



**COVID-19 infection and medicines in pregnancy – a multinational registry based study**

**Medication use in pregnant women with COVID-19: an interim report**

November 12, 2021

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<b>Research question and objectives</b>	<p>This study is based on electronic health care registry data from 9 health care databases in 8 European countries between 2018 and 2020. The primary objectives are:</p> <ol style="list-style-type: none"> <li><b>1)</b> To estimate the prevalence of medicines used, by trimester of pregnancy and compare this between pregnant women with COVID-19, pregnant women without COVID-19 and non-pregnant women of reproductive age with COVID-19.</li> <li><b>2)</b> To describe severity and clinical outcomes of COVID-19 in pregnant and non-pregnant women.</li> <li><b>3)</b> To compare the rates of adverse maternal and neonatal outcomes in pregnant women with and without COVID-19, using different medicines.</li> </ol>
<b>Country(-ies) of study</b>	<p>Participating electronic health care databases among CONSIGN partners:</p> <p>Denmark – nationwide registries*</p> <p>France – nationwide registries*</p> <p>Germany – 20% population coverage*</p> <p>Italy – regional registry (Tuscany)</p> <p>Norway – nationwide registries</p> <p>Spain – regional registries (Valencia and Aragon)</p> <p>Sweden – nationwide registries*</p> <p>UK – national registry (Wales)</p> <p>(*Not participating in this interim report)</p>

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## 1 List of abbreviations

ACCESS	vACCine covid-19 monitoring readinESS
ACOG	American College of Obstetricians and Gynaecologists
ADVANCE	Accelerated Development of VAccine beNefit-risk Collaboration in Europe
AESI	Adverse Event of Special Interest
ARDS	Acute respiratory distress requiring ventilation
ARS	Agenzia Regionale di Sanita' della Toscana
ATC	Anatomical Therapeutic Chemical
BMI	Body Mass Index
CDC	Centers for Disease Control and Prevention
CDM	Common Data Model
CI	Confidence interval
COVID-19	Coronavirus disease 2019
DAP	Data Access Provider
DDD	Daily defined dose
DNA	Desoxyribonucleic acid
DRE	Digital Research Environment
ECDC	European Centre for Disease Prevention and Control
EMA	European Medicines Agency
EMR	Electronic Medical Records
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
ETL	Extract, Transform, and Load
EU PAS	The European Union electronic Register of Post-Authorisation Studies
FICF	Catalan Institute of Pharmacology Foundation (FICF)
FISABIO -HSRU	Foundation for the Promotion of Health and Biomedical Research of Valencia Region - Health Services Research Unit
GDPR	General Data Protection Regulation
GP	General Practitioner
IACS	Instituto Aragonés de Ciencias de la Salud
ICD	International Classification of Diseases
ICU	Intensive Care Unit
LMP	Last menstrual period
mRNA	messenger Ribonucleic acid
NHS	National Health Service
ODHSI	Observational Health Data Sciences and Informatics
QC	Quality Control
SAIL	Secure Anonymised Information Linkage
SAP	Statistical Analysis Plan
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SWANSEA	Swansea University
UiO	University of Oslo



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## 3 Collaborating institutions

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<b>Data access provider (DAPs)</b>		
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## 4 Deliverables and milestones

Deliverable	Date
D2a. Protocol submitted to the EMA	16 October 2020
D3. Interim report, objective 1	16 July 2021
D4. Final report of study results	16 July 2022

Milestone	Planned date
Protocol submitted to the EMA	16 October 2020
Extract, Transform, and Load (ETL) design finalized	February 2020
Statistical analysis plan finalized	March 2021
Data extraction & ETL	March/ April 2021
Running quality & first analysis	April 2021
Interim report, objective 1	16 July 2021
Data extraction, objective 2 and 3	March 2022
Updated report of study results, objective 2-3	16 July 2022

## 5 Rationale and background

In the current pandemic, pregnant women are becoming infected with the SARS-CoV-2 virus and being treated for COVID-19 disease and its complications. EMA wishes to be prepared for situations where questions arise regarding the impact of medicine used for COVID-19 during pregnancy, on the unborn child. To answer such questions, insight is needed into drug utilisation in COVID-19 affected pregnancies compared with other pregnancies. The regulatory network will be better placed to judge the appropriateness of use in pregnancy, as well as the appropriateness of any proposed pregnancy-related risk minimisation measures, with better insight into how the disease, and treatments currently used, affect the pregnant woman and her infant.

The CONSIGN project is funded by the European Medicines Agency (EMA) (specific contract 04 implementing framework contract No EMA//28/PE, Lot 4) to undertake this research.

The project has led to the establishment of a new collaboration of over thirty researchers, harnessing data from nine electronic health care registries in eight European countries (Denmark (DK), Germany (DE), France (FR), Italy (IT), Norway (NO), Spain (ES), Sweden (SE), United Kingdom (UK)). Data sources include general practice databases (e.g. UK, ES), claims databases (FR, DE) and record linkage of demographic data, registers and dispensing (SE, NO, DK, IT, ES).

## 6 Research questions and objectives

The primary objectives of CONSIGN are:

- 1) To estimate the prevalence of medicines used, by trimester of pregnancy, and compare this among pregnant women with COVID-19, pregnant women without COVID-19, and non-pregnant women with COVID-19.
- 2) To describe severity and clinical outcomes of COVID-19 disease in pregnant women with COVID-19, according to treatments received during pregnancy, and compare these data with those of non-pregnant women of reproductive age with COVID-19.
- 3) To assess and compare the rates of adverse maternal and neonatal outcomes in pregnant women with and without COVID-19, using different medicines.

This **interim report** provides results for Objective 1. Specifically, it addresses the following objectives:

- a. To estimate the prevalence of medication use in pregnant women with COVID-19, by age and trimester of pregnancy.
- b. To compare these data with those collected for pregnant women without COVID-19, by age and trimester of pregnancy.

This interim report provides the prevalence of medication use in pregnant women with COVID-19 as part of objective 1, in data sources that had access to relevant data. The updated final report, answering all the research questions above, will be available in July 2022.

## 7 Research methods

### 7.1 Study design

The study is a multi-database drug utilisation study, conducted during the period June 2019 until the date of last data availability for each data source. This includes the first two periods of SARS-CoV-2 circulation in Europe. The source cohort includes pregnant women observed in one of the participating data sources whose pregnancy coincided with the COVID-19 pandemic; i.e. were pregnant on or after the start of the pandemic in Europe (set to 01.03.2020) and recorded in the data sources by the time of their most recent update.

### 7.2 Sources and study population

The CONSIGN project includes data from nine data sources in eight European countries. Five Data Access Providers (DAPs) participated in Objective 1 of the project, providing data for this interim report (Table 1). Details of these Data Access Providers and the data sources they have access to are provided in Appendix 1.

**Table 1 Overview of data sources to be used for the Interim report**

Data source	Country	DAP	Estimated births per year	Total population	Type of data source	Diagnoses recordings	Medical birth registry
ARS database (ARS)	Italy – Tuscany	ARS	25 000	3.6 million	Record linkage	Hospital*	Yes
Valencia Integrated Database (VID)	Spain – Valencia	FISABIO-HSRU	32 000	5 million	Record linkage	GP, specialist Hospital	Yes
SAIL database (SAIL)	UK – Wales	SWANSEA	33 000	3 million	Record linkage	GP, Hospital	Yes
PRECOVID Study and EpiChron Cohort (PRECOVID)**	Spain – Aragon	IACS	10 000	1.3 million	Cohort	GP, Hospital	No***
Linked national registries (Norway)	Norway	UiO	60 000	5.3 million	Record linkage	GP, Hospital	Yes

Notes: \*Also emergency admissions, exemptions from copayment for chronic conditions, access to mental health care.

\*\*The EpiChron Cohort Study links socio-demographic and clinical anonymized information of all the inhabitants of Aragon, built from the BIGAN platform. Aragon BIGAN platform integrates a technical infrastructure and a data lake gathering individual patient data from the regional health service information systems, including primary care, specialized care, hospitalizations, ER episodes, drug prescription, image diagnosis, laboratory analytical determinations, diagnostics, vaccination, anamnesis and demographics from the whole population of Aragon.

\*\*\*Information on pregnancies was retrieved from CARTILLA\_EMBARAZO ('pregnancy control'), not the medical birth registry which is available only for the 2 largest hospitals. Abbreviations: ARS = Agenzia Regionale di Sanita' della Toscana; DAP: Data Access Provider; FISABIO-HSRU = Foundation for the Promotion of Health and Biomedical Research of Valencia Region - Health Services Research Unit; GP: General practitioner; IACS = Instituto Aragonés de Ciencias de la Salud; SAIL = Secure Anonymised Information Linkage; SWANSEA = Swansea University; UiO = University of Oslo.

### **7.3 Inclusion criteria**

The study cohort consisted of women aged 12-55 years who were pregnant on the start date of the pandemic (defined as 01.03.2020), or whose pregnancy started after this date. A woman could contribute data on more than one pregnancy during the study period. Study participants were required to have a full year of coverage prior to the start of pregnancy to facilitate the identification of prior medical conditions.

The analyses were conducted at the level of the trimester of pregnancy, given its influence on decision making with respect to medication use. Hence, a woman could contribute data on more than one pregnancy, and more than one trimester, during the study period. Women who participated with multiple pregnancies were handled as individual pregnancies in the analyses.

Only trimesters coinciding with the pandemic (i.e., the end date for the trimester was after the start date of the pandemic (01.03.2020) and before the end of data availability) were eligible for inclusion. Trimesters of pregnancy that were completed prior to the pandemic start date were excluded. Trimesters that overlapped the start date of the pandemic were included, and medication used through the entire trimester was captured.

For those Data Access Providers (DAPS) providing data on prevalence of medication use in ongoing pregnancies (ARS and IACS), similarly, only those trimesters whose end date was after the start of the pandemic and before the end of data availability were included.

### **7.4 Study variables**

#### **7.4.1 Pregnancy start and end dates**

The start of pregnancy was defined as the estimated first day of the last menstrual period (LMP); end of pregnancy was the date of delivery or abortion (elective/spontaneous). Pregnancy start and end dates were assessed based on the data banks used to detect the pregnancy:

- medical birth registers
  - LMP: The first day of the LMP is estimated by subtracting the gestational age at delivery, as recorded in the register, from the pregnancy end date; if gestational age is estimated both by ultrasound and the woman's recall of LMP, the former is preferred.
- records of diagnostic codes (e.g. hospitalizations):
  - gestational age at the record date is estimated using the algorithm of Matcho et al<sup>1</sup>
- records of procedure codes:
  - gestational age at the record date is estimated using the algorithm of Matcho et al<sup>1</sup>, possibly adjusted per data source-specific predicted gestational age
- primary care medical records or hospitalisation records

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<sup>1</sup> Matcho, A., et al., *Inferring pregnancy episodes and outcomes within a network of observational databases*. PloS one, 2018. **13**(2): p. e0192033-e0192033.

- date of the pregnancy delivery or date of abortion are retrieved as recorded (specific to IACS)

Novel methods to identify ongoing pregnancies using diagnostic codes, procedure codes and primary care records are being developed as part of ConcePTION<sup>2</sup>. The ARS institute applied this methodology to extract ongoing pregnancies, censoring at 'end-of-trimester', up until 31.03.2021. Likewise, IACS extracted data on ongoing pregnancies, censoring at 31.12.2020.

**Table 2 DAP-specific method of identifying pregnancy start and end date**

DAP	Data banks used to identify pregnancy start and end	Explanation
<i>DAP includes both completed and ongoing pregnancies</i>		
Italy ARS	Birth registry, spontaneous abortion registry, termination registry, hospital discharge records, recordings of diagnostic procedures	Pregnancy start: date of record minus gestational age if extracted from a registry; otherwise, estimated based on the diagnostic code, or on the period of pregnancy when the procedure is first expected, based on a predictive model  pregnancy end: date of record if a registry; otherwise, estimated from due date based on estimation of start date
Spain IACS	The pregnancy control data bank (CARTILLA_EMBARAZO) captures information from all pregnancy related visits, including the date of the LMP, which is recorded at the first visit.  The end of pregnancy is obtained from the date of the pregnancy delivery or abortion recorded in primary care or hospital discharge. For those pregnancies without information of delivery or abortion prior to the end of the study (31th December 2020), these were considered that to be ongoing at that date.	Regarding the pregnancy database, pregnancy monitoring is carried out by the obstetrician (specialized care) after referral by the primary care physician if the pregnancy test is positive. Until 2018, all observations related to pregnancy care were written by the obstetrician in a notebook during each follow-up visit: laboratory test results, ultrasound results, other measurements (e.g., blood pressure, BMI). From 2018, this is the same process, but all annotations are made using an electronic form, although most of the information is free text providing comments regarding the evolution of pregnancy. Free text was not extracted for the study.

<sup>2</sup> Defined Background rates of Adverse Events of Special Interest for monitoring COVID-19 vaccines (ACCESS-BGR)

EU PAS Register Number: EUPAS37273 [www.encepp.eu/encepp/viewResource.htm?id=37274](http://www.encepp.eu/encepp/viewResource.htm?id=37274)

<b>DAP includes completed pregnancies only</b>		
Spain (FISABIO-HSRU)	<p>The Valencia Integrated Database (VID): - PMR (Perinatal Mortality Registry): Stillbirth, neonatal death - MDR (Metabolic Diseases Registry) Deliveries. In VID, a record is created for any pregnancy of gestational age 12 weeks or beyond (live, miscarriage, elective abortion, stillbirth) during pregnancy, but we are able to identify it at the end of pregnancy (not during pregnancy).</p>	<p>Start of pregnancy is the date of LMP, end of pregnancy is the date of delivery or abortion (elective/spontaneous). Pregnancy end: Date of delivery (live or stillbirth), date of abortion or miscarriage*. Pregnancy start: -For those with gestational age available (around 90% of deliveries) = Date of delivery minus gestational age in weeks. Gestational age is estimated based on ultrasound. - For those without gestational age available (around 10% of deliveries) = Date of delivery minus 40 weeks when newborns' weight is 2500 gr or above; AND through a linear regression model when newborns' weight under 2500 gr. * Currently working on availability of data and identification of miscarriages occurred in early pregnancy.</p>
Wales SWANSEA	National Community Child Health Database (NCCHD), Maternity Indicators Dataset (MIDS)	<p>Births (live and still) were identified as child IDs on NCCHD. NCCHD is based on birth registrations with the Office of National Statistics (ONS), which records all legal births in the UK. This data bank does not hold information on spontaneous and induced abortions. End date of pregnancy was defined as Monday of the subject's (infant's) week of delivery (live birth or stillbirth), to avoid use of identifiable data. Gestational age at birth, based on ultrasound scans, was obtained from NCCHD. Data were checked against MIDS. This improved the completeness of the data. If gestational age was missing or implausible, the pregnancy was excluded/ gestation was estimated for term births from the mean value for the database. In the event, all births had a gestational age.</p>
Norway UiO	<p>Birth registry (MBRN) A record is created for any pregnancy of gestational age 12 weeks or beyond (live, miscarriage, elective abortion, stillbirth), at the end of pregnancy (not during pregnancy).</p>	<p>Pregnancy end: Date of delivery Pregnancy start = Date of delivery – gestational length in days Gestational length is estimated based on ultrasound. Rarely, when UL is missing, GL is based on the woman's report of the LMP.</p>

Abbreviations: ARS = Agenzia Regionale di Sanita' della Toscana; FISABIO-HSRU = Foundation for the Promotion of Health and Biomedical Research of Valencia Region - Health Services Research Unit; IACS = Instituto Aragonés de Ciencias de la Salud; SWANSEA = Swansea University; UiO = University of Oslo.

