JIDC | THE JOURNAL OF INFECTION IN DEVELOPING COUNTRIES

Original Article

Increase in quinolones prescriptions for children (0–10 years old) in Brazil

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Abstract

Introduction: Quinolones are frequently associated with adverse effects such as tendinopathies and joint damage. However, the safety of quinolone use in pediatric patients remains inadequately established, with limited recommended applications. This study aimed to investigate the escalating consumption of quinolones among Brazilian children aged 0–10 years.

Methodology: An interrupted time series analysis was conducted to examine fluctuations in quinolone consumption within the pediatric population. Data were sourced from the Brazilian National Controlled Products Management System (SNGPC). Analysis of variance and joinpoint regression were employed to assess yearly variations in commercial unit sales of quinolones.

Results: Brazil witnessed the consumption of approximately 93 million commercial units of quinolones by the entire population, with 1 million units prescribed for children (0–10years). The surge in quinolone utilization among children during this period exceeded 50% ($p < 0.05$), a statistically significant increase compared to the 24% growth observed in the entire population. Regression analysis indicated an annual linear growth of around 9% (year on year) in Brazil for quinolone use among children.

Conclusions: Our study revealed a concerning rise in quinolone prescriptions for Brazilian children aged 0–10 years, underscoring the imperative for cautious use due to limited safety data and acknowledged risks, such as musculoskeletal damage. Healthcare providers should prioritize safer alternatives when possible, focusing on children's well-being and combating antimicrobial resistance. Advocacy for prudent prescribing practices and increased awareness is crucial, along with further research to comprehensively understand long-term effects and establish evidence-based guidelines for quinolone use in pediatric populations.

Key words: quinolones; children; tendinopathies; joint damage.

J Infect Dev Ctries 2025; 19(3):418-423. doi:10.3855/jidc.20177

(Received 02 April 2024 – Accepted 15 August 2024)

Introduction

The first quinolone, nalidixic acid, was introduced in the 1960s with initial approval by the Food and Drug Administration (FDA) for children older than 3 months, specifically for urinary tract infections [1]. Quinolones exhibit bactericidal activity by targeting bacterial DNA and RNA synthesis. They are effective against a wide range of microorganisms, including Gram-positive and Gram-negative bacteria, with additional anti-pseudomonal activity and high oral bioavailability [2]. Their concentration-dependent action on enzymes involved in bacterial DNA replication, such as DNA gyrase and topoisomerase IV, makes them effective [3]. Despite their efficacy in treating various bacterial infections in adults over the last 40 years; including urinary, respiratory, skin and soft tissue, ocular, and otological infections, their incorporation into pediatric anti-infective therapy has been limited due to significant adverse effects, particularly concerning cartilage and tendons [4–6].

In the 1980s and 1990s, new quinolones were introduced into clinical practice, and they became the most prescribed class of antibiotics in the United States in the 2000s, despite 42% of these prescriptions being considered nonapproved [7]. The current FDA authorization restricts quinolone use in children under 18 years to complicated urinary tract infections, pyelonephritis, and post-exposure prophylaxis and treatment of inhalation anthrax [8]. Nevertheless, concerns about safety and the treatment of multidrug-resistant infections have led to frequent off-label use of ciprofloxacin or levofloxacin in children [2].

The major concerns regarding quinolone use in children revolve around cartilage and tendon damage leading to associated arthropathy. The first report of childhood arthropathy related to nalidixic acid emerged in the 1960s [9]. A 2011 systematic review of over 16,000 young people (less than 17 years old) using ciprofloxacin reported 6.6% adverse events; with musculoskeletal events, primarily arthralgia, accounting for 1.6% [10]. Another study comparing

levofloxacin with other antimicrobial treatments in over 2,500 children revealed higher musculoskeletal adverse events with quinolones at 2 months (2.1% vs. 0.9%) and 1 year (3.4% vs. 1.8%) after treatment initiation [11].

Serious injuries, such as tendon rupture, are mostly associated with quinolone use in the elderly, athletes, and concurrent corticosteroid use or kidney disease [12]. Reports also exist of tendinopathies and Achilles tendon ruptures after using topical quinolones in ear drops for otitis treatment [13,14]. Less common effects in children include seizures and neurological damage, with a clinical trial involving over 100,000 children treated with ciprofloxacin showing similar rates of neurological events compared to other antibiotics [1].

