Universidade de Lisboa

Faculdade de Farmácia

Fluoroquinolone Antibiotics

The Impact of Direct Healthcare Professional Communications on Spontaneous Reporting

Benjamim Francisco da Silva

Trabalho de Campo orientado pela Professora Doutora Carla Torre, Professora Auxiliar da Faculdade de Farmácia da Universidade de Lisboa e co-orientado pelo Dr. João Paulo Fernandes, Técnico Superior da Direção de Gestão de Risco de Medicamentos do INFARMED I.P.

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Trabalho Final de Mestrado Integrado em Ciências Farmacêuticas apresentado à Universidade de Lisboa através da Faculdade de Farmácia

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As I insert the references for this document, resulting from the work of many months, I reminisce about everything that got me this far. I am in awe of my endeavour, and I know, without any doubts, that I wouldn't have made it this far without the support of so many people.

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Thanks for everything and everyone.

Declaro ter desenvolvido e elaborado o presente trabalho em consonância com o Código de Conduta e de Boas Práticas da Universidade de Lisboa. Mais concretamente, afirmo não ter incorrido em qualquer das variedades de fraude académica, que aqui declaro conhecer, e que atendi à exigida referenciação de frases, extratos, imagens e outras formas de trabalho intelectual, assumindo na íntegra as responsabilidades da autoria.

Resumo

Introdução: Notificações espontâneas de reações adversas músculo-esqueléticas duradouras motivaram a autoridade alemã do medicamento a solicitar, em 2017, um *referral procedure* ao PRAC (*Pharmacovigilance Risk Assessment Committee*) para as formas sistémica e inaladas dos antibióticos pertencentes às quinolonas e fluoroquinolonas. A revisão levou à remoção de todas as quinolonas do mercado, e à restrição do uso das fluoroquinolonas, associada a uma DHPC (*Direct Healthcare Professional Communication*), em 2019, e na comissão do estudo EUPAS37856, cujos resultados levaram à emissão de uma segunda DHPC em 2023.

Objetivos: Este estudo descritivo procura explorar o efeito destas ações regulamentares no padrão global de notificações espontâneas para as fluoroquinolonas, e no padrão de notificação para as fluoroquinolonas relativo às reações adversas para as quais as DHPC alertavam.

Métodos: Notificações espontâneas de fluoroquinolonas abrangidas por ambas DHPC, nas formas sistémica e inaladas, de 1 de abril de 2014 a 30 de abril de 2024, do EEE, foram recolhidas da base de dados EudraVigilance. Notificações provenientes da literatura e relativas a outras formas farmacêuticas foram excluídas. O conjunto de notificações foi então submetido a uma análise de todas as notificações, uma análise de casos com pelo menos um PT (*Preferred Term*) do MedDRA (*Medical Dictionary for Regulatory Activities*) pertencente às SOC (*System Organ Classes*) "Perturbações músculo-esqueléticas e do tecido conjuntivo" e "Perturbações do sistema nervoso", e uma análise selecionando apenas casos com PT relativos a tendinite.

Resultados: Obtivemos um total de 31681 casos de interesse. O total de notificações aumentou desde 2016, atingiu o pico em 2019 (5005) e diminuiu para um nadir em 2021 (1977). Seguiu-se um segundo pico mais fraco em 2023 (3005), que diminuiu até ao final do período de análise. Estes resultados repetiram-se nas análises subsequentes.

Conclusão: Casos aumentaram, devido a utilização incorreta, até à primeira DHPC, associada ao pico dos casos, e que levou à diminuição do uso de fluoroquinolonas ao alertar profissionais de saúde. O segundo pico pode ser atribuído à segunda DHPC, e o efeito menos dramático pode dever-se a dessensibilização e/ou efetividade parcial da primeira DHPC. As DHPC aumentarão a notificação espontânea, reforçando a sua importância.

Palavras-chave: Fluoroquinolonas, EudraVigilance, Medidas de Minimização de Risco, Reações Adversas, DHPC.

Abstract

Background: Case reports of long-lasting musculoskeletal side-effects motivated the German Medicines Authority to request, in 2017, a referral procedure to the PRAC (Pharmacovigilance Risk Assessment Committee), for systemic and inhaled quinolone and fluoroquinolone antibiotics. The review led to the removal from the market of all quinolones, and to a restriction in the use of fluoroquinolones, associated to a Direct Healthcare Professional Communication (DHPC) in 2019, and the commissioning of the study EUPAS37856, which results led the PRAC to issue a second DHPC in 2023.

Objectives: This descriptive study aims to explore these regulatory actions' effect on the overall pattern of spontaneous reports for the fluoroquinolones, as well as on the pattern of notification for the fluoroquinolones relative to the adverse reactions for which the DHPCs precautioned.

Methods: Case reports of fluoroquinolones ranged by both DHPCs, in their inhaled and systemic forms, from April 1, 2014, to April 30, 2024, from the EEA, were retrieved from the EudraVigilance database. Cases from literature, and other pharmaceutical forms were excluded. The set of reports was then submitted to an analysis of all notifications, an analysis of cases with at least one MedDRA (Medical Dictionary for Regulatory Activities) PT (Preferred Term) belonging to the "Musculoskeletal and connective tissue disorders" and "Nervous system disorders" SOCs (System Organ Classes), and a third analysis for cases containing a PT relative to tendinitis.

Results: A total of 31681 cases of interest were retrieved. The total number of reports for fluoroquinolones increased since 2016, peaked in 2019 (5005), and declined to a nadir in 2021 (1977). A second, weaker peak followed in 2023 (3005), which decreased until the end of the period of analysis. These results were mirrored in subsequent analyses.

Conclusion: Cases increased due to undue use until the first DHPC, which, associated with the peak in reports, alerted healthcare professionals and contributed to a decrease in fluoroquinolone use. The second peak can be attributed to the second DHPC, and its less dramatic effect may be due to desensitisation and/or partial effectiveness of the first DHPC. The DHPCs may lead to spontaneous reporting increases, reinforcing their importance.

Keywords: Fluoroquinolones, EudraVigilance, Risk Minimization Measures, Pharmacovigilance, DHPC.

List of Abbreviations

ADR – Adverse Drug Reaction

AFSSAPS - *Agence Française de Sécurité Sanitaire des Produits de Santé*

ANSM - *Agence nationale de sécurité du medicament et des produits de santé*

BfArM - *Bundesinstitut für Arzneimittel und Medizinprodukte*

CHMP - Committee for Medicinal Products for Human Use

DHPC - Direct Healthcare Professional Communication

EC - European Commission

EMA – European Medicines Agency

EPS – European Pharmacovigilance System

EU – European Union

GVPs – Good Pharmacovigilance Practices

HPs – Healthcare Professionals

MAH – Marketing Authorisation Holder

MedDRA - Medical Dictionary for Regulatory Activities

PAH - Pulmonary Arterial Hypertension

PASS - Post Authorisation Safety Study

PRAC - Pharmacovigilance Risk Assessment Committee

PT - Preferred Term

PSUR - Periodic Safety Update Reports

RMM - Risk Minimisation Measure

RMP – Risk Management Plan

SADR – Serious Adverse Drug Reaction

SOC - System Organ Class

SmPC - Summary of Product Characteristics

WHO – World Health Organization

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1 Introduction

1.1 The European Pharmacovigilance System

Member States shall operate a pharmacovigilance system for the fulfilment of their pharmacovigilance tasks and their participation in Union pharmacovigilance activities. The pharmacovigilance system shall be used to collect information on the risks of medicinal products as regards patients' or public health.

