



Fluoroquinolone and no risk of Achilles-tendinopathy in childhood pneumonia under eight years of age—a nationwide retrospective cohort

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Background: The emergence of macrolide-resistant *Mycoplasma pneumoniae* pneumonia (MRMP) has made its treatment challenging. A few guidelines have recommended fluoroquinolones (FQs) as second-line drugs of choice for treating MRMP in children under the age of eight, but concerns about potential adverse events (i.e., Achilles tendinopathy; AT) have been raised. The aim of this study was to investigate the relationship between the use of FQs and the risk of AT in pneumonia in children under eight years of age.

Methods: Children hospitalized with pneumonia (total of 2,213,807 episodes) from 2002 to 2017 were enrolled utilizing the Korean National Health Insurance Sharing Service (NHISS) database. The independent risk of FQs for AT was analyzed by a generalized estimating equation with adjustment for age, sex, and underlying diseases.

Results: Among 2,213,807 episodes of pneumonia hospitalization, children in a total of 6,229 episodes (0.28%) were treated with FQs (levofloxacin 40.9%, ciprofloxacin 36.1%, moxifloxacin 11.6%, and others 11.4%). The FQ-exposure group showed a 0.19% (12/6,229) incidence of AT within 30 days after the first administration of FQ. The use of FQs increased the risk of AT (OR 3.00; 95% CI: 1.71–5.29), but became null after adjusting for age, sex, and underlying diseases (aOR 0.85; 95% CI: 0.48–1.51). All AT related to the use of FQs occurred after the use of ciprofloxacin or levofloxacin, and not in children under eight years of age.

Conclusions: AT was a rare adverse event of FQ use for childhood pneumonia, particularly under eight years of age. Clinicians could consider using FQs as a second-line option in the treatment of childhood pneumonia when there are no alternative therapeutic options.

Keywords: Fluoroquinolones (FQs); Achilles tendon; tendinopathy; pneumonia; child

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Introduction

Community-acquired pneumonia (CAP) remains a leading cause of morbidity and mortality worldwide. *Streptococcus Pneumoniae* is the most prevalent cause of CAP in most countries. However, increasing numbers of *Mycoplasma pneumoniae* pneumonia (MPP) have been recognized, especially in children and young adults. MPP causes 40% or more of the CAP and as many as 18% of the cases in children requiring hospitalization (1).

M. pneumoniae lacks cell walls. Therefore, it is resistant to beta-lactams and all antimicrobials targeting the cell wall. Macrolides have long been regarded as the first-line treatments for MPP, mainly due to their low minimum inhibitory concentration and safety in children. However, the prevalence of macrolide-resistant *Mycoplasma pneumoniae* pneumonia (MRMP) has abruptly increased in recent years (2), particularly in East Asian countries, such as China, Japan, and Korea, with high macrolide pressure (3). This is evident by the highest macrolide resistance rates reported in countries with extensive macrolide use. However, the rate decreased by 43.6% in 2015 from its highest rate of 81.6% in 2012, along with a reduction in macrolide prescriptions in Japan (4).

The emergence of MRMP has made its treatment challenging. A few guidelines have recommended fluoroquinolones (FQs) as the second-line drugs of choice for treating MRMP in children (5,6), but concerns about its potential adverse events (i.e., Achilles tendinopathy; AT) have been raised. Therefore, recommendations for the use of FQs according to age still conflict among the guidelines. Although MPP is usually a mild, self-limited disease with a good response to macrolides, it can cause various extra-pulmonary complications and progress to severe life-threatening conditions. Clinicians should be aware of macrolide treatment failure and consider using alternative drugs if symptoms persist or if there are signs of clinical deterioration. Delayed decisions to use second-line antimicrobials may induce further complications, as well as a healthcare-related burden. The aim of this study was to investigate the relationship between the use of FQs and the risk of AT in children under eight years of age with pneumonia.

We present the following article in accordance with the STROBE reporting checklist (available at <http://dx.doi.org/10.21037/jtd-20-2256>).

