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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Prepared For:
European Medicines Agency

Domenico Scarlattilaan 6
1083 HS Amsterdam
The Netherlands

Prepared By:
Eileen Dareng, MD, MPH, PhD (Epidemiologist)
Alexandra Pacurariu, PhD (Senior Epidemiologist)

IQVIA Ltd
210 Pentoville Road,
London N1 9JY
United Kingdom

IQVIA Principal:
Deborah Layton, FRPharmS, PhD
Engagement Manager
DLayton@uk.imshealth.com

Protocol Approval and Sign-off

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

Epidemiologist & author	Alexandra Pacurariu		15th October 2020
	Print name, title here	Signature	Date
Principal Investigator	Deborah Layton		15th October 2020
	Print name, title here	Signature	Date
Senior QC	Deborah Layton		15th October 2020
	Print name, title here	Signature	Date

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
Protocol version identifier	V 0.3
Date of last version of protocol	*NA*
EU PAS register number	To be registered
Active substance	Fluoroquinolones class: J01MA01 Ofloxacin J01MA02 Ciprofloxacin J01MA06 Norfloxacin J01MA07 Lomefloxacin J01MA12 Levofloxacin J01MA14 Moxifloxacin
Medicinal product	Multiple
Product reference	NA
Procedure number	EMA/430636/2019
Marketing authorisation holder(s)	Multiple
Joint PASS	No
Research questions and objectives	The overall aim of this study is 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.
Country(-ies) of study	the Netherlands, Spain, UK, Belgium, Germany and France
Author	IQVIA Ltd.

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1 List of Abbreviations

Abbreviation	Definition
CAP	Community acquired pneumonia
CDM	Common Data Model
COPD	Chronic obstructive Pulmonary Disorder
DDD	Defined daily dose
DHPC	Dear Healthcare Professional Communications
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
FDA	Food and Drug Administration
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
OMOP	Observational Medical Outcomes Partnership
PRAC	Pharmacovigilance Risk Assessment Committee
SIDIAP	Information System for Research in Primary Care
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedure

2 Responsible Parties

Principal Investigator
Deborah Layton PhD,
IQVIA
Real World Solution,
London, UK, 210 Pentonville Road
Email: DLayton@uk.imshealth.com

Data Steward IQVIA
Christian Reich MD
IQVIA
Real World Solutions
201 Broadway
Cambridge, MA 02139, USA
Tel: +49 172 804 4129
Email: christian.reich@iqvia.com

Data Steward SIDIAP
Talita Duarte Salles, PhD
IDIAPJGol
Gran Via de les Corts Catalanes 587, àtic
08007, Barcelona, Spain
Tel.: +34934824243
Email: tduarte@idiapjgol.org

Data Steward IPCI
Katia Verhamme, MD, PhD
Erasmus MC
Department of Medical Informatics
POBOX 2040
3000 CA Rotterdam
The Netherlands
Tel: +31-10 704 4152
Email : k.verhamme@erasmusmc.nl

3 Abstract

Section	Description
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 certain bacterial infections. 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. 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 inhalational use. In November 2018, the EMA concluded that serious adverse reactions including tendon, muscle and joint disorders, neurologic and psychiatric disorders listed in the product information of different fluoroquinolones could in rare cases become long-lasting, and recommended cessation of prescriptions for milder, non-severe or self-limiting infections, and restrictions for other indications.
Research question and objectives	The overall aim of this study is to evaluate the impact of the regulatory actions taken for fluoroquinolone containing medicinal products following the 2018 referral procedure. The study objectives are: 1. To determine the drug utilisation and prescription patterns of fluoroquinolone containing medicinal products over the period 2016 and 2020 by a) estimating monthly incident drug use, stratified by on label indications (which includes first line and last line indications) and off label indications (mild infections for which fluoroquinolones are not indicated for). b) Estimation of early discontinuation proportion (prescribed courses that were discontinued prior to intended treatment end date)

	2. Evaluate the impact of regulatory interventions on fluoroquinolone prescribing patterns using time series analysis. 3. To determine prescribers' compliance with warnings as described in fluoroquinolones SmPC section 4.4, in particular on tendinitis and tendon rupture as well as on aortic aneurysm/dissection 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 aneurysm/dissection c) patients with recent (within 30 days prior) or concomitant prescribing of systemic corticosteroids 4. To determine monthly incident prescription rates for alternative antibiotics prescribed in patients where systemic or inhalation use fluoroquinolones have previously been prescribed and discontinued
Research methods	
Study design	A retrospective population-based cohort study will be conducted using electronic health care records from six databases from six European countries.
Setting	The study time period is 1st January 2016 until the latest available data cut-off. Limited inclusion and exclusion criteria will be used in order to achieve a broader representativeness of the population.
Variables	Demographics: age, sex Exposure specific: type of fluoroquinolone, indication of use, line of therapy, start and end date, early discontinuation, use of alternative medications, recent and concomitant use of systemic corticosteroids. Risk factors for tendinitis and tendon rupture and for aortic dissection. Calendar year
Data sources	Data from six databases from six European countries namely IPCI (the Netherlands), SIDIAP (Catalonia Spain) and IQVIA (UK IMRD, LPD Belgium, DA Germany and LPD France). Data from these databases have been mapped to the OMOP Common Data Model.

Data analysis	This is a drug utilization study with a time series analysis component to identify the potential impact of regulatory interventions on fluoroquinolones prescribing trends. An initial exploratory descriptive analysis will be conducted for each database-specific cohort. Crude and stratified incidence of drug use, drug discontinuation and use of alternative treatment use will be calculated. A Joinpoint regression model will be used to investigate changes in prescribing patterns over calendar time. Prescriber compliance with labelled warnings for use mentioned in the product information will be investigated, as well as, using incidence of drug use across indications and risk factors.
Plans for Disseminating and Communicating Study Results	The final study report will be written in accordance with the GVP guidelines module VIII, (EMA/813938/2011) and information about this PASS will be entered into the publicly available EU PAS register before start of data analysis.

