O5 September 2022

Data analysis report

Drug utilisation study of macrolide-containing medicinal products during pregnancy

Table of Contents

1. Rationale and background

Recently there have been a number of publications investigating risks associated with macrolide use during pregnancy.

To support a thorough review of this issue within regulatory evaluation procedures , a drug utilisation analysis of macrolide use in pregnancy (stratified by specific agent) was considered relevant to inform decision-making

While identifying clinical codes in electronic health records that indicate events related to pregnancy is simple, reliably detecting the start and end of pregnancy, to be able to assess exposure by trimester, is significantly more complicated.

Recently there has been a few papers attempting to validate phenotyping algorithms to detect gestational age, including by Moll et al, Drug Saf. 2021[(1)], Taylor et al, PDS. 2022[(2)] and Matcho et al, PLoS One. 2018[(3)]. These tend to be specific to one or a small number of databases and data models and thus a direct application of these in new datasets is unfeasible.

Hence, in this study, a short validation of a phenotyping algorithm for gestational age was performed across three databases in OMOP common data model format: IQVIA™ Disease Analyzer Germany, IQVIA™ Disease Analyzer France and IQVIA™ Medical Research Database UK EMIS.

2. Research question and objectives

1) Develop and validate a phenotyping algorithm that identifies gestational age.
2) Describe the use of macrolides and amoxicillin during pregnancy, specifically:
    a) Prescriptions by year, age, gravidity, and trimester of pregnancy, stratified by substance
    b) Number of prescriptions and number of distinct substances prescribed by pregnancy
    c) Indications by substance
3) Characterise the drug quantity, namely number of units prescribed in tablets or capsules, of Erythromycin by trimester of pregnancy

3. Research methods

3.1. Study design

This was a longitudinal observational cohort study.

3.2. Setting and study population

The study period was from start of data collection for each of the three databases to January 2022. See details of each database in Annex I. The population included all pregnant women identified according to the phenotyping algorithm as defined in Annex II.

3.3. Variables

3.3.1. Vocabularies

The medical vocabulary used was OMOP Concept ids. These concept ids use SNOMED CT as standard vocabulary and are mapped to several other vocabularies, including Read, ICD-9 and ICD-10 as well as to the national editions of SNOMED CT.

The medicinal product dictionary used was RxNorm and extensions.

3.3.2. Pregnancy

A phenotyping algorithm to identify pregnancy start and end dates was developed in OMOP concept id and assessed using three databases in the OMOP common data model, IQVIA™ Disease Analyzer Germany, IQVIA™ Disease Analyzer France and IQVIA™ Medical Research Data EMIS (IMRD UK). The details of the phenotyping algorithm are in Annex II. Only the databases that allowed for consistent and reliable identification of pregnancy trimester were used as per the algorithm.

OMOP Concept ids for pregnancy and related events were extracted from the paper by Matcho et al, PLoS One. 2018.

The threshold to separate any two pregnancies was defined as any two pregnancy-related OMOP concept ids separated by more than 365 days or any pregnancy related code 90 days after a OMOP concept id related to abortion or miscarriage.

The main analysis was conducted using patients that had temporal consistency for codes identifying start of pregnancy and end of pregnancy. A sensitivity analysis was conducted with patients that had delivery codes in OMOP CDM.

3.3.3. Exposure

3.3.3.1. Antibiotics

OMOP concept codes were identified for the following macrolides: Azithromycin, Clarithromycin, Erythromycin, Midecamycin, Oleandomycin, Roxithromycin, Spiramycin, Telithromycin. For comparison, the OMOP concept codes for Amoxicillin were also used.

3.3.3.2. Indications

All observations within +/- seven days of the prescription of macrolide or amoxicillin-containing products were identified and screened for children concepts of the SNOMED CT Infectious disorders concept, in OMOP concept ids.

3.4. Data sources

The study was conducted using three European databases: a French database (IQVIA™ Disease Analyzer France December 2021 version) a German database (IQVIA™ Disease Analyzer Germany December 2021 version) and a United Kingdom database (IQVIA™ Medical Research Database January 2022 version) (see Annex I for more details).

3.5. Statistical analysis

3.5.1. Main statistical methods

A descriptive analysis of the use of macrolides and amoxicillin in pregnant women identified using the phenotyping algorithm as defined in Annex II was performed.

Descriptive statistics and summary tabulations of prescriptions of macrolides and amoxicillin by year, age group, gravidity (refers to the pregnancy number), trimester and indications, stratified by substance were performed. In addition, the number of prescriptions per pregnancy were determined and stratified by substance.

Trends of use of each substance over time, relative to number of pregnancies as determined by the phenotyping algorithm were also plotted.

Drug quantity is reported as pack size, only for standard pack sizes for each solid oral formulation of erythromycin.

The main analysis was conducted using patients that had temporal consistency for codes identifying start of pregnancy and end of pregnancy.

3.5.2. Sensitivity analysis

A sensitivity analysis was conducted with patients that had OMOP concept ids for full-term delivery (See Annex II).

Analyses were conducted by EMA researchers using IHD and R software.

3.6. Quality control

The study was conducted according to the ENCePP code of conduct (European Medicines Agency 2018). Standard operating procedures or internal process guidance were adhered to for the conduct of the study. These procedures include rules for secure and confidential data storage, quality-control procedures for all aspects of the study from protocol development to the reporting of the results.

All documents undergo at least one round a review by an experienced reviewer, while the results from the statistical analysis are either reviewed or checked via double coding.

The quality control of the data is the responsibility of the data holder.

4. Results

4.1. Main analysis

Of the three databases IQVIA™ Disease Analyzer France, IQVIA™ Disease Analyzer Germany and IMRD UK, only IMRD UK met the criteria defined by the pregnancy phenotyping algorithm. Results are shown in Annex II.

There were 15,868 pregnancies that met the criteria established in the pregnancy phenotyping algorithm. Of these, 3,794 took at least one of the substances selected for this study during a pregnancy.

Only three macrolide antibiotics were identified in the database used (azithromycin, erythromycin, clarithromycin). Of these, erythromycin is the one that has the greatest number of prescriptions. The prescription of the selected antibiotics seems to be evenly distributed across trimesters with only marginally more prescriptions on the third trimester in general and for erythromycin (**Table 1**).

