Assessment of the risk of musculoskeletal adverse events associated with fluoroquinolone use in children: a meta-analysis

Ji-gan Wang, MD,[a,*] Hai-Rong Cui, MD[b], Yi-sen Hu, MD[b], Hua-Bo Tang, MD[a]  

Abstract

Background: The use of fluoroquinolone antibiotics has been restricted in children because of their potential to cause adverse musculoskeletal events. This study was performed to systematically evaluate whether there is a difference between fluoroquinolone and non-fluoroquinolone antibiotics in terms of their associated risk of adverse musculoskeletal events in children.

Methods: Cochrane Library, Embase, and PubMed databases were used to retrieve studies related to fluoroquinolone and non-fluoroquinolone-induced musculoskeletal adverse events in children. A meta-analysis was performed using Stata 11.

Results: A total of 10 studies were included in the analysis. The combined results showed that there was no statistical difference between fluoroquinolone and non-fluoroquinolone groups in terms of musculoskeletal adverse events in children (risk ratio $= 1.145$, 95% confidence interval = 0.974 – 1.345, $P = .101$). Subgroup analysis was performed using a random-effects model. Here, the effects on the trovafloxacin and levofloxacin groups were significantly different from that of the control group. However, musculoskeletal adverse events due to either drug was not reported after long-term follow-up.

Conclusions: The results showed that fluoroquinolone and non-fluoroquinolone antibiotics were not different in terms of their ability to cause musculoskeletal adverse events in children. For this reason, fluoroquinolone antibiotics can be used in children as appropriate.

PROSPERO registration number: CRD42019133900

Abbreviations: CI = confidence interval, FDA = food and drug administration, RCT = randomized controlled trial, RR = risk ratio.

Keywords: fluoroquinolone, musculoskeletal adverse events, side effects

1. Introduction

Fluoroquinolones are unique antimicrobial drugs. By targeting bacterial topoisomerase in the nucleus, including DNA helicase and topoisomerase IV, they block progression of the DNA replication enzyme complex and act as direct inhibitors of bacterial DNA synthesis. Therefore, fluoroquinolones exhibit bactericidal properties by causing bacterial DNA damage and rapid bacterial cell death.[1] With the increasing prevalence of drug-resistant infections, the prescription of quinolones seems to be a good choice in children; however, they are rarely used in the pediatric population. There is a concern regarding the potential toxicity of quinolones during chondrogenesis, which is based on animal studies conducted in the 1970s that demonstrated damage to articular cartilage in the weight-bearing joints of young beagle dogs exposed to high doses of quinolones.[2] As these findings were demonstrated only in animal models and there are physiological differences between humans and animals, investigating the adverse effects of quinolones on the bones and cartilage of children is required. This study was performed to systematically analyze the prescription of quinolone antibiotics to children to evaluate whether there was a difference between the risk associated with adverse musculoskeletal events with fluoroquinolone and non-fluoroquinolone antibiotic use.

2. Methods

2.1. Search strategy

The meta-analysis was reported in accordance with the preferred reporting items for systematic reviews and meta-analysis criteria. Cochrane Library, Embase, and PubMed databases were searched
for relevant published articles until June 1, 2019. The search terms included “quinolones,” “fluoroquinolones,” “ciprofloxacin,” “fleroxacin,” “enoxacin,” “enrofloxacin,” “gatifloxacin,” “gemifloxacin,” “moxifloxacin,” “norfloxacin,” “ofloxacin,” “levofoxacin,” “pefloxacin,” “children,” “child,” “kid,” “RCT (randomized controlled trial),” and “randomized controlled trial.” There were no restrictions on language or country, and an expanded search for the included studies was performed.

2.2. The following search sequence was performed in PubMed

- 1 (Fluoroquinolones [mh]) “quinolones” or ciprofloxacin) or fleroxacin) or enoxacin) or enrofloxacin) or gatifloxacin) or gemifloxacin) or moxifloxacin) or norfloxacin) or ofloxacin) or levofoxacin) or pefloxacin”
- 2 “RCT or randomized controlled trial”
- 3 “children” or child or kid
- #1, #2, and #3.

