The incidence of collagen-associated adverse events in pediatric population with the use of Fluoroquinolones: a nationwide cohort study in Taiwan

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fluoroquinolones (FQs), pediatric patients, collagen-associated adverse effects, prescription safety issue
Abstract

Background: To evaluate the safety of using fluoroquinolones (FQs) in pediatric population in Taiwan.

Methods: Patients aged 0~18-year-old with FQs prescriptions ≥3 consecutive days during year 2000 to 2013 were selected from the National Health Insurance Research Database, 4-time case number were selected as controls. We evaluated the patient’s outcome after the use of FQs by reviewing a newly diagnosis of the following collagen-associated adverse events by ICD-9-CM codes, covering tendons rupture, retinal detachments, gastrointestinal tract perforation, aortic aneurysm or dissection.

Results: Of the enrolled patients (n=167,105), collagen-associated adverse effects developed in 85 cases (0.051%) in 6-month tracking, including 0.051% in the FQs study cohort (17 in 33,421) and 0.051% (68 in 133,684) in the FQs free comparison cohort. The crude HR for collagen-associated adverse events in the FQs group was 0.997 (0.586-1.696; p=0.990). After adjusting for age, sex, catastrophic illness, low-income household, seasons, levels of urbanization, and healthcare, the corrected HR in 6-month tracking with FQs was 1.360 (95% CI; 0.795-2.326; p=0.261).

Conclusions: There is no significant difference of collagen-associated adverse effects between FQs group and FQs free group from our data. We propose that FQs for pediatric population in clinical practice may be not so harmful as previous references reported.

Background

Fluoroquinolones (FQs) are effective antimicrobial agents by directly inhibiting the
process of bacterial DNA synthesis. With the broad-spectrum antibacterial coverage, they are widely used in bacterial infections, like acute bacterial sinusitis, acute bacterial exacerbations of chronic bronchitis, and uncomplicated urinary tract infections for adults. In addition to the strength of broad-spectrum antibacterial coverage, other advantages, such as high oral bioavailability, large volume of distribution, ideal tissue penetration and long-lasting medicine, make FQs a favorable choice in treating infectious diseases. (1,2)

However, FQs are not the first choice in clinical guideline for treating infectious diseases, since they have been reported to be associated with collagen degradation, which may lead to severe and detrimental adverse effects like tendon ruptures, retinal detachments, gastrointestinal tract perforation, even aortic aneurysms in adults. (3–7) FQs were previously found to cause apoptotic changes in extracellular matrix and significantly decrease collagen type I and the β1-integrin receptors. (8) Collagen defects-related tissue damages are found not only in tendons, but also tissues composed of collagen, such as aortic wall, gastrointestinal tract, and retina. (5,9,10) All of these findings attribute to the cause of collagen-associated adverse effects. To alarm the risks of adverse effects of FQs, the U.S. FDA declared several warnings containing potential tendinitis, tendon ruptures, and even irreversible peripheral neuropathy. (11,12)

On the other hand, the original toxicological studies with quinolones documented the cartilage injury in weight-bearing joints in canine puppies. (13) With the concern of potential negative impacts on musculoskeletal development in growing children, systemically administered FQs are not recommended for routine use in children younger than 18 years old except for some complicated and complex infectious diseases cases. (14) To follow the clinical guidelines recommendations in treating
infectious diseases in children (15), the physicians tend to reserve the prescriptions of FQs as the last line antibiotics to tackle with fulminant and invasive bacterial infections at hospitals in Taiwan.

Although the use of FQs to treat bacterial infection in pediatric population has been decreasing with time, there is still a small pediatric group who needs FQs for treating serious and multiple drug-resistant bacterial infections rising in the community. (16,17) For this reason, it is urgently needed to evaluate the safety of FQs in clinical use. After reviewing the literatures, we found that most of the study subjects for adverse effects of FQs were over than 18-year old patients. (3–5,7,18) By contrast, there are still a few publications reporting benefits for using FQs in children. (19, 20) Since the lack of sufficient evidence-based articles found in pediatric population, the purpose of our study is to investigate the safety issue of FQs-induced collagen-associated adverse effects at the young age group.

Methods

Data sources

We performed a cohort study by using the National Health Insurance Research Database (NHIRD) of Taiwan. The National Health Insurance (NHI) system of Taiwan covers more than 99.6% of the Taiwanese population. (21) This database is representative of the population in Taiwan, and always used in generating evidence to support clinical decisions or healthcare policy-making. (22) All data from primary outpatient departments and inpatient hospital care settings after year 2000 were included in this database. This longitudinal health insurance database in year 2000-2013 in Taiwan was collected by randomly selecting individuals from the registry for beneficiaries of the NHI program. It contains complete outpatient and inpatient
electronic claim records, individual diagnoses, procedures, and medicine prescription. This database is commonly used in several population-based studies and pharmacoepidemiologic research in Taiwan. (https://nhird.nhri.org.tw/)

**Medication exposure and patient identification**

In this study, medication exposure is defined as receiving FQs in either oral or intravenous form of the following active compounds including ciprofloxacin, levofloxacin, ofloxacin, gemifloxacin, norfloxacin, and moxifloxacin. The prescription period is equal to (or longer than) three consecutive days to correspond with the inclusion criteria.