Table 1: Prescription of selected antibiotics by age at start of the antibiotic and gravidity. *Absolute frequency. Unit is prescription, not person.*

	Amoxicillin (N=4466)	**Azithromycin** (N=44)	**Erythromycin** (N=391)	**Clarithro-mycin** (N=111)	**Total** (N=5012)
Age group at start of antibiotic: n (%)					
Younger than 20	250 (5.6%)	7 (15.9%)	22 (5.6%)	8 (7.2%)	287 (5.7%)
20 to 29	2143 (48.0%)	22 (50.0%)	189 (48.3%)	46 (41.4%)	2400 (47.9%)
30 to 39	1919 (43.0%)	14 (31.8%)	161 (41.2%)	55 (49.5%)	2149 (42.9%)
40 to 49	154 (3.4%)	1 (2.3%)	19 (4.9%)	2 (1.8%)	176 (3.5%)
50 and older	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Gravidity: n (%)					
1st	2039 (45.7%)	24 (54.5%)	158 (40.4%)	51 (45.9%)	2272 (45.3%)
2nd	1517 (34.0%)	6 (13.6%)	144 (36.8%)	42 (37.8%)	1709 (34.1%)
3rd	591 (13.2%)	2 (4.5%)	65 (16.6%)	11 (9.9%)	669 (13.3%)
4th and following	319 (7.1%)	12 (27.3%)	24 (6.1%)	7 (6.3%)	362 (7.2%)
Trimester of exposure: n (%)					
1	1393 (31.2%)	22 (50.0%)	131 (33.5%)	53 (47.7%)	1599 (31.9%)
2	1547 (34.6%)	11 (25.0%)	124 (31.7%)	22 (19.8%)	1704 (34.0%)
3	1526 (34.2%)	11 (25.0%)	136 (34.8%)	36 (32.4%)	1709 (34.1%)

In absolute terms, the number of prescriptions of these selected antibiotics has been decreasing overall since 2015 (**Table 2**).

Table 2: Prescription of selected antibiotics by year. *Absolute frequency. Unit is prescription, not person.*

	Amoxicillin (N=4466)	**Azithromycin** (N=44)	**Erythromycin** (N=391)	**Clarithromycin** (N=111)	**Overall** (N=5012)
Year of start of antibiotic: n (%)					
< 2010	1331 (29.8%)	1 (2.3%)	106 (27.1%)	11 (9.9%)	1449 (28.9%)
2010	164 (3.7%)	1 (2.3%)	19 (4.9%)	2 (1.8%)	186 (3.7%)

	Amoxicillin (N=4466)	**Azithromycin** (N=44)	**Erythromycin** (N=391)	**Clarithromycin** (N=111)	**Overall** (N=5012)
2011	219 (4.9%)	1 (2.3%)	22 (5.6%)	3 (2.7%)	245 (4.9%)
2012	248 (5.6%)	4 (9.1%)	25 (6.4%)	5 (4.5%)	282 (5.6%)
2013	298 (6.7%)	0 (0%)	29 (7.4%)	8 (7.2%)	335 (6.7%)
2014	389 (8.7%)	4 (9.1%)	38 (9.7%)	10 (9.0%)	441 (8.8%)
2015	404 (9.0%)	6 (13.6%)	36 (9.2%)	16 (14.4%)	462 (9.2%)
2016	362 (8.1%)	4 (9.1%)	38 (9.7%)	9 (8.1%)	413 (8.2%)
2017	341 (7.6%)	14 (31.8%)	24 (6.1%)	11 (9.9%)	390 (7.8%)
2018	268 (6.0%)	7 (15.9%)	21 (5.4%)	8 (7.2%)	304 (6.1%)
2019	249 (5.6%)	0 (0%)	13 (3.3%)	14 (12.6%)	276 (5.5%)
2020	110 (2.5%)	1 (2.3%)	9 (2.3%)	10 (9.0%)	130 (2.6%)
2021	83 (1.9%)	1 (2.3%)	11 (2.8%)	4 (3.6%)	99 (2.0%)

The trend in absolute value seems to correspond to a decreasing trend, in relative terms, considering prescriptions by pregnancy, per year, even if the decrease seems small for most substances (**Figure 1**).

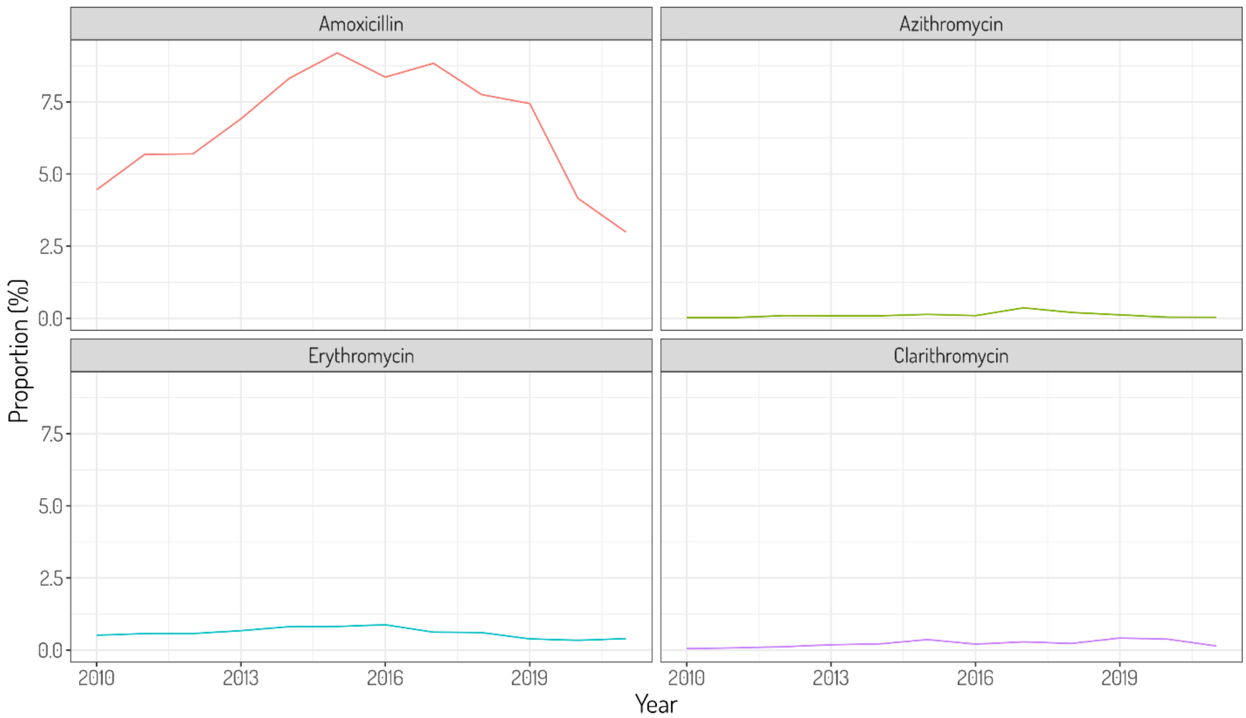


Figure 1: Trends of prescription of selected antibiotics over time relative to number of pregnancies. *Relative frequency. Unit is prescriptions not person.*

Most pregnant women were prescribed only one specific type of substance, among the selected list of antibiotics prescribed during pregnancy, across the trimesters (**Table 3**).

