Drugs in R&D (2025) 25:35–55
https://doi.org/10.1007/s40268-024-00499-x

ORIGINAL RESEARCH ARTICLE

Analyses of Adverse Drug Reactions to Fluoroquinolones in Spontaneous Reports Before and After the Referral and in Clinical Routine Cases

Diana Dubrall[1,2] · Julia Wicherski[2] · Maike Below[3] · Jan Görtzen-Patin[4,5] · Matthias Schmid[1] · Sven Zenker[1,4,5] · Britta Haenisch[2,6,7] · Bernhardt Sachs[2,8]

Accepted: 3 November 2024 / Published online: 21 January 2025

Abstract

Introduction In November 2018, the European Medicines Agency (EMA) restricted the use of fluoroquinolones (used by mouth, injections or inhalation) in the context of a referral due to long-lasting and potentially irreversible adverse drug reactions (ADRs). Fluoroquinolones should no longer be used to treat mild or moderate bacterial infections unless other antibacterials cannot be used.

Objectives The first aim of our study was to analyze whether in the period before compared with after the referral the characteristics of spontaneous ADR reports related to fluoroquinolones differed and whether specific ADRs were more frequently reported for fluoroquinolones compared with cotrimoxazole. Secondly, we analyzed whether the ADR profile differed between individual fluoroquinolones. Finally, the number of fluoroquinolone reports was considered in relation to the number of outpatient drug prescriptions.

Methods All spontaneous ADR reports from Germany received before the referral (01/2014–12/2019) and after the referral (01/2020–12/2022) for adults in which fluoroquinolones ($n = 2575$; $n = 967$) or cotrimoxazole ($n = 299$, $n = 275$) were reported as suspected/interacting were identified in the European ADR database, EudraVigilance. The ADR reports were descriptively analyzed concerning the reported characteristics. Odds ratios (ORs) and their 95% confidence intervals (CIs) were estimated by logistic regression analyses, which were performed to investigate whether aortic aneurysms, retinal detachments, cardiac arrhythmias, peripheral polyneuropathies, nervous system disorders, toxic liver diseases and non-traumatic injuries of muscles, tendons and synovialis were more frequently reported for fluoroquinolones compared with cotrimoxazole. Stratified analyses between fluoroquinolones were conducted by calculating ORs and their 95% CIs by using two-by-two tables. Reporting rates were calculated by dividing the number of fluoroquinolone reports by the number of fluoroquinolone prescriptions.

Results Reporting rates of fluoroquinolones clearly increased until 2019 and decreased afterward. Only minor differences in the characteristics of fluoroquinolone reports (e.g., regarding the indications) were observed in reports received before and after the referral. In both periods, peripheral neuropathies, nervous system, and muscle and tendon disorders were more often reported for fluoroquinolones than cotrimoxazole. In the pooled fluoroquinolone-stratified analyses, (i) peripheral neuropathies and nervous system disorders were more frequently reported for ciprofloxacin, (ii) non-traumatic injuries of muscle, tendon, and synovialis were more often reported for levofloxacin, and (iii) cardiac arrhythmias and toxic liver diseases were more frequently reported for moxifloxacin compared with the other fluoroquinolones.

Conclusion In accordance with a reminder sent by the EMA referring to prescribing trends for fluoroquinolones, our study showed that the characteristics of spontaneous ADR reports for fluoroquinolones after the referral were similar to those before the referral, underlining the importance of adhering to the recommended restrictions issued by the EMA. In addition, we observed individual differences between ciprofloxacin, levofloxacin, and moxifloxacin with regard to their ADR profile. Further studies are needed to confirm our results.

Disclaimer: The information and views set out in this manuscript are those of the authors and do not necessarily reflect the official opinion of the Federal Institute for Drugs and Medical Devices.

Extended author information available on the last page of the article

Key Points

Only minor differences were found in the characteristics of the spontaneous adverse drug reaction (ADR) reports from EudraVigilance before and after the referral, highlighting the importance of adhering to the recommended restrictions by the EMA.

In addition, we observed individual differences between ciprofloxacin, levofloxacin, and moxifloxacin with regard to their ADR profile. The reasons for these differences have to be analyzed in further studies.

1 Introduction

Fluoroquinolones are broad-spectrum antibiotics against both Gram-negative and Gram-positive bacteria (depending on the type of fluoroquinolone) and have been used for over 40 years [1]. During that time, their safety profile has been discussed and labeling updates have been conducted as a result of severe, long-lasting or potentially irreversible adverse drug reactions (ADRs), which came to light years after marketing authorization [2–9]. Some fluoroquinolones were withdrawn from the market due to safety issues (e.g., trovafloxacin [hepatotoxicity], gatifloxacin [hypoglycemia], and grepafloxacin [cardiotoxicity]) [1, 10, 11].

In November 2018, the European Medicines Agency (EMA) restricted the use of fluoroquinolones applied orally, intravenously or by inhalation following a referral initiated by the German Federal Institute for Drugs and Medical Devices (BfArM) [12]. As a result, fluoroquinolones should no longer be used as first-line treatment of mild or moderate bacterial infections (e.g., uncomplicated urinary tract infections) since the risks associated with their use may exceed their benefits.

Among others, collagen-associated ADRs (e.g., aortic aneurysms, retinal detachments, and tendon disorders), hepatic ADRs, cardiac arrhythmias, and peripheral and central nervous system disorders are known ADRs of fluoroquinolones [13]. In Germany, ciprofloxacin, enoxacin (no longer available on the market), levofloxacin, moxifloxacin, norfloxacin, ofloxacin, and delafloxacin (not yet on the market) are currently approved [8].

Some ADR-specific risk factors such as older age and concomitant corticoid therapy concerning tendon disorders [13, 14] or family histories of aortic aneurysms concerning aortic aneurysms and dissections [13] are described in literature. Sex- and fluoroquinolone-specific differences regarding the frequency of these ADRs were discussed [14–16], but further studies are needed to confirm these results.

The first aim of our study was to analyze whether there are differences in the characteristics of spontaneous ADR reports from Germany related to fluoroquinolones before and after the referral. In addition, we investigated whether aortic aneurysms, cardiac arrhythmias, peripheral neuropathies, nervous system disorders, non-traumatic injuries of muscles, tendons, and synovialis, toxic liver diseases, and retinal detachments were more frequently reported for fluoroquinolones compared with cotrimoxazole (combination of sulfamethoxazole and trimethoprim) before and after the referral. All of these specific ADRs were part of the referral and were in another research project of the BfArM identified as most relevant to gain further evidence [17]. The second aim was to evaluate whether these specific ADRs were more frequently reported for females or males or for one fluoroquinolone compared with another. Thirdly, we analyzed whether the number of fluoroquinolone and cotrimoxazole prescriptions in Germany and the number of spontaneous ADR reports in relation to the number of these prescriptions increased or decreased in the analyzed period of time. To address these questions, the spontaneous ADR reports in the European ADR database, EudraVigilance, were investigated. Additionally, we evaluated whether these ADRs were more commonly recorded as diagnoses in patients exposed to fluoroquinolones compared with those exposed to cotrimoxazole in clinical routine data from the University Hospital Bonn in the time period after the referral.

2 Material and Methods

In this retrospective study, we evaluated two different data sources: (i) spontaneous reports of suspected ADRs (hereafter for brevity, ADRs) from EudraVigilance (ADR definition described in literature [18–20]) and (ii) clinical routine data from the University Hospital Bonn. The spontaneous ADR reports include patients exposed to fluoroquinolones as outpatients and inpatients, while the clinical routine data only refer to patients exposed to fluoroquinolones as inpatients. Whereas the spontaneous ADR reports refer to suspected ADRs, the clinical routine data refer to diagnoses, which are in temporal association with the administration of the drug of interest.

2.1 Analyses of Spontaneous Adverse Drug Reaction (ADR) Reports from EudraVigilance

2.1.1 EudraVigilance

ADRs can be reported spontaneously by health care professionals (HCPs, e.g., physicians, pharmacists) who are obliged by their professional conduct code to report ADRs, or non-health care professionals (non-HCPs, e.g., consumers). The ADR database EudraVigilance of the European Medicines Agency contains all spontaneously reported ADR reports by the member states of the European Economic Area [21]. In EudraVigilance, ADRs are coded following MedDRA terminology [22] and drugs with the EudraVigilance medicinal product dictionary [23].

2.1.2 Identification of Reports

We identified all spontaneous ADR reports received between 01/2014 and 12/2022 reported for patients older than 17 years in which fluoroquinolones (ATC code J01M [$n = 3542$] [24]) were reported as suspected/interacting. A comparator group of spontaneous ADR reports referring to several antibiotics (entire comparator reports) with a similar profile of indications in clinical practice as the fluoroquinolones was generated. This dataset consisted of spontaneous ADR reports referring to amoxicillin (J01CA04), cefuroxime (J01DC02), azithromycin (J01FA10), clindamycin (J01FF01), amoxicillin/clavulanic acid (J01CR02), cephalexin (J01DB01), doxycycline (J01AA02, A01AB22) or cotrimoxazole (combination of sulfamethoxazole and trimethoprim, J01EE01) ($n = 5815$). In order to analyze whether the ADRs reported differed before and after the referral, both datasets were divided into reports received between 01/2014 and 12/2019 (fluoroquinolones $n = 2575$, comparator $n = 3428$) (before referral) and between 01/2020 and 12/2022 (fluoroquinolones $n = 967$, comparator $n = 2387$) (after referral). The first period does not exactly match the period before the referral, which was published in November 2018. We deliberately added the first year after referral to the period before the referral to address a potential reporting bias, since we expected an increased reporting directly after the referral as described in another analysis due to higher attention [25]. Furthermore, in order to obtain patients that are as similar as possible concerning the indication of the antibiotic therapy, we analyzed the indications reported in ADR reports of fluoroquinolones and ADR reports of each drug included in the comparator reports (Supplementary Information 1, see electronic supplementary material [ESM]). We found as a result that the reported indications in ADR reports related to cotrimoxazole were the most similar to those in the ADR reports of fluoroquinolones. For this reason, the comparator group was further restricted to reports in which cotrimoxazole was reported as suspected/interacting (2014–2019: $n = 299$; 2020–2022: $n = 275$) (cotrimoxazole reports). In the main manuscript, only the comparison of reports referring to fluoroquinolones or cotrimoxazole as suspected/interacting drugs is shown (see Fig. 1). The comparison to the entire comparator group is shown in Supplementary Information 2 (see ESM).

2.1.3 Descriptive Analyses of the Spontaneous ADR Reports

The identified ADR reports were analyzed with regard to the demographics of the patients, the seriousness of the ADR reports, the drugs most frequently reported as suspected/interacting, the most frequently reported drug indications, and the ADRs most frequently reported, as well as their primary reporting sources. Further on, the number of reports describing aortic aneurysms, retinal detachments, cardiac arrhythmias, peripheral polyneuropathies, nervous system disorders, toxic liver diseases, and non-traumatic injuries of muscles, tendons, and synovialis was determined (the respective MedDRA terms for identification of these reports are listed in Supplementary Information 3 in the ESM). Additionally, sex- and fluoroquinolone-stratified analyses concerning the aforementioned ADRs were performed.

Note that more than one seriousness criterion can be reported per ADR report. The classification of seriousness based on the legal definition does not correspond to the clinical definition of the severity of an ADR. In accordance with the legal definition [19], an ADR report is classified as serious if one of the reported ADRs was life-threatening, led to hospitalization or prolongation thereof, death, congenital anomalies or permanent disabilities.

The primary reporting source describes the person who reported the ADR [18]. Multiple reporters (e.g., a physician and patient independently reported on the same ADR) can report one ADR report. Note that we are not able to distinguish between a physician and a pharmacist working in a hospital or in primary care.

2.1.4 Statistical Analyses of Spontaneous ADR Reports

Means with standard deviations (SD) and medians with interquartile ranges (IQR) were calculated for patients' age. Frequency distributions with percentages were calculated for all other criteria.

