,1.08)	0.87(0.75,1.01)	0.80(0.75,0.84) ↓
	31 – 60 days	0.90(0.84,0.98) ↓	0.99(0.65,1.49)	0.91(0.84,0.99) ↓	0.95(0.81,1.11)	0.77(0.73,0.82) ↓
	≥ 61 days	1.07(1.05,1.09) ↑	1.02(0.91,1.15)	1.09(1.07,1.12) ↑	0.99(0.95,1.04)	0.71(0.70,0.72) ↓
LEX VS. NO LEX	≤ 30 days	1.31(1.22,1.41) ↑	1.93(1.35,2.75) ↑	1.19(1.09,1.29) ↑	1.79(1.56,2.06) ↑	1.04(0.98,1.10)
	31 – 60 days	1.05(0.95,1.15)	1.14(0.66,1.96)	1.06(0.96,1.18)	1.02(0.82,1.26)	1.01(0.94,1.08)
	≥ 61 days	1.08(1.05,1.11) ↑	1.00(0.85,1.16)	1.07(1.05,1.10) ↑	1.15(1.09,1.21) ↑	0.86(0.84,0.88) ↓
LVX VS. NO LVX	≤ 30 days	1.14(1.05,1.25) ↑	2.20(1.50,3.24) ↑	1.16(1.06,1.28) ↑	0.96(0.78,1.19)	2.19(2.11,2.28) ↑
	31 – 60 days	1.09(0.98,1.21)	1.91(1.17,3.10) ↑	1.09(0.97,1.22)	1.14(0.90,1.43)	1.80(1.71,1.89) ↑
	≥ 61 days	1.02(1.00,1.05)	1.22(1.03,1.43) ↑	1.03(1.00,1.07) ↑	0.97(0.91,1.03)	0.99(0.97,1.01)
CIP VS. NO CIP	≤ 30 days	0.96(0.89,1.03)	1.06(0.70,1.60)	0.96(0.88,1.04)	0.84(0.71,1.00) ↓	1.46(1.40,1.53) ↑
	31 – 60 days	0.92(0.85,1.01)	1.02(0.63,1.67)	0.91(0.82,1.00) ↓	0.95(0.78,1.14)	1.31(1.24,1.38) ↑
	≥ 61 days	0.96(0.94,0.98) ↓	1.16(1.02,1.32) ↑	0.96(0.94,0.99) ↓	0.92(0.88,0.97) ↓	0.86(0.84,0.88) ↓
MXF VS. NO MXF	≤ 30 days	0.59(0.37,0.93)	0.97(0.15,6.24)	0.52(0.30,0.91) ↓	0.76(0.33,1.77)	2.05(1.78,2.35) ↑
	31 – 60 days	0.71(0.43,1.15)	0.00(0.00,0.00)	0.63(0.35,1.13)	0.93(0.39,2.25)	1.43(1.18,1.72) ↑
	≥ 61 days	0.99(0.93,1.06)	1.02(0.69,1.51)	0.99(0.92,1.06)	1.10(0.95,1.27)	0.89(0.86,0.93) ↓
FLQ VS. AMX	≤ 30 days	1.00(0.84,1.19)	1.49(0.69,3.19)	0.94(0.77,1.16)	1.08(0.77,1.50)	2.86(2.61,3.13) ↑
	31 – 60 days	0.95(0.79,1.15)	0.07(0.04,0.12) ↓	0.94(0.75,1.17)	0.92(0.65,1.31)	2.18(1.96,2.44) ↑
	≥ 61 days	0.99(0.96,1.02)	1.14(0.94,1.40)	0.98(0.95,1.02)	1.03(0.96,1.11)	1.19(1.16,1.22) ↑
FLQ VS. AZM	≤ 30 days	0.87(0.73,1.03)	1.14(0.54,2.39)	0.83(0.68,1.02)	0.98(0.70,1.37)	2.35(2.18,2.53) ↑
	31 – 60 days	0.99(0.82,1.19)	0.06(0.04,0.09) ↓	0.93(0.75,1.16)	1.06(0.75,1.49)	1.94(1.77,2.13) ↑
	≥ 61 days	0.93(0.90,0.96) ↓	1.10(0.91,1.34)	0.91(0.88,0.94) ↓	1.00(0.93,1.08)	1.29(1.25,1.32) ↑
FLQ VS. LEX	≤ 30 days	0.66(0.55,0.78) ↓	0.68(0.32,1.42)	0.70(0.57,0.87) ↓	0.47(0.34,0.66) ↓	1.80(1.67,1.95) ↑
	31 – 60 days	0.85(0.70,1.04)	0.05(0.03,0.09) ↓	0.80(0.64,1.01)	0.99(0.68,1.44)	1.48(1.34,1.64) ↑
	≥ 61 days	0.92(0.89,0.95) ↓	1.13(0.92,1.40)	0.92(0.89,0.96) ↓	0.86(0.80,0.93) ↓	1.06(1.03,1.09) ↑
FLQ VS. AMC	≤ 30 days	0.93(0.77,1.11)	1.05(0.48,2.32)	0.96(0.77,1.19)	0.72(0.51,1.02)	1.37(1.27,1.48) ↑