### **Trimester of pregnancy**

The period of pregnancy was divided into trimesters. The American College of Obstetricians and Gynecologists (ACOG) definition of timing in pregnancy was used:

- Trimester 1: from Last Menstrual Period (LMP) to day < 98 after LMP; or end of pregnancy, whichever earlier
- Trimester 2: from day 98 after LMP to day <196 after LMP; or end of pregnancy, whichever earlier
- Trimester 3: from day 196 after LMP onwards until end of pregnancy

### **7.4.2 SARS-CoV-2 and COVID-19**

SARS-CoV-2 infections and COVID-19 were identified by records in surveillance systems, or diagnostic codes in health care records and/or laboratory results (Table 3).

**Table 3 Data banks(s) used by each DAP to identify COVID-19**

DAP	Type	Explanation
Italy ARS	Registry of positive COVID-19 tests	This is the official surveillance system
Spain FISABIO-HSRU	RedMIVA (Microbiological Surveillance Network of the Valencian Community)	All PCR or antigen test results are recorded
Wales SWANSEA	COVID-19 Test results dataset available from healthdatagateway.org	All test results and symptom trackers
Spain IACS	Registry developed for monitoring the evolution of the COVID-19 disease pandemic in the region of Aragon	All PCR or antigen test results are recorded
Norway UiO	MSIS (Norwegian surveillance system for communicable diseases)	Laboratory confirmed positive test

Abbreviations: ARS = Agenzia Regionale di Sanita' della Toscana; FISABIO-HSRU = Foundation for the Promotion of Health and Biomedical Research of Valencia Region - Health Services Research Unit; IACS = Instituto Aragonés de Ciencias de la Salud; PCR = polymerase chain reaction; SWANSEA = Swansea University; UiO = University of Oslo.

### **7.4.3 Medications**

Information on medication was retrieved from outpatient or primary care dispensing records, as recorded in the data banks of the data sources participating in the project. For each dispensing or prescribing record (as was the case in Wales), we assumed the dispensing (or prescribing) date to reflect timing of medication use (no stockpiling was considered). Table 4 gives an overview of the medication groups of special relevance to COVID-19 that are included in this interim report.

**Table 4 ATC-level 2 codes of medication groups of special relevance to COVID-19**

<ol style="list-style-type: none"> <li>1. Antihypertensives (C02, C03, C04, C07, C08 and/or C09)</li> <li>2. Antithrombotic agents (B01)</li> <li>3. Antivirals (J05)</li> <li>4. Antibacterials (J01)</li> <li>5. Antimycotics (J02)</li> </ol>
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6. Antimycobacterials (J04)
7. Immune sera and globulins (J06)
8. Vaccinations (J07)
9. Analgesics (N02)
10. Psycholeptics (N05)
11. Psychoanaleptics (N06)
12. Diabetes (A10)
13. Corticosteroids (H02)
14. Immunostimulants (L03)
15. Immunosuppressants (L04)
16. Anti-inflammatory drugs (M01)
17. Nasal preparations (R01)
18. Medicines for obstructive airway disease (R03)
19. Cough and cold medications (R05)

#### **7.4.4 Risk factors for severe COVID-19 infection**

##### **Age**

Age groups were defined based on age at the start date of the pregnancy, using two categories:<sup>3</sup>

- 12-34 years of age
- 35-55 years of age

##### **At-Risk Medical Conditions to develop severe COVID-19**

At-risk medical conditions for developing severe COVID-19 were defined based on scientific evidence available from the US Centres for Disease Control and Prevention (CDC website, July 2020) and UK National Health Services (NHS website, July 2020) websites. Table 5 lists the at-risk medical conditions, diagnostic codes and proxies, identified in line with the ACCESS project.<sup>4</sup> A composite 'at-risk' variable was created to indicate the presence of any one of these conditions<sup>5</sup>. Multi-morbidity was not considered; subjects could belong to more than one at-risk group. A one-year look back time-period prior to the start of pregnancy - to assess relevant diagnostic codes or ATC codes - was applied.

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<sup>3</sup> Lean, S. C., H. Derricott, R. L. Jones and A. E. P. Heazell (2017). "Advanced maternal age and adverse pregnancy outcomes: A systematic review and meta-analysis." PLoS One 12(10): e0186287.

<sup>4</sup> Defined Background rates of Adverse Events of Special Interest for monitoring COVID-19 vaccines (ACCESS-BGR)  
EU PAS Register Number: EUPAS37273 [www.encepp.eu/encepp/viewResource.htm?id=37274](http://www.encepp.eu/encepp/viewResource.htm?id=37274)

<sup>5</sup> In the current analysis we included obesity in the composite variable, 'risk factor for the development of severe COVID-19', based on diagnostic codes, medication use as proxy, or BMI  $\geq 30$ . We did not include obesity as a stand-alone stratification factor. However, we intend to do so in the final analysis presented in the report due July 2022. Smoking / alcohol will not be considered as a co-morbid condition owing to inconsistent data capture among DAPs

**Table 5 Co-morbid conditions with evidence of increased COVID-19 severity.**

At-risk medical conditions (diagnostic codes)	Medicinal product proxy(ies) (ATC code)
<b>Cardiovascular incl. blood</b>	
Cardiovascular disease/ Serious heart conditions includes: <ul style="list-style-type: none"> <li>heart failure,</li> <li>coronary artery disease</li> <li>cardiac myopathies</li> </ul>	Antiarrhythmics, class I and III (C01B) Cardiac stimulants excl. Cardiac glycosides (C01C) Vasodilators used in cardiac diseases (C01D) Other cardiac preparations (C01E) Antithrombotic agents (B01A)
Thalassemia and sickle cell disease	Hydroxyurea (L01XX05) Other hematological agents (B06AX)
<b>Respiratory</b>	
Chronic lung disease including COPD, medicated asthma	Drugs for obstructive airway diseases (R03) Lung surfactants (R07AA) Respiratory stimulants (R07AB)
<b>Endocrine and metabolic</b>	
Type 1 & 2 Diabetes	Insulin and analogues (A10A) Blood glucose lowering drugs (A10B)
Obesity diagnosis or having a BMI $\geq 30$ kg/m <sup>2</sup>	Peripherally acting antiobesity products (A08AB) Centrally acting antiobesity products (A08AA)
<b>Renal</b>	
Chronic kidney disease	Erythropoietin (B03XA01)
<b>Immunological</b>	
HIV	Protease inhibitors (J05AE) Combinations to treat HIV (J05AR) NRTI (J05AF) NNRTI (J05AG)
Immunosuppression	Immunosuppressants (L04A) Corticosteroids (H02)
<b>Cancer</b>	Alkylating agents (L01A) Antimetabolites (L01B) Plant alkaloids and other natural products (L01C) Cytotoxic antibiotics and related substances (L01D) Other antineoplastic agents (L01X) Hormones and related agents (L02A) Hormone antagonists and related agents (L02B) Immunostimulants (L03) Immunosuppressants (L04)

The data banks used by each Data Access Provider to identify the presence of an at-risk medical condition is presented in Table 6.

**Table 6 Data bank(s) used by each DAP use to identify presence of at-risk medical conditions**

DAP	Type
Italy ARS	Hospital discharge records, emergency admissions, exemptions from copayment, dispensings of medicines from community or hospital pharmacies for outpatient use or inpatient for cancer medications
Spain FISABIO-HSRU	Ambulatory Electronic Health Records (AEHR) includes primary and specialist care and active diagnoses (1 year look-back), Electronic pharmaceutical records (GAIA) (1 year look-back), Accident & Emergency Department record (AED) (1 year look-back)
Wales SWANSEA	Primary care (GP) database, Hospital admissions (PEDW). Maternity Indicators Dataset (MIDS)
Spain IACS	Dispensed medicines from community pharmacies (1 year look back)
Norway UiO	Norwegian Prescription Database (NorPD) (1 year look back) Medical Birth registry (MBRN) (BMI at start of pregnancy)

Abbreviations: ARS = Agenzia Regionale di Sanita' della Toscana; FISABIO-HSRU = Foundation for the Promotion of Health and Biomedical Research of Valencia Region - Health Services Research Unit; IACS = Instituto Aragonés de Ciencias de la Salud; SWANSEA = Swansea University; UiO = University of Oslo.

**Table 7 Data bank(s) used by each DAP use to identify obesity as part of the at-risk medical condition**

DAP	Type
Italy ARS	Obesity was identified from diagnostic codes retrieved during 365 days before estimated pregnancy start. Due to the nature of the ARS data source, this is expected to be severely underestimated. <sup>6</sup>
Spain FISABIO-HSRU	Obesity is identified as an obesity diagnosis (ICD9: 278 codes; ICD10: E65, E66 codes) from one year before the estimated LMP using date from Ambulatory Electronic Health Records.
Wales SWANSEA	Maternity Indicators Dataset (MIDS). Height and weight are entered at initial antenatal visit.
Spain IACS	Obesity was identified based on the consumption of drugs peripheral acting antiobesity products or centrally acting antiobesity products. <sup>7</sup>
Norway UiO	Obesity was identified as a BMI $\geq 30$ kg/m <sup>2</sup> at the start of pregnancy, extracted from the Medical Birth registry (MBRN)

<sup>6</sup> For the final report, obesity will also be identified using BMI  $\geq 30$  kg/m<sup>2</sup> at the start of pregnancy in all pregnancies that are retrieved from the birth registry.

<sup>7</sup> For the final report BMI  $\geq 30$  kg/m<sup>2</sup> at the start of pregnancy (from the pregnancy control data bank) will be included as an additional marker of obesity.

## **7.5 Analysis**

The prevalence of medication dispensed (or prescribed) was analysed according to trimester of pregnancy and COVID-19 status:

1. Analysis 1: Prevalence of medication dispensed (or prescribed) in trimesters with no positive COVID-19 test/diagnosis, nor any preceding COVID-19 infection during the pregnancy.
2. Analysis 2: Prevalence of medication dispensed (or prescribed) in the trimester when a first recorded positive COVID-19 test/diagnosis was received.
3. Analysis 3: Prevalence of medication dispensed (or prescribed) in trimesters following a trimester when a positive COVID-19 test/diagnosis was received.

In each analysis, the denominator was the count of women in the trimester of interest and the numerator the count of women having one or more dispensings of - or prescription for - the specific medication within that trimester.

Results were stratified by:

- age group
- presence of an 'at-risk medical condition'
- calendar month of positive COVID-19 test/diagnosis (where applicable)

## **8 Results**

### **8.1 Data sources and follow-up**

For this analysis, Data Access providers (DAPS) in 5 countries participated (Table 7). Three DAPS used medical birth registers to identify completed pregnancies: FISABIO-HSRU (Spain), UiO (Norway) and SWANSEA (Wales). This end date of data availability was 31.12.2020 for FISABIO-HSRU, 30.06.2020 for UiO, and 30.04.2021 for SWANSEA. ARS and IACS had access to data banks facilitating the examination of on-going pregnancy to include trimesters completed up to 31.03.2021 (ARS) and 31.12.2020 (IACS).

- ARS (Italy) had access to data until the end of March 2021 related to both completed and ongoing pregnancies
- IACS (Spain) had access to data until the end of December 2020 related to both completed and ongoing pregnancies
- FISABIO-HSRU (Spain) had access to data until the end of December 2020 on pregnancies completed by that date
- UiO (Norway) had access to data until the end of December 2020, though data from its birth register was only available on pregnancies completed by end of June 2020.
- SWANSEA (Wales) had access to data until the end of April 2021 on pregnancies completed by that date

**Table 8 End date of data availability for each data source**

Data Access Provider	Country	COVID-19 diagnoses and sequelae, at-risk medical conditions					Medication	Pregnancy status & outcomes
		Hospital	Emergency	Primary care	Outpatient specialist care	Surveillance (COVID-19 registry)	Prescription registry	Birth registry
ARS	Italy	March 2021	March 2021	-	-	March 2021	March 2021	March 2021
FISABIO-HSRU	Spain	MBDS* Dec 2020	AED Dec 2020	AEHR Dec2020	AEHR Dec 2020	RedMIVA Dec 2020	AEHR/G AIA Dec 2020	MDR/ PMR Dec 2020
SWANSEA	Wales	April 2021	*	April 2021	NA	April 2021	April 2021	NCCHD from UHBs ONS Dec 2020
IACS	Spain	December 2020	NA	December 2020	NA	December 2020	Dec 2020	Dec 2020**
UiO	Norway	NPR: Dec 2020	NA	KUHR: Dec 2020	KUHR: Dec 2020	MSIS Dec 2020	NorPD: Nov2020	MBRN: June 2020

Notes: \*Data sources not included for data delivery in Obj.1. \*\*Information on pregnancies was retrieved from CARTILLA\_EMBARAZO ('pregnancy control'), not its medical birth registry which is only available for the 2 largest hospitals.

Abbreviations: AED = Accident & Emergency Department record (Emergency room visits); AEHR = Ambulatory Electronic Health Records (Includes primary and specialist care); ARS = Agenzia Regionale di Sanita' della Toscana; FISABIO-HSRU = Foundation for the Promotion of Health and Biomedical Research of Valencia Region - Health Services Research Unit; GAIA (Electronic pharmaceutical records); IACS = Instituto Aragonés de Ciencias de la Salud; MBDS = Clinical Minimum Basic Dataset (Hospitalization data); MDR = Metabolic Disease Registry (acts as a Birth Registry); RedMIVA = Microbiological Surveillance Network of the Valencian Community (Includes all PCR or Antigen test results); PMR = Perinatal Mortality Registry; SWANSEA = Swansea University; UiO = University of Oslo.