4 Amendments and Updates

Major and Minor Amendments	
Major Amendments	**Minor Amendments**
• NA •	• Yes, see below

Number	Date	Section of the Protocol	Amendment or update	Reason
1	6th October 2020	8.2.3	The sentence 'An extra year – 2015 is considered as a lookback period for patients enrolled in 2016' was removed	Does not apply to the sensitivity analysis that will use all available lookback time
2	6th October 2020	8.3.5	Clarified that the list of antibiotics applies both for switch and add-on treatments	Clarification
3	6th October 2020	8.7.3.1	Specify that concomitant or recent systemic corticosteroid use is included in the risk factors.	Clarification
4	6th October 2020	8.7.3.1	Rewording implying that past users cannot become incident users instead of stating they are at risk of incident use. '….excluding past users **who cannot become incident users** ~~are no longer at risk of incident use~~'	Clarification
5	6th October 2020	8.7.5	rewording to ensure the data will be further stratified if numbers do permit	Clarification
6	6th October 2020	8.2.6 and 8.7.3.1	Addition of stratification by duration of fluoroquinolone treatment episode. 8.2.6.8 Sub-population by duration of fluoroquinolone episode Stratification by duration of Fluoroquinolone episode duration, as calculated in section 8.3.2 will be performed, The categories will be decided based on duration of use distribution observed.	Omission corrected.
7	6th October 2020	8.7.5	The word contraindicated removed to align with the wording in the SmPC	Clarification

5 Milestones

Milestone	Planned date
Milestone	**Planned date**
Approval Study Protocol by EMA	21st September 2020
Registration in the EU PAS register	October 2020
Start of data collection	NA. Data extraction start date is 1st January 2016
End of data collection	Data extraction start date is 1st January 2016
Final study report provided to EMA	6th September 2021
Manuscript to be provided to EMA	6th November 2021

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 ischemia (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 EU. In 2008, the 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 updated 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 the 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 (9). In November 2018, the EMA concluded that serious adverse reactions including tendon, muscle and joint disorders, neurologic and psychiatric disorders 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 communication (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 utilization study, coupled with a before and after analysis of prescribing trends is a commonly utilized approach for measuring the effect of risk minimization measures (10). In a systematic review of studies investigating analytical approaches used for impact studies, 55% of all included studies used drug utilization as a measure of impact (11).

In a previous descriptive study conducted in the UK, France and Germany prior to the recommendations in 2018, fluoro(quinolones) 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 (2,12). There have been no descriptive studies on fluoro(quinolone) drug utilization in the EU after the EMA recommendations were made.

7 Research Questions and Objectives

The overall aim of this study is 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 2020 by:

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

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

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

3. To determine prescribers' compliance with warnings in fluoroquinolones SmPC section 4.4, on tendinitis and tendon rupture as well as in aortic aneurysm/dissection 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 aneurysm/dissection

    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 and later switched to another treatment.

8 Research Methods

8.1 Study Design

A retrospective population-based cohort study will be created conducted using electronic health care records from six databases from six European countries. This is a drug utilization study with a time series analysis component to identify the potential impact of regulatory interventions on fluoroquinolones' prescribing trends.

8.2 Setting

This study will be conducted in six EU member state countries where fluoroquinolones are marketed. Data from six databases from six European countries namely IPCI (the Netherlands), SIDIAP (Catalonia Spain) and IQVIA (UK IMRD, LPD Belgium, DA Germany and LPD France). Data from these databases

have been mapped to the OMOP Common Data Model (see https://github.com/OHDSI/CommonDataModel/wiki for more details).

8.2.1 Study Time Period

The study time period is 1st January 2016 until the latest available data cut-off. A table with provisional data cut-off points is presented below:

Database	Data lock point
LPD Belgium	December 2020
LPD France	May 2020
DA Germany	June 2020
UK IMRD	January 2021
LPD Italy	December 2020
IPCI	January 2021
SIDIAP	January 2021

8.2.2 Index Date

For each patient, follow-up will start from the date on which they contribute active follow-up time.

8.2.3 Follow-up Period and Censoring

The follow-up period begins at the latest of:

- study start date
- patient registration date
- end of the 12 months continuous enrolment window (see inclusion criteria)

Patients are censored at the earliest of

- date of patient death
- date of patient exit (deregister) from a contributing data provider (GP practice)
- date that a contributing provider exits the data source (last collection date)
- end of the database's data collection
- end of study period (latest data cut-off)

The lookback window for evaluating risk factors is 'ever before'(from registration date until index date). This can introduce information bias if some patients have longer lookback window than others. A sensitivity analysis where the look back window will be restricted to one year will also be applied, see section 8.7.6.

8.2.4 Study Population

The study population in each database will include all patients who contribute observation person-time at risk in each database during the study time period and meet the study selection criteria.

8.2.5 Patient Selection

In each country, patients who meet all of the inclusion criteria and none of the exclusion criteria will be selected.

8.2.5.1 Inclusion Criteria

The inclusion criteria are:

- All patients with an active registration status during the study time period
- Continuous enrolment in the database for more than 12 months