31 – 60 days	0.94(0.77,1.15)	0.04(0.02,0.07)↓	0.90(0.72,1.14)	1.24(0.83,1.86)	1.19(1.08,1.31)↑
≥ 61 days	0.93(0.90,0.97)↓	1.19(0.95,1.49)	0.93(0.89,0.96)↓	0.98(0.90,1.06)	1.06(1.03,1.09)↑

Abbreviations: HR, hazard ratio; CI, confidence interval; FLQ, fluoroquinolone; CIP, ciprofloxacin; LVX, levofloxacin; MXF, moxifloxacin; AMX, Amoxicillin; AMC, Amoxicillin Clavulanate; AZT, Azithromycin; LEX, Cephalexin.

↑= significantly high with P-value < 0.001, ↑= significantly high with 0.001 ≤ P-value < 0.05

↓= significantly low with P-value < 0.001, ↓= significantly high with 0.001 ≤ P-value < 0.05

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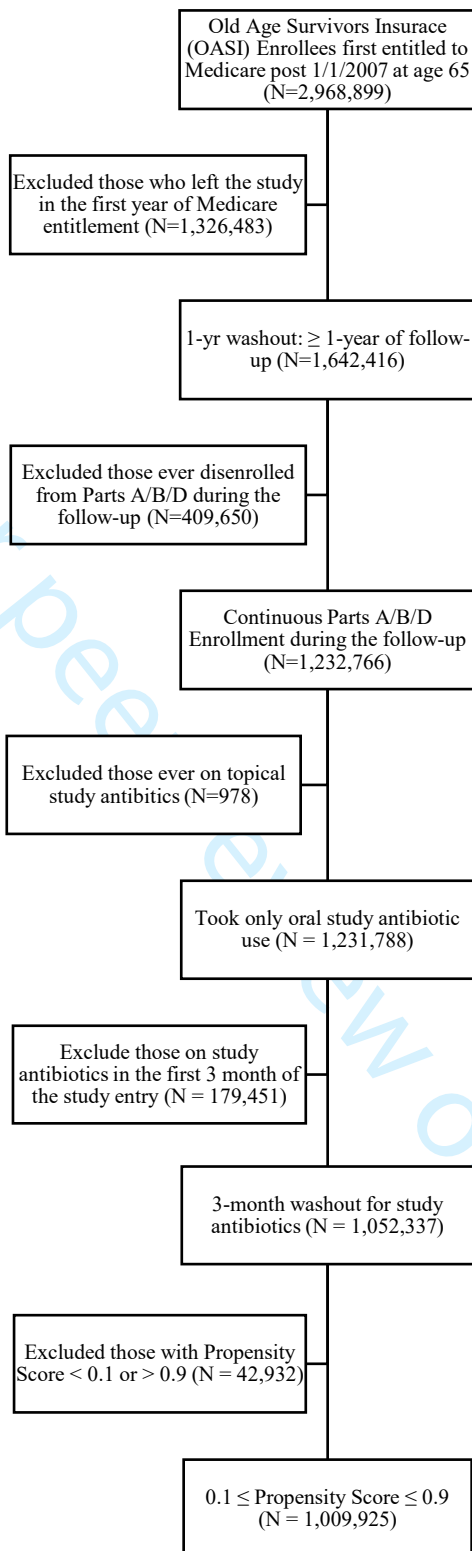
Table 4. Pairwise Comparisons