## 8.2 Description of the pregnancy cohort

The pregnancy cohort included 115,162 pregnant women; 2,022 (1.8%) of whom tested positive for, or were diagnosed with COVID-19, during their pregnancy (Table 8). Over 30% of the women were aged 35 years or older, with a considerably higher proportion of women in the older age category in Italy and Spain than in Norway and Wales; 26.7% were defined as at-risk of developing severe COVID-19, with a much larger percentage in Wales.

Among data sources, the rates of pregnant women who tested positive for or were diagnosed with COVID-19 during pregnancy ranged from 0.17% (UiO, Norway) to 4.0% (IACS, Spain). The duration of data availability influenced both the number of pregnant women in each DAP's cohort and the number of women with a positive test or diagnosis of COVID-19 during their pregnancy. Pregnant women who tested positive for COVID-19 in 2020, but who had not yet delivered by the end of December 2020 were not included in those countries using medical birth registries to create their pregnancy cohort with the exception of Wales, which had data on births until the end of April 2021. We expect that our rates of COVID-19 positive test/diagnosis mirror the testing pattern / infection pattern among women in

childbearing age in each region / country covered. There is currently no evidence that pregnant women are more susceptible to contracting the SARS-CoV2 virus.

In terms of the representativeness of the samples studied here, data from Norway covers the entire country and consequently is representative for the country. Wales has primary care data representative of approximately 80% of the country; women with primary care data have been shown to have slightly lower deprivation scores than those without.<sup>8</sup> The FISABIO-HSRU covers the entire Valencia Region, with approximately 5 million inhabitants, which accounts for 11% of the Spanish population. While the data is representative of the Valencia Region, this may not be generalizable to the whole Spanish population. Similarly, with the IACS data source from Aragon, this is a population-based study and therefore representative of the Aragon region, but may not be generalizable to the entire Spanish population. Data from ARS includes the complete activity of the regional healthcare system, and covers the entire population of legal inhabitants of Tuscany, an Italian region of approximately 3.6 million inhabitants.

**Table 9 Description of the pregnancy cohort**

	<b>Total pregnancies</b>	<b>Age 12-34 years</b>	<b>Age 35-55 years</b>	<b>At-risk medical condition*</b>	<b>COVID-19 positive test/diagnosis in pregnancy</b>
	N	N (%)	N (%)	N (%)	N (%)
<b><i>Cohort created using both completed and ongoing pregnancies</i></b>					
Italy -ARS	43,066	25,977 (60.3%)	17,089 (39.7%)	10,008 (23.2%)	722 (1.7%)
Spain - IACS	11,154	7,027 (63.0%)	4,127 (37.0%)	1,686 (15.1%)	441 (4.0%)
<b><i>Cohort created using only completed pregnancies</i></b>					
Wales - SWANSEA	19,098	15,866 (83.1%)	3,232 (16.9%)	9,087 (47.6%)	501 (2.6%)
Spain - FISABIO-HSRU	23,683	16,384 (69.2%)	7,299 (30.8%)	3,996 (16.9%)	327 (1.4%)
Norway- UiO	18,161	15,110 (83.2%)	3,051 (16.8%)	5,979 (24.7%)	31 (0.17%)

Notes: \*At-risk medical condition: any diagnosis/medication use indicating the presence of cardiovascular disease, respiratory disease, diabetes, obesity, renal disease, immunological disease or cancer, in the year prior to start of pregnancy.

Abbreviations: ARS = Agenzia Regionale di Sanita' della Toscana; FISABIO-HSRU = Foundation for the Promotion of Health and Biomedical Research of Valencia Region - Health Services Research Unit; IACS = Instituto Aragonés de Ciencias de la Salud; SWANSEA = Swansea University; UiO = University of Oslo.

<sup>8</sup> EUROMedCAT. (EMC) 2015 Selective Serotonin Reuptake Inhibitor (SSRI) antidepressants in Pregnancy and Congenital Anomalies: population cohort study using linked electronic data in 3 countries V2. Deliverable number 21. – ISBN 978-0956746252. Available at: <http://www.euromedicat.eu/content/2015-EUROMedCAT-SSRI-Deliverable-21.pdf>

In total, 228,491 trimesters which coincided with the pandemic<sup>9</sup> were included in the study, among the 115,162 pregnant women (Table 10). Over half (52.7%) of COVID-19 cases occurred during the third trimester of pregnancy. The time span of data available influenced the counts of each trimester. For example, there were fewer first trimesters in Norway than second or third trimesters, as a result of the combination of the inclusion criteria, and earlier end date of data (June 2020).

**Table 10 Count of trimesters of pregnancy included in each analysis**

	Trimesters with neither +ve COVID-19 test or diagnosis nor prior +ve test during pregnancy	Trimester when a first recorded +ve COVID-19 test or diagnosis was received	Trimesters following the trimester when a +ve COVID-19 test or diagnosis was received
	N	N	N
<b>Italy -ARS</b>			
Trimester 1	24,623	191	NA
Trimester 2	27,311	217	93
Trimester 3	30,887	314	144
Total	82,821	722	237
<b>Spain- FISABIO-HSRU</b>			
Trimester 1	10,130	8	NA
Trimester 2	17,660	33	8
Trimester 3	23,302	286	41
Total	51,092	327	49
<b>Wales - SWANSEA</b>			
Trimester 1	11,039	39	NA
Trimester 2	15,336	199	39
Trimester 3	18,449	263	230
Total	44,824	501	269
<b>Spain - IACS</b>			
Trimester 1	7,666	120	NA
Trimester 2	8,007	144	93
Trimester 3	7,137	177	139
Total	22,810	441	232
<b>Norway- UiO</b>			
Trimester 1	102	0	NA
Trimester 2	6,052	5	0
Trimester 3	17,976	26	5
Total	24,130	31	5

Abbreviations: ARS = Agenzia Regionale di Sanita' della Toscana; FISABIO-HSRU = Foundation for the Promotion of Health and Biomedical Research of Valencia Region - Health Services Research Unit; IACS = Instituto Aragonés de Ciencias de la Salud; SWANSEA = Swansea University; UiO = University of Oslo.

<sup>9</sup> Only trimesters coinciding with the pandemic (i.e., the end date for the trimester was after the start date of the pandemic (01.03.2020) and before the end of data availability) were eligible for inclusion in the study.

### 8.2.1 *Characteristics of trimesters of pregnancy included in each analysis*

Table 10 compares the characteristics of those trimesters free of COVID-19 infection (defined as with none of the following: a positive COVID-19 test or, a COVID-19 diagnosis or, any preceding positive test or diagnosis during pregnancy), with those trimesters where a positive COVID-19 test or diagnosis was recorded. Within data sources, age and presence of at-risk medical condition, were very similar.

**Table 11 Characteristics of trimesters of pregnancy with and without a COVID-19 +ve test/diagnosis**

	Trimesters with neither +ve COVID-19 test or diagnosis nor any preceding +ve test during pregnancy	Trimester when a first recorded +ve COVID-19 test or diagnosis was received
	N (%)	N (%)
<b>Italy - ARS</b>		
Age at start of pregnancy		
12-34y	50,634 (61.1%)	476 (65.9%)
35-55y	32,187 (38.9%)	246 (34.1%)
Presence of an at-risk medical condition	19,152 (23.1%)	158 (21.9%)
Total	82,821	722
<b>Spain - FISABIO-HSRU</b>		
Age at start of pregnancy		
12-34y	35,410 (69.3%)	228 (69.7%)
35-55y	15,682 (30.7%)	99 (30.3%)
Presence of an at-risk medical condition	8,765 (17.2%)	53 (16.2%)
Total	51,092	327
<b>Wales - SWANSEA</b>		
Age at start of pregnancy		
12-34y	37,245 (83.1%)	429 (85.6%)
35-55y	7,579 (16.9%)	72 (14.4%)
Presence of an at-risk medical condition	21,382 (47.7%)	249 (49.7%)
Total	44,824	501
<b>Spain - IACS</b>		
Age at start of pregnancy		
12-34y	14,429 (63.3%)	296 (67.1%)
35-55y	8,381 (36.7%)	145 (32.9%)
Presence of an at-risk medical condition	3,542 (15.5%)	67 (15.2%)
Total	22,810	441
<b>Norway - UiO</b>		
Age at start of pregnancy		
12-34y	20,062 (83.1%)	26 (83.9%)
35-55y	4,068 (16.9%)	5 (16.1%)
Presence of an at-risk medical condition	5,974 (24.5%)	5 (16.1%)
Total	24,130	31

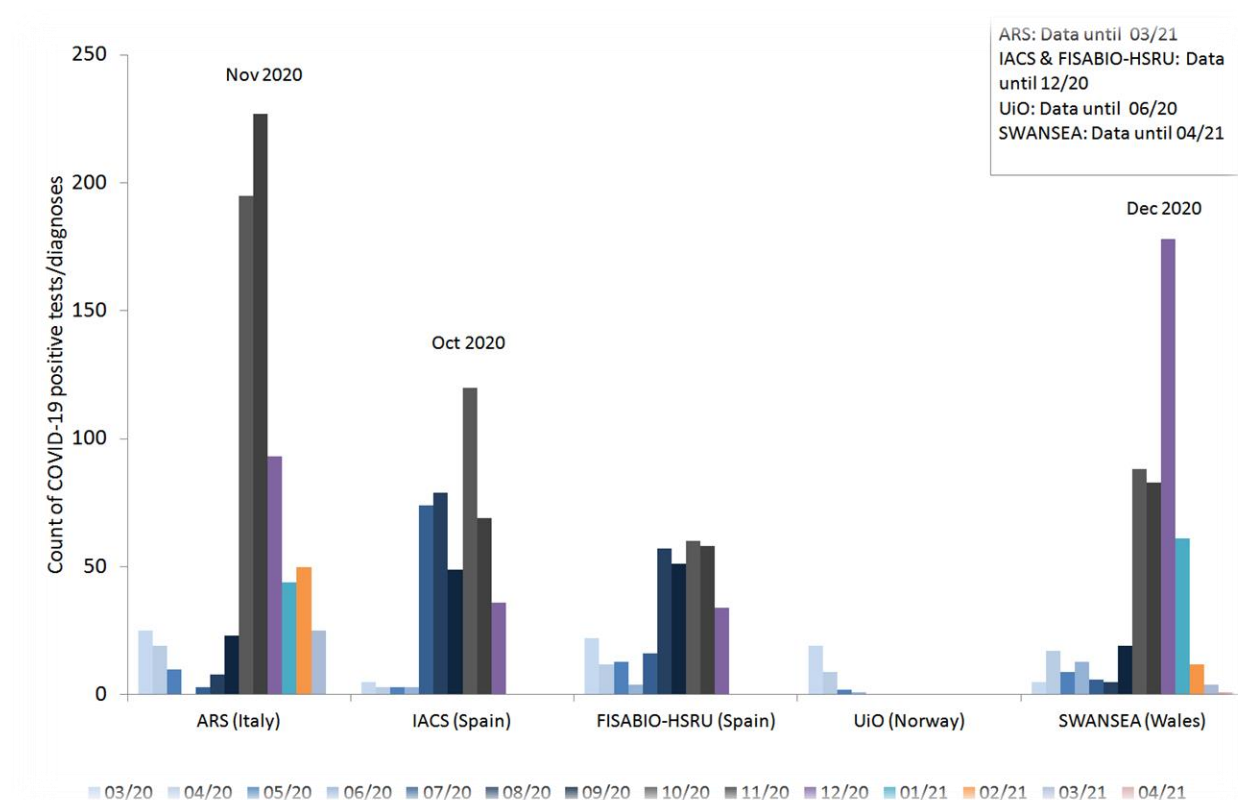
Abbreviations: ARS = Agenzia Regionale di Sanita' della Toscana; FISABIO-HSRU = Foundation for the Promotion of Health and Biomedical Research of Valencia Region - Health Services Research Unit; IACS = Instituto Aragones de Ciencias de la Salud; SWANSEA = Swansea University; UiO = University of Oslo.



### 8.2.2 Timing of COVID-19 infection in the pregnancy cohort

The peak in infections during Oct-Dec 2020 are clearly visible in Figure 1. As previously highlighted, it is important to recognize that end date of data availability, and the method used to create the pregnancy cohort creation (completed pregnancies, vs. completed & ongoing pregnancies), influenced the count of COVID-19 infections identified in the data sources in each month. For example, data from Wales include data from the birth registry on deliveries to the end of April 2021, therefore its cohort includes a sizable number of pregnant women who tested positive for COVID -19 in the latter half of 2020, prior to the completion of their pregnancy in the Spring of 2021.

**Figure 1. Timing of COVID-19 infection in the pregnancy cohort**



Abbreviations: ARS = Agenzia Regionale di Sanita' della Toscana; FISABIO-HSRU = Foundation for the Promotion of Health and Biomedical Research of Valencia Region - Health Services Research Unit; IACS = Instituto Aragonés de Ciencias de la Salud; SWANSEA = Swansea University; UiO = University of Oslo.

### 8.3 Description of medication use per pregnancy trimester and COVID-19 status

The results of the three analyses are presented together in the following tables to facilitate comparison. The numerator is the number of women having one or more dispensing/prescription (date of prescription/dispensing) of the medication within the specific trimester. The denominator is the number of pregnant women in the specific trimesters.

More detailed results stratified by age, the presence of at-risk medical condition, and calendar month of infection (where applicable) are presented in Annex 1 - 3. The absolute counts in terms of the numerators and denominators are provided in the Annexes.

Figures of drug categories of interest (antithrombotic agents (B01); antibacterials (J01); analgesics (N02); and psychoanaleptics (N06)), are provided in Appendix 2. The findings are discussed in the Discussion section.

**A note on the reporting of prevalence estimates**

The 95% CI reflects the measure of uncertainty around the prevalence estimate, which is greater for smaller sample sizes. The sample sizes (i.e., count of trimester of interest), are not provided in the following results tables to facilitate readability. They are provided in the Annexes.

In the case of a denominator (i.e., number of women in the trimester of interest) with a zero value, the prevalence estimate is returned as 'Not Applicable (NA)'. For denominators with a count less than five, the prevalence is returned as 'Not calculated (NC)'. In the case of a zero numerator (i.e., count of women exposed to relevant drug category), the prevalence is returned as 0.