8.2.5.2 Exclusion Criteria

Patients will be excluded if they are

- Missing age or sex

The design of the study presented is summarised in Figure 1 Study design

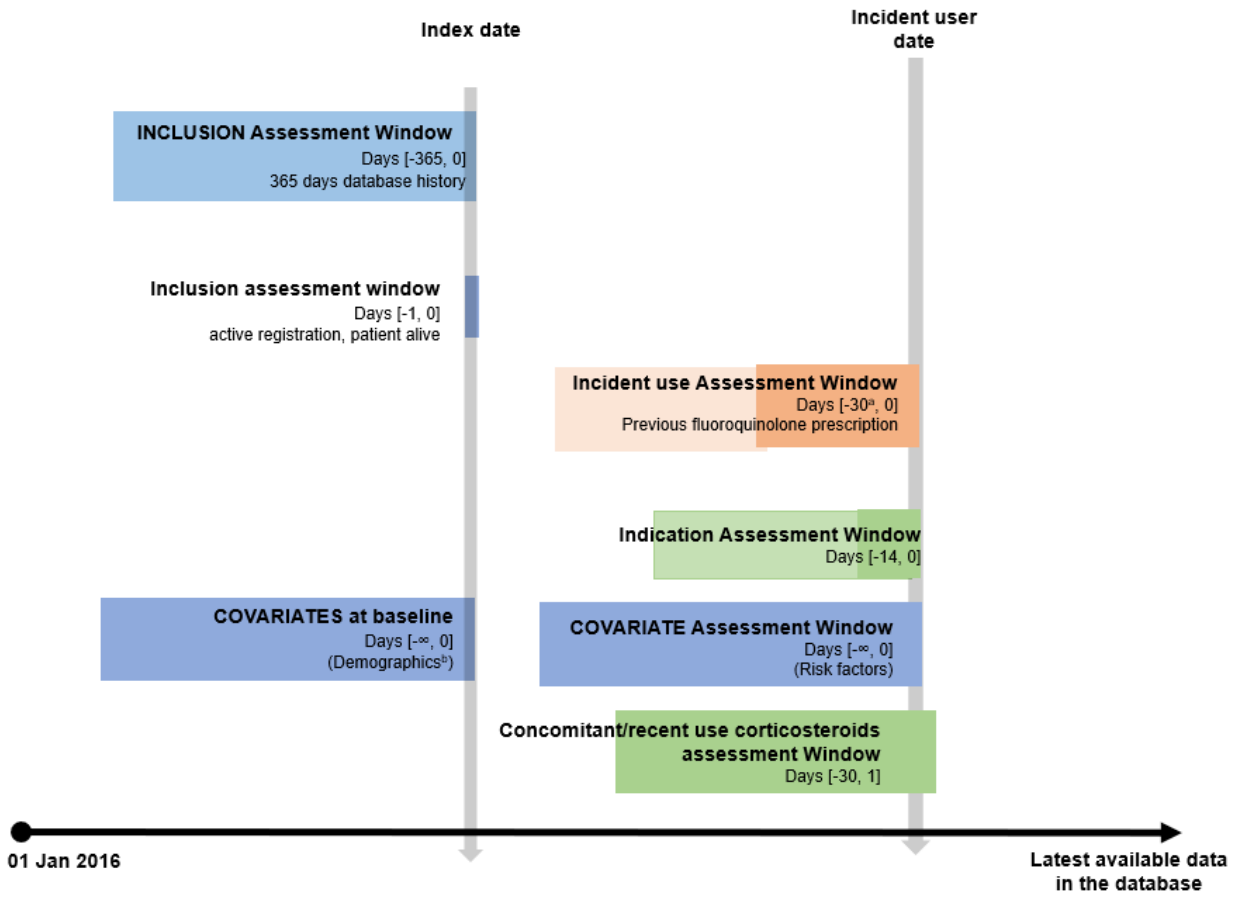

Figure 1 Study design

Legend:

a. Demographics: age, sex, calendar year or time period of index; b- Sensitivity analysis to vary this window will be applied. Incident use assessment window – is a lookback window of 30 days or more where used to check if the patient received another fluoroquinolone prescription and therefore is a prevalent user; Indication assessment window – is a lookback window of 14 days or more used to check the indication for which fluoroquinolones were prescribed.

8.2.6 Sub-Populations

Categories of sub-populations of interest are defined by indication, age group, sex, concomitant risk factors for tendinitis or tendon rupture, aortic aneurysm/dissection, active substance, route of administration, prescriber specialty and country as described below.

Not all subgroupings apply to all objectives and more details about the stratifications are presented in Section 8.7 Data analysis.

8.2.6.1 Sub-populations by indication

All fluoroquinolone exposed patients will be classified by the underlying diagnosis, where identifiable, into on-label indications (which includes first line and last line indications) and off-label indications (mild infections for which fluoroquinolones are not indicated for), see algorithms defined in section 8.3.3. All fluoroquinolone exposed patients, for whom an underlying diagnosis cannot be identified from the predefined list will be classified as “Unknown”.

The indications will be categorized into the following pre-specified groups, see section 8.3.3 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)

For some of the above groups, subcategories will be made to further stratify according to whether therapy is first or last line.

8.2.6.2 Sub-populations by age group

Sub-populations by age group will be defined using age at the start of each calendar year. Ten-year age categories will be 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 will be explored: <18 years, 18 -<=75 years, and >75 years.

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

8.2.6.3 Sub-populations by sex

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

8.2.6.4 Sub-populations by active substance

The fluoroquinolone exposed population will be further stratified by the type of fluoroquinolone.

8.2.6.5 Sub-populations by country

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

8.2.6.6 Sub-population by specialty

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

8.2.6.7 Sub-population by route of administration

Quinsair (levofloxacin), the only fluoroquinolone administered by inhalation will be analysed separately from the systemic (parenteral/oral) routes of administration.

8.2.6.8 Sub-population by duration of fluoroquinolone episode

Stratification by duration of Fluoroquinolone episode duration, as calculated in section 8.3.2 will be performed, The categories will be data driven and decided upon to reflect the distribution of duration of use observed.

8.3 Variables

In order to meet the study objectives, the following parameters will be obtained from each data source and analysed:

- Demographics
- Exposures of interest
- Indication of use
- At risk groups of interest
- Alternative antibiotics exposure

8.3.1 Demographics

Sex will be regarded as a fixed covariate throughout the study period.

Age will be assessed at the start of each calendar year.

8.3.2 Exposures of interest

From the study population, an exposed cohort will be 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 is not directly available from the Anatomical Therapeutic Class (ATC) codes. The exposed cohort will be further stratified by individual fluoroquinolones of interest, and also by route of administration (systemic or inhaled).

The fluoroquinolones of interest are ofloxacin, ciprofloxacin, norfloxacin, lomefloxacin, levofloxacin and moxifloxacin. The duration of each drug episode will be obtained from the DRUG_EXPOSURE table in the CDM. See Table 1.

The DRUG_EXPOSURE table in the CDM contains the drug_exposure_start_date and the drug_exposure_end_date. These are 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 1 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 is inferred by the extraction transform load (ETL), using other information or a default, see Table 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.
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 days_supply variable in each database is taken directly from the source. If days_supply is not provided it is calculated through logic described in table 2.

Table 2 Calculation of duration of use and end of treatment across databases

	IPCI	UK IMRD	Germany DA	Belgium LPD	SIDIAP	France LPD
If days_supply is missing	Use amount and dose extracted from the sig	Use daily dosage along with prescribed quantity	Impute with the most frequent daily dosage or DDD at a therapy level	Use calculated quantity/ units_per_day.	Use the quantity, daily dosage and DDD of each drug	Use the quantity and daily dosage of each drug
If still missing	Use the DDD and	Impute most frequent	-	-	-	-

	prescribed quantity	daily dose at the drug level
If still missing - imputation	Impute the DDD derived duration OR use the modal duration OR default to fixed duration depending on the drug of interest.	

DDD= defined daily dose; 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.

These are the rules applied before transformation in OMOP model. After this, the same imputations will be applied across databases.

Incident fluoroquinolone use is defined as a recorded prescription of fluoroquinolone in a patient with no fluoroquinolone use within the previous 30 days, calculated at substance level.

As the choice of 30 days to define monthly incident prescription is somewhat arbitrary, we will conduct a sensitivity analysis to examine the robustness of our definition, by varying the look back window used to define incident prescriptions. We will explore look back periods of 60, 90 and 180 days in the sensitivity analysis (see section 8.7.7) 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, up to 4-6 weeks for osteomyelitis. However, for most indications, fluoroquinolones treatment duration is usually between 7-14 days.

Duration of treatment episode for each exposed patient will be 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, will signal the end of the treatment episode, this is based on the average duration of treatment of 7-14 days (13).

Sensitivity analysis will be applied, see section 8.7.7.

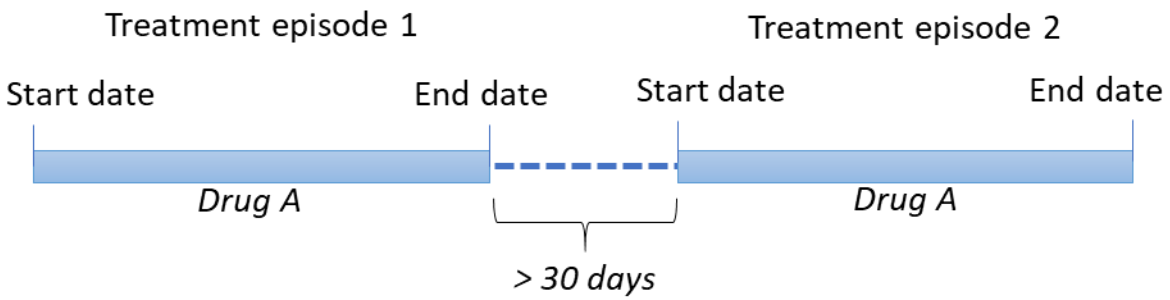

Figure 2 Schematic depiction ascertainment of treatment episodes

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 will have a hard stop at 5 or 7 days unless requested by a physician.