We utilized data between year 2000 and 2013 from NHIRD of a sub-dataset, longitudinal health insurance database (n = 989,753). All patients aged 0~18 years old with FQs prescriptions ≥3 consecutive days after January 1, 2000 were selected and included into this cohort. The patients without tracking information, with missing data on gender, those ever received FQs before index date, had collagen-associated adverse events, and primary or secondary collagen diseases prior to enrollment were excluded. Also, we excluded cases with the diagnosis of appendicitis (ICD-9-CM code: 540-543), peritonitis (ICD-9-CM code: 567), and typhoid fever (ICD-9-CM code: 002) because the symptoms of these diseases are similar to one of the primary outcomes (GI perforation) in this study. (4) Overall, the totally enrolled cases with the use of FQs were 33,421 individuals. Propensity score matching was used for selecting control group, and 4-fold case number were selected. (**Figure 1.**)

**Figure 1.** The flowchart of study sample selection.

**Outcome**

All of the diseases and adverse effects were defined by International Classification.
of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM). The outcome was evaluated and defined by the newly diagnosis of the collagen-associated adverse events, including tendons rupture (727.6), retinal detachments (361.0), gastric perforation (531.1, 531.2, 531.5, 531.6, 532.1, 532.2, 532.5, 532.6, 533.1, 533.2, 533.5, 533.6, 534.1, 534.2, 534.5, and 534.6), small or large intestinal perforation (569.83) (4), aortic aneurysm (441.1, 441.2, 441.3, 441.4, 441.5, 441.6, 441.7, and 441.9), and aortic dissection (441.0, 441.00, 441.01, 441.02, and 441.03). (18)

Covariates
In order to be as comprehensive as possible in adjusting for factors that might confound the studied association, we identified several covariates such as catastrophic illness to adjust the baseline health conditions of selected patients, and low-income household for individual financial conditions. Moreover, we also adjusted for selected other variables such as seasons, levels of urbanization and healthcare for minimizing potential biases.

Statistical analysis
Statistical analyses were performed using Chi-square/Fisher exact test on category variables and t-test on continuous variables. Characteristics and outcome events of cohort patients for the FQs and FQs free groups are reported as number and percentage, mean and standard deviation, as appropriate. The Kaplan-Meier analysis and log-rank test were used for calculating the cumulative incidence rates of collagen-associated adverse events between FQs group and FQs-free group. The multivariable Cox proportional hazard model was used to estimate the hazard ratio (HR) of collagen-associated adverse events associated with the use of FQs. Our definition of significant level was 0.05 to detect differences in collagen-associated adverse events between FQs group and FQs-free group. All analyses were performed
with SPSS version 22.

Results

This study involved a total of 33,421 for the FQs group and 133,684 for the FQs free controls. Of the enrolled patients (n=167,105), collagen-associate adverse effects developed in 85 (0.051%) in 6-month tracking, including 0.051% in the FQs study cohort (17 in 33,421) and 0.051% (68 in 133,684) in the FQs-free comparison cohort.

Baseline characteristics of patients

Baseline characteristics of case patients and comparators are listed in the Table 1. There were no significant differences between the FQs group and FQ-free group in the distributions of age and sex, but the proportion of catastrophic illness was slightly higher in the FQs group than the FQs-free groups (0.6 vs. 0.38).

Table 1. Characteristics of study

Collagen-associated adverse events

In the cohort, we did not observe any case of tendons rupture, retinal detachments, aortic aneurysms, and aortic dissection. Patients with collagen-associated adverse events (GI perforation) in FQs group included 1 individual in 7-day tracking, 3 individuals in 14-days tracking, 4 individuals in 28-days tracking, 12 individuals in 3-month tracking, and 17 individuals in 6-month tracking. However, patients with collagen-associated adverse events (GI perforation) in FQs free group were 2 individuals in 3-days tracking, 6 individuals in 7-days tracking, 10 individuals in 14-days tracking, 45 individuals in 3-month tracking, 68 individuals in 6-month tracking. (Figure.1) The crude HR for collagen-associated adverse events in FQs group was 0.997 (95% CIs; 0.586-1.696; p=0.990). (Table 2.)
Table 2. Factors of Gi perforation in 6-month tracking by using Cox regression.

Risk of collagen-associated adverse events

After adjusting for age, sex, catastrophic illness, low-income household, seasons, levels of urbanization and healthcare, the adjusted HR for collagen-associated adverse events in FQs group was 1.360 (95% CI; 0.795-2.326; p=0.261). After multivariate analysis, we noticed that patient’s age was associated with the risk of GI perforation. As shown in Table 2, the risk of collagen-associate adverse effect was lower in patients aged 5~9 years old (aHR=0.442; 95% CI=0.183-0.973; p=0.043), patients aged 10~14 years old (aHR=0.394; 95% CI=0.167-0.930; p=0.034).