Methods

Data source

The National Health Insurance Service (NHIS), a government-affiliated agency responsible for examining the accuracy of claims for the National Health Insurance and National Medical Aid in Korea, covers approximately 96.6% of the Korean population (7). The National Health Insurance Sharing Service (NHIS) provided by NHIS conducts reviews and assessments of all medical insurance claims in South Korea. The NHIS database includes information about demographics (age and sex), medical healthcare service data, including diagnostic codes (*International Statistical Classification of Disease and Related Health Problems* 10th Edition, ICD-10), dispensed or prescribed medications, and diagnostic tests and procedures. Preferably, it contains information on healthcare utilization at hospitals, emergency departments, outpatient clinics, and dispensed medication at pharmacies. There were missing or outlying values in key fields, such as drug names, quantities, date dispensed, and duration in less than 0.5% of all records. We used the NHIS data to identify the effects of FQs in the occurrence of AT in children with pneumonia under eight years of age.

Study population and design

We constructed a nationwide, population-based retrospective cohort of community-acquired childhood pneumonia (patients under 19 years of age) from 2002 to 2017 in Korea. We identified a total of 1,418,541 children hospitalized with pneumonia during the study period. We excluded individuals with missing or outlying values in demographic variables, such as birth year, birth quarter, sex, and age. We also excluded data from 2002 and 2017 to avoid the underdetection of AT or the use of FQs in the first and last year of the study period. As a result, we ended up with 2,213,807 pneumonia episodes requiring hospitalization. Pneumonia-related hospitalization was defined when a pneumonia diagnosis (J11-18 as the primary or first additional diagnosis) was made at the time of hospitalization.

Definitions of dependent and independent variables

AT was considered a dependent variable. For each child,

we checked whether he/she received an AT diagnostic code [(S86.08 and M76.6) and no S86.00] as the primary or first additional diagnosis within 30 days after the first administration of FQs. In the case of multiple episodes of AT, a six-month window was applied to ensure the independence of the episode.

FQ use was defined as the main independent variable when the drug code (i.e., J01MA) was observed at the time of hospitalization. For each subject, cumulative duration (days) and age at use were recorded and used for subgroup analyses. Detailed information on the FQs is described in [Table S1](#).

For the severity of pneumonia, we considered any case of chest computed tomography, oxygen administration, intensive care unit admission, intubation, ventilator care or cardiopulmonary resuscitation during the same hospitalization periods (detailed information is described in [Table S2](#)). Other potential covariates including underlying diseases, such as cardiovascular diseases, congenital respiratory diseases, neuromuscular diseases, genetic metabolic diseases, immunodeficiency, neoplasms, autoimmune disease, and transplantation within 12 months before the first administration of FQs, were included in the statistical model. [Table S3](#) presents the detailed information.

Ethical considerations

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The research protocol for this study was approved by the Ethical Review Board of Soonchunhyang University Seoul Hospital (approval number: SCHUH 2017-06-006). The requirement for informed consent was waived due to the retrospective nature of the study. The authors are accountable for all aspects of the work (if applied, including full data access, integrity of the data and the accuracy of the data analysis) in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Statistical analysis

We investigated the relationship between the use of FQs and the risk of AT using generalized estimation equation (GEE) models at the individual level. The GEE model was adjusted for sex, age group, pneumonia severity, and underlying diseases. AT was considered a dependent variable, and the logit link function was used. The correlation between the longitudinally observed dependent variables of each

subject was adjusted using sandwich estimators. In addition, potential confounders were adjusted for sex, age group, the index of severity, and the index of other diseases. We presented a crude model and an adjusted model to estimate the odds ratios (ORs) and 95% confidence intervals (CIs), respectively. Quasi-Akaike's Information Criteria (QIC) were used to select the optimal model from among several options and the predicted values were calculated using the selected model. In subgroup analyses, we further restricted the cohort groups according to the subtypes of FQs, age group, and the duration of FQ use. All statistical analyses were conducted using the statistical computing program, SAS Enterprise Guide software (version 7.1).

