Report 3 – Systemic glucocorticoids in the treatment of COVID-19 and risks of adverse outcomes in COVID-19 patients in the primary and secondary care settings

European Medicines Agency

FINAL REPORT

Study: Systemic glucocorticoids in the treatment of COVID-19 and risks of adverse outcomes in COVID-19 patients, within primary and secondary care settings

Prepared for: European Medicines Agency, Amsterdam, the Netherlands

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PASS Information

Section	Description
Title	Systemic glucocorticoids use in the treatment of COVID-19 and risks of adverse outcomes in COVID-19 patients in the primary and secondary care setting
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Research questions and objectives	Primary objective To describe utilization of systemic glucocorticoids (e.g., dexamethasone, prednisolone, methylprednisolone or hydrocortisone) for treatment of COVID-19 in two types of setting: hospitalized (in hospital care) and ambulatory (any care received outside the hospital) within 90 days following COVID-19 diagnosis. Secondary objectives 1. To describe at COVID-19 diagnosis date the demographic, health and clinical patient characteristics (stratified by setting and systemic glucocorticoid user type (naive, prevalent). 2. To quantify the crude and adjusted incidence rates and time to onset of adverse events of interest (i.e., infections, hyperglycaemia, hypertension, gastrointestinal bleeding and composite cardiovascular disease events) within 30 and 90 days post treatment index date, by setting, in various treatment groups, systemic glucocorticoid user type (naive, prevalent) and sub-populations of special interest. 3. To quantify the crude and adjusted incidence rates of mortality and other disease outcomes within 30- and 90-days post treatment index date, by setting, in various treatment groups, systemic glucocorticoid user type (naive, prevalent) and sub-populations of special interest. 4. To explore the performance of different coding definitions for COVID-19 and how they influence the size of the cohort
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Section 1.0 Acknowledgments

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Section 2.0 List of Abbreviations

Abbreviation	Definition
ARDS	Acute respiratory distress syndrome
ATC	Anatomical Therapeutic Chemical Classification System
CDM	Common Data Model
COPD	Chronic obstructive pulmonary disease
COVID-19	Coronavirus disease 2019
DDD	Defined daily dose
DIC	Disseminated intravascular coagulation
ECMO	Extracorporeal membrane oxygenation
EHDEN	European Health Data and Evidence Network
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
GI	Gastrointestinal
GP	General Practitioner
HIC	Health Informatics Centre
IMASIS	Information System of Parc Salut Mar
IMRD	IQVIA Medical Research Data
IPCI	Integrated Primary Care Information
LPD	Longitudinal Patient Database
MAS	macrophage activation syndrome
OMOP	Observational Medical Outcomes Partnership
PASS	Post-authorization safety *study*
PCR	Polymerase chain reaction
PDC	Proportion of days covered
PE	Pulmonary embolism
SARS Cov2	severe acute respiratory syndrome coronavirus 2
SIDIAP	Information System for Research in Primary Care
VTE	Venous thromboembolism
WHO	World Health Organization
HCDM	Hospital Charge Data Master