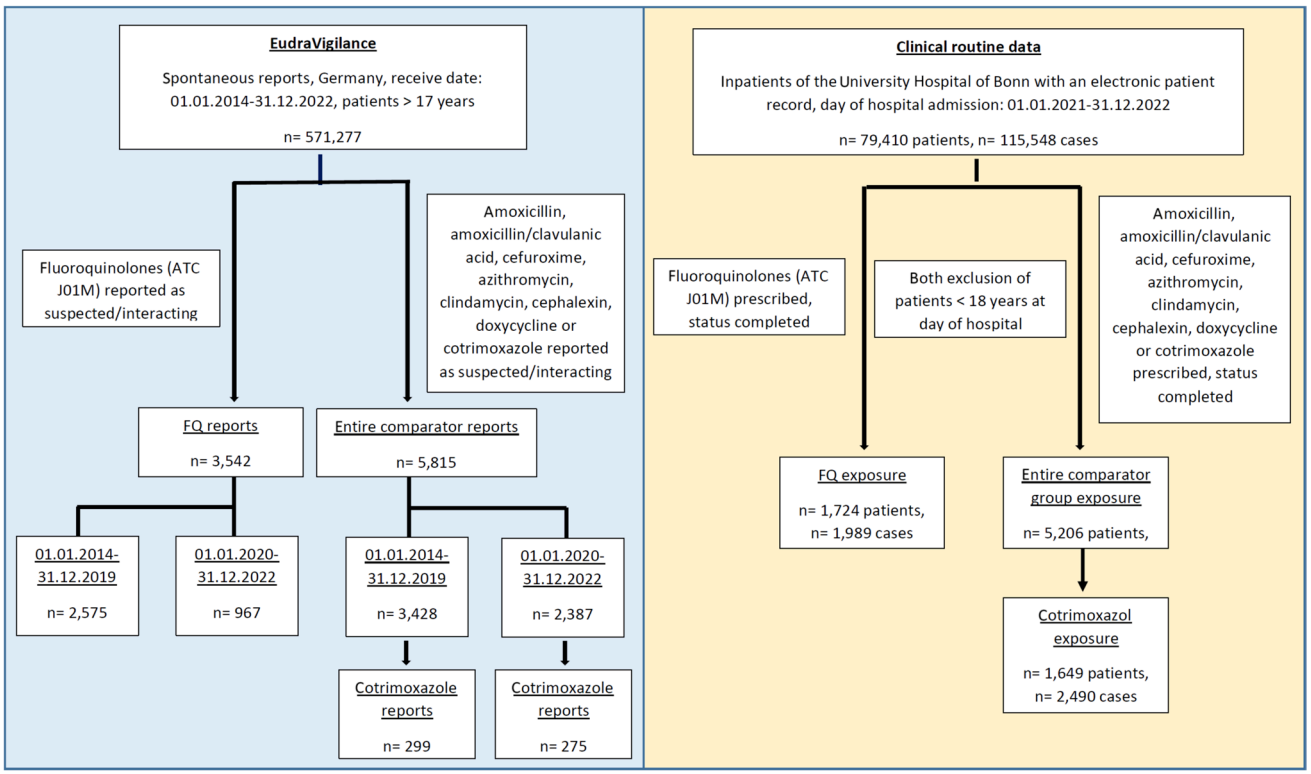


Fig. 1 Identification of Spontaneous reports and clinical routine cases

2.1.5 Logistic Regression Analyses of Spontaneous ADR Reports Comparing Reports Related to Fluoroquinolones and Cotrimoxazole

Logistic regression analyses were performed for fluoroquinolones versus cotrimoxazole as outcome variables, and age (> 64 years), sex, cardiac arrhythmias, peripheral polyneuropathies, nervous system disorders, toxic liver diseases, and non-traumatic injuries of muscles, tendons, and synovialis as covariates for both periods, before and after the referral. Results obtained from logistic regression analyses are reported in terms of odds ratios (OR) with 95% confidence intervals (CIs). If the lower CI exceeded 1, the specific ADR was assumed to be more frequently reported for fluoroquinolones. If the upper CI was lower than 1, the specific ADR was assumed to be more frequently reported for cotrimoxazole. The logistic regression analysis was also performed for ADR reports reported by physicians and consumers separately. However, the tendencies of the results were similar to those of the whole dataset.

2.1.6 Logistic Regression Analyses of Fluoroquinolone Reports Stratified by Sex and Individual Fluoroquinolones

In order to investigate whether there are differences in the frequency of the analyzed ADRs between females and males in the fluoroquinolone reports, and between one specific fluoroquinolone compared with another fluoroquinolone, logistic regression analyses were performed. Therefore, the reports before and after the referral were combined into one dataset. For logistic regression analyses, females and males or the respective fluoroquinolones under consideration were considered as outcome variables, and cardiac arrhythmias, peripheral polyneuropathies, nervous system disorders, toxic liver diseases (no reports describing toxic liver diseases in ofloxacin reports), and non-traumatic injuries of muscles, tendons, and synovialis as covariates. Results obtained from logistic regression analyses are reported in terms of OR with 95% CI. If the lower CI exceeded 1, the specific ADR was assumed to be more frequently reported for females (in the sex-stratified analysis), or for the fluoroquinolone under consideration (in the fluoroquinolone-stratified analyses). If the upper CI was lower than 1, the specific ADR was assumed to be more frequently reported for males (in the sex-stratified analysis), or for the other fluoroquinolone under consideration (in the fluoroquinolone-stratified analyses).

2.2 Number of Spontaneous ADR Reports from EudraVigilance in Relation to the Number of Drug Prescriptions Provided by the Central Research Institute for Ambulatory Health Care in Germany

2.2.1 Outpatient Drug Prescription Data

Prescription data according to § 300 SGB V were provided by the Central Research Institute for Ambulatory Health Care in Germany [26] for adults (≥ 18 years) with at least one fluoroquinolone or cotrimoxazole prescription between 01/2014 and 12/2021. The number of drug prescriptions represents the total number of outpatient prescriptions for patients with statutory health insurances (approximately 80–90% of the German population) dispensed in German pharmacies. Note that inpatient prescriptions are not covered, which is relevant to consider when interpreting prescription data of antibiotics.

2.2.2 Calculation of Reporting Rates of Spontaneous ADR Reports from EudraVigilance

Reporting rates were calculated by dividing the respective number of spontaneous ADR reports from EudraVigilance for a specific drug by the respective number of its outpatient prescriptions. Reporting rates were calculated for all of the analyzed drugs, the analyzed ADRs, and per year. They are presented as the number of spontaneous ADR reports per 100,000 prescriptions. ORs with 95% CIs were calculated using two-by-two tables to determine whether the analyzed ADRs were more frequently reported for fluoroquinolones compared with cotrimoxazole, taking their number of prescriptions into account. If the lower CI exceeded 1, the specific ADR was assumed to be more frequently reported for fluoroquinolones. If the upper CI was lower than 1, the specific ADR was assumed to be more frequently reported for cotrimoxazole.

2.3 Analyses of Clinical Routine Cases from the University Hospital Bonn

2.3.1 University Hospital Bonn

The University Hospital Bonn provided clinical routine data of patients with electronic health records (EHR) via the services of the Medical Informatics Initiative-supported Data Integration Center (DIC) [27, 28]. These data, including drug prescription data, were not available before 2021, which is why we could only analyze a period after the referral (2021–2022). In the clinical routine data, diagnoses are coded by ICD-10-GM [29], and drugs are coded with the ATC classification system [24]. The Bonn University Hospital data integration center pseudonymized data following hospital and federal regulations and only provided access to clinical staff (authors DD and MS) from onsite facilities. After analysis in a secure environment separated from the hospital network, results were reviewed by the data integration center coordinators (including author JG) to ensure patient data protection, and only non-identifiable, aggregated results were approved for export and handed over to the co-authors.

2.3.2 Identification of Clinical Routine Cases

We identified all patients hospitalized between 01 January 2021 and 31 December 2022 who were exposed to fluoroquinolones (ATC code J01M [24]) ($n = 1724$ patients, $n = 1989$ cases) or amoxicillin, cefuroxime, azithromycin, clindamycin, amoxicillin/clavulanic acid, cephalexin, doxycycline, or cotrimoxazole ($n = 5206$ patients, $n = 6329$ cases) (Fig. 1). As with the spontaneous reports, the comparator group was also restricted to cases with cotrimoxazole exposure ($n = 1649$ patients, $n = 2490$ cases). The comparative analysis with the entire comparator group is shown in Supplementary Information 2 (see ESM). Note that intensive care units were not included and that a patient could be admitted to the University Hospital Bonn more than once during the analyzed period.

2.3.3 Descriptive Analyses of Clinical Routine Cases

The identified clinical routine cases were analyzed with regard to the demographics of the patients, the type of hospital admissions (e.g., as an emergency), the drugs most frequently administered, the diagnoses most frequently reported, the duration of hospital stay, and the type of discharge diagnoses from the hospital. We identified all patients with diagnoses of aortic aneurysms, retinal detachments, cardiac arrhythmias, peripheral polyneuropathies, nervous system disorders, toxic liver diseases, and non-traumatic injuries of muscles, tendons, and synovialis after the first fluoroquinolone or cotrimoxazole exposure (the respective ICD-10 codes for identification of these diagnoses are shown in Supplementary Information 3 in the ESM) (Fig. 2). Patients in whom the corresponding diagnoses occurred before first fluoroquinolone or cotrimoxazole exposure documented in EHRs were excluded. We determined the number of days between the first fluoroquinolone or cotrimoxazole exposure and the first occurrence of the respective diagnoses.

To identify the drugs most frequently administered, all drug prescriptions with an application process stated as having been "carried out" were analyzed. Drug prescriptions with an application process stated as "ongoing" or "not carried out" were not considered.

The analysis of diagnoses represents all previous, concomitant, and acute illnesses that required any treatment in the hospital wards. Note that only recorded diagnoses but not laboratory parameters were taken into account.

2.3.4 Statistical Analyses of Clinical Routine Data

Means with standard deviations (SDs) and medians with interquartile ranges (IQRs) were calculated for patients' age, the number of days between first exposure to the respective drug and the occurrence of the diagnoses, and the duration of the hospital stay. Frequency distributions with percentages were calculated for all other criteria.

2.3.5 Logistic Regression Analyses of Clinical Routine Cases

Logistic regression analyses were performed for fluoroquinolones versus cotrimoxazole as outcome variables, and age (> 64 years), sex, aortic aneurysms, cardiac arrhythmias, peripheral polyneuropathies, nervous system disorders, toxic liver diseases, and non-traumatic injuries of muscles, tendons, and synovialis as covariates. Results obtained from logistic regression analyses are reported in terms of OR with 95% CI. If the lower CI exceeded 1, the specific diagnosis was assumed to be more frequently recorded for fluoroquinolones. If the upper CI was lower than 1, the specific diagnosis was assumed to be more frequently recorded for cotrimoxazole.

3 Results

3.1 Analyses of Spontaneous ADR Reports From EudraVigilance

3.1.1 Descriptive Analyses of the Spontaneous ADR Reports Before and After the Referral

Patients in the fluoroquinolone reports were slightly younger than those in the cotrimoxazole reports in both periods (2014–2019: 54.9 vs 56.1; 2020–2022: 52.1 vs 53.0) (Table 1). In fluoroquinolone and cotrimoxazole reports, patients of reports received between 2020 and 2022 were marginally younger than patients of reports received between 2014 and 2019. More females were included in cotrimoxazole compared with fluoroquinolones reports (2014–2019: 70.2% vs 58.4%, 2020–2022: 70.2% vs 62.3%). In fluoroquinolone and cotrimoxazole reports, hypertension, urinary tract infections, and drug hypersensitivities or allergies ranked among the patients' most frequently reported medical histories. The proportion of serious reports decreased for fluoroquinolone (−13.5%) and cotrimoxazole reports (−18.3%) between the analyzed periods. An increase in the proportion of reports from consumers (fluoroquinolones: +17.8%, cotrimoxazole: +22.9%) and a decrease in the proportion of reports from all other health care professionals was seen for fluoroquinolone and cotrimoxazole reports over time. Ciprofloxacin was the fluoroquinolone most frequently reported as suspected/interacting followed by levofloxacin. The proportion of moxifloxacin reports (− 4.5%) decreased while that of ofloxacin reports (+ 5.4%) increased in the time period 2014–2019 compared with the time period 2020–2022. Urinary tract infection was the indication most