**Table 12** Prevalence of medication prescribed/dispensed during trimesters of pregnancy, by COVID-19 status; by data source: **Antihypertensives (C02, C03, C04, C07, C08, C09)**

	Trimesters with no positive COVID-19 test or diagnosis nor any preceding COVID-19 infection during the pregnancy; % (95% CI)			Trimester when a first recorded positive COVID-19 test or diagnosis was received; % (95% CI)			Trimesters following the trimester when a positive COVID-19 test or diagnosis was received; % (95% CI)	
	First Trimester	Second Trimester	Third trimester	First Trimester -infect	Second Trimester -infect	Third Trimester - infect	Second Trimester	Third trimester
ARS	0.9 (0.8 to 1.1)	0.9 (0.8 to 1.0)	1.2 (1.0 to 1.3)	1.6 (0.0 to 3.3)	0.5 (0.0 to 1.4)	1.9 (0.4 to 3.4)	0	1.4 (0.0 to 3.3)
FISABIO-HSRU	0.8 (0.6 to 1.0)	1.0 (0.8 to 1.1)	1.9 (1.7 to 2.0)	0	3.0 (0.0 to 8.9)	1.4 (0.0 to 2.8)	12.5 (0.0 to 35.4)	2.4 (0.0 to 7.2)
SWANSEA	2.1 (1.8 to 2.3)	1.1 (0.9 to 1.2)	1.0 (0.9 to 1.1)	0	1.0 (0.0 to 2.4)	1.1 (0.0 to 2.4)	2.6 (0.0 to 7.5)	0.9 (0.0 to 2.1)
IACS	1.2 (0.9 to 1.4)	1.0 (0.8 to 1.2)	1.1 (0.9 to 1.4)	0	2.1 (0.0 to 4.4)	0.6 (0.0 to 1.7)	0	2.2 (0.0 to 4.6)
UiO	3.9 (0.2 to 7.7)	0.8 (0.6 to 1.1)	1.3 (1.1 to 1.4)	NA	0	0	NA	0

Abbreviations: ARS = Agenzia Regionale di Sanita' della Toscana; FISABIO-HSRU = Foundation for the Promotion of Health and Biomedical Research of Valencia Region - Health Services Research Unit; IACS = Instituto Aragonés de Ciencias de la Salud; SWANSEA = Swansea University; UiO = University of Oslo; NA = Not Applicable.

**Table 13** Prevalence of medication prescribed/dispensed during trimesters of pregnancy, by COVID-19 status; by data source: **Antithrombotic agents (B01)**

	Trimesters with no positive COVID-19 test or diagnosis nor any preceding COVID-19 infection during the pregnancy; % (95% CI)			Trimester when a first recorded positive COVID-19 test or diagnosis was received; % (95% CI)			Trimesters following the trimester when a positive COVID-19 test or diagnosis was received; % (95% CI)	
	First Trimester	Second Trimester	Third trimester	First Trimester -infect	Second Trimester -infect	Third Trimester - infect	Second Trimester	Third trimester
ARS	6.7 (6.4 to 7.1)	5.9 (5.6 to 6.2)	4.3 (4.0 to 4.5)	13.6 (8.7 to 18.5)	16.1 (11.2 to 21.0)	15.9 (11.9 to 20.0)	5.4 (0.8 to 10.0)	9.7 (4.9 to 14.6)
FISABIO-HSRU	4.3 (3.9 to 4.7)	5.6 (5.3 to 5.9)	5.2 (4.9 to 5.5)	25.0 (0.0 to 55.0)	15.2 (2.9 to 27.4)	25.9 (20.8 to 30.9)	25.0 (0.0 to 55.0)	12.2 (2.2 to 22.2)
SWANSEA	3.9 (3.5 to 4.2)	5.8 (5.4 to 6.2)	3.8 (3.5 to 4.0)	5.1 (0.0 to 12.1)	5.0 (2.0 to 8.1)	1.9 (0.3 to 3.6)	2.6 (0.0 to 7.5)	3.5 (1.1 to 5.8)
IACS	7.8 (7.2 to 8.4)	8.3 (7.7 to 8.9)	7.4 (6.8 to 8.0)	20.8 (13.6 to 28.1)	47.9 (39.8 to 56.1)	29.4 (22.7 to 36.1)	8.6 (2.9 to 14.3)	13.7 (8.0 to 19.4)
UiO	8.8 (3.3 to 14.3)	3.7 (3.3 to 4.2)	2.0 (1.8 to 2.2)	NA	0	0	NA	0

Abbreviations: ARS = Agenzia Regionale di Sanita' della Toscana; FISABIO-HSRU = Foundation for the Promotion of Health and Biomedical Research of Valencia Region - Health Services Research Unit; IACS = Instituto Aragonés de Ciencias de la Salud; SWANSEA = Swansea University; UiO = University of Oslo; NA = Not Applicable.

**Table 14** Prevalence of medication prescribed/dispensed during trimesters of pregnancy, by COVID-19 status; by data source: **Antivirals (J05)**

	Trimesters with no positive COVID-19 test or diagnosis nor any preceding COVID-19 infection during the pregnancy; % (95% CI)			Trimester when a first recorded positive COVID-19 test or diagnosis was received; % (95% CI)			Trimesters following the trimester when a positive COVID-19 test or diagnosis was received; % (95% CI)	
	First Trimester	Second Trimester	Third trimester	First Trimester -infect	Second Trimester -infect	Third Trimester - infect	Second Trimester	Third trimester
ARS	0.2 (0.2 to 0.3)	0.2 (0.1 to 0.2)	0.2 (0.2 to 0.3)	0.5 (0.0 to 1.5)	0	0.3 (0.0 to 0.9)	1.1 (0.0 to 3.2)	0
FISABIO-HSRU	0.2 (0.1 to 0.3)	0.1 (0.1 to 0.2)	0.2 (0.1 to 0.2)	0	0	0.7 (0.0 to 1.7)	0	0
SWANSEA	0.5 (0.3 to 0.6)	0.5 (0.4 to 0.6)	0.6 (0.5 to 0.7)	0	0	1.5 (0.0 to 3.0)	0	0
IACS	0.1 (0.0 to 0.1)	0.0 (0.0 to 0.1)	0.1 (0.0 to 0.2)	0	0	0	0	0
UiO	0	0.5 (0.3 to 0.7)	1.6 (1.4 to 1.7)	NA	0	0	NA	0

Abbreviations: ARS = Agenzia Regionale di Sanita' della Toscana; FISABIO-HSRU = Foundation for the Promotion of Health and Biomedical Research of Valencia Region - Health Services Research Unit; IACS = Instituto Aragonés de Ciencias de la Salud; SWANSEA = Swansea University; UiO = University of Oslo; NA = Not Applicable.

**Table 15** Prevalence of medication prescribed/dispensed during trimesters of pregnancy, by COVID-19 status; by data source: **Antibacterials (J01)**

	Trimesters with no positive COVID-19 test or diagnosis nor any preceding COVID-19 infection during the pregnancy; % (95% CI)			Trimester when a first recorded positive COVID-19 test or diagnosis was received; % (95% CI)			Trimesters following the trimester when a positive COVID-19 test or diagnosis was received; % (95% CI)	
	First Trimester	Second Trimester	Third trimester	First Trimester -infect	Second Trimester -infect	Third Trimester - infect	Second Trimester	Third trimester
ARS	12.1 (11.7 to 12.5)	9.1 (8.7 to 9.4)	6.9 (6.6 to 7.2)	14.1 (9.2 to 19.1)	13.4 (8.8 to 17.9)	9.2 (6.0 to 12.4)	3.2 (0.0 to 6.8)	4.2 (0.9 to 7.4)
FISABIO-HSRU	10.2 (9.6 to 10.8)	13.0 (12.5 to 13.4)	12.6 (12.1 to 13.0)	12.5 (0.0 to 35.4)	21.2 (7.3 to 35.2)	19.2 (14.7 to 23.8)	12.5 (0.0 to 35.4)	12.2 (2.2 to 22.2)
SWANSEA	13.6 (13.0 to 14.3)	13.8 (13.2 to 14.3)	8.8 (8.4 to 9.2)	7.7 (0.0 to 16.1)	17.6 (12.3 to 22.9)	11.8 (7.9 to 15.7)	25.6 (11.9 to 39.3)	7.8 (4.4 to 11.3)
IACS	10.3 (9.6 to 11.0)	9.7 (9.1 to 10.4)	7.9 (7.3 to 8.5)	12.5 (6.6 to 18.4)	13.2 (7.7 to 18.7)	10.2 (5.7 to 14.6)	4.3 (0.2 to 8.4)	4.3 (0.9 to 7.7)
UiO	8.8 (3.3 to 14.3)	11.0 (10.2 to 11.8)	7.3 (7.0 to 7.7)	NA	20.0 (0.0 to 55.1)	15.4 (1.5 to 29.3)	NA	0

Abbreviations: ARS = Agenzia Regionale di Sanita' della Toscana; FISABIO-HSRU = Foundation for the Promotion of Health and Biomedical Research of Valencia Region - Health Services Research Unit; IACS = Instituto Aragonés de Ciencias de la Salud; SWANSEA = Swansea University; UiO = University of Oslo; NA = Not Applicable.

**Table 16** Prevalence of medication prescribed/dispensed during trimesters of pregnancy, by COVID-19 status; by data source: **Antimycotics (J02)**

	Trimesters with no positive COVID-19 test or diagnosis nor any preceding COVID-19 infection during the pregnancy; % (95% CI)			Trimester when a first recorded positive COVID-19 test or diagnosis was received; % (95% CI)			Trimesters following the trimester when a positive COVID-19 test or diagnosis was received; % (95% CI)	
	First Trimester	Second Trimester	Third trimester	First Trimester -infect	Second Trimester -infect	Third Trimester - infect	Second Trimester	Third trimester
ARS	0.4 (0.3 to 0.5)	0.3 (0.2 to 0.4)	0.2 (0.2 to 0.3)	0	0.5 (0.0 to 1.4)	0.3 (0.0 to 0.9)	0	0
FISABIO-HSRU	0.1 (0.0 to 0.1)	0.1 (0.1 to 0.1)	0.1 (0.1 to 0.1)	0	0	0	0	0
SWANSEA	0.2 (0.1 to 0.3)	0.1 (0.0 to 0.1)	0.1 (0.0 to 0.1)	0	0	0.4 (0.0 to 1.1)	0	0
IACS	0.2 (0.1 to 0.3)	0.1 (0.0 to 0.1)	0.0 (0.0 to 0.1)	0	0	1.1 (0.0 to 2.7)	0	0
UiO	0	0.1 (0.0 to 0.2)	0.2 (0.1 to 0.2)	NA	0	0	NA	0

Abbreviations: ARS = Agenzia Regionale di Sanita' della Toscana; FISABIO-HSRU = Foundation for the Promotion of Health and Biomedical Research of Valencia Region - Health Services Research Unit; IACS = Instituto Aragonés de Ciencias de la Salud; SWANSEA = Swansea University; UiO = University of Oslo; NA = Not Applicable.

**Table 17** Prevalence of medication prescribed/dispensed during trimesters of pregnancy, by COVID-19 status; by data source: **Antimycobacterials (J04)**

	Trimesters with no positive COVID-19 test or diagnosis nor any preceding COVID-19 infection during the pregnancy; % (95% CI)			Trimester when a first recorded positive COVID-19 test or diagnosis was received; % (95% CI)			Trimesters following the trimester when a positive COVID-19 test or diagnosis was received; % (95% CI)	
	First Trimester	Second Trimester	Third trimester	First Trimester -infect	Second Trimester -infect	Third Trimester - infect	Second Trimester	Third trimester
ARS	0.0 (0.0 to 0.0)	0.0 (0.0 to 0.0)	0.0 (0.0 to 0.0)	0	0	0	0	0
FISABIO-HSRU	0	0.0 (0.0 to 0.0)	0.0 (0.0 to 0.0)	0	0	0	0	0
SWANSEA	0.0 (0.0 to 0.0)	0	0	0	0	0	0	0
IACS	0.0 (0.0 to 0.0)	0.0 (0.0 to 0.0)	0	0	0	0	0	0
UiO	0	0	0	NA	0	0	NA	0

Abbreviations: ARS = Agenzia Regionale di Sanita' della Toscana; FISABIO-HSRU = Foundation for the Promotion of Health and Biomedical Research of Valencia Region - Health Services Research Unit; IACS = Instituto Aragonés de Ciencias de la Salud; SWANSEA = Swansea University; UiO = University of Oslo; NA = Not Applicable.

**Table 18** Prevalence of medication prescribed/dispensed during trimesters of pregnancy, by COVID-19 status; by data source: **Immune sera and globulins (J06)**

	Trimesters with no positive COVID-19 test or diagnosis nor any preceding COVID-19 infection during the pregnancy; % (95% CI)			Trimester when a first recorded positive COVID-19 test or diagnosis was received; % (95% CI)			Trimesters following the trimester when a positive COVID-19 test or diagnosis was received; % (95% CI)	
	First Trimester	Second Trimester	Third trimester	First Trimester -infect	Second Trimester -infect	Third Trimester - infect	Second Trimester	Third trimester
ARS	0.2 (0.1 to 0.2)	0.4 (0.4 to 0.5)	0.9 (0.8 to 1.0)	0	0	1.0 (0.0 to 2.0)	1.1 (0.0 to 3.2)	0.7 (0.0 to 2.1)
FISABIO-HSRU	0.0 (0.0 to 0.1)	7.0 (6.7 to 7.4)	1.8 (1.6 to 2.0)	0	3.0 (0.0 to 8.9)	1.4 (0.0 to 2.8)	37.5 (4.0 to 71.0)	2.4 (0.0 to 7.2)
SWANSEA	0	0	0	0	0	0	0	0
IACS	0.0 (0.0 to 0.0)	1.0 (0.7 to 1.2)	1.1 (0.9 to 1.4)	0	2.1 (0.0 to 4.4)	1.7 (0.0 to 3.6)	0	0.7 (0.0 to 2.1)
UiO	0	0.2 (0.1 to 0.3)	0.3 (0.2 to 0.4)	NA	0	3.8 (0.0 to 11.2)	NA	0

Abbreviations: ARS = Agenzia Regionale di Sanita' della Toscana; FISABIO-HSRU = Foundation for the Promotion of Health and Biomedical Research of Valencia Region - Health Services Research Unit; IACS = Instituto Aragonés de Ciencias de la Salud; SWANSEA = Swansea University; UiO = University of Oslo; NA = Not Applicable.

