Study of impact of EU label changes for fluoroquinolone containing medicinal products for systemic and inhalation use - post-referral prescribing trends

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Final Study Report V3.0

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Report approval and sign-off

I confirm that I have read the contents of this report and its attachments. I approve the report in its current form.

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PASS Information

Section	Description
Title	Study of impact of EU label changes for fluoroquinolone containing medicinal products for systemic and inhalation use - post-referral prescribing trends
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Research questions and objectives	The overall aim of this study was to evaluate the impact of the regulatory actions taken for fluoroquinolone containing medicinal products following the 2018 referral procedure, using healthcare databases of six European countries. **Primary Objective(s):** 1. To determine the drug utilisation and prescription patterns of fluoroquinolone containing medicinal products over the period 2016 to 2021 by: a) monthly incident drug use overall and stratified by on-label indications (which include first line and last line indications) and off-label indications (which include mild infections for which fluoroquinolones are not indicated for). b) early discontinuation proportion (prescribed courses that were discontinued prior to intended treatment end date) 2. To evaluate the impact of regulatory interventions on fluoroquinolone prescribing patterns using time series analysis. 3.To determine prescribers' compliance with warnings in fluoroquinolones Summary of Product Characteristics (SmPC) Section 4.4, on tendinitis and tendon rupture as well as on aortic dissection and aneurysm specifically by calculation of monthly incident prescription rates in the subgroups at risk: a) risk groups for tendinitis and tendon rupture b) risk groups for aortic dissection and aneurysm c) patients with recent (30 days prior) or concomitant prescribing of systemic corticosteroids 4.To determine monthly incident prescription rates for alternative antibiotics prescribed in patients where systemic use of fluoroquinolones has previously been prescribed or discontinued.

Country(-ies) of study	Belgium, France, Germany, the Netherlands, Spain, and the United Kingdom
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Marketing authorisation holder(s)

Section	Description
Marketing authorisation holder(s) (MAH)	NA
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1 Abstract

Title

Study of impact of EU label changes for fluoroquinolone containing medicinal products for systemic and inhalation use - post-referral prescribing trends.

Version and Date

31 March 2022 – Version 2.0

Name and affiliation of main authors:

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Key words

Antibiotics, fluroquinolones, drug utilisation

Rationale and background

Fluoroquinolones are broad spectrum antibiotics that are active against both gram negative and gram-positive bacteria and are indicated in the management of various bacterial infections. The use of fluoroquinolones has been associated with the risk of serious adverse events, mainly involving the nervous system as well as tendons, muscles and joints, e.g., tendon rupture. The concerns of the persistence of side effects resulted in the European Medicines Agency (EMA) conducting a pharmacovigilance referral procedure focused on assessing adverse drug reactions, and the benefit-risk balance of fluoroquinolones for systemic and inhalation use. In November 2018, the EMA concluded that those serious adverse reactions in rare cases might become long-lasting, and recommended cessation of prescriptions for milder, non-severe or self-limiting infections, and restrictions of prescriptions in the at-risk population.

Prescribing patterns of fluoroquinolone containing medicinal products in Europe will inform the impact of the regulatory actions taken for these medicines following the 2018 referral procedure. With this drug utilisation study (DUS) using primary care data of six European Union (EU) countries over the period 2016 and 2021 we aimed to determine the potential impact of regulatory interventions on fluoroquinolones' prescriptions.

Research question and objectives

This DUS aimed to 1) estimate monthly incident fluoroquinolone prescriptions, both overall and stratified by on-label and off-label use, and estimate the proportion of early discontinuation of fluoroquinolone prescriptions, 2) evaluate the impact of regulatory interventions on fluoroquinolone prescribing patterns, 3) determine prescribers' compliance with warnings in fluoroquinolones Summary of Product Characteristics (SmPC) Section 4.4, in patients at risk of tendinitis and tendon rupture, at risk of aortic dissection and aneurysm and in patients with recent or concomitant prescribing of systemic corticosteroids, and 4) estimate monthly incident prescription rates for alternative antibiotics prescribed in patients where systemic use fluoroquinolones have previously been prescribed or discontinued.

Study design

A retrospective population-based cohort study was conducted using electronic health care records from six European countries namely Longitudinal Patient Database (LPD) Belgium, LPD France, Disease Analyser (DA) Germany, the Integrated Primary Care Information (IPCI) Netherlands, Information System for Research in Primary Care (SIDIAP) Catalonia Spain and IQVIA Medical Research Data United Kingdom (UK). These databases were mapped to the Observational Medical Outcomes Partnership (OMOP) Common Data Model (CDM). The final six months of each database were excluded because towards the end of the study period the number of patients drops substantially due to patients only being regarded as active until their last recorded contact with a health care professional in the data sources. This decline could have a significant impact on rate estimates as the denominator of active patients would be lower towards the end of the study period but the numerator (those receiving a fluoroquinolone would not) and the usage rate of fluoroquinolones would be artificially increased.

Variables

Firstly, monthly incident fluoroquinolone users were investigated by calculating the incident use (number of new users per 1,000 persons per month), and stratified in different subgroups of interest including age, sex, drug type, indications, on-label and off-label use. Incidence of off-label use of fluoroquinolone was calculated and presented as a ratio of off-label to on-label. Early discontinuation proportion was expressed as the number of patients identified as stopping treatment early per 1,000 incident users per month. Secondly, a time series analysis using joinpoint/segmented regression was used to analyse time points of changes in trends. Data were modelled by a Poisson model on the log-linear scale with monthly incidence rate as the independent variable and calendar month as the predictor. An additional model was specified for the age-standardised fluoroquinolone usage rate (standardised to European Standard Population 2013). This model used a linear regression model with the age-standardised rate per 1000 population as the independent variable and calendar month as the predictor. Thirdly, prescriber's compliance was investigated by calculating the incident use (number of new users per 1,000 persons per month) in patients at risk of tendinitis/tendon rupture, at risk of aortic dissection and aneurysm and in patients with recent or concomitant prescribing of systemic corticosteroids. Finally, monthly incident prescription rates for alternative antibiotics prescribed in

patients where fluoroquinolones have previously been prescribed or discontinued were investigated by calculating the incident use (number of new users who received alternative antibiotic per 1,000 incident users per month).

Key results

The study population included between 16 to 21 million patients each month during the study period (2016 - 2021). The total number of individuals ranged from 268,834 - 372,754 per month in Belgium, 1,946,954 -3,557,777 per month in France, 4,401,044 - 7,517,841 per month in Germany, 2,486,931 - 3,946,084 per month in the UK, 937,596 - 1,197,100 per month in the Netherlands and 5,623,617 - 5,713,682 per month in Spain over the study period. Patients could contribute information to more than one month.

The incidence of fluoroquinolone use in the six European countries studied was low and ranged from 0.7/1,000 persons per month (UK) to 8.0/1,000 persons per month (Spain) over all calendar years. Fluoroquinolone use was the highest in persons aged above 75 in all the countries. In addition, the most frequent indications were respiratory tract infections, urinary tract infections (uncomplicated) and ear infections. Nevertheless, a high percentage of patients could not have been attributed an indication (unknown indications ranged between 38.1% and 84.0%). Furthermore, other indicators of changes in prescribing behaviour by healthcare professionals such as early discontinuation or prescriptions rates for alternative antibiotics (prescribed in patients where systemic use fluoroquinolones had previously been used) or at-risk group show no changes after the regulatory interventions across countries.

Only the UK and possibly Germany had small to modest decreases in prescriptions that could be attributable to EMA interventions. In Germany, the regression analyses show a slight decrease in prescriptions of fluoroquinolones coinciding with the start of implementation of the SmPC changes (22 March 2019 to 11 December 2019) and the direct healthcare professional communications (DHPC) (8 April 2019). Seasonal fluctuations in monthly prescription rates seem to be lower than before implementation. In the UK, regression analyses suggested a decrease in prescriptions from 2019 onwards coinciding with SmPC changes (25 April 2019 to 23 December 2019 and 01 April 2020 to 18 May 2020) and DHPC (21 March 2019). This timing also corresponds to EMA communications regarding fluoroquinolone restrictions (16 Oct 2018 [PRAC Recommendation], November 2018 [CHMP Opinion] and March 2019 [European Commission Decision]). Yet these reductions should not be attributed to regulatory interventions only, considering changes have started already before.

Discussion

Findings do not support an effect of regulatory intervention on fluoroquinolone use. Several subgroup analyses in different countries show modest reductions in prescriptions during or after implementation of interventions, but effects are not consistent across groups. Moreover, decreases in prescriptions often occur before implementation of regulatory interventions, e.g., Germany and the UK. Co-occurring changes that already lower incident prescription of fluoroquinolones such as antimicrobial stewardship, may have hampered any effects of regulatory interventions that may have occurred. Nevertheless, if

any, effects should be considered of modest size. Lack of evidence and inconsistent findings may also indicate that the timeframe studied was too short to allow adequate dissemination of regulatory measures to healthcare practices and subsequent prescription rates. Yet, the absolute levels of fluoroquinolone prescriptions as well as the patterns across countries, age group, main indications and avoidance in risk groups align with known country differences and clinical guidelines.

Classification of key variables to determine subgroups based on algorithms and missing data for some subgroups such as fluoroquinolone indications limit the interpretation of the study. Also, we did not determine prescription patterns in secondary care. Strengths include the large study population size, and the CDM and analytics used to standardise data obtained from each source and to reduce methodological variability in the results.

Conclusion

The regulatory actions for fluoroquinolones associated with the 2018 referral seems to have had only a modest impact on fluoroquinolones prescribing. Observed decreases in prescriptions starting already before implementation of regulatory interventions may be attributed to increased antibiotic stewardship and local changes in clinical guidance.

2 List of abbreviations

Abbreviation	Definition
ATC	Anatomical Therapeutic Chemical
BIC	Bayesian Information Criterion
CAP	Community Acquired Pneumonia
CDM	Common Data Model
CI	Confidence Interval
COPD	Chronic Obstructive Pulmonary Disease
COVID-19	Corona Virus Disease-2019
DA	Disease Analyser
DHPC	Direct Healthcare Professional Communications
DUS	Drug Utilisation Study
EHR	Electronic Health Record
EMA	European Medicines Agency
ETL	Extraction Transform and Load
EU	European Union
FDA	Food and Drug Administration
GP	General Practitioner
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IMRD	IQVIA Medical Research Data
IPCI	Integrated Primary Care Information
LPD	Longitudinal Patient Database
MAH	Marketing Authorisation Holder
MC	Medical Centre
MPC	Monthly Percentage Change
NICE	National Institute for Health and Care Excellence
OHDSI	Observational Health Data Sciences and Informatics
OMOP	Observational Medical Outcomes Partnership
PCT	Primary Care Team
PI	Period of Implementation
PV	Pharmacovigilance

QMS	Quality Management System
SIDIAP	Information System for Research in Primary Care
SmPC	Summary of Product Characteristics
SWAB	Stichting Werkgroep Antibioticabeleid
UK	United Kingdom
US	United States

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4 Other responsible parties

Not Applicable

5 Milestones

Milestone	Planned date
Approval study protocol by EMA	21 September 2020
Registration in the EU PAS register	30 October 2020
Start of data collection	Not applicable. Data extraction start date was 1 January 2016
End of data collection	Data extraction start date was 1 January 2016
Final study report provided to EMA	31 March 2022
Manuscript to be provided to EMA	31 March 2022

6 Rationale and background

Quinolones and fluoroquinolones, subsequently referred to as fluoroquinolones are broad spectrum antibiotics that are active against both gram negative and gram-positive bacteria and are indicated in the management of certain bacterial infections (1,2). The use of fluoroquinolones has been associated with the risk of some serious adverse events, which involve the peripheral and central nervous system as well as tendons, muscles and joints (3–5). The mechanisms for these adverse events, though uncertain, are most likely multifactorial and involve oxidative stress, mitochondrial toxicity, inhibition of cell proliferation and migration, reduced extracellular matrix, apoptosis and ischaemia (2).

While most of the adverse events have been known, the severity and potential permanence were not included in earlier product information of fluoroquinolones authorised in the European Union (EU). In 2008, the United States (US) Food and Drug Administration (FDA) first added a boxed warning for increased risk of tendinitis and tendon rupture (6). In August 2013, the FDA required updates to the labelling to describe the potential for irreversible peripheral neuropathy and in 2016, the FDA enhanced warnings about the association of fluoroquinolones and potentially permanent side effects involving tendons, muscles, joints, nerves and central nervous system (7,8). As a result of the risks of these side effects, some indications were restricted and fluoroquinolones were used only for patients with no alternative treatment options.

Similarly, within the EU, fluoroquinolones have been subject to several EU referral procedures leading to restrictions in indications for moxifloxacin in 2007 – 2009, ciprofloxacin in 2008, and levofloxacin in 2012 (2). The concerns of the persistence of side effects resulted in the European Medicines Agency (EMA) conducting a pharmacovigilance referral procedure focused on assessing the severity and persistence of long-lasting, disabling and potentially irreversible adverse drug reactions, and the benefit-risk balance of fluoroquinolones for systemic and inhalation use (2). In November 2018, the EMA concluded that serious adverse reactions including tendon, muscle and joint disorders, neurologic and psychiatric disorders, all listed in the product information of different fluoroquinolones, could in rare cases become long-lasting, disabling and potentially even irreversible, and substantially disrupt patients' daily activities (2). Based on the conclusions of the assessment, the licence for medicinal products containing the quinolones nalidixic acid, pipemidic acid, cinoxacin and flumequine were suspended as no indication with a positive benefit-risk profile could be identified. To maintain a favourable benefit-risk balance for fluoroquinolone containing medicinal products for systemic use and use via inhalation, revised indications, warnings, and other measures as direct healthcare professional communications (DHPC) were implemented in EU member states, including recommendations for cessation of prescriptions for milder, non-severe or self-limiting infections, and restrictions for other indications (from first line to further lines of therapy). In some EU member states, the outcome of the referral was communicated at the national level through media campaigns, involving learned societies and medical associations to inform prescribing physicians and health care organisations about these changes.

While these regulatory interventions have the potential to lead to changes in the incidence of serious and/or long-lasting adverse events associated with fluoroquinolones, measuring the impact of these interventions on disease outcome has to be done, to prove effectiveness and to observe potential unintended consequences. A drug utilisation study (DUS), coupled with a before and after analysis of prescribing trends is a commonly utilised approach for measuring the effect of risk minimisation measures (9). In a systematic review of studies investigating analytical approaches used for impact studies, 55% of all included studies used drug utilisation as a measure of impact (10).

In a previous descriptive study conducted in the United Kingdom (UK), France and Germany prior to the recommendations in 2018, fluoroquinolones were most frequently indicated for the treatment of mild infections including acute sinusitis, acute bronchitis and uncomplicated urinary tract infections, all of which are restricted indications in the current EMA guidelines (2,11). There have been no descriptive studies on fluoroquinolone drug utilisation in the EU after the EMA recommendations were made.

7 Research questions and objectives

The overall aim of this study was to evaluate the impact of the regulatory actions taken for fluoroquinolone containing medicinal products following the 2018 referral procedure, using the healthcare databases of six European countries.

Primary Objective(s)

1. To determine the drug utilisation and prescription patterns of fluoroquinolone containing medicinal products over the period 2016 to 2021 by:

    a) estimating monthly incident drug use overall and stratified by on-label indications (which include first and last line indications) and off-label indications (which include mild infections for which fluoroquinolones are not indicated).

    b) estimation of early discontinuation proportion (prescribed courses that were discontinued prior to intended treatment end date)

2. To evaluate the impact of regulatory interventions on fluoroquinolone prescribing patterns using time series analysis.

3. To determine prescribers' compliance with warnings in fluoroquinolones Summary of Product Characteristics (SmPC) Section 4.4 on tendinitis and tendon rupture as well as on aortic dissection and aneurysm specifically by calculation of monthly incident prescription rates in the subgroups at risk:

    a) risk groups for tendinitis and tendon rupture

    b) risk groups for aortic dissection and aneurysm

    c) patients with recent (30 days prior) or concomitant prescribing of systemic corticosteroids

4. To determine monthly incident prescription rates for alternative antibiotics prescribed in patients where systemic use fluoroquinolones have previously been prescribed or discontinued.

8 Amendments and updates

The following changes were done in the statistical analysis plan, after the protocol was approved and were reflected as protocol amendments.

Topic	Justification	Protocol amendment
Censoring of observation time	For several databases, the end of an individual's observation period is their last observation, e.g., their last appointment with a health practitioner. It was observed that towards the end of the study period the number of active participants included in the denominator of the usage calculation dropped substantially and those that are retained are those that are recorded as having contact with service provider. This can result in an artificially increased rate of fluoroquinolone usage in the final months of each affected database (since the denominator decreases but the numerator (those receiving fluoroquinolone) would not). We therefore excluded the final 6 months of results since this is where the reduction in number of active patients is likely to have the most impact.	Yes
Segmented analysis	The monthly percentage change (MPC) instead of the annual percentage change was presented for each segment of the final model along with confidence intervals; this aligns better with the monthly incidence estimates.	Yes
Stratification by route of administration	The plan was to evaluate route of administration, but this could not be presented as record of other than 'systemic' or 'unknown' routes were not available. Therefore, this stratification is not presented in this report.	Yes
Gap between treatment episodes	Changing the interval for a new treatment had the same impact on the results as extending the incident user assessment window. Therefore, this sensitivity analysis is not presented in this report.	Yes

9 Research methods

9.1 Study design

A retrospective population-based cohort study was conducted using electronic health care records from six databases from six European countries. This cohort was used for a drug utilisation study with a time series analysis component to identify the potential impact of regulatory interventions on fluoroquinolones' prescribing trends. See Figure 1 for a visual depiction of the study design and time points, and refer to Section 9.4 for further details on the different covariates and risk factors.

This study was conducted in six European countries where fluoroquinolones are marketed: namely Belgium (Longitudinal Patient Database [LPD] Belgium), France (LPD France), Germany (Disease Analyser [DA] Germany),the Netherlands (Integrated Primary Care Information [IPCI]), Spain (Information System for Research in Primary Care [SIDIAP]) and the UK (IQVIA Medical Research Data [IMRD]). Data from these databases were mapped to the Observational Medical Outcomes Partnership (OMOP) Common Data Model (CDM). See https://github.com/OHDSI/CommonDataModel/wiki for more details.

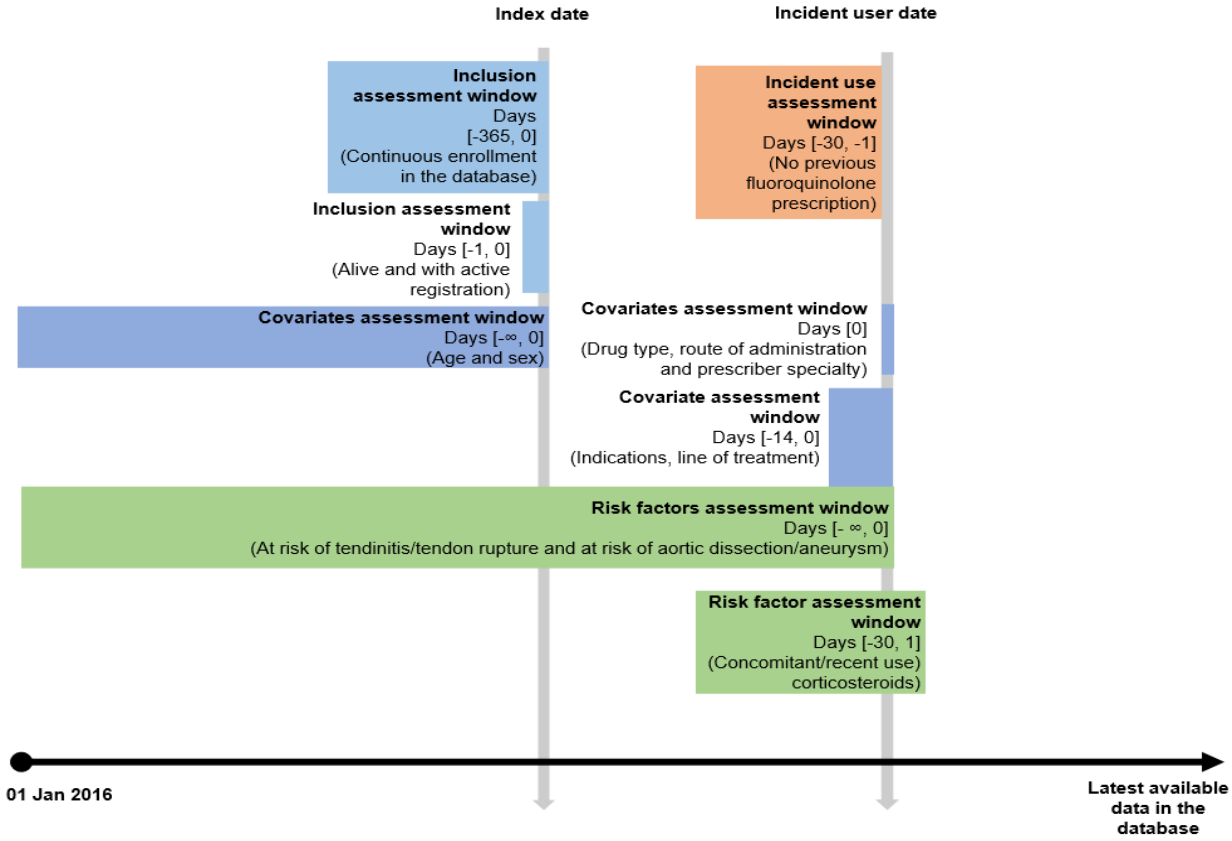

Figure 1. Study design

9.2 Setting

9.2.1 Study time period

The study time period was 1 January 2016 until the latest available data cut-off as shown in Table 1.

Table 1. Data cut-off points

Database	Data lock points as planned in the protocol	Data lock points without censoring	Actual data lock points with censoring[1]
LPD Belgium	December 2020	April 2021	October 2020
LPD France	May 2020	August 2021	February 2021
DA Germany	June 2020	June 2021	December 2020
IPCI Netherlands	January 2021	June 2021	December 2020
SIDIAP Catalonia Spain	January 2021	June 2021	December 2020
IMRD UK	January 2021	April 2021	October 2020

LPD: Longitudinal Patient Database; DA: Disease Analyser; IPCI: Integrated Primary Care Information; SIDIAP: Information System for Research in Primary Care; IMRD: IQVIA Medical Research Data; UK: United Kingdom.
[1]The final six months of each database were excluded to account for the drop in number of active subjects in the denominator.

9.2.2 Index date

For each individual, follow-up started from the date on which they had contributed active follow-up time during the study period.

9.2.3 Follow-up period and censoring

The follow-up period began (i.e., date of index date) at the latest of: study start date or end of the 12 months continuous enrolment window (see inclusion criteria). Patients were censored at the earliest of: date of patient death, date of patient exit (deregister) from a contributing data provider (general practitioner [GP]), date that a contributing provider exited the data source (last collection date), end of the database's data collection or end of study period (latest data cut-off). An additional censoring rule was applied to exclude the last six months of records within each database (Table 1).

The lookback window for evaluating risk factors was 'ever before' (from registration date until index date). This could introduce information bias if some patients had longer lookback window than others. A sensitivity analysis where the look back window was restricted to 1 year was applied, see Section 9.9.4.

9.3 Subjects

The study population in each database included all individuals who had contributed observation person-time in each database during the study time period and met the study selection criteria.

9.3.1 Patient selection

In each country, patients who met all of the inclusion criteria and none of the exclusion criteria were selected.

9.3.1.1 Inclusion criteria

The inclusion criteria were all patients with an active registration status during the study time period and continuous enrolment in the database for more than 12 months prior to index date.

9.3.1.2 Exclusion criteria

Patients were excluded if they were missing age or sex.

9.3.2 Sub-population

Categories of sub-populations of interest were defined by age group, sex, active substance, route of administration, indication, prescriber specialty and country as described below. Not all subgroupings were applied to all objectives. More details about the stratifications are presented in Section 9.9 Statistical methods.

9.3.2.1 Sub-populations by age group

Sub-populations by age group were defined using age at the start of each calendar year. Ten-year age categories were created (0-9, 10-19, 20-29, 30-39, 40-49, 50-59, 60-69, 70-79, 80-89, 90-100).

To provide insights into the use of fluoroquinolones in the elderly, alternative age categories were explored: <18 years, 18-75 years, and >75 years.

Similarly, additional categories were created to investigate potential use of fluoroquinolones in the paediatric population using cut-offs based on the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH): infants (<2 years); children (2-11 years); adolescents (12-18 years).

9.3.2.2 Sub-populations by sex

Sex was defined at start of follow-up as male or female, and two sub-populations were defined accordingly. Patients with missing sex data were excluded from the study.

9.3.2.3 Sub-populations by active substance

The fluoroquinolone exposed population was further stratified by the type of fluoroquinolone using individual Anatomical Therapeutic Chemical (ATC) code.

9.3.2.4 Sub-population by route of administration

Quinsair (levofloxacin), the only fluoroquinolone administered by inhalation was analysed separately.

9.3.2.5 Sub-population by duration of fluoroquinolone episode

Stratification by duration of fluoroquinolone episode duration, as calculated in Section 9.4.2 was performed. The categories were data driven and decided upon to reflect the distribution of duration of use observed.

9.3.2.6 Sub-populations by indication

All fluoroquinolone exposed patients were classified by the underlying diagnosis. These indications were categorised into the following pre-specified groups (see Section 9.4.3 for more details):

- respiratory tract infections
- urinary tract infections
- ear infections
- gastrointestinal infections
- genital, testicular, and prostatic infections
- skin and soft tissue infections
- bone infections
- prophylactic use
- other (septicaemia, meningitis, infection of cerebrovascular fluid, endocarditis)
- unknown (missing indication or indication not captured above)

All fluoroquinolone exposed patients for whom an underlying diagnosis could not be identified from the predefined list above were classified as “Unknown”. For analysis of each sub-population defined by indication, there was no differentiation according to on or off-label use. The indications categories contain both on- and off-label use. For example, respiratory tract infections could also include milder, non-severe or self-limiting infections such as acute bronchitis, pharyngitis, tonsilitis, laryngitis which were considered off-label indications. The on- and off-label stratification was made separately (see Section 9.4.4 for details on the definitions). Analyses relating to on- and off-label use are presented as per objective 1.a.

9.3.2.7 Sub-population by specialty

For databases where this was possible (Germany, France and Spain), the results were split by GP and different specialists.

9.3.2.8 Sub-populations by country

The country in which each database originates from were used for classification of country setting: Belgium (LPD Belgium), France (LPD France), Germany (LPD Germany), the UK (IMRD), the Netherlands (IPCI) and Spain (SIDIAP).

9.4 Variables

In order to meet the study objectives, the following parameters were obtained from each data source and analysed: demographics, exposures of interest, indication of use, on- and off-label use, risk groups of interest (at-risk of tendinitis and tendon rupture, at-risk of aortic dissection and aneurysm and concomitant or recent systemic corticosteroids exposure) and alternative antibiotics exposure.

9.4.1 Demographics

Sex was regarded as a fixed covariate throughout the study period.

Age was assessed at the start of each calendar year.

9.4.2 Exposures of interest

From the study population, an exposed cohort was defined based on patients exposed to any fluoroquinolone. Drug exposure in the CDM is standardised to RxNorm concepts. This has the advantage that the drug exposure contains details of ingredients, strength and formulation (clinical drug level) which are not directly available from the ATC codes. The exposed cohort was further stratified by individual fluoroquinolones of interest and by route of administration (systemic or inhaled). The fluoroquinolones of interest were ofloxacin, ciprofloxacin, norfloxacin, lomefloxacin, levofloxacin, and moxifloxacin. Quinsair (levofloxacin) was the only fluoroquinolone administered by inhalation.

The duration of each drug episode was obtained from the DRUG_EXPOSURE table in the CDM (see Table 2). The DRUG_EXPOSURE table in the CDM contains the drug_exposure_start_date and the drug_exposure_end_date. These were populated within each dataset based on the source data, where available, or by calculation during the extraction transform and load (ETL) process to the CDM, applying appropriate rules within the databases. This has the advantage that the drug exposure duration does not have to be inferred from other information at the time of analysis. It enables a consistent analytical pipeline for all the databases.

Table 2. Drug exposure table variables provided in the CDM

Field	Description
drug_exposure_start_date	The date of the prescription or dispensing.
drug_exposure_end_date	The end date for the current instance of drug exposure. Unless provided directly by the source, this was inferred by the extraction transform and load (ETL), using other information or a default (Figure 2).
Quantity	The total quantity of drug as recorded in the original prescription or dispensing record from the physician.
days_supply	The number of days of supply of the medication as prescribed. The days_supply variable in each database was taken directly from the source. If days_supply was not provided it was calculated through logic described in Figure 2.
Sig	The directions (‘signetur’) on the drug prescription as recorded in the original prescription (and printed on the container) or dispensing record from the physician.

The rules in Figure 2 were applied before transformation in the OMOP model. After this, the same imputations were applied across databases.

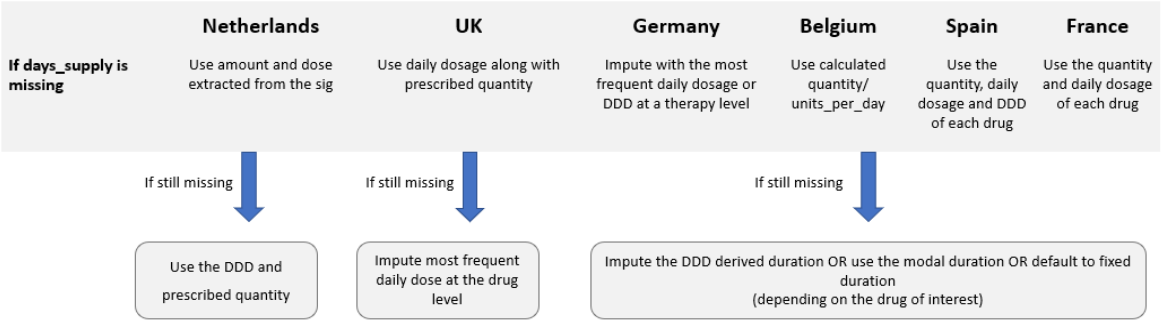

Figure 2. Calculation of duration of use and end of treatment across databases

DDD: Defined Daily dose; Sig: Signatur; UK: United Kingdom.

Incident fluoroquinolone use was defined as a recorded prescription of fluoroquinolone in a patient with no fluoroquinolone use within the previous 30 days, irrespective of indication, calculated at substance level. As the choice of 30 days to define monthly incident prescription was somewhat arbitrary, we conducted a sensitivity analysis to examine the robustness of our definition, by varying the look back window used to define incident prescriptions. We explored look back periods of 60, 90 and 180 days in the sensitivity analysis (see Section 9.9.4) to estimate the impact of the look back period on incident prescriptions. The exact period to determine an incident prescription depends on the average duration of treatment and the average fluoroquinolones treatment duration depends on the indication. It can range from 3 days for acute uncomplicated cystitis and up to 4-6 weeks for osteomyelitis. However, for most indications, fluoroquinolones treatment duration is usually between 7-14 days.

The duration of treatment episode for each exposed patient was calculated by subtracting the drug exposure start date from the drug exposure end date. A gap of more than 30 days between prescriptions, i.e., a gap of more than 30 days between the estimated end date of a drug and the start date of the same drug, signalled the end of the treatment episode. This was based on the average duration of treatment of 7-14 days (Figure 3) (12).