Comparison	Temporal Exposure	Any Tendon Rupture	Achilles Tendon Rupture	Complete Rupture of Rotator Cuff	Other Tendon Rupture	Death (Competing risk)
		HR(95% CI)	HR(95% CI)	HR(95% CI)	HR(95% CI)	HR(95% CI)
HRs comparing use of each FQ with use of each non-FQ antibiotics in a ≤30-day window						
CIP VS. LVX	≤ 30 days	0.84(0.75,0.94)↓	0.48(0.27,0.86) ↓	0.82(0.73,0.94) ↓	0.87(0.67,1.15)	0.67(0.63,0.71)↓
CIP VS. MXF	≤ 30 days	1.63(1.02,2.61)↑	1.08(0.16,7.29)	1.84(1.05,3.24)↑	1.10(0.47,2.60)	0.72(0.62,0.83)↓
LVX VS. MXF	≤ 30 days	1.95(1.21,3.13)↑	2.26(0.34,15.17)	2.24(1.27,3.94)↑	1.26(0.53,3.01)	1.07(0.93,1.24)
CIP VS. AMX	≤ 30 days	1.11(1.01,1.23)↑	1.20(0.66,2.16)	1.09(0.97,1.21)	1.06(0.84,1.34)	2.23(2.05,2.44)†
CIP VS. AZM	≤ 30 days	0.97(0.87,1.06)	0.91(0.53,1.57)	0.96(0.86,1.07)	0.96(0.77,1.21)	1.84(1.71,1.97)†
CIP VS. LEX	≤ 30 days	0.73(0.66,0.81)↓	0.55(0.31,0.95) ↓	0.81(0.72,0.91)↓	0.47(0.37,0.59)†	1.41(1.31,1.52)†
CIP VS. AMC	≤ 30 days	1.03(0.91,1.16)	0.84(0.46,1.56)	1.10(0.96,1.25)	0.71(0.56,0.92)↓	1.07(1.00,1.15)
LVX VS. AMX	≤ 30 days	1.33(1.19,1.49)†	2.50(1.45,4.29)↑	1.32(1.16,1.49)†	1.22(0.93,1.59)	3.34(3.07,3.64)†
LVX VS. AZM	≤ 30 days	1.15(1.03,1.29)↑	1.91(1.13,3.23)↑	1.16(1.03,1.31)↑	1.10(0.84,1.44)	2.75(2.57,2.95)†
LVX VS. LEX	≤ 30 days	0.87(0.78,0.98) ↓	1.14(0.68,1.92)	0.98(0.86,1.12)	0.54(0.41,0.69)†	2.11(1.97,2.27)†
LVX VS. AMC	≤ 30 days	1.23(1.08,1.40)↑	1.76(0.98,3.15)	1.33(1.15,1.54)†	0.82(0.62,1.08)	1.60(1.49,1.72)†
MXF VS. AMX	≤ 30 days	0.68(0.43,1.09)	1.10(0.16,7.41)	0.59(0.34,1.03)	0.96(0.41,2.27)	3.12(2.67,3.65)†
MXF VS. AZM	≤ 30 days	0.59(0.37,0.94) ↓	0.84(0.13,5.65)	0.52(0.30,0.91)↓	0.88(0.37,2.07)	2.57(2.21,2.98)†
MXF VS. LEX	≤ 30 days	0.45(0.28,0.72) ↓	0.50(0.08,3.35)	0.44(0.25,0.77)↓	0.43(0.18,1.00)	1.97(1.70,2.29)†
MXF VS. AMC	≤ 30 days	0.63(0.39,1.01)	0.78(0.11,5.33)	0.60(0.34,1.05)	0.65(0.28,1.53)	1.50(1.29,1.73)†
HRs comparing use of FQ as a class with use of each non-FQ antibiotics across different time window						
FLQ VS. AMX	Overall	0.98(0.90,1.07)	0.49(0.36,0.68)	0.95(0.86,1.06)	1.01(0.86,1.19)	1.95(1.86,2.05)†
FLQ VS. AZM	Overall	0.93(0.85,1.01)	0.42(0.30,0.57)	0.89(0.80,0.98)↓	1.01(0.86,1.19)	1.80(1.73,1.88)†
FLQ VS. LEX	Overall	0.80(0.73,0.88)	0.34(0.24,0.47)	0.80(0.72,0.89)	0.74(0.62,0.88)	1.42(1.35,1.48)†
FLQ VS. AMC	Overall	0.93(0.85,1.02)	0.37(0.26,0.52)	0.93(0.83,1.03)	0.96(0.80,1.15)	1.20(1.15,1.25)†