Results

The characteristics of the study population are presented in [Table 1](#). Among 2,213,807 episodes of childhood pneumonia requiring hospitalization, children in a total of 6,229 (0.28%) episodes were given FQs for the treatment of pneumonia. Most of the cases were under eight years of age (87.79%). The mean age was 3.31 ± 3.66 years and 53.74% of the total study population was boys. There were 1,943,555 episodes of hospitalizations for CAP in children under eight years of age and the numbers decreased with increasing age. Approximately 3.75% of the episodes met the operational diagnosis of severe pneumonia. The most common preexisting diseases were cardiovascular diseases (3.49%), followed by genetic metabolic diseases (1.18%), neuromuscular diseases (0.79%), neoplasms (0.24%), congenital respiratory diseases (0.16%), immunodeficiency (0.08%), autoimmune disease (0.07%), and transplantation (0.05%). A total of 1,429 cases of Achilles tendinitis was observed among the 2,213,807 CAP episodes (0.06%), but no Achilles tendon rupture was observed.

[Table 2](#) shows the characteristics of the subpopulation exposed to FQs. Among 6,229 exposures to FQs, levofloxacin (40.9%) and ciprofloxacin (36.1%) were the most common. The total duration of FQ use was 8.50 ± 5.95 days. Contrary to the age distribution in [Table 1](#), most cases here were in children over 12 years of age.

[Table 3](#) shows the GEE model results for the use of FQs on AT. The FQ-exposure group showed a 0.19% (12/6,229) incidence of AT, and a 3-fold higher risk than the non-exposure group (OR 3.00, 95% CI: 1.71–5.29, $P < 0.0001$), but the statistical significance became null after adjusting for age, sex, pneumonia severity, and underlying diseases (aOR 0.85, 95% CI: 0.48–1.51, $P = 0.57$). Compared to the group

Table 1 Demographics of the study population (2,213,807 episodes of childhood pneumonia requiring hospitalization) from 2002 to 2017 in Korea

Demographics	Variables	N	%
Use of FQ	No	2,207,578	99.72
	Yes	6,229	0.28
Achilles tendinopathy	No	2,213,807	100
	Yes	0	0
Achilles-tendinitis	No	2,212,378	99.94
	Yes	1,429	0.06
Age, years	<8	1,943,555	87.79
	8–12	155,787	7.04
	≥12	114,465	5.17
	Mean (SD)		3.31 (3.66)
	Median (min/max)		2 (0/18)
Severity of pneumonia	Non-severe	2,130,700	96.25
	Severe	83,107	3.75
Sex	Female	1,024,215	46.26
	Male	1,189,592	53.74
Cardiovascular diseases	No	2,136,537	96.51
	Yes	77,270	3.49
Congenital respiratory diseases	No	2,210,236	99.84
	Yes	3,571	0.16
Neuromuscular diseases	No	2,196,281	99.21
	Yes	17,526	0.79
Genetic metabolic diseases	No	2,187,582	98.82
	Yes	26,225	1.18
Immunodeficiency	No	2,211,993	99.92
	Yes	1,814	0.08
Neoplasms	No	2,208,545	99.76
	Yes	5,262	0.24
Autoimmune disease	No	2,212,309	99.93
	Yes	1,498	0.07
Transplantation	No	2,212,809	99.95
	Yes	998	0.05

Table 2 Characteristics of the subpopulation exposed to fluoroquinolones (6,229 episodes of childhood pneumonia requiring hospitalization) from 2002 to 2017 in Korea

	N	%
FQ subtypes		
Levofloxacin	2,545	40.9
Ciprofloxacin	2,249	36.1
Moxifloxacin	725	11.6
Gemifloxacin	168	2.7
Garenoxacin	0	0
Sparfloxacin	8	0.1
Lomefloxacin	23	0.4
Ofloxacin	351	5.6
Tosufloxacin	89	1.4
Others	71	1.1
Duration of use of FQs (day), Mean (SD)	8.50 (5.95)	
Age, years		
<8	933	14.98
8–12	501	8.04
≥12	4,795	76.98
Mean (SD)		13.87 (4.71)
Median (min/max)		16 (0/18)