Despite quinolones' widespread clinical use, their short- and long-term effects in children remain poorly understood and should be carefully monitored when necessary [15]. This study aimed to monitor the use of topical and parenteral quinolones in Brazilian children aged 0–10 years between 2014 and 2019, by comparing it with adult usage, identifying commonly used agents, and examining potential changes in usage growth rates within this age group.

Methodology

Study samples and data collection

An interrupted time series analysis was conducted to assess variations in quinolone consumption among 0–10-year-old children and the entire population from 2014 to 2019. Prescriptions from dentists and veterinarians were excluded, focusing solely on medical prescriptions for topical and oral quinolones. Data from hospitalized patients were not included in this study. The dataset, obtained from The National Controlled Products Management System (SNGPC) [16], exclusively captured the number of antibiotic units sold in pharmacies across Brazil. Data from 2020 onward were omitted due to the potential bias in antibiotic consumption resulting from the coronavirus disease 2019 (COVID-19) pandemic.

Statistical analysis

Joinpoint regression, a statistical technique widely employed in epidemiology to analyze time series data and identify significant changes in trends, was utilized to assess yearly variations in quinolone sales in both adults and children [17]. The Joinpoint model excels in precisely pinpointing "joinpoints" within a time series dataset, representing specific points in time where a statistically significant change in the trend occurs. In order to compare the means of consumption between 2014 and 2019, statistical analyses were performed using analysis of variance, followed by the Tukey-Kramer test. These analyses aimed to provide insights into any significant differences in quinolone consumption patterns during the specified time frame.

Results

The number of commercial units of quinolones sold between the years 2014 and 2019 in the entire population and the percentage change comparing 2014 to 2019 are summarized in Table 1. Ciprofloxacin emerged as the top-selling quinolone across all age groups throughout all the years examined, and experienced a notable growth of approximately 33.5% when comparing data from 2014 to 2019 (Table 1). The quinolone with the most significant overall growth in sales across diverse age demographics was moxifloxacin. This notable increase was attributed to its expansive spectrum of activity, encompassing *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis*, and atypical microorganisms such as *Chlamydia pneumoniae* and *Mycoplasma pneumonia* [18].

Conversely, norfloxacin experienced a decline in sales by 33%, which aligned with findings from other studies. This decrease in popularity was attributed to the emergence of resistant microorganisms, as documented in prior research [19]. The evolving landscape of antimicrobial resistance appeared to have influenced the market dynamics of quinolones, with certain members of this drug class experiencing shifts in demand and preference over the analyzed period.

Table 1. Number of commercial units of quinolones sold between the years 2014 and 2019 in the entire population and the percentage change comparing 2014 to 2019.

Quinolone	2014	2015	2016	2017	2018	2019	Total sales	Change (%) 2014–2019
Ciprofloxacin	7,064,607	7,239,114	7,888,587	8,358,098	9,331,305	9,430,376	49,312,086	33.49%
Levofloxacin	3,205,450	3,474,250	3,999,495	4,414,091	4,240,316	3,845,087	23,178,688	19.95%
Moxifloxacin	1,092,263	1,133,078	1,234,106	1,378,382	1,668,855	1,734,117	8,240,800	58.76%
Norfloxacin	1,458,290	1,433,096	1,344,578	1,239,810	1,128,505	973,542	7,577,820	– 33.24%
Gatifloxacin	574,845	578,348	583,119	623,569	670,342	717,985	3,748,207	24.90%
Ofloxacin	106,005	108,954	111,229	114,739	124,732	125,109	690,768	18.02%
Gemifloxacin	43,899	24,650	16,114	9,736	1,953	21	96,373	– 99.95%
Besifloxacin	21,402	10,745	9,466	8,932	7,878	6,169	64,592	– 71.18%
Total (year)	**13,568,774**	**14,004,250**	**15,188,709**	**16,149,374**	**17,175,903**	**16,834,424**	**92,909,333**	**24.06%**

Table 2. The number of commercial units of quinolones sold between the years 2014 and 2019 in children (0–10 years) and the percentage change comparing 2014 to 2019.