Table 3: Number of different substances prescribed (among the selected antibiotics) by trimester. *Absolute frequency. Unit is number of different prescriptions per pregnancy and trimester.*

	1st Trimester (N=1412)	**2nd Trimester** (N=1501)	**3rd Trimester** (N=1514)	**Total** (N=4427)
Number of different substances prescribed per pregnancy: n (%)				
1	1373 (97.2%)	1481 (98.7%)	1487 (98.2%)	4341 (98.1%)
2	39 (2.8%)	20 (1.3%)	27 (1.8%)	86 (1.9%)

About 80% of pregnant women received only one prescription of the same antibiotic during any single pregnancy. Fewer than 5% of pregnant women received 4 or more prescriptions of the same antibiotic (**Table 4**).

Table 4: Prescription of selected antibiotics by number of times it was prescribed during a pregnancy. *Absolute frequency. Unit is number of prescriptions.*

	Amoxicillin (N=3508)	**Azithromycin** (N=30)	**Erythromycin** (N=333)	**Clarithro-mycin** (N=103)	**Overall** (N=3974)
Number of prescriptions during each pregnancy: n (%)					
1	2764 (78.8%)	24 (80.0%)	286 (85.9%)	95 (92.2%)	3169 (79.7%)
2	591 (16.8%)	4 (13.3%)	41 (12.3%)	8 (7.8%)	644 (16.2%)
3	109 (3.1%)	1 (3.3%)	3 (0.9%)	0 (0%)	113 (2.8%)
4	37 (1.1%)	0 (0%)	1 (0.3%)	0 (0%)	38 (1.0%)
> 4	7 (0.2%)	1 (3.3%)	2 (0.6%)	0 (0%)	10 (0.3%)

The most common indication for the amoxicillin was urinary tract infection, whereas for erythromycin and clarithromycin it was respiratory infections, upper and lower tract (**Table 5**).

Table 5: Type of infection related to the prescription of selected antibiotics. *Absolute frequency. Unit is infections listed by person, not person.*

	Amoxicillin (N=1377)	**Azithro-mycin** (N=12)	**Erythro-mycin** (N=123)	**Clarithro-mycin** (N=49)	**Total** (N=1561)
Type of infection: n (%)					

	Amoxicillin (N=1377)	**Azithro-mycin** (N=12)	**Erythro-mycin** (N=123)	**Clarithro-mycin** (N=49)	**Total** (N=1561)
Acute lower respiratory tract infection	118 (8.6%)	0 (0%)	12 (9.8%)	6 (12.2%)	136 (8.7%)
Acute respiratory infections	81 (5.9%)	0 (0%)	9 (7.3%)	1 (2.0%)	91 (5.8%)
Candidal vulvovaginitis	31 (2.3%)	0 (0%)	1 (0.8%)	0 (0%)	32 (2.1%)
Candidiasis	13 (0.9%)	0 (0%)	3 (2.4%)	0 (0%)	16 (1.0%)
Candidiasis of vagina	34 (2.5%)	0 (0%)	1 (0.8%)	0 (0%)	35 (2.2%)
Common cold	21 (1.5%)	0 (0%)	0 (0%)	0 (0%)	21 (1.3%)
Genitourinary tract infection in pregnancy	21 (1.5%)	0 (0%)	1 (0.8%)	0 (0%)	22 (1.4%)
Infection of ear	13 (0.9%)	0 (0%)	1 (0.8%)	0 (0%)	14 (0.9%)
Infection of sebaceous cyst	2 (0.1%)	0 (0%)	7 (5.7%)	6 (12.2%)	15 (1.0%)
Infective otitis externa	9 (0.7%)	0 (0%)	3 (2.4%)	0 (0%)	12 (0.8%)
Lower respiratory tract infection	218 (15.8%)	0 (0%)	25 (20.3%)	16 (32.7%)	259 (16.6%)
Respiratory tract infection	16 (1.2%)	0 (0%)	0 (0%)	0 (0%)	16 (1.0%)
Streptococcus agalactiae infection	16 (1.2%)	1 (8.3%)	2 (1.6%)	0 (0%)	19 (1.2%)
Upper respiratory infection	272 (19.8%)	0 (0%)	25 (20.3%)	7 (14.3%)	304 (19.5%)
Urinary tract infection in pregnancy	54 (3.9%)	0 (0%)	2 (1.6%)	0 (0%)	56 (3.6%)
Urinary tract infectious disease	314 (22.8%)	1 (8.3%)	2 (1.6%)	1 (2.0%)	318 (20.4%)
Viral disease	13 (0.9%)	0 (0%)	1 (0.8%)	0 (0%)	14 (0.9%)
Viral upper respiratory tract infection	15 (1.1%)	0 (0%)	1 (0.8%)	1 (2.0%)	17 (1.1%)
Other	116 (8.4%)	10 (83.3%)	27 (22.0%)	11 (22.4%)	164 (10.5%)

Prescriptions of erythromycin by pregnancy trimester don’t vary significantly. Most presentations prescribed for erythromycin were of 28 dosage units (tablets or capsules) and about one fifth were of the 56 dosage units (**Table 6**).

Table 6: Drug quantity, in pack size (i.e., number of tablets or capsules), of Erythromycin prescribed by trimester. *Unit is pack prescribed, not person.*

	1st Trimester (N=98)	**2nd Trimester** (N=98)	**3rd Trimester** (N=96)	**Total** (N=292)
Drug quantity (in pack size)				
10	0 (0%)	1 (1.0%)	1 (1.0%)	2 (0.7%)
14	0 (0%)	1 (1.0%)	2 (2.1%)	3 (1.0%)
15	1 (1.0%)	0 (0%)	1 (1.0%)	2 (0.7%)
28	70 (71.4%)	70 (71.4%)	74 (77.1%)	214 (73.3%)
56	22 (22.4%)	22 (22.4%)	15 (15.6%)	59 (20.2%)
84	0 (0%)	0 (0%)	1 (1.0%)	1 (0.3%)
100	5 (5.1%)	4 (4.1%)	2 (2.1%)	11 (3.8%)

4.2. Sensitivity analysis

There are 107,749 pregnancies that meet the criteria established in the pregnancy phenotyping algorithm. Of these, 22,467 took at least one of the selected antibiotics (**Table 7**).