Subgroup analyses

Stratified by baseline demographic data, catastrophic illness, low-income household, seasons, levels of urbanization and healthcare

The association of fluoroquinolones with subsequent GI perforation was stratified by baseline demographic, catastrophic illness, low-income household, seasons, levels of urbanization and healthcare. Analyses of factors of GI perforation in 6-month tracking stratified by the aforementioned variables were performed by Cox regression as shown in Table 3. We did not observe any statistically significant difference between FQs group and FQs-free group after subgroup analyses of gender, age, catastrophic illness, low-income household, seasons, levels of urbanization and healthcare.

Table 3. Factors of Gi perforation in 6-month tracking by variables listed in the table by using Cox regression.

Stratified by fluoroquinolones

Also, we did the subgroup analysis to confirm the association of FQs subgroup with
subsequent GI perforation in different tracking periods by using Cox regression. In 3-day tracking period, we observed 2 events from FQs-free group. In 7-day tracking period, we observed 1 event from ofloxacin in the FQs group, and 6 events from FQs-free group. In 14-day tracking period, we observed 1 event from ciprofloxacin, 1 event from norfloxacin, and 1 event from ofloxacin in the FQs group, and 10 events from FQs-free group. In 28-day tracking period, we observed 1 event from ciprofloxacin, 1 event from norfloxacin, 2 events from ofloxacin in the FQs group, and 14 events from FQs-free group. In 3-month tracking period, we observed 1 event from ciprofloxacin, 3 events from norfloxacin, and 8 events from ofloxacin in the FQs group, and 45 events from FQs-free group. In 6-month tracking period, we observed 1 event from ciprofloxacin, 3 events from norfloxacin, and 13 events from ofloxacin in the FQs group, and 68 events from FQs-free group. The incidence rate and adjusted HR are listed in Table 4. None of them were statistically significant difference between FQs group and FQs-free group.

Table 4. Factors of GI perforation stratified by Fluoroquinolones subgroup in different tracking period by using Cox regression.

Discussion

Fluoroquinolones are highly effective antimicrobial agents with the following advantages: a broad spectrum of bactericidal activity, ideal bioavailability, both oral and intravenous formulations, high serum levels and a large volume of distribution. These advantages increase the FQs usage in a wide variety of infectious diseases, including skin and respiratory infections for adults. However; the post-marketing surveillance data indicates that FQs may cause subsequent collagen-associated adverse events. Since year 2008, the U.S. FDA has declared several warnings about
the association of FQs with disabling and potentially permanent side effects involving tendons, muscles, joints, nerves and the central nervous system in succession. (23) Additionally, due to the toxic effects observed from juvenile animals treated with FQs, the use of FQ-related drugs became rather limited in pediatric population. (13) Only ciprofloxacin and levofloxacin are approved by the U.S. FDA for the treatment of inhalation anthrax, complicated UTIs, and pyelonephritis in children aged 1 to 17 years old. (15) On the other hand, with the overuse of antimicrobial agents in clinical practice, the emergence of antibiotic resistant bacteria is rising in Taiwan. (24) To overcome the surge of drug resistant issues, the use of FQs is also increasing. To evaluate the safety issue of FQs, it is timely relevant for us to investigate serious collagen-associated adverse events in pediatric population.

The main findings of our study demonstrated that there was no difference in the risk of collagen-associated adverse events between FQs group and FQs-free group in pediatric population. By reviewing published studies, (3-7, 18) we realized that the reported higher risk of collagen-associate adverse effect in FQs-related cases were found in patients at the age of over 18 years old. However, most of these studies were designed in case-control studies and the subjects were patients older than 18 years old. (3-7, 18) After comparing the difference between our findings and previous reported results, we made the following to several explanations:

(i) The study design: the subjects from case-control studies were identified by evaluating the outcome status at the outset of the investigation. Enrolled cases with the outcome of interest are matched with a control group without it. The major and inevitable problems in case-control studies are the sampling bias, observation bias and recall bias. In contrast, cohort studies are usually used to confirm the disease
incidence, causes, and prognosis. Cohort studies are often utilized for measuring events in chronological order and clarifying the relationship between cause and effect. (25, 26) Consequently, we designed our study in the form of cohort study to assess the association between use of FQs and effect of collagen-associated adverse events. We believe that this cohort study provides more objective and reliable information than case-control studies.

(ii) Dosage adjustment and rigorous monitoring in pediatric population: dosage of FQs is calculated and adjusted for by body weight in children before prescriptions. Maximum dosage limitation is advised by clinical guideline and FDA. (15) Meanwhile, healthcare providers usually follow the recommendation strictly because of the concern of the adverse effects to this vulnerable population. Furthermore, physicians tend to avoid this class of antimicrobial agents in clinical practice and preserve them as the final therapy for difficult and serious bacterial infections. Therefore, the side effects become much less as expected attributing to precise dosage and strict indication.