That information shall in particular refer to adverse reactions in human beings, arising from use of the medicinal product within the terms of the marketing authorisation as well as from use outside the terms of the marketing authorisation, and to adverse reactions associated with occupational exposure.

Article 101, Directive 2001/83/EC

Currently, the amended Directive 2001/83/EC delineates the legal framework of medicines in the European Union. It stipulates what constitutes a medicinal product and any other subjacent terms (Title I), distinguishes the products to which it applies (Title II), the conditions needed for their marketing (Title III), manufacture (Title IV) and packaging (Title V), their classification (Title VI), distribution (Title VII) and advertisement (Title VIII), the existence of a dedicated pharmacovigilance system (Title IX), exceptions relating to products derived from human blood or plasma (Title X), the framework for evaluation of compliance with the code of law (Title XI), the EMA committee designated to communicate with the European Commission (EC) (Title XII), and finalizes with direct instructions on the operation of the framework (Titles XIII and XIV) (1).

The excerpt above has been cited from the first article of Title IX, "Pharmacovigilance". It presents the two key aspects of the European Pharmacovigilance System (EPS): the existence of a system that continuously collects information on any deleterious effects associated with the use of medicinal products, and the coordination of Member States to the completion of tasks that benefit the whole Union. It is important to know, however, that it has not always been structured in this manner.

1.1.1 The Foundations of the European Pharmacovigilance System (EPS)

The EPS was continuously developed as an answer to the challenges it encountered, developing regulatory processes to increase its resilience. Its complex structure can more easily be understood through the history that shaped it.

The story of regularized Pharmacovigilance Systems is often traced back to the crisis of thalidomide in the 1960s, but the monitoring of the correct use of medicines can be found as early as 1893, with the example of Hannah Greener in the United Kingdom. Hannah was a 15-year-old girl who died following a procedure for the removal of an ingrown nail, in which chloroform was used as an anaesthetic. The concerns that resulted from this incident eventually led the journal The Lancet to begin to gather and publish reports of anaesthesia-related deaths (2).

In the decades that followed, incidents occurred such as the sulphanilamide elixir crisis in 1937, in which the use of diethylene glycol, a nephrotoxic and neurotoxic agent, as a solvent for an elixir led to the death of at least 76 people in the United States. This incident was a great motivator for the passage of the 1938 Federal Food, Drug and Cosmetic Act, which mandated manufacturers to submit evidence of safety prior to marketing a medicinal product (3,4). This set of laws profoundly shaped the FDA, as until this point its role contemplated mostly supervising marketed products. In the same year, Douthwaite proposed gastrointestinal toxicity as an adverse reaction of acetylsalicylic acid (5). The causality of this adverse reaction would be proven only by a set of studies in the succeeding decades, starting with Muir and Cossar's experimental study in 1955 (6,7), likely affecting hundreds of patients in the meantime. Thalidomide constituted one in a series of disasters that reinforced the need of a robust pharmacovigilance system in our Healthcare Systems. Marketed worldwide as a sedative for pregnancy-associated nausea, thalidomide started to be commercialized in the 1950s and led to the birth of approximately thousands of children with phocomelia, a syndrome of extensive limb development atrophy, owing to the teratogenic effects of thalidomide that had not been properly documented and communicated to the medical community (8).

Observing these effects, Dr. McBride wrote a letter, in 1961, to the editor of The Lancet, in which he described having observed an increased incidence "of severe abnormalities" in the babies delivered by women who had taken a medicine with thalidomide as its active substance. McBride described the specific abnormalities observed and inquired if journal readers had seen similar abnormalities in women who had taken Thalidomide during pregnancy (9). This letter facilitated the acknowledgement of a geographically wider crisis, and constituted the archetypical spontaneous report, containing information to detail a cause-effect relationship between an adverse drug reaction (phocomelia) and a medicinal product (thalidomide).

In response to this tragedy, regulatory authorities began to require not just proof of a medicine's safety, but also proof of a medicine's efficacy (through clinical trials) for attainment of a

Marketing Authorisation. This development also led to the development of the first formalized Pharmacovigilance systems, designed to receive safety alerts. This evolution is seen in the Kefauver–Harris Amendment in the United States (1962) (10), the Yellow Card Scheme of the United Kingdom (1964) (11), Directive 65/65/EEC in Europe (1965) (12) and the WHO Programme for International Drug Monitoring (1968) (13).

Europe's Directive 65/65/EEC was eventually refined into the present Directive 2001/83/EC. The legislation now dedicated a section to describing the Pharmacovigilance System that Member States must put in place. 2001/83/EC's continuous amendments were a response to the new challenges that appeared since its conception, and an example of these challenges can be found in Merck's Vioxx (Rofecoxib): the challenge to create a structure in Pharmacovigilance Systems that assured a response to the risks that were now being more easily noticed and received.

Vioxx use was suspected, in 2000, of causing myocardial infarction, a Serious Adverse Drug Reaction (SADR) - an ADR that results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, is a birth defect, or constitutes any other medically important event (14–16) - following findings of a nested case control study (17). In spite of this suspicion, Vioxx stayed in the market for four more years before its eventual withdrawal from the market (2004), partly due to the use of misinformation strategy by Merck Sales Personnel (18). Overall, it included, but was not limited to, suppression of evidence and presentation of earlier, smaller studies, which indicated potential clinical benefits.

This incident raised growing concerns from policymakers, who noted the necessity of a more robust pharmacovigilance system, capable of systematically detecting and correctly managing safety signals – information arising from one or multiple sources which suggests a new, potentially causal association, or a new aspect of a known association between an intervention and an event or set of events, that is judged to be of sufficient likelihood to justify verificatory action (19) - in proportion to the risk they seem to represent (20), and added to the body of evidence that motivated the EC to, in 2005, initiate an extensive review of the EPS. This review aimed to find ways to better deal with the burden of ADRs, which caused around 197,000 deaths per year in the EU at the time of the review (21).

Another important challenge can be found few years later, in Servier's Mediator (Benfluorex). Mediator was granted a French Marketing Authorisation in 1976 as an antidiabetic for its appetite suppressant effect. Its active substance, Benfluorex, is a fenfluramine derivative. In

1997, Isoméride (Dexfenfluramine) and Ponderal (Fenfluramine), chemically similar anorexigenic agents, were withdrawn from the market due to cardiovascular side effects, which included Pulmonary Arterial Hypertension (PAH). These withdrawals initiated a period of greater suspicion, by the scientific community, of Mediator's safety, and yet, Mediator evaded suspension until 2009, with neither PAH, nor Cardiac Valvulopathy being documented as associated ADRs until the end of its lifecycle, despite being the reasons why it was eventually withdrawn.