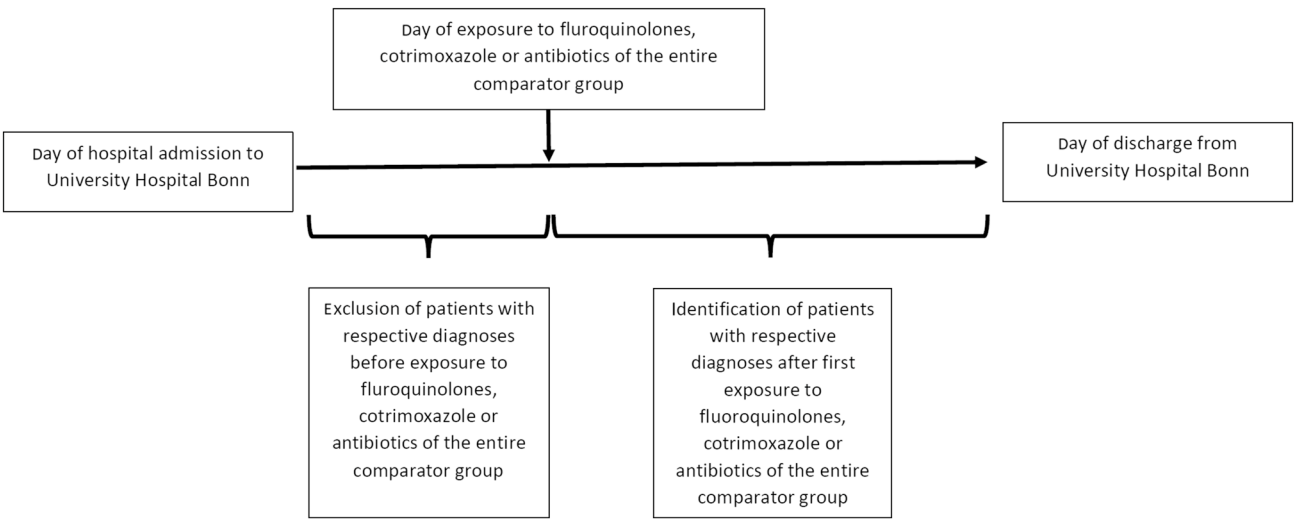


Fig. 2 Identification of patients with respective diagnoses in clinical routine cases considering the date of diagnoses and drug intake

frequently reported in fluoroquinolone and cotrimoxazole reports in both periods. In comparison, ADRs related to muscle and tendon disorders occurred as the most frequently reported ADRs in fluoroquinolone reports in both periods, while gastrointestinal and skin-related ADRs were commonly reported in cotrimoxazole reports.

Table 1 shows the descriptive analyses of the demographical parameters of the patients, the seriousness criteria of the ADR reports, the primary reporting source and the most frequently reported patients' histories, drugs reported as suspected/interacting, drug indications, and ADRs in fluoroquinolones and cotrimoxazole reports.

3.1.2 Logistic Regression Analyses of the Specific ADRs in the ADR Reports Comparing Fluoroquinolone and Cotrimoxazole Reports

Aortic aneurysms and retinal detachments were only reported in fluoroquinolone reports (2014–2019: $n = 5$, $n = 5$; 2020–2022: $n = 3$, $n = 0$, respectively) (Table 2). Cardiac arrhythmias were more frequently reported in fluoroquinolone compared with cotrimoxazole reports between 2014 and 2019 (OR 2.0 [1.2–3.4]), but not between 2020 and 2022 (OR 1.1 [0.6–2.0]). Peripheral polyneuropathies (2014–2019: OR 2.2 [1.4–3.6], 2020–2022: OR 2.9 [1.8–4.7]), nervous system disorders (2014–2019: OR 2.1 [1.3–3.5], 2020–2022: OR 3.4 [1.8–6.2]) and non-traumatic injuries of muscles, tendons, and synovialis (2014–2019: OR 14.0 [7.6–25.8], 2020–2022: OR 8.1 [4.7–14.0]) were clearly more often reported in fluoroquinolones compared with cotrimoxazole reports in both periods. Toxic liver diseases were almost equally often described for fluoroquinolones and cotrimoxazole reports (2014–2019: OR 1.2 [0.5–2.8], 2020–2022: OR 1.4 [0.4–4.6]).

Table 2 shows the results of the logistic regression analyses before and after the referral. If the lower confidence interval exceeds 1, the specific ADR was assumed to be more frequently reported for fluoroquinolones. If the upper confidence interval is lower than 1, the specific ADR was assumed to be more frequently reported for cotrimoxazole.

3.1.3 Sex-Stratified Analysis of the Specific ADRs in Fluoroquinolone Reports

In fluoroquinolone reports of both periods combined, nervous system disorders (OR 1.23 [1.03–1.47]) and peripheral neuropathies (OR 1.23 [1.05–145]) were more frequently reported for females compared with males (Fig. 3). In contrast, non-traumatic injuries of muscle, tendon, and synovialis (OR 0.78 [0.67–0.90]) were more commonly described in reports for males compared with females. No difference between the sexes was found for toxic liver diseases (OR 1.08 [0.66–1.74]) and cardiac arrhythmias (OR 1.22 [0.98–1.51]).

Figure 3 shows the odds ratios (ORs) and their 95% confidence intervals (CIs) concerning the specific adverse drug reactions (ADRs) in the sex-stratified analysis. ORs were calculated by logistic regression analysis. If the lower CI exceeded 1, the specific ADR was assumed to be more frequently reported for females. If the upper CI was lower than 1, the specific ADR was assumed to be more frequently reported for males

3.1.4 Fluoroquinolone-Stratified Analyses of the Specific ADRs in Fluoroquinolone Reports

For both periods combined, peripheral neuropathies and nervous system disorders were more frequently reported for ciprofloxacin compared with levofloxacin and moxifloxacin (Fig. 4). In addition, non-traumatic injuries of muscle, tendon, and synovialis were more commonly described in ciprofloxacin compared with moxifloxacin and ofloxacin reports. Non-traumatic injuries of muscle, tendon, and synovialis were clearly more often reported for levofloxacin compared with ciprofloxacin, moxifloxacin, and ofloxacin. Cardiac arrhythmias and toxic liver diseases were more frequently reported for moxifloxacin compared with ciprofloxacin, levofloxacin, and ofloxacin.

Figure 4 shows the odds ratios (ORs) and their 95% confidence intervals (CIs) concerning the specific adverse drug reactions (ADRs) in the fluoroquinolone-stratified analyses. ORs were calculated by logistic regression analysis. If the lower CI exceeded 1, the specific ADR was assumed to be more frequently reported for the respective fluoroquinolone under consideration. If the upper CI was lower than 1, the specific ADR was assumed to be more frequently reported for the respective other fluoroquinolone under consideration

3.2 Number of Spontaneous ADR Reports from EudraVigilance in Relation to the Number of Drug Prescriptions Provided by the Central Research Institute for Ambulatory Health Care in Germany

3.2.1 Number of Spontaneous ADR Reports, Number of Outpatient Drug Prescriptions, and Reporting Rates Per Year

The number of fluoroquinolone reports increased 3.8-fold (219–828 reports) and the number of cotrimoxazole reports increased 4.2-fold (26–109 reports) from 2014 to 2019 (Supplementary Information 4, see ESM). Between 2020 and 2022, the number of fluoroquinolone and cotrimoxazole reports declined 2.1-fold (460–224 reports) and 1.4-fold (107–75). While the number of fluoroquinolone

Table 1 Descriptive analyses of fluoroquinolone and cotrimoxazole reports before and after the referral

Period	2014–2019 (before referral)		2020–2022 (after referral)	
	Fluoroquinolones ($n = 2575$)	Cotrimoxazole ($n = 299$)	Fluoroquinolones ($n = 967$)	Cotrimoxazole ($n = 275$)
Demographical parameters of the patients				
Mean age (± SD)	54.9 (±17.3)	56.1 (±19.3)	52.1 (±17.8)	53 (±20.0)
Median age [IQR]	55.0 [42–69]	59.0 [39–72]	52.0 [37–66]	55.0 [35–75]
Female	58.4% ($n = 1504$)	70.2% ($n = 210$)	62.3% ($n = 602$)	70.2% ($n = 193$)
Male	40.8% ($n = 1050$)	28.8% ($n = 86$)	37.5% ($n = 363$)	29.8% ($n = 82$)
Sex NA	0.8% ($n = 21$)	1.0% ($n = 3$)	0.2% ($n = 2$)	0.0% ($n = 0$)
The three most frequently reported histories of the patients (PT level)[a]				
NA	41.2% ($n = 1062$)	35.5% ($n = 106$)	33.4% ($n = 323$)	37.5% ($n = 103$)
1.	10.3% hypertension ($n = 265$)	11.4% hypertension ($n = 34$)	9.3% drug hypersensitivity ($n = 90$)	9.1% drug hypersensitivity ($n = 25$)
2.	4.3% urinary tract infections ($n = 111$)	6.0% urinary tract infections ($n = 18$)	7.4% hypertension ($n = 72$)	8.7% hypertension ($n = 24$)
3.	3.7% drug hypersensitivity ($n = 95$)	4.7% drug hypersensitivity ($n = 14$)	6.2% seasonal allergy ($n = 60$)	6.9% urinary tract infection ($n = 19$)
Seriousness criteria of the ADR reports[b]				
Serious	43.3% ($n = 1114$)	44.8% ($n = 134$)	29.8% ($n = 288$)	26.5% ($n = 73$)
Death	1.6% ($n = 41$)	2.0% ($n = 6$)	0.5% ($n = 5$)	0.7% ($n = 2$)
Life-threatening	3.6% ($n = 93$)	6.7% ($n = 20$)	2.0% ($n = 19$)	2.5% ($n = 7$)
Hospitalization	16.2% ($n = 416$)	24.4% ($n = 73$)	10.8% ($n = 104$)	16.4% ($n = 45$)
Disabling	6.9% ($n = 178$)	0.3% ($n = 1$)	2.5% ($n = 24$)	0.4% ($n = 1$)
Primary reporting sources[c]				
Physicians	21.4% ($n = 552$)	27.1% ($n = 81$)	14.8% ($n = 143$)	15.6% ($n = 43$)
Pharmacists	15.6% ($n = 401$)	23.1% ($n = 69$)	8.9% ($n = 86$)	13.5% ($n = 37$)
Other HCPs	2.0% ($n = 52$)	4.0% ($n = 12$)	1.3% ($n = 13$)	1.8% ($n = 5$)
Consumers	48.4% ($n = 1247$)	41.5% ($n = 124$)	66.2% ($n = 640$)	64.4% ($n = 177$)
The five drugs most frequently reported as suspected/interacting[d]				
1.	58.4% ciprofloxacin ($n = 1505$)	100.0% cotrimoxazole ($n = 299$)	58.2% ciprofloxacin ($n = 563$)	100.0% cotrimoxazole
2.	26.7% levofloxacin ($n = 687$)	3.3% ciprofloxacin ($n = 10$)	24.4% levofloxacin ($n = 236$)	1.8% torasemide ($n = 5$)
3.	11.3% moxifloxacin ($n = 290$)	2.7% mycophenolate mofetil ($n = 8$)	9.9% ofloxacin ($n = 96$)	All other drugs <5 reports
4.	4.5% ofloxacin (n= 116)	2.7% valganciclovir (n= 8)	6.7% moxifloxacin (n= 65)	
5.	2.8% norfloxacin ($n = 72$)	2.3% tacrolimus ($n = 7$)	2.8% norfloxacin ($n = 27$)	
The five indications of fluoroquinolones or cotrimoxazole most frequently reported (PT level)[e]				
NA	25.6% ($n = 659$)	30.8% ($n = 92$)	24.3% ($n = 235$)	42.5% ($n = 117$)
1.	12.1% urinary tract infection ($n = 312$)	20.4% urinary tract infections ($n = 61$)	10.0% urinary tract infection ($n = 97$)	13.5% urinary tract infections ($n = 37$)
2.	6.1% bronchitis ($n = 158$)	8.7% cystitis ($n = 26$)	7.4% cystitis noninfective ($n = 7.4$)	8.4% cystitis noninfective ($n = 23$)
3.	5.4% cystitis noninfective ($n = 138$)	8.4% cystitis noninfective ($n = 25$)	5.4% cystitis ($n = 52$)	6.9% cystitis ($n = 19$)
4.	5.3% cystitis ($n = 136$)	2.3% antifungal prophylaxis ($n = 7$)	3.4% prostatitis ($n = 33$)	2.5% prophylaxis ($n = 7$)
5.	4.3% pneumonia ($n = 112$)	2.0% prophylaxis ($n = 6$)	2.6% diverticulitis ($n = 25$)	1.8% antifungal prophylaxis ($n = 5$) 1.8% pyelonephritis ($n = 5$)
The five ADRs most frequently reported (PT level)[f]				
1.	20.6% arthralgia ($n = 530$)	14.0% nausea ($n = 42$)	21.5% tendon pain ($n = 208$)	16.7% nausea ($n = 46$)