(iii) Comorbidity in elderly population: with regard to most of the FQs studies, (3-7, 18) the enrolled subjects were older than 18 years old, especially the elderly population with comorbidities, like cardiovascular diseases and diabetes. (27) For example, cardiovascular diseases such as hypertension and hyperlipidemia, make the blood vessels more vulnerable and subsequently increase the risk of aortic aneurysms. (28) Patients with diabetes have more problematic blood vessels and retinopathy, which increases the risk of retinal detachments. (29, 30) Thus, these underlying diseases may contribute to the side effects of FQs to some extent in elderly population, but much seldom in younger generation. These observational findings may partially explain why we found that pediatric patients in our cohort
have less side effects compared with previous reports. Though our findings differ from the previous studies, we believe that it reflects the real clinical situations in pediatric population by meticulously analyzing the database resource in Taiwan. The National Health Insurance Research Database (NHIRD) of Taiwan, which covers more than 99.6% of the Taiwanese population, makes our study results more statistically powerful and representative. (21) NHIRD has been also widely used in generating evidences to support clinical decisions or healthcare policy-making. (22)

Several limitations of the study should be noted. First, we are not sure about the compliance of the OPD patients because some of them may discontinue oral form of FQs abruptly. (31) It may cause underestimation of the adverse effects of FQs because the patients did not complete the treatment course. According to the results from previous studies, up to 52.7% of subjects reported that they did not precisely follow the physicians’ advice about antibiotics use. (32) Second, the clinical conditions and underlying diseases of the enrolled cases during the observation period were not available. Underlying illness and chronic diseases may predispose to develop the collagen-associated adverse effects significantly. Third, no supportive image reports and laboratory data from each medical record to confirm the diagnosis of collagen-associated adverse effects, we defined the outcome in this study by reviewing the registration of ICD-9-CM codes. The potential misclassification bias cannot be ruled out in our study. (33) Despite the potential limits, our study also has some strengths. The results of this study are based on a real-world database analysis. The enormous number of prescriptions records makes the results more reliable and unbiased. In addition, we tracked the patient’s outcome up to 6 months to see the long-term impact of the FQs exposure.
Conclusions

We designed this population-based, retrospective cohort study to evaluate the safety of FQs in pediatric population in Taiwan. In this study, we did not observe any statistically significant difference in the incidence of collagen-associated adverse events between FQs group and FQs-free group. FQs use in pediatric patients seems safe under instruction on the basis of our findings. Therefore, the risk of collagen-associated adverse events in pediatric population may be overestimated in previous studies. Since physicians still need FQs to treat serious and fulminant bacterial infections in children, our data suggests that physicians may prescribe FQs in seriously infected young patients as indicated in the guideline.

List of Abbreviations

Fluoroquinolones (FQ); National Health Insurance (NHI); National Health Insurance Research Database (NHIRD); International Classification of Diseases, Ninth Revision, Clinical Modification (ICD–9-CM); person-days (PDs); hazard ratio (HR); adjusted hazard ratio (aHR): confidence interval (CI)

Declarations

Ethics approval and consent to participate

This study was conducted following the Code of Ethics of the World Medical Association (Declaration of Helsinki). The Institutional Review Board of Tri-Service General Hospital approved this study and waived the need for individual written informed consent because all participants’ ID was removed or properly concealed (TSGH IRB No.2-105-05-082).
Consent for publication

Not applicable.

Availability of data and materials

The data that support the findings of this study are available from National Health Insurance Research Database (NHIRD) of Taiwan but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

PY and CH conceptualized and designed the study, drafted the initial manuscript, and reviewed and revised the manuscript.

JL, CC, and WC designed the data collection instruments, collected data, carried out the initial analyses, and reviewed and revised the manuscript.

CS and WC conceptualized and designed the study, coordinated and supervised data collection, and critically reviewed the manuscript for important intellectual content. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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References

1. Lode H, Hoffken G, Boeckk M, Deppermann N, Borner K, Koepppe P. Quinolone pharmacokinetics and metabolism. J Antimicrob Chemother. 1990;26 Suppl B:41–9.

2. Mant TG. Multiple-dose pharmacokinetics of lomefloxacin: rationale for once-a-day dosing. Am J Med. 1992;92(4a):26s–32s.

3. Daneman N, Lu H, Redelmeier DA. Fluoroquinolones and collagen associated severe adverse events: a longitudinal cohort study. BMJ open. 2015;5(11):e010077.

4. Hsu SC, Chang SS, Lee MG, Lee SH, TsaiYW, Lin SC, et al. Risk of gastrointestinal perforation in patients taking oral fluoroquinolone therapy: An analysis of nationally representative cohort. PloS one. 2017;12(9):e0183813.

5. Etminan M, Forooghian F, Brophy JM, Bird ST, Maberley D. Oral fluoroquinolones and the risk of retinal detachment. Jama. 2012;307(13):1414–9.

6. Stephenson AL, Wu W, Cortes D, Rochon PA. Tendon Injury and Fluoroquinolone Use: A Systematic Review. Drug Saf. 2013;36(9):709–21.

7. Pasternak B, Inghammar M, Svanstrom H. Fluoroquinolone use and risk of aortic aneurysm and dissection: nationwide cohort study. Bmj. 2018;360:k678.

8. Sendzik J, Shakibaei M, Schafer-Korting M, Stahlmann R. Fluoroquinolones cause changes in extracellular matrix, signalling proteins, metalloproteinases and caspase-3 in cultured human tendon cells. Toxicology. 2005;212(1):24–36.

9. Sykes EM, Jr. Colon perforation in Ehlers-Danlos syndrome. Report of two cases and review of the literature. Am J Surg. 1984;147(3):410–3.