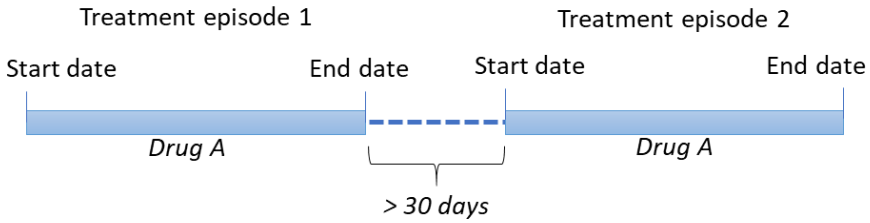

Figure 3. Schematic depiction ascertainment of treatment episodes

Early discontinuation of fluoroquinolone treatment episode is difficult to capture using prescription data as the actual duration of drug intake remains unknown. Due to the antibiotic stewardship, many prescriptions have a hard stop at 5 or 7 days unless requested to prolong treatment by a physician. Our discontinuation algorithm was based on the UK National Institute for Health and Care Excellence (NICE) recommendations which recommends a change within 48 hours ± 24 hours in accordance with either review of effectiveness, acute tolerability issues or confirmation of microorganism which required different antibiotics (13). The discontinuation was algorithmically determined as any of the following:

1. A generic treatment discontinuation code occurring during treatment episode (e.g., medication course shortened, patient informed of discontinuation of medication or treatment changed during treatment episode) OR

2. A code suggesting lack of effectiveness during treatment episode (e.g., infection resistant to antimicrobial drug, infection due to resistant bacteria) OR

3. Switch - an overlapping antibiotic prescription before the end of the current treatment episode.

9.4.3 Indication of use

The underlying indication for which a fluoroquinolone was used was defined by examining all medical codes in the patient medical record within 14 days (subject to sensitivity analysis) prior to and including the start date of a treatment episode. This operational definition was used as the underlying indication for which a fluoroquinolone was used is not directly captured. This time window had been previously used to identify underlying indications for antibiotic use in primary care data (11,14). If no indication was found and if another antibiotic was used in the 14 days' time window, the indication search was extended another 14 days before the respective antibiotic start date. If multiple indications were found, the patient was counted once for each indication. Counts of patients with more than one indication were reported.

The indications were categorised as mentioned in Section 9.3.2.6. Each code list was created with medical review of individual codes to decide if they relate to the indications of interest in this study, prior

the data extraction[1]. It should be noted that code lists for infections were created and reviewed by an epidemiologist and a medical doctor using the standardized vocabulary in the CDM. For each infection, relevant concepts were selected and all descendant codes/concepts, as well as all codes/concepts that mapped to the selected concept were included. Each of the descendant code and mapped codes were subsequently reviewed. Symptom-related codes which do not map to specific diagnosis were not included as these are not specific enough to determine exact diagnosis, and therefore would not map to any of the medical conditions of interest. Infections were then subsequently grouped by body system based on medical knowledge. For example, chronic sinusitis, tuberculosis, acute bronchitis etc were grouped as respiratory tract infections.

9.4.4 Off-label and on-label use

Off-label and on-label classification - In line with Good Pharmacovigilance Practices Module VI, off-label is defined as ''situations where the medicinal product is intentionally used for a medical purpose not in accordance with the terms of the marketing authorisation'' (15).

Information from the SmPCs, the Art 31 referral plus the UK and Dutch treatment prescribing guidelines were used in combination to classify fluoroquinolone indications at a class level as on-label or off-label. Notably, where a specific indication was restricted or removed, this was considered as off-label in the study. For example, acute bronchitis, pharyngitis, tonsilitis, prevention for traveller's diarrhoea and prevention of exacerbations in women with recurring urinary tract infections were removed or restricted in the referral and consequently considered as off-label in the study. When the recommendation was to use fluoroquinolones only in severe infection of a certain type (e.g., complicated urinary tract infections or complicated skin infection), an algorithm that considered additional clinical information was used to capture disease severity. As this algorithm required quite detailed clinical information that was likely not to be captured in less granular databases, the algorithm might have not worked equally well in all databases. The definitions of these indications are presented below:

- **Complicated urinary tract infection (on-label)** was defined as the presence of codes suggestive of a urinary tract infection AND one or more of the following factors:
    - Genitourinary congenital anomalies
    - Structural abnormalities of the urinary tract (abnormal size, raised echogenicity, hydronephrosis/hydroureter, urinary tract obstruction, ileocystoplasty)
    - Functional impairment of the kidneys (renal failure, vesicoureteric reflux, glomerular filtration rate <90 mL/min/1.73 m^2)

[1]Manual review of individual cases has not been performed to validate their identification using the code lists.

- Others (concomitant clinical conditions – diabetes mellitus, catheter associated urinary tract infection, irradiation cystitis, postoperative urinary tract infection, post renal transplantation)

- **Complicated skin infections (on-label)** were defined as the presence of cellulitis/erysipelas, local wound infection, major cutaneous abscesses, infected skin ulcers and skin infections in burns patients.

- **Recurrent cystitis in women (on-label)** was defined as the presence of [a code for recurrent cystitis OR 2 episodes of cystitis in the previous 6 months OR three episodes of cystitis in the previous 12 months] AND female sex.

- **Recurrent and non-responsive acute otitis media (on-label)** was defined as the occurrence of three episodes of acute otitis media in a period of 3 months OR four or more episodes in 12 months. Non-responsive acute otitis was defined as a code for acute otitis media AND a code for infection due to resistant bacteria.

- **Prevention of exacerbations in women with recurring urinary tract infections (off-label)** was defined as the prescription of any antibiotic regimen for at least 6 months or until the next episode of a urinary tract infection, including any dosing strategy (daily, weekly, monthly or postcoital use) after a diagnosis of recurrent cystitis, as described above. This definition was based on a systematic review, which indicated that a period of >6 months duration of treatment is often used to indicate prophylaxis in recurrent urinary tract infections management (16).

For indications where first line fluoroquinolone is not recommended as part of the referral, i.e., pneumonia due to gram negative bacteria, acute bacterial sinusitis, acute exacerbation of chronic obstructive pulmonary disease (COPD) and community acquired pneumonia (CAP), these were considered as off-label if used as first or second line and on-label if used as third line (see Appendix 1 for further details on how on- and off-label were defined). The proportions of fluoroquinolone prescriptions by off-label indications for each fluroquinolone type contributing to the overall data are presented in Appendix 2. It should be noted that out of the total classified indications, the proportions of indications that were considered as off-label for each fluoroquinolone type were very high across countries. For example, the majority of off-label indications for moxifloxacin and levofloxacin were attributed to off-label respiratory tract infections in all countries.

Limitations with these approaches are further described in Section 11.2.

9.4.5 Algorithms for line of treatment

For certain indications, usually mild infections, fluoroquinolones are indicated only as last line of treatment. These are:

- Acute bacterial sinusitis
- Acute exacerbation of COPD

- CAP
- Pneumonia due to gram negative bacteria
- Simple uncomplicated acute cystitis
- Recurrent cystitis in women

For these indications, we stratified if fluoroquinolones had been used as:

- **first line of treatment** defined in line with clinical guidance as ‘’the first treatment given for a disease. When used by itself, first line treatment is the one accepted as the best treatment” (17,18)
- **last line of treatment** defined as third line or higher – e.g., the use of at least two antibiotics from different classes in the previous 6 days, in accordance with NICE and ‘Stichting Werkgroep Antibioticabeleid’ (SWAB) (13,19).

As for on- and off-label use, the approach to define line of treatment was defined at the class level. It is understood that variations in prescribing policy across countries with some local modifications of SmPC by fluoroquinolone type and other data to support the need for a fluroquinolone (e.g., based on antibiotic susceptibility of the infectious agent) exist. Therefore, misclassification of line of treatment is possible between on- and off-label for individual fluoroquinolones. Limitations with this approach are further described in Section 11.2.

9.4.6 At risk groups of interest

This risk factors list was not exhaustive. When creating risk groups, we included only risk factors that had been consistently identified to be associated with the adverse events of interest in the literature. The factors mentioned in the Article 31 referral procedure were all considered (2). There was still some uncertainty about some other risk factors directly related to the long-lasting, disabling and potentially irreversible adverse drug reactions associated with fluoroquinolones.

9.4.6.1 Risk group for tendinitis and tendon rupture

Risk group for tendinitis and tendon rupture included individuals who had a medical history of any of the following:

- advanced age (>60)
- medical history of renal impairment, solid organ transplantation or prior tendon rupture or tendinitis (prior to fluoroquinolone use)
- tobacco user

This is based on information from Article 31 Assessment Report and available literature (2).

Note: Although physical activity is a known risk factor for tendon rupture this was not included as a risk group because data are not adequately captured in the databases.

Corticosteroid use is also a recognised factor for tendinitis and tendon rupture, and this was included as a separate risk factor due to its importance, see below.

Concomitant or recent systemic corticosteroid use - was defined to have occurred when a systemic corticosteroid treatment episode started recently before or during fluoroquinolone treatment episode. Recent systemic corticosteroid use was defined as a prescription of a systemic corticosteroid within 30 days of fluoroquinolone exposure, including the day of fluoroquinolone start date + 1 day.

All oral, intravenous, intramuscular, rectal and inhaled formulations of the following corticosteroids were included: prednisolone, methylprednisolone, beclomethasone, betamethasone, dexamethasone, hydrocortisone, cortisone and triamcinolone. Topical formulations of corticosteroids were excluded due to the lower dose and limited systemic effect.

9.4.6.2 Risk group for aortic dissection and aneurysm

Risk group for aortic dissection or aneurysm included individuals who had a medical history of any of the following:

- Advanced age (>60)
- Medical history of other vascular aneurysms
- Medical history of: hypertension, lipid disorder, cardiac or renal transplant, genetic conditions (Marfan's syndrome, vascular Ehlers-Danlos syndrome, Loeys-Dietz syndrome, Turner's syndrome), cardiovascular syphilis, traumatic motor vehicle accident, aortic valve disorder, COPD or ischaemic heart disease or cerebrovascular disease
- Tobacco user

The list was based on a literature review (20–22). Presence of these risk factors were based on at least one record in the entire patient medical records before fluoroquinolone prescription.

9.4.7 Alternative antibiotics exposure

Within the fluoroquinolone exposed cohort, exposure to alternative antibiotics was defined as a prescription for a new antibiotic during a fluoroquinolone treatment episode (switch). This translated into a prescription start date for an alternative medicine during the period of fluoroquinolone prescription, e.g., between fluoroquinolone episode start date and end date.

Exception: for very severe indications as tuberculosis, pelvic inflammatory disease, moderate to severe community acquired pneumonia and complicated anthrax infection which are likely to be treated with multiple antibiotics at the same time, an overlapping antibiotic during the current treatment episode did not signal switching but add-on. The following predefined categories were investigated as alternative medications (both switch and add-on): tetracyclines, penicillins, cephalosporins, macrolides, aminoglycosides and other antibiotics (sulphonamides and other combinations) (11).

9.5 Data sources and measurement

For this study, we included Electronic Health Record (EHR) data from six primary care databases throughout Europe, specifically LPD (Belgium), LPD (France), DA (Germany), IPCI (the Netherlands), SIDIAP (Catalonia, Spain) and IMRD (the UK). All of these databases have their data mapped to the OMOP CDM. Characteristics of these databases with regard to the total number of individuals and database update are described in Table 3.

Table 3. Characteristics of databases

Database	Managing organisation	Country	Individuals	History
LPD	IQVIA	Belgium	1.1 M	2005 - present
LPD	IQVIA	France	7.8 M	1994 - present
DA	IQVIA	Germany	34 M	1992 - present
IPCI	Erasmus MC	Netherlands	2.6 M	1996 – present[1]
SIDIAP	IDIAP Jordi Gol	Spain	5.6 M	2006 - present
IMRD	IQVIA	UK	15.2 M	1996 - present

LPD: Longitudinal Patient Database; DA: Disease Analyser; IPCI: Integrated Primary Care Information; SIDIAP: Information System for Research in Primary Care; IMRD: IQVIA Medical Research Data; UK: United Kingdom. [1]Although historical data (1996 - present) were available, the most recent data extraction (2008 - present) was used.

Longitudinal Patient Database (LPD) Belgium (IQVIA)

LPD Belgium is a computerised network of GPs who contribute to a centralised database of anonymised data of patients with ambulatory visits. Currently, around 300 GPs from 234 practices are contributing to the database covering 1.1 M patients from a total of 11.5 M Belgians (10.0%). The database covers a time period from 2005 through the present. Observation time is defined by the first and last consultation dates. Drug information is derived from GP prescriptions. Drugs obtained over the counter by the patient outside the prescription system are not reported. No explicit registration or approval is necessary for drug utilisation studies.

Longitudinal Patient Database (LPD) France (IQVIA)

LPD France is a computerised network of physicians including GPs who contribute to a centralised database of anonymised patient EHR. Currently, >1200 GPs from 400 practices are contributing to the database covering 7.8 M patients in France. The database covers a time period from 1994 through the present. Observation time is defined by the first and last consultation dates. Drug information is derived from GP prescriptions. Drugs obtained over the counter by the patient outside the prescription system are not reported. No explicit registration or approval is necessary for drug utilisation studies.

Disease Analyser (DA) Germany (IQVIA)

DA Germany is collected from extracts of patient management software used by GPs and specialists practicing in ambulatory care settings. Data coverage includes more than 34 M distinct person records out of at total population of 80 M (42.5%) in the country and collected from 2,734 providers. Patient visiting more than one provider is not cross identified for data protection reasons and therefore recorded as separate in the system. Dates of service include from 1992 through present. Observation time is defined by the first and last consultation dates. Germany has no mandatory GP system and patient have free choice of specialist. As a result, data are collected from visits to 28.8% General, 13.4% Orthopaedic Surgery, 11.8% Otolaryngology, 11.2% Dermatology, 7.7% Obstetrics/Gynaecology, 6.2% various Neurology and Psychiatry 7.0% Paediatric, 4.6% Urology, 3.7% Cardiology, 3.5% Gastroenterology, 1.5% Pulmonary and 0.7% Rheumatology practices. Drugs are recorded as prescriptions of marketed products. No registration or approval is required for drug utilisation studies.

Integrated Primary Care Information, Erasmus MC, University Medical Center Rotterdam, the Netherlands

IPCI is collected from EHRs of patients registered with their GPs throughout the Netherlands. The selection of 391 GPs is representative of the entire country. The database contains records from 2.6 million patients out of a Dutch population of 17 M (8.2%) starting in 1996. The median follow-up is 2.2 years. The observation period for a patient is determined by the date of registration at the GP and the date of leave/death. The observation period start date is refined by many quality indicators, e.g., exclusion of peaks of conditions when registering at the GP. All data before the observation period is kept as history data. Drugs are captured as prescription records with product, quantity, dosing directions, strength and indication. Drugs not prescribed in the GP setting might be underreported. Indications are available as diagnoses by the GPs and, indirectly and not necessarily complete, from secondary care providers reporting back to the GP for continuity of care. Approval needs to be obtained for each study from the Governance Board (23).

Information System for Research in Primary Care, SIDIAP Jordi Gol, Catalonia, Spain

SIDIAP is also collected from EHR records of patients receiving primary care delivered through Primary Care Teams (PCT), of the Catalan Health Institute. The Catalan Health Institute manages 286 out of 370 such PCT with a coverage of 5.6 M patients, out of 7.5 M people living in Catalonia (74%). The database started to collect data in 2006. The mean follow-up is 10 years. The observation period for a patient can be the start of the database (2006), or when a person is assigned to a Catalan Health Institute primary care centre. Date of exit can be when a person is transferred-out to a primary care centre that does not pertain to the Catalan Health Institute, or date of death, or date of end of follow-up in the database. Drug information is available from prescriptions and from dispensing records, however only prescribed data was used in this study. Drugs not prescribed in the GP setting might be underreported; and disease diagnoses made at specialist care settings are not included. Studies using SIDIAP data require previous approval by both a Scientific and an Ethics Committee (24).

IQVIA Medical Research Data (IMRD) – UK

IMRD UK is a large database of anonymised electronic medical records collected at Primary Care clinics throughout the UK. Data coverage includes 15.2 M patients, 5.6 M providers, 793 care sites and more than 5 billion service records, covering 22.5% of a population of 67.5 M. Dates of service include from 1996 through present. Quality indicators define the start date for that patient (e.g., each patient's observation period began at the latest of: the patient's registration date, the acceptable mortality recording date of the practice, the Vision date). Drug treatment is recorded as prescriptions. All protocols have to be submitted to an independent Scientific Review Committee prior to study conduct.

9.6 Bias

As we are using primary care databases, some data are not recorded or may be poorly recorded. For example, the use of fluoroquinolones within a hospital setting. Some indications and incident users may have been missed, particularly for last line therapy and for severe indications. This missing data was likely to be differential and, skewed towards the more serious and the last line indications. In addition, reasons for discontinuation were not always available, and consequently the early discontinuation (which was algorithmically derived) might has been misclassified. Non-adherence to antibiotic therapy is a well-known phenomenon and consequently there was a potential of overestimating fluoroquinolone use since the actual drug intake might be lower.

With regard to the indication of use, as the databases do not record indication, a condition code proximal to prescription was used. Prior to data extraction, the code lists were constructed with clinical inputs from a clinical research fellow who specifically decided if they related to the indications of interest in this study. This may reduce misclassification and proportion of missing indications. If multiple indications were found, the patient was counted once for each indication. Furthermore, fluoroquinolone was stratified by on- and off-label use based on the SmPC, Art. 31 referral plus the UK and Dutch treatment prescribing guidelines.

When the recommendation was to use fluoroquinolones only in severe infection of a certain type, an algorithm that considered additional clinical information was used to capture the disease severity (e.g., complicated urinary tract infections defined as the presence of codes suggestive of a urinary tract infection AND one or more of the following factors: genitourinary congenital anomalies, structural abnormalities of the urinary tract (abnormal size, raised echogenicity, hydronephrosis/hydroureter, urinary tract obstruction, ileocystoplasty), functional impairment of the kidneys (renal failure, vesicoureteric reflux, glomerular filtration rate <90 mL/min/1.73 m^2), others (concomitant clinical conditions – diabetes mellitus, catheter associated urinary tract infection, irradiation cystitis, postoperative urinary tract infection, post renal transplantation)). As this algorithm required quite detailed clinical information that was likely not to be captured in less granular databases, the algorithm might have not worked equally well in all databases.

For indications for which first line fluoroquinolone is not recommended as part of the referral, i.e., pneumonia due to gram negative bacteria, acute bacterial sinusitis, acute exacerbation of COPD and CAP, these were considered as off-label if used as first or second line and on-label if used as third line (see Appendix 1) for further details on how on- and off-label were defined). For instance, the distinction between first and last of treatment for indication such as pneumonia due to gram negative bacteria and community acquired pneumonia can vary for specific molecules. Moxifloxacin and ofloxacin are approved for last line of treatment for the management of pneumonia, based on the information from the Article 31 PV assessment report and the request for information from national regulators (NUI – Fluroquinolone EMA/302225/202). However, the UK SmPCs does not always specify what line of treatment for a given disease, except for levofloxacin which states that levofloxacin should be used when it is considered inappropriate to use other antibacterials that are commonly recommended for the initial treatment of community acquired pneumonia. Therefore, we determined line of treatment based on treatment prescribing guidelines such as NICE prescribing guideline (https://www.nice.org.uk/guidance/ng138/resources/visualsummary-pdf-9130723021) which does not list any fluroquinolone as a first line treatment for pneumonia. Variations in prescribing policy across countries with some local modifications of SmPC by fluoroquinolone type and other data to support the need for a fluroquinolone (e.g., based on antibiotic susceptibility of the infectious agent) exist. Therefore, these methodological aspects might have introduced misclassifications in the on- and off-label use. In addition, as prescribing and use in each country are likely to be influenced by local guidelines, it was beyond the scope of this study to consider these differences. The drug use was described and not interpreted in view of country-specific clinical guidance.

Finally, the databases were a subsample of the full population using primary care records. Hence, results should be used with caution when attempting to generalise overall fluoroquinolone use as secondary care records were not included.

9.7 Study size

This study was a characterisation of all patient data captured in the data sets and meeting inclusion criteria for exposure to systemic fluoroquinolones of interest. No hypothesis was tested. Therefore, sample size calculation for the ability to reject the null hypothesis given an effect size was not conducted.

9.8 Data transformation

To assess and analyse multiple data sources in a distributed or federated network, the data needed to be harmonised into a common data standard. This standard is provided by a CDM. The CDM, combined with its standardised content ensures that research methods can be systematically applied to any database producing correct, meaningful, comparable and reproducible results.

All databases included in this network were standardised to the OMOP CDM. This CDM covers the specification for all variables and its content that can be collected during the study. The OMOP CDM is developed and maintained by the Observational Health Data Sciences and Informatics (OHDSI) initiative and is described in detail at: https://ohdsi.github.io/CommonDataModel/ and in The Book of OHDSI: http://book.ohdsi.org. For further details, please refer to the protocol which is available online (EUPAS37856).

9.9 Statistical methods

9.9.1 Main summary measures

Continuous variables were described using mean, standard deviation, median, first and third quartiles, minimum and maximum. Categorical variables were described by the number and percentage of patients in each category. The number of patients with missing data for key variables were reported and no imputation was performed to handle missing data (apart from treatment duration that was specified previously). Confidence intervals (CIs) of 95% were presented for means using a normal approximation. All results are presented separately by database and pooled over the different databases as appropriate. To prevent the identification of individuals, cells containing low frequency counts of (1-5) were suppressed.

9.9.2 Main statistical methods

Each of the analysis described below were repeated within each dataset: LPD (Belgium), LPD (France), DA (Germany), IPCI (the Netherlands), SIDIAP (Spain), and IMRD (the UK).

9.9.2.1 Objective 1: Overall monthly incident fluoroquinolone use and stratified by on-label and off-label indications, and early discontinuation proportion over the period 2016 to 2021

To address primary objective 1, crude (overall) and stratum specific estimates are presented by calendar year. Stratifications according to age, sex, indications, drug type, route of administration and prescriber speciality are provided if numbers allowed stratification. In addition, stratification by duration of treatment is provided for objective 1a.

Overall monthly incident fluoroquinolone use

Incident fluoroquinolone drug use was described per calendar month as a rate per 1,000 population calculated as (i) = $\frac{Incident\ new\ fluoroquinolone\ users\ in\ the\ month}{active\ population\ in\ the\ month} * 1000$

The numerator (i.e., new users) was the number of incident users in each month. An incident user was defined as a patient with start date for fluoroquinolone in that calendar month, and no record for a prescription of a fluoroquinolone within the previous 30 days (substance specific definition, not class level). The denominator (i.e., active population) consisted of the total active patient population

contributing at least 1 day of follow-up time in that calendar month excluding past users that cannot become incident users, that is those that had a fluoroquinolone in the past month.

Note: Individuals could be exposed to fluoroquinolone multiple times in the study period. Therefore, an individual could be defined as an incident user on multiple occasions during the study period. Additionally, if a patient switched from one fluoroquinolone to another, that patient may be counted as an incident user for each of the fluoroquinolones used.

Age standardised monthly incident fluoroquinolone use rate

The age-standardised monthly usage rate was calculated as a weighted sum of the age specific incident rates each month. The European Standard Population 2013 was used as the standard population for all time points and countries. Each age-specific rate was multiplied by the associated weight given in the Box 1 below and summed to give the total age-standardised rate per month:

Box 1 The European Standard Population 2013

Age band (yrs)	Weight
0-9	0.105
10-19	0.11
20-29	0.12
30-39	0.135
40-49	0.14
50-59	0.135
60-69	0.115
70-79	0.09
80-89	0.04
90+	0.01

Monthly incidence of on-label fluoroquinolone use (which includes first line and last line indications)

On-label incident fluoroquinolone drug use was described per calendar month as a rate per 1,000 population calculated as in (i) above where the numerator (i.e., new users) was the number of incident users in each month where 'on-label indication = Yes'. The denominator (i.e., active population) consisted of the total active patient population contributing at least 1 day of follow-up time in that calendar month. The denominator also includes the patients with unknown indications.

Monthly incidence of off-label fluoroquinolones use (mild infections for which fluoroquinolones are not indicated for)

Off-label incident fluoroquinolone drug use was described per calendar month as a rate per 1,000 population as calculated in (i) where the numerator, new users, was the number of incident users in each month for an off-label indication, where 'on-label indication = No'. The denominator, total population, consisted of the total active patient population contributing at least 1 day of follow-up time in that calendar month. The denominator includes the unknown indications.

Early discontinuation proportion over the period 2016 to 2021

Early discontinuation proportion per month was expressed as the number of patients identified as stopping treatment early per 1,000 incident users per month and presented by calendar year and per quarter[2].

For estimation of early discontinuation proportions per calendar month, the denominator consisted of all incident user patients in that month. The numerator consisted of the number of these incident users that were identified as having discontinued treatment prematurely. The discontinuation was applied to the month that the treatment episode begins in, i.e., if an incident treatment episode was expected to run from 25 January 2018 to 18 February 2018 but was discontinued on 05 February 2018 it was considered an incident episode in January and was counted as a discontinuation in January.

9.9.2.2 Objective 2: Impact of regulatory interventions on fluoroquinolone prescribing patterns using time series analysis

A time series analysis using joinpoint/segmented regression was used to analyse time points of changes in trends. Data were modelled by a Poisson model on the log-linear scale with monthly incidence rate as the independent variable and calendar month as the predictor. Seasonality and the specific regulatory intervention time points have not been modelled in the data; the joinpoint analysis was data driven thus allowing for changes in trends associated with these two factors to be observed as breakpoints in the model, if identified. An additional model was specified for the age-standardised fluoroquinolone usage rate (standardised to European Standard Population 2013) (25). This model used a linear regression model with the age--standardised rate (described in section 9.9.2.1) per 1,000 population as the independent variable and calendar month as the predictor. It is important to be aware that there may be slight differences in results of the two models because of the model specification as well as the age-standardisation.

The joinpoint/segmented regression model was conducted using the *'segmented'* package in R software. The number of break points included in the model to give the best fit to the data was chosen automatically using Bayesian Information Criterion (BIC) via the '*segmented'* command in the R package. A maximum of 20 break points was considered which is higher than expected to ensure that the best model is achieved. The final model which gives the lowest BIC was chosen. For the Poisson model the monthly percentage change (MPC) was presented for each segment of the final model along with CIs (utilising the *slope* command of the *segmented* package). For the age-standardised model using linear regression, the coefficient and 95% CI were presented. The final model was described by

[2]The results are also presented quarterly (e.g., discontinuation rates were calculated based on the number of individuals who discontinued in the quarter divided by the number of incident fluoroquinolone users in this quarter). Although a few patients may have been incident more than one time, they will get counted only once in the quarter. Hence, a slightly lower number than by summing 3 months together in the calendar year results.

the time periods of the breaks and the corresponding MPC (or coefficient for age--standardised linear model) for each segmented block of time with 95% CIs.

The model was fitted to explore incidence over time of all fluoroquinolones and repeated for each fluoroquinolone separately since implementation dates vary between the specific drugs. Age--standardised rates were not modelled for individual fluoroquinolones. The last 6 months of data points were not included in the time-trend analysis due to population attrition in the datasets which would be expected to result in artificially increased monthly usage rates.

The final model predicted moments of change in trend and was described in relation to the known times of regulatory interventions in each country. The implementation dates vary by country and by fluoroquinolone type, the dates specified in Table 4 are shown below.

Table 4. Summary of implementation time periods for all fluoroquinolones and by drug type for each country

	Belgium	France	Germany	Netherlands	Spain (Catalonia)	UK
DHPC date	1 Apr. 2019	10 Apr. 2019	8 Apr. 2019	9 Apr. 2019	8 Apr. 2019	21 Mar. 2019
SmPC and PI implementation for all drugs	24 Feb. 2019 to 17 Apr. 2020	2 Aug. 2019 2 Oct. 2019 23 Dec. 2019 2 Apr. 2020 7 May 2020 28 May 2020	22 Mar. 2019 to 11 Dec. 2019	14 Feb. 2019 to 30 Mar. 2020	27 Mar. 2019 to 2 Jul. 2020 31 Jul. 2020	25 Apr. 2019 to 23 Dec. 2019 01 Apr. 2020 to 18 May 2020
Pefloxacin	NA	NA	NA	NA	NA	NA
Lomefloxacin	NA	2 Aug. 2019	NA	NA	NA	NA
Ciprofloxacin	12 Apr. 2019 to 13 Dec. 2019	2 Apr. 2020	29 Mar. 2019 to 19 Oct. 2019	29 Apr. 2019 to 30 Mar. 2020	4 Jun. 2019 to 11 Jun. 2020	25 Apr. 2019 to 23 Dec. 2019
Levofloxacin	24 Feb. 2019 to 27 Nov. 2019	7 May 2020	26 Mar. 2019 to 26 Jun. 2019	14 Feb. 2019 to 17 Feb. 2020	27 Mar. 2019 to 2 Jul. 2020	01 Aug. 2019 to 11 Nov. 2019
Ofloxacin	9 Oct. 2019 to 1 Nov. 2019	28 May 2020	22 Mar. 2019 to 11 Dec. 2019	23 Jul. 2019 to 11 Dec. 2019	31 Jul. 2020	15 Aug. 2019

Moxifloxacin	9 May 2019 to 17 Apr. 2020	23 Dec. 2019	26 Mar. 2019 to 26 Jun. 2019	21 May 2019 to 21 Feb. 2020	4 Jun. 2019 to 2 May 2020	1 Apr. 2020 to 18 May 2020
Norfloxacin	5 Jun. 2019	2 Oct. 2019	22 Mar. 2019 to 5 Apr. 2019	10 Jul. 2019 to 6 Jan. 2020	25 Sep. 2019 to 17 Mar. 2020	NA
Prulifloxacin	NA	NA	NA	NA	NA	NA
Rufloxacin	NA	NA	NA	NA	NA	NA

DHPC: Direct Healthcare Professional Communications; NA: Not Authorised (or not used in the respective country); PI: Period of Implementation; SmPC: Summary of Product Characteristics; UK: United Kingdom.

9.9.2.3 Objective 3: Prescribers' compliance with warnings in fluoroquinolones SmPC Section 4.4 in the subgroups at risk

For each of the analysis described in primary objective 3, stratifications according to individual fluoroquinolones of interest, age category (10 years) and sex were provided if numbers allowed stratification. In addition, date is also examined for evidence of seasonal fluctuations.

Monthly incident fluoroquinolone use in risk groups for tendinitis and tendon rupture

Incident fluoroquinolone drug use in at risk groups was described per calendar month as a rate per 1,000 population calculated as in (i) for individuals at risk of tendinitis and tendon rupture. The numerator (i.e., new users) was the number of incident users in each month in individuals defined as being at risk of tendonitis or tendon rupture. The denominator (i.e., total population) consisted of the total active patient population contributing at least 1 day of follow-up time in that calendar month.

Monthly incident fluoroquinolone use in those at risk of aortic dissection and aneurysm

Incident fluoroquinolone drug use was described per calendar month as a rate per 1,000 population calculated as in (i) for individuals at risk of aortic dissection and aneurysm. The numerator (i.e., new users) was the number of incident users in each month in individuals defined as being at risk of aortic dissection and aneurysm. The denominator (i.e., total population) consisted of the total active patient population contributing at least 1 day of follow-up time in that calendar month.