12 years old or older, the 8- to 11-year age group showed approximately two-fold higher risk (aOR 1.95, 95% CI: 1.70–2.24, $P < 0.0001$), but the group under eight years of age showed 93% less risk for AT (aOR 0.07, 95% CI: 0.06–0.09, $P < 0.0001$). Genetic metabolic diseases and autoimmune diseases increased the risk of AT, independently of the use of FQs (aOR 1.68, 95% CI: 1.15–2.45) (aOR 2.35, 95% CI: 1.02–5.4, $P = 0.044$) after multiple regression analysis.

Table 4 shows the association between the exposure to FQs and the risk of AT according to the subtypes of FQs. Eight cases of AT occurred after exposure to ciprofloxacin (0.36%, 8/2,249), and four cases occurred after exposure to levofloxacin (0.16%, 4/2,545), but no case occurred after exposure to other FQs. There was no case of AT in children under eight years of age. No duration-dependent response was observed (aOR 0.93, 95% CI: 0.79–1.1).

Discussion

In this study, we investigated the use of FQs and the risk

of AT in a nationwide childhood pneumonia cohort from 2002 to 2017 and found that the incidence of AT related to the use of FQs was rare (0.19%, 12/6,229), and most cases of AT were related to underlying diseases, such as genetic metabolic diseases or autoimmune disease, not from the use of FQs alone. In addition, we found no case of AT in children under eight years of age, and no duration-dependent response to FQ use.

Emerging resistance to macrolides is of great concern because it creates a therapeutic conundrum, particularly for young children in whom second-line antimicrobials are relatively contraindicated. Recent studies have reported that MRMP showed more rapid progression; and higher extra-pulmonary complications than macrolide-sensitive mycoplasma pneumonia (29.6% extra-pulmonary complications in children with MRMP) (8). Acute respiratory distress syndrome or acute respiratory failure are the most well known and most serious intrapulmonary complications (9). The importance of the early administration of antibiotics for MPP patients was

Table 3 Generalized estimating equation model for the use of fluoroquinolones on Achilles tendinopathy among Korean children with pneumonia (2,213,807 of episodes) from 2002 to 2017

		No. of population	No. of AT (%)	Univariate			Multivariate		
				OR	95% CI	P	aOR	95% CI	P
Use of FQ	No	2,207,578	1,417 (0.06)		Ref.			Ref.	
	Yes	6,229	12 (0.19)	3.00	(1.71–5.29)	0.0001	0.85	(0.48–1.51)	0.5715
Age	<8	1,943,555	368 (0.02)	0.07	(0.06–0.09)	<0.0001	0.07	(0.06–0.09)	<0.0001
	8–12	155,787	771 (0.49)	1.95	(1.70–2.24)	<0.0001	1.93	(1.68–2.22)	<0.0001
	≥12	114,465	290 (0.25)		Ref.			Ref.	
Severity of pneumonia	Non-severe	2,130,700	1,387 (0.07)		Ref.			Ref.	
	Severe	83,107	42 (0.05)	0.78	(0.57–1.05)	0.102	0.66	(0.49–0.91)	0.0098
Sex	Female	1,024,215	649 (0.06)		Ref.			Ref.	
	Male	1,189,592	780 (0.07)	1.03	(0.93–1.15)	0.5283	1.09	(0.98–1.21)	0.1072
Cardiovascular diseases	No	2,136,537	1,392 (0.07)		Ref.			Ref.	
	Yes	77,270	37 (0.05)	0.74	(0.53–1.03)	0.0717	1.03	(0.73–1.44)	0.8858
Congenital respiratory diseases	No	2,210,236	1,428 (0.06)		Ref.			Ref.	
	Yes	3,571	1 (0.03)	0.43	(0.06–3.22)	0.4104	1.08	(0.15–7.72)	0.9413
Neuromuscular diseases	No	2,196,281	1,413 (0.06)		Ref.			Ref.	
	Yes	17,526	16 (0.09)	1.44	(0.88–2.35)	0.1491	1.16	(0.7–1.92)	0.5628
Genetic metabolic diseases	No	2,187,582	1,399 (0.06)		Ref.			Ref.	
	Yes	26,225	30 (0.11)	1.78	(1.23–2.59)	0.0025	1.68	(1.15–2.45)	0.0069
Immunodeficiency	No	2,211,993	1,429 (0.06)	–	–	–	–	–	–
	Yes	1,814	0 (0)	–	–	–	–	–	–
Neoplasms	No	2,208,545	1,422 (0.06)		Ref.			Ref.	
	Yes	5,262	7 (0.13)	2.07	(0.99–4.33)	0.0538	1	(0.48–2.09)	0.9956
Auto-immune disease	No	2,212,309	1,423 (0.06)		Ref.			Ref.	
	Yes	1,498	6 (0.4)	5.96	(2.54–13.97)	<0.0001	2.35	(1.02–5.4)	0.044
Transplantation	No	2,212,809	1,428 (0.06)		Ref.			Ref.	
	Yes	998	1 (0.10)	1.45	(0.17–12.12)	0.7311	0.68	(0.09–4.97)	0.7012