Mediator's regulatory process gained great infamy following Irène Frachon's 2010 publications, namely a book, "Mediator 150 mg" (whose initial subtitle, *how many deaths?*, was censored after a court decision), and a decisive Case-Control Study, "Benfluorex and Unexplained Valvular Heart Disease: A Case-Control Study" that provided near irrefutable evidence of Mediator's unacceptable risk to public health: an astonishing odds ratio of 40.4 (95% confidence interval 9.7 to 168.3) for "unexplained", i.e. without a previously known and identifiable cause, mitral regurgitation in Benfluorex users, in comparison to a control group of patients with "explained", mitral regurgitation (22). These publications further validated the withdrawal decision and guided the judicial procedures that followed in 2010. The case-control study was also, along with the clinical trial data, scientific journals and Individual Case Safety Reports, among the evidence reviewed during the Referral Procedure (RP) that ensued the suspension by the French Medicines Authority (at the time, *Agence Française de Sécurité Sanitaire des Produits de Santé* (AFSSAPS)).

When sufficient evidence has been gathered, the EC, a Member State or a pharmaceutical company may request a Referral Procedure – a rigorous evaluation of the benefit-risk balance of a medicine or class of medicines - to the EMA, in order to efficaciously resolve a concern relative to safety or the benefit-risk balance (23,24).

A Referral Procedure allows for a centralized analysis of an issue on behalf of the EU, solving potential disagreements between Member States and creating an EEA-wide solution to public health issues. They are currently characterized by the Directive 2001/83/EC article that regulates the conditions for their initiation and development, and which establishes the EMA committees which will be tasked with its realization. Due to continual amendment of the law, there have been many types of RPs, and the Mediator (Benfluorex) Referral Procedure constitutes a type of RP that is no longer in use, as it has been supplanted: an Article 107 procedure, which was *triggered when a Member State varied, suspended or revoked the marketing authorisation for a medicine in its territory because of a safety issue* (EMA) (24).

The Mediator Referral Procedure allowed for a rapid EU-wide evaluation of the medicine's safety. The EMA Committee responsible for the Referral, the Committee for Medicinal Products for Human Use (CHMP) (25), *concluded that the benefits of benfluorex-containing medicines do not outweigh their risks, and therefore recommended that the marketing authorisation of these medicines be revoked* (26).

Numerous factors have been identified as the complex, conglomerative cause for this tragedy. Servier's misinformation efforts towards healthcare professionals (HPs) included a misguiding strategy concerning Benfluorex's pharmacological similarity to the aforementioned anorexigenic agents. Regarding AFSSAPS' role, many internal causes were investigated during the trials that ensued the crisis, such as potential conflicts of interest, and a lack of protocols put in place to prevent such malpractice. Externally, Irène Frachon herself spoke in hearings at the French Senate, describing the intense pressure she and other scientists who aimed to provide an honest analysis of the medicine and discern safety signals risks fell under, citing examples such as a cardiologist who could not, in 2004, publish his dissertation on Mediator due to his superior's fear of publishing such a work with insufficient proof, and the censorship of her own book's subtitle, due to a judge judging that the phrase "How many deaths?" could denigrate a medicine that had, already at the time, been withdrawn from the market (27).

These events were recognized as a failure from a major European Regulatory Authority: AFSSAPS effectively allowed the exposure of Mediator to the French population for 33 years, from its introduction to the market in the September 1, 1976, to its suspension on November 30, 2009 (27). The severity of this public health crisis motivated the design of a more robust French Pharmacovigilance System, with the new *Agence nationale de sécurité du medicament et des produits de santé*, ANSM, at its helm.

Mediator was also an important incident on an European level. New Regulations and Directives introduced frameworks such as the Risk Management Plans (RMPs) (28) and Periodic Safety Update Reports (PSURs) already in 2004 (Directive 2004/27/EC). Following the Mediator incident, these Pharmacovigilance tools were further developed with subsequent amendments, particularly the reforms of Directive 2010/84/EU (29–32), which made RMPs obligatory for all new medicines and expanded the definition of ADRs to include not only noxious and unintended responses to the expected, authorised, use of a medicine, but also medications errors and uses outside the terms of marketing authorisations (32,33).

Marketing Authorisation Holders (MAHs) are obligated, through the RMP, to document the risks that have been identified, risks that are more likely to be identified (e.g. a risk associated

with the pharmacological class of the active substance), missing information (e.g. relevant populations in which the safety of the medicine has not been tested), and plans to minimise the risk associated with these three different categories of risks. Such plans may include alterations to the Summary of Product Characteristics (SmPC), or even the realization of a Post Authorisation Safety Study (PASS), and they assure the existence a plan of activities to actively ascertain a medicine's inevitably changing benefit-risk balance (34). A structured follow-up is assured for any risks that are detected.

Directive 2010/84/EU also predicted the creation of the Pharmacovigilance Risk Assessment Committee (PRAC) of the EMA, dedicated to the Agency's Pharmacovigilance efforts, and which consolidated the importance of Pharmacovigilance for the European Union. Directive 2012/26/EU continued these reforms, renovating the framework of Referral Procedures (35).

1.1.2 The EMA's Array of Regulatory Actions

Referral Procedures are just one of many regulatory processes that have been developed to maintain the benefit-risk balance of medicines. Other processes include the Risk Minimisation Measures (RMMs), that are designed to reduce the risks of the safety concerns that are found in earlier stages of the RMP. Their need is re-evaluated at regular intervals, according to generated data, and their effectiveness is assessed in equal manner (34).

Risk Minimisation Measures are constituted by two components: RMM messages, the key information about the risk and the actions intended to be taken by HPs, caregivers and patients, and RMM tools, the tools by which RMM messages are disseminated and adherence to the risk minimising action is supported or controlled (36). It is important to note that the RMM message is not necessarily a verbally explicit message. For example, the tool of restricting the pack size can (non-verbally) implicit the message that overdose is a risk associated to a certain medicine. RMM tools are categorized into routine and additional RMM tools.

Routine RMMs (rRMMs) apply to every medicinal product and tools of rRMMs include changes to the SmPC, the fundamental routine RMM tool, as well as changes to: the package leaflet, the labelling, the pack size(s) and the legal status of the product (e.g. restricting the medicine's availability to medical prescription).

Additional RMMs (aRMMs) aim to emphasise the importance of a risk contained in the SmPC and the actions intended to minimise it, being put in place only when it is perceived that they are essential to maintain the benefit-risk balance of a medicine. Tools of aRMM are sub-categorised into Educational/Safety advice tools and risk minimisation control tools.

Educational/Safety advice tools can target patients, caregivers or HPs and aim to support adherence to the actions that minimise a risk. An example of such is Thalidomide's risk awareness form. This medicine is currently indicated as a part of a combination treatment for multiple myeloma (a condition in which its benefit-risk balance is realized) and the aRMM aims to assure that a patient is fully informed of the SADRs associated with the use of the medicine prior to initiation of the treatment (37).

Risk minimisation control tools aim, alternatively, to facilitate adherence to actions that minimise a risk through the establishment of a set of conditions that need to be fulfilled before the patient is granted access to the medicine, such as Thalidomide's Pregnancy Prevention Plan, which restricts the prescription of Thalidomide to women of child-bearing potential unless all of the conditions of the plan are fulfilled (38).