**Table 19** Prevalence of medication prescribed/dispensed during trimesters of pregnancy, by COVID-19 status; by data source: **Vaccinations (J07)**

	Trimesters with no positive COVID-19 test or diagnosis nor any preceding COVID-19 infection during the pregnancy; % (95% CI)			Trimester when a first recorded positive COVID-19 test or diagnosis was received;% (95% CI)			Trimesters following the trimester when a positive COVID-19 test or diagnosis was received; % (95% CI)	
	First Trimester	Second Trimester	Third trimester	First Trimester -infect	Second Trimester -infect	Third Trimester - infect	Second Trimester	Third trimester
ARS	4.8 (4.5 to 5.0)	9.1 (8.8 to 9.4)	25.0 (24.5 to 25.4)	7.3 (3.6 to 11.0)	17.1 (12.0 to 22.1)	35.4 (30.1 to 40.6)	7.5 (2.2 to 12.9)	32.6 (25.0 to 40.3)
FISABIO-HSRU	0	0.0 (0.0 to 0.1)	0.0 (0.0 to 0.1)	0	0	0	0	0
SWANSEA	0.3 (0.2 to 0.4)	6.4 (6.0 to 6.8)	2.0 (1.8 to 2.2)	0	4.5 (1.6 to 7.4)	1.1 (0.0 to 2.4)	5.1 (0.0 to 12.1)	1.7 (0.0 to 3.4)
IACS	0.0 (0.0 to 0.0)	0	0	0	0	0	0	0
UiO	2.0 (0.0 to 4.7)	5.9 (5.3 to 6.5)	1.1 (0.9 to 1.2)	NA	0	0	NA	0

Abbreviations: ARS = Agenzia Regionale di Sanita' della Toscana; FISABIO-HSRU = Foundation for the Promotion of Health and Biomedical Research of Valencia Region - Health Services Research Unit; IACS = Instituto Aragonés de Ciencias de la Salud; SWANSEA = Swansea University; UiO = University of Oslo; NA = Not Applicable.

Note: Information on vaccination is usually registered in vaccination registries, not in the prescribing and dispensing databases which were used in this analysis.

**Table 20** Prevalence of medication prescribed/dispensed during trimesters of pregnancy, by COVID-19 status; by data source: **Analgesics (N02)**

	Trimesters with no positive COVID-19 test or diagnosis nor any preceding COVID-19 infection during the pregnancy; % (95% CI)			Trimester when a first recorded positive COVID-19 test or diagnosis was received; % (95% CI)			Trimesters following the trimester when a positive COVID-19 test or diagnosis was received; % (95% CI)	
	First Trimester	Second Trimester	Third trimester	First Trimester -infect	Second Trimester -infect	Third Trimester - infect	Second Trimester	Third trimester
ARS	0.6 (0.5 to 0.7)	0.3 (0.2 to 0.4)	0.3 (0.3 to 0.4)	0.5 (0.0 to 1.5)	0	0.3 (0.0 to 0.9)	0	0
FISABIO-HSRU	11.9 (11.3 to 12.5)	13.7 (13.2 to 14.2)	10.1 (9.8 to 10.5)	25.0 (0.0 to 55.0)	45.5 (28.5 to 62.4)	22.0 (17.2 to 26.8)	0	9.8 (0.7 to 18.8)
SWANSEA	4.7 (4.3 to 5.1)	3.7 (3.4 to 4.0)	2.9 (2.7 to 3.2)	10.3 (0.7 to 19.8)	6.0 (2.7 to 9.3)	1.9 (0.3 to 3.6)	7.7 (0.0 to 16.1)	7.0 (3.7 to 10.2)
IACS	12.5 (11.7 to 13.2)	10.0 (9.3 to 10.6)	6.5 (6.0 to 7.1)	27.5 (19.5 to 35.5)	22.9 (16.1 to 29.8)	13.6 (8.5 to 18.6)	8.6 (2.9 to 14.3)	4.3 (0.9 to 7.7)
UiO	1.0 (0.0 to 2.9)	4.1 (3.6 to 4.6)	2.8 (2.6 to 3.1)	NA	0	3.8 (0.0 to 11.2)	NA	0

Abbreviations: ARS = Agenzia Regionale di Sanita' della Toscana; FISABIO-HSRU = Foundation for the Promotion of Health and Biomedical Research of Valencia Region - Health Services Research Unit; IACS = Instituto Aragonés de Ciencias de la Salud; SWANSEA = Swansea University; UiO = University of Oslo; NA = Not Applicable.

**Table 21** Prevalence of medication prescribed/dispensed during trimesters of pregnancy, by COVID-19 status; by data source: **Psycholeptics (N05)**

	Trimesters with no positive COVID-19 test or diagnosis nor any preceding COVID-19 infection during the pregnancy; % (95% CI)			Trimester when a first recorded positive COVID-19 test or diagnosis was received; % (95% CI)			Trimesters following the trimester when a positive COVID-19 test or diagnosis was received; % (95% CI)	
	First Trimester	Second Trimester	Third trimester	First Trimester -infect	Second Trimester -infect	Third Trimester - infect	Second Trimester	Third trimester
ARS	0.3 (0.3 to 0.4)	0.3 (0.2 to 0.4)	0.3 (0.2 to 0.3)	0.5 (0.0 to 1.5)	0	1.0 (0.0 to 2.0)	1.1 (0.0 to 3.2)	0
FISABIO-HSRU	2.1 (1.8 to 2.4)	1.5 (1.3 to 1.7)	1.4 (1.3 to 1.6)	0	0	1.4 (0.0 to 2.8)	0	0
SWANSEA	2.1 (1.9 to 2.4)	1.2 (1.0 to 1.4)	0.9 (0.8 to 1.0)	0	1.5 (0.0 to 3.2)	1.9 (0.3 to 3.6)	0	2.2 (0.3 to 4.1)
IACS	3.4 (2.9 to 3.8)	1.6 (1.3 to 1.8)	1.0 (0.8 to 1.3)	3.3 (0.1 to 6.5)	5.6 (1.8 to 9.3)	1.1 (0.0 to 2.7)	1.1 (0.0 to 3.2)	1.4 (0.0 to 3.4)
UiO	5.9 (1.3 to 10.4)	1.0 (0.7 to 1.2)	0.7 (0.6 to 0.8)	NA	0	0	NA	0

Abbreviations: ARS = Agenzia Regionale di Sanita' della Toscana; FISABIO-HSRU = Foundation for the Promotion of Health and Biomedical Research of Valencia Region - Health Services Research Unit; IACS = Instituto Aragonés de Ciencias de la Salud; SWANSEA = Swansea University; UiO = University of Oslo; NA = Not Applicable.

**Table 22** Prevalence of medication prescribed/dispensed during trimesters of pregnancy, by COVID-19 status; by data source: **Psychoanaleptics (N06)**

	Trimesters with no positive COVID-19 test or diagnosis nor any preceding COVID-19 infection during the pregnancy; % (95% CI)			Trimester when a first recorded positive COVID-19 test or diagnosis was received; % (95% CI)			Trimesters following the trimester when a positive COVID-19 test or diagnosis was received; % (95% CI)	
	First Trimester	Second Trimester	Third trimester	First Trimester -infect	Second Trimester -infect	Third Trimester - infect	Second Trimester	Third trimester
ARS	1.9 (1.7 to 2.1)	1.6 (1.4 to 1.7)	1.6 (1.5 to 1.7)	1.0 (0.0 to 2.5)	0.9 (0.0 to 2.2)	1.0 (0.0 to 2.0)	2.2 (0.0 to 5.1)	0.7 (0.0 to 2.1)
FISABIO-HSRU	1.5 (1.3 to 1.8)	1.1 (0.9 to 1.2)	0.9 (0.8 to 1.0)	0	0	0.3 (0.0 to 1.0)	0	0
SWANSEA	13.3 (12.6 to 13.9)	9.0 (8.5 to 9.4)	7.7 (7.3 to 8.1)	7.7 (0.0 to 16.1)	12.1 (7.5 to 16.6)	8.7 (5.3 to 12.2)	12.8 (2.3 to 23.3)	10.9 (6.8 to 14.9)
IACS	2.1 (1.8 to 2.4)	1.0 (0.8 to 1.2)	0.8 (0.6 to 1.0)	4.2 (0.6 to 7.7)	2.1 (0.0 to 4.4)	0.6 (0.0 to 1.7)	2.2 (0.0 to 5.1)	2.2 (0.0 to 4.6)
UiO	2.9 (0.0 to 6.2)	1.3 (1.0 to 1.6)	1.0 (0.9 to 1.1)	NA	0	0	NA	0

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**Table 23** Prevalence of medication prescribed/dispensed during trimesters of pregnancy, by COVID-19 status; by data source: **Diabetes (A10)**

	Trimesters with no positive COVID-19 test or diagnosis nor any preceding COVID-19 infection during the pregnancy; % (95% CI)			Trimester when a first recorded positive COVID-19 test or diagnosis was received; % (95% CI)			Trimesters following the trimester when a positive COVID-19 test or diagnosis was received; % (95% CI)	
	First Trimester	Second Trimester	Third trimester	First Trimester -infect	Second Trimester -infect	Third Trimester - infect	Second Trimester	Third trimester
ARS	1.1 (0.9 to 1.2)	1.6 (1.5 to 1.8)	2.6 (2.4 to 2.7)	1.6 (0.0 to 3.3)	1.4 (0.0 to 2.9)	3.2 (1.2 to 5.1)	1.1 (0.0 to 3.2)	2.1 (0.0 to 4.4)
FISABIO-HSRU	1.1 (0.9 to 1.3)	1.7 (1.5 to 1.9)	2.7 (2.5 to 3.0)	0	3.0 (0.0 to 8.9)	4.9 (2.4 to 7.4)	0	4.9 (0.0 to 11.5)
SWANSEA	1.5 (1.3 to 1.8)	1.8 (1.6 to 2.0)	3.3 (3.0 to 3.5)	0	2.5 (0.3 to 4.7)	3.0 (1.0 to 5.1)	0	3.9 (1.4 to 6.4)
IACS	1.0 (0.7 to 1.2)	1.9 (1.6 to 2.2)	3.5 (3.1 to 3.9)	0	4.2 (0.9 to 7.4)	2.8 (0.4 to 5.3)	1.1 (0.0 to 3.2)	3.6 (0.5 to 6.7)
UiO	1.0 (0.0 to 2.9)	1.8 (1.5 to 2.2)	2.8 (2.6 to 3.1)	NA	0	15.4 (1.5 to 29.3)	NA	0

Abbreviations: ARS = Agenzia Regionale di Sanita' della Toscana; FISABIO-HSRU = Foundation for the Promotion of Health and Biomedical Research of Valencia Region - Health Services Research Unit; IACS = Instituto Aragonés de Ciencias de la Salud; SWANSEA = Swansea University; UiO = University of Oslo; NA = Not Applicable.



**Table 24** Prevalence of medication prescribed/dispensed during trimesters of pregnancy, by COVID-19 status; by data source: **Corticosteroids (H02)**

	Trimesters with no positive COVID-19 test or diagnosis nor any preceding COVID-19 infection during the pregnancy; % (95% CI)			Trimester when a first recorded positive COVID-19 test or diagnosis was received; % (95% CI)			Trimesters following the trimester when a positive COVID-19 test or diagnosis was received; % (95% CI)	
	First Trimester	Second Trimester	Third trimester	First Trimester -infect	Second Trimester -infect	Third Trimester - infect	Second Trimester	Third trimester
ARS	2.4 (2.2 to 2.6)	1.7 (1.6 to 1.9)	1.8 (1.7 to 2.0)	6.8 (3.2 to 10.4)	6.5 (3.2 to 9.7)	2.2 (0.6 to 3.9)	1.1 (0.0 to 3.2)	2.1 (0.0 to 4.4)
FISABIO-HSRU	0.4 (0.3 to 0.6)	0.4 (0.3 to 0.5)	0.4 (0.3 to 0.5)	0	0	1.4 (0.0 to 2.8)	0	0
SWANSEA	0.9 (0.7 to 1.0)	0.7 (0.6 to 0.9)	0.5 (0.4 to 0.6)	5.1 (0.0 to 12.1)	2.0 (0.1 to 4.0)	0.4 (0.0 to 1.1)	0	0.4 (0.0 to 1.3)
IACS	1.0 (0.8 to 1.2)	0.5 (0.3 to 0.6)	0.4 (0.3 to 0.6)	1.7 (0.0 to 4.0)	1.4 (0.0 to 3.3)	1.1 (0.0 to 2.7)	0	0.7 (0.0 to 2.1)
UiO	2.0 (0.0 to 4.7)	0.5 (0.3 to 0.7)	0.3 (0.2 to 0.4)	NA	0	0	NA	0

Abbreviations: ARS = Agenzia Regionale di Sanita' della Toscana; FISABIO-HSRU = Foundation for the Promotion of Health and Biomedical Research of Valencia Region - Health Services Research Unit; IACS = Instituto Aragonés de Ciencias de la Salud; SWANSEA = Swansea University; UiO = University of Oslo; NA = Not Applicable.

**Table 25** Prevalence of medication prescribed/dispensed during trimesters of pregnancy, by COVID-19 status; by data source: **Immunostimulants (L03)**

	Trimesters with no positive COVID-19 test or diagnosis nor any preceding COVID-19 infection during the pregnancy; % (95% CI)			Trimester when a first recorded positive COVID-19 test or diagnosis was received; % (95% CI)			Trimesters following the trimester when a positive COVID-19 test or diagnosis was received; % (95% CI)	
	First Trimester	Second Trimester	Third trimester	First Trimester -infect	Second Trimester -infect	Third Trimester - infect	Second Trimester	Third trimester
ARS	0.1 (0.0 to 0.1)	0.1 (0.0 to 0.1)	0.1 (0.0 to 0.1)	0	0	0	0	0
FISABIO-HSRU	0.0 (0.0 to 0.0)	0.0 (0.0 to 0.0)	0.0 (0.0 to 0.0)	0	0	0	0	0
SWANSEA	0	0.0 (0.0 to 0.0)	0	0	0	0	0	0
IACS	0	0	0	0	0	0	0	0
UiO	0	0	0.0 (0.0 to 0.0)	NA	0	0	NA	0

Abbreviations: ARS = Agenzia Regionale di Sanita' della Toscana; FISABIO-HSRU = Foundation for the Promotion of Health and Biomedical Research of Valencia Region - Health Services Research Unit; IACS = Instituto Aragonés de Ciencias de la Salud; SWANSEA = Swansea University; UiO = University of Oslo; NA = Not Applicable.