Our discontinuation algorithm is based on the 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 requires different antibiotics.(14)

The discontinuation will be 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, see full list in the Annex 4 Code lists)

OR

2. A code suggesting lack of effectiveness during treatment episode (e.g., infection resistant to antimicrobial drug, infection due to resistant bacteria), see full list in the Annex 4 Code lists

OR

3. Switch - an overlapping antibiotic prescription before the end of the current treatment episode. See 8.3.5

8.3.3 Indication of use

The underlying indication for which a fluoroquinolone is used will be 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 time window has been previously used to identify underlying indications for antibiotic use in primary care data. (12,15)

If no indication is found, and if another antibiotic is used in the 14 days' time window, the indication search will be extended another 14 days before the respective antibiotic start date.

If multiple indications are found, the patient will be counted once for each indication. Counts of patients with more than one indication will be reported.

The indications will be categorized as mentioned in section 8.2.6.1.

Off label and on label classification - In line with GVP 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''.(16) Information from the SmPC and art 31 referral will be used to classify indications as on-label or off-label, see Annex 3.

8.3.3.1 Algorithms for on label indications that require severity/recurrence assessment

When the recommendation is to use fluoroquinolones only in severe infection of a certain type (e.g., complicated urinary tract infections or complicated skin infection), an algorithm that considers additional clinical information will be used to capture disease severity.

As this algorithm requires quite detailed clinical information that is likely not to be captured in less granular databases, the algorithm might not work equally well in all databases.

Complicated urinary tract infection is 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 < 90ml/min/1.73m^2)

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

Complicated skin infections are 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 is defined as the presence of [a code for recurrent cystitis OR (two episodes of cystitis in the previous six months) OR three episodes of cystitis in the previous 12 months)] AND female sex

Recurrent and non-responsive acute otitis media is defined as the occurrence of three episodes of acute otitis media in a period of three months OR four or more episodes in twelve months. Nonresponsive acute otitis is 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 is defined as the prescription of any antibiotic regimen for at least six 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 is based on a systematic review, which indicated a period of > 6 months duration of treatment is often used to indicate prophylaxis in recurrent UTI management (17).

8.3.3.2 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

- Community acquired pneumonia

- Pneumonia due to Gram negative bacteria

- Simple uncomplicated acute cystitis
- Recurrent cystitis in women

For these indications, we will stratify if fluoroquinolones were used as first line or last line.

For this study, first line of treatment is 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”(18,19).

Last line for fluoroquinolones used in primary care for the infections listed above, is 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). (14,20)

8.3.4 At risk groups of interest

This risk factors list is not exhaustive. When creating risk groups, we have included only risk factors that have been consistently identified to be associated with the adverse events of interests in the literature. The factors mentioned in the Art31 referral procedure were all considered. (9)Thereas there is still some uncertainty about some other risk factors directly related to the long-lasting, disabling and potentially irreversible adverse drug reactions associated with (flouro)quinolones.

Risk Group for tendinitis and tendon rupture

Risk group for tendinitis and tendon rupture:

- 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) (full code list provided in the Annex 4).

Note: Physical activity is a known risk factor for tendon rupture that was deliberately ignored as it is not adequately captured in the databases.

Corticosteroid use is also a recognized 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 - is defined to have occurred when a systemic corticosteroid treatment episode started recently before or during fluoroquinolone treatment episode. Recent systemic corticosteroid use is 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 will be included: prednisolone, methylprednisolone, beclomethasone, betamethasone, dexamethasone, hydrocortisone, cortisone and triamcinolone. Topical formulations of corticosteroids are excluded due to the lower dose and limited systemic effect.

Risk Group for aortic rupture or aneurysm

Risk group for aortic rupture or aneurysm include individuals who have 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, ischemic heart disease or cerebrovascular disease.
- Tobacco user

The list is based on a literature review and NHS websites (21–23) (code list provided in the Annex 4).

Presence of these risk factors will be based on at least one record in the entire patient medical records before fluoroquinolone prescription.

8.3.5 Alternative antibiotics exposure

Within the fluoroquinolone exposed cohort, exposure to alternative antibiotics is defined as a prescription for a new antibiotic during a fluoroquinolone treatment episode (switch). This translates 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, complicated anthrax infection which are likely to be treated with multiple antibiotics at the same time, an overlapping antibiotic during the current treatment episode will not signal switching but add-on.

The following predefined categories will be investigated as alternative medications (both switch and add-on): tetracyclines, penicillins, cephalosporins, macrolides, aminoglycosides and other antibiotics (sulphonamides and other combinations).(12)

8.4 Data Sources

For this study, we will include Electronic Health Record data from six primary care databases throughout Europe, specifically IPCI (the Netherlands), SIDIAP (Spain), IMRD (UK), LPD (Belgium), DA Germany and LPD France. 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 Belgium	IQVIA	Belgium	1.1 M	2005 - present
LPD France	IQVIA	France	7.8M	1994 - present
DA Germany	IQVIA	Germany	34M	1992 - present
UK IMRD	IQVIA	UK	15.2M	1996 - present
IPCI	Erasmus MC	Netherlands	2.6M	1996 - present

SIDIAP	IDIAP Jordi Gol	Spain	5.6M	2006 - present

8.4.1 Integrated Primary Care Information, Erasmus MC, the Netherlands

IPCI is collected from EHR records 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 17M (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, from secondary care providers but the latter might not be complete. Approval needs to be obtained for each study from the Governance Board. (24)

8.4.2 Information System for Research in Primary Care, IDIAP Jordi Gol, Spain

SIDIAP is also collected from EHR records of patients receiving primary care delivered through Primary Care Teams (PCT), consisting of GPs, nurses and non-clinical staff. The Catalan Health Institute manages 286 out of 370 such PCT with a coverage of 5.6M patients, out of 7.5M people in the Catalan population (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 in pharmacies. 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. (25)

8.4.3 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 1.1M patients from a total of 11.5M 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 utilization studies.

8.4.4 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 34M distinct person records out of at total population of 80M (42.5%) in the country and collected from 2,734 providers. Patient visiting more than one provider are 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% Orthopedic Surgery, 11.8% Otolaryngology, 11.2% Dermatology, 7.7% Obstetrics/Gynecology, 6.2% various Neurology and Psychiatry 7.0% Pediatric, 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 utilization studies.

