INTRODUCTION

Fluoroquinolones were first introduced for use in the 1980s as broad-spectrum antimicrobial agents. In 2002, fluoroquinolones became the most commonly prescribed antibiotic class in the USA, accounting for 22 million outpatient visits, representing a threefold increase since 1995 (Linder et al., 2005). The excellent oral bioavailability and tissue penetration, ease of administration as well as their broad-spectrum activity make fluoroquinolones a very attractive class of antimicrobials. The rising patterns of fluoroquinolone use in adults have been followed by decreased fluoroquinolone susceptibility against a variety of common bacteria. This is particularly true amongst Escherichia coli, the most common pathogen associated with urinary tract infections (Boyd et al., 2008). A recent report of E. coli urine isolates in adults with community-acquired or healthcare-associated infections showed that 9 and 37 %, respectively, were resistant to levofloxacin (Fleming et al., 2014). Despite the well-documented rise in resistance to these agents in adults, they continue to be the drugs of choice for a variety of indications in both adults and children. However, limited epidemiological data are available for children. We conducted a 10 year epidemiological study to assess the trend of fluoroquinolone susceptibilities amongst children with E. coli urinary isolates.

METHODS

The study was conducted at Alfred I. duPont Hospital for Children (AIDHC; Wilmington, DE, USA), a 180-bed tertiary paediatric teaching hospital affiliated with Thomas Jefferson University (Philadelphia, PA, USA), between 1 March 2000 and 28 February 2010. Urine cultures (midstream clean-catch and catheterized specimens) were retrieved by querying the clinical microbiology laboratory database (Misys; Misys Healthcare System). Cultures that reported more than one organism were discarded. Demographic data were retrieved from AIDHC electronic medical records.

Identification and susceptibility testing of E. coli were performed following the standard procedures at the AIDHC microbiology laboratory, using a semi-automated system (MicroScan; Dade Behring) according to the Clinical Laboratory Standards Institute. The percentage susceptibility for fluoroquinolones was calculated by examining the first isolate per patient per year consistent with the 2006 Clinical Laboratory Standards Institute recommendations (CLSI, 2006).

Fluoroquinolone use amongst hospitalized patients was retrieved by querying the electronic administration record of ciprofloxacin and levofloxacin, as reported previously (Rose et al., 2014). Annual intravenous and oral fluoroquinolone use was calculated as days of treatment (DoT) per 1000 patient-days, where DoT represented the number of days that a patient received either ciprofloxacin or levofloxacin, regardless of the number of doses administered or dosage strength.

For analysis of data, quantitative variables were summarized by mean, median and range. Categorical variables were summarized using frequencies and percentages.

A test of trends was used to test the evolution of fluoroquinolone susceptibility rates over time. The Pearson correlation coefficient was
used to evaluate the association between fluoroquinolone use and resistance rates amongst hospitalized patients. All tests were two-tailed with a level of significance of 0.05. Analyses were performed using SPSS software (version 22; SPSS) and statistical software R (version 2.10.1). The Nemours Institutional Review Board approved this protocol.

RESULTS

In total, 4522 E. coli urinary isolates were recorded over a 10 year period from 3122 unique patients. The median age for all patients was 5 years (range 0–21 years). Females comprised 3858 of all isolates (85 %). Most patients seeking care were from the community (3982; 88 %), with the majority of these isolates being recovered from the emergency room (60 %; 2389/3982) followed by an outpatient clinic (40 %; 1593/3982).

From 2000 to 2010, E. coli susceptibility to fluoroquinolones oscillated over time from 100 to 92 %, without showing a significant trend ($\chi^2=0.4; P=0.5$) (Fig. 1). Susceptibilities to ciprofloxacin had a strong correlation with levofloxacin susceptibilities ($r=0.99; P<0.001$). Males were most likely to have fluoroquinolone-resistant E. coli urinary isolates than females [odds ratio (OR): 2.1; 95 % confidence interval (CI): 1.4–3; $P<0.0001$]. Gender differences remained present for males with catheterized specimens (OR: 2; 95 % CI: 1.3–2.9; $P<0.001$), but not for specimens obtained by midstream clean-catch (OR: 1.3; 95 % CI: 0.5–3.5; $P=0.6$). Males between 1 and 5 years of age had the highest rate of resistant isolates (OR: 7; 95 % CI: 3.2–15; $P<0.0001$). Females with catheterized specimens were more likely to exhibit fluoroquinolone resistance (OR: 1.5; 95 % CI: 1–2.2; $P=0.02$).