10. Germain DP. Clinical and genetic features of vascular Ehlers-Danlos syndrome. Ann Vasc Surg. 2002;16(3):391–7.

11. Administration. USFaD. FDA warns about increased risk of ruptures or tears in
the aorta blood vessel with fluoroquinolone antibiotics in certain patients [Available from: https://www.fda.gov/drugs/drug-safety-and-availability/fda-warns-about-increased-risk-ruptures-or-tears-aorta-blood-vessel-fluoroquinolone-antibiotics.

12. Administration. USFaD. FDA Drug Safety Communication: FDA updates warnings for oral and injectable fluoroquinolone antibiotics due to disabling side effects [Available from: https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-fda-updates-warnings-oral-and-injectable-fluoroquinolone-antibiotics.

13. Jackson MA, Schutze GE. The Use of Systemic and Topical Fluoroquinolones. Pediatrics. 2016;138(5).

14. Pediatric Infectious Diseases Society of Taiwan CHRC, National Health Research Institutes. Recommendations for the Use of New Quinolone Antibiotics in Children.

15. Patel K, Goldman JL. Safety Concerns Surrounding Quinolone Use in Children. Journal of clinical pharmacology. 2016;56(9):1060-75.

16. Yi FH. The Prescribing Pattern of Fluoroquinolone in Pediatric Patients in Taiwan. Tainan City: National Cheng Kung University; 2013.

17. Pediatric Infectious Diseases Society of Taiwan CHRC, National Health Research Institutes. Recommendations for the Diagnosis and Management of Acute Otitis Media in Children [Available from: http://www.pids.org.tw/index.php?route = news/news_detail&news_id = 96.

18. Lee CC, Lee MT, Chen YS, Lee SH, Chen YS, Chen SC, et al. Risk of Aortic Dissection and Aortic Aneurysm in Patients Taking Oral Fluoroquinolone. JAMA Intern Med. 2015;175(11):1839-47.

19. Dixit A, Karandikar MV, Jones S, Nakamura MM. Safety and Tolerability of Moxifloxacin in Children. J Pediatric Infect Dis Soc. 2018;7(3):e92-e101.
20. Choi S-H, Kim EY, Kim Y-J. Systemic use of fluoroquinolone in children. Korean Journal of Pediatrics. 2013;56(5):196-201.

21. Lin L-Y, Warren-Gash C, Smeeth L, Chen P-C. Data resource profile: the National Health Insurance Research Database (NHIRD). Epidemiol Health. 2018;40:e2018062-e.

22. Hsieh C-Y, Su C-C, Shao S-C, Sung S-F, Lin S-J, Kao Yang Y-H, et al. Taiwan’s National Health Insurance Research Database: past and future. Clin Epidemiol. 2019;11:349-58.

23. Administration. USFDA. FDA updates warnings for fluoroquinolone antibiotics [Available from: https://www.fda.gov/news-events/press-announcements/fda-updates-warnings-fluoroquinolone-antibiotics.

24. Wu CT, Lee HY, Chen CL, Tuan PL, Chiu CH. High prevalence and antimicrobial resistance of urinary tract infection isolates in febrile young children without localizing signs in Taiwan. J Microbiol Immunol Infect. 2016;49(2):243-8.

25. Mann CJ. Observational research methods. Research design II: cohort, cross sectional, and case-control studies. Emergency Medicine Journal. 2003;20(1):54-60.

26. Song JW, Chung KC. Observational studies: cohort and case-control studies. Plast Reconstr Surg. 2010;126(6):2234-42.

27. Lloyd-Jones DM, Larson MG, Beiser A, Levy D. Lifetime risk of developing coronary heart disease. Lancet. 1999;353(9147):89-92.

28. Sidloff D, Choke E, Stather P, Bown M, Thompson J, Sayers R. Mortality from thoracic aortic diseases and associations with cardiovascular risk factors. Circulation. 2014;130(25):2287-94.

29. Cheung N, Mitchell P, Wong TY. Diabetic retinopathy. The Lancet. 2010;376(9735):124-36.
30. Marso SP, Hiatt WR. Peripheral Arterial Disease in Patients With Diabetes. Journal of the American College of Cardiology. 2006;47(5):921-9.

31. Kardas P. Noncompliance in Current Antibiotic Practice. Infectious Diseases in Clinical Practice. 2006;14(4):S11-S4.

32. Chen C, Chen YM, Hwang KL, Lin SJ, Yang CC, Tsay RW, et al. Behavior, attitudes and knowledge about antibiotic usage among residents of Changhua, Taiwan. J Microbiol Immunol Infect. 2005;38(1):53-9.