2.3. The inclusion criteria were as follows

1. Type of participants: the studies was children, and age was defined as ranging 0 to 18 years old; the criteria was not limited by sex, race, disease type, or region. The criteria were not limited by sex, race, disease type, or region.
2. Type of intervention: the source of conventional treatment, dosage form, dosage approach, and dose were clear for the quinolone group, whereas the non-quinolone group received only conventional treatment without any quinolone antibiotics.
3. Outcomes: suffering from musculoskeletal adverse events: joint pain, joint swelling, reduced movement of joint or radiographic evidence of joint damage, and any other musculoskeletal adverse event.
4. Research type: RCT, case-control, cohort study.

2.4. The exclusion criterion was as follows

1) study subjects were adults or newborns;
| ‘Reference’ or ‘Source’                  | Publication year | Number of patients | Number of non-patients | Complication type | Quinolone drugs     | Non-quinolone drugs | Follow-up time | Treatment type                      |
|----------------------------------------|------------------|--------------------|------------------------|-------------------|---------------------|---------------------|-----------------|-------------------------------------|
| FDA2004                                | USA              | 31                 | 304                    | Arthropathy       | Ciprofloxacin       | Ceftiraxone         | 6 wk           | Complicated urinary tract infections (including pyelonephritis) |
| FDA2004                                | USA              | 46                 | 289                    | Arthropathy       | Ciprofloxacin       | Ceftiraxone         | 1 yr           | Complicated urinary tract infections (including pyelonephritis) |
| Mohammed Abdus Salam, 1998             | Bangladesh       | 13                 | 58                     | Arthropathy       | Ciprofloxacin       | Pivamidinocillin    | 6 mo           | Shigellosis in children              |
| Leibovitz 2000                         | USA              | 1                  | 94                     | Arthropathy       | Ciprofloxacin       | Ceftriaxone sodium  | 4 wk           | Acute aggressive diarrhea            |
| Xavier Sáez-Llorens 2002               | S Africa         | 1                  | 61                     | Arthropathy       | Trovafl oxacin      | Ceftriaxone         | 5-7 wk         | Bacterial meningitis in children     |
| Xavier Sáez-Llorens 2002               | S Africa         | 1                  | 149                    | Arthropathy       | Trovafl oxacin      | Ceftriaxone         | 5-7 wk         | Bacterial meningitis in children     |
| Chuen L. Yee 2002                      | USA              | 34                 | 1871                   | Joint deformities | Ofloxacin           | Azithromycin        | 60 d           | -                                   |
| Chuen L. Yee 2002                      | USA              | 1                  | 37                     | Tendon-joint disorder | Ofloxacin           | Azithromycin        | 60 d           | -                                   |
| Chuen L. Yee 2002                      | USA              | 128                | 5776                   | Tendon-joint disorder | Ofloxacin           | Azithromycin        | 60 d           | -                                   |
| Chuen L. Yee 2002                      | USA              | 30                 | 1580                   | Tendon-joint disorder | Ofloxacin           | Azithromycin        | 60 d           | -                                   |
| Chuen L. Yee 2002                      | USA              | 0                  | 16                     | Tendon-joint disorder | Ofloxacin           | Azithromycin        | 60 d           | -                                   |
| Chuen L. Yee 2002                      | USA              | 103                | 4494                   | Tendon-joint disorder | Ofloxacin           | Azithromycin        | 60 d           | -                                   |
| Martin Chalumea 2003                   | France           | 10                 | 254                    | Musculoskeletal diseases | Fluoroquinolone     | Amoxicillin         | 15 d           | -                                   |
| Xavier Sáez-Llorens 2003               | Mexico, USA      | 6                  | 271                    | Arthralgia, myalgia | Gatifloxacin        | Amoxicillin         | 5-7 wk         | Recurrent and nonreactive otitis media in children |
| Lawrence Sher 2005                     | USA, Costa Rica  | 1                  | 175                    | Arthralgia        | Gatifloxacin        | Amoxicillin         | 30 d           | Recurrent and nonreactive otitis media in children |
| Gary J. Noel 2007                      | USA              | 28                 | 1312                   | Musculoskeletal diseases | Levofloxacin       | Non-quinolone antibiotics | 2 mo       | -                                   |
| Gary J. Noel 2007                      | USA              | 46                 | 1294                   | Musculoskeletal diseases | Levofloxacin       | Non-quinolone antibiotics | 1 yr       | -                                   |
| John S. Bradley 2007                   | Argentina        | 19                 | 514                    | Arthralgia, myalgia | Levofloxacin       | Amoxicillin-clavulanate potassium | 5 wk       | Community acquired pneumonia in children |
Table 2