**Table 26** Prevalence of medication prescribed/dispensed during trimesters of pregnancy, by COVID-19 status; by data source: **Immunosuppressants (L04)**

	Trimesters with no positive COVID-19 test or diagnosis nor any preceding COVID-19 infection during the pregnancy; % (95% CI)			Trimester when a first recorded positive COVID-19 test or diagnosis was received; % (95% CI)			Trimesters following the trimester when a positive COVID-19 test or diagnosis was received; % (95% CI)	
	First Trimester	Second Trimester	Third trimester	First Trimester -infect	Second Trimester -infect	Third Trimester - infect	Second Trimester	Third trimester
ARS	0.2 (0.2 to 0.3)	0.2 (0.1 to 0.2)	0.2 (0.1 to 0.2)	0	0	0	0	0
FISABIO-HSRU	0.1 (0.1 to 0.2)	0.2 (0.1 to 0.2)	0.1 (0.1 to 0.2)	0	0	0	0	0
SWANSEA	0.2 (0.1 to 0.2)	0.2 (0.1 to 0.2)	0.1 (0.1 to 0.2)	0	0.5 (0.0 to 1.5)	0	0	0.4 (0.0 to 1.3)
IACS	0.1 (0.1 to 0.2)	0.1 (0.0 to 0.2)	0.1 (0.0 to 0.2)	0	0	0	0	0
UiO	2.0 (0.0 to 4.7)	0.2 (0.1 to 0.4)	0.2 (0.1 to 0.3)	NA	0	0	NA	0

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**Table 27** Prevalence of medication prescribed/dispensed during trimesters of pregnancy, by COVID-19 status; by data source: **Anti-inflammatory drugs (M01)**

	Trimesters with no positive COVID-19 test or diagnosis nor any preceding COVID-19 infection during the pregnancy; % (95% CI)			Trimester when a first recorded positive COVID-19 test or diagnosis was received; % (95% CI)			Trimesters following the trimester when a positive COVID-19 test or diagnosis was received; % (95% CI)	
	First Trimester	Second Trimester	Third trimester	First Trimester -infect	Second Trimester -infect	Third Trimester - infect	Second Trimester	Third trimester
ARS	1.0 (0.9 to 1.1)	0.6 (0.5 to 0.7)	0.7 (0.6 to 0.8)	1.6 (0.0 to 3.3)	0.9 (0.0 to 2.2)	0.3 (0.0 to 0.9)	0	0
FISABIO-HSRU	2.4 (2.1 to 2.7)	0.9 (0.7 to 1.0)	0.7 (0.6 to 0.8)	0	0	0.7 (0.0 to 1.7)	0	0
SWANSEA	1.5 (1.3 to 1.7)	0.2 (0.1 to 0.2)	0.1 (0.1 to 0.2)	2.6 (0.0 to 7.5)	0	0	0	0
IACS	6.9 (6.3 to 7.5)	1.6 (1.4 to 1.9)	1.0 (0.8 to 1.2)	10.0 (4.6 to 15.4)	2.1 (0.0 to 4.4)	2.8 (0.4 to 5.3)	1.1 (0.0 to 3.2)	0.7 (0.0 to 2.1)
UiO	2.0 (0.0 to 4.7)	0.3 (0.1 to 0.4)	0.2 (0.1 to 0.2)	NA	0	0	NA	0

Abbreviations: ARS = Agenzia Regionale di Sanita' della Toscana; FISABIO-HSRU = Foundation for the Promotion of Health and Biomedical Research of Valencia Region - Health Services Research Unit; IACS = Instituto Aragonés de Ciencias de la Salud; SWANSEA = Swansea University; UiO = University of Oslo; NA = Not Applicable.

**Table 28** Prevalence of medication prescribed/dispensed during trimesters of pregnancy, by COVID-19 status; by data source: **Nasal preparations (R01)**

	Trimesters with no positive COVID-19 test or diagnosis nor any preceding COVID-19 infection during the pregnancy; % (95% CI)			Trimester when a first recorded positive COVID-19 test or diagnosis was received; % (95% CI)			Trimesters following the trimester when a positive COVID-19 test or diagnosis was received; % (95% CI)	
	First Trimester	Second Trimester	Third trimester	First Trimester -infect	Second Trimester -infect	Third Trimester - infect	Second Trimester	Third trimester
ARS	0.1 (0.0 to 0.1)	0.1 (0.0 to 0.1)	0.0 (0.0 to 0.1)	0	0	0	0	0
FISABIO-HSRU	0.7 (0.5 to 0.9)	0.8 (0.6 to 0.9)	0.5 (0.4 to 0.6)	0	0	1.0 (0.0 to 2.2)	0	2.4 (0.0 to 7.2)
SWANSEA	2.3 (2.0 to 2.6)	2.5 (2.2 to 2.7)	1.3 (1.1 to 1.5)	7.7 (0.0 to 16.1)	2.5 (0.3 to 4.7)	1.5 (0.0 to 3.0)	5.1 (0.0 to 12.1)	2.2 (0.3 to 4.1)
IACS	1.5 (1.2 to 1.8)	1.1 (0.8 to 1.3)	0.6 (0.5 to 0.8)	4.2 (0.6 to 7.7)	2.1 (0.0 to 4.4)	0.6 (0.0 to 1.7)	0	1.4 (0.0 to 3.4)
UiO	0	2.7 (2.3 to 3.1)	3.3 (3.1 to 3.6)	NA	0	7.7 (0.0 to 17.9)	NA	0

Abbreviations: ARS = Agenzia Regionale di Sanita' della Toscana; FISABIO-HSRU = Foundation for the Promotion of Health and Biomedical Research of Valencia Region - Health Services Research Unit; IACS = Instituto Aragonés de Ciencias de la Salud; SWANSEA = Swansea University; UiO = University of Oslo; NA = Not Applicable.

**Table 29** Prevalence of medication prescribed/dispensed during trimesters of pregnancy, by COVID-19 status; by data source: **Medicines for obstructive airway disease (R03)**

	Trimesters with no positive COVID-19 test or diagnosis nor any preceding COVID-19 infection during the pregnancy; % (95% CI)			Trimester when a first recorded positive COVID-19 test or diagnosis was received; % (95% CI)			Trimesters following the trimester when a positive COVID-19 test or diagnosis was received; % (95% CI)	
	First Trimester	Second Trimester	Third trimester	First Trimester -infect	Second Trimester -infect	Third Trimester - infect	Second Trimester	Third trimester
ARS	1.9 (1.7 to 2.0)	1.8 (1.6 to 1.9)	1.5 (1.3 to 1.6)	3.1 (0.7 to 5.6)	0.5 (0.0 to 1.4)	1.3 (0.0 to 2.5)	1.1 (0.0 to 3.2)	2.1 (0.0 to 4.4)
FISABIO-HSRU	1.8 (1.5 to 2.1)	1.9 (1.7 to 2.1)	1.5 (1.4 to 1.7)	12.5 (0.0 to 35.4)	3.0 (0.0 to 8.9)	3.5 (1.4 to 5.6)	0	7.3 (0.0 to 15.3)
SWANSEA	6.3 (5.8 to 6.7)	6.6 (6.2 to 7.0)	5.1 (4.8 to 5.5)	10.3 (0.7 to 19.8)	8.0 (4.3 to 11.8)	7.2 (4.1 to 10.4)	17.9 (5.9 to 30.0)	6.5 (3.3 to 9.7)
IACS	2.1 (1.8 to 2.5)	1.7 (1.4 to 2.0)	1.5 (1.2 to 1.8)	3.3 (0.1 to 6.5)	6.3 (2.3 to 10.2)	3.4 (0.7 to 6.1)	0	0
UiO	2.9 (0.0 to 6.2)	3.1 (2.7 to 3.6)	2.4 (2.2 to 2.6)	NA	0	3.8 (0.0 to 11.2)	NA	0

Abbreviations: ARS = Agenzia Regionale di Sanita' della Toscana; FISABIO-HSRU = Foundation for the Promotion of Health and Biomedical Research of Valencia Region - Health Services Research Unit; IACS = Instituto Aragonés de Ciencias de la Salud; SWANSEA = Swansea University; UiO = University of Oslo; NA = Not Applicable.

**Table 30** Prevalence of medication prescribed/dispensed during trimesters of pregnancy, by COVID-19 status; by data source: **Cough and cold medications (R05)**

	Trimesters with no positive COVID-19 test or diagnosis nor any preceding COVID-19 infection during the pregnancy; % (95% CI)			Trimester when a first recorded positive COVID-19 test or diagnosis was received; % (95% CI)			Trimesters following the trimester when a positive COVID-19 test or diagnosis was received; % (95% CI)	
	First Trimester	Second Trimester	Third trimester	First Trimester -infect	Second Trimester -infect	Third Trimester - infect	Second Trimester	Third trimester
ARS	0.0 (0.0 to 0.1)	0.0 (0.0 to 0.1)	0.0 (0.0 to 0.0)	0	0	0	0	0
FISABIO-HSRU	-	-	-	-	-	-	-	-
SWANSEA	0.2 (0.1 to 0.3)	0.3 (0.2 to 0.4)	0.2 (0.1 to 0.3)	0	0.5 (0.0 to 1.5)	0.8 (0.0 to 1.8)	0	0.9 (0.0 to 2.1)
IACS	0.2 (0.1 to 0.3)	0.2 (0.1 to 0.3)	0.0 (0.0 to 0.1)	1.7 (0.0 to 4.0)	0	0.6 (0.0 to 1.7)	0	0
UiO	1.0 (0.0 to 2.9)	1.8 (1.4 to 2.1)	0.8 (0.7 to 1.0)	NA	0	0	NA	0

Notes: \*Due to an omission in the original statistical analysis plan, FISABIO-HSRU were not in a position to extract data for R05 for this report.

Abbreviations: ARS = Agenzia Regionale di Sanita' della Toscana; FISABIO-HSRU = Foundation for the Promotion of Health and Biomedical Research of Valencia Region - Health Services Research Unit; IACS = Instituto Aragoes de Ciencias de la Salud; SWANSEA = Swansea University; UiO = University of Oslo; NA = Not Applicable.

## 9 Discussion

This first interim report from Work Package 1 of the CONSIGN project using electronic health care registry data, presents preliminary findings on drug utilisation patterns in a cohort of 115,162 pregnant women, 2,022 (1.8%) of whom tested positive for COVID-19 during their pregnancy.

Five Data Access Providers from four European countries (Italy, Norway, Spain and Wales) participated in this first study, providing outpatient or primary care drug utilisation data from prescribed or dispensed prescriptions, covering a period from June 2019 up to the end of data availability.<sup>10</sup> Analyses were conducted at the level of trimester of pregnancy. Comparison was made between the prevalence of medication use in trimesters with no positive COVID-19 test/diagnosis nor any preceding COVID-19 infection during the pregnancy, with that observed in trimesters when a first recorded positive COVID-19 test/diagnosis was received, and subsequent trimesters.

### 9.1 Main findings

#### 9.1.1 Pregnant women without a COVID-19 diagnosis

There were large differences observed between the data sources in the prevalence of use of several drug categories. For example, in Italy, approximately 1 in 4 women in the third trimester of their pregnancy were dispensed a vaccine compared to 10% in the second trimester. In comparison, the SAIL data source in Wales - which also included dispensing over the winter months of 2020/2021, and should therefore include the administration of influenza vaccine - showed that only 2% of women in the third trimester and 6% in the second trimester were dispensed a vaccine. In the other countries, there was minimal or no vaccines dispensed to pregnant women. This warrants further examination to elicit whether this is simply an artifact of different reimbursement systems and data capture; or truly represents different patterns of vaccination in pregnant women in these countries.

There was a pronounced difference in the rates of psychoanaleptics (N06) dispensed to pregnant women in the SAIL data source in Wales. Over 13% of women in their first trimester of pregnancy were dispensed a medication for this drug category; reducing to 8% of women in the third trimester. In the other data

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<sup>10</sup> End of data availability differed by Data Access Provider. The most recent end date of data availability was April 2021.

sources, rates were approximately 1-2% throughout pregnancy. These high rates have been identified in prior cross-European studies.<sup>11, 12</sup>

Likewise, pregnant women in the SAIL data source had higher rates of use of medicines for obstructive airway disease (5-7%, compared with 2-3% in the other data sources); this contrast is in line with earlier work.<sup>13</sup> Differences in prevalence estimates were also seen among 'Analgesics (N02)', which were significantly higher in the two Spanish groups. This may however be due to differing reimbursement systems providing payment for pain medication bought over-the-counter in other countries.

We observed almost identical patterns of dispensing of medication for diabetes (A10) at the trimester level, across the data sources - approximately 1% in the first trimester, 2% in the second trimester, and 3% in the third trimester. Interestingly, we did not observe as large a discrepancy in the use of antibacterials (J01), as anticipated, given the high rates historically observed in Italy and Spain.<sup>14</sup> The use of antibacterials was likely to be influenced by public health interventions such as lock downs, and infection control measures (mask wearing, hand sanitization, social distancing) reducing the spread of infections, and encounters with health care providers.

Finally, there was low or practically nil use of on prescription antivirals (J05), antimycotics (J02), antimycobacterials (J04), immune sera and globulins (J06), corticosteroids (H02), immunostimulants (L03), immunosuppressants (L04), nasal preparations (R01), and cough and cold medications (R05).

### ***9.1.2 Pregnant women who received a positive test or diagnosis of COVID-19 during their pregnancy***

#### ***Antithrombotic agents (B01)***

Among trimesters with a positive test or diagnosis of COVID-19, this was the most commonly dispensed drug category of all 19 examined.

In ARS (Italy), IACS (Spain), and FISABIO-HSRU (Spain), there was approximately a threefold increase in the prevalence of use of medication from this drug category, compared to use in trimesters without a COVID-19 diagnosis.

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<sup>11</sup> Charlton, RA. et al. (2015) SSRI use before, during and after pregnancy: a population-based study in 6 European regions *BJOG: An International Journal of Obstetrics and Gynecology*. 122(7):1010-20. doi: 10.1111/1471-0528.13143.

<sup>12</sup> Jordan, S. et al. (2016) Selective Serotonin Reuptake Inhibitor (SSRI) antidepressants in Pregnancy and Congenital Anomalies: analysis of linked databases in Wales, Norway and Funen, Denmark. *Plos One* 11(12): e0165122. doi: 10.1371/journal.pone.0165122

<sup>13</sup> Charlton, R.A., et al. (2016) Asthma medication prescribing before, during and after pregnancy: a study in seven European regions. *BMJ Open*, 6(1): p. e009237

<sup>14</sup> European Centre for Disease Prevention and Control, Antimicrobial consumption in the EU/EEA – Annual Epidemiological Report 2019. 2020, ECDC: Stockholm

In the IACS data source, approximately half of the 144 women who contracted COVID-19 during their second trimester were dispensed a prescription for an antithrombotic agent (B01), as were approximately a third of the 177 women in their third trimester. For those who contracted COVID-19 in the first or second trimester of their pregnancy, rates of use in the third trimester were considerably higher than those who were in the third trimester of a pregnancy without a COVID-19 infection (13.7%, 95% CI: 8.0 to 19.4 vs. 7.4%, 95% CI: 6.8 to 8.0). Data provided by ARS showed a similar pattern, in that there was a three-fold increase in prevalence, with prevalence remaining higher in the third trimester following infection in an earlier trimester. These prevalence estimates were not as high as those seen in IACS however, nor were there clear differences in use between the second and third trimester.