8.4.5 .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 EMR. Currently, >1200 GPs from 400 practices are contributing to the database covering 7.8M 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 utilization studies.

8.4.6 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 15.2M patients, 5.6M providers, 793 care sites and more than 5 billion service records, covering 22.5% of a population of 67.5M. 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.

8.5 Sample Size

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

Table 4 describes the number of users per fluoroquinolone entity in the databases based on a count conducted for years 2016-2019 inclusive but this number might change based on new available data.

Table 4 Number of patients treated with fluoroquinolones in each database

	Ofloxacin J01MA01	Ciprofloxacin J01MA02	Norfloxacin J01MA06	Lomefloxacin J01MA07	Levofloxacin J01MA12	Moxifloxacin J01MA14
IPCI	11,388	47,890	3,167	0	2,199	1,347
SIDIAP	8,737	387,336	75,854	0	172,515	47,158
LPD BELGIUM	5,358	28,263	2,422	0	3,233	17,845
LPD FRANCE	123,659	55,198	34,804	22,977	25,916	7,377
DA GERMANY	139,026	472,296	22,313	0	100,514	42,127
IMRD UK	1,373	6,264	0	0	72	3

Prulifloxacin and Rufloxacin have 0 counts; Enoxacin is no longer authorised in the EU.

8.6 Data Management

This study will follow relevant ENCePP guidelines and International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guidelines for data management.

Usually processes for database management differ by country. Generally, the data is stored at the database level and analysed locally thus files from the various data sources will be kept separate behind firewalls, and patient-level data will not be merged across data sources. The proposed databases to be used in this study are standardised to the OMOP common data model. This covers the specification for all variables that will be collected throughout the study and enables the use of standardised analytics and tools across the network since the structure of the data and the terminology system is harmonized. The OMOP CDM is developed and maintained by the Observational Health Data Sciences and Informatics (OHDSI) initiative and is described in detail on the wiki page of the CDM: https://github.com/OHDSI/CommonDataModel/wiki and in The Book of OHDSI: http://book.ohdsi.org.

For this study an open source Drug Utilisation R package will be developed suitable for the functionality needed for this study.

Each data partner will execute a Study R package against their database to generate the data for the drugs of interests, indications etc. After review of the results the data custodian returns them to the coordinating centre (IQVIA Ltd UK). The results from all six databases will then be combined in tables and figures for the study report.

8.6.1 CDM Data Quality Checks

OHDSI and the European Health Data & Evidence Network (EHDEN) have developed multiple quality control mechanisms for the Common Data Model. These are described in high detail in Chapter 15 of The Book of OHDSI (http://book.ohdsi.org/DataQuality.html).The Data Quality Dashboard (DQD) has been developed in the EHDEN project in close collaboration with OHDSI. The goal of the DQD is to design and develop an open-source tool to expose and evaluate observational data quality. This package will run a series of data quality checks against an OMOP CDM instance (currently supports v5.3.1 and v5.2.2). It systematically runs the checks, evaluates the checks against some pre-specified threshold, and then communicates what was done in a transparent and easily understandable way. The quality checks were

organised according to the Kahn Framework, which uses a system of categories and contexts that represent strategies for assessing data quality.

Using this framework, the Data Quality Dashboard takes a systematic-based approach to running data quality checks. Instead of writing thousands of individual checks, we use “data quality check types”. These “check types” are more general, parameterised data quality checks into which OMOP tables, fields, and concepts can be substituted to represent a singular data quality idea.

Version 1 of the tool includes 20 different check types organised into Kahn contexts and categories. Additionally, each data quality check type is considered either a table check, field check, or concept-level check. Table-level checks are those evaluating the table at a high-level without reference to individual fields, or those that span multiple event tables. These include checks making sure required tables are present or that at least some of the people in the PERSON table have records in the event tables. Field-level checks are those related to specific fields in a table. The majority of the check types in version 1 are field-level checks. These include checks evaluating primary key relationship and those investigating if the concepts in a field conform to the specified domain. Concept-level checks are related to individual concepts. These include checks looking for sex-specific concepts in persons of the wrong sex and plausible values for measurement-unit pairs. For a detailed description and definition of each check type, you can refer to the GitHub documentation: https://ohdsi.github.io/DataQualityDashboard/articles/CheckTypeDescriptions. After systematically applying the 20 check types to an OMOP CDM version approximately 3,351 individual data quality checks are resolved, run against the database, and evaluated based on a pre-specified threshold. The R package then creates a json object that is read into an RShiny application to view the results. Results from the DQD may be used to inform supplemental investigations into ETL processes and identify opportunities for enhancement of each local CDM.

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concepts. These include checks looking for sex-specific concepts in persons of the wrong sex and plausible values for measurement-unit pairs. For a detailed description and definition of each check type, you can refer to the GitHub documentation: https://ohdsi.github.io/DataQualityDashboard/articles/CheckTypeDescriptions. After systematically applying the 20 check types to an OMOP CDM version approximately 3,351 individual data quality checks are resolved, run against the database, and evaluated based on a pre-specified threshold. The R package then creates a json object that is read into an RShiny application to view the results. Results from the DQD may be used to inform supplemental investigations into ETL processes and identify opportunities for enhancement of each local CDM.

Each data source custodian will maintain any patient-identifying information securely on site according to internal standard operating procedures (SOPs). If the study is sub-contracted by IQVIA to a third party, the datasets and analytics programmes will be stored according to the vendor's procedures. Security processes will be in place to ensure the safety of all systems and data. Every effort will be made to ensure that data are kept secure so that they cannot be accessed by anyone except selected study staff. Appropriate data storage and archiving procedures will be followed. Standard procedures to restore files in the event of a hardware or software failure will be in place at each data source. It is expected that the principle of the CDM will be applied to data sources outside of the OMOP network in order to standardise the study outputs where possible. The results from all databases will then be combined in tables and figures for the study report.

The study sponsor will not have access to health records at the level of the individual patient but only to tables with aggregated data.

8.7 Data Analysis

8.7.1 General considerations

Continuous variables will be described using mean, standard deviation, median, first and third quartiles, minimum, and maximum. Categorical variables will be described by the number and percentage of patients in each category. The number of patients with missing data for key variables will be reported- no imputation will be performed to handle missing data (apart from treatment duration that was specified previously). Confidence intervals (CIs) of 95% will be presented for means using a normal approximation. All results will be 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) will be suppressed.

8.7.2 Descriptive analyses

An initial exploratory descriptive analysis will be conducted for each database-specific cohort to provide insight into general patterns, functional form and any outliers of exposure variables and covariates. These initial data will be further summarized using descriptive statistics as outlined in the previous section. Additionally, variable distribution will be explored visually using bar charts, boxplots or histograms where relevant. Baseline characteristics as observed on the index date will be summarized for each country. This includes age, sex, and other covariates (indications, risk factors and exposures of interest).