Monthly incident fluoroquinolone use in those with recent (30 days prior) or concomitant prescribing of systemic corticosteroids

Incident fluoroquinolone drug use was described per calendar month as a rate per 1,000 population calculated as in (i) for individuals in those with recent (30 days prior) or concomitant prescription of systemic corticosteroids. The numerator (i.e., new users) was the number of incident users in each month in individuals defined as having a recent (30 days prior) or concomitant prescription of systemic corticosteroids. The denominator (i.e., total population) consisted of the total active patient population contributing at least 1 day of follow-up time in that calendar month.

9.9.2.4 Objective 4: Monthly incident prescription rates for alternative antibiotics prescribed in patients where systemic use fluoroquinolones have previously been prescribed or discontinued

For the analysis described in primary objective 4, stratifications according to indication, age group and sex are provided.

The incidence of alternative antibiotic prescription per month was expressed as the number of patients identified as starting an alternative antibiotic per 1,000 incident users per month presented by calendar year and per quarter.

For estimation of proportions receiving an alternative antibiotic per calendar month, the denominator consisted of all incident user patients in that month. The numerator consisted of the number of these incident users that were identified as having received an alternative antibiotic. The alternative antibiotic was applied to the month that the treatment episode begins in i.e., if an incident treatment episode was expected to run from 25 January 2018 to 18 February 2018, but an alternative antibiotic was received on 05 February 2018 it was considered an incident episode in January and was counted as an alternative antibiotic in January.

Note that these patients were therefore a sub-cohort of incident users.

9.9.3 Missing values

No imputation of missing values was applied; only those with relevant information were included.

9.9.4 Sensitivity analysis

Sensitivity analyses varying the time periods used in the main definition to alternative definitions were conducted (Table 5).

Table 5. Sensitivity analyses

	Main definition	Alternative definition	Analyses to be applied to
1. Incident fluoroquinolone use assessment window	No fluoroquinolone exposure in the last 30 days	• No fluoroquinolone exposure in last 60 days • No fluoroquinolone exposure in last 90 days • No fluoroquinolone exposure in last 180 days	Objective 1a overall incident fluoroquinolone rates

	Main definition	Alternative definition	Analyses to be applied to
2. Gap between treatment episodes	Interval between treatment episodes of >30 days indicates new treatment episode	• Interval between treatment episodes of >14 days indicates new treatment episode • Interval between treatment episodes of >60 days	Objective 1a overall incident fluoroquinolone rates
3. Indication of use assessment window	Underlying medical condition within the previous 14 days of fluoroquinolone exposure	• Underlying medical condition within the previous 30 days of fluoroquinolone exposure • Underlying medical condition within the previous 60 days of fluoroquinolone exposure	Objective 1a incident fluoroquinolone use stratified by indication
4. Lookback window for risk factors	Any time prior fluoroquinolone exposure	• 365 days prior fluoroquinolone exposure	Objectives 3a-c incident fluoroquinolone rates in those with risk factors

9.10 Quality control

IQVIA Quality Management System (QMS)

As the coordinating centre for this collaboration, the IQVIA Quality Management System (QMS) was applied. This IQVIA QMS is built upon the quality and regulatory compliance principles established by the standards and guidelines from the International Standards Organisation and ICH. The QMS encompasses all matters that individually or collectively influence the quality and regulatory compliance of the offerings in scope, and defines systems, processes and tools that enable the proposal to meet the appropriate quality standards and Good clinical practice compliance requirements. IQVIA has implemented an effective support network to ensure that the QMS is embedded across all projects.

At the study level, all aspects of the study from protocol development to the reporting of the results were conducted within the work-frame of IQVIA QMS and in accordance to the appropriate global procedure.

A Quality Control checklist were developed and executed for the study, which included quality control on study methodology, statistical analysis plan, programming, data management and analysis, study results, conclusions and study report. Furthermore:

1. The study Quality Control plan establishes ownership for the execution of the individual Quality Control steps. The principle of the independence of Quality Control applies.

2. Individuals responsible for the execution of the specific Quality Control steps must have knowledge, capability and experience which are adequate for the task.

3. The result of the execution of the individual steps of the Quality Control plan are documented, and include the required correction actions, if any.

4. The execution of any required corrective action is documented.

Also, the Principal Investigator and Senior Quality controller of the study collectively verify training compliance of IQVIA employees contributing to the study, as per IQVIA procedure. Examples might be to check the following:

- The data are correctly anonymised
- The variables are in the expected format
- The range of each variable is as expected (e.g., no negative ages)
- Patients' data of birth precedes data of death.

10 Results

In the following sections, the incidence of drug use is usually presented as min-max ranges across the entire period and for each country, then stratified by sex, age categories, active substance, on- and off-label use, indication and line of treatment, depending on the objective. When certain trends are visible, this is indicated. Although with the exception of Section 10.6, the trends were never formally tested, and they should be interpreted with caution.

This report is focused on the main findings and therefore not all results are presented. The Electronic Supplementary Material (link: https://ecorecoviddashboard.shinyapps.io/shiny-fq/) contains all results of fluoroquinolones use by database, including all required stratifications, sensitivity analyses and supplementary tables and will be referred to when needed to complement the report.

Please note that the following restrictions apply:

Data privacy

- Cells which contain counts ≤5 were masked. The incidence rates could not be calculated in these instances.

Interpretation

- No formal comparison was made for incidence rates between countries or between strata. Therefore, any attempts of comparing should be made with caution.
- Interpretation of the incidence of fluoroquinolone use at the end of the follow-up could be hampered because of the Corona Virus Disease-2019 (COVID-19) pandemic.

10.1 Participants

The number of active patients across the study period for each database is presented in Table 6. Overall, the use of fluoroquinolones was investigated in 16 to 21 million patients each month during the study period (January 2016 to February 2021).[3]

[3] The study period differed for each database (depending on the data lag time) and was chosen in order to maximise the use of available data. The final six months of each database were excluded to remove the drop towards the end of the study as the number of participants dropped substantially and those that are retained are those that seeing a health practitioner (see Table 1).

Table 6. Number of individuals with observation time, by country

	Belgium	France	Germany	Netherlands	Spain (Catalonia)	UK
Study period	Jan 2016 - Oct 2020	Jan 2016 – Feb 2021	Jan 2016 – Dec 2020	Jan 2016 – Dec 2020	Jan 2016 – Dec 2020	Jan 2016 – Oct 2020
Number of patients across study period (Min – max)[1]	268,834 - 372,754	1,946,954 - 3,557,777	4,401,044 - 7,517,841	937,596 - 1,197,100	5,623,617 - 5,713,682	2,486,931 - 3,946,084

Max: Maximum; Min: Minimum; UK: United Kingdom. [1]Mininum and maximum of monthly count range.

10.2 Incidence of fluoroquinolone use (objective 1a)

The overall monthly incidence of fluoroquinolone users over calendar time is presented in Figure 4 and Figure 5 and further stratifications are shown in Figure 6 and Figure 7. The incidence rate is expressed as the number of new users of fluoroquinolones/1,000 persons per month.

The highest overall incidence rates were reported in Spain (range: 2.8 to 8.0/1,000 persons per month), followed by Belgium (range: 2.0-5.7/1,000 persons per month), Germany (range: 1.3 to 2.9/1,000 persons per month), France (range: 1.3-2.5/1,000 persons per month) and the Netherlands (range: 1.5-2.0/1,000 persons per month). The lowest overall incidence rates were in the UK (range: 0.7-1.2/1,000 persons per month) (Figure 4). A similar pattern was observed in the overall age-standardised incidence rates (ranges: 2.6 to 7.6/1,000 persons per month in Spain, 1.8 to 5.5/1,000 persons per month in Belgium, 1.2 to 2.8/1,000 persons per month in Germany, 1.3 to 2.4/1,000 persons per month in France, 1.4 to 2.0/1,000 persons per month in the Netherlands and 0.7 to 1.2/1,000 persons per month in the UK) (Figure 5).

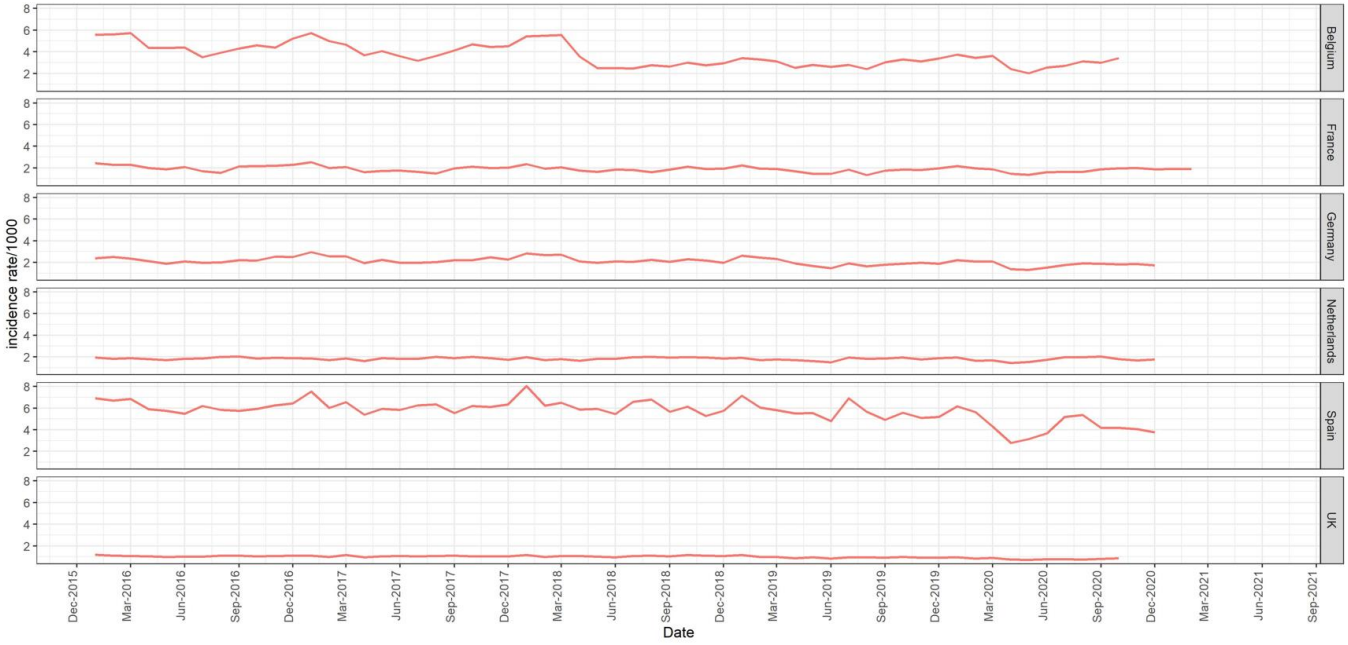

Figure 4. Monthly incidence fluoroquinolone use crude rates over the study period

Legend: The incidence rate is expressed as the number of new users of fluoroquinolones/1,000 persons per month.

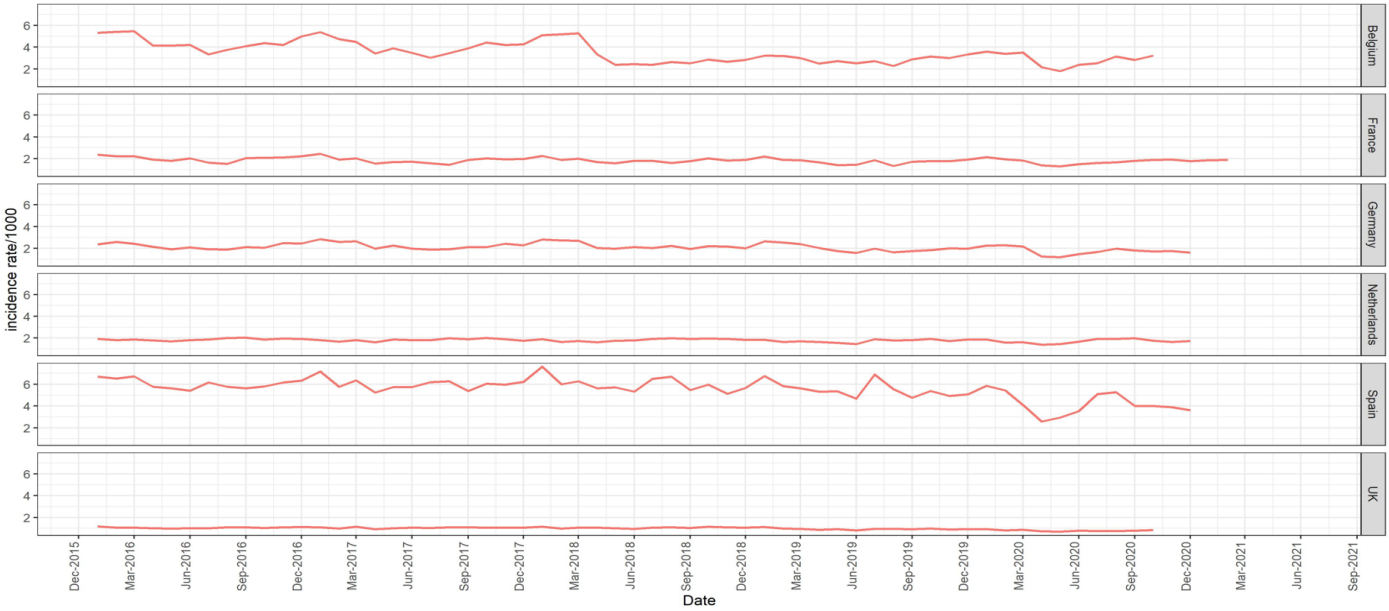

Figure 5. Monthly incidence fluoroquinolone use age-standardised rates over the study period

Legend: The incidence rate is expressed as the number of new users of fluoroquinolones/1,000 persons per month.

When stratified by sex, fluoroquinolone use was slightly higher in females than males in Belgium, France, Germany, and Spain, whereas it remained similar in the Netherlands and in the UK[4] (Figure 6).

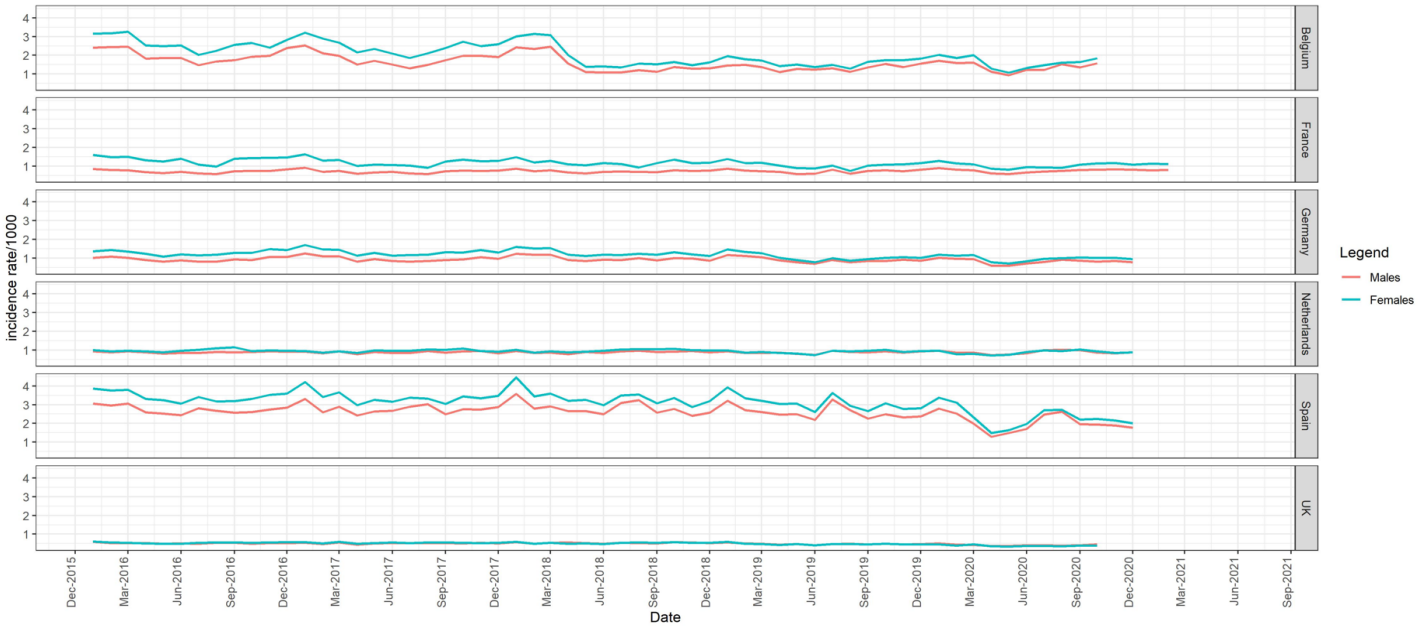

Figure 6. Monthly incident fluoroquinolone use rates over the study period, stratified by sex

Legend: The incidence rate is expressed as the number of new users of fluoroquinolones/1,000 persons per month.

When stratified by age group (<18, 18-75 and >75), the highest monthly median incidence rates were in persons aged above 75 in all countries Figure 7. In this age category, the monthly incidence rates ranged from 10.0 to 27.3/1,000 persons per month in Spain, 2.8 to 7.7/1,000 persons per month in Belgium, 4.8 to 7.4/1,000 persons per month in the Netherlands, 1.7 to 4.1/1,000 persons per month in Germany, 1.6 to 3.4/1,000 persons per month in the UK and 1.5 to 2.9/1,000 persons per month in France[5]. The monthly median incidence rates were slightly higher in persons aged above 18 compared to those who were aged less 18 across all the countries (except Germany). In Germany, the monthly incidence rates ranged from 1.0 to 4.5/1,000 persons per month in persons aged below 18 (Table 7).

[4]No statistical test was performed to test the difference in trend or between male and female subgroups.
[5]Alternative age categories based on 10 years age bands and in the paediatric population can be viewed in the Electronic Supplementary Material.

Table 7. Monthly median incident fluoroquinolone use rates over the study period, stratified by age

	Belgium		France		Germany		Netherlands		Spain		UK	
	Min-Max	Med.	Min-Max	Med.	Min-Max	Med.	Min-Max	Med.	Min-Max	Med.	Min-Max	Med.
<18 years old	0.9-4.7	2.2	0.7-2.5	1.3	1.0-4.5	2.6	0.4-1.8	0.6	0.5-9.9	2.6	0.2-0.3	0.2
18-75 years old	2.0-6.2	3.6	1.3-2.7	1.9	1.2-2.7	1.8	1.2-1.9	1.6	2.3-6.6	4.9	0.7-1.2	1.0
>75 years old	2.8-7.7	**4.5**	1.5-2.9	**2.2**	1.7-4.1	**2.9**	4.8-7.4	**6.4**	10.0-27.3	**17.1**	1.6-3.4	**2.8**

Max: maximum; Med: median; Min: minimum; UK: United Kingdom.

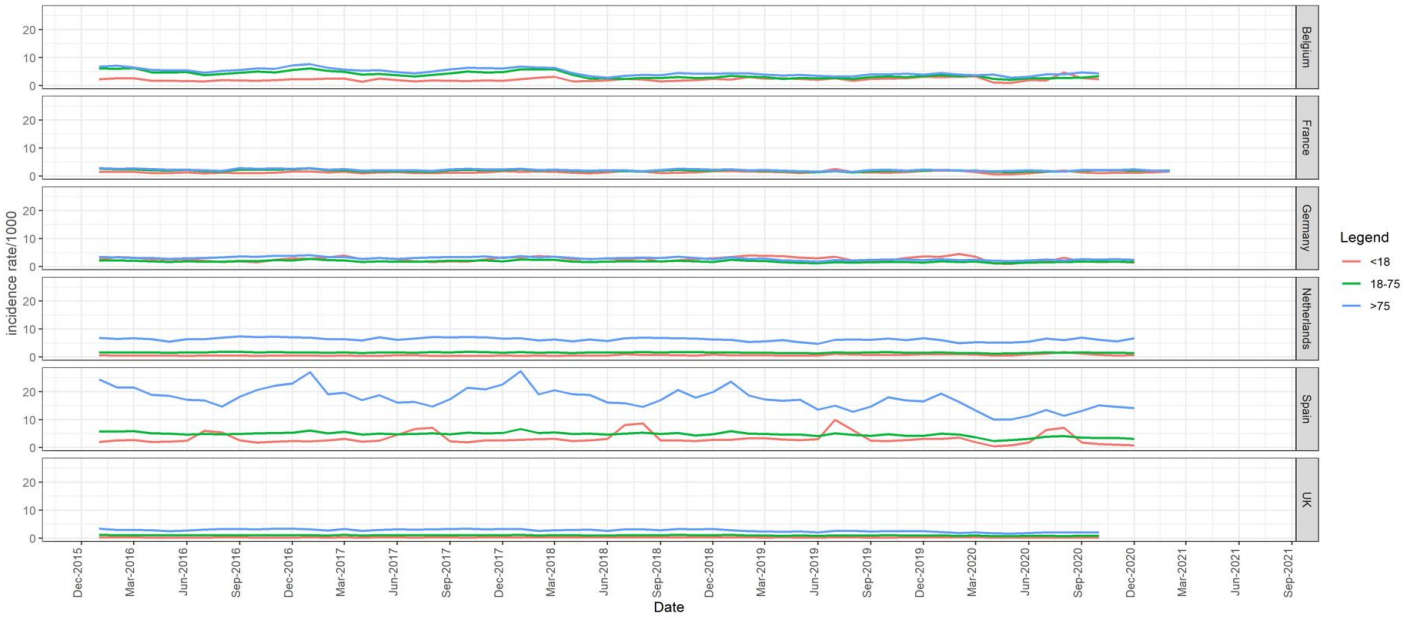

Figure 7. Monthly incident fluoroquinolone use rates over the study period, stratified by age

Legend: The incidence rate is expressed as the number of new users of fluoroquinolones/1,000 persons per month.

When stratified by fluoroquinolone type, ciprofloxacin was the most prescribed in Spain, where incidence rates ranged between 1.8 to 5.2/1,000 persons per month. The most common fluoroquinolones prescribed in Belgium were ciprofloxacin and moxifloxacin where incidence rates ranged between 1.3 and 2.4/1,000 persons per month and 0.2 to 2.9/1,000 persons per month, respectively. In France, ciprofloxacin and ofloxacin were the most frequently prescribed, with incidence rates ranging from 0.3 to 0.5/1,000 persons per month and 0.7 to 1.1/1,000 persons per month, respectively. In Germany, the UK and the Netherlands, ciprofloxacin was the most commonly prescribed. Lomefloxacin was authorised and used only in France (Figure 8).

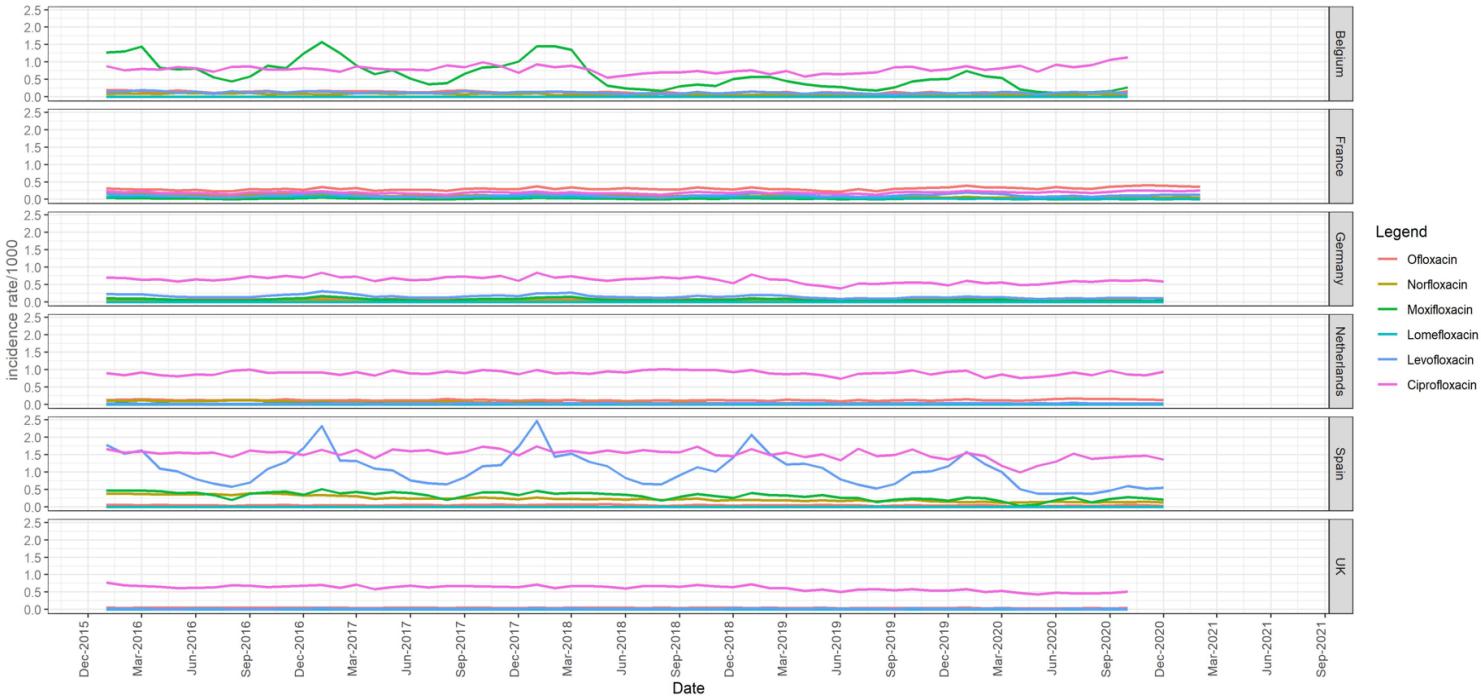

Figure 8. Monthly incident fluoroquinolone use rates over the study period, by fluoroquinolone type

Legend: The incidence rate is expressed as the number of new users of fluoroquinolones/1,000 persons per month.

When stratified by duration of treatment, the incidence of fluoroquinolone use was the highest for short duration (0-6 days) in the Netherlands, the UK, Germany and France, short-medium duration (7-13 days) in Belgium and Spain. In Germany, the UK and the Netherlands, high incidence of fluoroquinolone use for short-medium duration (7-13 days) and very-long duration (≥28 days) were observed. Long duration (21-27 days) had the lowest incidence of fluoroquinolone across countries (Figure 9).

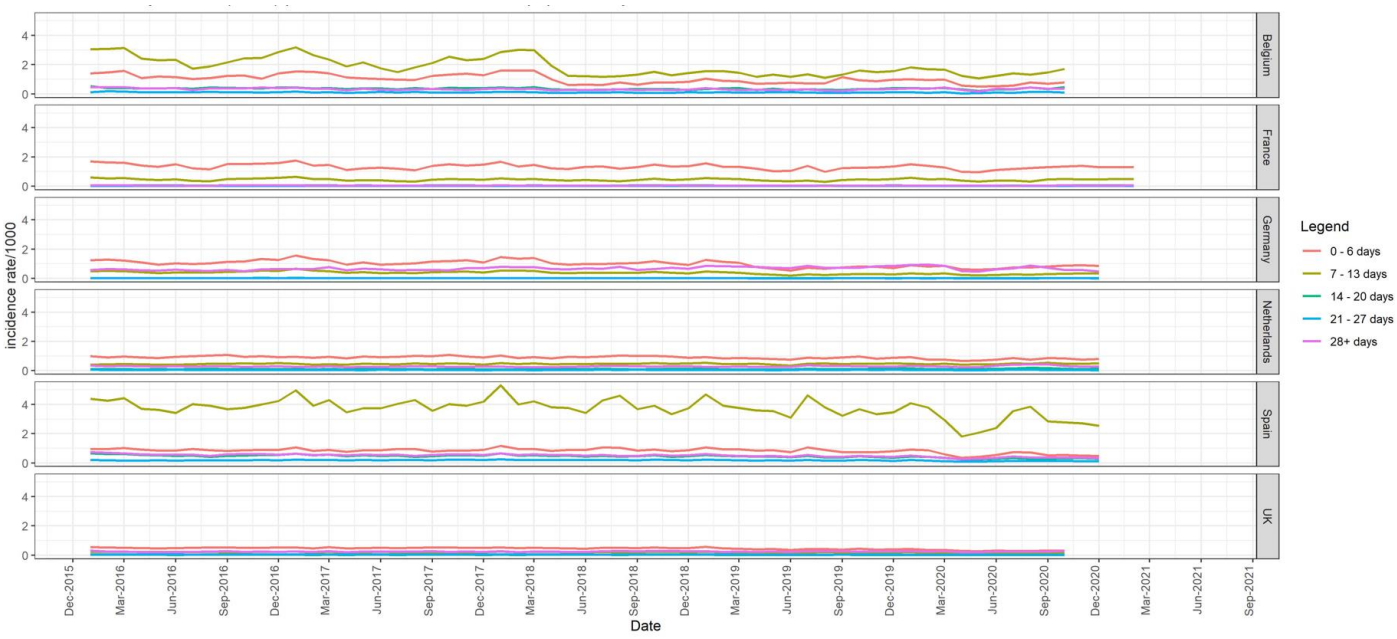

Figure 9. Monthly incident fluoroquinolone use rates over the study period, by duration of fluoroquinolone treatment episode

Legend: *Short duration* ranged between 0 and 6 days; *short-medium duration* between 7 and 13 days; *medium duration* between 14 and 20 days; *medium-long duration* was between 14 and 20 days; *long duration* was between 21 and 27 days; *very-long duration* was ≥28 days. The incidence rate is expressed as the number of new users of fluoroquinolones/1,000 persons per month.

When stratified by line of treatment, the overall incidence of fluoroquinolone use was higher in the first line of treatment (1st line), with rates ranged from 2.6 to 7.7/1,000 persons per month in Spain, 1.9 to 5.5/1,000 persons per month in Belgium, 1.3 to 2.9/1,000 persons per month in Germany, 1.3 to 1.9/1,000 persons per month in the Netherlands, 1.3 to 2.4/1,000 persons per month in France and 0.6 to 1.1/1,000 persons per month in the UK. The second (2nd line) and third line (3rd+ line) of treatment remained low or non-existent in all countries (Figure 10).