aORs, adjusted for age, severity, sex, cardiovascular diseases, congenital respiratory diseases, neuromuscular diseases, genetic metabolic diseases, neoplasms, autoimmune disease, and transplantation. AT, occurrence of Achilles tendinopathy.

reinforced by a study reporting that the hospital mortality for MP-infected and ICU-admitted patients was 29.4% (10).

Most guidelines recommend respiratory FQs as first-line therapy for adult CAP (11). FQs act against topoisomerases and inhibit DNA synthesis and replication, and are highly effective against MP *in vitro* (12). The therapeutic efficacy of FQs has been reported in adolescents and adults with MRMP (13), and also in children (14). The Pediatric

Infectious Diseases Society and the Infectious Diseases Society of America recommend azithromycin as the first-line antibiotic, and clarithromycin, erythromycin, doxycycline (for children aged ≥8 years), levofloxacin or moxifloxacin (for adolescents) as second-line drugs (15), whereas the Japanese guidelines and the 2015 Hong Kong Pediatric CAP guidelines recommend tosufloxacin (in Japan) (5), and levofloxacin (in Hong Kong) (6) as second-

Table 4 Generalized estimating equation (GEE) model for the subtypes of fluoroquinolones on Achilles tendinopathy Korean children with pneumonia exposed to fluoroquinolones (6,229 episodes) from 2002 to 2017

		No. of population	AT (%)	Univariate			Multivariate		
				OR	95% CI	P	aOR	95% CI	P
FQ subtypes	Ciprofloxacin	2,249	8 (0.36)	Ref.			Ref.		
	Levofloxacin	2,545	4 (0.16)	0.44	(0.13–1.46)	0.1809	0.49	(0.14–1.66)	0.2501
	Moxifloxacin	725	0	–	–	–	–	–	–
	Gemifloxacin	168	0	–	–	–	–	–	–
	Garenoxacin	0	0	–	–	–	–	–	–
	Sparfloxacin	8	0	–	–	–	–	–	–
	Lomefloxacin	23	0	–	–	–	–	–	–
	Ofloxacin	351	0	–	–	–	–	–	–
	Tosufloxacin	89	0	–	–	–	–	–	–
	Others	71	0	–	–	–	–	–	–
Duration of FQs (per 1 day increment)				0.92	(0.77–1.1)	0.3679	0.93	(0.78–1.1)	0.3905
Age	<8	933	0	–	–	–	–	–	–
	8–12	501	3 (0.6)	3.2	(0.86–11.87)	0.0816	2.98	(0.79–11.18)	0.1054
	≥12	4,795	9 (0.19)	Ref.					

aORs, adjusted for age, severity, sex, cardiovascular diseases, congenital respiratory diseases, neuromuscular diseases, genetic metabolic diseases, neoplasms, autoimmune disease, and transplantation. AT, occurrence of Achilles tendinopathy.

line drugs in children under eight years of age. However, there are no evidence-based guidelines.