Table 1 (continued)

Period	2014–2019 (before referral)		2020–2022 (after referral)	
	Fluoroquinolones ($n = 2575$)	Cotrimoxazole ($n = 299$)	Fluoroquinolones ($n = 967$)	Cotrimoxazole ($n = 275$)
2.	19.9% tendon pain ($n = 513$)	12.0% pruritus ($n = 36$)	20.2% arthralgia ($n = 195$)	14.9% headache ($n = 41$)
3.	16.7% myalgia ($n = 431$)	10.4% headache ($n = 31$)	19.2% myalgia ($n = 186$)	13.1% rash ($n = 36$)
4.	12.7% dizziness ($n = 328$)	10.0% rash ($n = 30$)	14.2% pain in extremity ($n = 137$)	9.1% diarrhea ($n = 25$)
5.	11.8% fatigue ($n = 303$)	8.7% dizziness ($n = 26$)	13.8% fatigue ($n = 133$)	9.1% dizziness ($n = 25$)

ADRs adverse drug reactions, *HCPs* health care providers, *IQR* interquartile range, *NA* information was not available, *PT level* preferred term level, *SD* standard deviation

[a]The histories of the patients were analyzed based on the PT level of MedDRA terminology [22]. More than one history can be reported per ADR report. Thus, the number of histories reported may exceed the number of reports. NA in respect of the patient's history means that the patient did not have any comorbidities or that the patient's history was not provided

[b]The analysis of seriousness criteria is based on the legal definition [19]. Note that more than one seriousness criterion can be reported per ADR report

[c]The primary reporting source describes the person/s who reported the ADR. One ADR report can be reported by more than one person (with different qualifications). The table shows the number of reports provided by one reporting source only

[d]More than one drug can be reported as suspected/interacting per ADR report. Thus, the number of drugs may exceed the number of ADR reports. Note that in the case of reports with fluoroquinolones reported as suspected/interacting, the most frequently reported drugs were fluoroquinolones. In the case of reports in which cotrimoxazole was reported as suspected/interacting also, other antibiotics and non-antibiotic drugs appear among the most frequently reported drugs

[e]The indications of fluoroquinolones or cotrimoxazole therapy were analyzed based on the PT level of MedDRA terminology [22]

[f]The ADRs were analyzed based on the PT level of MedDRA terminology [22]. Note that more than one ADR can be reported per ADR report. Thus, the number of ADRs may exceed the number of reports

prescriptions decreased between 2014 and 2021, especially ciprofloxacin and levofloxacin prescriptions after 2019, the number of cotrimoxazole prescriptions was relatively constant with a slight increase in 2019 and a slight decrease in 2020. The reporting rates (number of spontaneous ADR reports/number of outpatient drug prescriptions) for ciprofloxacin, levofloxacin, moxifloxacin, and norfloxacin clearly increased until 2019 and decreased afterward, while the reporting rates for ofloxacin and cotrimoxazole were relatively constant (Fig. 5).

Figure 5 shows the number of spontaneous ADR reports per 100,000 prescriptions per year (reporting rate). Reporting rates were calculated by dividing the respective number of spontaneous ADR reports from EudraVigilance by the respective number of outpatient prescriptions provided by the Central Research Institute for Ambulatory Health Care in Germany.

3.2.2 Number of Spontaneous ADR Reports from EudraVigilance per 100,000 Outpatient Drug Prescriptions for the Specific ADRs

All outcomes, especially non-traumatic injuries of muscles, tendons, and synovialis, peripheral polyneuropathies, and nervous system disorders, were more frequently reported for fluoroquinolones compared with cotrimoxazole per 100,000 outpatient drug prescriptions in both periods (Table 3). The highest reporting rates were calculated for non-traumatic injuries of muscles, tendons, and synovialis per 100,000 fluoroquinolone prescriptions (2014–2019: 2.8 reports per 100,000 outpatient drug prescriptions, 2020–2021: 4.4 reports per 100,000 outpatient drug prescriptions).

Table 3 shows the number of spontaneous ADR reports for the specific ADRs per 100,000 outpatient fluoroquinolones or cotrimoxazole prescriptions (reporting rates) before and after the referral. Odds ratios were calculated to investigate whether the specific ADRs were more frequently reported for fluoroquinolones compared with cotrimoxazole taking the number of outpatient prescriptions into account. If the lower confidence interval exceeds 1, the specific ADR was assumed to be more frequently reported for fluoroquinolones. If the upper confidence interval is lower than 1, the specific ADR was assumed to be more frequently reported for cotrimoxazole.

Table 2 Logistic regression analyses of the analyzed ADRs in fluoroquinolones and cotrimoxazole reports before and after the referral

Period	2014–2019 (before referral)			2020–2022 (after referral)		
Analyzed variables	Fluoroquinolones ($n = 2559$)[a]	Cotrimoxazole ($n = 283$)[a]	Logistic regression analysis: OR [±95% CI][b]	Fluoroquinolones ($n = 963$) [c]	Cotrimoxazole ($n = 271$)[c]	Logistic regression analysis: OR [±95% CI][b]
Age (> 64 years)	32.4% ($n = 828$)	41.0% ($n = 116$)	0.9 [0.7–1.2]	27.7% ($n = 267$)	32.5% ($n = 88$)	1.1 [0.8–1.5]
Female	58.3% ($n = 1492$)	70.0% ($n = 198$)	0.6 [0.5–0.8]	62.3% ($n = 600$)	70.5% ($n = 191$)	0.7 [0.5–1.0]
Aortic aneurysms[d]	0.2% ($n = 5$)	0.0% ($n = 0$)	-	0.3% ($n = 3$)	0.0% ($n = 0$)	-
Retinal detachments[d]	0.2% ($n = 5$)	0.0% ($n = 1$)	-	0.0% ($n = 0$)	0.0% ($n = 0$)	-
Cardiac arrhythmias[d]	13.6% ($n = 348$)	6.0 % ($n = 17$)	2.0 [1.2–3.4]	10.6% ($n = 102$)	6.6% ($n = 18$)	1.1 [0.6–2.0]
Peripheral polyneuropathies[d]	26.9% ($n = 689$)	7.4% ($n = 21$)	2.2 [1.4–3.6]	32.3% ($n = 311$)	8.1% ($n = 22$)	2.9 [1.8–4.7]
Nervous system disorders[d]	20.9% ($n = 535$)	7.8% ($n = 22$)	2.1 [1.3–3.3]	20.5% ($n = 197$)	4.8% ($n = 13$)	3.4 [1.8–6.2]
Non-traumatic injuries of muscle, tendon and synovialis[d]	42.6% ($n = 1091$)	3.9% ($n = 11$)	14.0 [7.6–25.8]	39.8% ($n = 383$)	5.5% ($n = 15$)	8.1 [4.7–14.0]
Toxic liver diseases[d]	2.3% ($n = 59$)	2.5% ($n = 7$)	1.2 [0.5–2.8]	1.6% ($n = 15$)	1.5% ($n = 4$)	1.4 [0.4–4.6]

ADRs adverse drug reactions, *CI* confidence interval, *OR* odds ratio

[a]In 16 reports, fluoroquinolones and cotrimoxazole were reported as suspected/interacting; thus, these reports were excluded from logistic regression analysis

[b]In logistic regression analyses, fluoroquinolones and cotrimoxazole were considered as outcome variables, and age (> 64 years), sex, cardiac arrhythmias, peripheral polyneuropathies, nervous system disorders, non-traumatic injuries of muscle, tendon, and synovialis, and toxic liver diseases as covariates. Aortic aneurysms and retinal detachments were not included in the logistic regression models since neither of these ADRs were reported in cotrimoxazole reports

[c]In 4 reports, fluoroquinolones and cotrimoxazole were reported as suspected/interacting. Thus, these reports were excluded from logistic regression analysis

[d]For a more detailed description of the identification of the respective ADRs, see Supplementary Information 3 in the electronic supplementary material (ESM)

3.3 Analyses of Clinical Routine Cases from the University Hospital Bonn

3.3.1 Descriptive Analysis of Clinical Routine Cases

Patients exposed to fluoroquinolones or cotrimoxazole were on average 68.0 and 65.0 years old (Table 4). Fewer females than males were exposed to fluoroquinolones (44.4% vs 55.6%) and cotrimoxazole (45.5% vs 54.5%). Ciprofloxacin was the fluoroquinolone most frequently prescribed (77.8% of fluoroquinolone-exposed patients) and pantoprazole was the most frequently applied non-anti-infective drug in both groups. Concerning the diagnoses, urinary tract infections and essential hypertension were the most frequently recorded diagnoses in patients exposed to fluoroquinolones and cotrimoxazole.

Table 4 shows the descriptive analyses of the demographics of the patients, types of hospital admissions, duration of hospital stay, the three most frequently recorded types of discharge diagnoses, the five most frequently applied drugs and the five most frequently recorded diagnoses of fluoroquinolone- and cotrimoxazole-exposed patients.

3.3.2 Logistic Regression Analysis of the Specific Diagnoses in Clinical Routine Cases

Patients exposed to fluoroquinolones were more often older than 64 years compared with those exposed to cotrimoxazole (OR 1.37 [1.21–1.54]). None of the analyzed specific diagnoses were recorded more frequently in patients exposed to fluoroquinolones or cotrimoxazole. However, considering only the effect estimates without the associated confidence intervals, a tendency towards a higher risk of aortic aneurysms of fluoroquinolone-exposed compared with cotrimoxazole-exposed patients could be assumed (Table 5).

Table 5 shows the results of the logistic regression analysis in clinical routine cases of patients admitted to the University Hospital Bonn in 2021 and 2022. If the lower confidence interval exceeds 1, the specific diagnoses were assumed to be more frequently recorded in

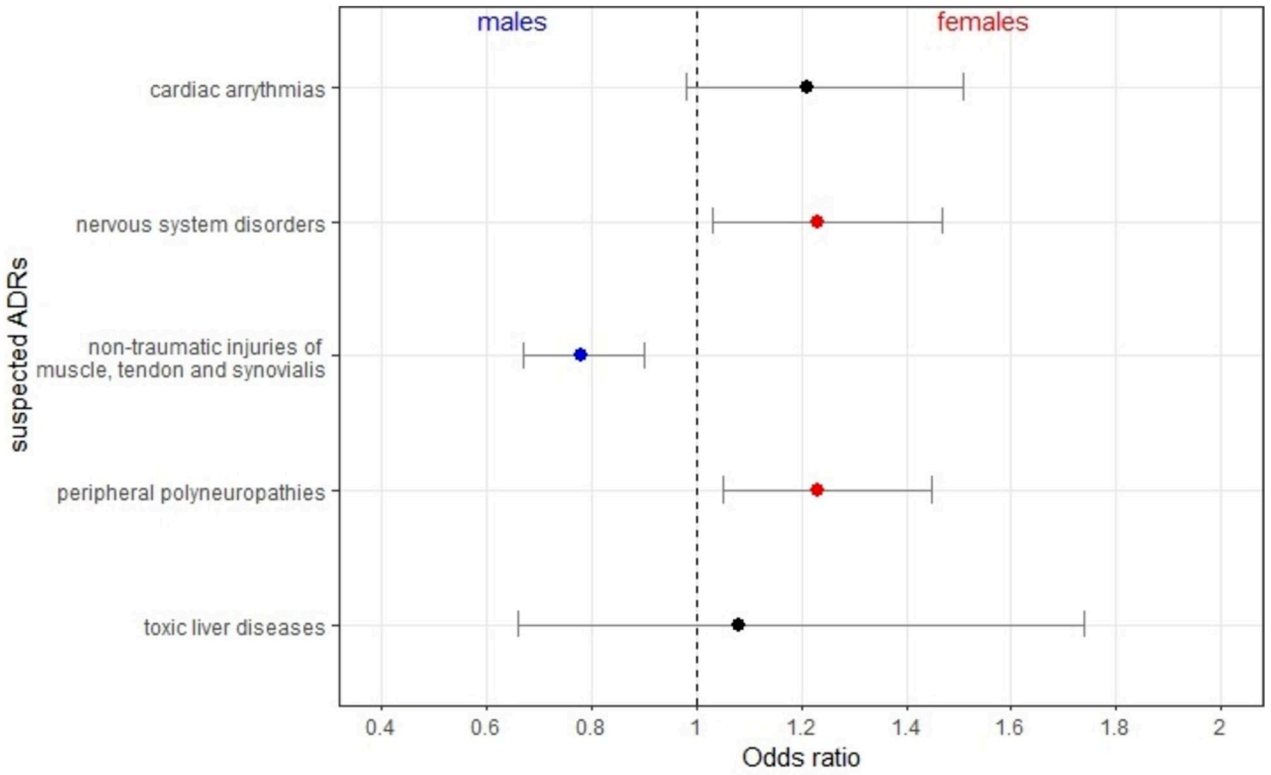


Fig. 3 Sex-stratified analysis of the specific ADRs

fluoroquinolone-exposed patients. If the upper confidence interval is lower than 1, the specific diagnoses were assumed to be more frequently recorded in cotrimoxazole-exposed patients.