Table 7: Prescription of selected antibiotics by age at start of the antibiotic and gravidity. *Absolute frequency. Unit is prescription, not person.*

	Amoxicillin (N=26284)	**Azithromycin** (N=232)	**Erythromycin** (N=3126)	**Clarithro-mycin** (N=912)	**Total** (N=30554)
Age group at start of antibiotic: n (%)					
Younger than 20	1362 (5.2%)	51 (22.0%)	159 (5.1%)	44 (4.8%)	1616 (5.3%)
20 to 29	12327 (46.9%)	113 (48.7%)	1369 (43.8%)	379 (41.6%)	14188 (46.4%)
30 to 39	11508 (43.8%)	56 (24.1%)	1461 (46.7%)	439 (48.1%)	13464 (44.1%)
40 to 49	1053 (4.0%)	12 (5.2%)	137 (4.4%)	49 (5.4%)	1251 (4.1%)
50 and older	34 (0.1%)	0 (0%)	0 (0%)	1 (0.1%)	35 (0.1%)
Gravidity: n (%)					
1st	11990 (45.6%)	124 (53.4%)	1338 (42.8%)	387 (42.4%)	13839 (45.3%)
2nd	8790 (33.4%)	59 (25.4%)	1096 (35.1%)	275 (30.2%)	10220 (33.4%)
3rd	3561 (13.5%)	25 (10.8%)	456 (14.6%)	138 (15.1%)	4180 (13.7%)
4th and following	1943 (7.4%)	24 (10.3%)	236 (7.5%)	112 (12.3%)	2315 (7.6%)
Trimester of exposure: n (%)					
1	7534 (28.7%)	117 (50.4%)	870 (27.8%)	351 (38.5%)	8872 (29.0%)

	Amoxicillin (N=26284)	**Azithromycin** (N=232)	**Erythromycin** (N=3126)	**Clarithro-mycin** (N=912)	**Total** (N=30554)
2	9403 (35.8%)	56 (24.1%)	1008 (32.2%)	193 (21.2%)	10660 (34.9%)
3	9347 (35.6%)	59 (25.4%)	1248 (39.9%)	368 (40.4%)	11022 (36.1%)

In line with the main analysis, the number of prescriptions of these selected antibiotics has been decreasing overall since 2014/2015 (**Table 8**).

Table 8: Prescription of selected antibiotics by year. *Absolute frequency. Unit is prescription, not person.*

	Amoxicillin (N=26284)	**Azithromycin** (N=232)	**Erythromycin** (N=3126)	**Clarithromycin** (N=912)	**Overall** (N=30554)
		Year of start of antibiotic: n (%)			
< 2010	8695 (33.1%)	49 (21.1%)	1136 (36.3%)	115 (12.6%)	9995 (32.7%)
2010	1104 (4.2%)	7 (3.0%)	159 (5.1%)	13 (1.4%)	1283 (4.2%)
2011	1216 (4.6%)	13 (5.6%)	140 (4.5%)	30 (3.3%)	1399 (4.6%)
2012	1522 (5.8%)	11 (4.7%)	186 (6.0%)	51 (5.6%)	1770 (5.8%)
2013	1674 (6.4%)	21 (9.1%)	218 (7.0%)	70 (7.7%)	1983 (6.5%)
2014	2045 (7.8%)	25 (10.8%)	219 (7.0%)	74 (8.1%)	2363 (7.7%)
2015	1997 (7.6%)	20 (8.6%)	238 (7.6%)	74 (8.1%)	2329 (7.6%)
2016	2011 (7.7%)	26 (11.2%)	199 (6.4%)	99 (10.9%)	2335 (7.6%)
2017	1815 (6.9%)	26 (11.2%)	172 (5.5%)	90 (9.9%)	2103 (6.9%)
2018	1440 (5.5%)	15 (6.5%)	130 (4.2%)	88 (9.6%)	1673 (5.5%)
2019	1317 (5.0%)	8 (3.4%)	140 (4.5%)	89 (9.8%)	1554 (5.1%)
2020	839 (3.2%)	4 (1.7%)	107 (3.4%)	74 (8.1%)	1024 (3.4%)
2021	607 (2.3%)	7 (3.0%)	82 (2.6%)	44 (4.8%)	740 (2.4%)

In relative terms, the proportion of prescriptions on the selected antibiotics per year follows a similar pattern to the main analysis (**Figure 2**).

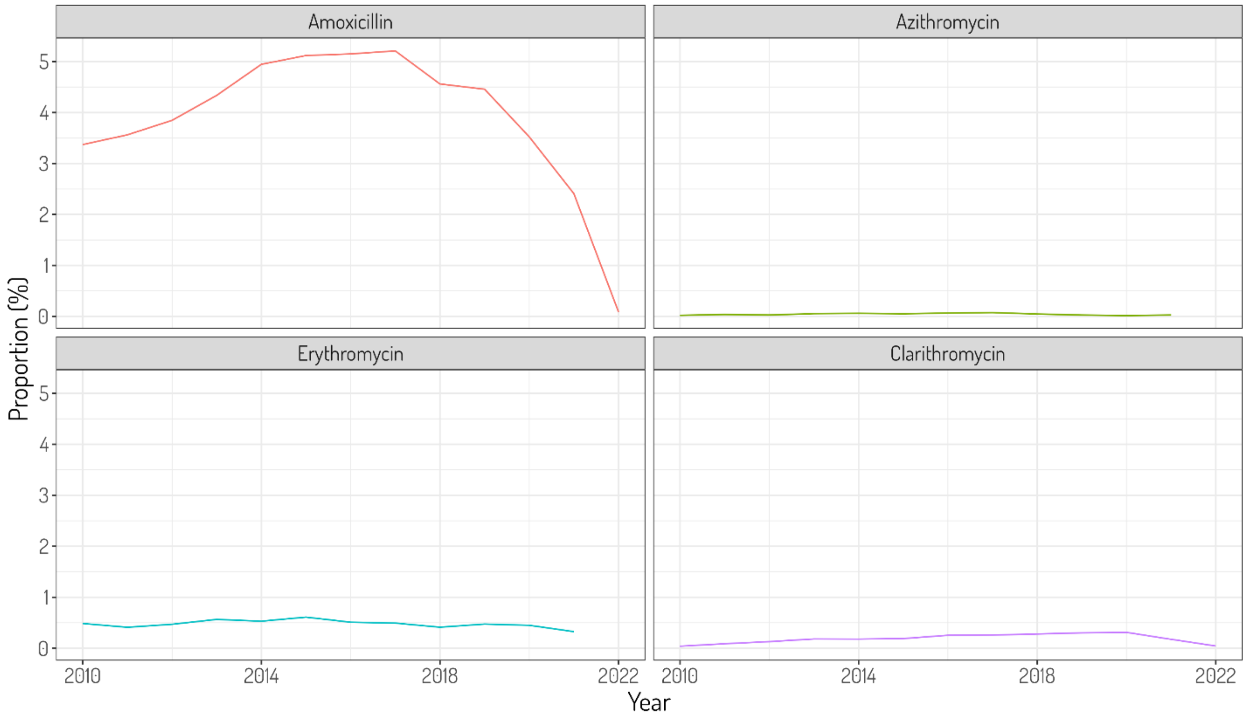


Figure 2: Trends of prescription of selected antibiotics over time relative to number of pregnancies. *Relative frequency. Unit is prescriptions not person.*

The distribution of the number of different drugs prescribed per pregnancy across the trimesters is similar to the main analysis, with a vast majority ~98% being only one of the selected substances (**Table 9**).