Quinolone	2014	2015	2016	2017	2018	2019	Total sales	Change (%) 2014–2019
Ciprofloxacin	60.834	72.387	85.751	97.781	103.968	98.135	518.856	61.32%
Levofloxacin	28.198	34.119	43.194	48.184	47.414	42.921	244.030	52.21%
Moxifloxacin	9.262	10.944	12.610	15.006	19.628	19.208	86.658	107.39%
Norfloxacin	17.741	17.756	19.879	19.584	17.506	15.209	107.675	– 14.27%
Gatifloxacin	5.310	6.025	7.200	8.035	8.287	8.317	43.174	56.63%
Ofloxacin	1.115	1.138	1.131	1.288	1.413	1.326	7.411	18.92%
Gemifloxacin	343	173	156	98	42	0	812	– 100.00%
Besifloxacin	152	83	131	85	64	57	572	– 62.50%
Total (year)	**122.955**	**142.625**	**170.052**	**190.061**	**198.322**	**185.173**	**1.009.188**	**50.60%**

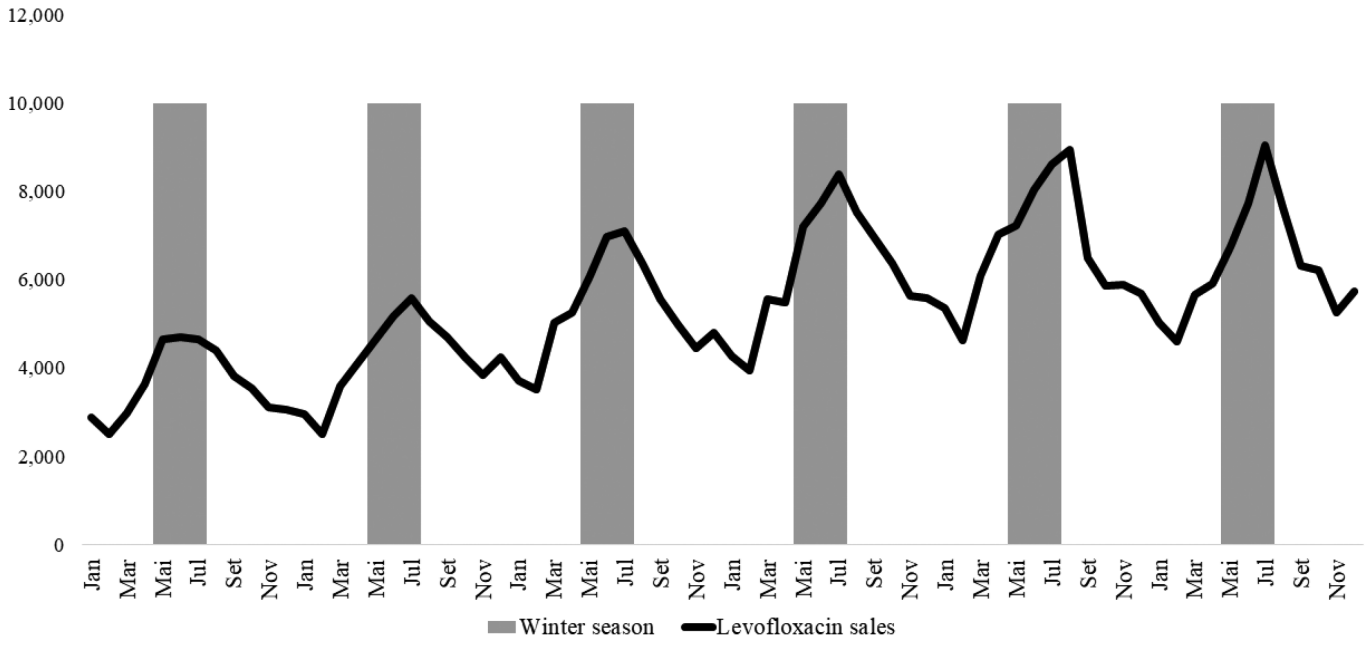
Table 2 summarizes the consumption of quinolones among children aged 0–10 years in Brazil from 2014 to 2019. The data revealed a substantial increase in consumption of 50.6% when comparing 2019 prescriptions with those from 2014 ($p < 0.05$). Notably, this growth far exceeded the overall population increase of 24.0% during the same period, as outlined in Table 1.

Particularly noteworthy was the remarkable growth ($p < 0.01$) observed in pediatric prescriptions of moxifloxacin, which soared by 107% within the study duration, from approximately 9,000 to 19,000 annual pediatric prescriptions nationwide. The literature lacks reports of significant problems or adverse effects associated with moxifloxacin use in children. However, it is crucial to emphasize its recommended application solely for the treatment of tuberculosis resistant to other antibiotics in this age group, discouraging its use for upper respiratory tract infections [20–22].

Another quinolone demonstrating substantial growth ($p < 0.01$) in pediatric prescriptions was levofloxacin, which witnessed a notable 52% increase over the study period. Despite not being recommended as a first-choice treatment for acute respiratory infections in children, its utilization surged during the winter months in Brazil, aligning with a rise in respiratory infections. This seasonal variation is graphically represented in Figure 1.