Section 3.0 Abstract

Section	Description
Title	Systemic glucocorticoids in the treatment of COVID-19 and risks of adverse outcomes in COVID-19 patients, within primary and secondary care settings
Rationale and background	Approximately 10-20% of COVID-19 positive patients, many of whom are older or have co-morbidities, suffer from pneumonia and acute respiratory distress syndrome (ARDS), requiring hospitalization and ventilatory support. It has been suggested that this population is also at higher risk of inflammatory immune system disorders. As a result, current treatment recommendations are to combine anti-viral therapy with immunosuppressive or immunomodulatory drugs to mitigate these immunologic complications, reducing COVID-19 associated morbidity and mortality. While the search for appropriate anti-viral therapy is ongoing, there have been some positive results with respect to systemic glucocorticoid use, such as dexamethasone, which has been associated with reduced mortality in ventilated patients and those on supplemental oxygen therapy. This has mobilised efforts to repurpose some of these steroids for the treatment of severe COVID-19 cases, however, a lot of information on steroid use in COVID-19 patients is currently missing. Treatment type, dosage, timing of administration, as well as the side effects of steroids in these patients, are inadequately explored.
Research question and objectives	**Primary Objective**: To describe utilization of systemic glucocorticoids (e.g., dexamethasone, prednisolone, methylprednisolone or hydrocortisone) for treatment of COVID-19 in two settings: hospitalized (in hospital care) and ambulatory (any care received outside of hospital) within 90 days following COVID-19 diagnosis. The following variables were described: • Prevalent use or naïve (incident) use of systemic glucocorticoids at date of diagnosis of COVID-19 • Concomitant use of other medications (number and type) and invasive/non-invasive respiratory support during follow up • Type of systemic glucocorticoid received • Time to systemic glucocorticoid initiation from COVID-19 diagnosis • Route of administration • Systemic glucocorticoid daily dose at initiation (treatment index date), cumulative duration, distribution of duration of use and cumulative dose of systemic glucocorticoid received • For prevalent users: proximity of previous glucocorticoid use to COVID-19 diagnosis (current use (concomitant on date of COVID-19 diagnosis, very recent use (end date within 30 days before date of COVID-19

	diagnosis) or recent use (use ended more than 30 days before date of COVID-19 diagnosis) **Secondary Objectives:** 1. To describe **at COVID-19 diagnosis date and at treatment index date** the demographic, health and clinical patient characteristics). The following variables were described: - demographics - comorbidities (number and type) - symptoms (number and type) preceding and/or on the date of diagnosis the diagnosis if captured time from onset of COVID-19 illness symptoms to confirmed diagnosis date Some of these characteristics were stratified by setting, glucocorticoid exposure type (naive, prevalent) and subgroups of special interest (e.g., chronic cardiac and pulmonary disease, diabetes, renal insufficiency). 2. To quantify the crude and adjusted incidence rates and time to onset of adverse events of interest (e.g., infections, hyperglycaemia, GI bleeding, composite of cardiovascular disease events) within **30 and 90 days post treatment index date**, in various treatment groups, stratified by setting, glucocorticoid exposure type (naive, prevalent) and subgroups of special interest. 3. To quantify the crude and adjusted incidence rates of mortality and other disease outcomes within **30- and 90-days post treatment index date**, in **various treatment groups**, stratified by setting glucocorticoid exposure type (naive, prevalent) and subgroups of special interest. 4. To explore the performance of **different coding definitions** for COVID-19 and how they influence the size of the cohort
Study design	This was a PASS study with a descriptive cohort study design and using secondary data sources (electronic medical records).
Setting	COVID-19 diagnosed patients across primary and secondary care settings in eight European countries and the US, with the study time period from 1st January 2020 to July 2021 (at the latest). Cut-off dates for data inclusion i.e. data lock points varied based on the country and database used. Four different cohorts based on healthcare setting (ambulatory or hospital setting) and systemic glucocorticoid user type (naïve or prevalent) were created. *Ambulatory data sources*: • Belgium - Longitudinal Patient Database (IQVIA) • France - Longitudinal Patient Database (IQVIA) • Italy – Longitudinal Patient Database (IQVIA) • Germany – Disease Analyser (IQVIA)