In contrast, there was no increase in the dispensing of medication from this drug category in the SAIL data source from Wales.

### ***Antivirals (J05)***

There was no increase in the prevalence of antiviral use in these trimesters. In fact, across all data sources, less than ten pregnant women with COVID-19 were dispensed an antiviral medication during the trimester when they received a positive COVID-19 diagnosis.

### ***Antibacterials (J01)***

While there was a tendency to a greater use of antibacterials during trimesters when a COVID-19 positive test or diagnosis was recorded compared to those without, few of these increases were statistically significant given the wider confidence intervals in the prevalence estimates of the former group.

### ***Analgesics (N02)***

In the two Spanish databases (FISABIO-HSRU and IACS), which showed high rates of use of analgesics in the earlier analysis compared with the other data sources - likely to be an artifact of reimbursement models. Prevalence rates in those trimesters with a COVID-19 diagnosis were two to three times higher compared to those trimesters without COVID-19.

### ***Corticosteroids (H02)***

As with other drug categories, there was a tendency towards a higher prevalence of use in trimesters with a COVID-19 diagnosis compared to those without, but numbers were low.

Use in ARS was twice as high in first trimesters with COVID-19 compared to those without (6.8 %, 95% CI: 3.2 - 10.4 vs. 2.4%, 95% CI: 2.2 - 2.6); while use in the second trimester was three times higher (6.5%, 95% CI: 3.2 - 9.7 vs. 1.7%, 95% CI: 1.6 - 1.9). There was no difference between third trimesters with and without a COVID-19 diagnosis.

### ***9.1.3 Caveats on interpretation of the findings***

There are several caveats that need to be taken into consideration when interpreting these findings.

Firstly, this interim report presents data on dispensing (or prescribing) in the outpatient setting only. It does not include medication administered to women during hospitalization for COVID-19. CONSIGN WP2 and WP3 cover such use. Therefore, the patterns of medication use are likely to differ from those studies in the in-patient setting, which will have a higher proportion of women with severe COVID-19 and use of injectable medications.

Secondly, it is likely that the differences in the diverse health systems examined here, as well as their models of reimbursements for pharmaceuticals, will have contributed to the differences observed in patterns of medication use across the data sources. For example, paracetamol is reimbursed in FISABIO, IACS, but only in the Norwegian registries if prescribed by a physician. All prescriptions are free of charge in Wales, but many analgesics can be conveniently bought in pharmacies and supermarkets. It is not feasible to disentangle these influences from differences in prescribing patterns.

Thirdly, small sample sizes lead to less precise prevalence estimates, as seen by the wide confidence intervals. This needs to be taken into consideration when comparing across data sources. The tables in the ANNEXES provide details on the number of trimesters included in the derivation of each of the estimates.

## ***9.2 Comparison with the literature***

A recent systematic review and meta-analysis of 62 observational studies (both case series and cohort studies) published between December 2019 and February 2021, included data on 31,016 pregnant women with confirmed COVID-19. The review found that among those studies that reported on the pharmacotherapeutic management of COVID-19, approximately half of the pregnant women were given antibiotics, anticoagulants, and hydroxychloroquine, one in three were given antivirals, and nearly one in five were managed with either corticosteroids or immunotherapy.<sup>15</sup>

A key difference in the studies examined in this meta-analysis was that the majority were conducted in the hospital setting, thus not directly comparable with our study.

A preprint published by the OHDSI network of 6 databases consisting of electronic medical records and claims data from France, Spain, and the United States included 8,598 pregnant women with COVID-19

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<sup>15</sup> Lassi, Z. S., et al. (2021). A systematic review and meta-analysis of data on pregnant women with confirmed COVID-19: Clinical presentation, and pregnancy and perinatal outcomes based on COVID-19 severity. *Journal of global health* 11: 05018-05018.



(2,031 hospitalized) between January 2020 and June 2020. Most pregnancies occurred in the US.<sup>16</sup> The ten most common inpatient treatments (US only) were systemic corticosteroids (29.6%), enoxaparin (24.0%), immunoglobulins (21.4%), famotidine (20.9%), azithromycin (18.1%), heparin (15.8%), ceftriaxone (7.9%), aspirin (7.0%), hydroxychloroquine (5.4%) and amoxicillin (3.5%).

Data was not presented on medication prescribed or dispensed in the outpatient setting, thereby precluding comparison of the findings with our study. Additionally, between country results were not presented or discussed, and data from France and Spain could not be seen or compared.

### ***9.3 Strengths and limitations***

To the best of our knowledge, this report is the first to provide detailed analysis of outpatient drug utilisation patterns, in pregnant women with and without COVID-19 across Europe, presenting data from five different data sources in four diverse European countries. It therefore fills an important knowledge gap on outpatient pharmacotherapeutic management of pregnant women with COVID-19.

The next phases of this project will expand upon this work, firstly providing updated drug utilisation data, secondly, describing the severity and clinical outcomes of COVID-19 disease in pregnant women with COVID-19, according to treatments received during pregnancy, and thirdly, examining the rates of adverse maternal and neonatal outcomes in pregnant women with and without COVID-19, using different medicines.

An important strength of the study is that the analysis was conducted at the level of the trimester of pregnancy; an important factor taken into consideration when making decisions about the pharmacological management of illness in pregnancy. Additionally, those trimesters in which there was no COVID-19 diagnosis among the same cohort of pregnant women, served as a natural reference group enabling comparison of medication use in the two groups.

The study had several limitations. Data are presented at ATC 2nd level only. This prohibits us making direct comparison with the data above published by Lai et al<sup>5</sup>, and an in-depth examination of whether there are any concerns regarding the use of specific medications in pregnancy. The final analysis will include substance-level analysis.

A second limitation is the low number of COVID-19 cases, especially in the first trimester of pregnancy, in some data sources (Norway). This was unavoidable given the time frame of data extracted, with some data access providers having a longer lag time for data access, as well as the fact that in 3 out of the 5

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<sup>16</sup> Lai, L. Y. H., et al. (2020). Clinical characteristics, symptoms, management and health outcomes in 8,598 pregnant women diagnosed with COVID-19 compared to 27,510 with seasonal influenza in France, Spain and the US: a network cohort analysis. medRxiv: 2020.10.13.20211821

data sources pregnancies could only be included if they had ended as well. Importantly, this is an interim report with preliminary findings; the final report in July 2022, will have updated data composed of a larger number of pregnant women exposed to COVID-19 during pregnancy, and we will use novel algorithms to detect ongoing pregnancies.

A further limitation is that we will underestimate the total prevalence of medication use as we do not capture in-patient drug utilisation, and a proportion of the women with COVID-19 will be admitted to hospital for treatment. This includes treatments with antithrombotics, antivirals, corticosteroids and immunoglobulins. The underestimation will be largest for the women with more severe COVID-19 disease as they will have the longest periods of hospital admissions.

Finally, misclassification of both medication exposure and COVID-19 status may occur. Medications may not be used as the exact time as they are prescribed/dispensed, and may be stockpiled. COVID-19 is not always tested; this was especially the case early on in the pandemic, as surveillance systems were getting established, and only those with more severe symptoms were tested initially. However, this is unlikely to have impacted the result of this study, as those who contracted COVID-19 in the first wave of the pandemic were mostly older and therefore less likely to be included in a pregnancy cohort. We now have the opposite challenge; widescale screening of populations resulting in asymptomatic positive patients who would have not been identified if not for screening.

#### ***9.4 Concluding remarks***

This interim drug utilisation study was conducted among 115,162 pregnant women of whom 2,022 (1.8%), had a COVID-19 diagnosis in pregnancy. Electronic health care registry data from five data sources in four diverse European countries between 2018 and 2021 were used. We found large differences in the prevalence of medication use for several drug categories between and within countries. Further studies will be conducted in July 2022 to consolidate these results and to investigate the consequences of such medications use among pregnant women with COVID-19.

## Appendix 1. Description of data access providers and data banks used

### Italy: ARS database

The Italian National Health care System is organized at regional level: the national government sets standards of assistance and a tax-based funding for each region, and regional governments are responsible to provide to all their inhabitants. Tuscany is an Italian region, with around 3.6 million inhabitants. **The Agenzia Regionale di Sanita' della Toscana (ARS)** is a research institute of the Tuscany Region. The ARS database comprises all information that are collected by the Tuscany Region to account for the health care delivered to its inhabitants. Moreover, ARS collects data from regional initiatives. All the data in the ARS data source can be linked with each other at the individual level, through a pseudo-anonymous identifier. The ARS database routinely collects primary care and secondary care prescriptions of drugs for outpatient use, and is able to link them at the individual level with hospital admissions, admissions to emergency care, records of exemptions from copayment, diagnostic tests and procedures, causes of death, mental health services registry, birth registry, spontaneous abortion registry, induced terminations registry. Mother-child linkage is possible through the birth registry. Vaccine data is available since 2016 for children and since 2019 for adults. **COVID-19:** COVID-19 is identified via the Tuscan section of the national COVID surveillance registry, which records and follows all persons with a positive test result. This can be integrated with other sources to improve the quality of follow-up study variables.

### Quality of the data banks and linkage

The data banks are all originated by the local health units, which have access to a shared regional inhabitant register, therefore identification of the patient in the original data is of high quality. Conversion to the pseudonym at the moment of sharing data with ARS is also managed centrally. Each data bank is subject to control at regional level, according to the purpose of the data bank (reimbursement and/or surveillance). Subsequently at the moment of the (approximately bimonthly) transmission to ARS, data is subject to internal consistency control by comparing monthly prevalence or records and of main variables with the past data. Control is shared with investigators in a dashboard.

Data bank	Type	Dates covered
ARS_ANAG_MED_RES_storico	inhabitant registry	from 2003
CAP	birth registry	from 2003
ABS	spontaneous abortions	from 2003
IVG	induced abortions	from 2003
SDO	hospital discharge records	from 2003
SPF	dispensation of medicines in	from 2003

	community pharmacies	
FED	dispensations of medicines from hospital pharmacies for outpatient use	from 2003
SEA	exemptions from copayment	from 2003
PS	emergency admissions	from 2010
SPA	ambulatory procedures	from 2004
SALM	mental health services	from 2010
VCN	vaccinations	from 2019
COVID_DATASET	covid vaccination registry	from 2020
SPC	primary care community activities	from 2010

### Norway: Norwegian linked registries

The core data that UIO has access to is the health care administrative databases of the entire Norwegian population, which amounts to approximately 5.3 million inhabitants. Norway has a universal public health care system, consisting of primary health care services and specialist health care services. Many population-based health registries were established in the 1960s, with use of a unique personal identifier facilitating linkage between registries. The mandatory national health registries were established to maintain national functions. They are used for health analysis, health statistics, improving the quality of health care, research, administration and emergency preparedness. Since January 2004, all pharmacies in Norway have been obliged to send data electronically to the Norwegian Institute of Public Health on all prescribed drugs (irrespective of reimbursement) dispensed to individuals in ambulatory care.

The Norwegian data sources, in this project are the national, mandatory Norwegian Surveillance System for Communicable Diseases (MSIS), which will be linked to four national health registries, i.e. the Medical Birth Registry (MBRN), the National Patient Register, the Norwegian Immunisation Registry, and the National Prescription Registry. Information about all Norwegian National Registries can be found here: [www.fhi.no/en/more/access-to-data/about-the-national-health-registries2/](http://www.fhi.no/en/more/access-to-data/about-the-national-health-registries2/)

### Quality of the data banks and linkage

All registries have extensive quality control procedures, and deliver quality assured data files to researchers. University of Oslo (UiO) is the Data Access Provider for Norwegian linked registry data in CONSIGN. UiO performs additional internal quality controls of variable missingness, outliers checks, etc. In general data, data have low degree of missingness with a few exceptions (e.g. MBRN: smoking in pregnancy, previous pregnancy loss and employment > 7% missing).

Linkage between data banks is complete as the linkage is performed using the personal ID allocated to every citizen in Norway and all the registries are mandatory by law.

Data bank	Type	Dates covered
MSIS	Communicable diseases registry – COVID-19 positive test	01.01.2018 - 31.12.2020
MBRN	Birth Registry – identification of pregnancies	01.01.2018 - 30.06.2020
NorPD	Prescription registry – identification of medication use	01.01.2018 - 30.11.2020
NPR*	Patient registry (secondary care) - COVID-19 diagnosis	01.01.2008 - 31.08.2020
SYSVAK*	Vaccine registry – identification of vaccines	01.01.2008 - 31.12.2020

\*Not used for this interim report; will be used in the final report.

### **Spain: IACS Aragon**

The EpiChron Research Group at the **Instituto Aragonés de Ciencias de la Salud (IACS)** provides the data. The source of data for this study will be the PRECOVID study and the EpiChron Cohort. The PRECOVID study includes all individuals with laboratory-confirmed infection by SARS-CoV-2 from an ad hoc registry developed by the Aragon Health System for monitoring the evolution of the COVID-19 disease pandemic in the region of Aragon. This registry links, at a patient level and in a pseudo-anonymized way, the information contained in the users' database, primary care EHRs and primary care and hospital pharmaceutical billing records. The EpiChron Cohort Study links socio-demographic and clinical anonymized information of all the inhabitants of Aragon, built from the BIGAN platform. Aragon BIGAN platform integrates a technical infrastructure and a data lake gathering individual patient data from the regional health service information systems, including primary care, specialized care, hospitalizations, ER episodes, drug prescription, image diagnosis, laboratory analytical determinations, diagnostics, vaccination, anamnesis and demographics from the whole population of Aragon, about 2M subjects with historic data, and 1.3 M active population subjects. Mother-child linkage and some information regarding labour outcomes are possible through hospital birth registry.

### Quality of the data banks and linkage

The BIGAN platform includes several mechanisms to control and improve the quality of its data, mainly in the ETL processes of capture and persistence in the data lake. Among these mechanisms, there are validation rules (for example, for dates and time intervals) or crosses with master tables, requiring that

certain coded data exist in a standardized dictionary. Analysis of the distribution of variables is also carried out periodically, in search of "outliers" that identify errors in the data capture or transformation processes. As a general rule, records that do not validate QA procedures are kept in a "staging" area, in order to be reviewed and discarded or reprocessed.

Linkage between data banks is complete as the linkage is performed using an anonymized ID based on personal ID allocated to every citizen in Aragon.