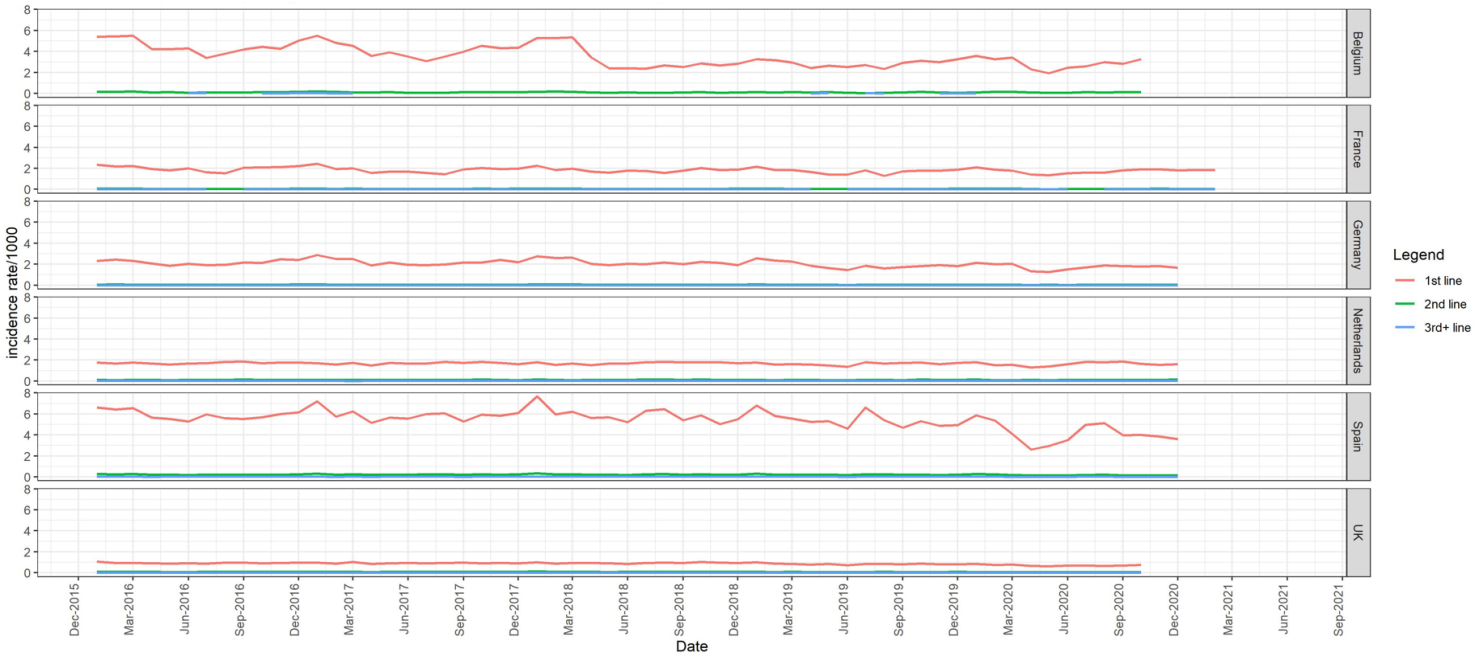

Figure 10. Monthly incident fluoroquinolone use rates over the study period, by line of treatment

Legend: The incidence rate is expressed as the number of new users of fluoroquinolones/1,000 persons per month.

10.3 Incidence of fluoroquinolone use stratified by indications (objective 1a)

The overall monthly incidence rates of fluoroquinolone users stratified by indications over calendar time are presented in Figure 11. In addition, the monthly incidence proportion is expressed as the number of incident users for whom the indication of use is known or unknown out of the new users of fluoroquinolones per month.

The proportion of patients for whom the indication of use is unknown was high; the monthly median percentage was 38.1% in Belgium, 57.1% in France, 65.6% in Germany, 84.0% in the UK, 59.3% in the Netherlands and 72.3% in Spain. This stratification was removed from Figure 11 to allow comparisons between the known indications.

For those patients where an indication of use was specified, the majority of use was for respiratory infections, urinary tract infections and ear infections across all countries and over the full study period. For respiratory tract infections, seasonal variations were observed in Belgium, Germany and Spain across the study period. These variations suddenly dropped from May 2018 in Belgium (Figure 11). In Germany, respiratory infections and ear infections were the most common with a median of monthly percentage of 12.6% and 11.4%, respectively. Similarly, these indications were also the most common with a median monthly percentage of 11.2% for indication in Spain. In Belgium, respiratory tract infections and urinary tract infections were the most common indications with a median of monthly percentage of 26.2% and 19.1%, respectively. Urinary tract infections were the most common indication in France (19.1%) and in the Netherlands (32.7%) while ear infections were the most common indication

in the UK (5.3%). Very few patients were prescribed fluoroquinolones for bone infections, skin infections, gastrointestinal infections and other use. Note that one patient could have more than one indication, consequently the monthly number of indications was slightly higher than the number of patients. Summing the total incident fluoroquinolones by indication and comparing to the overall incident fluoroquinolone users we have an average of 1,355 indications per 1,294 patients in Belgium, 14,798 indications per 14,541 users in Germany, 6,003 indications per 5,885 patients in France, 3,260 per 3,222 patients in the UK, 2,159 per 2,086 patients in the Netherlands and 32,631 indications per 32,296 patients in Spain.

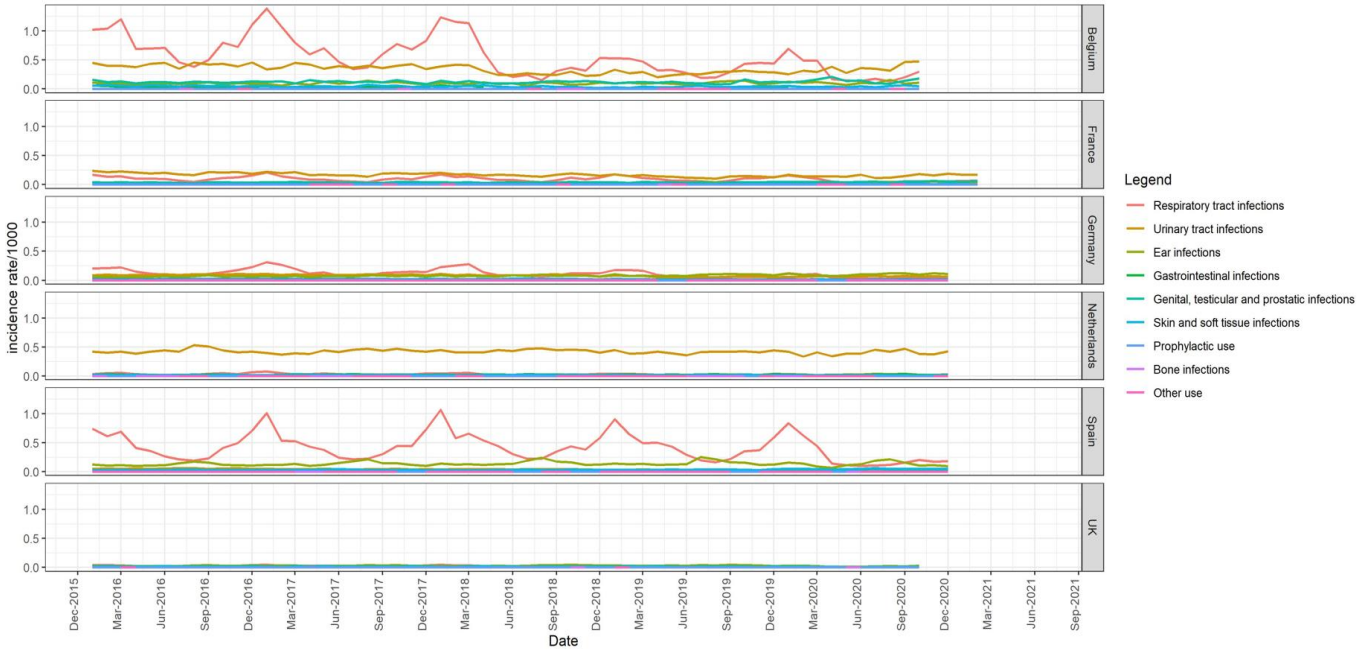

Figure 11. Monthly incident fluoroquinolone use rates over the study period, by indications

Legend: Other use = infections in immunocompromised, septicaemia, meningitis, infection of cerebrovascular fluid and endocarditis. The incidence rate is expressed as the number of new users of fluoroquinolones/1,000 persons per month.

10.4 Incidence of fluoroquinolone stratified by on-label and off-label use (objective 1a)

The incidence of fluoroquinolone was higher in the off-label use[6] than in the on-label use in all countries (except the UK). The minimum and maximum monthly ratio of off-label to on-label across the entire period varied between 1.9 and 4.8 in Belgium, 1.9 and 4.2 in France, 3.5 and 6.6 in Germany, 3.2 and 5.3 in the Netherlands and 2.3 and 5.9 in Spain. In the UK, the ratios of off-label to on-label were lower and included 1 (min and max: 0.9 and 2.1) (Figure 12).

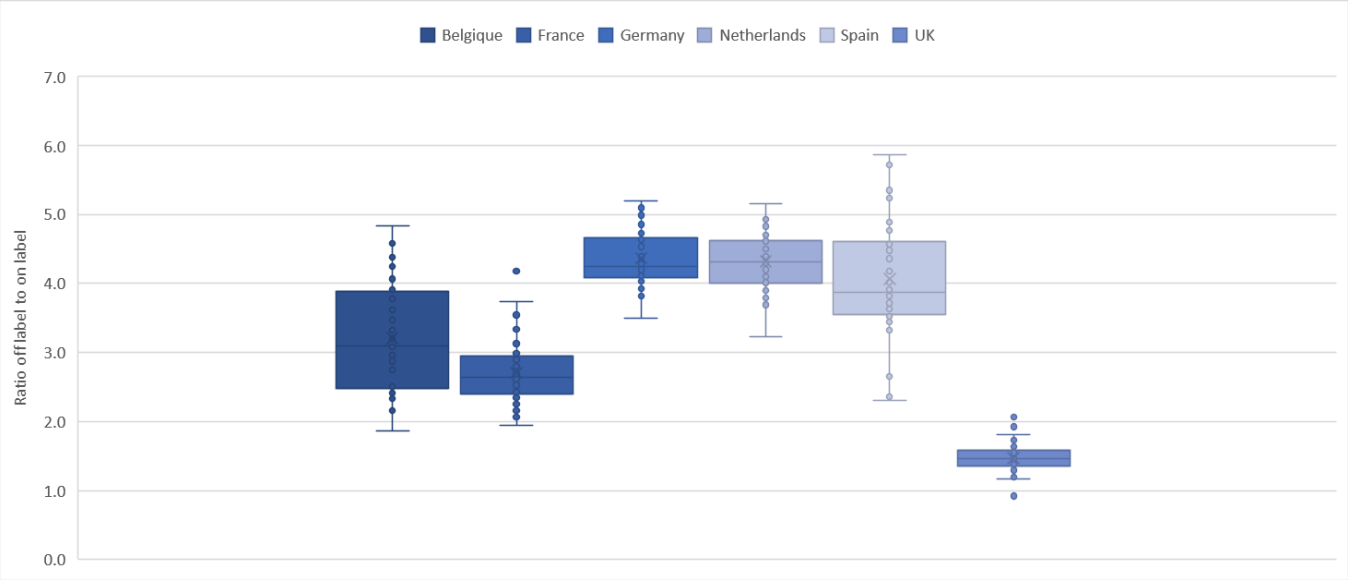

Figure 12. Ratio of off-label vs on-label use rates for fluoroquinolones

Legend: A patient could be counted in both on-label and off-label groups depending on the indication considered. Only known indications were classified as on-label and off-label.

Overall, the observed incidence of fluoroquinolone trends were similar in the on- and off-label in France, Germany and the Netherlands even though the magnitude was different in these two groups[7]. In Belgium, a decrease in the off-label use was observed around 2018 followed by lower levels of variation. In the UK, a steep decrease in the on- and off-label was observed from 2020 followed by lower variations. Similarly, a sharp decrease was observed from 2020, but followed by seasonal variations at

[6]Information from the SmPC and Art. 31 referral plus the UK and Dutch treatment prescribing guidelines were used in combination to classify indications as on-label or off-label. When the recommendation was to use fluoroquinolones only in severe infection of a certain type (e.g., complicated urinary tract infections), an algorithm that considered additional clinical information was used to capture the disease severity. Moreover, when specific indication was being removed or restricted based on Art. 31, this was considered as off-label use in the study. For indications where first line fluoroquinolone is not recommended as part of the Referral, i.e., pneumonia due to Gram negative bacteria, acute bacterial sinusitis, acute exacerbation of COPD and CAP, these were considered as off-label if used as first or second line and on-label if used as third line. See Section 9.4.4 and 9.4.5, and Appendix 1 for further details on how on- and off-label were defined.

[7]No formal comparison was made for incidence rates between countries or between strata.

the same level as before in Spain. Stratification by on and off-label are presented in Figure 13-Figure 18.

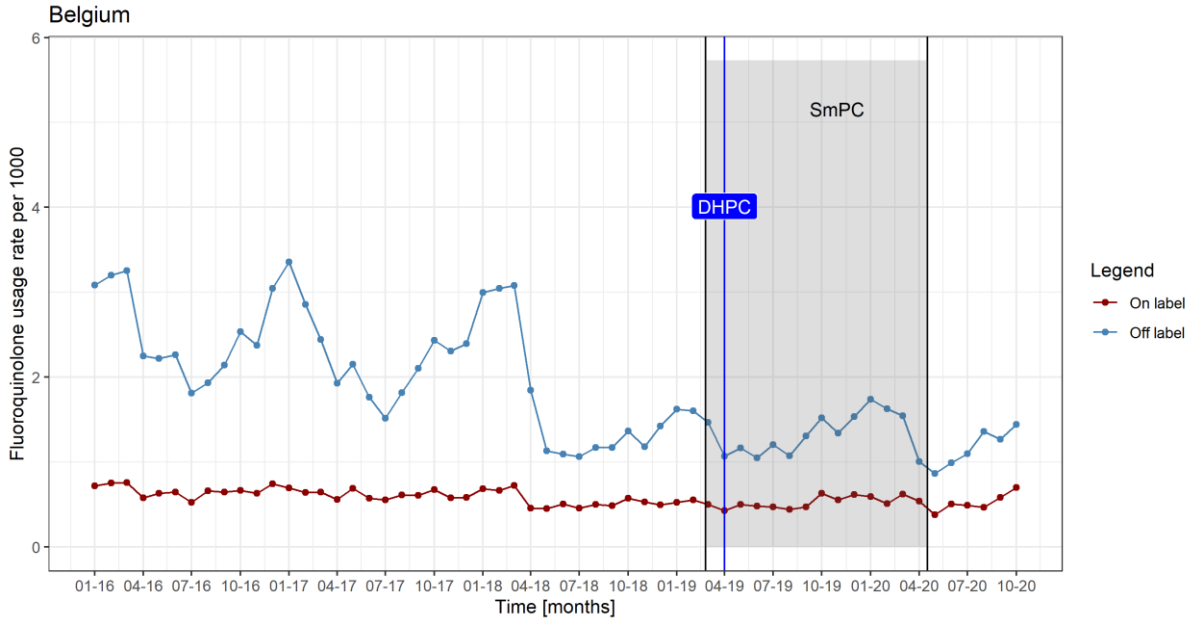

Figure 13. Incidence rate of fluoroquinolone use for Belgium, stratified by on- and off-label

Legend: A patient could be counted in both on-label and off-label groups depending on the indication considered. Only known indications were classified as on-label and off-label. The grey shaded interval represents the summary of product characteristics (SmPC) implementation period for the fluoroquinolone warnings (24 Feb. 2019 to 17 Apr. 2020) and the associated direct healthcare professional communications (DHPC) (1 Apr. 2019) (vertical blue line). See Table 4 for the exact dates in each country.

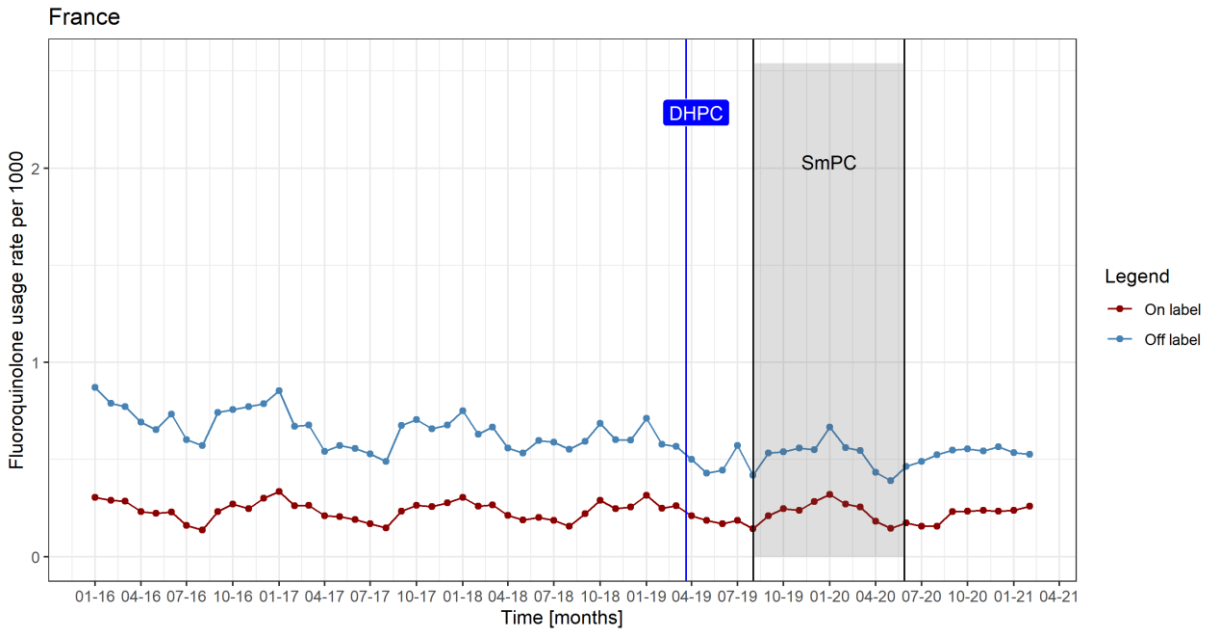

Figure 14. Incidence rate of fluoroquinolone use for France, stratified by on- and off-label

Legend: A patient could be counted in both on-label and off-label groups depending on the indication considered. Only known indications were classified as on-label and off-label. The grey shaded interval represents the summary of product characteristics (SmPC) implementation dates for the fluoroquinolone warnings (2 Aug. 2019 to 28 May 2020) and the associated direct healthcare professional communications (DHPC) date (10 Apr. 2019) (vertical blue line). Although several dates were reported for the SmPC implementations in France (see Table 4 for the exact dates), this graph shows the interval between the first and the last date.

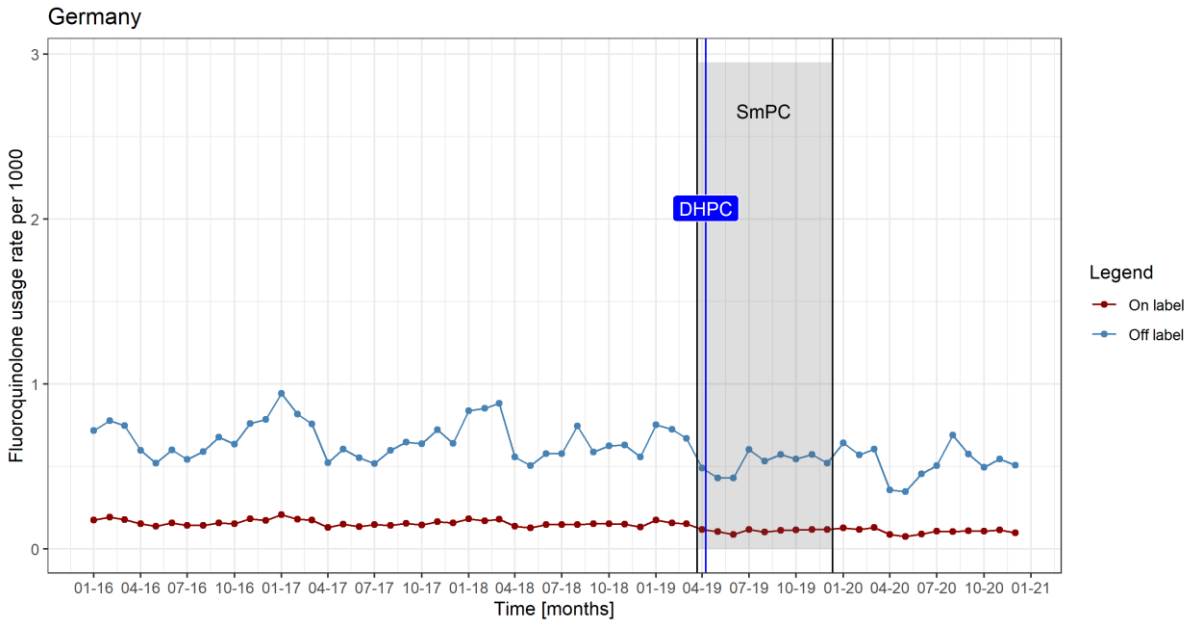

Figure 15. Incidence rate of fluoroquinolone use for Germany, stratified by on- and off -label

Legend: A patient could be counted in both on-label and off-label groups depending on the indication considered. Only known indications were classified as on-label and off-label. The grey shaded interval represents the summary of product characteristics (SmPC) implementation period for the fluoroquinolone warnings (22 Mar. 2019 to 11 Dec. 2019) and the associated direct healthcare professional communications (DHPC) date (8 Apr. 2019) (vertical blue line). See Table 4 for the exact dates in each country.

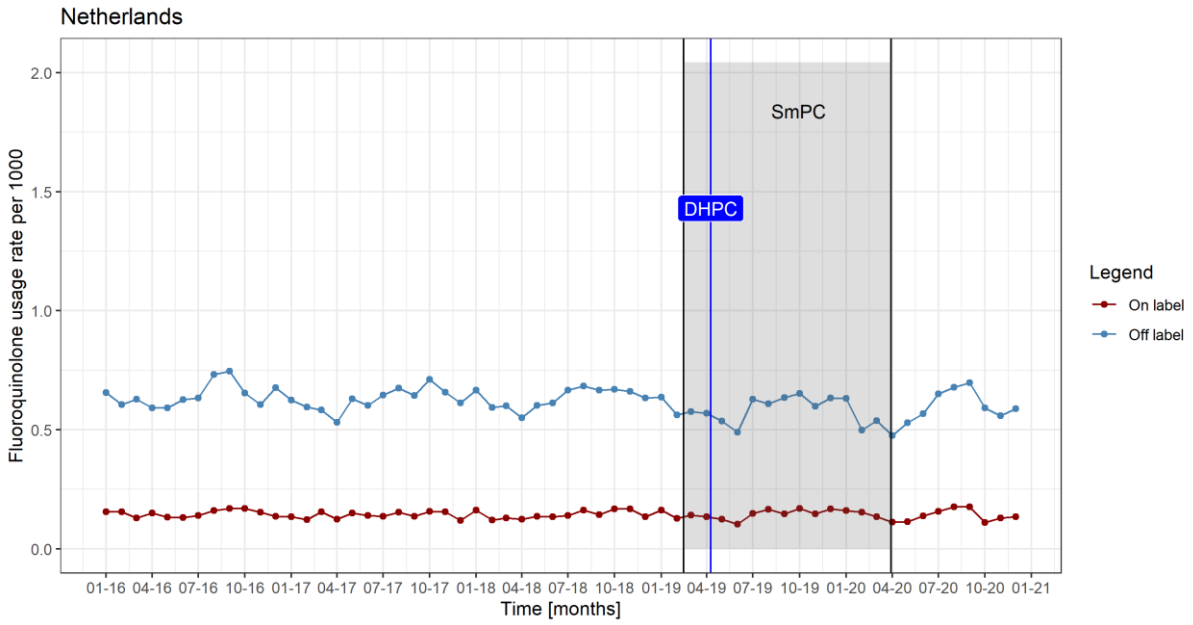

Figure 16. Incidence rate of fluoroquinolone use for the Netherlands, stratified by on- and off-label

Legend: A patient could be counted in both on-label and off-label groups depending on the indication considered. Only known indications were classified as on-label and off-label. The grey shaded interval represents the summary of product characteristics (SmPC) implementation period (14 Feb. 2019 to 30 Mar. 2020) for the fluoroquinolone warnings and the associated direct healthcare professional communications (DHPC) date (9 Apr. 2019) (vertical blue line). See Table 4 for the exact dates in each country.

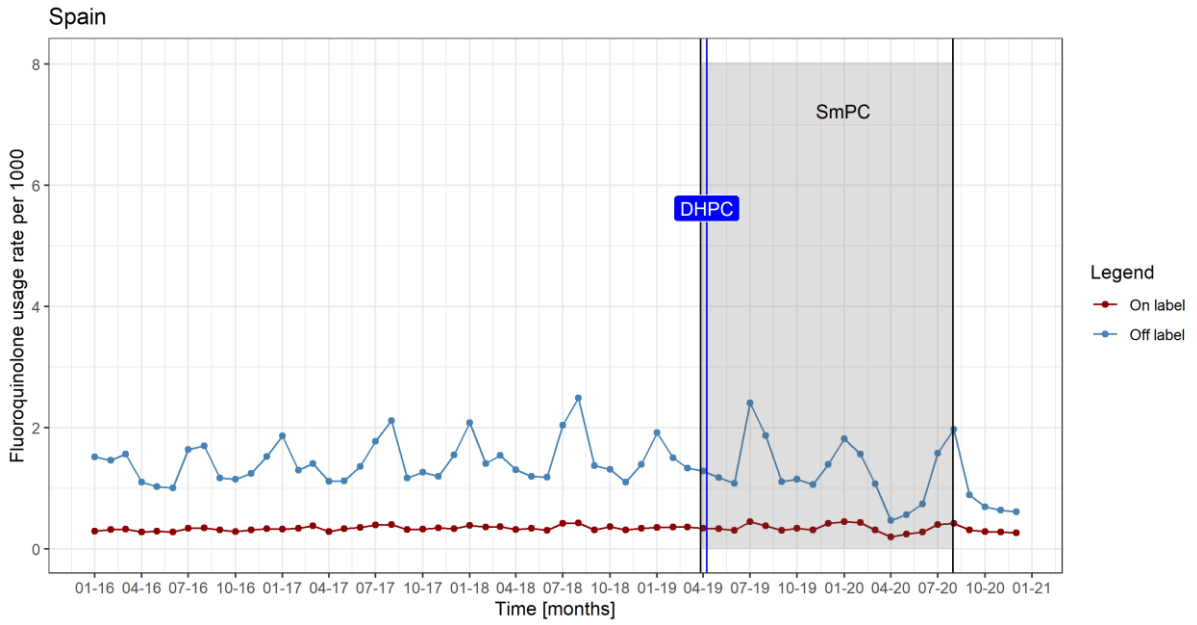

Figure 17. Incidence rate of fluoroquinolone use for Spain, stratified by on- and off-label

Legend: A patient could be counted in both on-label and off-label groups depending on the indication considered. Only known indications were classified as on-label and off-label. The grey shaded interval represents the summary of product characteristics (SmPC) implementation dates/period for the fluoroquinolone warnings (27 Mar. 2019 to 2 Jul. 2020 and 31 Jul. 2020) and the associated direct healthcare professional communications (DHPC) date (8 Apr. 2019) (vertical blue line). See Table 4 for the exact dates in each country.

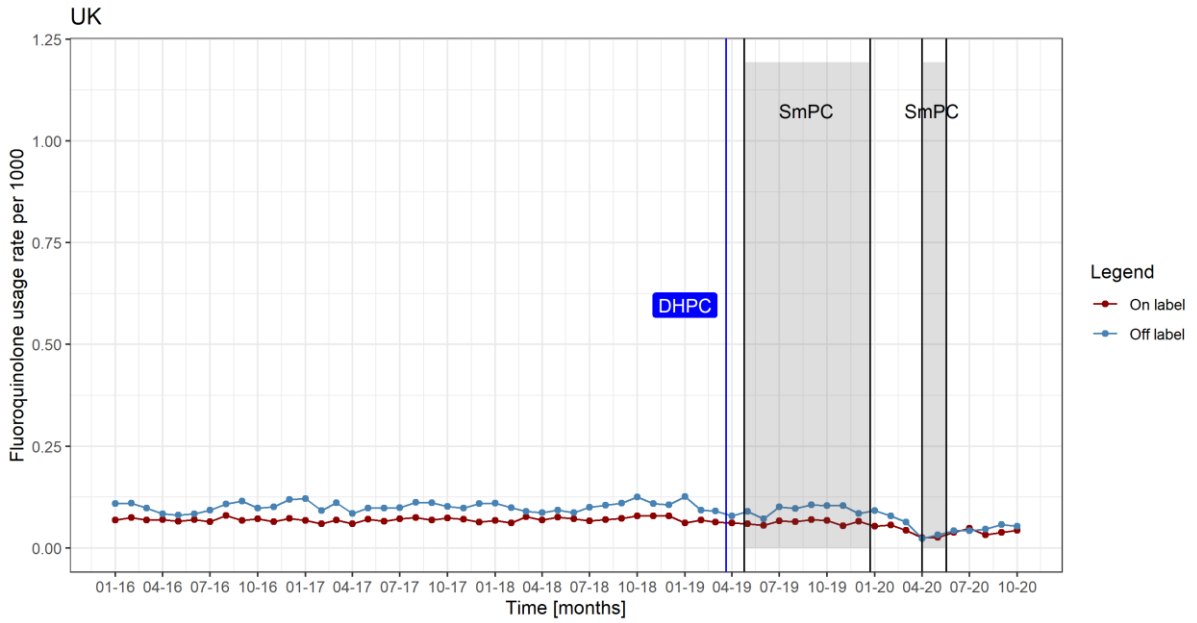

Figure 18. Incidence rate of fluoroquinolone use for the UK, stratified by on- and off-label

Legend: A patient could be counted in both on-label and off-label groups depending on the indication considered. Only known indications were classified as on-label and off-label. The grey shaded interval represents the summary of product characteristics (SmPC) implementation periods for the fluoroquinolone warnings (25 Apr. 2019 to 23 Dec. 2019 and 01 Apr. 2020 to 18 May 2020) and the associated direct healthcare professional communications (DHPC) date (21 Mar. 2019) (vertical blue line). See Table 4 for the exact dates in each country.

10.5 Early discontinuation proportion in incident fluoroquinolone users (objective 1b)

The overall monthly early discontinuation in fluoroquinolone over calendar time is presented in Figure 19 and further stratifications (by age, sex, indication, drug type, route of administration and prescriber's speciality) are shown in the Electronic Supplementary Material. The early discontinuation[8] in

[8]Early discontinuation was defined as evidence of any of the following in incident fluoroquinolone users: a generic treatment discontinuation code, code suggesting lack of effectiveness, an overlapping antibiotic prescription before the end of the current treatment episode. Note that the discontinuation will be applied to the month that the treatment episode begins in. Please refer to Section 9.4.2 for the early discontinuation definition.

fluoroquinolone users is expressed as the number of patients identified as stopping treatment early per 1,000 incident fluoroquinolone users per month.

The highest rates were in the UK (range: 80.6-123.6/1,000 persons per month), followed by the Netherlands (range: 62.7-106.5/1,000 persons per month), in Spain (range: 39.0-61.1/1000 persons per month), in Belgium (range: 27.1-56.5/1,000 persons per month), in Germany (range: 24.8 and 46.1/1,000 persons per month), and finally in France (range: 16.9-30.5/1,000 persons per month) (Figure 19). The proportion of early discontinuations seemed stable across time and countries.