4 Discussion

To the best of our knowledge, this is the first analysis of spontaneous ADR reports of fluoroquinolones investigating differences in reported characteristics before and after the referral. Only minor differences in the characteristics of reports were observed before and after the referral. Females and males seemed to be more prone to develop specific ADRs, respectively. Differences concerning the ADRs were observed between individual fluoroquinolones.

4.1 Analyses of Characteristics Reported in Fluoroquinolone Reports Before and After the Referral

It may be speculated that high-risk groups (e.g., older patients) were less often treated with fluoroquinolones after the restriction of use following the referral of the EMA [12], explaining the younger age of patients (roughly 3 years younger) in the reports after (2020–2022) compared with before (2014–2019) the referral. This may also account for the lower proportion of serious fluoroquinolone reports after compared with before the referral. However, the lower proportion of serious reports may also result from the general increase in non-serious reports from consumers in recent years, as observed in other studies [30, 31], and may be related to amendments of the regulatory obligations with regard to forwarding non-serious ADR reports by pharmaceutical companies to the European Medicines Agency [32]. Urinary tract infection remained the most frequently reported indication with fluoroquinolone therapy after the referral (also assumed based on the clinical routine data). We cannot evaluate the severity of the treated urinary tract infections; however, this could indicate that the restrictions [12] to use fluoroquinolones only for complicated urinary tract infections but not for uncomplicated urinary tract infections have not been complied with.

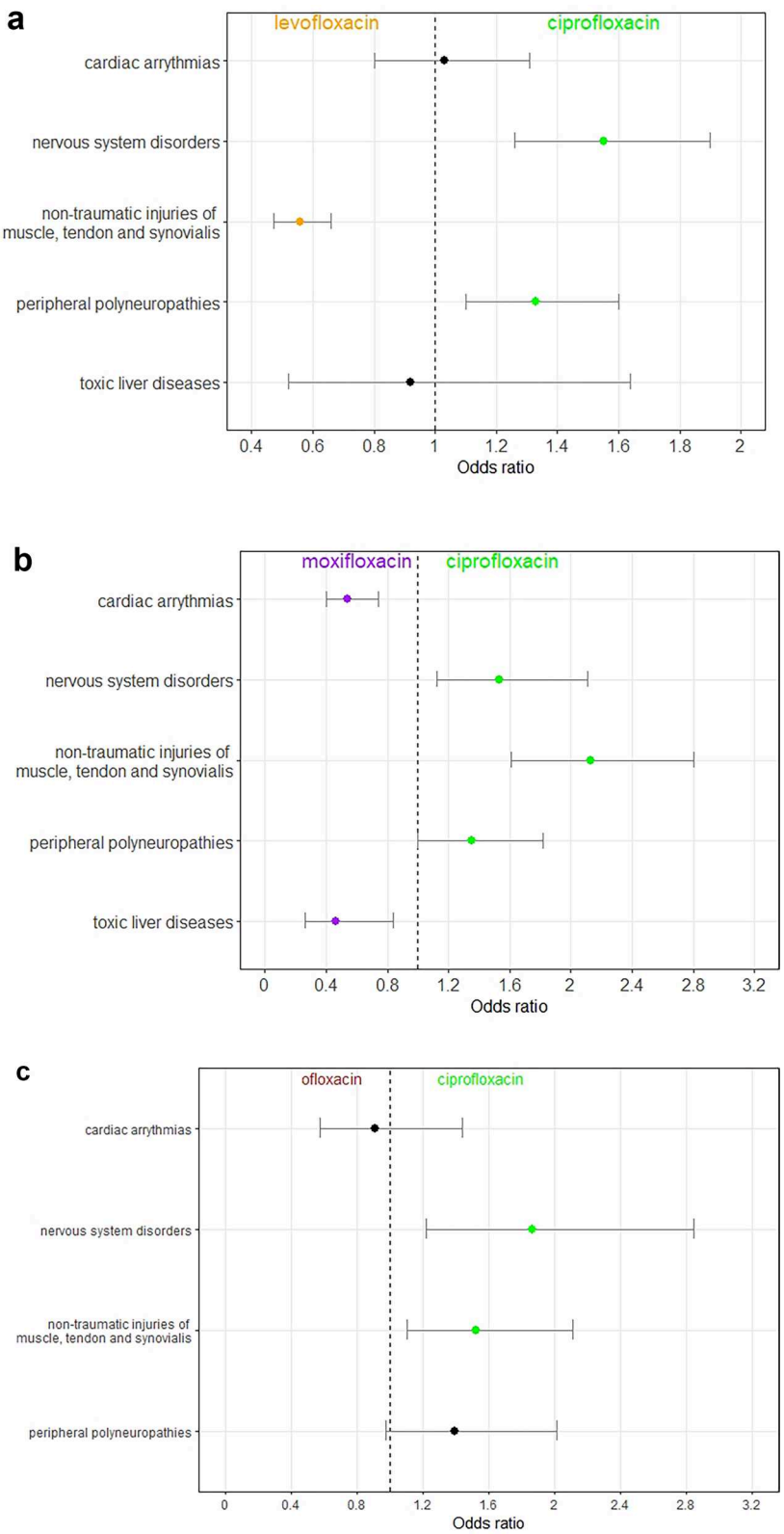
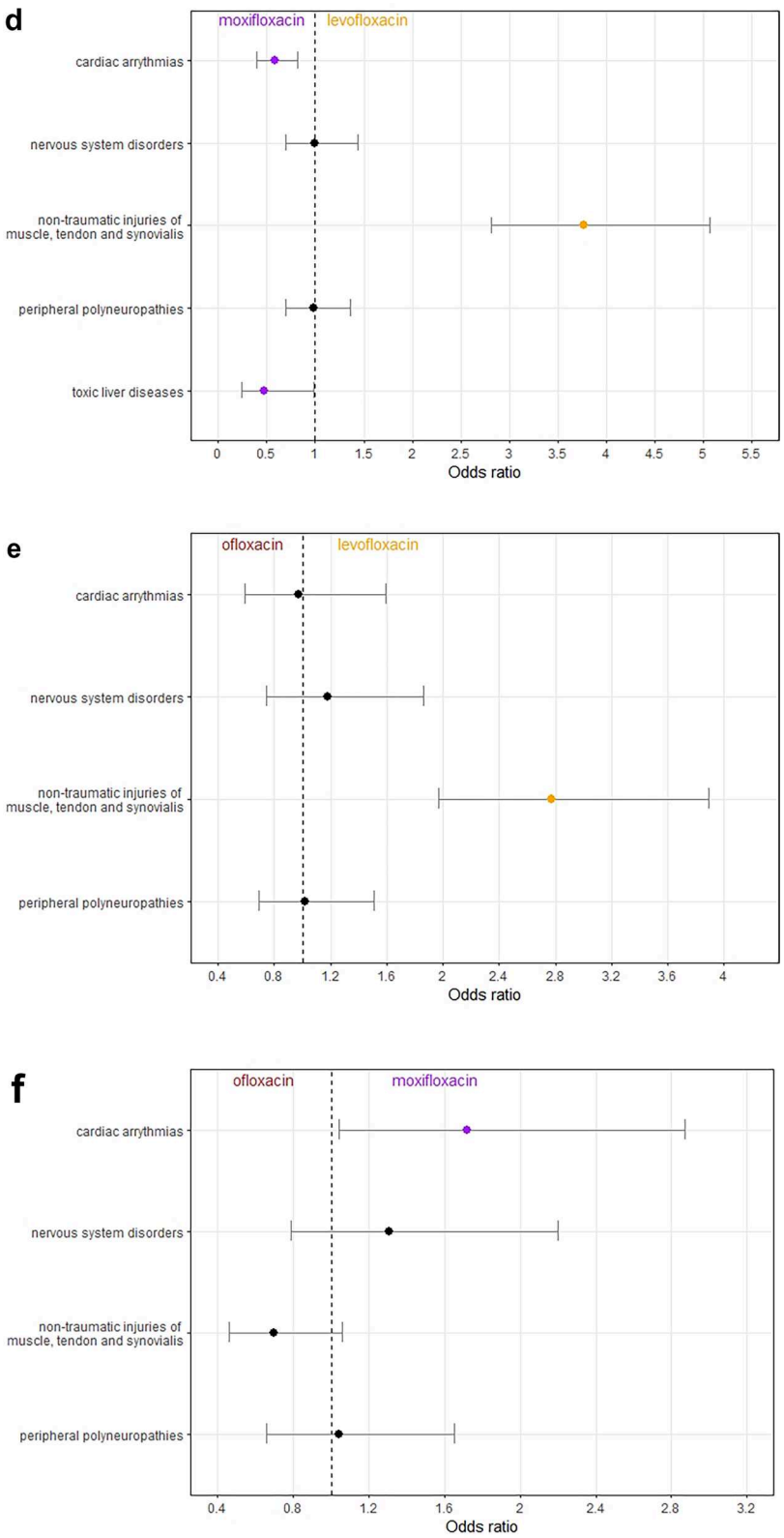


Fig. 4 Fluoroquinolone-stratified analyses of the specific ADRs

Fig. 4 (continued)



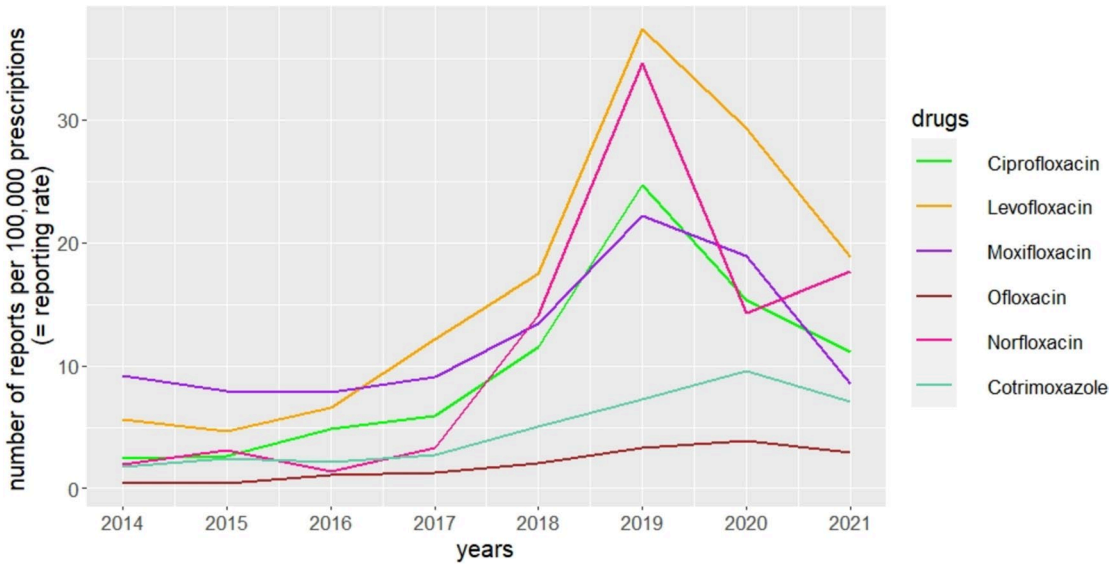


Fig. 5 Reporting rates per year

Table 3 Number of spontaneous ADR reports for the specific ADRs per 100,000 outpatient fluoroquinolone or cotrimoxazole prescriptions