The Newcastle-Ottawa Scale (NOS) for assessing the quality of studies included into present meta-analyses.

The Newcastle-Ottawa Scale (NOS)

We downloaded the following scale from: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp, to evaluate the included studies qualities. The studies that met at least five NOS criteria were considered to be high-quality studies.

Note: A study can be awarded a maximum of 1 star for each numbered item within the selection and exposure categories. A maximum of 2 stars can be given for comparability.

### Selection
1. Is the case definition adequate?
   a) yes, with independent validation
   b) yes, for example, record linkage or based on self reports
   c) no description
2. Representativeness of the cases
   a) consecutive or obviously representative series of cases
   b) potential for selection biases or not stated
3. Selection of controls
   a) community controls
   b) hospital controls
   c) no description
4. Definition of controls
   a) no history of disease (endpoint)
   b) no description of source

### Comparability
1. Comparability of cases and controls on the basis of the design or analysis
   a) study controls for __________ (Select the most important factor.)
   b) study controls for any additional factor (This criteria could be modified to indicate specific control for a second important factor.)

### Exposure
1. Ascertainment of exposure
   a) secure record (e.g. surgical records)
   b) structured interview where blind to case/control status
   c) interview not blinded to case/control status
   d) written self report or medical record only
   e) no description
2. Same method of ascertainment for cases and controls
   a) yes
   b) no
3. Non-response rate
   a) same rate for both groups
   b) non respondents described
   c) rate different and no designation

### 2. Newcastle-Ottawa Quality Assessment Scale: cohort studies

Note: A study can be awarded a maximum of 1 star for each numbered item within the selection and outcome categories. A maximum of 2 stars can be given for comparability.

### Selection
1. Representativeness of the exposed cohort
   a) truly representative of the average describe in the community
   b) somewhat representative of the average in the community
   c) selected group of users eg nurses, volunteers
   d) no description of the derivation of the cohort
2. Selection of the non exposed cohort
   a) drawn from the same community as the exposed cohort
   b) drawn from a different source
   c) no description of the derivation of the non exposed cohort

### Comparability
1. Comparability of cohorts on the basis of the design or analysis
   a) study controls for __________ (select the most important factor)
Two researchers extracted data independently (without using any tools) from all eligible studies. The quality of the studies was evaluated by 2 reviewers, and a third researcher assessed the study when there was a difference in opinion. The following data were extracted: name of the first author, research site, year of publication, type of complications, drugs used in the quinolone and non-quinolone groups, disease types, and follow-up duration. The quality of included studies was assessed using the Newcastle-Ottawa Scale template for randomized controlled trials or the The Newcastle-Ottawa Scale template for non-randomized controlled trials. The full criteria for grading has been provided online in the supplementary file: Newcastle-Ottawa Scale, http://links.lww.com/MD/E728. It has 3 categories (selection, comparability, and exposure) and 8 items. Two researchers performed quality assessments individually. In the selection category (adequate definition of the cases, representativeness of the cases, selection of non-quinolones, and definition of non-quinolones) and exposure category (ascertainment of exposure, same method of ascertainment for cases and non-quinolones, and non-response rate), a quality research item received 1 star, and a comparable category (comparability of cases and non-quinolones on the basis of the design or analysis) could receive at most 2 stars. The quality assessment values ranged from 0 to 9 stars. Each band indicates the percentage of the included studies that met each of these quality criteria. A higher score represented better methodological quality. We regarded scores of 0 to 3, 4 to 6, and 7 to 9 as reflecting low, moderate, and high quality, respectively. This scale was a risk of bias assessment tool for observational studies, especially case-control or cohort studies. It was recommended by the Cochrane Collaboration. However, this assessment tool was lack of methodological details in published studies, which may potentially deviate the risk of bias assessment.