33. Mazzali C, Duca P. Use of administrative data in healthcare research. Intern Emerg Med. 2015;10(4):517-24.

Tables

| Table 1. Characteristics of study |
|-----------------------------------|
| Fluoroquinolone                  | Total | With |
| Variables                        | n     | %    | n    | %    |
| Total                            | 167,105 |     | 33,421 | 20.00 |
| Collagen-associated adverse events |       |     |       |      |
| Without                          | 167,020 | 99.95 | 33,404 | 99.95 |
| With                             | 85      | 0.05  | 17     | 0.05  |
| Collagen-associated adverse events subgroup |     |     |       |      |
| Without                          | 167,020 | 99.95 | 33,404 | 99.95 |
| Tendons rupture                  | 0      | 0.00  | 0      | 0.00  |
| Retinal detachments              | 0      | 0.00  | 0      | 0.00  |
| Gl perforation                   | 85     | 0.05  | 17     | 0.05  |
| AA / AD                          | 0      | 0.00  | 0      | 0.00  |
| Gender                           |       |     |       |      |
| Male                             | 85,990 | 51.46 | 17,198 | 51.46 |
| Female                           | 81,115 | 48.54 | 16,223 | 48.54 |
| Age (years)                      | 9.78 ± 5.58 | | 9.83 ± 5.35 | |
| Age group (years) | Count  | % | Count  | % |
|------------------|--------|---|--------|---|
| <1               | 5,100  | 3.05 | 1,020  | 3.05 |
| 1                | 7,145  | 4.28 | 1,429  | 4.28 |
| 2                | 7,970  | 4.77 | 1,594  | 4.77 |
| 3                | 9,060  | 5.42 | 1,812  | 5.42 |
| 4                | 10,680 | 6.39 | 2,136  | 6.39 |
| 5-9              | 46,670 | 27.93| 9,334  | 27.93|
| 10-14            | 42,785 | 25.60| 8,557  | 25.60|
| ≥15              | 37,695 | 22.56| 7,539  | 22.56|

| Catastrophic illness | Count  | %  | Count  | %  |
|----------------------|--------|---|--------|---|
| Without              | 166,398| 99.58 | 33,222 | 99.40 |
| With                 | 707    | 0.42  | 199    | 0.60  |

| Low-income household | Count  | %  | Count  | %  |
|----------------------|--------|---|--------|---|
| Without              | 164,089| 98.20 | 32,561 | 97.40 |
| With                 | 3,016  | 1.80  | 860    | 2.57  |

| Season               | Count  | %  | Count  | %  |
|----------------------|--------|---|--------|---|
| Spring (Mar - May)   | 43,867 | 26.25| 8,757  | 26.24|
| Summer (Jun - Aug)   | 42,836 | 25.63| 8,435  | 25.24|
| Autumn (Sep - Nov)   | 41,287 | 24.71| 8,289  | 24.82|
| Winter (Dec - Feb)   | 39,115 | 23.41| 7,940  | 23.76|

| Location             | Count  | %  | Count  | %  |
|----------------------|--------|---|--------|---|
| Northern Taiwan      | 74,080 | 44.33| 11,139 | 33.33 |
| Middle Taiwan        | 46,900 | 28.07| 11,100 | 33.21 |
| Southern Taiwan      | 39,124 | 23.41| 9,994  | 29.96 |
| Eastern Taiwan       | 5,748  | 3.44 | 795    | 2.38  |
| Outlets islands      | 1,253  | 0.75 | 393    | 1.18  |

| Urbanization level   | Count  | %  | Count  | %  |
|----------------------|--------|---|--------|---|
| 1 (The highest)      | 45,240 | 27.07| 7,343  | 21.97 |
| 2                    | 62,222 | 37.24| 11,929 | 35.66 |
| 3                    | 27,980 | 16.74| 6,433  | 19.25 |
| 4 (The lowest)       | 31,663 | 18.95| 7,716  | 23.05 |
### Level of care

| Hospital center          | 7,559 | 4.52 | 1,268 | 3.79 |
|--------------------------|-------|------|-------|------|
| Regional hospital        | 11,858| 7.10 | 1,939 | 5.80 |
| Local hospital           | 8,762 | 5.49 | 1,588 | 4.94 |
| Physician Clinics        | 138,926| 83.14| 28,626| 85.6 |

*P*: Chi-square / Fisher exact test on category variables and t-test on continue variables