The FQs are generally well-tolerated, but they damaged the cartilage in the weight-bearing joints of juvenile animals (16). The pathophysiology of FQ-induced tendinopathy is still largely unknown. Various pathogenetic mechanisms have been postulated for arthropathies, such as the inhibition of collagen and glycosaminoglycans synthesis; the inhibition of mitochondrial function, resulting in the generation of free radicals; and oxidative stress, or the chelation of magnesium ions, all culminating in cartilage and tendon damage (17,18). Animal models showed an increase in matrix-degrading activity and a decrease in matrix synthesis and fibroblast cell proliferation, thereby weakening the tendon and increasing the risk of rupture (19). FQ-induced tendinopathy has been reported in the literature and its incidence was estimated to be 0.14–0.4% (20). FQ-induced tendinopathy preferentially occurs in adolescents during their pubertal growth spurt following long-term treatment. The time to the development of arthropathy ranged from 15 min to 30 days (median six days) after the administration of FQs (21). Achilles

tendon rupture is also a well-known complication associated with FQs in elderly patients with preceding steroid use or underlying disease, but there have been no reports in healthy children to date (22).

On May 12, 2016, the U.S. Food and Drug Administration (FDA) advised restricting FQ antibiotic use for certain uncomplicated infections due to serious adverse reactions, such as tendinitis, tendon rupture, the worsening of myasthenia gravis, the risk of peripheral neuropathy and central nervous system effects, dermatologic, cardiac, and hypersensitivity reactions (23). The black box warning (FDA's strongest warning) for the drug was updated on July 26, 2016, for all oral and injectable FQ antibiotics due to side effects, such as disabling and potentially permanent effects on tendons, muscles, joints, nerves, and the central nervous system (24). Ciprofloxacin, gemifloxacin, levofloxacin, lomefloxacin, moxifloxacin, norfloxacin, ofloxacin, and tosufloxacin are currently available Korean FDA-approved FQs, but none of them have been approved by the Korean FDA for children under 18 years of age. However, FQ use has been expanded off-label to pediatric patients with conditions for which no alternative treatment

was possible because of bacterial resistance or because other active antibiotics could not be given orally. Although FQs are not recommended as a first-line antibiotic because they have age-related contraindications, their use may be required in cases where macrolide resistance is suspected. Our study showed that 0.28% of childhood pneumonia was treated by the off-label use of FQs in real-world practice.

Increasing cases of FQ-associated tendinopathy have been reported since the first description of norfloxacin-associated Achilles tendinitis was published in 1983 (25). However, studies for children exposed to FQ have not clearly demonstrated the development of lesions consistent with those observed in animals (26,27), and all musculoskeletal adverse effects reported in the literature were reversible following withdrawal of the treatment (28).

In a prospective study in France, among 276 children exposed to FQs, musculoskeletal adverse events occurred more frequently in FQs-treated children than in children not given FQ therapy (29). The Levaquin Pediatric Program phase three trials to assess the efficacy and safety of levofloxacin in children identified more musculoskeletal adverse events (arthralgia, arthritis, gait abnormality, or tendinopathy) in levofloxacin-treated children than in children not given FQ therapy (OR 2.4, 95% CI: 1.1–5.2 at two months; OR 1.9; 95% CI: 1.1–3.5 at one year) (30). In contrast, FQ-treated children with cystic fibrosis consistently showed a low risk for arthropathy (26,31). A healthcare claims study in the USA involving 7,897 children who had been prescribed any FQs reported no risk of tendon or joint disorders (TJD) with a <1% incidence within 60 days after the first prescription of FQs (27).