### Table 2

The Newcastle-Ottawa Scale (NOS)

| Outcome | (continued). |
|---------|--------------|
| b) study controls for any additional factor* (This criteria could be modified to indicate specific control for a second important factor.) |
| 1) Assessment of outcome |
| a) independent blind assessment* |
| b) record linkage |
| c) self report |
| d) no description |
| 2) Was follow-up long enough for outcomes to occur |
| a) Yes (select an adequate follow up period for outcome of interest)* |
| b) No |
| 3) Adequacy of follow up of cohorts |
| a) Complete follow-up - all subjects accounted for* |
| b) Subjects lost to follow up unlikely to introduce bias - small number lost - > ___ % (select an adequate %) follow up, or description provided of those lost* |
| c) Follow up rate - < ___ % (select an adequate %) and no description of those lost |
| d) No statement |

(2) no control group was found in the literature;
(3) conference papers, case reports, or review articles;
(4) insufficient original data provided;
(5) side effects did not mention musculoskeletal adverse events.

### 2.5. Data extraction and quality evaluation and bias risk assessment

Two researchers extracted data independently (without using any tools) from all eligible studies. The quality of the studies was evaluated by 2 reviewers, and a third researcher assessed the study when there was a difference in opinion. The following data were extracted: name of the first author, research site, year of publication, type of complications, drugs used in the quinolone and non-quinolone groups, disease types, and follow-up duration. The quality of included studies was assessed using the Newcastle-Ottawa Scale template for randomized controlled trials or the The Newcastle–Ottawa Scale template for non-randomized controlled trials. The full criteria for grading has been provided online in the supplementary file: Newcastle-Ottawa Scale, http://links.lww.com/MD/E728. It has 3 categories (selection, comparability, and exposure) and 8 items. Two researchers performed quality assessments individually. In the selection category (adequate definition of the cases, representativeness of the cases, selection of non-quinolones, and definition of non-quinolones) and exposure category (ascertainment of exposure, same method of ascertainment for cases and non-quinolones, and non-response rate), a quality research item received 1 star, and a comparable category (comparability of cases and non-quinolones on the basis of the design or analysis) could receive at most 2 stars. The quality assessment values ranged from 0 to 9 stars. Each band indicates the percentage of the included studies that met each of these quality criteria. A higher score represented better methodological quality. We regarded scores of 0 to 3, 4 to 6, and 7 to 9 as reflecting low, moderate, and high quality, respectively. This scale was a risk of bias assessment tool for observational studies, especially case-control or cohort studies. It was recommended by the Cochrane Collaboration. However, this assessment tool was lack of methodological details in published studies, which may potentially deviate the risk of bias assessment.

### 2.6. Statistical analysis

Stata 11 software was used for data processing and analysis. The risk ratio (RR) and 95% confidence interval (CI) were calculated to determine the effect size for dichotomous variables. The mean difference and 95% CI were used to calculate the effect size for continuous variables. Heterogeneity tests were assessed using I^2 and Q statistics, and I^2 > 50% was considered for the existence of heterogeneity among the studies. The data were analyzed using the random-effects model. Publication bias was evaluated by the rank sum test and a funnel chart.

### 2.7. Ethical statement

This study was carried out in accordance with the recommendations and in the preferred reporting items for systematic reviews and meta-analyses guidelines. Hence, permission from the ethics committee or the institutional review board is not required.