The dissemination plan of aRMMs should specify the materials to be used, the target populations, timeframes and, if applicable, the use of supportive dissemination channels, such as HP organisations. For the implementation of certain actions, a Direct Healthcare Professional Communication (DHPC), may be needed. DHPCs deliver information from a MAH, or a competent authority, directly to individual HPs, with the aim of changing their practices in relation to a medicinal product (e.g. the cases in which they are prescribed). Their preparation involves cooperation between a(the) MAH(s) and the competent authority, and an agreement on the content and communication plan should be reached before the DHPC is issued (39).

RMMs are a part of a learning cycle. Following their implementation (e.g. addition of information to the SmPC), their impact on the intended outcome is evaluated and the evidence gathered updates the benefit-risk balance, which may or not require further adjustment through new RMMs. The results of rRMMs are monitored through regular pharmacovigilance activities, such as PSURs, but aRMMs require Post-Authorisation Safety Studies (PASS) in order to monitor their effectiveness.

These studies are defined in relation to the intended outcomes of RMMs, investigating the extent to which they have been disseminated to target populations, led to the acquisition of the intended knowledge and behaviours in this group, and the extent to which the intended health outcomes have been achieved. These studies must consider possible variations in the RMMs' implementation between Member States, and are subject to a specific timeframe, which is dependent on the type of RMM and must allow enough time for the measure to have realized its planned impact (36).

1.1.3 The Current landscape of the EPS

The framework created by the hitherto mentioned legislation and further characterized in the Good Pharmacovigilance Practices (GVPs) shapes the current form of the EPS.

All the stakeholders of the system have independent, yet mutual motivations to engage in pharmacovigilance activities. Member States' National Health Authorities aim to manage the risks of their approved medicines in a myriad of forms. The EMA is tasked with the coordination of the EPS. When a Member State sends a safety signal for analysis by the EMA, it gains access to the expertise assembled by the agency, which may coordinate a quick, EU-wide response that prevents damage done by the identified risk in all Member States.

1.2 The Fluoroquinolones' Referral Procedure

Directed by reports of long-lasting musculoskeletal side-effects from its national safety database and from literature, the German Medicines Authority (*Bundesinstitut für Arzneimittel und Medizinprodukte*, BfArM), requested an Article 31 Referral Procedure for systemic and inhaled forms of quinolone and fluoroquinolone antibiotics, a family of broad-spectrum antibacterials. This review was initiated on the 9th of February 2017 (40).

Article 31 Referrals are *triggered when the interest of the Union is involved, following concerns relating to the quality, safety or efficacy of a medicine or a class of medicines* (EMA) (41) - Quinolone and fluoroquinolones antibiotics were, at the time, marketed in several Member States. In this type of Referral, the EMA committee initially responsible for the evaluation is the PRAC, which recommendations are forwarded to the CHMP and, if endorsed by this committee, forwarded to the EC, which issues a final and legally binding decision applicable in the EEA.

As the procedure progressed, the EMA observed an increase in the public interest in these medicinal products and invited citizens to communicate directly with the committee by holding a public hearing during its meeting on the 13th of June of 2018 (42). From a total of 115 applications to attend, 23 speakers from 11 Member States were selected to speak (43). The rare side-effects and their impact were described in vivid detail: "one patient, a medical specialist herself, told me she thought the side-effects are way worse than the side-effects of chemo(therapy). At one point, she suffered so much she considered going to Switzerland to be euthanised", with many stakeholders noting the importance of communicating more information on the benefit-risk balance of the referred medicines to all Member States.

The PRAC continued its assessment throughout the following months, concluding the Referral Procedure in October of 2018. The result of this assessment was a recommendation for the removal from the market of all medicines containing a quinolone antibiotic, cinoxacin, flumequine, nalidixic acid and pipemidic acid, as these medicines were authorised only for infections that should no longer be treated with this class of antibiotics, and restriction of the usage (an aRMM) for the nine remaining fluoroquinolones: ciprofloxacin, levofloxacin, lomefloxacin, moxifloxacin, norfloxacin, ofloxacin, pefloxacin, prulifloxacin and rufloxacin, to a set of conditions in which the now refined benefit-risk balance was fulfilled.

The PRAC's recommendations were forwarded to the CHMP who, agreeing with the preceding committee, adopted its position as the EMA's position, forwarding it to the EC, which issued the execution of the PRAC's recommendations. The dissemination of the aRMM was assisted by DHPCs, which started to be emitted in April 2019.

The DHPCs explained that owing to the notification of incapacitating, long-lasting and potentially irreversible ADRs related to the musculoskeletal and nervous systems, the benefit-risk balance of fluoroquinolones was reviewed, and followed to instruct HPs not to prescribe fluoroquinolone antibiotics for the treatment of: self-limiting or minor infections (such as pharyngitis, tonsillitis and acute bronchitis), non-bacterial infections (such as non-bacterial prostatitis), and mild or moderate bacterial infections, unless other antibacterial medicines commonly used for the treatment of such conditions could not be used.

HPs were also instructed not to prescribe fluoroquinolone antibiotics for prevention of traveller's diarrhoea, recurring lower urinary tract infections, or to patients who had previously had SADRs when taking quinolone or fluoroquinolone antibiotics (44,45), and informed also that the class of medicines should be used with special caution in the elderly, patients with kidney disease and patients who had had an organ transplantation, as these patients are at a higher risk of tendon injury, one of the initially reported musculoskeletal side-effects. Finally, the DHPCs recommended avoiding the combination of fluoroquinolones and corticosteroids, as their combined use also contributes to a higher risk of tendon injury.

The PRAC subsequently sought to evaluate the effectiveness of the aRMM at fulfilling its objective through the commissioning of a PASS, drug utilization study EUPAS37856 (46). The study evaluated data from Belgium, France, Germany, the Netherlands, Spain and the United Kingdom from 2016 to 2021, and revealed only a modest reduction in fluoroquinolone use – the medicines seemed to still be prescribed outside of their recommended uses (47).

Consequently, the PRAC sought the emission of a second, reminding, DHPC, disseminated in EU Member States starting June 2023 (48,49).

These DHPCs notified HPs that the results of the aforementioned study indicated that fluoroquinolone antibiotics were likely still being prescribed outside of their recommended uses and listed the conditions in which these medicines should and should not be used. The conditions listed were the same as the ones listed in the first set of DHPCs. They add however, two new fluoroquinolones to the list: delafloxacin and nadifloxacin. A summary of the fluoroquinolones' regulatory process at the EMA can be found in figure 1.