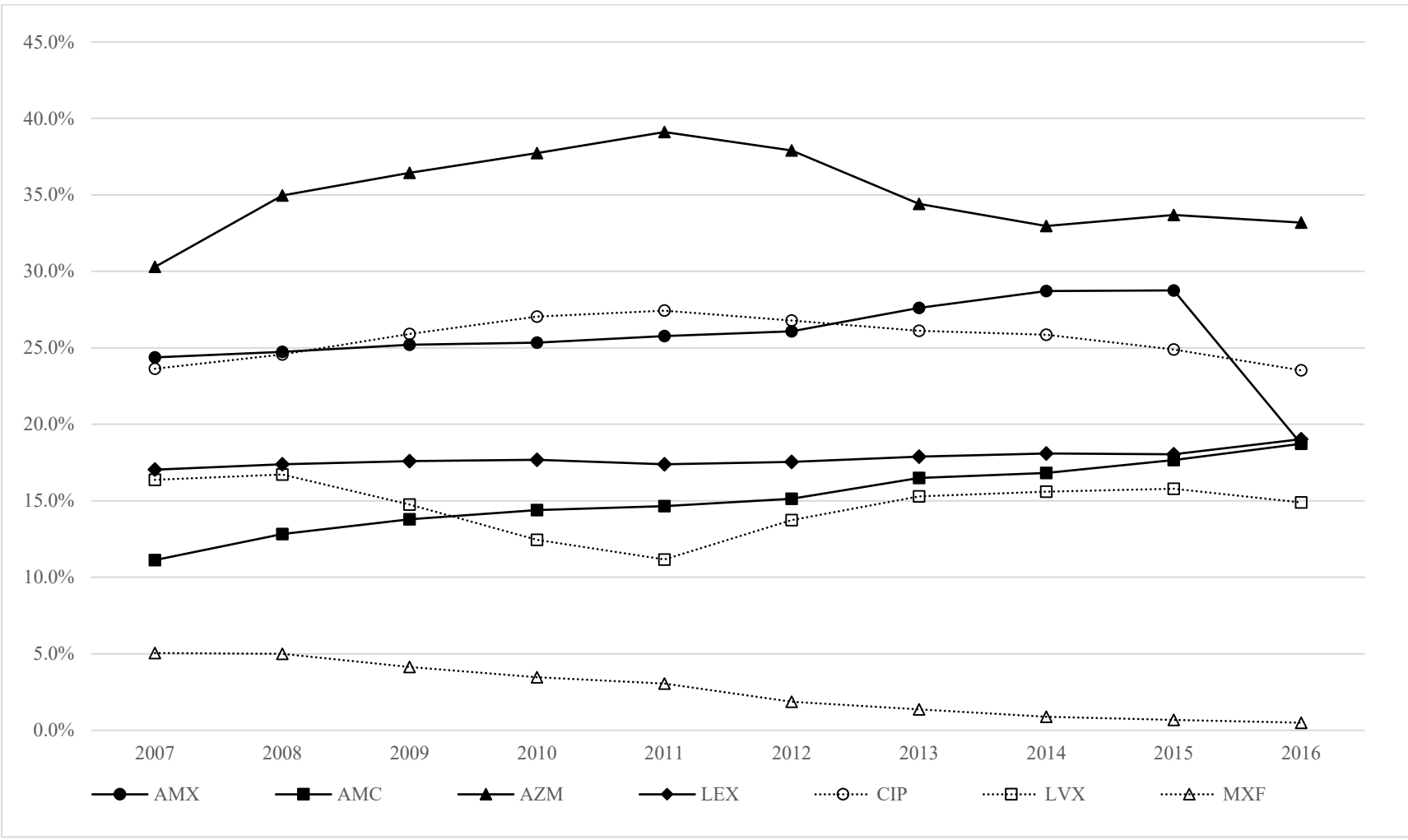
Abbreviations: HR, hazard ratio; CI, confidence interval; FLQ, fluoroquinolone; CIP, ciprofloxacin; LVX, levofloxacin; MXF, moxifloxacin; AMX, Amoxicillin; AMC, Amoxicillin Clavulanate; AZT, Azithromycin; LEX, Cephalexin.

†= significantly high with P-value < 0.001, †= significantly high with 0.001 ≤ P-value < 0.05

‡= significantly low with P-value < 0.001, ‡= significantly high with 0.001 ≤ P-value < 0.05



Supplementary Figure. Secular Trend of Study Antibiotic Use



X-axis: Calendar year.

Y-axis: % of patients on each drug class.

STROBE Statement—Checklist of items that should be included in reports of *case-control studies*

	Item No	Recommendation	Page No
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	1
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(a) Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls	6
		(b) For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7
Bias	9	Describe any efforts to address potential sources of bias	8-9
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	7-9
		(b) Describe any methods used to examine subgroups and interactions	n/a
		(c) Explain how missing data were addressed	n/a
		(d) If applicable, explain how matching of cases and controls was addressed	n/a
		(e) Describe any sensitivity analyses	n/a
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	9
		(b) Give reasons for non-participation at each stage	9
		(c) Consider use of a flow diagram	9
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9-10
		(b) Indicate number of participants with missing data for each variable of interest	n/a
Outcome data	15*	Report numbers in each exposure category, or summary measures of exposure	10