Figure 1 underscores the seasonality in levofloxacin usage, with a pronounced upswing during the winter months (depicted by gray bars) and a decline in warmer seasons. It is crucial to note that numerous safer alternatives exist for treating acute respiratory infections in children, as outlined by the Centers for Disease Control and Prevention (CDC), eliminating the necessity of resorting to medications with limited clinical experience in pediatrics [23]. Furthermore, in May 2016, the FDA expressed concerns about adverse events associated with quinolones, emphasizing that "serious side effects associated with fluoroquinolone antibacterial drugs generally outweigh the benefits for patients with acute sinusitis, acute bronchitis, and

Figure 1. Number of commercial units of levofloxacin sold in Brazilian pharmacies for children (0–10 years) between 2014 and 2019.



uncomplicated urinary tract infections who have other treatment options" [24].

A joinpoint regression model (Figure 2) was employed to assess annual trends in quinolone sales, illustrate the yearly percentage change, and its statistical significance. The regression analysis revealed a 5.13% annual growth in quinolone sales for the entire population (all ages) and a more substantial increase of 9.41% for children aged 0–10 years. Notably, the regression analysis indicated a consistent linear growth in these percentages, with no discernible trend changes during the years 2014 to 2019, for both studied groups. In other words, there was a linear increase in the indicated percentages without alterations in the growth trends between the studied years.

Discussion

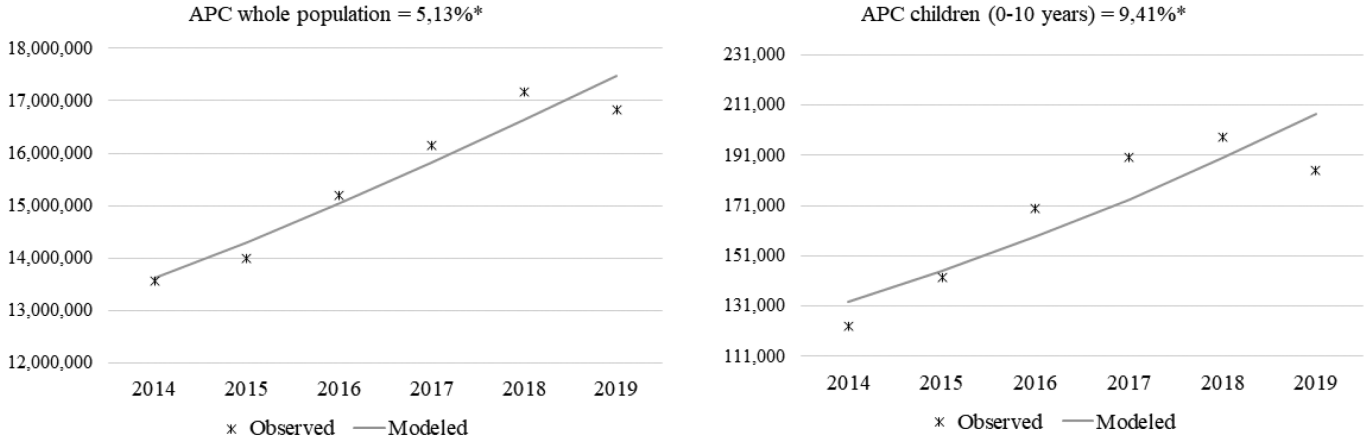
The increase in moxifloxacin consumption among children observed in this study is concerning, especially when considering findings from the study by Greenberg *et al.* [22]. Their research highlighted the limited pharmacokinetic data and potential for toxicity associated with moxifloxacin use in pediatric populations. Specifically, the study reported high variability in oral bioavailability and concerns regarding the drug's clearance and volume distribution, which were found to be significantly different from previous studies. Given the complex pharmacokinetics and the lack of comprehensive safety data, the rising use of moxifloxacin in children, as observed in our study, may not be appropriate, particularly in cases where safer alternatives exist.

The present study revealed a substantial (50.6%) increase in quinolone consumption among children aged 0–10 years in Brazil between 2014 and 2019, a rise that significantly outpaced the 24.0% growth observed in the general population over the same period. This trend mirrors global concerns highlighted in several studies. For instance, Patel *et al*. emphasized the growing use of quinolones in children, often in off-label contexts, raising serious concerns about the potential for severe adverse effects, such as musculoskeletal issues [8]. The lack of robust long-term safety data exacerbates these concerns, making the increased use of quinolones in pediatric populations particularly worrisome. Similarly, Adefurin *et al.* conducted a systematic review that documented a rise in ciprofloxacin use in children despite limited evidence supporting its safety [10]. Their findings, like those observed in Brazil, suggest that the expanding use of quinolones may be inappropriate, particularly given the significant risk of adverse events and the paucity of conclusive data on their long-term safety in children.