Hospitalized children were more likely to have resistant strains when compared with outpatients (OR: 2.8; 95 % CI: 1.9–4; $P<0.0001$) (Fig. 1). In this setting, we found no significant differences in age amongst children with susceptible and resistant strains ($P=0.06$). Emergence of ciprofloxacin and levofloxacin resistance was strongly associated with fluoroquinolone use ($r=0.9; P=0.002$). Fig. 2 depicts the susceptibility of E. coli in children from the community and from the hospital by year and gender. Hospitalized males with E. coli urinary isolates had a significant decrease in fluoroquinolone susceptibility over time ($\chi^2=8.1; P=0.004$).

Rates of fluoroquinolone-resistant E. coli were similar amongst children who received care in the emergency room and in outpatient clinics (OR: 0.9; 95 % CI: 0.6–1.5; $P=0.6$).

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**Fig. 1.** Fluoroquinolone susceptibilities amongst children with E. coli urinary isolates, 2000–2009. Test for trend in proportions: community-acquired E. coli isolates, $\chi^2=0.42, P=0.5$; hospital-associated E. coli isolates, $\chi^2=1.2, P=0.2$; all isolates, $\chi^2=0.46, P=0.5$. 
**DISCUSSION**

To the best of our knowledge, this is the first report illustrating the evolution of fluoroquinolone resistance in *E. coli* amongst children with positive urinary isolates over a 10 year period. Previously reported rates of ciprofloxacin-resistant *E. coli* amongst paediatric males and females with community-acquired urinary tract infections obtained from The Surveillance Network database increased from 1 to 10 % and 0.6 to 4 % between 2002 and 2009, respectively (Edlin et al., 2013). In our experience, a significant trend was not found for inpatient and outpatient children over the study period, except in hospitalized males. Despite decreased urinary *E. coli* susceptibilities in more recent years, particularly for males, a trend for either gender was not found. Gender differences have been described previously; however, differences between catheterized and clean-catch specimens have not been addressed (Edlin et al., 2013). A limitation of this study is that we did not evaluate clinical criteria, and whilst urinary colonization is unlikely in this population, we cannot make inferences regarding infection status or outcomes.

Fluoroquinolone resistance is of particular importance in paediatrics as this population has not yet been faced with the same resistance challenges as the adult population, likely due to the lower overall usage of fluoroquinolone in paediatrics. In the past, fluoroquinolone use in paediatric patients has been somewhat limited due to the potential risk for cartilaginous abnormalities described in weight-bearing joints of juvenile animals. Nevertheless, in 2002, children <18 years of age accounted for > 500 000 fluoroquinolone prescriptions written (Bradley & Jackson, 2011).

We previously reported a strong correlation between increased usage of fluoroquinolones and a rise in resistance amongst hospitalized children, although still relatively low compared with the adult population (Rose et al., 2014). Studies evaluating this correlation in paediatrics are relatively limited and those that are published show conflicting evidence (Rose et al., 2014). A case-control study performed by Kim et al. (2008) did not observe a correlation between prior fluoroquinolone use and fluoroquinolone resistance. However, in this study only eight of the 271 isolates were resistant to fluoroquinolones. A limitation of our study is that outpatient exposure to fluoroquinolone could not be assessed.

As previously described in adults, the increased use of fluoroquinolone in children is indeed impacting the efficacy of this antibiotic class against infections due to *E. coli* (Rose et al., 2014). Although fluoroquinolone
resistance remains more pronounced for adults, the paediatric population is also facing a similar problem, albeit at a slower rate. Stewardship monitoring of fluoroquinolone use amongst children is warranted, in both the outpatient and inpatient setting, to preserve the lifespan and efficacy of this antibiotic class.

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REFERENCES