Table 9: Number of different substances prescribed (among the selected antibiotics) by trimester. *Absolute frequency. Unit is number of different prescriptions per pregnancy and trimester.*

	1st Trimester (N=8057)	**2nd Trimester** (N=9616)	**3rd Trimester** (N=9905)	**Total** (N=27578)
Number of different drugs prescribed per pregnancy: n (%)				
1	7842 (97.3%)	9447 (98.2%)	9703 (98.0%)	26992 (97.9%)
2	212 (2.6%)	168 (1.7%)	200 (2.0%)	580 (2.1%)
3	3 (0.0%)	1 (0.0%)	2 (0.0%)	6 (0.0%)

Again, about 80% of pregnant women received only one prescription of the same antibiotic during any single pregnancy and fewer than 5% of pregnant women received 4 or more prescriptions of the same antibiotic. The substance that had the highest number of prescriptions during a pregnancy was erythromycin (**Table 10**).

Table 10: Prescription of selected antibiotics by number of times it was prescribed during a pregnancy. *Absolute frequency. Unit is number of prescriptions.*

	Amoxicillin (N=21305)	**Azithromycin** (N=202)	**Erythromycin** (N=2587)	**Clarithromycin** (N=831)	**Total** (N=24925)
Number of prescriptions during each pregnancy: n (%)					
1	17381 (81.6%)	182 (90.1%)	2195 (84.8%)	769 (92.5%)	20527 (82.4%)
2	3118 (14.6%)	16 (7.9%)	315 (12.2%)	53 (6.4%)	3502 (14.1%)
3	622 (2.9%)	3 (1.5%)	44 (1.7%)	3 (0.4%)	672 (2.7%)
4	145 (0.7%)	0 (0%)	14 (0.5%)	3 (0.4%)	162 (0.7%)
> 4	39 (0.2%)	1 (0.5%)	19 (0.7%)	3 (0.4%)	62 (0.2%)

The most common indication for the selected antibiotics was upper respiratory tract infection in general, and lower respiratory tract infection for erythromycin (**Table 11**).

Table 11: Type of infection related to the prescription of selected antibiotics. Absolute frequency. *Unit is infections listed by person, not person.*

	Amoxicillin (N=7530)	**Azithro-mycin** (N=94)	**Erythro-mycin** (N=929)	**Clarithro-mycin** (N=315)	**Total** (N=8868)
Type of infection: n (%)					
Acute lower respiratory tract infection	642 (8.5%)	3 (3.2%)	83 (8.9%)	43 (13.7%)	771 (8.7%)
Acute respiratory infections	533 (7.1%)	2 (2.1%)	77 (8.3%)	13 (4.1%)	625 (7.0%)
Candidal vulvovaginitis	118 (1.6%)	4 (4.3%)	14 (1.5%)	2 (0.6%)	138 (1.6%)
Candidiasis	98 (1.3%)	4 (4.3%)	8 (0.9%)	4 (1.3%)	114 (1.3%)
Candidiasis of vagina	245 (3.3%)	1 (1.1%)	12 (1.3%)	9 (2.9%)	267 (3.0%)
Common cold	105 (1.4%)	0 (0%)	13 (1.4%)	0 (0%)	118 (1.3%)
Genitourinary tract infection in pregnancy	163 (2.2%)	1 (1.1%)	7 (0.8%)	0 (0%)	171 (1.9%)
Infection of ear	74 (1.0%)	0 (0%)	11 (1.2%)	2 (0.6%)	87 (1.0%)
Infection of sebaceous cyst	9 (0.1%)	0 (0%)	13 (1.4%)	7 (2.2%)	29 (0.3%)
Infective otitis externa	75 (1.0%)	0 (0%)	34 (3.7%)	3 (1.0%)	112 (1.3%)
Lower respiratory tract infection	1062 (14.1%)	3 (3.2%)	147 (15.8%)	72 (22.9%)	1284 (14.5%)
Respiratory tract infection	97 (1.3%)	0 (0%)	9 (1.0%)	1 (0.3%)	107 (1.2%)

	Amoxicillin (N=7530)	**Azithro-mycin** (N=94)	**Erythro-mycin** (N=929)	**Clarithro-mycin** (N=315)	**Total** (N=8868)
Streptococcus agalactiae infection	79 (1.0%)	1 (1.1%)	9 (1.0%)	4 (1.3%)	93 (1.0%)
Upper respiratory infection	1472 (19.6%)	0 (0%)	130 (14.0%)	36 (11.4%)	1638 (18.5%)
Urinary tract infection in pregnancy	298 (4.0%)	0 (0%)	3 (0.3%)	0 (0%)	301 (3.4%)
Urinary tract infectious disease	1546 (20.5%)	1 (1.1%)	32 (3.4%)	7 (2.2%)	1586 (17.9%)
Viral disease	81 (1.1%)	0 (0%)	12 (1.3%)	8 (2.5%)	101 (1.1%)
Viral upper respiratory tract infection	90 (1.2%)	0 (0%)	10 (1.1%)	5 (1.6%)	105 (1.2%)
Other	743 (9.9%)	74 (78.7%)	305 (32.8%)	99 (31.4%)	1221 (13.8%)

As for the main analysis, prescriptions of erythromycin by pregnancy trimester don't vary significantly. Most presentations prescribed for erythromycin are of 28 dosage units (tablets or capsules) and about one fifth are of the 56 dosage units (**Table 12**).

Table 12: Drug quantity, in pack size, of Erythromycin prescribed by trimester. *Unit is pack prescribed, not person.*

	1st Trimester (N=650)	**2nd Trimester** (N=749)	**3rd Trimester** (N=937)	**Total** (N=2336)
Drug quantity (in pack size)				
10	3 (0.5%)	8 (1.1%)	4 (0.4%)	15 (0.6%)
14	5 (0.8%)	9 (1.2%)	15 (1.6%)	29 (1.2%)
15	2 (0.3%)	4 (0.5%)	3 (0.3%)	9 (0.4%)
28	485 (74.6%)	564 (75.3%)	717 (76.5%)	1766 (75.6%)
56	129 (19.8%)	145 (19.4%)	170 (18.1%)	444 (19.0%)
84	2 (0.3%)	0 (0%)	2 (0.2%)	4 (0.2%)
100	24 (3.7%)	19 (2.5%)	26 (2.8%)	69 (3.0%)

5. Discussion

Of the three databases IQVIA™ Disease Analyzer France, IQVIA™ Disease Analyzer Germany and IMRD UK, only IMRD UK met the criteria defined by the pregnancy phenotyping algorithm. For the main analysis, there were 15,868 pregnancies that met the criteria established in the pregnancy phenotyping algorithm and of these, 3,794 (24%) took at least one of the substances selected for this study during a pregnancy. For the sensitivity analysis the pregnancies were 107,749 and 22,467 (21%) took at least one of the selected antibiotics.

Only three macrolide antibiotics were identified in the database used. Amoxicillin was the most prescribed product, but of the three macrolides, erythromycin was the most prescribed. The prescriptions of any of the selected antibiotics seem to be evenly distributed across the trimesters, with marginally higher prescriptions in the third trimester, which may reflect random statistical dispersion.