### 3. Results

#### 3.1. Study selection

A total of 802 articles were screened through e Cochrane Library, Embase, and PubMed, and 1 article was obtained from another source. After eliminating duplicate literature, 617 potentially relevant articles remained. After a second round of screening of titles and abstracts based on the exclusion criteria, 152 articles remained for further evaluation. Ten articles were included after screening,\(^1\) as shown in Figure 1. Only 1 of the included articles was a historical cohort study,\(^3\) and the rest were prospective cohort studies. The characteristics of the included studies are shown in Table 1. According to the Newcastle–Ottawa scale, the quality of all studies were > 5 points (Table 2): Stata 11 software was used for meta-analysis. \(I^2\) and Q tests were used to test heterogeneity. \(I^2\) was found to be 26.7% \((P=.143)\). We used a random effects model for Meta-analysis. There were no statistically significant differences between fluoroquinolone and non- fluoroquinolone groups \((RR=1.145, \, 95\% \, CI=0.974–1.345, \, P=.101)\) in terms of bone and muscle damage (Fig. 2).
3.2. Subgroup analysis based on different quinolones

Two statistical methods, $I^2$ statistics and Q, were used to test heterogeneity. We observed an absence of any heterogeneity, and the random-effects model was used. Meta-analysis showed that the trovafloxacin and levofloxacin subgroups were significantly different from the control group. (Table 3; Fig. 3).

3.3. Sensitivity analysis

To test the stability and reliability of the results, a sensitivity analysis was performed. The results showed that removing individual studies did not have any significant effect on the combined effect size RR value, indicating that the results were stable and reliable (Fig. 4).

3.4. Publication bias

To check for publication bias, a funnel plot was constructed, and Egger test was performed. The funnel plot showed a roughly symmetrical distribution and the Egger test $P$ value was .688 (95% CI: $-0.7348835$ to $1.086832$), indicating that there was no publication bias (Fig. 5).

4. Discussion

Although fluoroquinolones are routinely used to treat common infections such as adult urinary tract infections and pneumonia, its use in the pediatric population is limited due to concerns about significant adverse effects. In a systematic review, Adefurin et al.\textsuperscript{14} reported 1065 cases of adverse events among 16,184

| Drug          | Number of studies | Heterogeneity | Method | RR     | 95% CI      | $P$  |
|---------------|-------------------|---------------|--------|--------|-------------|------|
| Ciprofloxacin | 6                 | 0.0%          | .559   | Random | 1.125       | .0866, 1.282 | .079 |
| Trovafloxacin | 2                 | 0.0%          | .673   | Random | 0.209       | .045, 0.972  | .046 |
| Ofloxacin     | 2                 | 0.0%          | .860   | Random | 0.895       | .695, 1.154  | .393 |
| Levofoxacin   | 5                 | 0.0%          | .754   | Random | 1.761       | 1.187, 2.612 | .005 |
| Gatifloxacin  | 2                 | 0.0%          | .454   | Random | 1.053       | .281, 3.951  | .039 |

Table 3
Subgroup analysis among the different quinolones.
pediatric patients on ciprofloxacin therapy (7% risk; 95%, CI 3.2–14.0%). The adverse event was musculoskeletal, which was significantly higher in the fluoroquinolone group than in the non-fluoroquinolone group, although all joint injuries were reversible. Data on the safety of fluoroquinolones in children are still limited, and safety issues have led to the termination of research with fluoroquinolones in the pediatric population during clinical development. Therefore, several fluoroquinolones have been withdrawn from the US market, including temafloxacin, trovafloxacin, and gatifloxacin.[15] The most common adverse effects of fluoroquinolones in adults are gastrointestinal symptoms (nausea, vomiting, and diarrhea), severe allergic skin reactions, and central nervous system effects such as dizziness, headache, and anxiety.[16] In August 2013, the FDA requested that all fluoroquinolones be updated with labels and drug guidelines to better describe the severe adverse effects of peripheral neuropathy. A review of the adverse event reporting system database shows that the onset of peripheral neuropathy with fluoroquinolones is fast and can be severe, disabling, and permanent. Unfortunately, there are no clinical predictors to identify the population at risk.[17] Animal toxicity studies have shown that young beagle dogs experience joint toxicity in weight-bearing joints after receiving a first-generation quinolone, namely piperacillin. Since then, all quinolones have resulted in adverse effects on joints in juvenile animals,[2] and the extent of adverse drug reactions varies according to drug and animal species. Of all animals studied, dogs are most sensitive to joint toxicity caused by fluoroquinolones.[18]