Among the FQs, levofloxacin and ofloxacin seem to be associated with a higher risk of tendon damage relative to other FQs, and tendinitis-risk seems to be dependent upon the dose and duration of use (32). However, a systematic review of ciprofloxacin safety in those under 17 years of age did not find dose- and duration-dependent relationships in humans (28). Our study also showed no duration-dependent response.

The knowledge of this association is critical to ensuring timely diagnosis and management of these adverse events. FQ-induced tendinitis is distinguished from other forms of tendinitis by its abrupt-onset of sharp pain that occurs spontaneously upon walking or palpation, and substantial swelling (33). Early diagnosis and management are required and treatment consists of immediate discontinuation of the FQs with placement of the tendon at rest. Edema may persist from weeks to several months. The cardinal

sign of tendinitis is tenderness and pain on movement or at rest, whereas the pain of tendon rupture is sudden. New or worsening pain in a patient on an FQ should lead the clinician to consider the possibility of tendinopathy. Therefore, clinicians should pay attention to joint pain, and switch to alternative treatments when joint pain occurs during FQ use. FQ can increase the susceptibility to further injury and should be ceased immediately when tendinopathy is suspected (23).

Compared to previous studies, the strengths of our study are as follows. The large sample size facilitated the analysis of the relationship between the use of FQs and the risk of AT and provided generalized information. Similar to our study, Yee *et al.* (27) demonstrated no relationship between the use of FQs and the risk of tendinopathy. However, they did not consider both the severity of the disease and baseline underlying diseases in the estimation models, whereas our study did. Furthermore, we considered longitudinally observed measurements of AT. For longitudinal data analysis, within-subject covariates are robust against between-subject confounders. We also considered sandwich estimators, which are robust for choosing variance-covariance structure among longitudinally observed measurements for each subject. Our study considered preexisting diseases and pneumonia severity as confounders by indication, and controlled their influence on the interpretation of our results.

Despite these contributions, some limitations should be considered in interpreting our findings. First, our study was based on the use of claims data. Because radiological and medical records are not available from the NHISS, the diagnostic reliability and validity of AT can be of concern. However, it is notable that AT caused by traffic accidents has not been covered by national health insurance. Therefore, no accidental AT cases could be included in these analyses. Second, mild symptoms of AT may not be reflected. Lastly, a certain number of potential confounders, such as a family history of musculoskeletal diseases, and personal status for nutrition, could not be used because they were not available in the NHISS.

Nonetheless, our results showed that the association between the use of FQs and AT was negligible in children under eight years of age. Rather, some underlying diseases may increase the risk of tendinopathy. Therefore, physicians could consider using FQs as a second-line option in the treatment of childhood pneumonia when there are no alternative therapeutic options.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The research protocol for this study was approved by the Ethical Review Board of Soonchunhyang University Seoul Hospital (approval number: SCHUH 2017-06-006). The requirement for informed consent was waived due to the retrospective nature of the study.

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Table S1 Types, categorization, classifications, and Anatomical Therapeutic Chemical (ATC) classification system codes, and Korea Food & Drug Administration drug classification numbers of study medications