Prescription trends seem to indicate a reduction since 2015/2016 in both the main and sensitivity analysis. Most women (>80%) receive only one prescription of one antibiotic during each pregnancy. The most common indication for the selected antibiotics was urinary tract infection for amoxicillin, lower and upper respiratory tract infection for erythromycin, and lower respiratory tract infection for clarithromycin. Among the oral solid formulations of erythromycin, the 28 tablets/capsule packs were the most frequently prescribed across trimesters.

Overall, erythromycin seems to be the most commonly used macrolide in pregnancy, in the IMRD UK database. The most commonly prescribed pack size is 28 tablets of capsules, and the number of prescriptions is fundamentally equally distributed by pregnancy, suggesting that prescribers don't assume a risk with exposure during the early phase of pregnancy.

This study has several limitations. To identify the gestational age of each patient, a phenotyping algorithm had to be defined and tested. The main phenotyping algorithm required the presence of codes indicating start of pregnancy and end of pregnancy. Considering that the presence of both sets of codes depleted the sample of pregnant women significantly, it may be that these patients, that have a well described pregnancy are not representative of the overall population of pregnant women as it suggests they had more healthcare interactions than several other pregnant women. In addition, a sensitivity algorithm, the presence of delivery codes to determine day 280 of pregnancy, may not accurately reflect the duration of pregnancy. To mitigate the risk of misclassifying gestational age, all codes for elective delivery were removed.

Furthermore, only successful deliveries are included in the study because it is difficult to establish the gestational age of women with miscarriage. However, the effects of exposure in this sub-group of women are extremely relevant for drug safety studies.

Another limitation is that the indication was inferred, this is because it can happen that the date at which a prescription is made is not the same as the date at which the corresponding diagnosis is made. A seven-day interval was defined whereby any infection indication within +/- 7 days of prescription was considered the indication. The 7-day threshold was defined empirically. Several intervals, from 1 to 60 days were tested, suggesting a linear relationship between the number of days used in the interval and the number of extra indications found.

References

1. Moll K, Wong HL, Fingar K, et al. Validating Claims-Based Algorithms Determining Pregnancy Outcomes and Gestational Age Using a Linked Claims-Electronic Medical Record Database. Drug Saf. 2021;44(11):1151-1164. doi:10.1007/s40264-021-01113-8
2. Taylor LG, Bird ST, Stojanovic D, et al. Utility of fertility procedures and prenatal tests to estimate gestational age for live-births and stillbirths in electronic health plan databases. Pharmacoepidemiol Drug Saf. 2022;31(5):534-545. doi:10.1002/pds.5414
3. Matcho A, Ryan P, Fife D, Gifkins D, Knoll C, Friedman A. Inferring pregnancy episodes and outcomes within a network of observational databases. PLoS One. 2018;13(2):e0192033. Published 2018 Feb 1. doi:10.1371/journal.pone.0192033

Annexes

Annex I – Databases

IQVIA Disease Analyser Germany

IQVIA Disease Analyser (IDA) Germany collects computerised information from specialised and general primary care practices throughout Germany since 1992. Around 3% of general practitioners (GP) practices are included, which covers all patients consulting a practice. Data from IDA Germany have been shown to be reasonably representative of German healthcare statistics for demographics and certain diseases and is considered one of the largest national medical databases worldwide. IDA Germany includes more than 2,500 practices and 3,100 physicians (13 speciality groups) representing over 15,000,000 patients. This database used to be named IMS Germany and some use of this terminology may persist.

The March 2022 OMOP version of this database was used.

IQVIA Disease Analyzer France

IDA France collects anonymised patient medical records since 1997 through a representative panel of GPs. The physician sample represents approximately 2% of physicians and is weighted by age and gender of the physician, doctor region and the SNIR of the physician (National Official Indicator of the GP volume of activity in terms of visits and consultations). Some 99% of the French population is insured, but there are differences regarding level of coverage. IDA France includes around 1,000 GPs and represents more than 4,000,000 of patients and considered representative for the French population. This database used to be named IMS France and some use of this terminology may persist.

The March 2022 OMOP version of this database was used.

IQVIA Medical Research Data EMIS UK

IQVIA Medical Research Data (IMRD) EMIS UK is a primary care database from the UK. GPs play a gatekeeper role in the healthcare system in the UK, as they are responsible for delivering primary health care and specialist referrals. Over 98% of the UK-resident population is registered with a GP, so that GP patient records are broadly representative of the UK population in general. Patients are affiliated to a practice, which centralizes the medical information from GPs, specialist referrals, hospitalizations, and tests.

The May2022 OMOP version of this database was used.

Annex II – Phenotyping algorithm to identify gestational age

Methodology

Patients with any OMOP concept code from the Matcho et al, PLoS One, 2018[3] paper were identified and extracted from IDA France, IDA Germany and IMRD UK (available online and upon request).

Gravidity thresholds were defined as any two pregnancy-related OMOP concept ids separated by more than 365 days or any pregnancy related code 90 days after a OMOP concept id related to abortion or miscarriage.

Within each pregnancy, the first codes recorded were profiled and codes likely identifying pregnancy where extracted.

The duration between codes indicating start of pregnancy and full-term delivery was determined and profiled. As there is a lag time between conception and first medical appointment for pregnancy of about six to seven weeks, the calculated duration was adjusted to include those days.

Codes that indicating gestational age, postnatal care and miscarriage were also profiled.

Pregnancies that matched 280 +/- 7 days between starting codes and full-term codes and pregnancies that matched their gestational age reported +/- 7 days (e.g., if code was premature at 38 weeks, a valid duration would be 266 +/- 7 days) were included in the main cohort.

Where reasonable consistent codes indicating delivery or end of pregnancy were identified, even without temporal consistency, i.e., without a starting code, pregnant women identified by these codes were included in a sensitivity cohort.