Chalumeau et al conducted a multicentric, observational, comparative cohort study in France from 1998 to 2000 based on 276 fluoroquinolone-treated pediatric patients and 249 cases treated with other antibiotics for different kinds of infections (respiratory infection and pneumonia, intestinal infection, sepsis and meningitis, urinary tract infection, and prevention of neutropenia).[9] Compared to that in the non-quinolone-treated group, musculoskeletal adverse events were more prevalent in the
quinolone-treated group (3.8% vs 0.4%), and no severe or sustained musculoskeletal damage was found after a single follow-up. Further, Noel et al. evaluated the safety and tolerability of levofloxacin based on 2523 children (a total of 2233 children completed 1-year follow-up, including 1340 in the levofloxacin treatment group and 893 in the control group, aged 6 months–16 years). The results showed that the incidence of skeletal muscle adverse events in the levofloxacin treatment group was higher than that in the non-quinolone control group. Moreover, the incidences of skeletal muscle adverse events in the 2-month follow-up and control groups were 2.1% and 0.9% (P = .04), respectively, and the incidences of adverse reactions were 3.4% and 1.8% (P = .03). Bradley et al. conducted a 5-year long-term follow-up of 207 children with adverse skeletal muscle reactions (124 of them from the levofloxacin treatment group and 83 from the non-quinolone treatment group). At the end of the 5-year follow-up, only 2 children (1 in each of the 2 groups) had skeletal muscle adverse events that might have been caused by drug therapy. The data safety and monitoring committee concluded that neither of the 2 adverse events was “possibly related” to the study drug.

Animal studies have shown that joint disease occurs earlier in young animals. However, a neonatal matched case-control study found that ciprofloxacin does not affect chondrogenesis. Thirty neonates with multidrug-resistant sepsis were treated with intravenous ciprofloxacin for 14 days and 30 matched neonates with sepsis were treated with non-quinolone antibiotics. There were no significant differences in mean serum electrolyte, liver, kidney, and hematological parameters between the 2 groups. Continuous ultrasound examinations of the knee cartilage after 1 and 6 months showed no difference between the 2 groups. In addition, a systematic review by Kaguelidou et al. on newborns found no serious adverse events, particularly joint toxicity, with ciprofloxacin. A single-center observational cohort study in Australia revealed that levofloxacin prophylaxis during induction therapy for pediatric acute lymphoblastic leukemia can reduce the risk of infection by 70%. Further, for the treatment and prevention of multidrug-resistant tuberculosis in children, quinolone antibiotics have achieved good benefits and have been used for a long time without reports of severe articular cartilage damage. Therefore, in a statement in 2011, the American
Academy of Pediatrics concluded that “fluoroquinolones are quite safe in children” and outlined the rationale for their use.[24]

Despite this available evidence, the perception of risk with fluoroquinolone remains high. Arthropyxia is the most common arthropathic symptom in children (50%), which mainly affects the knee joint. Tendon or joint disease and reduced movement also account for a large proportion of joint disease cases (19% and 15%, respectively). However, these musculoskeletal events are reversible with management.[25] In 2016, the American Academy of Pediatrics recommended that fluoroquinolones can be used for the following infections in children:[26]