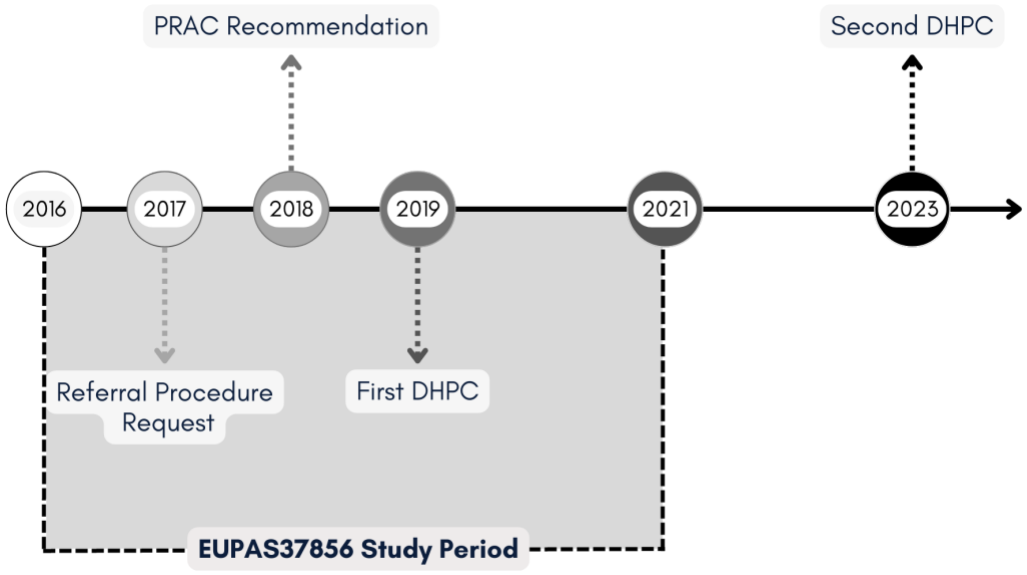

Figure 1 - Timeline of regulatory events relating to fluoroquinolone antibiotics

2 Objectives

Following a request from BfArM, quinolone and fluoroquinolone antibiotics were subjected to a Referral Procedure. The review led to a re-evaluation of the benefit-risk balance of these medicines, and it was discerned that Risk Minimization Measures needed to be taken to maintain the benefit-risk balance for the fluoroquinolones. The dissemination of these RMMs was assisted by two Direct Healthcare Professional Communications detailing the conditions in which, in accordance with the newly calibrated benefit-risk balance, the prescription of fluoroquinolone antibiotics was justified.

This descriptive study aims to evaluate the effect of the DHPCs on the overall pattern of spontaneous reports for the fluoroquinolones included in both DHPCs: ciprofloxacin, levofloxacin, lomefloxacin, moxifloxacin, norfloxacin, ofloxacin, pefloxacin, prulifloxacin and rufloxacin. Within the overall pattern of spontaneous reports, we also aim to discern the pattern for notifications that referred to specific ADRs mentioned in the DHPCs, namely tendinitis.

3 Methodology

3.1 Study Design

Our descriptive study aimed to illustrate the pattern of spontaneous reporting relative to the systemic and inhaled forms of the nine fluoroquinolones covered on both DHPCs in order to analyse the plausibility of the DHPCs influencing the pattern of spontaneous reports.

The overall pattern of spontaneous reports for the nine selected fluoroquinolones was illustrated, along with the pattern for spontaneous reports relative to the MedDRA SOCs representing the ADRs mentioned in the DHPCs ("Musculoskeletal and connective tissue disorders" and "Nervous system disorders"), and the pattern for spontaneous reports related to the MedDRA PTs representing specifically one of the ADRs mentioned in the DHPCs, tendinitis: "Tendonitis" and "Tendon rupture". This ADR was chosen due to its seriousness, clinical relevance and for being a well-defined clinical entity, compared with other reactions that may be less specific.

3.2 Study Setting

Cases from spontaneous reports received through the EudraVigilance gateway, dated from the 1st of April 2014 (five years before the emission of the first DHPC) to the 30th of April 2024 (time of initiation of our study) from the EEA, that concerned the systemic and inhaled forms of the nine fluoroquinolones covered on both DHPCs, were gathered and illustrated with Microsoft Excel, Version 16.88.24081116. The EudraVigilance database is maintained by the EMA and compiles suspected ADRs of medicines developed and/or marketed in the European Economic Area (EEA) (50).

Cases collected from literature review were excluded to minimize temporal bias. Cases concerning fluoroquinolones in other pharmaceutical forms were also excluded, as the DHPCs concerned specifically the aforementioned pharmaceutical forms. For the SOCs analysis, cases were retrieved in a multiaxial manner.

Before the analyses, changes in membership in the EEA for the study period were assessed, along with the uniformity of the dates of emission of the DHPCs, when such data was available in the national medicine registers (51).

3.3 Data Analysis

The computed total of spontaneous reports for each month, for each fluoroquinolone, was graphed into a 2D line chart through Microsoft Excel, Version 16.88.24081116. The Y axis was defined as “Number of Spontaneous Cases”, and the X axis was defined as “Year”.

4 Results

A total of 31681 cases of interest were retrieved from April 2014 to April 2024.

The data used to create the graphs that follow can be found in table format in Annex A1.

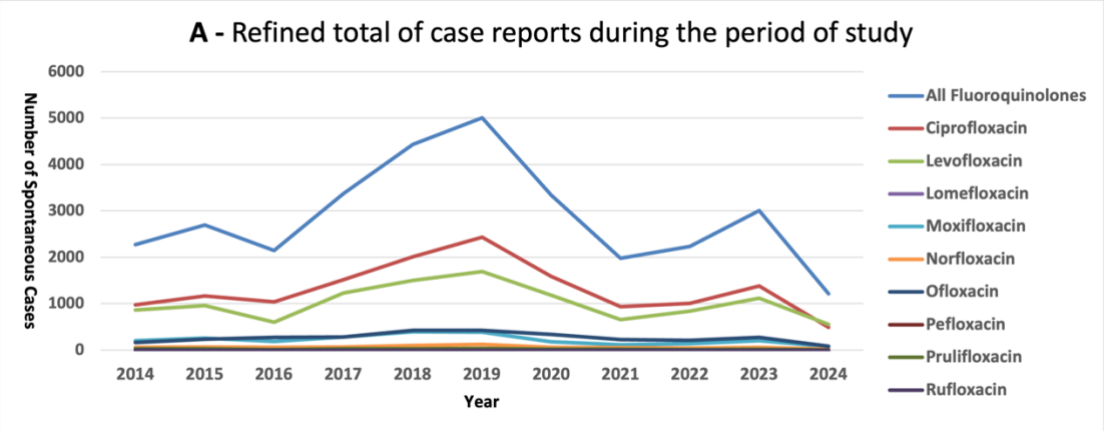

Figure 2 – Spontaneous cases reported for marketed fluoroquinolones in the EEA*, from April 2014 to April 2024

* As EudraVigilance can receive cases from the USA or China, as long as they relate to medicinal products marketed in the EEA, some cases may come from these countries. This observation applies to all subsequent graphs.

The total number of case reports for fluoroquinolones increased since 2016, peaked in 2019 (5005 cases), and then declined to a nadir in 2021 (1977 cases). This nadir was followed by a weaker, second crescendo that peaked again in 2023 (3005 cases) and then decreased until the end of the period of analysis.

The three fluoroquinolones with the highest number of case reports were Ciprofloxacin (14518 cases), Levofloxacin (11180 cases) and Ofloxacin (2911 cases).