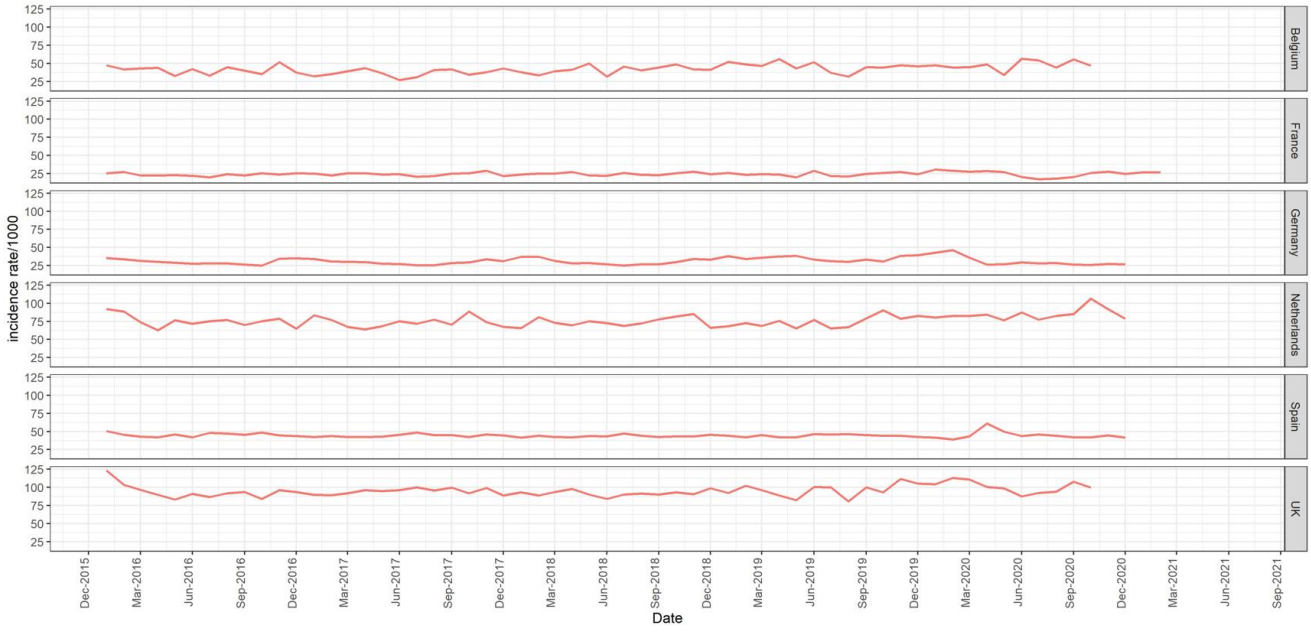

Figure 19. Early discontinuation proportion in incident fluoroquinolone users over the study period

Legend: The early discontinuation in fluoroquinolone users is expressed as the number of patients identified as stopping treatment early per 1,000 incident fluoroquinolone users per month.

10.6 A joinpoint regression analysis of Impact of regulatory interventions on fluoroquinolone prescribing patterns (objective 2)

A time series analysis using joinpoint/segmented regression was used to analyse time points of changes in trends of fluoroquinolones utilisation. The model was carried out for incidence of all fluoroquinolones and repeated for each fluoroquinolone separately and for each country since implementation dates and utilisation trends vary between the specific drugs and countries. Age-standardised rates were modelled for all fluoroquinolone usage. This analysis is presented per country.

10.6.1 Belgium

For the overall fluoroquinolones use, some seasonal patterns were observed with peak use every year in January/February and lowest levels in June/July. There was a large drop in use around February/May

2018 (MPC −33.3%, 95% CI [−35.9, −30.7]) (Table 8). After May 2018, seasonal fluctuations continued, albeit at a lower level (Figure 20). A similar pattern was seen in the analysis of age-standardised rates.

Each substance trends are presented in Figure 21.

Ciprofloxacin use was approximately constant during the first 27 months of study, followed by a drop in starting from around September 2017 until May 2018 where rates plateaued. An increase in usage was observed from May to October 2020 (MPC 5.4%, 95% CI [2.8, 8.1]). Moxifloxacin showed strong seasonal variation with peaks in January and troughs in July. A large drop in use was observed around February/June 2018 (MPC -49.4%, 95% CI [−51.9, −46.7]). Norfloxacin showed very little change over the time period, the trend indicated a slight decrease in use over the first 2 years (MPC -0.6%, 95% CI [-1.2, 0.02]), followed by a sharper drop between February 2018 and April 2018 and then an increasing trend (MPC 0.4%, 95% CI [-0.4, 1.3]) though the CIs for each linear trend were wide and encompass zero. Levofloxacin showed a decrease over the first 44 months of the study from January 2016 to August 2019 (MPC −1.1%, 95% CI [−1.4, −0.8]) followed by a gradual increase though the CI contains zero. No break points were observed for ofloxacin that would improve the fit of the model.

Table 8. Segmented regression model for all-fluoroquinolone usage crude rate - Belgium

Breakpoint Number	Breakpoint Month	MPC (%)	MPC 95% CI	
0	Jan-16	-7.3	-8.1	-6.5
1	Jul-16	6.8	5.2	8.5
2	Jan-16	-8.6	-9.6	-7.5
3	Jun-17	7.4	6.6	8.2
4	Feb-18	-33.3	-35.9	-30.7
5	May-18	4.0	3.0	5.0
6	Jan-19	-6.9	-9.5	-4.3
7	May-19	5.3	4.3	6.3
8	Jan-20	-15.7	-19.5	-11.9
9	Apr-20	9.4	7.6	11.3

CI: Confidence Interval; MPC: Monthly Percentage Change

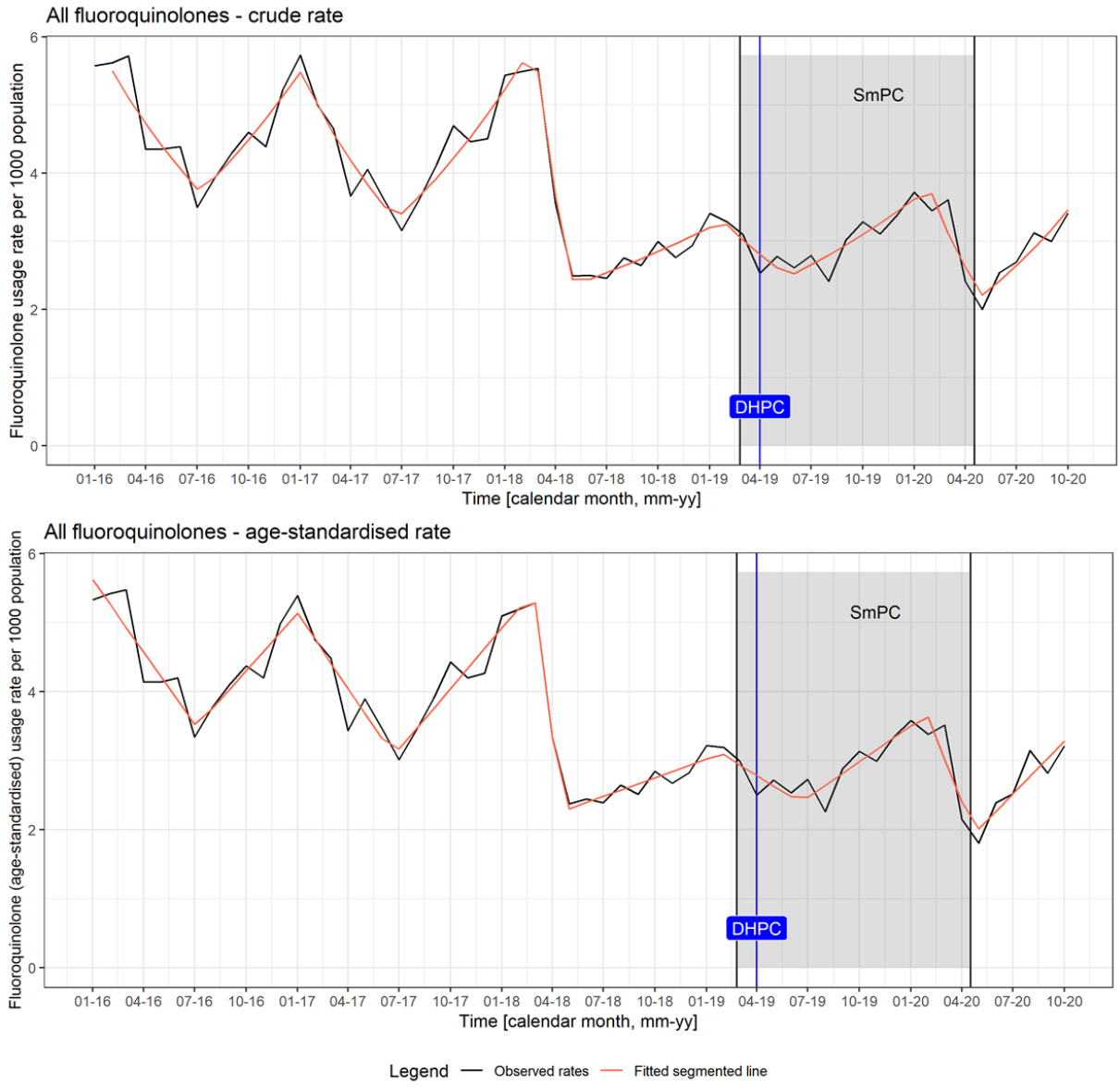

Figure 20. Incidence rate of all fluoroquinolone use with segmented regression for Belgium

Legend: The grey shaded interval represents the summary of product characteristics (SmPC) implementation period for the fluoroquinolone warnings (24 Feb. 2019 to 17 Apr. 2020) and the associated direct healthcare professional communications (DHPC) (1 Apr. 2019) (vertical blue line). The black line is the observed trend and the red line is the predicted trend. See Table 4 for the exact dates in each country.

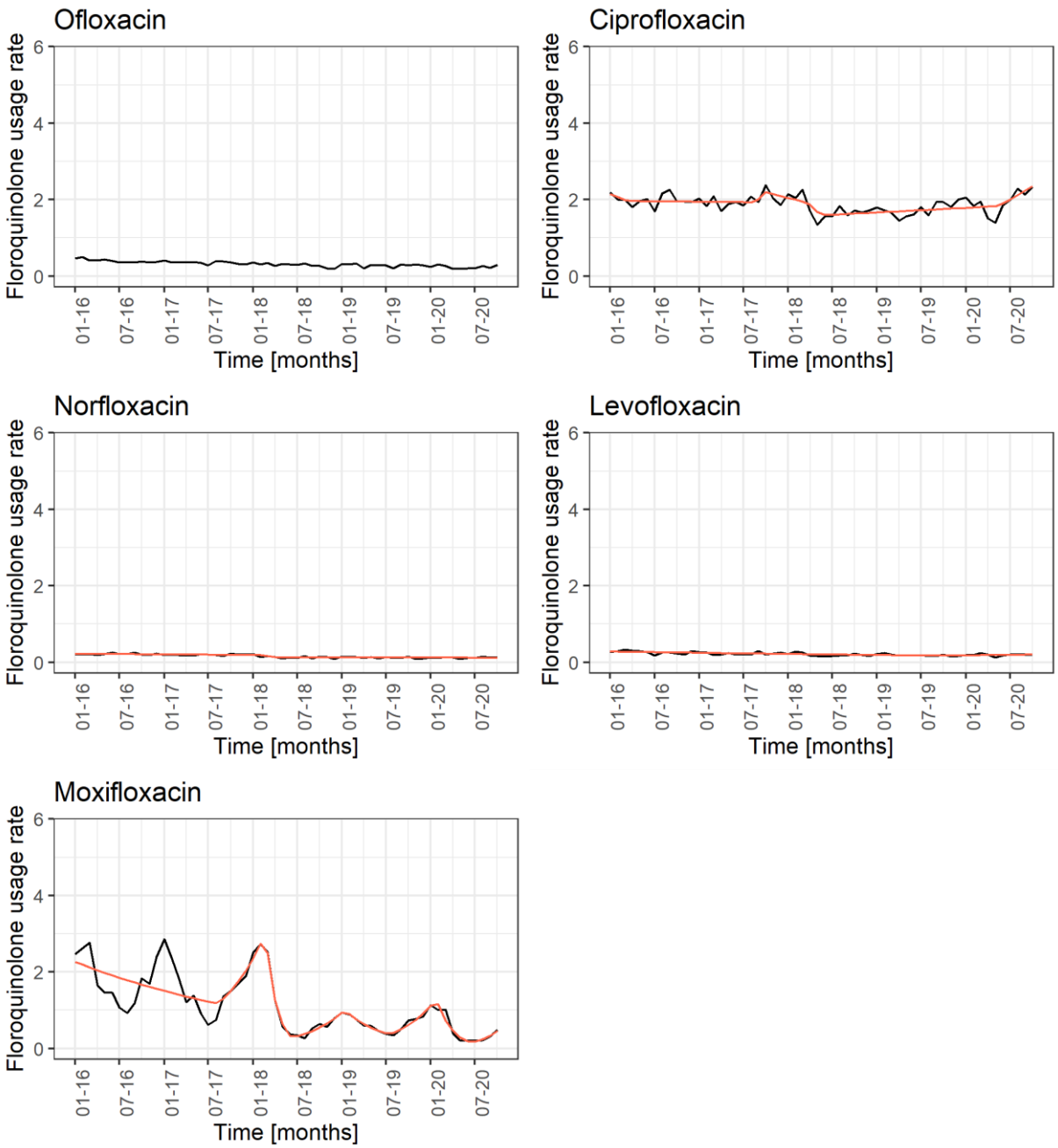

Figure 21. Incidence rate of fluoroquinolone use with segmented regression for Belgium, stratified by substance

10.6.2 France

For the overall fluoroquinolones use we see some seasonal variation in the 2016 with highs in the winter and lows in the summer. Over time we can see the peaks gradually getting lower (Table 9 and Figure 22). The analysis of the age-standardised rates using linear regression did not identify the changes seen in the analysis of the crude rates. The addition of breakpoints did not improve the model fit. The

linear regression with no breakpoints estimates a gradual reduction in age-standardised rate per 1000 population of -0.005 per month (95% CI -0.009, -0.002) over the course of the study.

Each substance trends are presented in Figure 23.

Ciprofloxacin showed some seasonal variation in the first year of the study followed by a gradual increase in usage since April 2017 (MPC 0.6%, 95% CI [0.5, 0.7]). Moxifloxacin and levofloxacin showed seasonal variations with peaks around January and troughs in July/August though the overall rates are low. Norfloxacin showed a decrease in use over time. Ofloxacin showed some small fluctuations over time but staying relatively flat. Lomefloxacin showed some broadly seasonal fluctuations (highs around September/October, lows around March/April) with an overall decrease in usage over time.

Table 9. Segmented regression model for all-fluoroquinolone usage crude rate - France

Breakpoint Number	Breakpoint Month	MPC (%)	MPC 95% CI	
0	Jan-16	-5.1	-5.5	-4.7
1	Jul-16	10.0	8.9	11.2
2	Nov-16	-5.9	-6.2	-5.5
3	Jul-17	9.5	8.3	10.7
4	Nov-17	-3.1	-3.5	-2.7
5	Jul-18	6.5	5.3	7.7
6	Nov-18	-4.0	-4.4	-3.6
7	Jul-19	7.7	7.0	8.4
8	Jan-20	-13.1	-14.9	-11.3
9	Apr-20	3.4	3.0	3.7

CI: Confidence Interval; MPC: Monthly Percentage Change

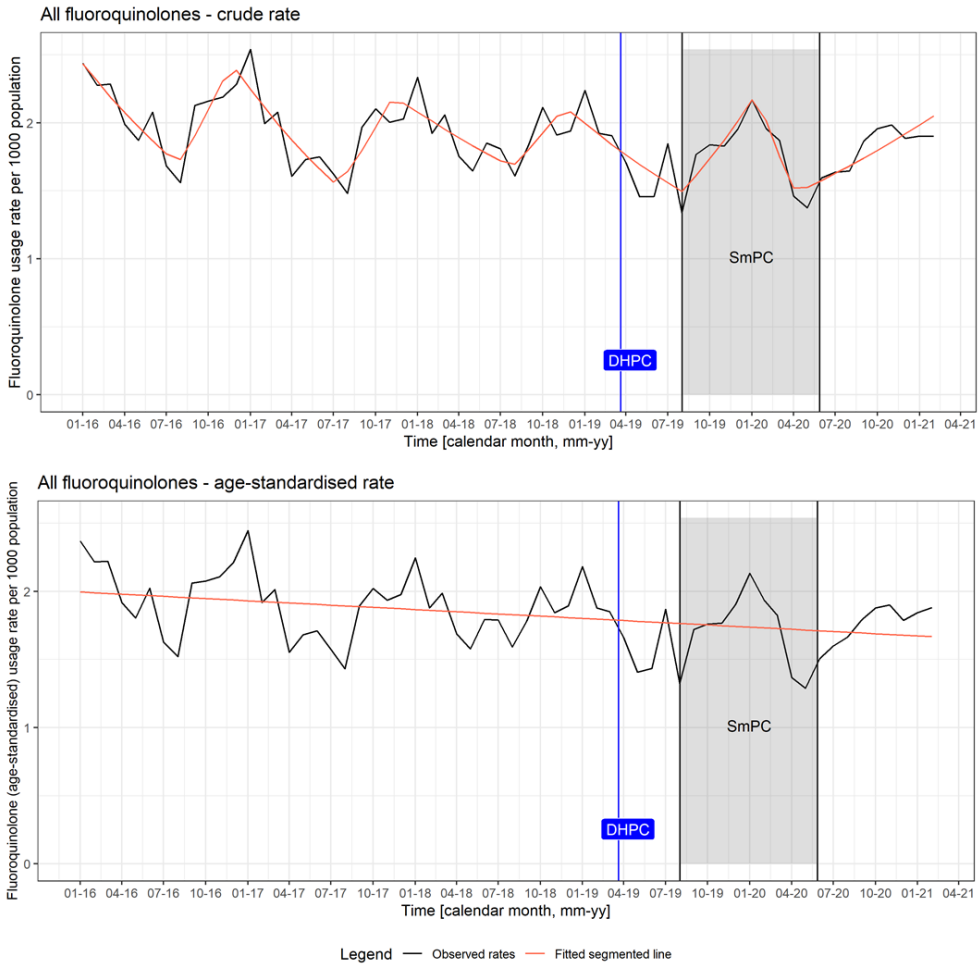

Figure 22. Incidence rate of all fluoroquinolone use with segmented regression for France

Legend: The grey shaded interval represents the summary of product characteristics (SmPC) implementation dates for the fluoroquinolone warnings (2 Aug. 2019 to 28 May 2020) and the associated direct healthcare professional communications (DHPC) date (10 Apr. 2019) (vertical blue line). Although several dates were reported for the SmPC implementations in France (see Table 4 for the exact dates), the graph shows the interval between the first and the last date. The black line is the observed trend and the red line is the predicted trend.

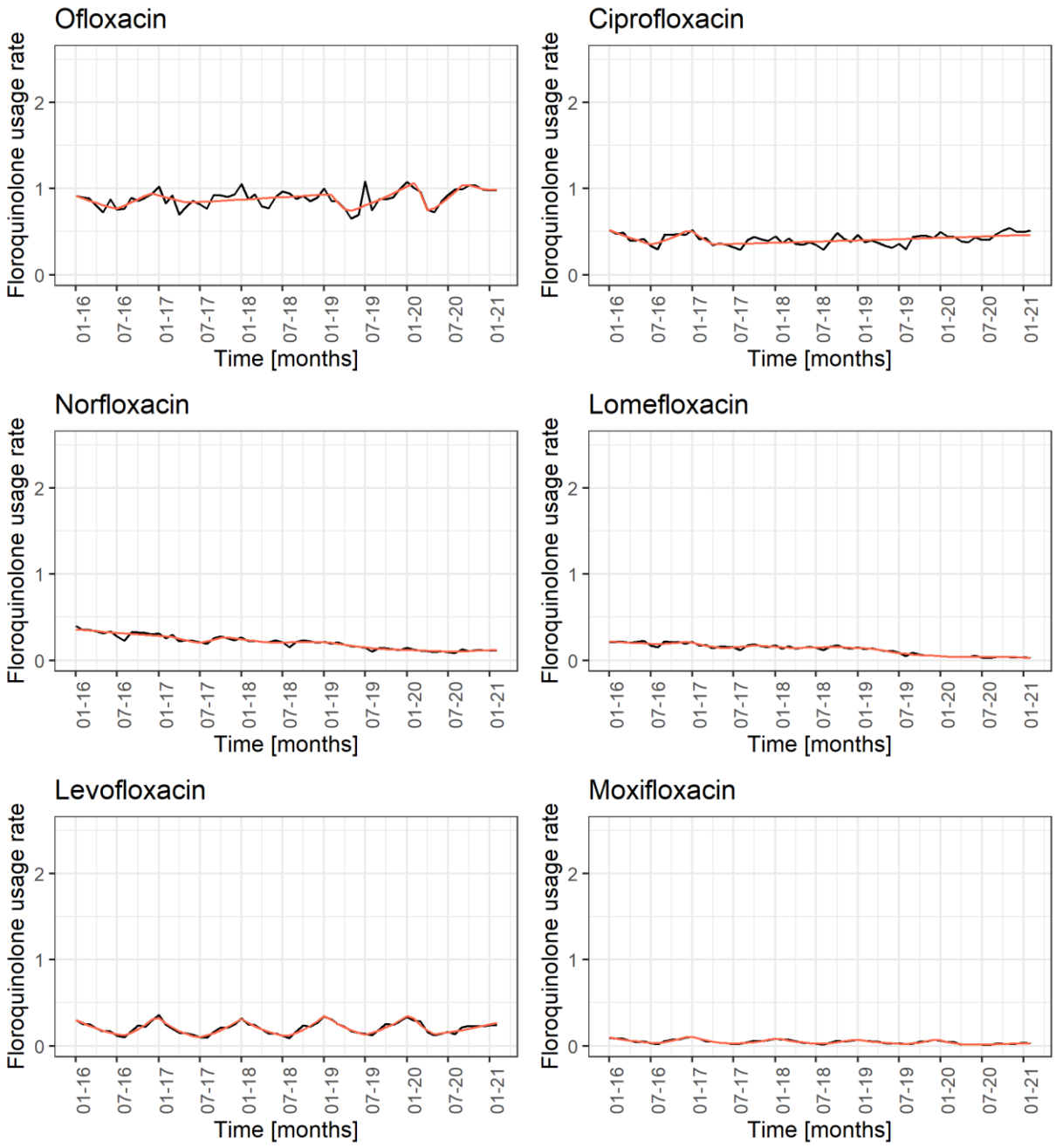

Figure 23. Incidence rate of fluoroquinolone use with segmented regression for France, stratified by substance

10.6.3 Germany

For the overall fluoroquinolones use, there is not a clear seasonal pattern though there does seem to be higher rates in winter and lower in the summer. A sharper decrease is seen from February to May 2019 (MPC −12.6%, 95% CI [-13.7, -11.6]) with variations at a lower level after this (Table 10 and Figure 24). The analysis of the age-standardised rates using linear regression does not identify these

fluctuations seen in the crude analysis. The addition of breakpoints does not improve the fit of the model.

Each substance trends are presented in Figure 25.

Ciprofloxacin usage rates changed little until February 2019 where we see a decrease until April 2019 (MPC -13.1%, 95% CI [-15.7, -10.4]). After this the rates have been increasing gradually. Rates of ofloxacin, moxifloxacin and levofloxacin use were low, but the time series analysis indicated seasonal variation. The rate of norfloxacin use was very low and fluctuated over the study period, with a gradual decrease from September 2017 to April 2019, followed by an increase again until December 2020.

Table 10. Segmented regression model for all-fluoroquinolone usage crude rate - Germany

Breakpoint Number	Breakpoint Month	MPC (%)	MPC 95% CI	
0	Jan-16	1.3	1.2	1.4
1	Feb-17	-6.0	-6.7	-5.4
2	Jun-17	4.4	3.9	4.9
3	Nov-17	-0.7	-0.8	-0.6
4	Feb-19	-12.7	-13.7	-11.6
5	May-19	4.7	4.5	5.0
6	Jan-20	-13.7	-15.8	-11.5
7	Mar-20	2.3	2.1	2.6

CI: Confidence Interval; MPC: Monthly Percentage Change

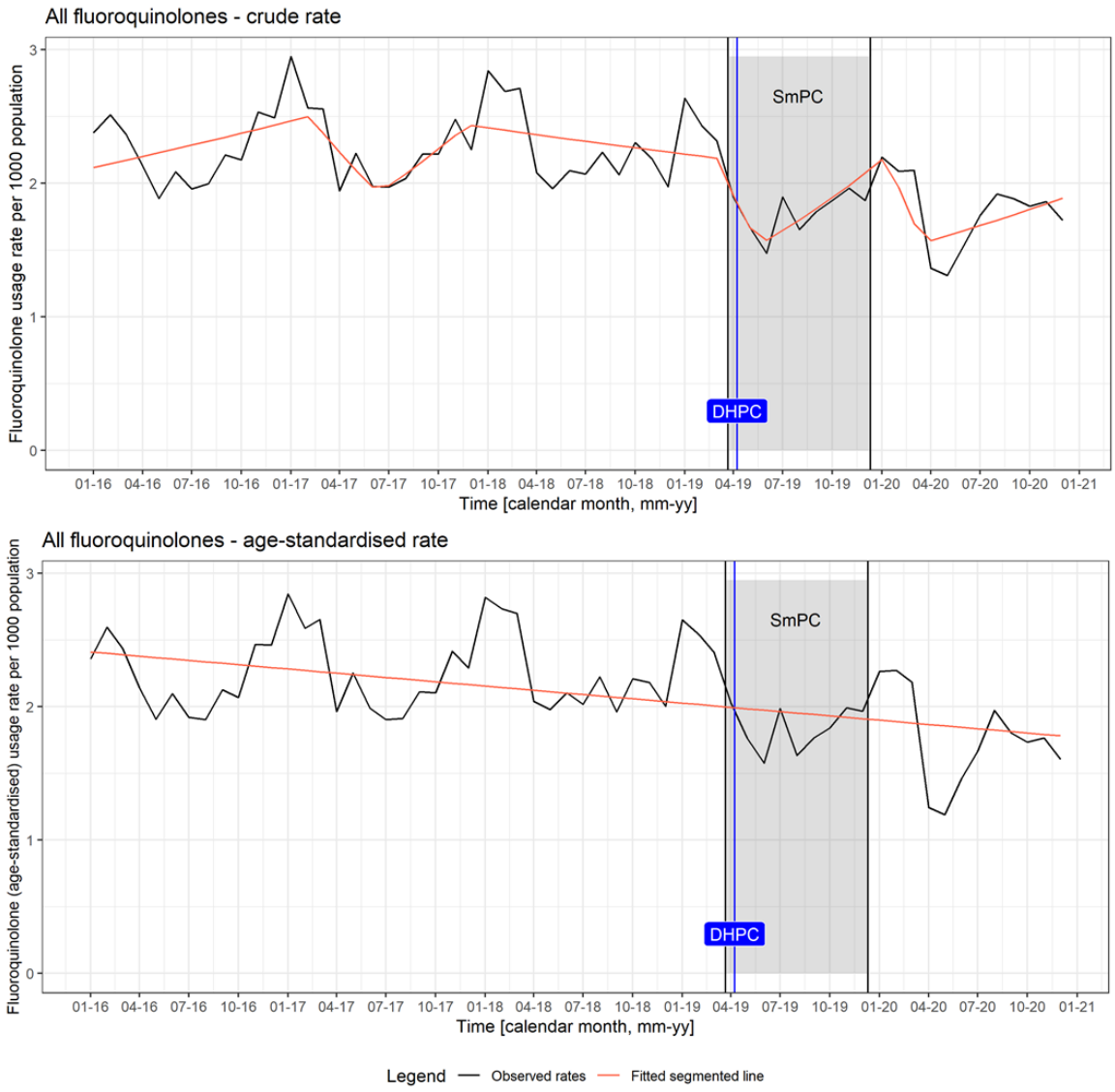

Figure 24. Incidence rate of all fluoroquinolone use with segmented regression for Germany

Legend: The grey shaded interval represents the summary of product characteristics (SmPC) implementation period for the fluoroquinolone warnings (22 Mar. 2019 to 11 Dec. 2019) and the associated direct healthcare professional communications (DHPC) date (8 Apr. 2019) (vertical blue line). The black line is the observed trend and the red line is the predicted trend. See Table 4 for the exact dates in each country.

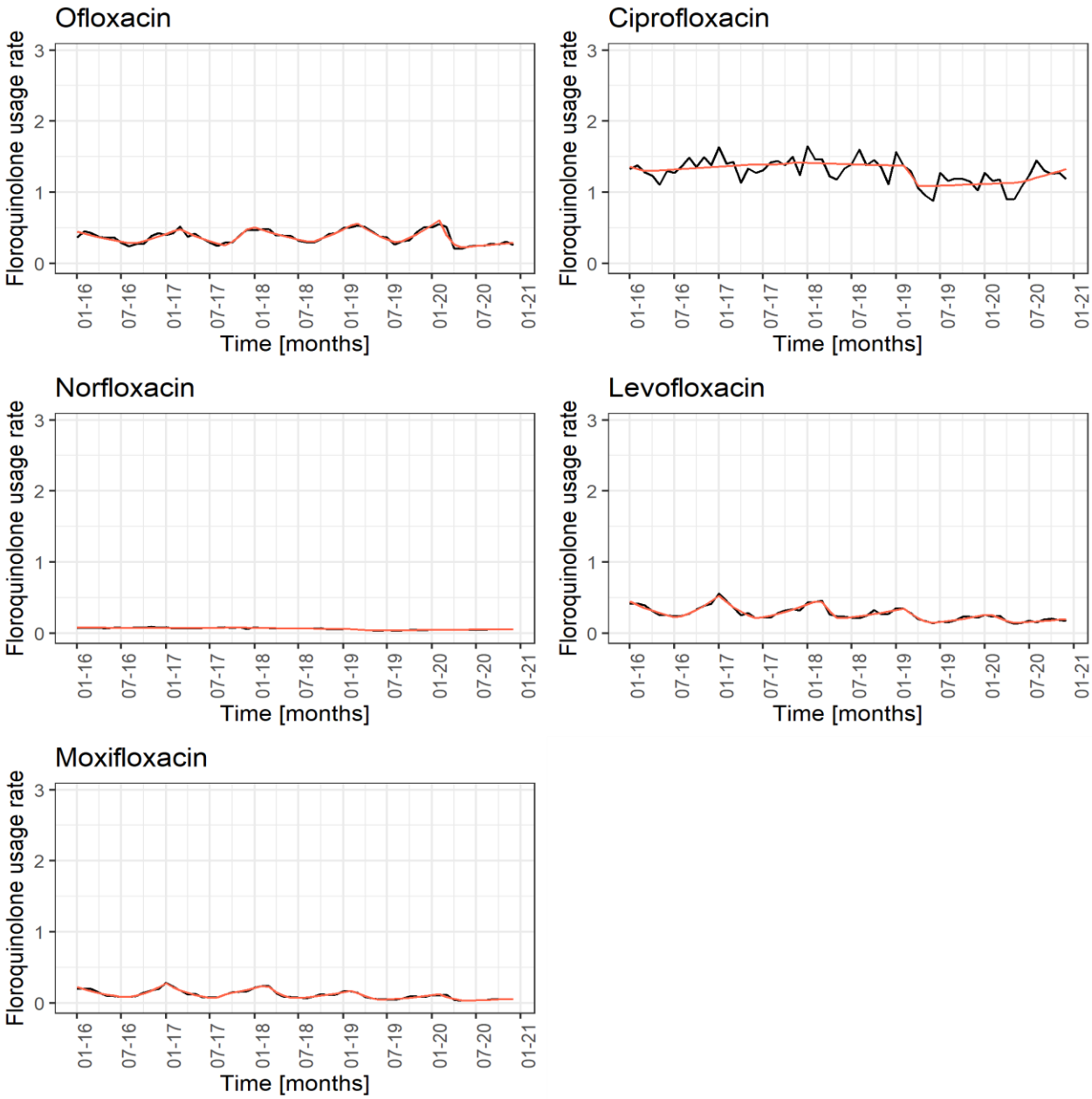

Figure 25. Incidence rate of fluoroquinolone use with segmented regression for Germany, stratified by substance

10.6.4 Netherlands

For the overall fluoroquinolones use, there was a drop in use seen around December 2019 (MPC −6.5%, 95% CI [-9.4, -3.4]), followed by an increase around April 2020 (MPC 9.3%, 95% CI [7.2,11.4]) and another decrease from August 2020 (MPC -5.0%, 95% CI [-6.7, -3.2]) (Table 11 and Figure 26). The analysis of the age-standardised rates using linear regression does not identify the last fluctuation found in the analysis of the crude rates. The addition of breakpoints does not improve the model. A linear regression indicates that age-standardised usage rates per 1000 population decrease very

slightly by -0.003 per month (95% CI -0.005, -0.0005, note this is a direct change in rates not a percentage change).