1. exposure to anthrax Bacillus (also approved by the FDA);
2. urinary tract infection caused by Pseudomonas aeruginosa or other multidrug-resistant gram-negative bacilli (FDA-approved for treatment of complicated urinary tract infections and pyelonephritis caused by Escherichia coli);
3. chronic suppurative otitis media or malignant otitis externa caused by P. aeruginosa;
4. acute or chronic osteomyelitis caused by P. aeruginosa;
5. deterioration of pulmonary functions in patients with cystic fibrosis colonized by P. aeruginosa;
6. infection caused by susceptible mycobacteria;
7. gram-negative bacillus infection in immunosuppressed patients resistant to other alternative antibacterial agents;
8. gastrointestinal infections caused by a variety of resistant species such as Shigella, Salmonella, Vibrio cholerae, or Campylobacter;
9. severe infections in children with a history of severe allergies to conventional antibacterial agents.

This study showed that fluoroquinolones have no differential effect on musculoskeletal adverse events when compared to that with other antibiotics. Therefore, restricting fluoroquinolones in children should not be recommended, although a low risk of fluoroquinolone-induced joint damage cannot be excluded. A study investigating 657,950 cases of adult patients found that quinolones are indeed a risk factor for tendon rupture.[27] Hence, it is advisable to use fluoroquinolones in children with life-threatening diseases where other antibiotics are considered ineffective. Specific recommendations made by the American Academy of Pediatrics, 2016, on the use of fluoroquinolones in children can thus be followed.[26]

There are some limitations to this study. Among the 10 included studies, 1 was a retrospective study,[18] in which adjustment for multivariate analysis was not performed; therefore, the potential side effects of quinolones might have been ignored or underestimated in this study. In addition, the included studies are relatively old, and there is a lack of relevant randomized controlled trials in recent years. In addition, most of the studies had a short follow-up period (several weeks–1 year). Therefore, large-scale prospective studies in children and adults with a considerably longer follow-up duration are warranted.

In conclusion, this meta-analysis revealed that there was no difference in the adverse musculoskeletal events caused by fluoroquinolone and non-quinolone antibiotics. Fluoroquinolone antibiotics may be appropriate for use in children when other antibiotics prove ineffective.

Author contributions
Ji-gan Wang and Hai-Rong Cui conceived and designed the study. Ji-gan Wang and Hua-Bo Tang searched the literature and extracted data. Yi-sen Hu performed statistical analyses. All authors wrote and reviewed the manuscript.

Conceptualization: Ji-gan Wang.
Data curation: Ji-gan Wang, Hai-Rong Cui, Yi-sen Hu.
Investigation: Ji-gan Wang, Yi-sen Hu.
Resources: Hua-Bo Tang.
Software: Hai-Rong Cui, Yi-sen Hu.
Writing – original draft: Ji-gan Wang, Hai-Rong Cui, Hua-Bo Tang.
Writing – review & editing: Ji-gan Wang.