These patterns were mirrored in the second (SOCs) and third (PTs) analyses:

The total number of case reports for fluoroquinolones which contained at least one MedDRA PT belonging to the two SOCs of interest was 15059, which corresponds to 48% of all retrieved case reports.

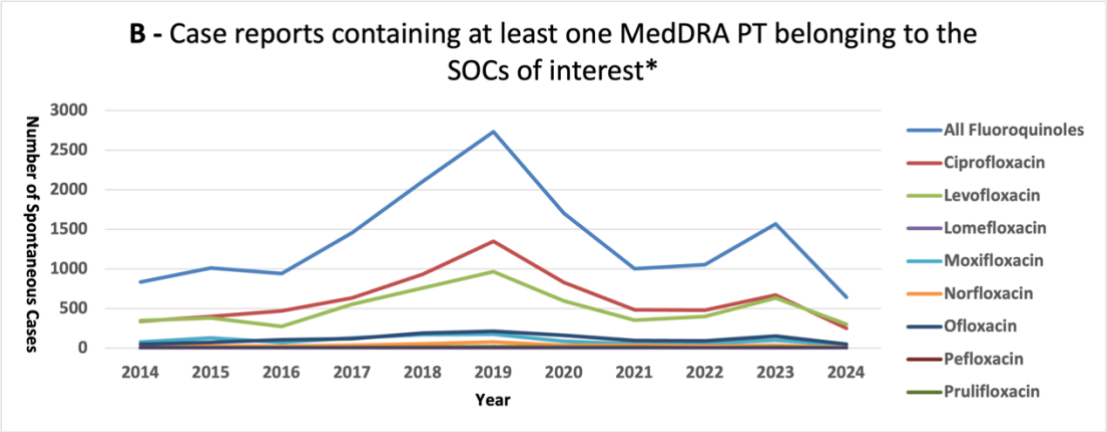

Figure 3 – Spontaneous cases reported for marketed fluoroquinolones in the EEA, from April 2014 to April 2024, that contained at least one MedDRA PT belonging to the SOCs "Musculoskeletal and connective tissue disorders" or "Nervous system disorders"

* The line for Rufloxacin could not be graphed, as only one report was received for this antibiotic (2014).

Cases start to increase after 2016, peak in 2019 (2732 cases) and decline to a nadir in 2021 (1004 cases). A second crescendo follows, to peak in 2023 (1569 cases), and then decrease until the end of the period of analysis.

The total number of case reports for fluoroquinolones which contained at least one MedDRA PT representing the ADR "tendinitis", was 5539, which corresponds to 17% of all retrieved case reports.

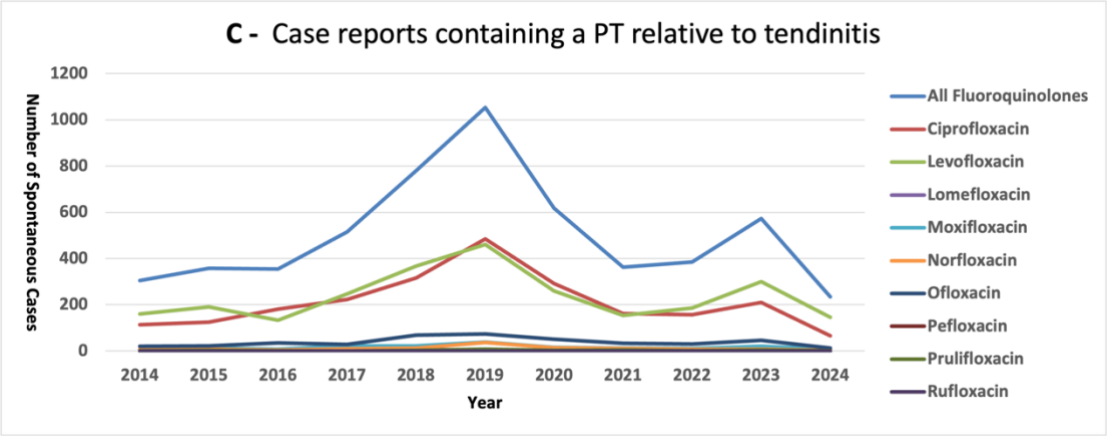

Figure 4 – Number of spontaneous cases reported for marketed fluoroquinolones in the EEA, from April 2014 to April 2024, that contained at least one of the MedDRA PTs "Tendonitis" and "Tendon rupture"

Similarly, cases increased after 2016, to a maximum of 1054 cases in 2019, then decreased to a nadir in 2021 (363 cases), before growing to a second, but weaker peak in 2023 (573 cases) that declines until the end of the period of analysis.

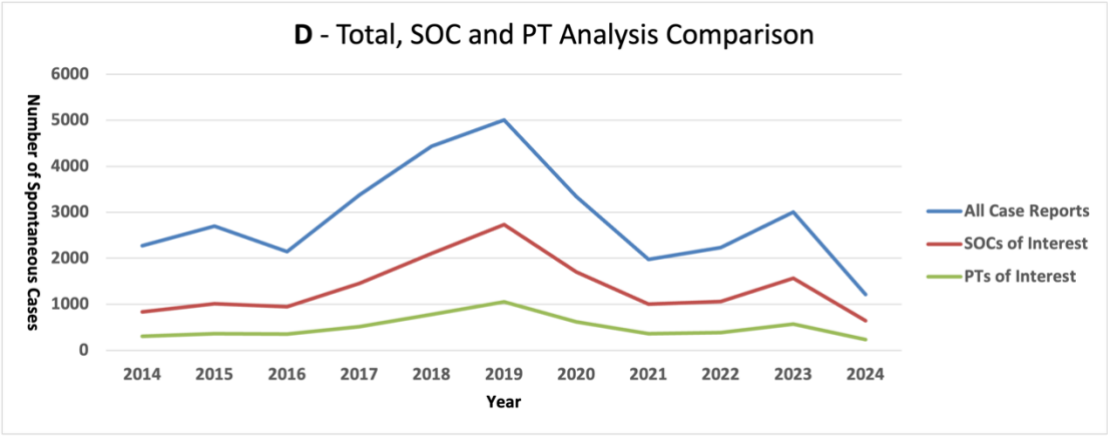

Figure 5 – Comparison between the Total, SOC and PT analyses.

The peaks observed in each analysis roughly overlap: an absolute maximum in 2019, a nadir that follows in 2021, and a new peak in 2023 followed by a decrease to the end of the period of analysis.

Analysis of the dates of emission of the DHPCs in the different countries of the European Economic Area reveal that most of the countries for which data could be found had emitted the first DHPC by the month of April 2019 (25 countries out of 26), and for the second DHPC, most countries had emitted the DHPC by the month of June 2023 (28 countries out of 29).