	• United Kingdom – IQVIA Medical Research Data (IMRD) UK and Health Informatics Centre (HIC) • The Netherlands – Integrated Primary Care Information (IPCI) • Spain – Information System for Research in Primary Care (SIDIAP) *Hospital data source:* • France – Assistance Publique – Hopitaux de Marseille (APHM) • Spain - Parc Salut Mar Barcelona (IMASIS) and HM Hospitales • Serbia –University Clinical Center of Serbia (Clinerion and Heliant, UCCS) • Germany – Academic Hospital • United States - Hospital Charge Data Master
Variables	**COVID-19 Case Definition** • Main analysis: Catch-all definition based on the earliest of a first diagnosis confirmed for COVID-19 or first SARS-CoV-2 positive PCR test • Alternative definitions: Diagnosis confirmed (diagCOVID-19), laboratory confirmed (labCOVID-19), symptomatic COVID-19 and suspected COVID-19 cases **Exposure** (based on prescription data) • Glucocorticoids used in COVID-19 indication (dexamethasone, prednisolone, prednisone, methylprednisolone or hydrocortisone) • Glucocorticoid for pre-existing conditions, described by metrics by metrics such as recent use of medication based on prescription records. • Other COVID-19 treatments (e.g., antiviral, antibiotic, statin therapy) • Respiratory support For secondary objectives 2 and 3 where the index date was based on treatment, the treatment groups were categorized as follows: • Use of systemic glucocorticoids without other treatments for COVID-19 • Use of systemic glucocorticoids plus other treatments for COVID-19 • Only other treatments and respiratory support with no systemic glucocorticoids • No specific treatments for COVID-19 infection **Outcomes** (Secondary objectives 2 and 3) • Adverse events such as composite cardiovascular events, hypertension, arrhythmia, gastritis, gastric ulcer, and hyperglycaemia • Disease outcomes:

	○ Ambulatory: Hospital admission, venous thromboembolism, disseminated intravascular coagulation, death of any cause ○ Hospital: Intensive services, venous thromboembolism, disseminated intravascular coagulation, discharge from hospital, death of any cause **Demographic and clinical variables**: age, sex, month of diagnosis, comorbidities
Data analysis	Continuous variables were described using mean, standard deviation, median, 1st and 3rd quartiles, minimum and maximum. Categorical variables were described by the number and percentage of patients in each category. **Primary Objective:** • Descriptive analysis for systemic glucocorticoid use patterns was carried out and stratified by setting, glucocorticoid exposure type (naive, prevalent) and subgroups of special interest. • Kaplan-Meier methods to estimate time to systemic glucocorticoid initiation from COVID-19 diagnosis, stratified by route of administration **Secondary Objective 1**: • Cohort-specific descriptive statistics summarizing demographic, health and clinical patient characteristics, stratified by setting, glucocorticoid exposure type glucocorticoid (naive, prevalent), and other subgroups of interest **Secondary Objectives 2 and 3:** • Crude incidence (both proportions and rates) for the relevant outcomes for each treatment exposure group were calculated. • The cumulative incidence rates were reported at the end of follow-up (30 and 90 days). • Data was stratified by setting, glucocorticoid exposure type (naive, prevalent), and subgroups of special interest • Cox regression models used to compute the adjusted incidence rates. **Secondary Objective 4:** • The performance of different COVID-19 disease definitions based on rule-based phenotype algorithms were explored using diagnostic predictive modelling
Results	Data from a total of 13 databases from eight countries were included where sufficient numbers of COVID-19 patients were identified. This study summarised the characteristics, prescribing patterns, adverse events, and disease outcomes of four different treatment cohorts (glucocorticoids only, other COVID treatments only, glucocorticoid and other

COVID treatments, and no COVID related treatments) among 9,719 ambulatory prevalent patients (seven databases from six countries), 497,723 ambulatory naïve patients (eight databases from six countries), 14,026 hospitalised prevalent patients (four databases from four countries) and 94,916 hospitalised naïve patients (six databases from five countries).

Glucocorticoids prescribing pattern

In the **ambulatory naïve cohort**, a total of 8,627 out of 497,723 COVID-19 patients received glucocorticoids. The top three prescribed glucocorticoids were prednisolone (range: 0.0% (n=0) in Italy-LPD to 92.1% (n=443) in UK-IMRD), prednisone (range: 3.8% (n=18) in Netherlands-IPCI to 68.6% (n=96) in Italy-LPD), and dexamethasone (range: 0.0% (n=0) in France-LPD to 40.3% (n=154) in Germany-DA). Median time from diagnosis to treatment with glucocorticoids ranged from 2.0 days in the Germany-DA to 10.0 days in the Spain-SIDIAP while the median cumulative duration of treatment ranged from 4.0 days in the France-LPD to 25.0 days in Italy-LPD. In addition, the median daily dose at treatment initiation ranged from 1.0mg in Italy-LPD to 15.0mg in France-LPD. The median cumulative dose of all glucocorticoids to 90 days across the included countries was between 29.9mg in UK-IMRD to 74.6mg in Germany-DA. No patient received respiratory support in the ambulatory setting.