Type of medications	Classification	ATC codes*	KFDA-DCN [†]
Fluoroquinolones	Ofloxacin	J01MA01	203901ATB, 203904ATB, 203902BIJ, 203907BIJ, 203940BIJ
	Ciprofloxacin	J01MA02	134103ATB, 134105ATB, 134109ATB, 134103ACH, 134108ATR, 134101BIJ, 134104BIJ, 134106BIJ, 134133BIJ, 134134BIJ, 134135BIJ
	Pefloxacin	J01MA03	209501ATB
	Enoxacin	J01MA04	152001ATB, 152002ATB
	Norfloxacin	J01MA06	203301ATB, 203302ATB, 203303ATB, 203302ACH, 203303ACH
	Lomefloxacin	J01MA07	184901ATB, 184903ATB, 184904ATB, 184901ACH
	Fleroxacin	J01MA08	159401ATB, 159402ATB
	Sparfloxacin	J01MA09	230701ATB, 230702ATB
	Rufloxacin	J01MA10	358801ATB
	Grepafloxacin	J01MA11	167401ATB
	Levofloxacin	J01MA12	183201ATB, 183202ATB, 183203ATB, 183205ATB, 183202BIJ, 183203BIJ, 183205BIJ, 183206BIJ, 183233BIJ, 183234BIJ, 183235BIJ, 183236BIJ
	Moxifloxacin	J01MA14	380301ATB, 380302BIJ, 380335BIJ, 801601BIJ
	Gemifloxacin	J01MA15	442901ATB, 442902BIJ
	Gatifloxacin	J01MA16	434801ATB
	Prulifloxacin	J01MA17	552901ATB
	Pazufloxacin	J01MA18	566901BIJ
	Garenoxacin	J01MA19	560301ATB
Tosufloxacin	J01MA22	242201ATB, 242202ATB	

*, ATC codes: Anatomical Therapeutic Chemical (ATC) classifications system codes; [†], KFDA-DCN: Korea Food & Drug Administration drug classification numbers.

Table S2 Definition of severe pneumonia based on the Solutions for Korean Medical Fee Contract System

	Codes in Korean Medical Fee Contract System
Chest CT	HA424 or HA434 or HA464 or HA474 or HA444
Oxygen supply	M0040
ICU admission	AJ0, AJ1, AJ2, AJ3, AJ4, AJ5, 19001, 19002, 19003, 19004, 19005, 19400, 19402, 19412, 19422, 19442, 19410, 19420, 19430, 19450, 19200, 19202, 19212, 19222, 19242, 19210, 19220, 19230, 19240, 19250, 19260, 19280, 19290, 19300, 19302, 19312, 19322, 19342, 19310, 19320, 19330, 19340, 19350, 19360, 19380, 19390, 19500, 19510, 19520, 19530, 1954-, 19550, 19560, 19580, 19590
Tracheal intubation	M5859
Ventilator care or cardiopulmonary resuscitation	M08XX, M58XX

Table S3 Diagnoses and their matched coding criteria based on the Korean Classification of Disease 6 (KCD-6) and the International Classification of Disease 10 codes (ICD-10)

Categories	ICD-10
Achilles tendinopathy	S86.08 or M76.6, not S86.00
Cardiovascular diseases	I0X.X or I1X.X or I2X.X or I3X.X or I40.9 or I42.X or I45.X or I47.X or I48.X or I49.X or I50.X or I51.X or P29.X or I7X.X or Q2X.X or S06.X
Congenital respiratory diseases	E84.X or P26.8 or P26.9 or P27.X or P28.5 or Q32.X or Q33.X or Q34.X
Neuromusculoskeletal diseases	G04.X or G05.X or G06.X or G11.X or G12.X or G31.X or G37.X or G7X.X or G80.X or G8X.X or G90.X or G91.X or G92.X or G93.X or G94.X or G95.X or I61.X or I62.X or I63.X or I64.X or I67.X or I69.X or I82.X or I84.X or Q00.X or Q01.X or Q02.X or Q03.X or Q04.X or T90.X
Genetic metabolic diseases	E03.X or E2X.X or E7X.X or E80.X or E81.X or E82.X or E83.X or E84.X or E85.X
Immunodeficiency	B20.4 or B24.X or B25.X or B37.1 or B37.5 or B37.7 or B59.X or D8X.X
Neoplasms	C2X.X or C3X.X or C4X.X or C5X.X or C6X.X or C7X.X or C8X.X or C9X.X or D03.X or D05.X or D38.X or D4X.X or D76.X or Z51.X or Z54.X
Autoimmune diseases	M06.X or M08.X or M32.9 or M33.0 or M33.1 or M35.0 or M35.9
Transplant and complications	Z94.X or T85.X or T86.X