Table 1 – DHPCs' dates of emission in the European Economic Area

COUNTRY	DATE OF EMISSION OF THE FIRST DHPC (DD/MM/YYYY)	DATE OF EMISSION OF THE SECOND DHPC (DD/MM/YYYY)
AUSTRIA	04/09/2019 (52)	15/06/2023 (53)
BELGIUM	XX/04/2019 (54)	XX/06/2023 (55)
BULGARIA	XX/04/2019 (56)	20/06/2023 (57)
CROATIA	09/04/2019 (58)	13/06/2023 (59)
CYPRUS*	XX/XX/XXXX	XX/XX/XXXX
CZECHIA	09/04/2019 (60)	08/06/2023 (61)
DENMARK	10/04/2019 (62)	08/06/2023 (63)
ESTONIA	08/04/2019 (64)	08/06/2023 (65)
FINLAND	05/04/2019 (66)	08/06/2023 (67,68)
FRANCE	10/04/2019 (69)	02/08/2023 (70)
GERMANY	08/04/2019 (71)	07/06/2023 (72)
GREECE	05/10/2019 (73)	02/06/2023 (74)
HUNGARY	08/04/2019 (75)	08/06/2023 (76)
IRELAND	09/04/2019 (77)	12/06/2023 (78)
ITALY	08/04/2019 (79)	08/06/2023 (80)
LATVIA	08/04/2019 (81)	08/06/2023 (82)
LIECHTENSTEIN	04/09/2019 (52)	15/06/2023 (53)
LITHUANIA	XX/04/2019 (83)	XX/05/2023 (84)
LUXEMBOURG	XX/XX/XXXX	08/06/2023 (85)
MALTA	10/04/2019 (86)	19/06/2023 (87)
NETHERLANDS	XX/XX/XXXX	09/06/2023 (88)
POLAND	08/04/2019 (89)	07/06/2023 (90)
PORTUGAL	25/03/2019 (91)	30/05/2023 (92)
ROMANIA	02/04/2019 (93)	06/06/2023 (94)
SLOVAKIA	08/04/2019 (95)	08/06/2023 (96)
SLOVENIA	08/04/2019 (97)	08/06/2023 (98)
SPAIN	XX/XX/XXXX	XX/06/2023 (99)
SWEDEN	XX/XX/XXXX	08/06/2023 (100)
UNITED KINGDOM	21/03/2019 (101)	NA
ICELAND	XX/04/2019 (102)	XX/06/2023 (103)
NORWAY	XX/04/2019 (104)	XX/06/2023(105)

NA, not applicable; X, information not found.

* No online register has been made available for Cyprus as of yet

The only country of the EEA to experience a change in membership was the United Kingdom (106), which officially exited the EEA on the 31st of January 2020 and, as such, presents only the date of emission for the first DHPC.

5 Discussion

Previous research has investigated the effectiveness of DHPCs on their immediate objectives, i.e. informing HPs of a specific risk and/or lowering the prescription and dispense of certain medicines. The results varied across published literature. Positive examples include a 2024 web-based survey administered to medical doctors (N = 613) from France, Germany, Poland, Spain and the Netherlands, which revealed that 75% were aware of the increased risk of meningioma in cyproterone acetate users, precautioned in a DHPC in 2020 (107). Positive results can also be seen in a 2021 survey administered to 1153 physicians from France, Germany, the United Kingdom, Spain and Sweden, that showed that at least 66.5% of the participants followed the precautions stipulated in the educational materials and the DHPCs for Valproate, sent in 2014, with physicians who had acknowledged receiving the materials and the DHPCs (25.8%) registering higher endpoint rates (108).

However, negative examples can also be found, such as the aforementioned EUPAS37856, which indicated that the first DHPC was not effective (46).

The results of these studies suggest that despite having a significant impact in the behaviour of HPs, DHPCs have not always achieved their intended effect, which further establishes their importance as tools of dissemination, while also re-affirming the importance of evaluating their effectiveness. There are few studies, however, on the effect of these dissemination tools, or of other regulatory actions, on spontaneous reporting. Our study investigated the pattern of spontaneous reporting of adverse drug reactions suspected to be associated to the use of fluoroquinolone antibiotics, through the analysis of cases received by EudraVigilance from the countries of the European Economic Area, from April 2014 to April 2024.

We observed that the number of spontaneous reports for fluoroquinolone antibiotics started to steadily increase between 2016 and 2017. Cases continued to increase to a peak of 5005 cases in 2019, the year in which the first DHPC was emitted. Afterwards, the yearly number of cases received started to decline, to an eventual nadir in 2021 (1977 cases), which was followed by a second, weaker crescendo, that grew until 2023 (3005 cases), the year in which the second DHPC, reminding the contents of the preceding communication, was emitted.

We hypothesize that cases increased until the emission of the first DHPC, due to incorrect usage of fluoroquinolones. A peak in case reports followed, very likely due to an increase in visibility attributable to this DHPC. HPs were alerted and contributed to a decrease in the use of fluoroquinolones (both directly, and indirectly, i.e. by influencing patients, to, for example,

report more often) and, as such, case reports proceeded to decline. We note that this decline might also be, at least in part, due to a perceived decrease in the importance of already known (due to the aforementioned DHPC) ADRs. We hypothesize that the second peak could be explained by the second DHPC, which once again alerted HPs to the importance of the precautioned ADRs. This second peak was weaker, which suggests that the occurrence of the ADRs was itself lower, possibly due to partial effectiveness of earlier RMM, and/or that the (repeated) message was less effective - HPs may be receiving an high number of communications on the safety of medicinal products, becoming desensitized to them, especially if there aren't new, substantial in these communications. Additionally, it is possible that repeated communications confer a lower sense of urgency, as the danger posed by the proceeding communications might seem less important.

These results suggest that regulatory events associated to fluoroquinolone antibiotics, namely the emission of the DHPCs, led to an increase in the visibility of these medicinal products, leading to an increase in spontaneous reporting, allowing further characterization of the safety profile of medicinal products. This hypothesis is supported by the results of a Romanian study published in 2021 that sought to evaluate the knowledge of physicians and pharmacists of the safety issues described in the first DHPC. Despite the relatively low number of participants (N = 127), the study concluded that a high percentage (79.5%) of participants were aware of new safety issues (109), and thus more inclined to submit spontaneous reports.

More research is needed in order to confidently assert that these effects occurred, or that they can be expected of any medicinal products subjected to a DHPC. A 2020 case-population study investigated the reporting rates of severe hypersensitivity reactions following intravenous iron administration. The study was based on EudraVigilance data, as well as IQVIA MIDAS sales data for calculation of the rate of exposure, and suggested, despite heterogenous reporting rates for individual products, that the RMMs had had no significant impact on the reporting rates (110). Another study from 2020 which sought, through interrupted time series analysis, to evaluate the influence of additional monitoring status on spontaneous reporting, using EudraVigilance data, and PSURs for calculation of the rate of exposure, found mixed results, with few medicinal products undergoing a significant increase in reporting rates (111).

5.1 Strengths and Limitations

A strength of our study lies in the use of the EudraVigilance database, which ranges all the countries of the EEA, and allowed us to retrieve a very high number of cases of interest (31681).

Another strength lies in the wide period of our study, ranging from 2014 to 2024, and the high number of active substances covered (112).