### Table 2. Factors of GI perforation in 6-month tracking by using Cox regression

| Variables                  | Crude HR | 95% CI  | 95% CI  | P   | Adjusted HR | 95% CI  | 95% CI  |
|----------------------------|----------|---------|---------|-----|-------------|---------|---------|
| Fluoroquinol               |          |         |         |     |             |         |         |
| one                        |          |         |         |     |             |         |         |
| Without                    | Reference|         |         |     | Reference   |         |         |
| With                       | 0.997    | 0.586   | 1.696   | 0.990 | 1.359       | 0.794   | 2.325   |
| Gender                     |          |         |         |     |             |         |         |
| Male                       | 1.153    | 0.753   | 1.764   | 0.513 | 1.063       | 0.809   | 1.370   |
| Female                     | Reference|         |         |     | Reference   |         |         |
| Age (yrs)                  |          |         |         |     |             |         |         |
| <1                         | Reference|         |         |     |             |         |         |
| 1                          | 1.835    | 0.708   | 4.756   | 0.212 |             |         |         |
| 2                          | 0.620    | 0.106   | 2.290   | 0.473 |             |         |         |
| 3                          | 1.802    | 0.715   | 4.540   | 0.212 |             |         |         |
| 4                          | 0.368    | 0.079   | 1.703   | 0.201 |             |         |         |
| 5-9                        | 0.441    | 0.193   | 1.008   | 0.052 |             |         |         |
| 10-14                      | 0.415    | 0.177   | 0.971   | 0.043 |             |         |         |
| ≥15                        | 0.944    | 0.442   | 2.014   | 0.881 |             |         |         |
| Catastrophic illness       |          |         |         |     |             |         |         |
| Without                    | Reference|         |         |     | Reference   |         |         |
| With                       | 5.972    | 0.014   | 161.782 | 0.985 | 2.802       | 0.297   | 13.722  |
| Low-income household       |          |         |         |     |             |         |         |
| Without                    | Reference|         |         |     | Reference   |         |         |
| With                       | 1.643    | 0.090   | 4.620   | 0.661 | 1.581       | 0.080   | 4.197   |
| Season   | Reference | Spring | Summer | Autumn | Winter |
|----------|-----------|--------|--------|--------|--------|
|          |           | 0.218  | 0.127  | 0.377  | <0.001 |
|          |           | 0.017  | 0.006  | 0.047  | <0.001 |
|          |           | 0.056  | 0.032  | 0.098  | <0.001 |
| Urbanization level |           | Reference | Reference | Reference | Reference |
| 1 (The highest) | 1.993 | 1.032 | 3.849 | 0.040 | 2.080 | 1.057 | 4.090 |
| 2          | 0.596 | 0.276 | 1.288 | 0.188 | 0.537 | 0.246 | 1.170 |
| 3          | 2.357 | 1.184 | 4.691 | 0.015 | 2.639 | 1.324 | 5.261 |
| 4 (The lowest) | Reference | Reference | Reference | Reference | Reference |

| Level of care | Reference | Reference | Reference | Reference | Reference |
|---------------|-----------|-----------|-----------|-----------|-----------|
| Hospital center | 2.909 | 1.232 | 6.871 | 0.015 | 2.830 | 1.161 | 6.901 |
| Regional hospital | 7.613 | 4.608 | 12.579 | <0.001 | 8.538 | 5.123 | 14.228 |
| Local hospital | 6.213 | 3.425 | 11.269 | <0.001 | 5.429 | 2.979 | 9.897 |

| Physician Clinics | Reference | Reference |
|-------------------|-----------|-----------|
| HR = hazard ratio, CI = confidence interval, Adjusted HR: Adjusted variables listed in the table |

Table 3. Factors of GI perforation in 6-month tracking stratified by variables by using Cox regression

| Fluoroquinolone | With | PDs | Rate (per 10^5 PDs) | Without | PDs | Rate (per 10^5 PDs) |
|-----------------|------|-----|---------------------|---------|-----|---------------------|
| Stratified      | Events |      |                      | Events |      |                      |
| Total           | 17    | 5,940,776.06 | 0.29                | 68      | 23,707,602.7 | 0.29                |
| Gender          |       |      |                      |         |       |                      |
| Male            | 10    | 3,060,435.00 | 0.33                | 31      | 12,297,000.6 | 0.25                |
| Female          | 7     | 2,880,341.06 | 0.24                | 37      | 11,410,602.1 | 0.32                |
| Age group (yrs) |       |      |                      |         |       |                      |
| <1              | 1     | 183,600.00  | 0.54                | 4       | 820,422.12  | 0.49                |
| 1               | 2     | 256,265.94  | 0.78                | 3       | 876,927.19  | 0.34                |
| 2               | 1     | 286,506.19  | 0.35                | 4       | 1,024,530.50 | 0.39                |
| 3               | 2     | 325,930.75  | 0.61                | 5       | 1,282,879.44 | 0.39                |
| 4               | 1     | 384,465.19  | 0.26                | 6       | 1,542,322.12 | 0.39                |
| 5-9             | 3     | 1,677,499.81 | 0.18               | 14      | 6,622,008.94 | 0.21                |
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10-14  2  1,521,852.94  0.13  10  6,123,547.69  0.16
≥15    5  1,304,655.25  0.38  22  5,414,964.75  0.41

Catastrophic illness
Without  16  5,907,063.87  0.27  68  23,616,531.1  0.29
With  1  33,712.19  2.97  0  91,071.62  0.00

Low-income household
Without  16  5,789,090.44  0.28  68  23,320,517.2  0.29
With  1  151,685.62  0.66  0  387,085.50  0.00

Season
Spring  5  1,209,564.81  0.41  23  6,731,139.19  0.34
Summer  3  1,211,624.37  0.25  12  5,549,493.38  0.22
Autumn  2  1,596,290.69  0.13  10  5,377,612.87  0.19
Winter  7  1,923,296.19  0.36  23  6,049,357.31  0.38

Urbanization level
1 (The highest)  6  1,305,977.19  0.46  30  6,700,633.87  0.45
2  2  2,119,226.31  0.09  12  8,911,079.56  0.13
3  7  1,142,905.31  0.61  19  3,835,392.81  0.50
4 (The lowest)  2  1,372,667.25  0.15  7  4,260,496.50  0.16