8.7.3 Incidence of drug use

8.7.3.1 Crude and stratified incidence of drug use

Monthly incident drug use will be expressed as the number of users per 1,000 persons per month presented by calendar year, see example below. Presentation by quarter will be also provided in the Supplementary tables.

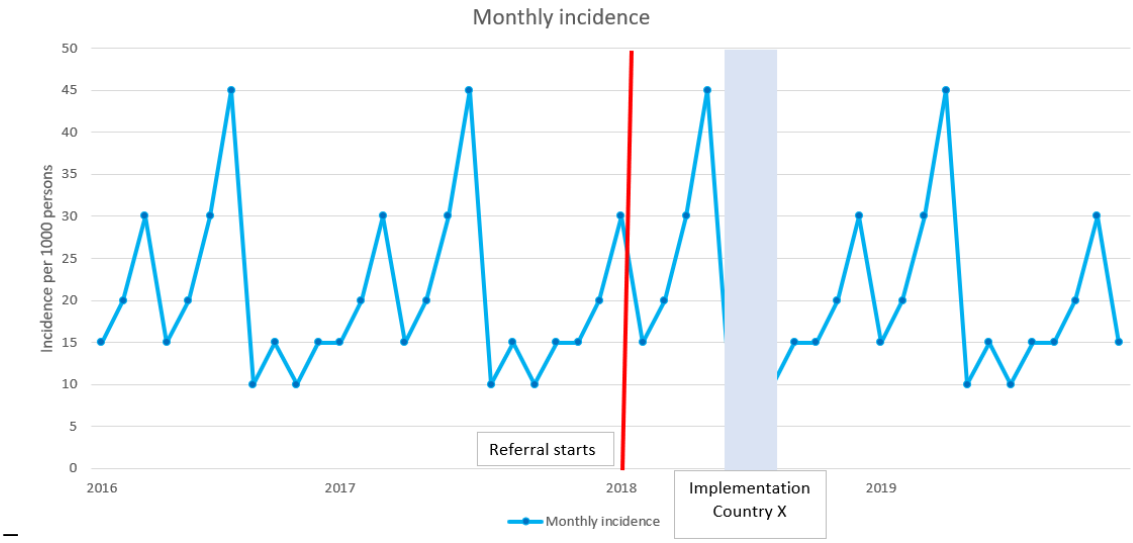

Figure 3: Mock depiction of incident use of fluoroquinolone per month for the study period.

The numerator will consist of the number of incident users in each month. An incident user is defined as a patient with a recorded prescription of the drug of interest, and no record for a prescription of the same drug within the previous 30 days (substance specific definition, not class level, details provided in Section 8.3.2). Planned sensitivity analysis varying the time period as described in section 8.7.6.

The denominator will consist of the total active patient population for each calendar month in each database contributing at least one day of follow-up time in that calendar month, excluding past users who cannot become incident users. , unless there is more than 30 days (or more, in the sensitivity analysis) between prescriptions.

Individuals can be exposed to fluoroquinolone multiple times in the study time period. Therefore, an individual can be defined as an incident user on multiple occasions during the study period.

Additionally, if a patient switches from one fluoroquinolone to another, that patient may be counted as an incident user for each of the fluoroquinolones used.

For each calendar year, stratum specific estimates will be presented separately according to: age at start of calendar year (categorical), sex, baseline concomitant risk factors for tendinopathy and aortic

dissection (grouped, see Section 8.3.4) including systemic corticosteroids indications (grouped, see section 8.2.6.1) and duration of fluoroquinolone treatment episode.

8.7.3.2 Crude and stratified early discontinuation proportion

Monthly early discontinuation proportion will be expressed as the number of patients identified as stopping treatment early (see definition in Section 8.3.2) per 1,000 incident users per month presented by calendar year and per quarter.

For estimation of early discontinuation proportions per calendar month, the numerator will consist of the number of incident users in each month identified as having discontinued treatment prematurely (see section 8.3.3). These patients will therefore be a sub-cohort of incident users. The denominator will consist of all patients as defined in section above (incident users). This implies that an individual can be flagged as discontinuing treatment prematurely on multiple occasions during the study period.

For each calendar year, stratum specific estimates will be presented according to: age at start of calendar year (categorical), sex and indication and type of practice if available, see section 8.2.6.

8.7.4 Time-series analysis of changes in prescribing patterns following the regulatory intervention

A Joinpoint regression model will be used to investigate changes in prescribing patterns over calendar time as recommended by Annex 2 of ENCePP Methodological Guide. Joinpoint regression calculates time points of trend line changes and offer an alternative if the date of the intervention is unknown (26) or if there are multiple intervention points.

A Joinpoint regression model will be used to investigate changes in prescribing patterns over calendar time. The response variable will be prescribing incidence proportion, and the independent variable will be calendar year 2016 to 2020. The minimum number of joinpoints specified will be zero, the maximum number of joinpoints will equate to the total number of regulatory interventions and major milestones of the referral regulatory procedures. The predicted moments of change in trend can be then compared with the known times of regulatory interventions in each country. Analysis will start with zero joinpoints, and test whether ≥1 joinpoints improves the model (based on a 5% significance level).

8.7.5 Prescriber compliance with labelled warnings for use

Stratum specific estimates of monthly incidence drug use will be presented according to: concomitant risk factors for tendinopathy and for aortic aneurysm , systemic corticosteroids, indications and line of therapy for each indications. These data willbe further stratified according to individual fluoroquinolones of interest, age category (10 years) and sex, if numbers allow stratification. Data will also be examined for evidence of seasonal fluctuations.

8.7.6 Alternative antibiotics prescribing

Monthly incidence prescribing rates for alternative medicines used by patients where systemic fluoroquinolones have been switched to another antibiotic.will be presented.

These patients will therefore be a sub-cohort of incident users (as defined in section 8.7.3). The denominator will consist of anyone with a prescription for fluoroquinolone as described in section 8.7.3.1. The numerator will be all patients who had a fluoroquinolone prescription in the medical history and were switched to another antibiotic before the end of the fluoroquinolone treatment episode. An individual can be flagged as using alternative medications on multiple occasions during the study period.

Stratum specific estimates of monthly incidence prescribing rates for alternative medicines used by patients where systemic fluoroquinolones have previously been prescribed **or** discontinued will be presented according to: indication (grouped), age group and sex.

8.7.7 Sensitivity analysis

Sensitivity analysis varying the time periods used in the main definition to alternative definitions will be conducted.