Each substance trends are presented in Figure 27.

Ciprofloxacin use showed a slight increase from January 2016 to around August 2018 (MPC 0.2%, 95% CI [-0.1, 0.3]) followed by a slight reduction to January 2020 (MPC -0.7%, 95% CI [-0.9, -0.4]). There was a sharper decrease between January to March 2020 with the confidence interval spanning zero we cannot be certain that this is a true decrease in rates (MPC -5.8%, 95% CI [-12.8, 1.7]). Moxifloxacin had very small use and some seasonal fluctuations with peak use around December and lowest use in July/August. Norfloxacin and levofloxacin had very small use and also little variation over time. Ofloxacin showed an increase from around May 2020 (MPC 24.8%, 95%CI [18.3, 31.7]), to a peak in August 2020 followed by a decrease after this time.

Table 11. Segmented regression model for all-fluoroquinolone usage crude rate - Netherlands

Breakpoint Number	Breakpoint Month	MPC (%)	MPC 95% CI	
0	Jan-16	-0.05	-0.10	-0.01
1	Dec-19	-6.5	-9.4	-3.4
2	Apr-20	9.3	7.2	11.4
3	Aug-20	-5.0	-6.7	-3.2

CI: Confidence Interval; MPC: Monthly Percentage Change

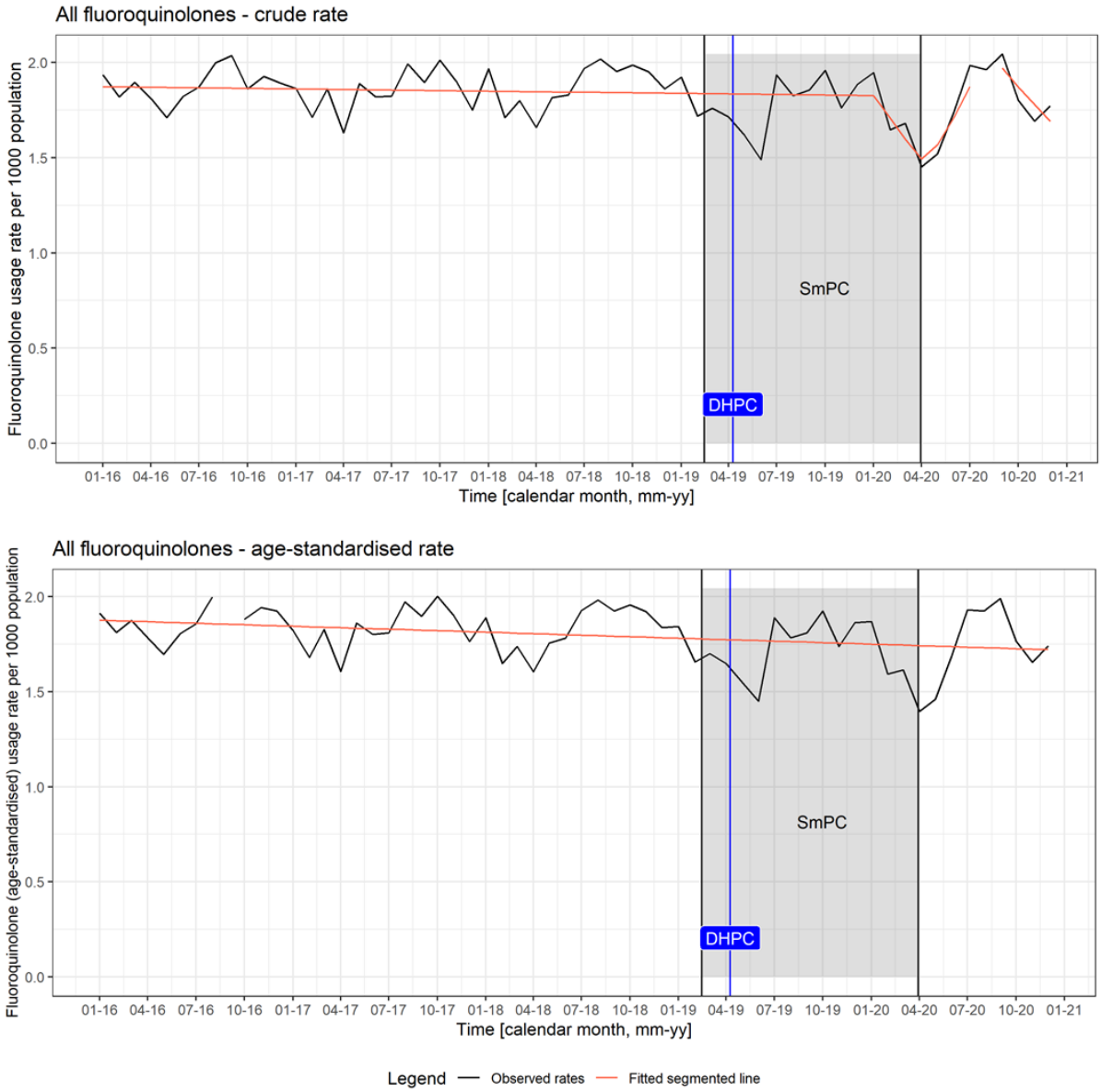

Figure 26. Incidence rate of all fluoroquinolone use with segmented regression for the Netherlands

Legend: The grey shaded interval represents the summary of product characteristics (SmPC) implementation period (14 Feb. 2019 to 30 Mar. 2020) for the fluoroquinolone warnings and the associated direct healthcare professional communications (DHPC) date (9 Apr. 2019) (vertical blue line). The black line is the observed trend and the red line is the predicted trend. See Table 4 for the exact dates in each country.

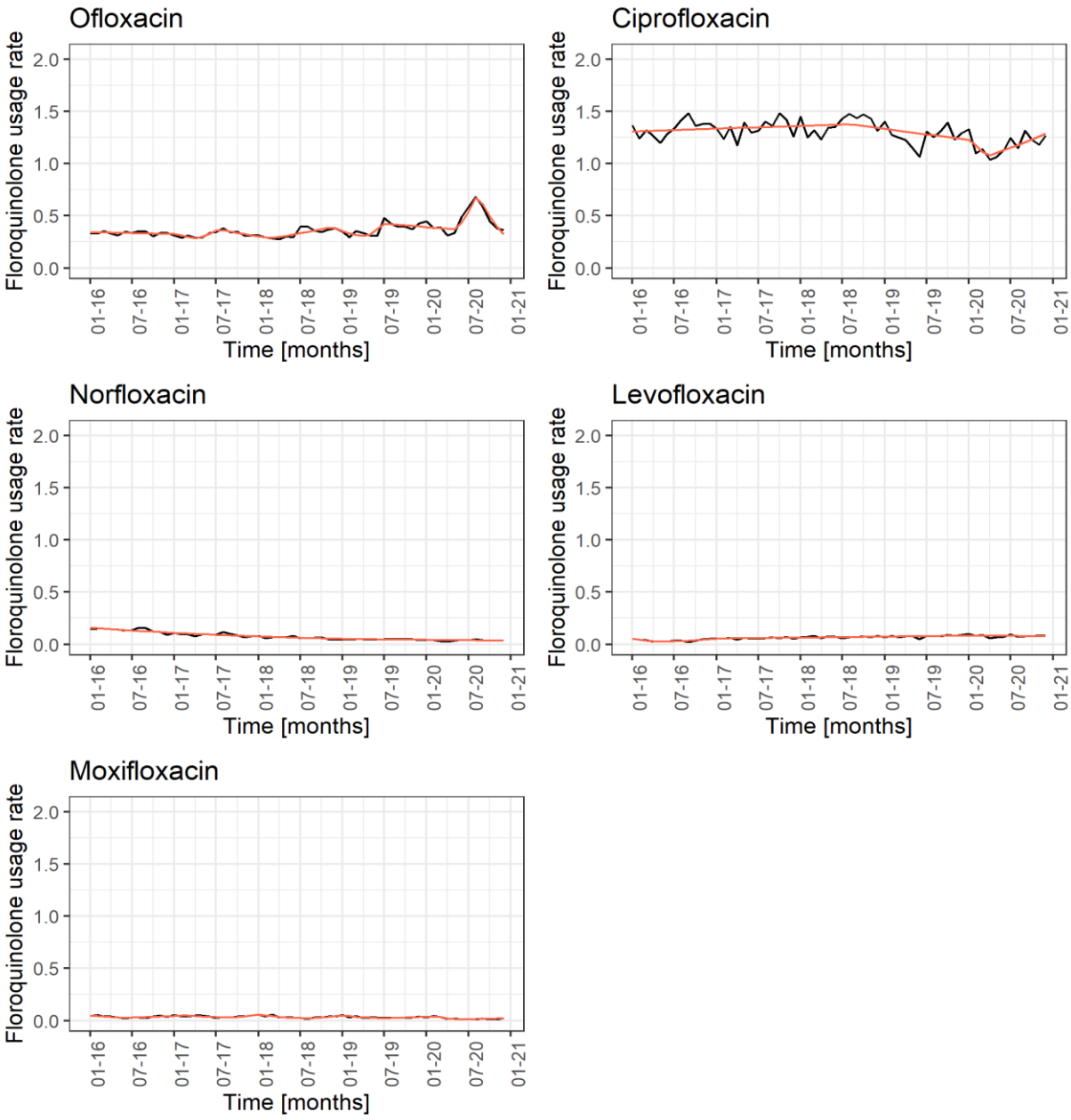

Figure 27. Incidence rate of fluoroquinolone use with segmented regression for the Netherlands, stratified by substance

10.6.5 Spain

For the overall fluoroquinolones use, after an initial drop in usage in the first three months of 2016 there is a gradual increase over the first 20 months (MPC 0.4%, 95% CI [0.4, 0.5]) followed by a gradual drop from around December 2017 to June 2019 (MPC -0.7%, 95% CI [-0.7, -0.6]) and a steeper decrease thereafter (MPC -2.3%, 95% CI [-2.3, -2.2]) (Table 12 and Figure 28). The linear regression of the age-standardised rates shows a similar pattern with no substantial change in usage over the first three years

of the study followed by a decline from around December 2018 to December 2020 (MPC -9.4%, 95% CI [-13.0, -5.6]).

Each substance trends are presented in Figure 29.

Although ciprofloxacin seemed to show seasonal variations, the pattern was similar to the overall pattern described with little change over the first few years of the study and some fluctuations in 2020. Ofloxacin use rates were very low with small increases and decreases over time. Levofloxacin showed seasonal variations with peaks in December/January and troughs in July/August. Norfloxacin was prescribed at low levels, some seasonal fluctuations were seen with a general decrease in usage overall. Moxifloxacin rates were also very low and generally decreasing over the study period.

Table 12. Segmented regression model for all-fluoroquinolone usage crude rate - Spain

Breakpoint Number	Breakpoint Month	MPC (%)	MPC 95% CI	
0	Jan-16	-4.4	-4.8	-3.9
1	May-16	0.4	0.4	0.5
2	Dec-17	-0.7	-0.7	-0.6
3	Jun-19	-2.3	-2.3	-2.2

CI: Confidence Interval; MPC: Monthly Percentage Change

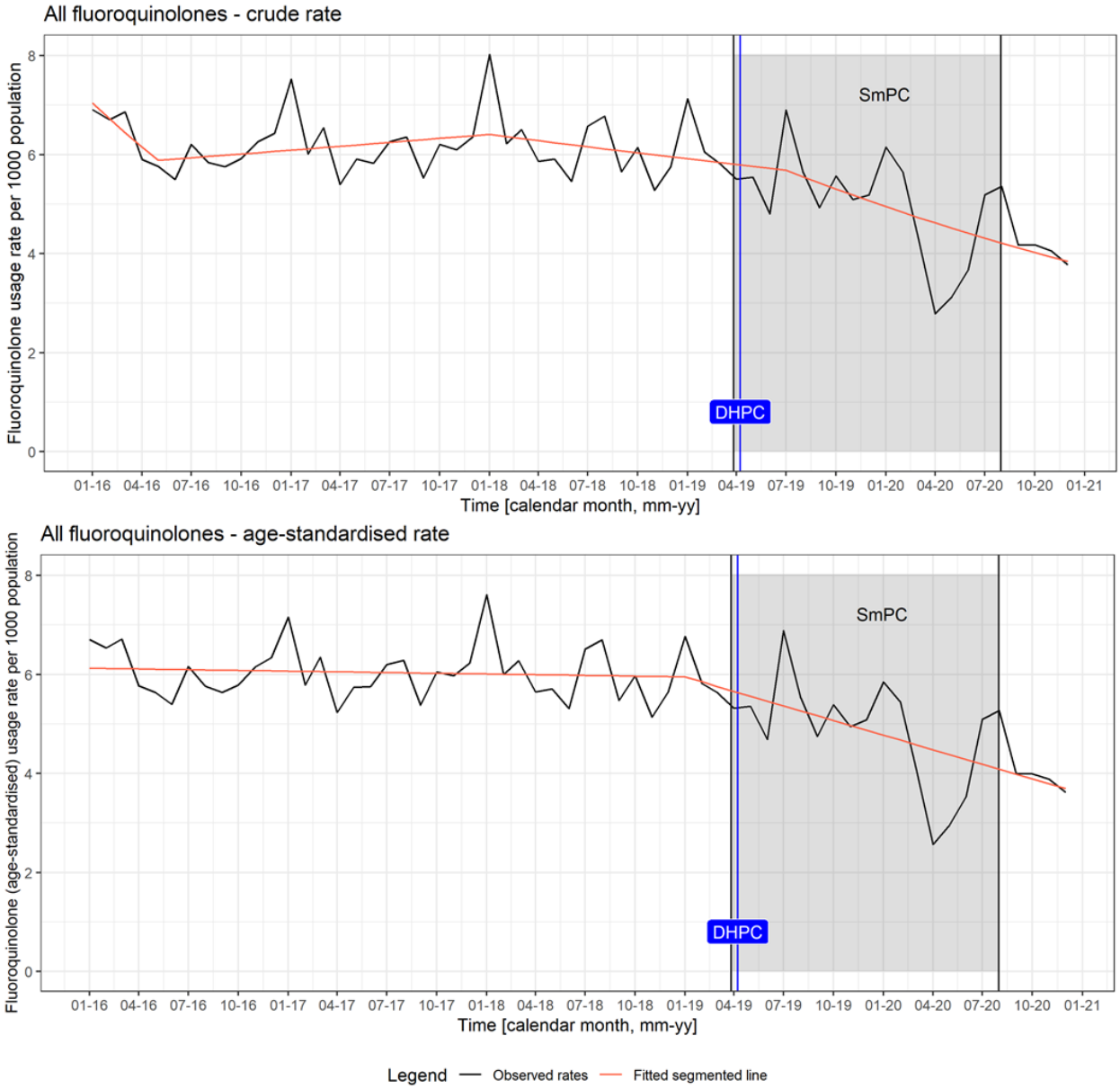

Figure 28. Incidence rate of all fluoroquinolone use with segmented regression for Spain

Legend: The grey shaded interval represents the summary of product characteristics (SmPC) implementation dates/period for the fluoroquinolone warnings (27 Mar. 2019 to 2 Jul. 2020 and 31 Jul. 2020) and the associated direct healthcare professional communications (DHPC) date (8 Apr. 2019) (vertical blue line). The black line is the observed trend and the red line is the predicted trend. See Table 4 for the exact dates in each country.

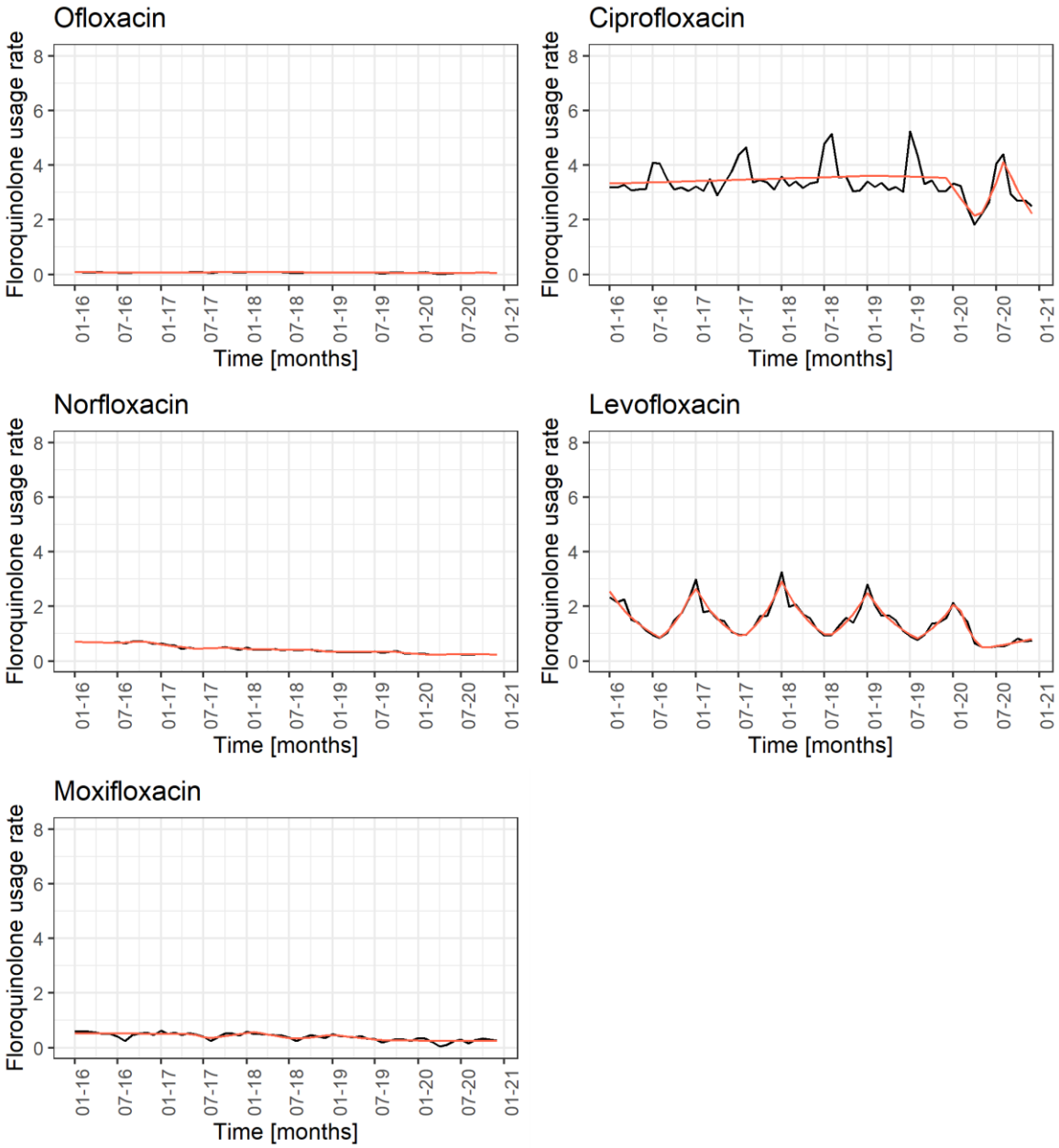

Figure 29. Incidence rate of all fluoroquinolone use with segmented regression for Spain, stratified by substance

10.6.6 UK

For the overall fluoroquinolones use, there was a drop in the first 3.5 months of the study, (MPC -4.9%, 95% CI [-6.2, -3.6]) (Table 13). Over the next 3 years the rates stay around the same level but with some fluctuations, peaks occurring around the winter. From November 2018 there is a general reduction in usage. Some seasonality is indicated in the Poisson based model (Figure 30). The linear regression of the age-standardised rates does not identify the seasonal fluctuations seen in the crude analysis, however the general trend is the same with relatively stable usage until the end of 2018 when it then reduces.

Each substance trends are presented in Figure 31.

Very similar patterns were seen for ciprofloxacin which are also aligned with the overall use pattern. Rates are approximately the same with small fluctuations over the first few years of the study. From November 2018 we see a general decrease in usage with fluctuations, lows around April/May and highs around October/November.

The rates of ofloxacin and levofloxacin were much lower. Ofloxacin has been decreasing throughout the time period (MPC -0.3%, 95% CI [-0.4, -0.1] Jan 2016 to Nov 2019, -3.5% [-4.8, -2.1] from Nov 2019). Levofloxacin saw a very gradual increase over the first 3 years (MPC 1.0%, 95% CI [0.7, 1.3]) followed by a gradual decrease to the end of the study (MPC -1.4%, 95% CI [-2.1, -0.7]) however the regression indicated a similar pattern over time as seen for ciprofloxacin; an initial drop at first, followed by a plateauing or slight increase in use and then a decrease from around January 2019.

No lomefloxacin use and very limited use for norfloxacin or moxifloxacin precluded the analysis for these substances, this is expected as per clinical practice.

Table 13. Segmented regression model for all-fluoroquinolone usage crude rate - UK

Breakpoint Number	Breakpoint Month	MPC (%)	MPC 95% CI	
0	Jan-16	-4.9	-6.2	-3.6
1	Apr-16	1.4	0.8	2.0
2	Nov-16	-3.4	-7.6	0.9
3	Jan-17	0.4	0.1	0.7
4	Dec-17	-1.4	-2.8	0.1
5	Apr-18	1.4	0.8	2.1
6	Nov-18	-5.4	-6.4	-4.3
7	Apr-19	1.5	0.6	2.4
8	Oct-19	-4.1	-4.9	-3.4
9	May-20	2.3	1.0	3.8

CI: Confidence Interval; MPC: Monthly Percentage Change

Figure 30. Incidence rate of all fluoroquinolone use with segmented regression for UK

Legend: The grey shaded interval represents the summary of product characteristics (SmPC) implementation periods for the fluoroquinolone warnings (25 Apr. 2019 to 23 Dec. 2019 and 01 Apr. 2020 to 18 May 2020) and the associated direct healthcare professional communications (DHPC) date (21 Mar. 2019) (vertical blue line). The black line is the observed trend and the red line is the predicted trend. See Table 4 for the exact dates in each country.

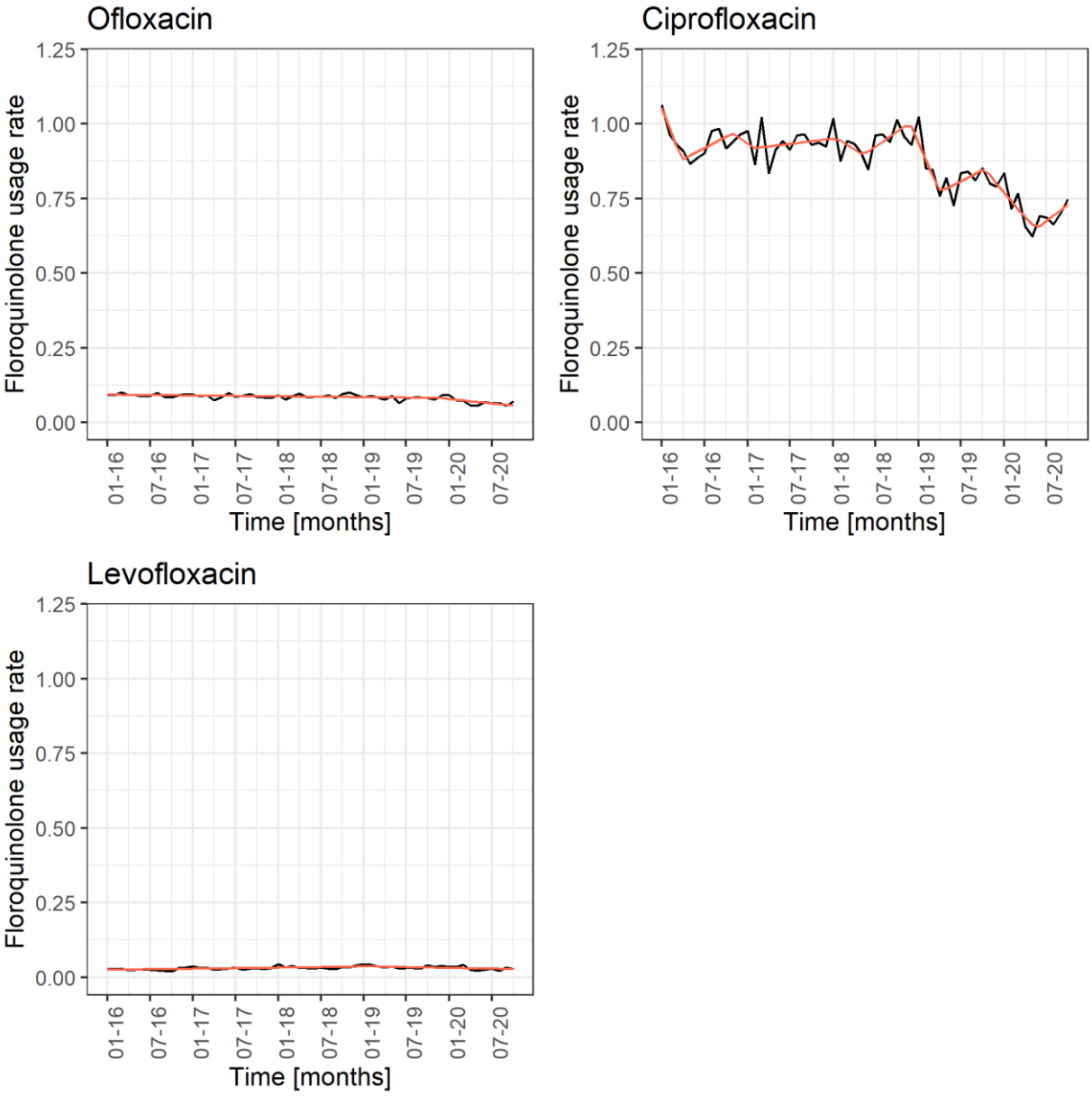

Figure 31. Incidence rate of fluoroquinolone use with segmented regression for UK, stratified by substance

10.7 Prescribers' compliance with warnings in fluoroquinolones SmPC Section 4.4

10.7.1 Monthly incident fluoroquinolones prescription rates in the risk group for tendinitis and tendon rupture

The monthly incidence of fluoroquinolone prescription rates in patients at risk of tendinitis and tendon rupture[9] over calendar time and by line of treatment are presented in Figure 32 and Figure 33, respectively, and further stratifications (by age, sex, indication, drug type and duration) are shown in the Electronic Supplementary Material. The monthly incidence is expressed as the number of new users of fluoroquinolones being at risk of tendinitis and tendon rupture/1,000 persons per month. The denominator consists of the monthly total active population.

The monthly incidence of prescribing fluroquinolones in the patients at risk of tendinitis and tendon rupture was very low in all countries, ranging from 0.5/1,000 persons per month in the UK to 5.0/1,000 persons per month in Spain.

Over the study period, the monthly incidence rates of fluoroquinolones in the at-risk group of tendinitis and tendon rupture were reported (from the highest to the lowest):

- 1.7 to 5.0/1,000 persons per month in Spain
- 1.1 to 2.8/1,000 persons per month in Belgium
- 0.5 to 1.1/1,000 persons per month in France
- 0.6 and 1.5/1,000 per persons per month in Germany
- 0.9 to 1.3/1,000 persons per month in the Netherlands
- 0.5 and 0.9/1,000 persons per month in the UK.

France, Germany, the Netherlands and the UK had low incidence rates of fluoroquinolones in the at-risk group of tendinitis. Seasonal variations were observed in Spain with lower levels towards the end of the study period.

[9]Risk factors for tendinitis and tendon rupture: advanced age (>60 years), a medical history of renal impairment, solid organ transplantation or prior tendon rupture or tendinitis, or tobacco user. This group is not mutually exclusive, i.e., patients can contribute to multiple risk groups.

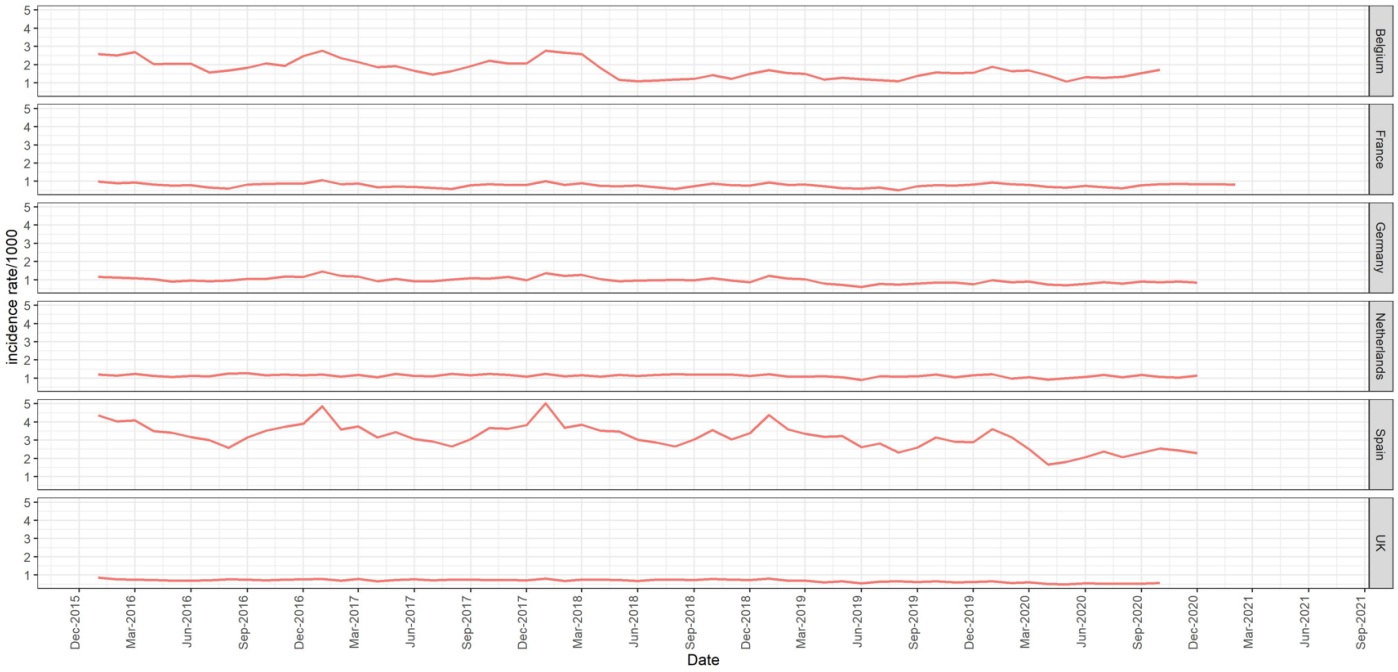

Figure 32. Monthly incident fluoroquinolones prescription rates in the risk group for tendinitis and tendon rupture

Legend: The incidence rate is expressed as the number of new users of fluoroquinolones/1,000 persons per month

As shown in Figure 33, when stratified by line of treatment, the overall incidence of fluoroquinolone prescription rates in patients at risk of tendinitis and tendon rupture were higher in the first line of treatment (1st line), with rates ranged (from the highest to the lowest):

- 1.6 to 4.8/1,000 persons per month in Spain
- 1.0 to 2.7/1,000 persons per month in Belgium
- 0.6 to 1.4/1,000 persons per month in Germany
- 0.8 to 1.2/1,000 persons per month in the Netherlands
- 0.5 to 1.0/1,000 persons per month in France
- 0.4 to 0.8/1,000 persons per month in the UK.