Level of care
Hospital center  6  222,455.87  2.70  26  1,083,958.87  2.40
Regional hospital  5  343,936.38  1.45  19  1,737,590.94  1.09
Local hospital  4  281,046.94  1.42  15  1,249,182.12  1.20
Physician Clinics  2  5,093,336.87  0.04  8  19,636,870.8  0.04

PDs = Person-days; Adjusted HR = Adjusted Hazard ratio: Adjusted for the variables listed in Table 2.; CI = confidence interval

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**Table 4. Factors of GI perforation stratified by Fluoroquinolone in different tracking period by using Cox regression**

| Adjusted HR | 95% CI | Population | Events | PDs | Rate (per 10^5 PDs) |  |
|-------------|--------|------------|--------|-----|---------------------|---|
| 3-day       |        |            |        |     |                     |  |
| Without     |        | 133,684    | 2      | 23,707,602 .75 | 0.01 Reference | |
| With        |        | 33,421     | 0      | 5,940,776.06   | 0.00 0.000 - | - |
| Levofloxacln|        | 653        | 0      | 112,735.69   | 0.00 - | |
| Ciprofloxax |        | 1,843      | 0      | 316,411.56   | 0.00 - | |

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| Duration | Treatment | Days | Total Cost | Additional Cost | MOX | Reference |
|----------|-----------|------|------------|-----------------|-----|-----------|
| 7-day    | Without MOX | 6   | 23,707,602 | 0.03 | | Reference |
|          | With MOX   | 1   | 5,940,776.06 | 0.02 | | 0.524 | 0.083 | 2 |
|          | With LevoMOX | 0  | 112,735.69 | 0.00 | | | | |
| 14-day   | Without MOX | 10  | 23,707,602 | 0.04 | | Reference |
|          | With MOX   | 3   | 5,940,776.06 | 0.05 | | | 1.048 | 0.045 | 1 |
|          | With LevoMOX | 0  | 112,735.69 | 0.00 | | | | |
| 28-day   | Without MOX | 14  | 23,707,602 | 0.06 | | Reference |
|          | With MOX   | 4   | 5,940,776.06 | 0.07 | | | 1.163 | 0.087 | 1 |
|          | With LevoMOX | 0  | 112,735.69 | 0.00 | | | | |
| 3-month  | Without MOX | 45  | 23,707,602 | 0.19 | | Reference |
|            | With 33,421 | 12 | 5,940,776.06 | 0.20 | 1.073 | 0.160 | 1 |
|------------|------------|----|---------------|------|-------|-------|---|
|            | Levofloxacin 653 | 0 | 112,735.69 | 0.00 | |
|            | Ciprofloxacin 1,843 | 1 | 316,411.56 | 0.32 | |
|            | Moxifloxacin 139 | 0 | 24,500.00 | 0.00 | |
|            | Gemifloxacin 12 | 0 | 2,160.00 | 0.00 | |
|            | Norfloxacin 7,041 | 3 | 1,261,596.87 | 0.24 | |
|            | Ofloxacin 23,733 | 8 | 4,223,371.94 | 0.19 | |
| **6-month** | Without 133,684 | 68 | 23,707,602 | 0.29 | Reference 0.75 |
| With 33,421 | 17 | 5,940,776.06 | 0.29 | 1.360 | 0.795 | 2 |
|            | Levofloxacin 653 | 0 | 112,735.69 | 0.00 | |
|            | Ciprofloxacin 1,843 | 1 | 316,411.56 | 0.32 | |
|            | Moxifloxacin 139 | 0 | 24,500.00 | 0.00 | |
|            | Gemifloxacin 12 | 0 | 2,160.00 | 0.00 | |
|            | Norfloxacin 7,041 | 3 | 1,261,596.87 | 0.24 | |
|            | Ofloxacin 23,733 | 13 | 4,223,371.94 | 0.31 | |

PDs = Person-days; Adjusted HR = Adjusted Hazard ratio: Adjusted for the variables listed in Table 2.; CI = confidence interval

**Figures**
### Inclusion criteria
Fluoroquinolone with aged 0-18
33,537 individuals

### Exclusion criteria
1. Fluoroquinolone before index date (n=65)
2. Collagen-associated adverse events before tracking (n=4)
3. Appendicitis / Peritonitis / Typhoid fever (n=18)
4. Without tracking (n=22)
5. Gender unknown (n=7)
   **Total:** 116 individuals

### With Fluoroquinolone (Study cohort)
33,421 individuals

- In 3-day tracking: 0 individual with tendons rupture
- In 7-day tracking: 0 individual with tendons rupture
- In 14-day tracking: 0 individual with tendons rupture
- In 28-day tracking: 0 individual with tendons rupture
- In 3-month tracking: 0 individual with tendons rupture
- In 6-month tracking: 0 individual with tendons rupture

### Without Fluoroquinolone (Comparison cohort)
133,684 individuals

- In 3-day tracking: 0 individual with tendons rupture
- In 7-day tracking: 0 individual with tendons rupture
- In 14-day tracking: 0 individual with tendons rupture
- In 28-day tracking: 0 individual with tendons rupture
- In 3-month tracking: 0 individual with tendons rupture

**Total:** 116 individuals

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**Figure 1**

The flowchart of study sample selection.