Data bank	Type	Dates covered
COVID-19	Ad-hoc registry developed for monitoring the evolution of the COVID-19 disease pandemic	March 2020 – December 2020
DISPENSACIONES	Medications dispensed by a community pharmacy office	2018 - 2020
DIAGNOSTICOS	Reason for consultation Primary care	All episodes active at least 1 day from 2018 to 2020
CMBD	Hospital discharge reports	2018 - 2020
BDU	Users database	2018 - 2020
CARTILLA_EMBARAZO	First visit for pregnancy control	2018 - 2020

### Spain: Valencia Integrated Databases (VID)

**The Foundation for the Promotion of Health and Biomedical Research of Valencia Region (FISABIO)** is Data Access Provider for Valencia Integrated Databases (VID). The Valencia health system integrated database (VID) is a set of multiple, public, population-wide electronic databases for the Valencia Region, the fourth most populated Spanish region, with ≈5 million inhabitants and an annual birth cohort of 32,000 newborns, representing 10.7% of the Spanish population and around 1% of the European population. The VID provides exhaustive longitudinal information including sociodemographic and administrative data (sex, age, nationality, etc.), clinical (diagnoses, procedures, diagnostic tests, imaging, etc.), pharmaceutical (prescription, dispensation) and health care utilisation data from hospital care, emergency departments, specialized care (including mental and obstetrics care), primary care and other public health services. It also includes a set of associated population databases and registries of significant care areas such as cancer, rare diseases, vaccines, congenital anomalies, microbiology and others, and also public health databases from the population screening programmes. All electronic health systems in the VID use the ICD-9-CM and the ICD-10-CM. The databases were initiated at different moments in time, but all in all the VID provides comprehensive individual-level data fed by all the databases from 2008 to date. Information on PCR test results as well as serological/antibody tests results for the whole population of the Valencia region is available and linkable from the Microbiological Surveillance Network (RedMIVA).

### Quality of the data banks and linkage

The extraction of data for any study from the VID to the FISABIO-HSRU is performed following the ENCePP's Guide. After the protocol is presented, it is revised through three supervising committees to obtain the corresponding approvals/classifications (Ethical Committee, Spanish Medicines Agency, and Data Access Commission). Once the extraction is completed, quality control is performed by two

independent senior data managers and the outputs are reviewed by a senior epidemiologist. After a double quality check, the extracted data are persisted or corrected, and the statistical analyses are performed using adequate statistical software (Stata and/or R). All results are reviewed by at least one researcher who is not involved in the analysis and a senior epidemiologist.

All the information in the VID databases can be linked at the individual level through a single personal identification code.

Data bank	Type	Dates covered
AEHR	Ambulatory Electronic Health Records (Includes primary, specialist care and active diagnoses)	2018-01-01/2020-12-31
GAIA	Electronic Pharmaceutical records;	2018-01-01/2020-12-31
AED	Accident & Emergency Department record (Emergency room visits);	2018-01-01/2020-12-31
MDR & PMR	Metabolic Disease Registry and Perinatal Mortality Registry to identify pregnancies	2018-01-01/2020-12-31
RedMIVA	Microbiological Surveillance Network of the Valencian Community (Includes all PCR or Antigen test results).	2020-03-01/2020-12-31

#### United Kingdom: Wales, Swansea University

The Secure Anonymised Information Linkage (SAIL) Databank sources, accesses, links and analyses prospectively collected routine health and population data, within a governed infrastructure that is safe and secure. All datasets are anonymised and encrypted by a third party, and returned to SAIL for linkage. Data are held on 5, 400,000 people, since 1998. Data are available within 3 months of events. SAIL holds linkable, anonymised national datasets, including: Accident and emergency care from 2009, Critical care from 2016, Congenital Anomaly Register and Information Service for Wales (CARIS), In-patient and out-patient PEDW records, Maternity dataset from 2015 for additional data on childbirth, National Community Child Health Database (NCCHD, includes gestation (ultrasound), birth centiles, childbirth, infant feeding, developmental screening and vaccinations), National Pupil Database Wales (education attainment to 16), ONS births and deaths (compulsory registration), Primary care data (including all prescriptions and diagnoses) from ~75% of Welsh GP practices. **COVID-19:** SAIL receives a daily extract from the national laboratory system containing COVID-19 test results from all sources (both public and private testing). This dataset is available in SAIL and previously linked to other datasets in the data bank, as above. **Swansea University** will be Data Access Provider for the SAIL data in this project.

### Quality of the data banks and linkage

Swansea University is the Data Access Provider for the Wales national linked registry data (SAIL databank)<sup>17</sup> which is used in CONSIGN. Swansea University performs additional internal quality controls of variable missingness, outliers' checks, and correspondence between datasets. In general data, data have low degree of missingness with a few exceptions (e.g., 11.04% women do not have credible data for obesity. In contrast, ~1% have missing data on socio-economic status, <1% have missing data for birth weight, and gestation is available for all birth. Approximately 20% of women do not have primary care data in SAIL, because some primary care providers, general practitioners (GPs) do not contribute to the national databank. (GPs are independent contractors to the NHS Health Boards, and cannot be compelled to provide data; they are not reimbursed for participation.) Individuals' presence in the data is determined by an algorithm.<sup>18</sup>

The SAIL Programme has implemented an ISO 27001 Information Security Management System (ISMS), which was externally certified by independent industry assessors in DEC 2015. <https://saildatabank.com/faq/>

Linkage between data banks is complete as the linkage is performed using each person's unique ALF (anonymous linking field) based on personal information and the NHS (National Health Service) number, when available (<https://saildatabank.com/about-us/data-linkage/>).<sup>19</sup>

Data bank	Type	Dates covered
SAIL	Linked databank	2018-April 2021
NCCHD	Birth registrations	2018-April 2021
MIDS	Maternity indicators dataset	2018-April 2021
GP records and prescribing	Primary care records	2018-April 2021
Hospital admissions	By ICD10 codes (not included here)	

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<sup>17</sup> Ford DV, Jones KH, Verplancke JP, Lyons RA, John G, Brown G, Brooks CJ, Thompson S, Bodger O, Couch T, Leake K. The SAIL Databank: building a national architecture for e-health research and evaluation. BMC Health Serv Res. 2009 Sep 4;9:157. doi: 10.1186/1472-6963-9-157. PMID: 19732426; PMCID: PMC2744675.

<sup>18</sup> Thayer D, Rees A, Kennedy J, Collins H, Harris D, Halcox J, Ruschetti L, Noyce R, Brooks C. Measuring follow-up time in routinely-collected health datasets: Challenges and solutions. PLoS One. 2020 Feb 11;15(2):e0228545. doi: 10.1371/journal.pone.0228545. PMID: 32045428; PMCID: PMC7012444.

<sup>19</sup> Jones KH, Ford DV, Thompson S, Lyons RA. A Profile of the SAIL Databank on the UK Secure Research Platform. Int J Popul Data Sci. 2019 Nov 20;4(2):1134. doi: 10.23889/ijpds.v4i2.1134. PMID: 34095541; PMCID: PMC8142954.



## **Appendix 2. Figures**

Figure 1. Antithrombotic agents (B01)

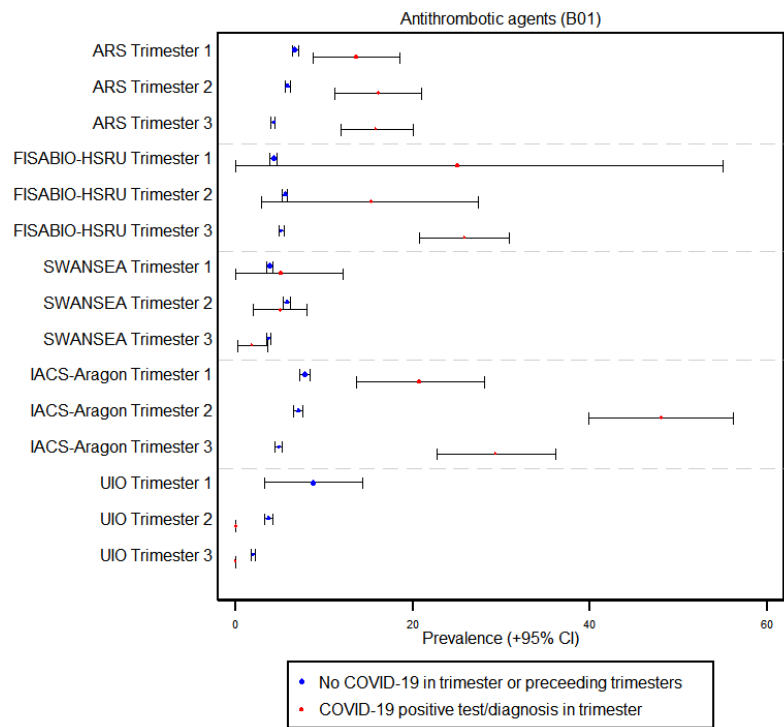


Figure 2. Antibacterials (J01)

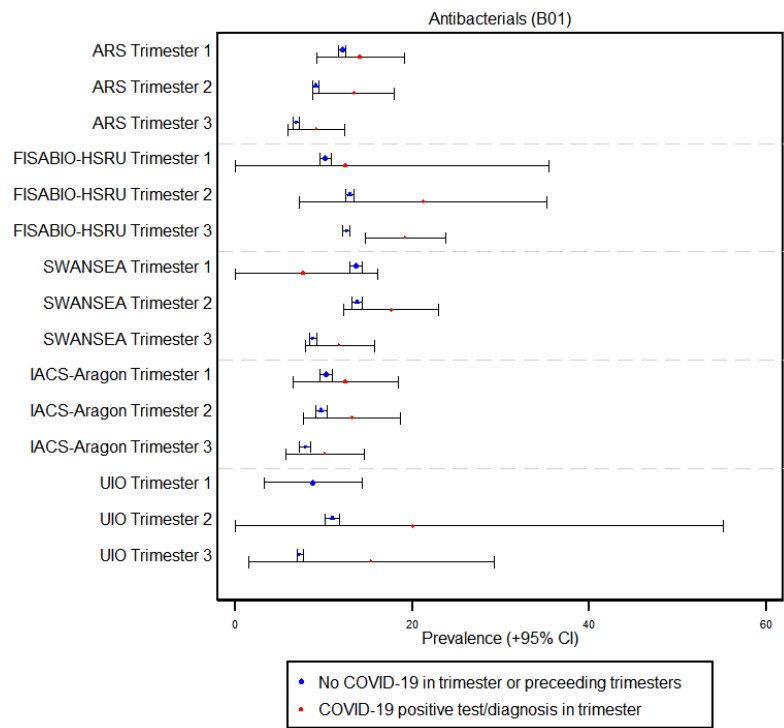


Figure 3. Analgesics (N02)

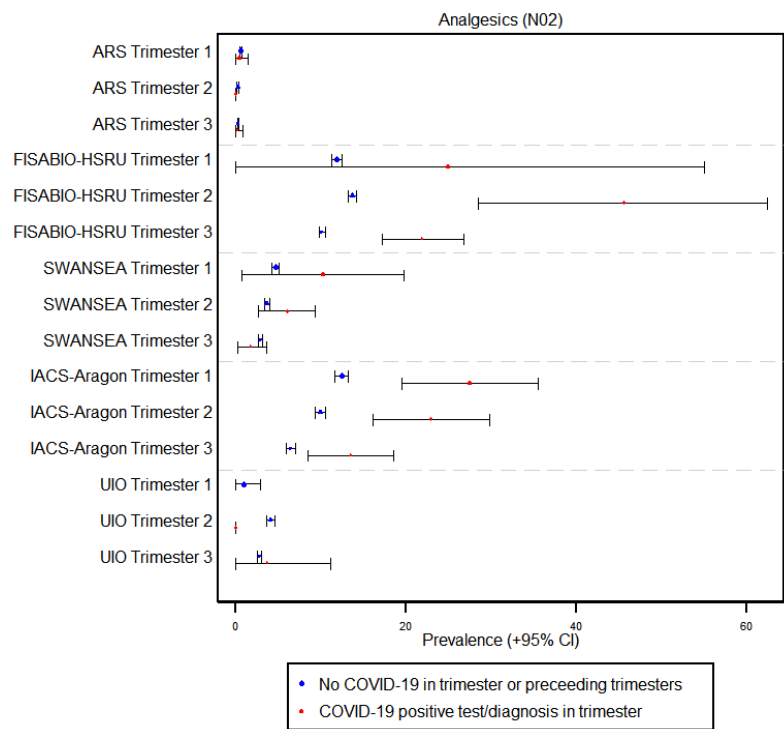
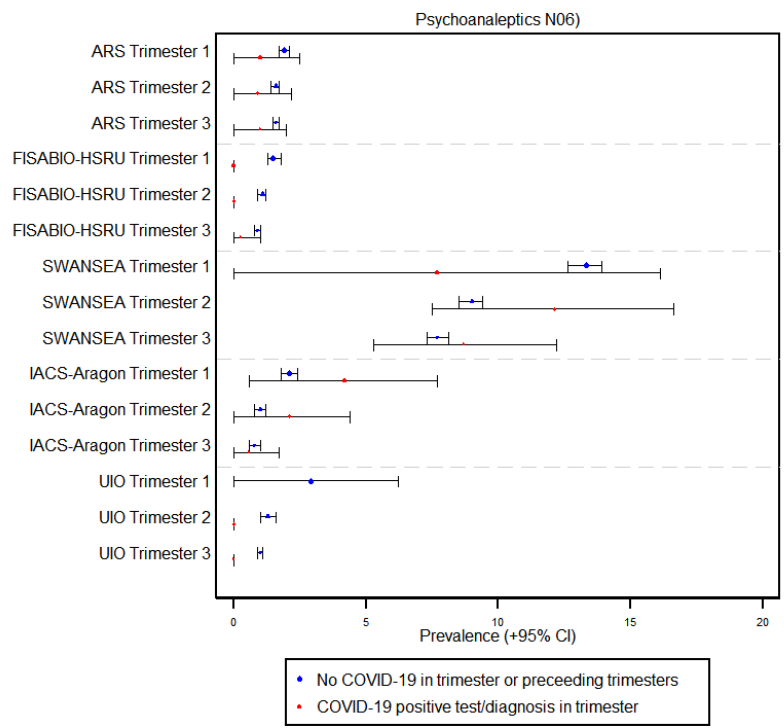


Figure 4. Psycholeptics (N06)



### Appendix 3. List of stand-alone documents

Number	Document reference number	Title
1	<i>Annex 1</i>	<i>Medication prescribed/dispensed in trimesters with no positive COVID-19 test/diagnosis nor any preceding COVID-19 infection during the pregnancy</i>
2	<i>Annex 2</i>	<i>Medication prescribed/dispensed in the trimester when a first recorded positive COVID-19 test/diagnosis was received</i>
3	<i>Annex 3</i>	<i>Medication prescribed/dispensed in trimesters following the trimester when a positive COVID-19 test/diagnosis was received</i>