The second (2nd line) and third line (3rd+ line) of treatment remained low or non-existent in all countries.

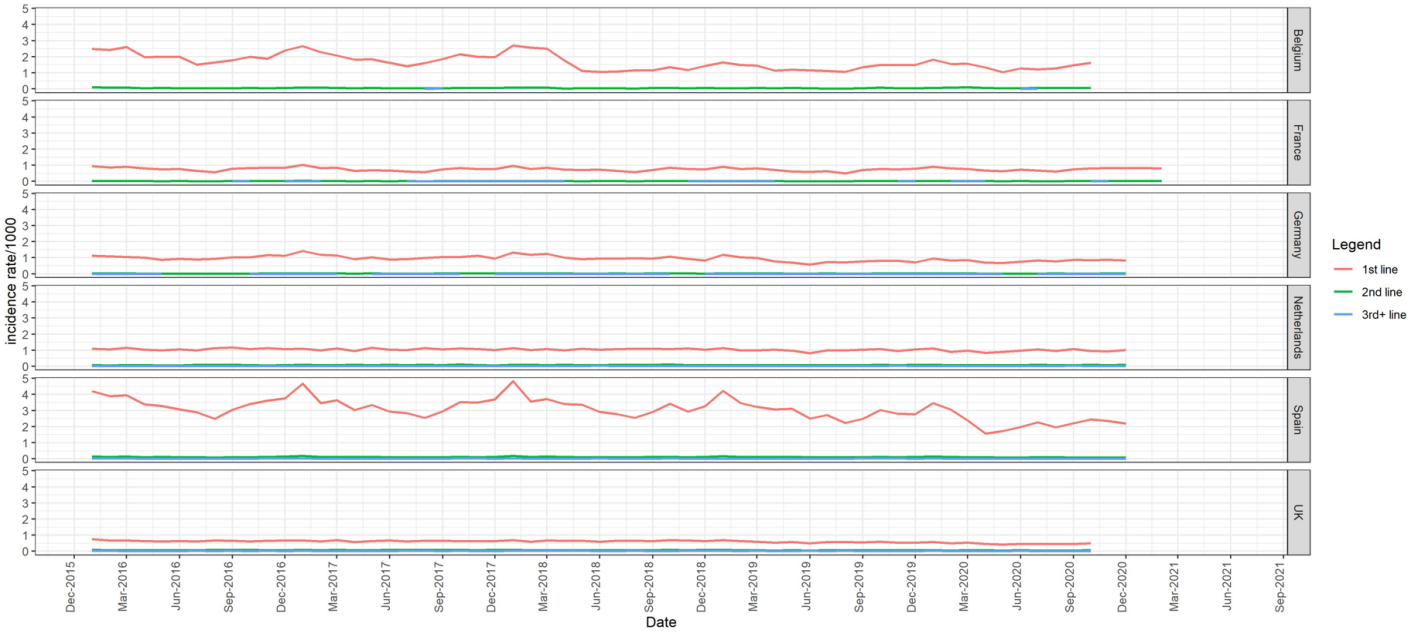

Figure 33. Monthly incident fluoroquinolones prescription rates in the risk group for tendinitis and tendon rupture by line of treatment

Legend: The incidence rate is expressed as the number of new users of fluoroquinolones/1,000 persons per month

10.7.2 Monthly incident fluoroquinolones prescription rates in the risk group for aortic dissection and aneurysm

The monthly incidence of fluoroquinolone prescription rates in patients at-risk of aortic dissection and aneurysm[10] over calendar time and by line of treatment are presented in Figure 34 and Figure 35, respectively, and further stratifications (by age, sex, indication, drug type, and duration) are shown in the Electronic Supplementary Material. The monthly incidence is expressed as the number of new users of fluoroquinolones being at risk of aortic dissection and aneurysm/1,000 persons per month. The denominator consists of the total active patient population.

The incidence rates of prescribing in the patients at risk of aortic dissection and aneurysm were very low in all countries, ranging from 0.5/1,000 persons per month in the UK to 5.6/1,000 persons per month in Spain.

[10] Risk factors for aortic dissection and aneurysm: advanced age (>60 years), a medical history of any other vascular aneurysms, hypertension, lipid disorder, cardiac or renal transplant, genetic conditions (Marfan's syndrome, vascular Ehlers-Danlos syndrome, Loeys-Dietz syndrome, Turner's syndrome), cardiovascular syphilis, traumatic motor vehicle accident, aortic valve disorder, COPD, ischaemic heart disease or cerebrovascular disease or being a tobacco user.

Over the study period, the monthly incidence rates of fluoroquinolones in the at-risk group of aortic dissection and aneurysm were reported (from the highest to the lowest):

- 1.9 to 5.6/1,000 persons per month in Spain
- 1.4 to 3.8/1,000 persons per month in Belgium
- 0.8 to 1.9/1,000 persons per month in Germany
- 0.9 to 1.4/1,000 persons per month in the Netherlands
- 0.6 to 1.2/1,000 persons per month in France
- 0.5 and 0.9/1,000 persons per month in the UK.

Similarly, France, Germany, the Netherlands and the UK had low incidence rates of fluoroquinolones in the at-risk group of aortic dissection and aneurysm. Seasonal variations were observed in Spain with lower levels towards the end of the study period.

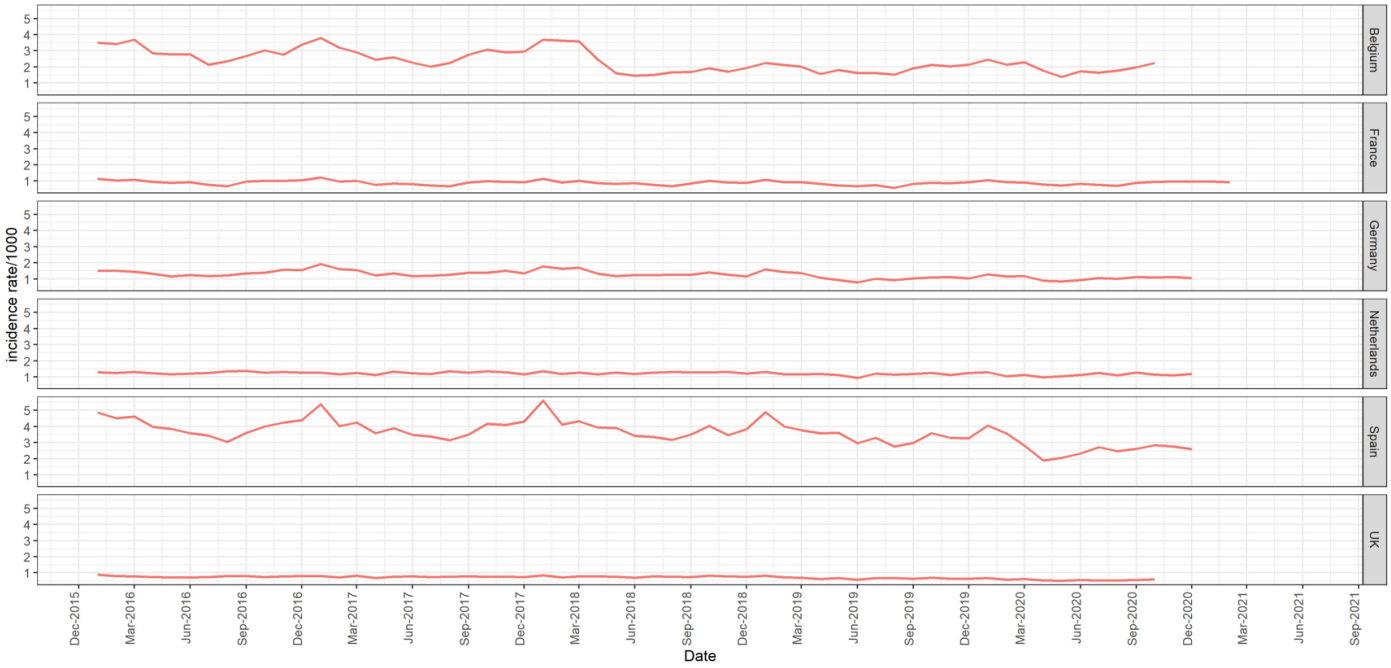

Figure 34. Monthly incident fluoroquinolones prescription rates in the risk group for aortic dissection and aneurysm

Legend: The incidence rate is expressed as the number of new users of fluoroquinolones/1,000 persons per month

As shown in Figure 35, when stratified by line of treatment, the overall incidence of fluoroquinolone prescription rates in patients at risk of aortic dissection and aneurysm were higher in the first line of treatment (1st line) with rates ranged (from the highest to the lowest):

- 1.8 to 5.4/1,000 persons per month in Spain
- 1.3 to 3.6/1,000 persons per month in Belgium

- 0.8 to 1.9/1,000 persons per month in Germany
- 0.6 to 1.2/1,000 persons per month in France
- 0.9 to 1.3/1,000 persons per month in the Netherlands
- 0.4 to 0.8/1,000 persons per month in the UK.

The second (2nd line) or third line (3rd+ line) of treatment remained low or non-existent in all countries.

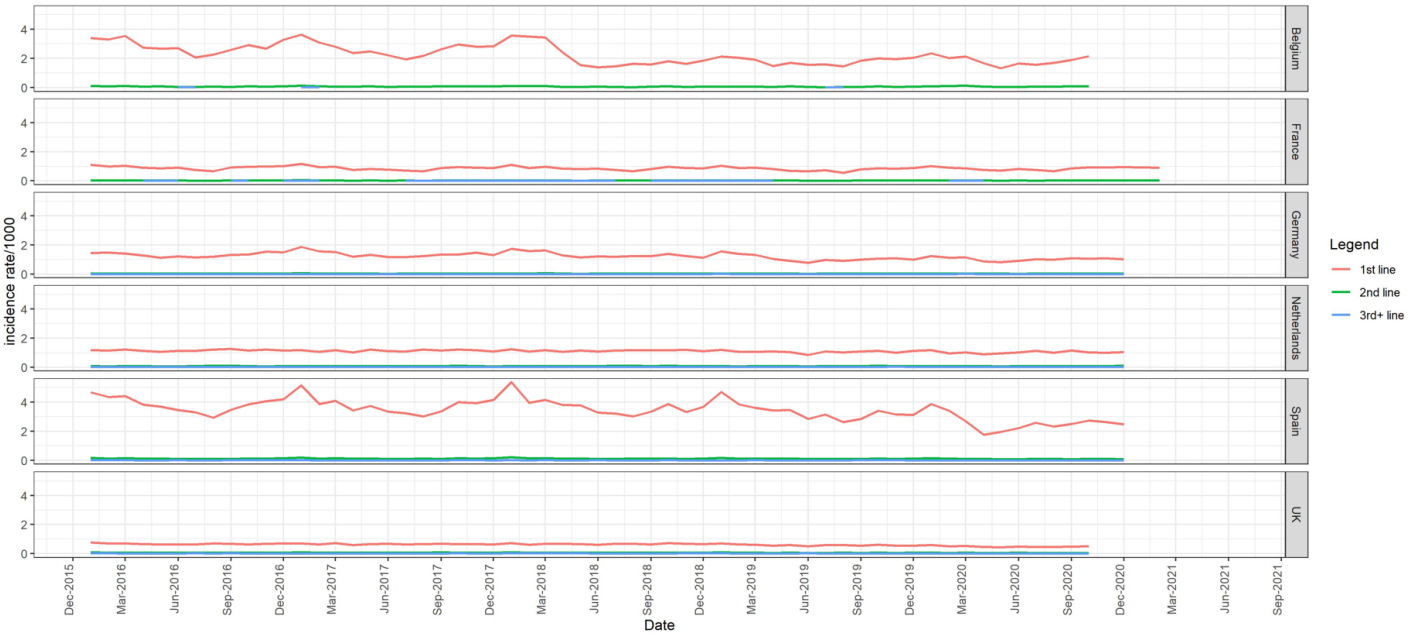

Figure 35. Monthly incident fluoroquinolones prescription rates in the risk group for aortic dissection and aneurysm by line of treatment

Legend: The incidence rate is expressed as the number of new users of fluoroquinolones/1,000 persons per month

10.7.3 Monthly incident fluoroquinolones prescription rates in patients with recent (30 days prior) or concomitant prescribing of systemic corticosteroids

The monthly incidence of fluoroquinolone prescription rates in patients with recent (30 days prior) or concomitant prescriptions of systemic corticosteroids over calendar time is presented in Figure 36, and further stratifications (by age, sex, indication, drug type, line of treatment and duration) are shown in the Electronic Supplementary Material. The monthly incidence is expressed as the number of new users of fluoroquinolones with recent or concomitant prescriptions of systemic corticosteroids/1,000 persons per month. The denominator consists of the total active patient population.

The incidence rates of monthly prescribing in patients with recent (30 days prior) or concomitant prescriptions of systemic corticosteroids remained low or non-existent in all countries, ranging from 0.03/1,000 persons in the UK to 0.5/1,000 persons in Spain.

Over the study period, the monthly incidence rates of fluoroquinolones prescribed in patients with recent (30 days prior) or concomitant prescriptions of systemic corticosteroids were reported (from the highest to the lowest):

- 0.1 to 0.5/1,000 persons per month in Spain
- 0.1 to 0.5/1,000 persons per month in France
- 0.04 to 0.4/1,000 persons per month in Belgium
- 0.1 to 0.2/1,000 persons per month in the Netherlands
- 0.03 and 0.1/1,000 persons per month in Germany
- 0.04 and 0.1/1,000 persons per month in the UK.

Seasonal variations were observed in Belgium, France and Spain with lower levels in Belgium and Spain towards the end of the study period.

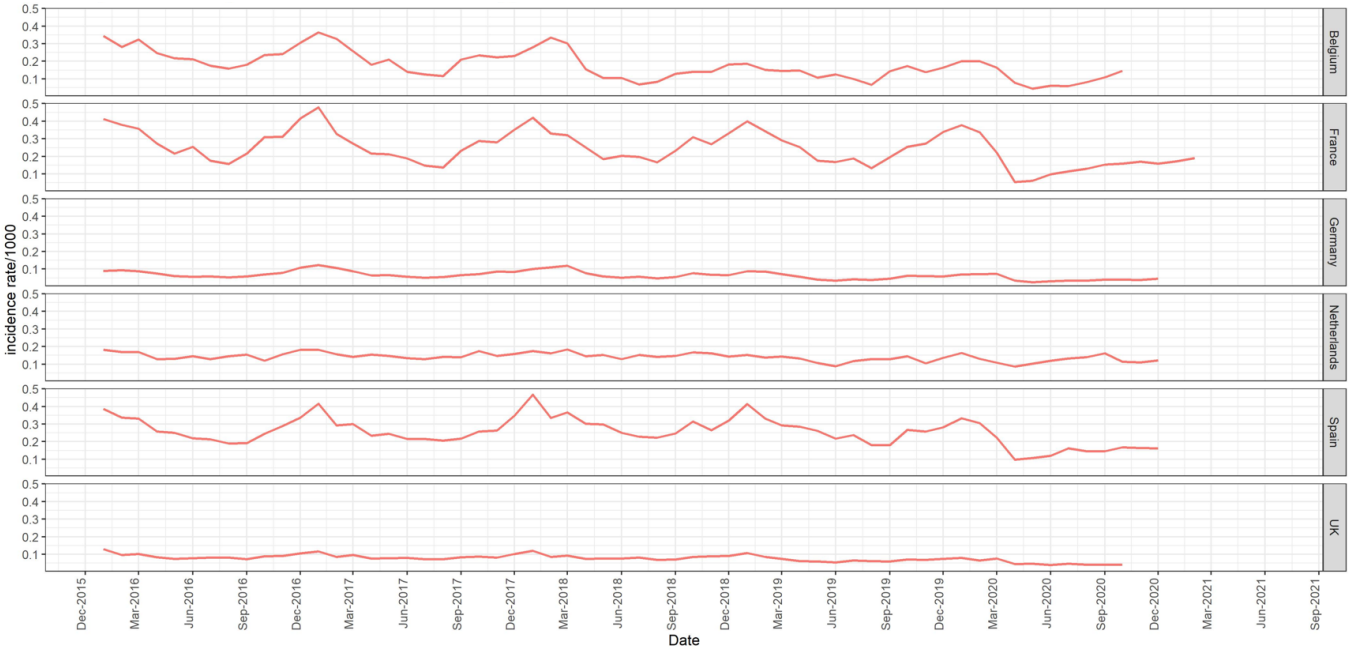

Figure 36. Monthly incident fluoroquinolones prescription rates in patients with recent (30 days prior) or concomitant prescriptions of systemic corticosteroids

Legend: The incidence rate is expressed as the number of new users of fluoroquinolones/1,000 persons per month

10.8 Monthly incident prescription rates for alternative antibiotics prescribed in incident fluoroquinolone users

The monthly incidence of alternative antibiotic prescription rates in incident fluoroquinolone users over calendar time is presented in Figure 37, and further stratifications (by age, sex, indication, and drug type) are shown in the Electronic Supplementary Material. The monthly incidence is expressed as the number of incident fluoroquinolone users who received alternative antibiotic/1,000 incident fluoroquinolone users per month. Note that these patients were therefore a sub-cohort of incident users.

Over the study period, the monthly median rates of prescribing alternative antibiotics were different across countries with (from the highest to the lowest):

- 93.8/1,000 incident users per month in the UK
- 76.0/1,000 incident users per month in the Netherlands
- 44.1/1,000 incident users per months in Spain
- 42.9/1,000 incident users per month in Belgium
- 30.1/1,000 incident users per month in Germany
- 24.4/1,000 incident users per month in France

The highest incidence rate of alternative antibiotics prescribed was reported in the UK with rates ranged from 80.6 to 123.6/1,000 incident users per month. The monthly incidence rates ranged from 62.7 to 106.5/1,000 incident users per month in the Netherlands, 39.0 to 61.1/1,000 incident users per month in Spain, and 23.1 to 57.7/1,000 incident users per month in Belgium. The lowest rates were reported in France (range: 16.9 to 30.5/1,000 incident users per month) and Germany (range: 24.8-46.1/1,000 incident users per month).

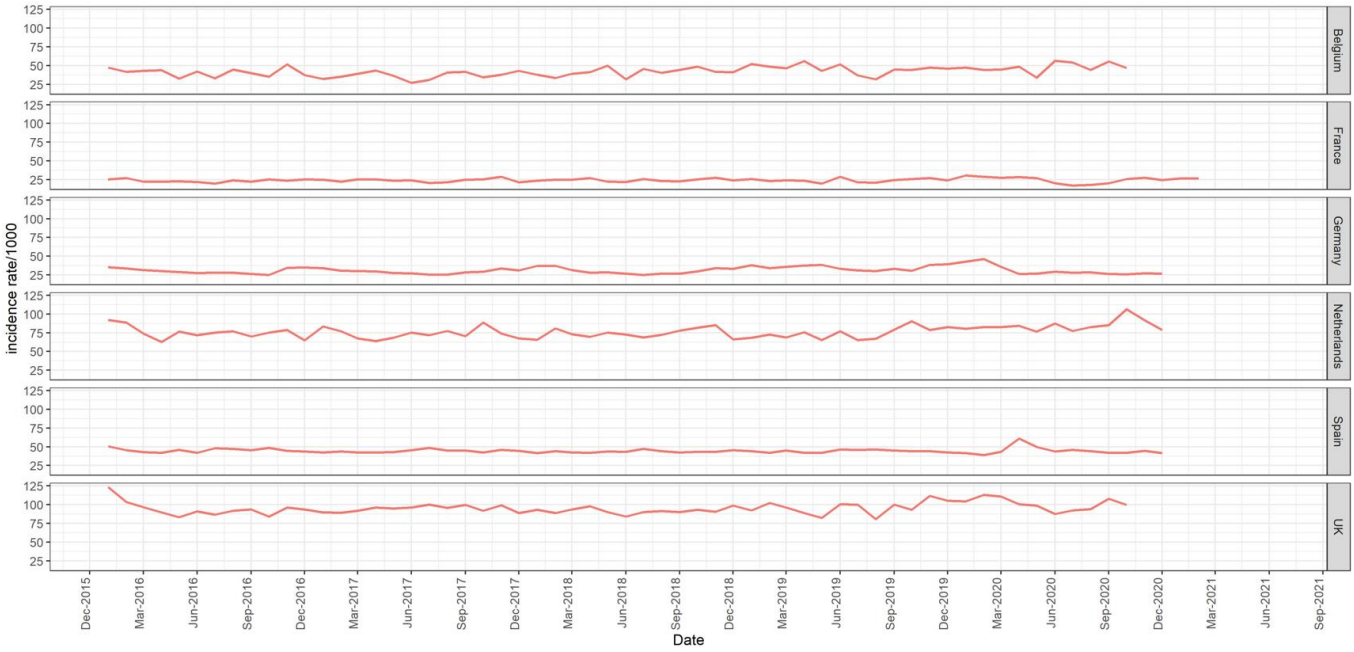

Figure 37. Monthly incident prescription rates of alternative antibiotics in incident fluoroquinolone users

Legend: The incidence rate is expressed as the number of patients identified as starting an alternative antibiotic per 1,000 incident users per month

10.9 Sensitivity analyses

10.9.1 Incident fluoroquinolone use assessment window

The impact of extending the incident user assessment window from 30 days (default) to 60 days resulted in a reduction of the monthly incident fluoroquinolone rate between 2.8% and 6.7% in average and across countries. Extending to 90 days reduced the monthly incident fluoroquinolone incident rate by an average between 5.3% and 10.8% across countries. Extending to 180 days reduced the monthly incident fluoroquinolone rate by an average between 11.1 and 17.7% across countries. The most pronounced effect was observed in the UK. The sensitivity analysis shows that the extension of the incident user assessment window from 30 days to 60 days or 90 days did not have a huge impact across countries. Applying an extended window from 30 days to 180 days would decrease the misclassification of prevalent users as incident at the cost of reducing the sample size (See Table 14 and Electronic Supplementary Material).

Table 14. Average reduction of monthly incident fluoroquinolone users when extending the incident user assessment window from 30 days (default) to 60, 90 and 180 days

	Belgium	France	Germany	Netherlands	Spain	UK
Extending to 60 days	2.8%	2.9%	3.3%	5.0%	4.8%	6.7%
Extending to 90 days	5.3%	5.7%	6.2%	8.8%	8.6%	10.8%
Extending to 180 days	11.1%	11.3%	12.5%	15.9%	16.4%	17.7%

UK: United Kingdom.

10.9.2 Indication of use assessment window

The impact of extending the assessment window for the indication from 14 days (default) to 30 days resulted in a reduction of the monthly incident fluoroquinolone rate for unknown indications category by an average of 2.4-4.1%. The impact of extending the assessment window for the indication from 14 days (default) to 60 days resulted in a reduction of the monthly incident fluoroquinolone rate for unknown indications by an average of 6.2-9.4% across countries. Applying an extended window to capture more indications did not manage to achieve a satisfactory decrease in the number of unknown indications and considering the increased risk of misclassification, it is not recommended (See Table 15 and Electronic Supplementary Material).

Table 15. Average reduction of monthly incident fluoroquinolone users when extending the assessment window for the unknown indication from 14 days (default) to 30 and 60 days

	Belgium	France	Germany	Netherlands	Spain	UK
Extending to 30 days	3.4%	2.4%	2.4%	4.1%	3.1%	2.9%
Extending to 60 days	8.6%	6.2%.	6.2%	9.4%	7.7%	7.0%

UK: United Kingdom.

10.9.3 Lookback window for risk factors

The impact of restricting the lookback window for risk factors from anytime in the past to 365 days resulted in a reduction of the population of overall incident fluoroquinolone use in those at risk of tendinopathy by an average between 3.2-19.2%. In addition, the overall incident fluoroquinolone use in those at risk of aortic dissection and aneurysm is reduced by an average between 5.4-21.0% across countries (Table 16 and Electronic Supplementary Material).

Table 16. Average reduction of the population of overall incident fluoroquinolone use in those at risk when restricting the lookback window for risk factors from anytime in the past (default) to 365 days prior to fluoroquinolone exposure

	Belgium	France	Germany	Netherlands	Spain	UK
Risk of tendinopathy (365 days prior to fluoroquinolone exposure)	3.2%	5.1%	3.7%	5.2%	2.4%	19.2%
Risk of aortic dissection and aneurysm (365 days prior to fluoroquinolone exposure)	9.4%	5.4%	13.1%	7.6%	12.1%	21.0%

UK: United Kingdom.

11 Discussion

11.1 Key results and interpretation

This retrospective drug utilisation study examined the use of fluoroquinolones through prescriptions in primary care in six countries between 2016 and 2021, and the impact of EMA regulatory interventions to reduce risk of harm implemented throughout 2018-2019. When visually evaluating the main results across countries, there were no substantial or consistent reductions observed in fluoroquinolone use after regulatory interventions. Similarly, joinpoint regression analyses were also unable to support changes directly corresponding to the implementation of regulatory interventions per country. Furthermore, other indicators of changes in prescribing behaviour by healthcare professionals, such as early discontinuation or prescriptions rates for alternative antibiotics (prescribed in patients where systemic use fluoroquinolones have previously been used), showed no changes after the regulatory interventions across countries. Although there were some modest reductions in prescriptions during or after the implementation of interventions in different subgroups in some countries, which are further discussed below, findings did not support a relevant effect of regulatory intervention on fluoroquinolone use.

The lack of evident changes concerning interventions in most countries could indicate that interventions had, at best low effectiveness which were not detectable in the primary care setting in these countries. Lack of evidence and inconsistent findings may also suggest that the timeframe studied was too short to allow adequate dissemination of regulatory measures to healthcare practices and subsequent prescription rates. A systematic review on the effectiveness of UK regulatory risk communications assumed a 12-month lag time to evaluate the effects of country-wide interventions (26). In contrast, no lag time was implemented in our study. Although no lag time was implemented in our study, even considering that a six-month follow-up time at study end was excluded, we would still have been able to observe any changes in prescriptions of fluoroquinolones. Possibly, the lack of detectable changes associated with regulatory intervention may suggest that the data were not well reflective of clinical practice. Yet, the absolute levels of fluoroquinolone, the prescription patterns across countries, the age group, the main indications, and the avoidance in risk groups aligned well with known country differences and clinical guidelines (11,27,28).

Several subgroup analyses for other countries showed decreases in prescriptions coinciding, or following, regulatory interventions, although not all provide clear support for the impact of interventions.

In Belgium, a modest absolute reduction, as well as a reduction of seasonally fluctuating peaks in prescriptions, was found to occur not later than the summer of 2018. This change was most substantial in the subgroup of ciprofloxacin prescriptions, in respiratory tract infections and prescriptions of short to moderate duration. Yet, DHPC and SmPC changes were not implemented before the beginning of 2019 and thus cannot be considered causal to the observed changes. This sudden drop was related to changes in reimbursement criteria for fluoroquinolone in Belgium. As of May 2018, fluoroquinolones

including ofloxacin, ciprofloxacin, norfloxacin, levofloxacin and moxifloxacin are no longer reimbursed for treating respiratory tract infections or uncomplicated urinary tract infections (29).

In Germany, the regression analyses showed a slight decrease in prescriptions of fluoroquinolones coinciding with the start of implementation of the SmPC changes and the DHPC. The seasonally fluctuating highest and lowest monthly prescription rates seemed to be lower than before implementation. This seasonality was not clearly reflected when visualising the segmented regression model stratified by substance. This change was not sufficiently evident overall and per substance to be appreciable in the visual representations of the crude and age-adjusted rates. Also, the decrease observed in crude and age-adjusted rates were already evident before the implementation of EMA interventions, e.g., as evaluated by a slightly lower seasonal peak. Another German study based on dispensing data from community pharmacies found a significant downward trend starting before the regulatory interventions examined here in our study, suggesting other factors may have been at play that influenced the observed changes in Germany's risk assessment procedure in Europe (30).

In the Netherlands, compared to Germany, a similar but even less pronounced drop of prescription rates in the regression analyses could be observed after implementation of regulatory interventions, also seen in ciprofloxacin prescriptions. Changes were at best modest and for example not reflected as a breakpoint when flexibly modelling age-adjusted rates.

In Spain, a decrease in prescriptions could be seen in the overall rates, in the off-label subgroup and both the subgroups of levofloxacin and ciprofloxacin prescriptions. When examined more closely, this drop took place around March/April 2020 and thus coincided with the first wave of the COVID-19 pandemic hitting Western Europe. Considering the important changes that the pandemic and associated population-level interventions, may have made, e.g., dynamics of infectious diseases, or willingness and possibilities of visiting primary care physicians, this drop was unlikely attributable to the regulatory interventions taken for fluoroquinolones, especially in Spain. Further research may consider examining why specifically in Spain, this time period was associated with falls in prescription rates of fluoroquinolones. Also, studying prescriptions of other antimicrobials around this time in Spain may help evaluate possible causes of the observed drop in fluoroquinolone prescriptions, as prescriptions indicated for the respiratory disease may, for example, have increased during the COVID pandemic.

In the UK, regression analyses suggested a decrease in prescriptions from 2019 onwards, coinciding with SmPC changes and DHPC. This timing also corresponds to EMA communications regarding fluoroquinolone restrictions (16 Oct 2018 [PRAC Recommendation], Nov 2018 [CHMP Opinion] and March 2019 European Commission Decision) (31,32). Prescriptions in the subset of persons stratified for on- and off-label use suggested a decrease about one year after the start of implementing SmPC changes and DHPC. The subgroup of ciprofloxacin prescriptions also showed a visually clearly appreciable reduction from 2019 onwards. Overall, most recent prescription rates were about 25% lower than baseline rates in our study. These were the most substantial reductions in prescriptions observed throughout our study. Yet this should not be attributed to regulatory interventions only, considering changes started already before.

Prescription rates also decreased over time regardless of regulatory interventions, or the COVID-19 pandemic, which suggested other factors also influenced prescription behaviour such as antibiotic stewardships or local changes in clinical guidance. We could not determine whether such factors also contributed to changes observed in relation to regulatory interventions. Dynamics of prescription rates of fluoroquinolones in recent years have been understudied in Europe. One US study reported a significant decrease in outpatient fluoroquinolone prescribing (by 39% decrease in total prescriptions per 1,000 patient visits) between 2016 and 2018 after a multimodal stewardship intervention (33). Yet, fluoroquinolone use declined both before and after a FDA black box warning on fluoroquinolones in 2016, suggesting limited impact of regulatory changes (34). Another US study in a large outpatient academic centre did not find a significant impact after the FDA black box warning on fluoroquinolone prescribing trends between 2013 and 2018 (35). To further determine how influences on prescribing of antimicrobials over time may have affected our observations, future research should consider using prescriptions of fluoroquinolones as a proportion of the total volume of antimicrobials.

To conclude, prescription rates of fluoroquinolones, as well as early discontinuation rates and prescription of alternative antimicrobials remained largely unchanged during and after regulatory interventions by EMA. Only in some analyses for some countries, especially the UK and possibly Germany, were some small to modest decreases in prescriptions which could be attributable to EMA interventions. For future work, researchers may consider looking into potential country-specific changes or including longer follow-up time.