Period	Reporting rate per 100,000 outpatient prescriptions[a]					
	2014–2019 (before referral)			2020–2021 (after referral)[b]		
	Fluoroquinolones (n = 38,996,900 outpatient prescriptions)	Cotrimoxazole (n = 8,200,422 outpatient prescriptions)	OR [± 95% CI][c]	Fluoroquinolones (n = 6,591,767 outpatient prescriptions)	Cotrimoxazole (n = 2,424,560 outpatient prescription)	OR [± 95% CI][c]
Cardiac arrhythmias[d]	0.9	0.2	4.3 [2.6–7.0]	1.2	0.5	2.2 [1.2–3.9]
Peripheral polyneuropathies[d]	1.8	0.3	6.9 [4.5–10.7]	3.5	0.7	5.3 [3.2–8.9]
Nervous system disorders[d]	1.4	0.3	5.1 [3.3–7.8]	2.4	0.5	4.8 [2.7–8.7]
Non-traumatic injuries of muscle, tendon, and synovialis[d]	2.8	0.1	20.9 [11.5–37.8]	4.4	0.5	8.9 [5.0–15.8]
Toxic liver diseases[d]	0.2	0.1	1.8 [0.8–3.9]	0.2	0.1	2.4 [0.5–10.6]

CI confidence interval, *OR* odds ratio

[a]The reporting rate is calculated by dividing the respective number of spontaneous ADR reports by the respective number of outpatient prescriptions. The reporting rate is presented as the number of spontaneous ADR reports per 100,000 outpatient prescriptions

[b]Outpatient prescriptions were not yet fully available for 2022 at the time of the analysis; thus, reporting rates were calculated for the period 2020–2021

[c]Odds ratios and their 95% confidence intervals were calculated using two-by-two tables

[d]For a more detailed description of the identification of the respective ADRs see Supplementary Information 3

4.2 Number of Reporting Rates and Fluoroquinolone Outpatient Prescriptions in Germany

The considerable increase in the number of fluoroquinolone reports per 100,000 outpatient fluoroquinolone prescriptions (reporting rate) between 2014 and 2019 might be related to stimulated reporting due to the referral and Dear Doctor letters [6–9, 12] increasing awareness and reporting of (specific) ADRs of fluoroquinolones. The general rise of ADR reports in EudraVigilance during this period [20, 31], especially after 2017, may also have contributed to an unknown

Table 4 Descriptive analyses of fluoroquinolone- and cotrimoxazole-exposed patients in clinical routine cases

	Period: 2021–2022	
	Fluoroquinolone exposure	Cotrimoxazole exposure
Number of patients[a]	1724	1649
Number of cases	989	2490
Demographical parameters		
Mean age (±SD)	68.0 (±16.2)	65.0 (±16.3)
Median age [IQR]	68.0 [57–79]	65.0 [55–75]
Female	44.4% ($n = 883$)	45.5% ($n = 1133$)
Male	55.6% ($n = 1106$)	54.5% ($n = 1357$)
Type of hospital admission		
Information available[b]	99,3% ($n = 1975$)	99.3% ($n = 2472$)
By physician	40.7% ($n = 809$)	59.4% ($n = 1480$)
By emergency	47.7% ($n = 948$)	31.8% ($n = 792$)
By transfer (duration < 24 h in the transferring hospital)	11.0% ($n = 218$)	8.0% ($n = 200$)
Duration of hospital stay		
Mean number of days (±SD)	12 (±24.8)	10 (±22.9)
Median number of days [IQR]	12 (6–24)	10 (4–22)
The three most frequently coded types of discharge diagnoses		
Information available	99.3% ($n = 1975$)	99.2% ($n = 2470$)
Treatment regularly finished	84.3% ($n = 1677$)	87.7% ($n = 2184$)
Death	5.5% ($n = 109$)	3.7% ($n = 92$)
Transfer to another hospital	4.3% ($n = 86$)	3.0% ($n = 75$)
The five most frequently prescribed drugs (status—completed)[c]		
1.	79.0% pantoprazole ($n = 1572$)	100.0% cotrimoxazole ($n = 2490$)
2.	77.8% ciprofloxacin ($n = 1548$)	80.0% pantoprazole ($n = 1991$)
3.	53.3% enoxaparin ($n = 1060$)	62.0% enoxaparin ($n = 1543$)
4.	51.7% metamizole ($n = 1029$)	42.0% metamizole ($n = 1045$)
5.	42.2% torasemide ($n = 839$)	41.6% aciclovir ($n = 1037$)
The five most frequently coded diagnoses[d]		
1.	29.2% urinary tract infections, location unknown ($n = 580$)	31.7% essential hypertension ($n = 790$)
2.	25.7% essential hypertension ($n = 512$)	29.0% urinary tract infections, location unknown ($n = 723$)
3.	25.6% Escherichia coli and other Enterobacterales ($n = 509$)	19.1% Escherichia coli and other Enterobacterales ($n = 475$)
4.	23.8% hypokalemia ($n = 474$)	15.7% hypokalemia ($n = 390$)
5.	17.4% acute bleeding anemia ($n = 359$)	12.8% secondary thrombocytopenia ($n = 319$)

IQR interquartile range, *SD* standard deviation

[a]Note that one patient could be admitted more than once to the University Hospital Bonn during the analyzed period of time

[b]The admission to the University Hospital Bonn could have taken place as an emergency, as a referral from another hospital or by a physician

[c]The drugs most frequently used were identified by analyzing all prescribed drugs for which the application process was stated as "carried out" (status completed). Drug prescriptions for which the application process was stated as "ongoing" or "not performed" were not considered

[d]Only the five most frequent diagnoses of diseases are presented. Laboratory tests and drug exposures in patient anamnesis were not taken into account

Table 5 Logistic regression analysis of specific diagnoses in clinical routine cases

Analyzed covariates	Period: 2021–2022		
	Fluoroquinolone ($n = 1933$)[a]	Cotrimoxazole ($n = 2429$)[a]	Logistic regression analysis: OR [± 95% CI][b]
Age (> 64 years)	58.8% ($n = 1137$)	51.1% ($n = 1242$)	1.37 [1.21–1.54]
Female	45.0% ($n = 870$)	45.7% ($n = 1,109$)	0.97 [0.86–1.09]
Aortic aneurysms[c]	0.4% ($n = 7$)	0.1% ($n = 1$)	2.58 [0.66–10.02]
Retinal detachments[c]	0.0% ($n = 0$)	0.0% ($n = 0$)	–
Cardiac arrhythmias[c]	7.0% ($n = 135$)	6.3% ($n = 153$)	1.04 [0.81–1.32]
Peripheral neuropathies[c]	1.4% ($n = 27$)	1.6% ($n = 40$)	0.79 [0.48–1.30]
Nervous system disorders[c]	3.3% ($n = 63$)	3.2% ($n = 78$)	1.00 [0.71–1.40]
Non-traumatic injuries of muscle, tendon, and synovialis[c]	0.5% ($n = 9$)	0.5% ($n = 13$)	0.84 [0.36–1.97]
Toxic liver diseases[c]	0.2% ($n = 3$)	0.3% ($n = 8$)	0.45 [0.12–1.70]

[a]Cases in which the patient's age was unknown were excluded from logistic regression analysis

[b]In logistic regression analysis, fluoroquinolone and cotrimoxazole exposures were considered as outcome variables, and age (> 64 years), sex, aortic aneurysms, cardiac arrhythmias, peripheral polyneuropathies, nervous system disorders, non-traumatic injuries of muscle, tendon, and synovialis, and toxic liver diseases as covariates. Retinal detachments were not included in the logistic regression model because retinal detachments were not observed after fluoroquinolone or cotrimoxazole exposure in clinical routine cases

[c]For a more detailed description of the identification of the respective diagnoses, see Supplementary Information 3 in the electronic supplementary material (ESM). Cases in which patients were exposed to fluoroquinolones and cotrimoxazole before the respective diagnoses were not considered

extent since the increase was also seen for cotrimoxazole. However, stimulated reporting seems likely since the number of fluoroquinolone reports per 100,000 outpatient drug prescriptions dropped clearly after 2019.

In Germany, the number of outpatient fluoroquinolone prescriptions decreased between 2014 and 2021. This may be related to the restrictions from the EMA [12], national initiatives to reduce antibiotic prescriptions [33–35] and their decrease of use in general [36], as well as a further decrease of antibiotic prescriptions during the COVID-19 pandemic between 2020 and 2021 [37, 38]. Analyses of fluoroquinolone prescriptions via the publicly available PharMaAnalyst database [39] showed an increasing number of fluoroquinolone prescriptions again in 2022. A recent study of primary care settings from six European countries (Belgium, France, Germany, the Netherlands, Spain, and the United Kingdom) between 2016 and 2021 suggested that despite the restriction of use, these measurements had only a modest impact on prescribing trends [40]. For this reason, the EMA published a reminder of the measures to reduce the risk of long-lasting, disabling, and potentially irreversible ADRs to fluoroquinolones and a respective Direct Healthcare Professional Communication (DHPC) was sent to healthcare professionals in the EU [41].

4.3 Analyses of Specific ADRs Before and After the Referral, for Females and Males and Individual Fluoroquinolones

The small number of reports describing aortic aneurysms ($n = 8$) and retinal detachments ($n = 5$) may be related to the fact that both ADRs are assumed to occur rarely [42, 43]. Additionally, since both may occur months after the fluoroquinolone therapy, recognizing these conditions as ADRs of fluoroquinolone therapy may be challenging. Neither of these two ADRs were reported for cotrimoxazole or the entire comparator group. Hence, they could not be included in the logistic regression models of the spontaneous report analyses. In the clinical routine data, a higher risk of aortic aneurysms for fluoroquinolones compared with cotrimoxazole or the entire comparator group may be assumed. This finding would be in line with other studies [42–44]. Concerning risk factors, asking patients about family histories of aortic aneurysms is of great importance, as this could increase the risk of developing aortic aneurysms [13, 45]. In patients with family histories of aortic aneurysms and patients with known aortic aneurysms, alternative antibiotics may be considered as recommended by the EMA [45]. Concerning retinal detachments, no cases with fluoroquinolone exposure could be observed in clinical routine cases. The literature is inconsistent whether there is a higher risk of retinal detachments with fluoroquinolone therapy [44, 46, 47].

Cardiac arrhythmias were also more frequently reported for fluoroquinolones compared with amoxicillin in VigiBase, which is the database of the World Health Organisation (WHO) [48]. In our study, this was only the case before but not after the referral. As in our study, others also observed a higher risk of cardiac arrhythmias for moxifloxacin [10] compared with amoxicillin [49] or compared with ciprofloxacin and levofloxacin [10, 13, 50]. Additionally, a higher risk for females to develop drug-induced cardiac arrhythmias (in general) compared with males is described in literature [51]. In our study, only a higher tendency for females considering the OR may be assumed. Alternative antibiotics might be preferable when treating patients with pre-existing cardiac disease, as already recommended by the EMA [52].

In literature, nervous system disorders including psychiatric disorders and peripheral polyneuropathies were disproportionally more frequently reported for fluoroquinolones in VigiBase (WHO database) [53], too. In Germany, more females than males are diagnosed with depression [54, 55] and females may generally be more prone to develop neuropathic pain [56]. Both aspects may increase the risk of developing nervous system disorders and peripheral neuropathies to fluoroquinolones, and might explain the higher number of females than males with these ADRs in our analyses. As in our study, both ADRs occurred more frequently for ciprofloxacin than for other fluoroquinolones in other studies [11, 57]. Differences in the chemical structure between the fluoroquinolones have been discussed to impact on their central nervous system (CNS) activity. In particular, the substituent at C7 of ciprofloxacin might explain some of the more frequent CNS effects of ciprofloxacin since it affects γ-aminobutyric acid (GABA) affinity [11]. The occurrence of nervous system disorders may further be increased by concomitant use of non-steroidal anti-inflammatory drugs (NSAIDs) as also mentioned in the assessment report of the EMA [58]. Because some NSAIDs are also available as over-the-counter drugs, it may be considered that physicians and pharmacists inform patients directly about the increased risk when both drugs are used concomitantly.