Gendrel and Moulin also identified a global trend toward increasing fluoroquinolone use in pediatric settings, despite guidelines that recommended restrictions due to the high risk of adverse effects, such as arthropathies [6]. The parallel observed in Brazil's rising quinolone consumption aligns with this international trend, underscoring the need for caution. These studies collectively highlight the potential dangers of this growing practice, particularly in light of the limited clinical experience and safety data regarding quinolone use in children. The findings from the present study, when compared with these international concerns, suggest an urgent need for a reassessment of prescribing practices and greater awareness of the risks associated with quinolone use in pediatric populations.

Data on the safety of quinolones in children remain incompletely established, particularly concerning

Figure 2. Joinpoint regression analysis of quinolone sales in Brazil for the entire population (all ages) and for children (0–10 years).



* Indicates that annual percentage change (APC) is significantly different from o at the α = 0.05 level.

events related to the musculoskeletal system. Thus, opting for safer antimicrobials is currently the preferred choice. The indiscriminate use of quinolones in children not only poses an individual risk to the child but also contributes to the emergence of resistant microorganisms [3,25].

Prescriptions of quinolones for children require careful consideration, balancing the risk-benefit ratio, as effective treatment for respiratory infections must be provided without unnecessarily exposing children to the potential risks of joint damage. Quinolones should be reserved as a second or third option in pediatric therapy, specifically for infections unresponsive to the safer antibiotics recommended in pediatric guidelines and consensus [26].

The observed increase in quinolone prescriptions in this study raises concerns about potential risks associated with their use in this vulnerable populations. Despite their proven efficacy in treating bacterial infections in adults, the safety profile of quinolones in children remains inadequately established. Recognized adverse effects, such as tendinopathies and joint damage, underscore the necessity for caution when prescribing these antibacterials to pediatric patients. Our study's findings indicate a significant surge in quinolone consumption among children, surpassing the overall population growth rate. This trend, coupled with the substantial rise in pediatric prescriptions for moxifloxacin and levofloxacin, prompts questions about the appropriateness of their use, especially in treating respiratory infections. Safer alternatives exist for such conditions, and the potential risks associated with quinolones should be meticulously weighed against their perceived benefits.

The study underscores the critical need for promoting judicious antibiotic prescribing practices in pediatric populations. While quinolones may have a role in specific clinical scenarios where other treatments have failed, they should be considered as second or third-line options. The well-documented adverse effects, including musculoskeletal damage and neurological events, highlight the necessity for healthcare providers to prioritize the use of safer antimicrobials in children. Guidelines and consensus statements should be developed and disseminated to offer clear recommendations for the appropriate use of quinolones in pediatrics. Additionally, efforts should be made to enhance healthcare professionals' awareness regarding the potential risks associated with quinolones and to encourage adherence to evidence-based prescribing practices [27] .

The study has limitations that must be acknowledged. First, the data utilized were obtained exclusively from the SNGPC, which captures sales data from pharmacies but does not include information from hospital settings. Additionally, the study did not account for potential confounding factors, such as regional variations in prescribing practices, socioeconomic status, or healthcare access; which could influence the observed trends. These limitations suggest that while the study provides valuable insights into quinolone consumption trends, the findings should be interpreted with caution; and further research is needed to comprehensively understand the factors driving these trends and their implications for pediatric healthcare.

Conclusions

The study highlights a significant and concerning increase in quinolone prescriptions for children aged 0-10 years in Brazil, which far surpassed the growth seen in the general population. This trend is particularly alarming given the well-documented risks associated with quinolone use in pediatric populations, including musculoskeletal damage and the potential for long-term adverse effects. The findings underscore the urgent need for healthcare providers to exercise greater caution when prescribing these antibiotics to children, and reserving them for situations where safer alternatives have been exhausted. There is a critical need for more stringent prescribing guidelines, increased awareness of the risks, and further research to establish evidence-based practices that prioritize the safety and well-being of pediatric patients.

Acknowledgements

We would like to thank the University of Sorocaba for providing support for the teachers to conduct this study.

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Conflict of interests

No conflict of interests is declared.

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