11.2 Limitations

First, data on medicine prescriptions did not equate to actual use. Particularly for determining early discontinuation of fluoroquinolones, the algorithm used may have underestimated the instances of early discontinuation. Vice versa, the early discontinuation proportion may have been overestimated due the definition used (start of a new antibiotic before finishing the course of fluoroquinolone) as switching followed by early discontinuation might be actual add-on treatments.

Second, due to the retrospective nature of this study and use of data collected in a variety of primary care practices across different countries, it was not feasible to (manually) validate the automatic classification of key supporting variables, e.g., indications for use of fluoroquinolones, and subsequently on- or off-label use. Indications could also be only indirectly identified through presence of other data on comorbidities. Although this study used a comprehensive list of codes for indication, it was possible that some indications were nonspecific or coded via symptoms and might have been missed

Third, the high percentage of unknown indications (37.7%-84.1%) made our stratified analyses for indication potentially more vulnerable to any potential selection bias. Although sensitivity analyses showed that extending the retrospective window to classify indication may increase the number of persons with data on indications, this may also decrease the validity of indications which need to be defined cross-sectionally.

Fourth, although primary care well reflected an important part of fluoroquinolone use, we could not determine any potential impact of regulatory interventions on prescriptions in secondary care, including hospitals. Considering the density of healthcare professionals in hospitals is higher, and hospitals may possess more professionalized or matured networks of disseminating safety information on medications, the impact of regulatory interventions may be stronger and swifter there. Differences across settings of care may be more pronounced in indications where infections are more often treated in hospital.

Fifth, we used UK NICE and Dutch prescribing guidelines to determine line of treatment across all countries, which are acceptable evidence-based guidelines but may differ from guidelines relevant to the other countries in this study. In addition, although the use of fluoroquinolones as second- or third-line treatments may be relatively low regardless of the healthcare setting, complicated infections requiring additional lines of treatment are differentially more often treated in secondary care. This may explain the relatively low numbers of non-first line treatments we found.

Last, there was limited information to classify lines of treatment within on-label treatments robustly, and where the label could not be defined, off-label use was classified by default. Therefore, off-label results suggested changes after regulatory interventions may also pertain to certain on-label treatments.

11.3 Strengths and generalisability

Through using data from a large number of patients per country and using flexible regression modelling over monthly rates, this study was able to sensitively show any potential changes across time. Also, use of the OMOP CDM increased comparability of results across countries. In addition, findings seemed generalisable to the primary care situation in countries with a similar healthcare system where similar regulatory interventions were implemented.

12 Other information

Not applicable

13 Conclusions

The regulatory action for fluoroquinolones associated with the 2018 referral seems to have had only a modest impact on fluoroquinolones prescribing in primary care setting, magnitude and type in some countries. Other alternative explanations such as antibiotic stewardships and local changes in clinical guidance might count as contributing factors. Nonetheless, the use of fluoroquinolones in Europe is aligned with previous reports and with what is expected from clinical guidance in terms of age groups, main indications and avoidance of prescribing in risk groups. A higher than expected off-label use was observed in most of the countries which may be attribute to the methodology.

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15 Appendix 1

Fluoroquinolone indications by on- and off-label use

Fluoroquinolone exposures will be categorised as on-label or off-label exposure if the prescription of fluoroquinolone is associated with one of those listed in the table below:

On-label		**Off-label**	
Respiratory tract infections			
Indication	**How is it captured**	**Indication**	**How is it captured**
Chronic sinusitis	Code only	Acute bronchitis	Code only
Broncho-pulmonary infections in cystic fibrosis or in bronchiectasis	Code based. Combination of codes to identify both infection and the chronic disease. (cystic fibrosis AND broncho-pulmonary infection) OR (bronchiectasis AND broncho-pulmonary)	Pharyngitis	Code only
Pneumonia due to gram negative bacteria (last line)*	Code based. Code for CAP diagnosis AND last line treatment	Pneumonia due to gram negative bacteria (1st or 2nd line)	Code based. Code for CAP diagnosis AND not last line treatment
Tuberculosis	Code only	Tonsillitis	Code only
Inhalation anthrax (post exposure prophylaxis and curative treatment)	Code only	Laryngitis	Code only
Acute bacterial sinusitis (last line)*	Code AND last line of treatment	Acute bacterial sinusitis (1st or 2nd line)	Code AND not last line of treatment
Acute exacerbation of COPD (last line)*	Code AND last line of treatment	Acute exacerbation of COPD (1st or 2nd line)	Code AND not last line of treatment
Community acquired pneumonia (last line)*	Code AND last line of treatment	Community acquired pneumonia (1st and 2nd line)	Code AND not last line of treatment
		Nosocomial pneumonia	Code based. Might be missing in some databases

Urinary tract infections			
Complicated urinary tract infections	Algorithm to identify severity	Prevention of exacerbations in women with recurring urinary tract infections	Algorithm based on dose and duration of treatment
Acute pyelonephritis	Code only		
Simple uncomplicated acute cystitis (last line)	Code AND last line of treatment	Simple uncomplicated acute cystitis (1st or 2nd line)	Code AND not last line of treatment
Recurrent cystitis in women (last line)	Algorithm to identify recurrence AND last line of treatment	Recurrent cystitis in women (1st or 2nd line)	Algorithm to identify recurrence AND not last line of treatment
Genital tract infections			
Prostatitis	Code only	Vaginal infections	Code only (might be missing in some databases)
Epididymo-orchitis	Code only		
Gonococcal urethritis	Code only		
Gonococcal Cervicitis	Code only		
Genital tract and gynaecological infections	Code only		
Pelvic inflammatory disease	Code only		
Ear infections			
Malignant external otitis	Code only	External otitis	Code only
Chronic suppurative otitis media	Code only		
Acute otitis media (recurrent, non-responsive)	Algorithm		
Skin infections			
Complicated skin and soft tissue infections	Algorithm		
Gastrointestinal infections			

Gastrointestinal infections	Code only	Prophylaxis of travellers' diarrhoea	Code only (might be missing in some databases)
Intra-abdominal infections	Code only	Selective decontamination of gastrointestinal tract in patients with compromised immune system	Code only (might be missing in some databases)
Bone and joint infections			
Bone and joint infections	Code only		
Prophylaxis use			
Prophylaxis of invasive infections due to Neisseria meningitidis	Code only (not all databases will be specific enough)	Preoperative preparations for chronic cholesteatomatous otitis and chronic otitis spreading to bone	Code only
Prophylaxis of bacterial infections in neutropenic patients	Code based: Neutropenic patients AND prophylaxis of bacterial infections		
Others			
Infection in immunocompromised patients	Code based – identify immunocompromised patients	Septicaemia	Code only
		Meningitis	Code only
		Infection of cerebrospinal fluid	Code only
		Endocarditis	Code only

COPD: Chronic Obstructive Pulmonary Disease; CAP: Community Acquired Pneumonia. *The line of treatment was considered in the off-label/on-label algorithm only for some selected indications, for which first line is not recommended. These indications were: pneumonia due to gram negative bacteria, acute bacterial sinusitis, acute exacerbation of COPD and CAP. These were considered off-label if fluoroquinolones were used as first or second line and on-label if used as third line.

16 Appendix 2

Fluroquinolone usage by indication on/off label and by substance across countries

In Belgium, the proportion of known indications for which fluroquinolones were used was: 45.0% for ofloxacin, 65.1% for norfloxacin, 77.5% for moxifloxacin, 64.5% for levofloxacin and 63.1% for ciprofloxacin. The majority of these prescriptions were attributed to off-label indications. Out of the 1966 off-label indications for ofloxacin, ear infections, respiratory tract infections and urinary tract infections were attributed to 31.2%, 34.3% and 34.0%, respectively. For moxifloxacin and levofloxacin, the majority of off-label indications were attributed to respiratory tract infections with 98.0% and 60.6%, respectively. Urinary tract infections accounted for 90.1% of norfloxacin off-label indications and 49.8% of ciprofloxacin off-label indications. See Table 1 below.

Table 1. Fluroquinolone usage by indication on/off-label and by substance in Belgium

	Ofloxacin				Norfloxacin				Moxifloxacin				Levofloxacin				Ciprofloxacin			
		All indications (%)	Off-label (%)	On-label (%)		All indications (%)	Off-label (%)	On-label (%)		All indications (%)	Off-label (%)	On-label (%)		All indications (%)	Off-label (%)	On-label (%)		All indications (%)	Off-label (%)	On-label (%)
Total (classified + unclassified)	7,160				3,570				28,693				5,112				44,603			
Total classified	3,225	45.0			2,324	65.1			22,231	77.5			3,299	64.5			28,163	63.1		
Total Off-label	1,966	61.0			2131	91.7			20,086	90.4			1,766	53.5			18,987	67.4		
Total On-label	1,259	39.0			193	8.3			2,145	9.6			1,533	46.5			9,176	32.6		
Total unclassified (unknown indication)	3,935	55.0			1,246	34.9			6,462	22.5			1,813	35.5			16,440	36.9		
Off-label indications																				
Ear infections	614	19.0	31.2	n.a	10	0.4	0.5	n.a	192	0.9	1.0	n.a	47	1.4	2.7	n.a	5,594	19.9	29.5	n.a
Other use	8	0.2	0.4	n.a	1	0.0	0.0	n.a	35	0.2	0.2	n.a	7	0.2	0.4	n.a	71	0.3	0.4	n.a
Respiratory tract infections	675	20.9	34.3	n.a	200	8.6	9.4	n.a	19,688	88.6	98.0	n.a	1,070	32.4	60.6	n.a	3,871	13.7	20.4	n.a
Urinary tract infections	669	20.7	34.0	n.a	1,920	82.6	90.1	n.a	171	0.8	0.9	n.a	642	19.5	36.4	n.a	9,451	33.6	49.8	n.a
On-label indications																				
Bone infections	12	0.4	n.a	1.0	3	0.1	n.a	1.6	20	0.1	n.a	0.9	17	0.5	n.a	1.1	52	0.2	n.a	0.6
Ear infections	142	4.4	n.a	11.3	7	0.3	n.a	3.6	155	0.7	n.a	7.2	14	0.4	n.a	0.9	1,961	7.0	n.a	21.4
Gastrointestinal infections	328	10.2	n.a	26.1	28	1.2	n.a	14.5	207	0.9	n.a	9.7	130	3.9	n.a	8.5	697	2.5	n.a	7.6
Genital, testicular and prostatic infections	511	15.8	n.a	40.6	71	3.1	n.a	36.8	169	0.8	n.a	7.9	837	25.4	n.a	54.6	2,792	9.9	n.a	30.4
Respiratory tract infections	38	1.2	n.a	3.0	16	0.7	n.a	8.3	994	4.5	n.a	46.3	67	2.0	n.a	4.4	298	1.1	n.a	3.2

Skin and soft tissue infections	157	4.9	n.a	12.5	34	1.5	n.a	17.6	506	2.3	n.a	23.6	273	8.3	n.a	17.8	1,058	3.8	n.a	11.5
Urinary tract infections	71	2.2	n.a	5.6	34	1.5	n.a	17.6	94	0.4	n.a	4.4	195	5.9	n.a	12.7	2,318	8.2	n.a	25.3

n.a: not applicable.

In Germany, the proportion of known indications for which fluroquinolones were used was: 17.9% for ofloxacin prescriptions, 28.8% for norfloxacin prescriptions, 55.2% for moxifloxacin, 43.1% for levofloxacin and 41.5% for ciprofloxacin. The majority of these prescriptions were attributed to off-label indications with respiratory tract infections accounting for 60.3% of ofloxacin off-label indications, 98.3% of moxifloxacin off-label indications and 81.8% of levofloxacin off-label indications; urinary tract infections for 95.1% of norfloxacin off-label indications; and ear infections for 54.2% of ciprofloxacin off-label indications. See Table 2 below.

Table 2. Fluroquinolone usage by indication on/off-label and by substance in Germany

	Ofloxacin				Norfloxacin				Moxifloxacin				Levofloxacin				Ciprofloxacin			
		All indications (%)	Off-label (%)	On-label (%)		All indications (%)	Off-label (%)	On-label (%)		All indications (%)	Off-label (%)	On-label (%)		All indications (%)	Off-label (%)	On-label (%)		All indications (%)	Off-label (%)	On-label (%)
Total (classified + unclassified)	164,054				26,678				54,812				125,330				590,671			
Total classified	29,390	17.9			7,694	28.8			30,278	55.2			53,977	43.1			245,315	41.5		
Total Off-label	21,820	74.2			7,008	91.1			25,413	83.9			41,058	76.1			201,051	82.0		
Total On-label	7,570	25.8			686	8.9			4,865	16.1			12,919	23.9			44,264	18.0		
Total unclassified (unknown indication)	134,664	82.1			18,984	71.2			24,534	44.8			71,353	56.9			345,356	58.5		
Off-label indications																				
Ear infections	2,845	9.7	13.0	n.a	9	0.1	0.1	n.a	159	0.5	0.6	n.a	277	0.5	0.7	n.a	108,871	44.4	54.2	n.a
Other use	47	0.2	0.2	n.a	14	0.2	0.2	n.a	79	0.3	0.3	n.a	233	0.4	0.6	n.a	791	0.3	0.4	n.a
Respiratory tract infections	13,162	44.8	60.3	n.a	318	4.1	4.5	n.a	24,973	82.5	98.3	n.a	33,602	62.3	81.8	n.a	48,692	19.8	24.2	n.a
Urinary tract infections	5,766	19.6	26.4	n.a	6,667	86.7	95.1	n.a	202	0.7	0.8	n.a	6,946	12.9	16.9	n.a	42,697	17.4	21.2	n.a
On-label indications																				
Bone infections	15	0.1	n.a	0.2	0	0.0	n.a	0.0	34	0.1	n.a	0.7	113	0.2	n.a	0.9	245	0.1	n.a	0.6
Ear infections	438	1.5	n.a	5.8	1	0.0	n.a	0.1	33	0.1	n.a	0.7	51	0.1	n.a	0.4	5,140	2.1	n.a	11.6
Gastrointestinal infections	956	3.3	n.a	12.6	57	0.7	n.a	8.3	229	0.8	n.a	4.7	374	0.7	n.a	2.9	2,855	1.2	n.a	6.4
Genital, testicular and	1,073	3.7	n.a	14.2	310	4.0	n.a	45.2	211	0.7	n.a	4.3	2,856	5.3	n.a	22.1	11,233	4.6	n.a	25.4

prostatic infections																			
Respiratory tract infections	1,652	5.6	n.a	21.8	68	0.9	n.a	9.9	2,918	9.6	n.a	60.0	5,290	9.8	n.a	40.9	10,153	4.1	n.a	22.9
Skin and soft tissue infections	3,174	10.8	n.a	41.9	100	1.3	n.a	14.6	1417	4.7	n.a	29.1	3,626	6.7	n.a	28.1	11,675	4.8	n.a	26.4
Urinary tract infections	262	0.9	n.a	3.5	150	1.9	n.a	21.9	23	0.1	n.a	0.5	609	1.1	n.a	4.7	2,963	1.2	n.a	6.7

n.a: not applicable.

In Netherlands, the proportion of known indications for which fluroquinolones were used was: 20.0% for ofloxacin prescriptions, 51.9% for norfloxacin prescriptions, 24.5% for moxifloxacin, 8.8% for levofloxacin and 51.6% for ciprofloxacin. The majority of these prescriptions were attributed to off-label indications with respiratory tract infections accounting for 90.8% of moxifloxacin off-label indications and for 49.8% of levofloxacin off-label indications; urinary tract infections for 98.0% for norfloxacin off-label indications, 47.3% of levofloxacin off-label indications and 93.5% of ciprofloxacin off-label indications; and ear infections for 85.0% of ofloxacin off-label indications. See Table 3 below.

Table 3. Fluroquinolone usage by indication on/off-label and by substance in Netherlands

	Ofloxacin				Norfloxacin				Moxifloxacin				Levofloxacin				Ciprofloxacin			
		All indications (%)	Off-label (%)	On-label (%)		All indications (%)	Off-label (%)	On-label (%)		All indications (%)	Off-label (%)	On-label (%)		All indications (%)	Off-label (%)	On-label (%)		All indications (%)	Off-label (%)	On-label (%)
Total (classified + unclassified)	27,257				5,358				2,412				5,016				101,738			
Total classified	5,448	20.0			2,779	51.9			591	24.5			441	8.8			52,521	51.6		
Total Off-label	3,347	61.4			2,524	90.8			490	82.9			275	62.4			39,407	75.0		
Total On-label	2,101	38.6			255	9.2			101	17.1			166	37.6			13,114	25.0		
Total unclassified (unknown indication)	21,809	80.0			2,579	48.1			1,821	75.5			4,575	91.2			49,217	48.4		
Off-label indications																				
Ear infections	2,844	52.2	85.0	n.a	15	0.5	0.6	n.a	4	0.7	0.8	n.a	7	1.6	2.5	n.a	595	1.1	1.5	n.a
Other use	4	0.1	0.1	n.a	0	0.0	0.0	n.a	0	0.0	0.0	n.a	1	0.2	0.4	n.a	39	0.1	0.1	n.a
Respiratory tract infections	185	3.4	5.5	n.a	36	1.3	1.4	n.a	445	75.3	90.8	n.a	137	31.1	49.8	n.a	1,927	3.7	4.9	n.a
Urinary tract infections	314	5.8	9.4	n.a	2,473	89.0	98.0	n.a	41	6.9	8.4	n.a	130	29.5	47.3	n.a	36,846	70.2	93.5	n.a
On-label indications																				
Bone infections	0	0.0	n.a	0.0	0	0.0	n.a	0.0	0	0.0	n.a	0.0	3	0.7	n.a	1.8	36	0.1	n.a	0.3
Ear infections	1,256	23.1	n.a	59.8	2	0.1	n.a	0.8	8	1.4	n.a	7.9	4	0.9	n.a	2.4	170	0.3	n.a	1.3
Gastrointestinal infections	39	0.7	n.a	1.9	53	1.9	n.a	20.8	9	1.5	n.a	8.9	11	2.5	n.a	6.6	3,890	7.4	n.a	29.7
Genital, testicular and prostatic infections	483	8.9	n.a	23.0	65	2.3	n.a	25.5	16	2.7	n.a	15.8	73	16.6	n.a	44.0	2,408	4.6	n.a	18.4

Respiratory tract infections	10	0.2	n.a	0.5	4	0.1	n.a	1.6	28	4.7	n.a	27.7	10	2.3	n.a	6.0	107	0.2	n.a	0.8
Skin and soft tissue infections	291	5.3	n.a	13.9	28	1.0	n.a	101.0	33	5.6	n.a	32.7	44	10.0	n.a	26.5	1,422	2.7	n.a	10.8
Urinary tract infections	22	0.4	n.a	1.0	103	3.7	n.a	40.4	7	1.2	n.a	6.9	21	4.8	n.a	12.7	5,081	9.7	n.a	38.7

n.a: not applicable.

In Spain, the proportion of known indications for which fluroquinolones were used was: 1.9% for ofloxacin prescriptions, 11.5% for norfloxacin prescriptions, 12.2% for moxifloxacin prescriptions, 37.6% for levofloxacin prescriptions and 32.4% for ciprofloxacin prescriptions. The majority of these prescriptions were attributed to off-label indications with respiratory tract infections accounting for 86.3% of ofloxacin off-label indications, 98.0% of moxifloxacin off-label indications and 99.0% of levofloxacin off-label indications; urinary tract infections for 75.5% for norfloxacin off-label indications; and ear infections for 81.3% for ciprofloxacin off-label indications. See table 4 below.

Table 4. Fluroquinolone usage by indication on/off-label and by substance in Spain

	Ofloxacin				**Norfloxacin**				**Moxifloxacin**				**Levofloxacin**				**Ciprofloxacin**			
		All indications (%)	Off-label (%)	On-label (%)		All indications (%)	Off-label (%)	On-label (%)		All indications (%)	Off-label (%)	On-label (%)		All indications (%)	Off-label (%)	On-label (%)		All indications (%)	Off-label (%)	On-label (%)
Total (classified + unclassified)	24,249				155,241				145,665				530,273				1,258,008			
Total classified	465	1.9			17,807	11.5			17,819	12.2			199,258	37.6			407,642	32.4		
Total Off-label	306	65.8			14,947	83.9			16,160	90.7			189,089	94.9			285,188	70.0		
Total On-label	159	34.2			2,860	16.1			1,659	9.3			10,169	5.1			122,454	30.0		
Total unclassified (unknown indication)	23,784	98.1			137,434	88.5			127,846	87.8			331,015	62.4			850,366	67.6		
Off-label indications																				
Ear infections	30	6.5	9.8	n.a	118	0.7	0.8	n.a	241	1.4	1.5	n.a	900	0.5	0.5	n.a	231,994	56.9	81.3	n.a
Other use	*			n.a	12	0.1	0.1	n.a	18	0.1	0.1	n.a	196	0.1	0.1	n.a	602	0.1	0.2	n.a
Respiratory tract infections	264	56.8	86.3	n.a	1,372	7.7	9.2	n.a	15,829	88.8	98.0	n.a	187,263	94.0	99.0	n.a	385,48	9.5	13.5	n.a
Urinary tract infections	12	2.6	3.9	n.a	13,445	75.5	90.0	n.a	72	0.4	0.4	n.a	730	0.4	0.4	n.a	14,044	3.4	4.9	n.a
On-label indications																				
Bone infections	0	0.0	n.a	n.a	0	0.0	n.a	0.0	24	0.1	n.a	1.4	420	0.2	n.a	4.1	408	0.1	n.a	0.3
Ear infections	13	2.8	n.a	n.a	32	0.2	n.a	1.1	201	1.1	n.a	12.1	1,112	0.6	n.a	10.9	64,036	15.7	n.a	52.3

Gastrointestinal infections	28	6.0	n.a	n.a	920	5.2	n.a	32.2	226	1.3	n.a	13.6	1,475	0.7	n.a	14.5	11,306	2.8	n.a	9.2
Genital, testicular and prostatic infections	41	8.8	n.a	25.8	953	5.4	n.a	33.3	120	0.7	n.a	7.2	1,563	0.8	n.a	15.4	16,968	4.2	n.a	13.9
Respiratory tract infections	6	1.3	n.a	3.8	12	0.1	n.a	0.4	450	2.5	n.a	27.1	1,179	0.6	n.a	11.6	566	0.1	n.a	0.5
Skin and soft tissue infections	71	15.3	n.a	44.7	255	1.4	n.a	8.9	612	3.4	n.a	36.9	3,979	2.0	n.a	39.1	2,4025	5.9	n.a	19.6
Urinary tract infections	*		n.a	n.a	688	3.9	n.a	24.1	26	0.1	n.a	1.6	441	0.2	n.a	4.3	5,145	1.3	n.a	4.2

n.a: not applicable.

In the UK, the proportion of known indications for which fluroquinolones were used was: 14.4% for ofloxacin prescriptions, 12.8% for norfloxacin prescriptions, 10.8% for moxifloxacin prescriptions, 17.8% for levofloxacin prescriptions and 16.8% for ciprofloxacin prescriptions. These prescriptions were attributed to on-label indications for 62.1% for ofloxacin, and to off-label indications for 80.0% for norfloxacin, 89.7% for moxifloxacin, 65.6% for levofloxacin and 56.3% for ciprofloxacin. In the on-label indications, genital, testicular and prostatic infections were attributed to 87.1% for ofloxacin. In the off-label indications, respiratory tract infections were attributed to 97.1% for moxifloxacin and 91.2% for levofloxacin. In addition, urinary tract infections were attributed to 75.0% for norfloxacin. Ear infections were attributed to 56.1% for ciprofloxacin. See Table 5 below.

Table 5. Fluroquinolone usage by indication on/off-label and by substance in the UK

	Ofloxacin				**Norfloxacin**				**Moxifloxacin**				**Levofloxacin**				**Ciprofloxacin**			
		All indications (%)	Off-label (%)	On-label (%)		All indications (%)	Off-label (%)	On-label (%)		All indications (%)	Off-label (%)	On-label (%)		All indications (%)	Off-label (%)	On-label (%)		All indications (%)	Off-label (%)	On-label (%)
Total (classified + unclassified)	16,830				39				719				6,139				176,451			
Total classified	2,422	14.4			5	12.8			78	10.8			1,094	17.8			29,705	16.8		
Total Off-label	918	37.9			4	80.0			70	89.7			718	65.6			16,724	56.3		
Total On-label	1,504	62.1			1	20.0			8	10.3			376	34.4			12,981	43.7		
Total unclassified (unknown indication)	14,408	85.6			34	87.2			641	89.2			5,045	82.2			146,746	83.2		
Off-label indications																				
Ear infections	749	30.9	81.6	n.a	0	0.0	0.0	n.a	1	1.3	1.4	n.a	34	3.1	4.7	n.a	9,376	31.6	56.1	n.a
Other use	1	0.0	0.1	n.a	0	0.0	0.0	n.a	1	1.3	1.4	n.a	13	1.2	1.8	n.a	259	0.9	1.5	n.a
Respiratory tract infections	142	5.9	15.5	n.a	1	20.0	25.0	n.a	68	87.2	97.1	n.a	655	59.9	91.2	n.a	4,737	15.9	28.3	n.a
Urinary tract infections	26	1.1	2.8	n.a	3	60.0	75.0	n.a	0	0.0	0.0	n.a	16	1.5	2.2	n.a	2,352	7.9	14.1	n.a
On-label indications																				
Bone infections	0	0.0	n.a	0.0	0	0.0	n.a	0.0	0	0.0	n.a	0.0	11	1.0	n.a	2.9	142	0.5	n.a	1.1
Ear infections	53	2.2	n.a	3.5	0	0.0	n.a	0.0	0	0.0	n.a	0.0	5	0.5	n.a	1.3	626	2.1	n.a	4.8

Gastrointestinal infections	37	1.5	n.a	2.5	0	0.0	n.a	0.0	0	0.0	n.a	0.0	22	2.0	n.a	5.9	2,789	9.4	n.a	21.5
Genital, testicular and prostatic infections	1,310	54.1	n.a	87.1	0	0.0	n.a	0.0	1	1.3	n.a	12.5	239	21.8	n.a	63.6	4,797	16.1	n.a	37.0
Respiratory tract infections	5	0.2	n.a	0.3	0	0.0	n.a	0.0	2	2.6	n.a	25.0	20	1.8	n.a	5.3	137	0.5	n.a	1.1
Skin and soft tissue infections	90	3.7	n.a	6.0	0	0.0	n.a	0.0	5	6.4	n.a	62.5	75	6.9	n.a	19.	2,321	7.8	n.a	17.9
Urinary tract infections	9	0.4	n.a	0.6	1	20.0	n.a	100.0	0	0.0	n.a	0.0	4	0.4	n.a	1.1	2,169	7.3	n.a	16.7

N.A: Not Applicable; UK: United Kingdom.

In France, the proportion of known indications for which fluroquinolones were used was: 41.5% for ofloxacin, 47.5% for norfloxacin, 64.9% for moxifloxacin, 56.5% for levofloxacin, 41.9% for ciprofloxacin and 59.7% for lomefloxacin. These prescriptions were attributed to on-label indications for 54.0% for moxifloxacin, and to off-label indications for 71.3 for ofloxacin, 88.8% for norfloxacin, 53.5% for levofloxacin, 67.6% for ciprofloxacin and 94.8% for lomefloxacin. In the on-label indications, genital, testicular and prostatic infections were attributed to 40.1% for norfloxacin. In the off-label indications, respiratory tract infections were attributed to 86.2% for levofloxacin. In addition, urinary tract infections were attributed to 39.8% for ofloxacin, 92.0% for norfloxacin, 65.3% for ciprofloxacin and 95% for lomefloxacin. Ear infections were attributed to 36.4% for ofloxacin. France is the only country where lomefloxacin was used. See Table 6 below.

Table 6. Fluroquinolone usage by indication on/off-label and by substance in the France

	Ofloxacin				Norfloxacin				Moxifloxacin			Levofloxacin				Ciprofloxacin				Lomefloxacin			
		All indications (%)	Off-label (%)	On-label (%)		All indications (%)	Off-label (%)	On-label (%)		All indications (%)	Off-label (%)	On-label (%)		All indications (%)	Off-label (%)	On-label (%)		All indications (%)	Off-label (%)	On-label (%)		All indications (%)	Off-label (%)	On-label (%)
Total (classified + unclassified)	18,9252				44,629				10,712				46,483				87,892				27,523			
Total classified	78,484	41.5			21,181	47.5			6,952	64.9			26,266	56.5			36,816	41.9			16,420	59.7		
Total Off-label	55,945	71.3			18,816	88.8			3,198	46.0			14,041	53.5			24,903	67.6			15,572	94.8		
Total On-label	22,539	28.7			2,365	11.2			3,754	54.0			12,225	46.5			11,913	32.4			848	5.2		
Total unclassified (unknown indication)	11,0768	58.5			23,448	52.5			3,760	35.1			20,217	43.5			51,076	58.1			11,103	40.3		
Off-label indications																								
Ear infections	20,370	26.0	36.4	n.a	117	0.6	0.6	n.a	38	0.5	1.2	n.a	134	0.5	1.0	n.a	2,765	7.5	11.1	n.a	42	0.3	0.3	n.a
Other use	50	0.1	0.1	n.a	9	0.0	0.0	n.a	3	0.0	0.1	n.a	19	0.1	0.1	n.a	22	0.1	0.1	n.a	7	0.0	0.0	n.a
Respiratory tract infections	13,250	16.9	23.7	n.a	1,387	6.5	7.4	n.a	3,000	43.2	93.8	n.a	12,099	46.1	86.2	n.a	5,851	15.9	23.5	n.a	733	4.5	4.7	n.a
Urinary tract infections	22,275	28.4	39.8	n.a	17,303	81.7	92.0	n.a	157	2.3	4.9	n.a	1,789	6.8	12.7	n.a	16,265	44.2	65.3	n.a	14,790	90.1	95.0	n.a
On-label indications																								
Bone infections	73	0.1	n.a	0.3	27	0.1	n.a	1.1	5	0.1	n.a	0.1	44	0.2	n.a	0.4	60	0.2	n.a	0.5	1	0.0	n.a	0.1

Ear infections	6,468	8.2	n.a	28.7	58	0.3	n.a	2.5	27	0.4	n.a	0.7	80	0.3	n.a	0.7	426	1.2	n.a	3.6	4	0.0	n.a	0.5
Gastrointestinal infections	400	0.5	n.a	1.8	64	0.3	n.a	2.7	24	0.3	n.a	0.6	123	0.5	n.a	1.0	420	1.1	n.a	3.5	25	0.2	n.a	2.9
Genital, testicular and prostatic infections	6,615	8.4	n.a	29.3	948	4.5	n.a	40.1	236	3.4	n.a	6.3	2,099	8.0	n.a	17.2	5,167	14.0	n.a	43.4	361	2.2	n.a	42.6
Respiratory tract infections	4,207	5.4	n.a	18.7	419	2.0%	n.a	17.7	3,332	47.9	n.a	88.8	8,696	33.1	n.a	71.1	2,950	8.0	n.a	24.8	170	1.0	n.a	20.0
Skin and soft tissue infections	1,854	2.4	n.a	8.2	439	2.1	n.a	18.6	119	1.7	n.a	3.	472	1.8	n.a	3.9	960	2.6	n.a	8.1	221	1.3	n.a	26.1
Urinary tract infections	2,922	3.7	n.a	13.0	410	1.9	n.a	17.3	11	0.2	n.a	0.3	711	2.7	n.a	5.8	1,930	5.2	n.a	16.2	66	0.4	n.a	7.8

n.a: not applicable.