References
[1] Aldred KJ, Kerns RJ, Osheroff N. Mechanism of quinolone action and resistance. Biochemistry 2014;53:1565–74.
[2] Ingham R, Brentnall DW, Dale EA, et al. Arthropyxia induced by antibacterial fused N-alkyl-4-pyridone-3-carboxylic acids. Toxicol Lett 1977;1:21–6.
[3] Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. Eur J Epidemiol 2010;25:603–5.
[4] Clinical Review for New Drug Applications. 19-537/S-049, 20-780/S-013, 19-8478-027, and 19-8578-031.
[5] Salam MA, Dhar U, Khan WA, et al. Randomised comparison of ciprofloxacin suspension and pivmecillinam for childhood shigellosis. Lancet 1998;352:522–7.
[6] Leibovitz E, Janco J, Piglansky L, et al. Oral ciprofloxacin vs. intramuscular ceftriaxone as empirical treatment of acute invasive diarrhea in children. Pediatr Infect Dis J 2000;19:1060–7.
[7] Sáez-Llorens X, McCog C, Fers JM, et al. Quinolone treatment for pediatric bacterial meningitis: a comparative study of trovafloxacin and ceftriaxone with or without vancomycin. Pediatr Infect Dis J 2002;21:14–22.
[8] Yee CL, Duffy C, Gerbino PG, et al. Tendon or joint disorders in children after treatment with fluoroquinolones or azithromycin. Pediatr Infect Dis J 2002;21:525–9.
[9] Chalumeau M, Tonnelier S, D’Athis P, et al. Fluoroquinolone safety in pediatric patients: a prospective, multicenter, comparative cohort study in France. Pediatrics 2003;111:e714–9.
[10] Sáez-Llorens X, Rodriguez A, Arguedas A, et al. Randomized, investigator-blinded, multicenter study of gatifloxacin versus moxifloxacin and levofloxacin for pediatric use. Pediatr Infect Dis J 2005;24:293–300.
[11] Shen L, Arguedas A, Husseman M, et al. Randomized, investigator-blinded, multicenter, comparative study of gatifloxacin versus moxifloxacin in children with acute otitis media treatment failure in children. Pediatr Infect Dis J 2005;24:301–18.
[12] Noel GJ, Bradley JS, Kaufman RE, et al. Comparative safety profile of levofloxacin in 2523 children with a focus on four specific musculoskeletal disorders. Pediatr Infect Dis J 2007;26:879–91.
[13] Bradley JS, Arguedas A, Blumer JS, et al. Comparative study of levofloxacin in the treatment of children with community-acquired pneumonia. Pediatr Infect Dis J 2007;26:688–78.
[14] Aderfuri A, Sammons H, Jacqz-Aigrain E, et al. Ciprofloxacin safety in paediatrics: a systematic review. Arch Dis Child 2011;96:874–80.
[15] Patel K, Goldman JL. Safety concerns surrounding ciprofloxacin use in children. J Clin Pharmacol 2016;56:1060–75.
[16] Humpel R, Mullmann R, Schmidt H. Ciprofloxacin in pediatrics: worldwide clinical experience based on compassionate use/safety report. Pediatr Infect Dis J 1997;16:160–2.
[17] Chaudhari S, Suryawanshi P, Ambardhkar S, et al. Safety profile of ciprofloxacin used for neonatal sepsis. Indian Pediatr 2004;41:1246–51.
[18] Yabe K, Satoh H, Ishi Y, et al. Early pathophysiological feature of arthropathy in juvenile dogs induced by ofloxacin, a quinolone antimicrobial agent. Vet Pathol 2004;41:673–81.
[19] Sudha C, Pradeep S, Shrikant A, et al. Safety profile of ciprofloxacin used for neonatal sepsis. Indian Pediatr 2004;41:1246–51.
[21] Wolf J, Tang L, Flynn P, et al. Levoflaxacin prophylaxis during induction therapy for pediatric acute lymphoblastic leukemia. Clin Infect Dis 2017;65:1790–8.

[22] Garcia-Prats AJ, Draper HR, Finlayson H, et al. Clinical and cardiac safety of long-term levofloxacin in children treated for multidrug-resistant tuberculosis. Clin Infect Dis 2018;67:1777–80.

[23] Seddon JA, Hesseling AC, Finlayson H, et al. Preventive therapy for child contacts of multidrug-resistant tuberculosis: a prospective cohort study. Clin Infect Dis 2013;57:1676–84.

[24] Bradley JS, Mary Anne J. Committee on Infectious Diseases. The use of systemic and topical fluoroquinolones. Pediatrics 2011;128:1034–45.

[25] Absodan A, Helen S, Evelyne JA, et al. Ciprofloxacin safety in paediatrics: a systematic review. Arch Dis Child 2011;96:874–80.

[26] Jackson MA, Schutze GE. Committee on Infectious Diseases. The use of systemic and topical fluoroquinolones. Pediatrics 2016;138:e20162706.

[27] Daneman N, Lu H, Redelmeier DA. Fluoroquinolones and collagen associated severe adverse events: a longitudinal cohort study. BMJ Open 2015;5:e010077.

[28] Bradley JS, Kaufman RE, Balis DA, et al. Assessment of musculoskeletal toxicity 5 years after therapy with levofloxacin. Pediatrics 2014;134:e146–153.