Results

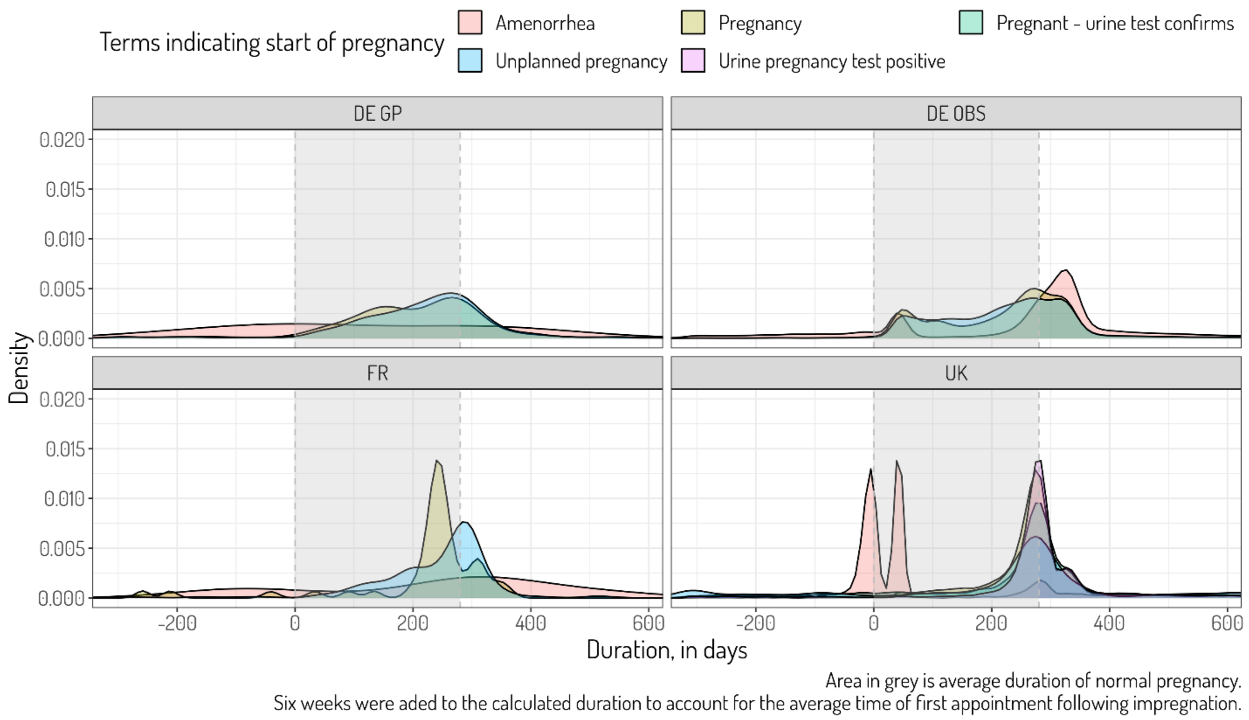
Concepts that identify start of pregnancy were defined as Amenorrhea, Patient currently pregnant, Unplanned pregnancy, Pregnant - urine test confirms, Urine pregnancy test positive. The first three concepts are present in every database, but the urine test information is only available for the UK database.

	DE General Practice (N=85086)	**DE Obstetrics and Gynecology** (N=1621478)	**FR General Practice** (N=60840)	**UK General Practice** (N=1095284)
Concepts that identify start of pregnancy				
Amenorrhea	4658 (5.5%)	247295 (15.3%)	8634 (14.2%)	69075 (6.3%)
Patient currently pregnant	24860 (29.2%)	741456 (45.7%)	6538 (10.7%)	972507 (88.8%)
Unplanned pregnancy	55568 (65.3%)	632727 (39.0%)	45668 (75.1%)	2949 (0.3%)
Pregnant - urine test confirms	0 (0%)	0 (0%)	0 (0%)	6804 (0.6%)
Urine pregnancy test positive	0 (0%)	0 (0%)	0 (0%)	43949 (4.0%)

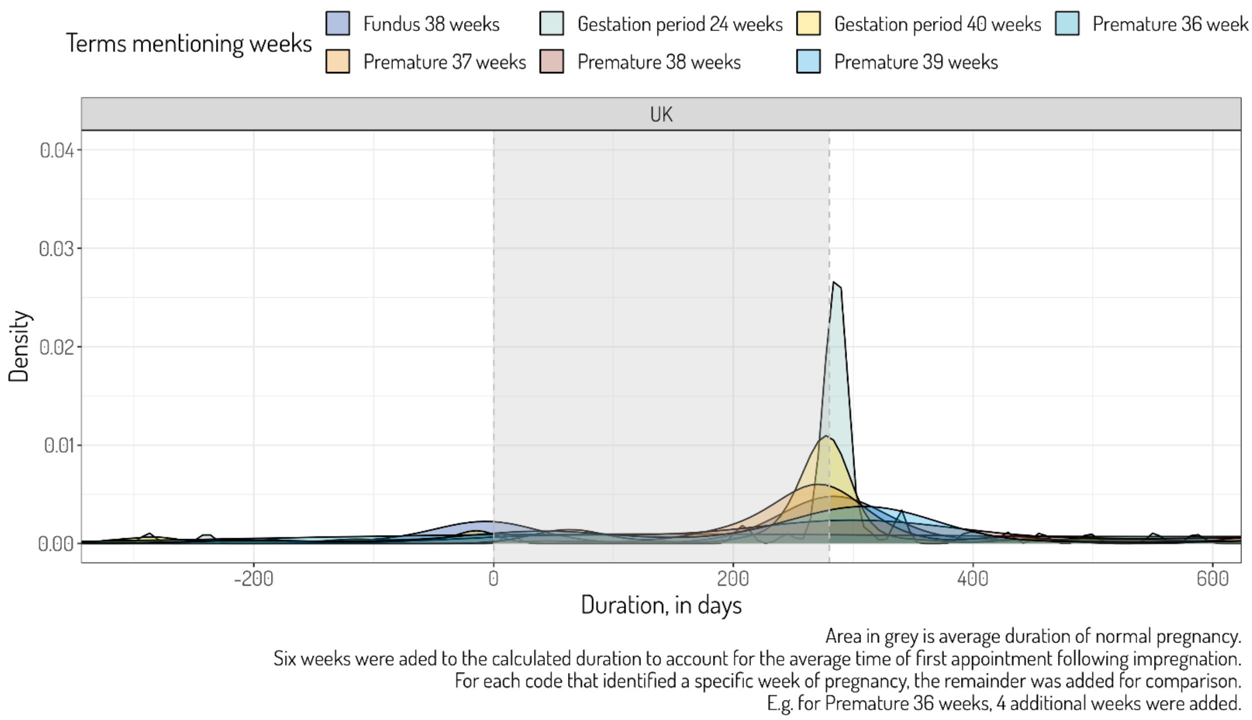
All databases include delivery codes referring to full-term delivery and post-natal care (lists are not show due to size, available on request). Concepts that refer to gestational age or time of delivery are only found in the UK database.