Non-traumatic injuries of muscle, tendon, and synovialis were more frequently reported for fluoroquinolone users compared with non-users or users of other antibiotics in other studies [14, 44], also. Alves et al. [14] reported in their review a higher risk of tendinopathy for ofloxacin and norfloxacin but not for ciprofloxacin and levofloxacin. In contrast, Bidell and Lodise [59] reported in their review a higher risk for levofloxacin and ofloxacin compared with other fluoroquinolones in studies of varying study designs. Since ofloxacin is a racemic mixture whose active ingredient is levofloxacin [11], it seems likely that their ADR profile is similar. A higher risk for patients with kidney diseases and older patients with reduced renal function may be expected since levofloxacin is eliminated via the kidneys [59]. Hence, dose adjustment may be considered in these patients and levofloxacin should be avoided in patients with severe renal impairment as recommended in the summary of product characteristics (SmPC) [60]. In our study, a higher risk for non-traumatic injuries of muscle, tendon, and synovialis for males compared with females was observed. In literature, some studies also reported a higher risk for males [15, 16], while others did not observe any sex-differences [61]. Further studies are needed in order to confirm or rule out any sex differences concerning non-traumatic injuries of muscle, tendon, and synovialis found in our study.

Toxic liver diseases were equally often reported in fluoroquinolone and cotrimoxazole reports in our analysis. Contrary to our study, the risk of acute liver injury with fluoroquinolones was higher than for amoxicillin in a Swedish registry [62]. A higher risk of toxic liver disease for moxifloxacin may be assumed based on our analysis. Toxic liver diseases are known for moxifloxacin [52, 63, 64], however, whether there is a higher risk compared with other fluoroquinolones needs to be investigated in further studies.

The differences in the ADR profile of individual fluoroquinolones may be related to differences between the chemical structures of fluoroquinolones, which also lead to differences in bacterial activity and pharmacokinetics [11]. Thus, fluoroquinolones may not be interchangeable. Additionally, some patients may be more prone (e.g., based on their comorbidities) to develop specific ADRs to individual fluoroquinolones. The ADR profile and differences in the efficacy regarding the bacterial activity have to be considered when selecting fluoroquinolones. Finally, other antibiotics may be more appropriate.

4.4 Different Results of Logistic Regression Analyses of Spontaneous Reports and Clinical Routine Cases

There are several reasons which might have led to the observed difference between the results of the logistic regression analyses of spontaneous reports and clinical routine cases. First of all, the study populations differ substantially. The spontaneous ADR reports include patients who developed an ADR as suspected by the reporter following outpatient and inpatient prescriptions of fluoroquinolones from all over Germany. In contrast, the routine data includes all inpatients from the University Hospital Bonn with documented intra-hospital exposure to either fluoroquinolones or cotrimoxazole, not only those with suspected ADRs, and do not include any outpatient data. In addition, since drug therapy before hospital admission is unknown, patients who were admitted to the hospital due to specific ADRs to fluoroquinolones following outpatient prescriptions are not covered. Some of the analyzed diagnoses may not need in-hospital treatment or are less easily recognized by

physicians such as subjectively perceived symptoms (e.g., mood swings) and patients may not have informed their physician about subjectively perceived symptoms for various reasons. Also, the clinical routine data primarily covers the duration of the hospital treatment, while the development of possible ADRs such as those induced by possible connective tissue effects may take longer than the typical duration of hospital treatment for other unrelated causes, thus preventing detection of such ADRs in the routine data. Thus, theses diagnoses may not be recorded or may be underestimated in clinical routine cases or may be reported more often in spontaneous ADR reports. Additionally, the time frames of the analyses of spontaneous reports and clinical routine cases differed which may also have impacted on the results. Finally, ADRs in spontaneous ADR reports were identified by selected MedDRA terms [22] and diagnoses in clinical routine cases by selected ICD-10 codes [29] (see Supplementary Information 3 in the ESM). The identification of the respective ADRs or diagnoses is thus not identical.

4.5 Strengths and Limitations

The strength of our analysis is the inclusion of a very diverse study population, such as older patients and patients with comorbidities taking concomitant drugs [20], and the consideration of two different databases.

One of the general limitations of spontaneous report analyses is the unknown amount of underreporting [65], which may also differ depending on the respective drug and ADR [66]. In the case of our study, stimulated reporting [67] for fluoroquinolones and underreporting for cotrimoxazole may be possible and might have influenced our results, also regarding specific ADRs. Since the exact number of patients exposed to fluoroquinolones or the reference antibiotics is unknown, too, incidences cannot be calculated based on analyses of spontaneous reports [20]. In addition, it may be possible that the Dear Doctor letters, which emerged before and during our "before the referral" period, already had an influence on the prescribing and reporting behavior of fluoroquinolones and their ADRs to an unknown extent. Further, the quality of documentation of the ADR reports might vary. Overall, a mean vigiGrade completeness score of 0.66 ($\pm$ 0.25) was calculated [68]. The vigiGrade completeness score is a measure to evaluate the completeness of structured information provided in each ADR report and was originally developed by the Uppsala Monitoring Center to analyze the completeness of ADR reports included in VigiBase.

In the case of clinical routine data, the causal relationship between the recorded diagnoses and drug exposure is not established but may be assumed based on the chronological occurrence of an ADR following the administration of a drug in a reasonable time frame. We have not assessed the causal relationship between the reported ADR(s) and the suspected/interacting drug(s) in the spontaneous reports either, however, unlike the clinical routine data, all spontaneous reports are suspected cases of ADRs by their intention. In contrast, the routine dataset includes all patient records and diagnoses and is thus not specifically constrained to cases with suspected or actual ADRs. Some of the dates of diagnoses in clinical routine data may not be correctly recorded and may have been recorded at discharge from the hospital or afterward for billing purposes. This is an inherent limitation of the clinical routine data, which may lead to incorrect representation of the chronological sequence of exposure and potential ADRs as identified by ICD-10 codes, although we excluded diagnoses recorded before first exposure from our analysis. Note that only ICD-10 diagnoses but not the diagnostic surrogates based on laboratory parameters were considered.

5 Conclusion

Just like the reminder of the EMA [41] based on prescribing trends of fluoroquinolones, our study also highlights that there were only minor differences in the characteristics of ADR reports (e.g., regarding indications) for fluoroquinolones before and after the referral. We also observed a trend of increasing fluoroquinolone prescriptions in 2022 again [39], underlining the importance of adhering to the recommended restrictions by the EMA [12]. In our analyses, differences in developing specific ADRs between individual fluoroquinolones were observed. This finding may be explained by differences between individual fluoroquinolones or by differences between patient populations with some patients (with specific co-morbidities) at higher risk of developing specific ADRs to individual fluoroquinolones. However, this needs to be confirmed in further studies.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40268-024-00499-x.

Acknowledgments We thank the ADR database research team of the Federal Institute for Drugs and Medical Devices (BfArM) pharmacovigilance division for their excellent support.

Declarations

Funding ANKA is funded by own resources from the German Federal Institute for Drugs and Medical Devices' (BfArM) and the Institute for Medical Biometry, Informatics, and Epidemiology (IMBIE), University Hospital Bonn, Germany (V-2020.2/68502/2020-2024). The data provisioning services provided by the data integration center (DIC) Bonn were created with and/or are currently supported, in part, via funding by the Federal Ministry of Education and Science (BMBF)

under grant numbers (FKZ): 01ZZ1602C, 01ZZ1803Q, 01ZZ2303G, and 01KX2121.

Competing interests DD and MS are supported by the ANKA project, which is founded by the Federal Institute for Drugs and Medical Devices and the Institute for Medical Biometry, Informatics and Epidemiology at the University Hospital Bonn.

Ethics approval The ethics committee of the Medical Faculty of Bonn waved the need for approval since this is not required for retrospective analyses based on pseudonymized spontaneous reports from EudraVigilance and clinical routine data from the University Hospital Bonn and stated that fthere are no ethical concerns (file no. 458/20 and 100/21). Thus, consent to participate is not required and was not obtained.

Consent to participate Not applicable.

Consent for publication Not applicable.

Availability of data and materials The pseudonymized ADR reports from EudraVigilance are not publicly accessible due to data protection requirements. Distinct levels of access are provided for various stakeholders (https://www.ema.europa.eu/en/human-regulatory/research-development/pharmacovigilance/eudravigilance/access-eudravigilance-data). Being one of the competent authorities in Germany, the highest level of access is granted to the Federal Institute for Drugs and Medical Devices (BfArM). Nevertheless, even with the lowest access level, researchers can perform the same analysis in EudraVigilance (EV) with aggregated data (public access: http://www.adrreports.eu/en/index.html). For further information regarding processing personal data in the context of the operation of EudraVigilance Human we refer to the European Medicines Agency's Data Protection Notice for EudraVigilance Human.

Code availability Not applicable.

Author's contributions DD, JW, BH, and BS contributed to the conception and design of the study. DD selected the statistical methods, performed the analysis and created all tables and figures. The results were discussed by all authors. The first draft of the manuscript was written by DD. All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

References

1. Pham TDM, Ziora ZM, Blaskovich MAT. Quinolone antibiotics. Medchemcomm. 2019;10(10):1719–39.
2. Tanne JH. FDA adds "black box" warning label to fluoroquinolone antibiotics. BMJ. 2008;337(7662):135.
3. US Food and Drug Administration (FDA). FDA updates warnings for fluoroquinolone antibiotics. Limits use for acute bacterial sinusitis, acute bacterial exacerbation of chronic bronchitis and uncomplicated urinary tract infections, 2016. https://www.fda.gov/news-events/press-announcements/fda-updates-warnings-fluoroquinolone-antibiotics. Accessed 15 Nov 2024.
4. US Food and Drug Administration (FDA). Fluoroquinolone Antimicrobial Drugs Information. https://www.fda.gov/drugs/information-drug-class/fluoroquinolone-antimicrobial-drugs-information. Accessed 15 Nov 2024.
5. US Food and Drug Administration (FDA). FDA In Brief: FDA warns that fluoroquinolone antibiotics can cause aortic aneurysm in certain patients. https://www.fda.gov/news-events/fda-brief/fda-brief-fda-warns-fluoroquinolone-antibiotics-can-cause-aortic-aneurysm-certain-patients. Accessed 15 Nov 2024.
6. European Medicines Agency (EMA). Quofenix / Quinsair—direct healthcare professional communication (DHPC). https://www.ema.europa.eu/en/medicines/dhpc/quofenix-quinsair. Accessed 15 Nov 2024.
7. Arzneimittelkommission der deutschen Ärzteschaft. Rote-Hand-Brief. https://www.akdae.de/fileadmin/user_upload/akdae/Arzneimittelsicherheit/RHB/Archiv/2019/20190408.pdf. Accessed 15 Nov 2024.
8. Federal Institute for Drugs and Medical Devices. Fluorchinolone: Schwere und langanhaltende Nebenwirkungen im Bereich Muskeln, Gelenke und Nervensystem. https://www.bfarm.de/SharedDocs/Risikoinformationen/Pharmakovigilanz/DE/RV_STP/a-f/fluorchinolone-bewegungsapparat.html. Accessed 15 Nov 2024.
9. Gorelik E, Masarwa R, Perlman A, et al. Fluoroquinolones and cardiovascular risk: a systematic review, meta-analysis and network meta-analysis. Drug Saf. 2019;42:529–38.
10. Krahn A. Zur toxikologie der antibiotikagruppe der gyrasehemmer/chinolone unter besonderer berücksichtigung der fluorchinolone.
11. European Medicines Agency (EMA). Quinolone- and fluoroquinolone-containing medicinal products—referral. https://www.ema.europa.eu/en/medicines/human/referrals/quinolone-and-fluoroquinolone-containing-medicinal-products. Accessed 15 Nov 2024.
12. Baggio D, Ananda-Rajah MR. Fluoroquinolone antibiotics and adverse events. Aust Prescr. 2021;44:161–4.
13. Alves C, Mendes D, Marques FB. Fluoroquinolones and the risk of tendon injury: a systematic review and meta-analysis. Eur J Clin Pharmacol. 2019;75:1431–43.
14. Baik S, Lau J, Huser V, et al. Association between tendon ruptures and use of fluoroquinolone, and other oral antibiotics: a 10-year retrospective study of 1 million US senior Medicare beneficiaries. BMJ Open. 2020;10: e034844.
15. Seeger JD, West WA, Fife D, et al. Achilles tendon rupture and its association with fluoroquinolone antibiotics and other potential risk factors in a managed care population. Pharmacoepidemiol Drug Saf. 2006;15(11):784–92.
16. Federal Institute for Drugs and Medical Devices. Pharmacoepidemiology - Serious Adverse Drug Reactions of Fluoroquinolones: pharmacoepidemiological analyses. https://www.bfarm.de/EN/BfArM/Tasks/Research/Pharmacoepidemiology/_node.html. Accessed 15 Nov 2024.
17. European Medicines Ageny (EMA). Guideline on good pharmacovigilance practices (GVP) Module VI—collection, management and submission of reports of suspected adverse reactions to medicinal products (Rev 2). 2017. https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/guideline-good-pharmacovigilance-practices-gvp-module-vi-collection-management-submission-reports_en.pdf.11. Accessed 15 Nov 2024.
18. European Medicines Agency (EMA). Guideline on good pharmacovigilance practices (GVP) Annex I—definitions (Rev 4).