Regarding limitations, our descriptive study aims to generate hypothesis but is hampered by limited control of confounding factors such as other regulatory actions, new medical guidelines and media attention, which lessens the strength of the evidence we presented, even if the increases in spontaneous reporting associated to the terms specifically mentioned by the DHPCs suggests a causal relationship. Access to high quality consumption data of fluoroquinolones would allow for an Interrupted time series analysis such as autoregressive integrated moving average, which has its advantages, namely allowing us to account for trends over time and assess, with a reasonable degree of confidence, the statical significance of the described trends (112,113). Such data would also allow us to evaluate the effectiveness of the DHPCs, as we would then be analysing the effect of the DHPCs on their direct target: the use of the fluoroquinolones.

Two other limitations are the fact that the UK's exit from the EEA might have led to a lower number of cases in the later periods of analysis, and the fact that the cases we've analysed codified the date of delivery to the EudraVigilance gateway, and not to the date in which they were received by the MAH or competent authority.

Our study is also subject to the limitations of any other study which analyses cases reports. It is possible for case reports identified in these databases to be, in truth, cases from literature. Many spontaneous reports lack an associated pharmaceutical form, or other such information that would allow us to discern the correct ATC code (e.g. differing between the topical and oral forms of a medicine). It is possible that we have included pharmaceutical forms that were not contemplated by the DHPCs, despite our effort to remove them when possible. Another issue in case reports lies in the quality of MedDRA coding, which is inherently inconsistent in these databases (114). It is expected that this issue affected the third analysis the most, as we searched for cases with specific PTs.

6 Conclusion

The EPS has been developed as a response to its challenging duties. As a result, its framework has grown in both size and complexity, and its activities are no longer (merely) passive.

Generated data indicated a need for a review of quinolone and fluoroquinolone antibiotics. It was found that an acceptable benefit-risk balance for the former group could no longer be realized, and their marketing authorisations were revoked. For the latter group, an adjustment was needed: the restriction of their prescription to a narrower set of conditions. To ensure that this aRMM was realised, the EMA served itself of the DHPCs. The evaluation of the aRMM tools revealed that the first DHPC likely did not achieve its intended objective. As such, a second DHPC was sent.

While the evaluation of the effectiveness of regulatory tools such as DHPCs is now routine, the evaluation of their effect in spontaneous reporting has not been extensively done, despite its utility. In this study, we aimed to analyse the effect of the DHPCs on the pattern of spontaneous reporting for fluoroquinolone antibiotics.

Following our observations, we hypothesize that cases increased due to undue use until the first DHPC, which, associated with a peak in reports, alerted HPs and contributed to a decrease in fluoroquinolone use. We hypothesize that the second, lower peak can be attributed to the second DHPC, which once again alerted HPs, but had a less dramatic effect due to desensitization of and/or partial effectiveness of the first DHPC. These findings, along with the limited existing data for the effectiveness of the DHPCs, suggest that the regulatory events associated with this class of antibiotics, namely the DHPCs, led to an important increase in spontaneous reporting through increased visibility for these medicinal products. This emphasizes the importance of these dissemination tools.

More research is needed to understand the effect of RMMs tools on spontaneous reporting, adding to the expertise that the EPS has extensively developed in signal detection and management.

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Annexes

A1. Tables corresponding to the graphs in "Results"

Table 2 – All retrieved case reports, distributed by medicinal product

	ALL	CIP	LEV	LOM	MOX	NOR	OFL	PEF	PRU	RUF
2014	2269	971	865	10	199	57	159	2	26	1
2015	2696	1165	954	13	258	63	232	5	26	0
2016	2142	1037	597	11	181	53	274	5	6	0
2017	3374	1515	1226	15	284	64	278	7	23	0
2018	4434	2006	1497	16	393	95	426	11	24	0
2019	5005	2430	1691	19	384	117	421	10	31	0
2020	3339	1587	1182	8	176	59	338	3	17	0
2021	1977	934	658	4	115	50	224	4	20	0
2022	2229	1007	837	2	134	43	209	4	6	0
2023	3005	1380	1118	0	204	58	270	1	15	0
2024	1211	486	555	0	75	20	80	2	4	0
TOTAL	31681	14518	11180	98	2403	679	2911	54	198	1

CIP, ciprofloxacin; LEV, levofloxacin; LOM, lomefloxacin; Mox, moxifloxacin; NOR, norfloxacin; OFL, ofloxacin; PEF, pefloxacin; PRU, prulifloxacin; RUF, rufloxacin.

Table 3 - Retrieved case reports which contained at least one MedDRA PT belonging to the SOCs "Musculoskeletal and connective tissue disorders" and "Nervous system disorders", distributed by medicinal product

	ALL	CIP	LEV	LOM	MOX	NOR	OFL	PEF	PRU	RUF
2014	836	339	349	3	76	20	49	0	9	1
2015	1010	399	380	5	126	27	71	2	8	0
2016	944	468	275	9	73	25	103	1	5	0
2017	1457	635	552	7	126	34	118	0	7	0
2018	2106	934	760	8	171	54	188	2	11	0
2019	2732	1350	964	14	177	78	214	2	18	0
2020	1704	831	597	8	84	36	160	2	10	0
2021	1004	482	352	1	52	34	96	1	10	0
2022	1056	479	399	1	60	26	91	3	4	0
2023	1569	672	633	0	100	33	151	1	11	0
2024	641	250	303	0	35	9	48	2	1	0
TOTAL	15059	6839	5564	56	1080	376	1289	16	94	1

CIP, ciprofloxacin; LEV, levofloxacin; LOM, lomefloxacin; Mox, moxifloxacin; NOR, norfloxacin; OFL, ofloxacin; PEF, pefloxacin; PRU, prulifloxacin; RUF, rufloxacin.

Table 4 - Retrieved case reports which contained at least one of the MedDRA PTs Tendonitis" and "Tendon rupture", distributed by medicinal product

	ALL	CIP	LEV	LOM	MOX	NOR	OFL	PEF	PRU	RUF
2014	304	114	160	0	8	7	20	0	1	0
2015	358	125	190	3	12	7	22	1	3	0
2016	355	180	133	2	8	4	34	0	1	0
2017	515	223	246	3	21	9	28	0	0	0
2018	780	315	367	6	21	12	68	1	2	0
2019	1054	485	461	4	38	36	73	0	8	0
2020	618	291	259	2	15	14	50	1	2	0
2021	363	161	153	0	12	11	33	0	4	0
2022	385	157	185	0	11	7	30	1	1	0
2023	573	209	300	0	20	7	46	0	4	0
2024	234	66	145	0	8	3	13	0	1	0
TOTAL	5539	2326	2599	20	174	117	417	4	27	0

CIP, ciprofloxacin; LEV, levofloxacin; LOM, lomefloxacin; Mox, moxifloxacin; NOR, norfloxacin; OFL, ofloxacin; PEF, pefloxacin; PRU, prulifloxacin; RUF, rufloxacin.

Table 5 - Comparison of spontaneous reports from the Total, SOC and PT Analyses

	ALL CASE REPORTS	SOCS OF INTEREST	PTS OF INTEREST
2014	2269	836	304
2015	2696	1010	358
2016	2142	944	355
2017	3374	1457	515
2018	4434	2106	780
2019	5005	2732	1054
2020	3339	1704	618
2021	1977	1004	363
2022	2229	1056	385
2023	3005	1569	573
2024	1211	641	234
TOTAL	31681	15059	5539