Table 5: Sensitivity analyses

	Main Definition	Alternative Definition
Incident fluoroquinolone	No fluoroquinolone exposure in the last 30 days	• No fluoroquinolone exposure in last 60 days • No fluoroquinolone exposure in last 90 days

use assessment window		• No fluoroquinolone exposure in last 180 days
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
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
Lookback window for risk factors	Any time prior fluoroquinolone exposure	• 365 days prior fluoroquinolone exposure

8.8 Quality Control

IQVIA Quality Management System (QMS)

As the coordinating centre for this collaboration, the IQVIA QMS will be applied. This IQVIA QMS is built upon the quality and regulatory compliance principles established by the standards and guidelines from the International Standards Organisation (ISO) and International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (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 are conducted within the work-frame of IQVIA Quality Management System (QMS) and in accordance to the appropriate global procedure.

A Quality Control checklist will be developed and executed for the study, which will include 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 will establish 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 will be documented, and include the required correction actions, if any.

4. The execution of any required corrective action will be documented.

Also, the Principal Investigator and Senior QC of the study will 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.

8.9 Limitations of the Research Methods

For this study we will use real world data from electronic health care records from six different countries. There may be differences between the databases with regard to how certain data are captured. For this study, we are interested in the indication for the use of fluoroquinolones as well as underlying comorbidities, with particular emphasis on the risk factors for serious adverse events. Both the indications and the presence of underlying comorbidities might be underreported in the source databases.

Indication of use – as the databases do not record indication, a condition code proximal to prescription will be used. This may lead to missing some indications and misclassification of some. This limitation is addressed by looking specifically for fluoroquinolone indications and by varying the lookback window. A single prescription can have more than one indication.

Very specific indications – some of the fluoroquinolones indications are very specific (e.g., Pneumonia due to Gram negative bacteria, infections in neutropenic patients, complicated urinary infections) and although we are trying to capture as much clinical information as possible via constructed algorithms, this might be very challenging in less granular databases and a degree of misclassification is expected.

Non-adherence to antibiotic therapy is a well-known phenomenon. Therefore, there is a potential of overestimating fluoroquinolone use since the actual drug intake might be lower. The early discontinuation, which is algorithmically derived, might be misclassified as not all reasons for discontinuation will be captured.

As we are using primary care databases, the use of fluoroquinolones within a hospital setting is absent. The implication for this is that we may miss some indications and incident users, particularly for last line therapy and indications for severe conditions. This missing data is likely to be differential, skewed towards the more serious and the last line indications.

Local and regional clinical guidelines – as this is a multi-country studies, prescribing and use in each country are influenced by local guidelines which might also differ between each other. It is beyond the scope of this study to consider these differences, the drug use will be just described and not interpreted in view of the clinical guidances.

Finally, the databases are a subsample of the full population and results should be used with caution when attempting to infer the results nation-wide.

9 Protection of Human Subjects

For this study, participants from various EU member states will process personal data from individuals which is collected in national/regional electronic health record databases. Due to the sensitive nature of this personal medical data, it is important to be fully aware of ethical and regulatory aspects and to strive to take all reasonable measures to ensure compliance with ethical and regulatory issues on privacy.

All the databases used in this study are already used for pharmaco-epidemiological research and have a well-developed mechanism to ensure that European and local regulations dealing with ethical use of the data and adequate privacy control are adhered to.

In agreement with these regulations, rather than combining person level data and performing only a central analysis, local analyses will be run, which generate non-identifiable aggregate summary results. The output files will not contain any data that allow identification of subjects included in the study. IQVIA has an internal set of rules and processes associated with Data quality assurance. Patient confidentiality will be protected according to the EU General Data Protection Regulation (GDPR)] on the protection of individuals. Security of the data will be maintained at all times. Access will be limited to authorized individuals.

9.1 Required submissions and approvals in the study target countries

The protocols will be reviewed by the Institutional Review Boards of the respective databases. As this is a non-interventional observational study, there is no need for ethical approval in the Netherlands, UK, Belgium, Germany and France. For SIDIAP (Spain), both the scientific committee for SIDIAP studies and the local ethics committee will evaluate the protocol before the study can be carried out. IQVIA follow best practice guidelines for the conduct of pharmacoepidemiologcal studies. (27)

10 Management and Reporting of Adverse Events/ Adverse Reactions

This study will adhere to the International Society for Pharmacoepidemiology (ISPE) good pharmacoepidemiology practice guidelines. This is a non-interventional study design, which is based on secondary data use. Expedited reporting of Adverse Events (AE) and Adverse Drug Reactions (ADR) is not required.

11 Plans for Disseminating and Communicating Study Results

11.1 Final Analyses and reporting

The final study report will be written in accordance with the GVP guidelines module VIII, (EMA/813938/2011). In accordance with the 2010 EU pharmacovigilance legislation (Articles 10 or 10a of Regulation (EC) No 726/2004; Articles 21a or 22a of Directive 2001/83/EC), information about this PASS will be entered into the publicly available EU PAS register before the start of data collection. Updates to the study protocol in case of substantial amendments, progress reports where applicable, and the final study report will also be entered in the register.

11.2 Publications

Study findings will be considered for publication as open access. Any publication will be guided by the Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Writing and Editing for Biomedical Publication of the International Committee of Medical Journal Editors (ICMJE). (28) Reporting will be consistent with the RECORD-PE guidelines for reporting of studies conducted using observational routinely collected health data.(29)

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Annexes

Annex 1. List of stand-alone documents

NA

Annex 2. ENCePP Checklist for Study Protocols

Doc.Ref. EMA/540136/2009

ENCePP Checklist for Study Protocols (Revision 4)

Adopted by the ENCePP Steering Group on 15/10/2018

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) welcomes innovative designs and new methods of research. This Checklist has been developed by ENCePP to stimulate consideration of important principles when designing and writing a pharmacoepidemiological or pharmacovigilance study protocol. The Checklist is intended to promote the quality of such studies, not their uniformity. The user is also referred to the ENCePP Guide on Methodological Standards in Pharmacoepidemiology, which reviews and gives direct electronic access to guidance for research in pharmacoepidemiology and pharmacovigilance.

For each question of the Checklist, the investigator should indicate whether or not it has been addressed in the study protocol. If the answer is "Yes", the section number of the protocol where this issue has been discussed should be specified. It is possible that some questions do not apply to a particular study (for example, in the case of an innovative study design). In this case, the answer 'N/A' (Not Applicable) can be checked and the "Comments" field included for each section should be used to explain why. The "Comments" field can also be used to elaborate on a "No" answer.

This Checklist should be included as an Annex by marketing authorisation holders when submitting the protocol of a non-interventional post-authorisation safety study (PASS) to a regulatory authority (see the Guidance on the format and content of the protocol of non-interventional post-authorisation safety studies). The Checklist is a supporting document and does not replace the format of the protocol for PASS presented in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

Study title:

EU PAS Register® number: **Study reference number (if applicable):**

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	8.2.1
1.1.2 End of data collection[2]	☒	☐	☐	
1.1.3 Progress report(s)	☐	☐	☒	
1.1.4 Interim report(s)	☐	☐	☒	
1.1.5 Registration in the EU PAS Register®	☒	☐	☐	5

[1] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.
[2] Date from which the analytical dataset is completely available.