2017. https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-good-pharmacovigilance-practices-annex-i-definitions-rev-4_en.pdf. Accessed 15 Nov 2024.
19. Dubrall D, Schmid M, Alesik E, et al. Frequent adverse drug reactions, and medication groups under suspicion. Dtsch Arztebl Int. 2018;115(23):393–440.
20. European Medicines Agency. EudraVigilance. https://www.ema.europa.eu/en/human-regulatory/research-development/pharmacovigilance/eudravigilance. Accessed 15 Nov 2024.
21. Medical Dictionary for Regulatory Activities (MedDRA). https://www.meddra.org/. Accessed 15 Nov 2024.
22. European Medicines Agency. Medicinal product dictionary. https://www.ema.europa.eu/en/human-regulatory/post-authorisation/data-medicines-iso-idmp-standards/extended-eudravigilance-medicinal-product-dictionary-xevmpd-training. Accessed 15 Nov 2024.
23. Federal Institute for Drugs and Medical Devices. ATC code. https://www.bfarm.de/SharedDocs/Downloads/DE/Kodiersysteme/ATC/atc-ddd-amtlich-2023.pdf?__blob=publicationFile. Accessed 15 Nov 2024.
24. Motola D, Vargiu A, Leone R, et al. Influence of regulatory measures on the rate of spontaneous adverse drug reaction reporting in Italy. Drug Saf. 2008;31(7):609–16.
25. Central Research Institute for Ambulatory Health Care in Germany. https://www.zi.de/. Accessed 15 Nov 2024.
26. Semler SC, Wissing F, Heyder R. German medical informatics initiative. Methods Inf Med. 2018;57(S 01):e50–6.
27. Winter A, Stäubert S, Ammon D, Aiche S, Beyan O, Bischoff V et al. Smart medical information technology for healthcare (SMITH). Methods Inf Med. 2018;57(S 01):e92–105.
28. Federal Institute for Drugs and Medical Devices. ICD-10_GM. https://www.bfarm.de/EN/Code-systems/Classifications/ICD/ICD-10-GM/_node.html. Accessed 15 Nov 2024.
29. European Medicines Agency. Annual Report 2022. https://www.ema.europa.eu/en/documents/annual-report/2022-annual-report-european-medicines-agency_en.pdf. Accessed 15 Nov 2024.
30. Christ P, Dubrall D, Schmid M, Sachs B. Comparative analysis of information provided in German adverse drug reaction reports sent by physicians, pharmacists and consumers. Drug Saf. 2023;46:1363–79.
31. European Medicines Agency. Legal framework: pharmacovigilance. https://www.ema.europa.eu/en/human-regulatory-overview/pharmacovigilance-overview/legal-framework-pharmacovigilance. Accessed 15 Nov 2024.
32. Kassenärztliche Bundesvereinigung (KBV): RESIST. Antibiotika bewusst anwenden—resistenzen vermeiden. http://www.kbv.de/html/resist.php. Accessed 15 Nov 2024.
33. Altiner A, Berner R, Diener A, et al. Converting habits of antibiotic prescribing for respiratory tract infections in German primary care—the cluster-randomized controlled CHANGE-2 trial. BMC Fam Pract. 2012;13:124.
34. Bundesamt für Verbraucherschutz und Lebensmittelsicherheit (BVL): GERMAP 2015. Antibiotika-Resistenz und -Verbrauch, Bericht über den Antibiotikaverbrauch und die Verbreitung von Antibiotikaresistenzen in der Human- und Veterinärmedizin in Deutschland. file:///C:/Users/jholstiege/Downloads/germap2015.pdf
35. Holstiege J, Schulz M, Akmatov M, et al. The decline in outpatient antibiotic use an analysis of Nationwide Prescription Data From 2010 to 2018. Dtsch Arztebl Int. 2020;117:679–86.
36. Central Research Institute for Ambulatory Health Care in Germany. https://www.zi.de/themen/arznei-und-heilmittel/verordnungsdaten/rx-trendbericht/wirkstoffgruppen. Accessed 15 Nov 2024.
37. Schuster R, Emcke T,von Arnstedt E, et al. Antibiotic prescriptions before, during and after the corona pandemic in Schleswig-Holstein. 30. Jahrestagung der Gesellschaft für Arzneimittelanwendungsforschung und Arzneimittelepidemiologie (GAA).
38. PharMaAnalyst. https://arzneimittel.wido.de/PharMaAnalyst/;jsessionid=9EAC86F92D41F462382A7C34700FE9F9?0. Accessed 15 Nov 2024.
39. European Medicines Agency. Study of impact of EU label changes for fluoroquinolone containing medicinal products for systemic and inhalation use—post-referral prescribing trends. https://www.encepp.eu/encepp/openAttachment/studyResult/48007. Accessed 15 Nov 2024.
40. European Medicines Agency. Fluoroquinolone antibiotics: reminder of measures to reduce the risk of long-lasting, disabling and potentially irreversible side effects. https://www.ema.europa.eu/en/news/fluoroquinolone-antibiotics-reminder-measures-reduce-risk-long-lasting-disabling-potentially. Accessed 15 Nov 2024.
41. Wee I, Chin B, Syn N, et al. The association between fluoroquinolones and aortic dissection and aortic aneurysms: a systematic review and meta-analysis. Sci Rep. 2021;11:11073.
42. Bennett AC, Bennett CL, Witherspoon BJ, Knopf KB. An evaluation of reports of ciprofloxacin, levofloxacin, and moxifloxacin-association neuropsychiatric toxicities, long-term disability, and aortic aneurysms/dissections disseminated by the Food and Drug Administration and the European Medicines Agency. Expert Opin Drug Saf. 2019;18(11):1055–63.
43. Gatti M, Bianchin M, Raschi E. Assessing the association between fluoroquinolones and emerging adverse drug reactions raised by regulatory agencies: an umbrella review. Eur J Internal Med. 2020;75:60–70.
44. European Medicines Agency. PRAC recommendations on signals. https://www.ema.europa.eu/en/documents/prac-recommendation/prac-recommendations-signals-adopted-31-august-3-september-2020-prac-meeting_en.pdf. Accessed 15 Nov 2024.
45. Etminan M, Forooghian F, Brophy JM, Bird ST, Maberley D. Oral fluoroquinolones and the risk of retinal detachment. JAMA. 2012;307(13):1414–9.
46. Chui CS, Man KK, Cheng CL, et al. An investigation of the potential association between retinal detachment and oral fluoroquinolones: a self-controlled case series study. J Antimicrob Chemother. 2014;69(09):2563–7.
47. Bonaldo G, Andriani LA, D'Annibali O, et al. Cardiovascular safety of macrolide and fluoroquinolone antibiotics: an analysis of the WHO database of adverse drug reactions. Pharmacoepidemiol Drug Saf. 2019;28:1457–63.
48. Falagas ME, Rafailidis PI, Rosmarakis ES. Arrhythmias associated with fluoroquinolone therapy. Int J Antimicrob Agents. 2007;29(04):374–9.
49. Lapi F, Tuccori M, Motola D, et al. Safety profile of the fluoroquinolones analysis of adverse drug reactions in relation to prescription data using four regional pharmacovigilance databases in Italy. Drug Saf. 2010;33(9):789–99.
50. Ebert SM, Liu XK, Woolsley RL. Female gender as a risk factor for drug-induced cardiac arrhythmias: evaluation of clinical and experimental evidence. J Womens Health. 1998;7(5):547–57.
51. European Medicines Agency. Referral Avelox. https://www.ema.europa.eu/en/documents/referral/avelox-article-6-12-referral-annex-i-ii-iii_en.pdf. Accessed 15 Nov 2024.
52. Huruba M, Farcas A, Leucuta DC, et al. A VigiBase descriptive study of fluoroquinolone-associated peripheral nervous system disorders. Pharmaceuticals. 2022;15:143.
53. Steffen A, Thom J, Jakobi F, et al. Trends in prevalence of depression in Germany between 2009 and 2017 based on nationwide ambulatory claims data. J Affect Dis. 2020;271:239–47.
54. Streit F, Zillich L, Frank J, et al. Lifetime and current depression in the German National Cohort (NAKO). World J Biol Psychiatry. 2023;24(10):865–80.

55. Colloca L, Ludman T, Bouhassira D, et al. Neuropathic pain. Nat Rev Dis Primers. 2017;3:17002.
56. Tomé AM, Filipe A. Quinolones—review of psychiatric and neurological adverse reactions. Drug Saf. 2011;34(6):465–88.
57. European Medicines Agency. Assessment report. https://www.ema.europa.eu/en/documents/referral/quinolone-and-fluoroquinolone-article-31-referral-assessment-report_en.pdf. Accessed 15 Nov 2024.
58. Bidell MR, Lodise TP. Fluoroquinolone-associated tendinopathy: does levofloxacin pose the greatest risk? Pharmacotherapy. 2016;36(6):679–93.
59. European Medicines Agency. Quinsair product information. https://www.ema.europa.eu/en/documents/product-information/quinsair-epar-product-information_en.pdf. Accessed 15 Nov 2024.
60. van der Linden PD, Sturkenboom MCJM, Herings RMC, et al. Increased risk of achilles tendon rupture with quinolone antibacterial use, especially in elderly patients taking oral corticosteroids. Arch Intern Med. 2003;163(15):1801–7.
61. Nibell O, Svanström H, Inghammer M. Oral Fluoroquinolone use and the risk of acute liver injury: a nationwide cohort study. CID; 74/12:2152–2158.
62. Hu T, Sun Y, An Z. Dose- and time-dependent manners of moxifloxacin induced liver injury by targeted metabolomics study. Front Pharmcol. 2022;13: 994821.
63. Chalasani N, Bonkovsky HL, Fontana R, et al. Features and outcomes of 899 patients with drug-induced liver injury: the DILIN prospective study. Gastroenterol. 2015;148(7):1340–1352.
64. Hazell L, Shakir SAW. Under-reporting of adverse drug reactions: a systematic review. Drug Saf. 2006;29(5):385–96.
65. Hasford J, Goettler M, Munter KH, et al. Physicians' knowledge and attitudes regarding the spontaneous reporting system for adverse drug reactions. J Clin Epidemiol. 2002;55(9):945–50.
66. Hoffman KB, Demakas AR, Dimbil M, et al. Stimulated reporting: the impact of US food and drug administration-issued alerts on the adverse event reporting system (FAERS). Drug Saf. 2014;37(11):971–80.
67. Bergvall T, Norén GN, Lindquist M. vigiGrade: a tool to identify well-documented individual case reports and highlight systematic data quality issues. Drug Saf. 2014;37:65–77.

Authors and Affiliations

Diana Dubrall[1,2] · Julia Wicherski[2] · Maike Below[3] · Jan Görtzen-Patin[4,5] · Matthias Schmid[1] · Sven Zenker[1,4,5] · Britta Haenisch[2,6,7] · Bernhardt Sachs[2,8]

✉ Diana Dubrall
Diana.Dubrall@bfarm.de

1 Institute for Medical Biometry, Informatics and Epidemiology, University Hospital Bonn, Venusberg-Campus 1, 53127 Bonn, Germany

2 Research Division, Federal Institute of Drugs and Medical Devices (BfArM), Kurt-Georg-Kiesinger-Allee 3, 53175 Bonn, Germany

3 Central Research Institute for Ambulatory Health Care in Germany, Salzufer 8, 10587 Berlin, Germany

4 Department of Anesthesiology and Intensive Care Medicine, University Hospital Bonn, Venusberg-campus 1, 53127 Bonn, Germany

5 Staff Unit for Medical and Scientific Technology Development and Coordination (MWTek), University Hospital Bonn, Venusberg-Campus 1, 53127 Bonn, Germany

6 German Center for Neurodegenerative Diseases (DZNE) e. V., Venusberg-Campus 1/99, 53127 Bonn, Germany

7 Germany Center for Translational Medicine, University Hospital Bonn, Venusberg-Campus 1, 53127 Bonn, Germany

8 Department for Dermatology and Allergy, University Hospital RWTH Aachen, Morillenhang 27, 52074 Aachen, Germany