	DE General Practice (N=0)	DE Obstetrics and Gynecology (N=0)	FR General Practice (N=0)	UK General Practice (N=38279)
Concepts that refer to week gestation/delivery				
Baby premature 36 weeks	0 (0%)	0 (0%)	0 (0%)	1688 (4.4%)
Baby premature 37 weeks	0 (0%)	0 (0%)	0 (0%)	3050 (8.0%)
Baby premature 38 weeks	0 (0%)	0 (0%)	0 (0%)	2425 (6.3%)
Baby premature 39 weeks	0 (0%)	0 (0%)	0 (0%)	3276 (8.6%)
Gestation period, 24 weeks	0 (0%)	0 (0%)	0 (0%)	473 (1.2%)
Gestation period, 40 weeks	0 (0%)	0 (0%)	0 (0%)	2938 (7.7%)
O/E -fundus 38 weeks-term size	0 (0%)	0 (0%)	0 (0%)	24429 (63.8%)

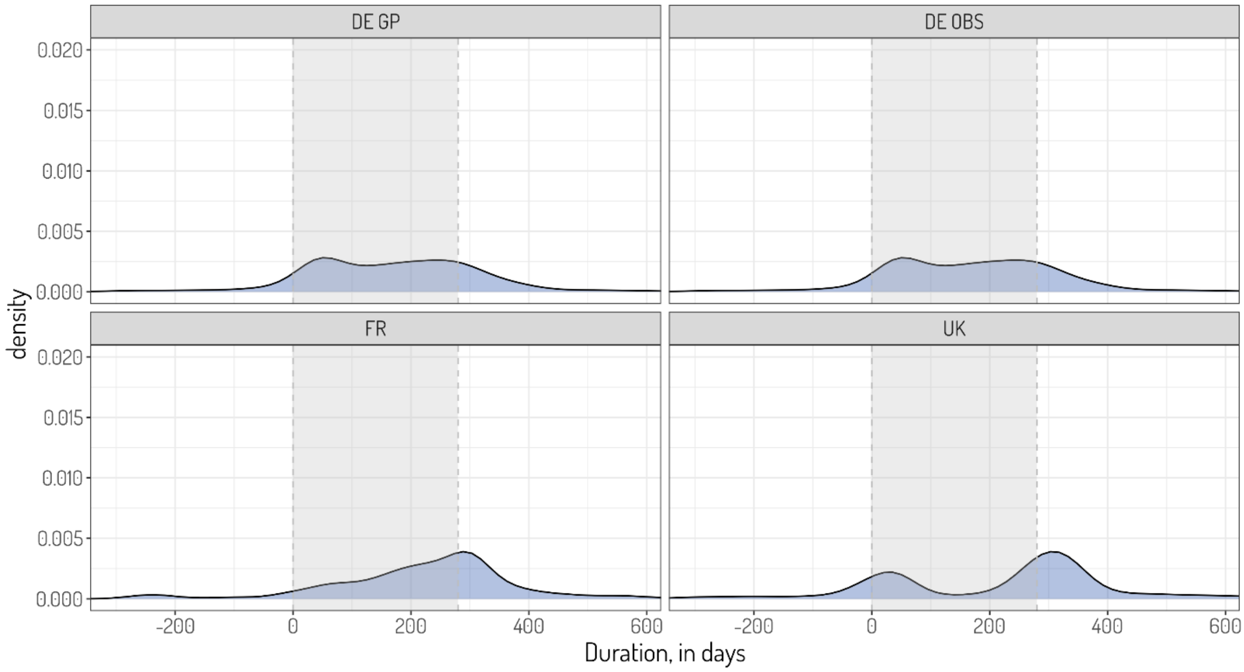
Duration between codes suggesting start of pregnancy and full-term delivery only seem to show some consistency for the UK database. All other databases seem to have a peak of durations around the 280-day mark, but it is either not as striking as for the UK data or presents bi/multi-modal distribution. For the UK database, Amenorrhea has a good temporal consistency but does not seem to be highly specific to start of pregnancy. Some amenorrhea codes seem to be used just before delivery codes.



Terms indication gestational age seem to show some consistency with the expected duration.

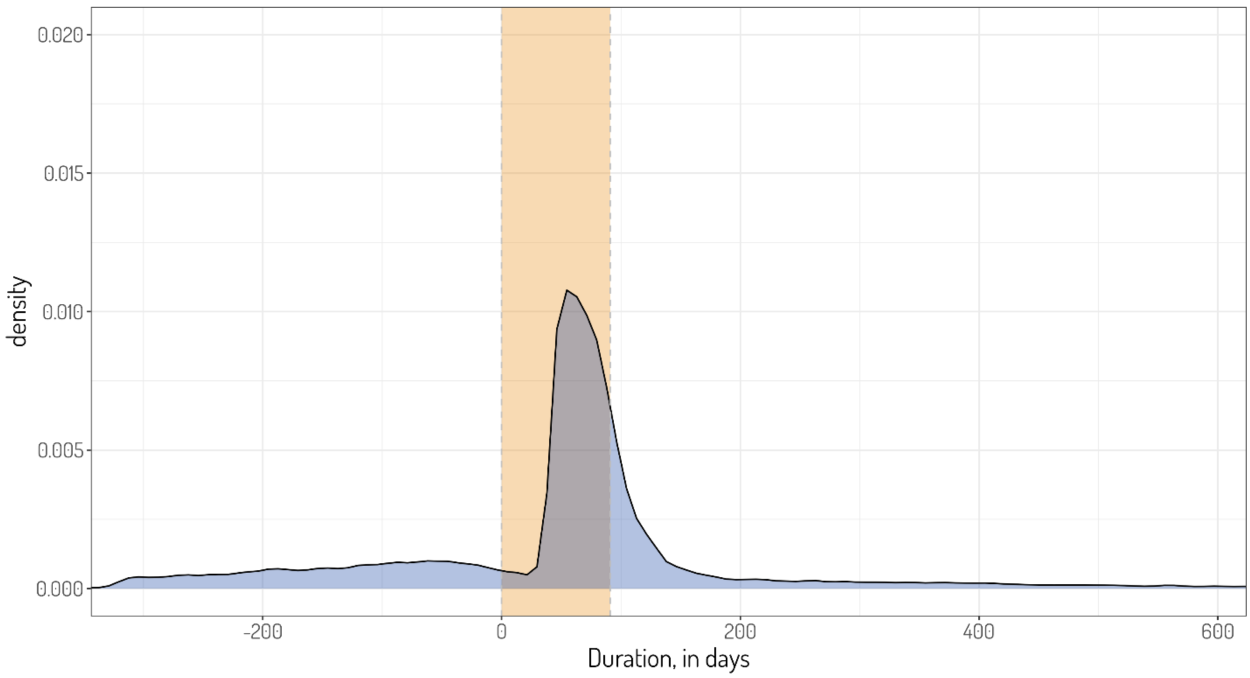


Terms for postnatal care do not seem to indicate a temporal consistency.



Area in grey is average duration of normal pregnancy.
Six weeks were aded to the calculated duration to account for the average time of first appointment following impregnation.

When including only those cases with a duration within the 280 days of pregnancy, the code for miscarriage falls 82% within the first trimester, this matches the expected 80% of miscarriages within the first trimester. However, it would not be correct to assume that all miscarriage concepts correctly identify the first trimester.



Area in orange is first trimester.
Six weeks were aded to the calculated duration to account for the average time of first appointment following impregnation.

Cohort

Main cohort will include pregnancies with temporal consistency between code indicating pregnancy and code indicating end of pregnancy (full term or premature) as well as consistency with a code with gestational information, in IMRD UK.

Sensitivity cohort will include all pregnancies with a full-term delivery code, in IMRD UK.

Annex 2 – Codelists

Codelists for pregnancy-related codes are available on the Matcho et al, PLoS One publication[(3)], as supplementary material and are available upon request.

Codelists for infections and for the substances are available upon request.