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1.6 Final report of study results.	☒	☐	☐	5

Comments:

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1 Does the formulation of the research question and objectives clearly explain:	☐	☐	☐	
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	6
2.1.2 The objective(s) of the study?	☒	☐	☐	7.1
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	8.2.4
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☒	☐	☐	7.1

Comments:

Section 3: Study design	**Yes**	**No**	**N/A**	**Section Number**
3.1 Is the study design described? (e.g. cohort, case-control, cross-sectional, other design)	☒	☐	☐	8.1
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	8.4
3.3 Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☒	☐	☐	8.7
3.4 Does the protocol specify measure(s) of association? (e.g. risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))	☐	☐	☒	
3.5 Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☐	☐	☒	

Comments:

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
4.1 Is the source population described?	☐	☒	☐	
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period	☒	☐	☐	8.2.1
4.2.2 Age and sex	☒	☐	☐	
4.2.3 Country of origin	☒	☐	☐	8.2.4
4.2.4 Disease/indication	☒	☐	☐	
4.2.5 Duration of follow-up	☒	☐	☐	8.2.3
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	8.2.5

Comments:

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
5.1 Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	
5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☐	☒	☐	
5.3 Is exposure categorised according to time windows?	☐	☒	☐	
5.4 Is intensity of exposure addressed? (e.g. dose, duration)	☐	☒	☐	
5.5 Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☒	☐	
5.6 Is (are) (an) appropriate comparator(s) identified?	☐	☐	☒	

Comments:

Section 6: Outcome definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☐	☐	☒	
6.2 Does the protocol describe how the outcomes are defined and measured?	☐	☐	☒	
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	☐	☐	☒	
6.4 Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease or treatment, compliance, disease management)	☐	☐	☒	

Comments:

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol address ways to measure confounding? (e.g. confounding by indication)	☐	☐	☒	
7.2 Does the protocol address selection bias? (e.g. healthy user/adherer bias)	☐	☐	☒	
7.3 Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	☒	☐	☐	8.9

Comments:

Section 8: Effect measure modification	**Yes**	**No**	**N/A**	**Section Number**
8.1 Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	☐	☐	☒	

Comments:

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	8.4

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☐	☐	☒	
9.1.3 Covariates and other characteristics?	☒	☐	☐	8.4
9.2 Does the protocol describe the information available from the data source(s) on:				
9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	8.4
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☐	☐	☒	
9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	8.4
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☒	☐	☐	8.4
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☐	☐	☒	8.4
9.3.3 Covariates and other characteristics?	☐	☐	☐	
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	☒	

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Are the statistical methods and the reason for their choice described?	☒	☐	☐	8.7
10.2 Is study size and/or statistical precision estimated?	☐	☒	☐	
10.3 Are descriptive analyses included?	☒	☐	☐	8.7.2
10.4 Are stratified analyses included?	☒	☐	☐	8.7
10.5 Does the plan describe methods for analytic control of confounding?	☐	☐	☒	
10.6 Does the plan describe methods for analytic control of outcome misclassification?	☐	☐	☒	
10.7 Does the plan describe methods for handling missing data?	☐	☒	☐	
10.8 Are relevant sensitivity analyses described?	☒	☐	☐	8.7.6

Comments:

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section Number**
11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☐	☒	☐	
11.2 Are methods of quality assurance described?	☒	☐	☐	8.8
11.3 Is there a system in place for independent review of study results?	☒	☐	☐	

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☐	☐	☒	
12.1.2 Information bias?	☒	☐	☐	8.9
12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods).	☐	☐	☒	
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	☐	☐	☒	

Comments:

Section 13: Ethical/data protection issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☐	☐	☒	
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☒	☐	☐	8.6

Comments:

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Section Number**
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	4

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Section Number**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	11
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	11

Comments:

Name of the main author of the protocol: Alexandra Pacurariu

Date: 15/October/2020

Signature: 

Annex 3. On label and off label fluoroquinolones indications

On label		Off-label	
Respiratory tract infections			
Indication	**How is it captured**	**Indication**	**How is it captured**
Chronic sinusitis	Code based	Acute bronchitis	Code based
Chronic pulmonary infections in patients with cystic fibrosis	Code based	Pharyngitis	Code based
Broncho-pulmonary infections in cystic fibrosis or in bronchiectasis	Code based. Combination of codes to identify both infection and the chronic disease.	Tonsillitis	Code based
Pneumonia due to Gram negative bacteria (last line)	Code based. This is included in the broader CAP diagnosis and the same codes will be used. + algorithm to identify line of treatment	Laryngitis	Code based
		Nosocomial pneumonia	Code based. Might be missing in some databases.
Tuberculosis	Code based		
Inhalation anthrax (post exposure prophylaxis and curative treatment)	Code based		
Acute bacterial sinusitis (last line)	Algorithm to identify line of treatment		
Acute exacerbation of COPD (last line)	Algorithm to identify line of treatment		
Community acquired pneumonia (last line)	Algorithm to identify line of treatment		
Urinary tract infections			

On label		Off-label	
Complicated urinary tract infections	Algorithm to identify severity (see section 8.3.3)	Prevention of exacerbations in women with recurring urinary tract infections	Algorithm based on dose and duration of treatment (see section 8.3.3)
Acute pyelonephritis	Code based		
Simple uncomplicated acute cystitis (last line)	Code based Algorithm to identify line of treatment		
Recurrent cystitis in women (last line)	Algorithm to identify line of treatment and recurrence (see section 8.3.3)		
Genital tract infections			
Prostatitis	Code based	Vaginal infections	Code based. Might be missing in some databases.
Epididymo-orchitis	Code based		
Gonococcal urethritis	Code based		
Gonococcal Cervicitis	Code based		
Genital tract and gynaecological infections	Code based		
Pelvic inflammatory disease	Algorithm to identify line of treatment Disease definition is Code based		
Ear infections			
Malignant external otitis	Code based	External otitis	Code based
Chronic suppurative otitis media	Code based		
Acute otitis media (recurrent, non-responsive)	Algorithm to identify recurrence and lack of response		
Skin infections			
Complicated skin and soft tissue infections	Code based. Only specific skin infections which are always serious will be selected by a medic.		
Gastrointestinal infections			
Gastrointestinal infections	Code only	Prophylaxis of travellers' diarrhoea	Might be missing in some databases.

On label		Off-label	
Intra-abdominal infections	Code only	Selective decontamination of gastrointestinal tract in patients with compromised immune system	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 based
Prophylaxis of bacterial infections in neutropenic patients.	Code based - Identify neutropenic patients		
Others			
Infection in immunocompromised patients	Code based – identify immunocompromised patients	Septicaemia	Code based
		Meningitis	Code based
		Infection of cerebrospinal fluid	Code based
		Endocarditis	Code based

Annex 4 Exemplar code lists (standard concepts and data source codes)