In the ambulatory naïve cohort, monthly incidence of glucocorticoids utilisation in COVID-19 patients was constantly low in most countries. From the available databases, it seems that glucocorticoids utilisation in Germany-DA and Spain-SIDIAP had increased after RECOVERY results were published, while this did not have an impact in Netherlands-IPCI and UK-IMRD. No trend testing was performed.

In the **hospital naïve cohort**, a total of 30,483 out of 94,916 COVID-19 patients were treated with glucocorticoids. The three most commonly prescribed glucocorticoids were dexamethasone (range: 19.7% (n=220) in Spain-Hospitales to 80.7% (n=582) in Germany-Academic Hospital), methylprednisolone (range: 17.7% (n=60) in France-APHM to 72.5% (n=3,035) in Serbia-UCCS), and hydrocortisone (range: 2.2% (n=495) in US-HCDM to 21.3% (n=74) France-APHM). Median time from diagnosis to treatment with glucocorticoids ranged from 0.0 days in Serbia-Clinerion and Heliant and US-HCDM to 6.0 days in France-APHM while the median cumulative duration ranged from 4.0 days in the France-APHM to 10.0 days in Spain-Hospitales. Additionally, the median daily dose at treatment initiation ranged from 2.0mg in Spain-IMASIS to 22.5mg in France-APHM. The median cumulative dose of all glucocorticoids to 90 days across the included countries ranged between 22.5mg in Spain-IMASIS to 135.6mg in Serbia-UCCS. No patient received respiratory support in the hospital setting.

In the hospital naïve cohort, the monthly proportion of glucocorticoid utilisation in COVID-19 patients had increased in France-APHM, Spain-IMASIS and Serbia-UCCS and US-HCDM after RECOVERY results were published. No trend testing was performed.

Based on available data there was no suggestion of repurposing the chronic steroid treatment for COVID-19 in the prevalent glucocorticoid use cohort,

therefore glucocorticoids prescribing pattern could not be studies in the prevalent cohorts.

Patients characteristics

Seven databases contributed information to **the ambulatory prevalent cohort**, France-LPD, Italy-LPD, Germany-DA, Netherlands-IPCI, Spain-SIDIAP, UK-IMRD and UK-HIC. In **ambulatory prevalent cohort**, the majority of patients were adults (18-65 years) ranging from 44.7% (n=443) in the Netherlands-IPCI to 81.9% (n=908) in France-LPD except the UK-HIC where 55.8% (n=155) of the patients were older adults (75+ years). A similar gender distribution was observed across the included geographies with a higher proportion of female patients (range: 51.1% [n=142] in UK-HIC to 67.4% [n=747] in France-LPD). Hypertension (ranging from 1.8% [n=22] in the UK-IMRD to 46.0% [n=87] in Italy-LPD) was found to be most reported co-morbidity. The proportion of patients with one or more COVID-19 symptoms varied from 4.8% (n=9) in Italy-LPD to 21.6% (n=60) in the UK-HIC. In addition, the proportion of patients receiving any other COVID-19 treatment except glucocorticoids varied from 5.8% (n=16) in UK-HIC to 23.8% (n=45) in Italy-LPD. No patients were receiving glucocorticoid only or glucocorticoid plus other COVID-19 treatment at diagnosis and across all the included databases.

Seven databases contributed information to the **ambulatory naive cohort**, France-LPD, Italy-LPD, Germany-DA, Netherlands-IPCI, Spain-SIDIAP, UK-IMRD, and UK-HIC. In **ambulatory naive cohort,** most of the patients were adults (18-65 years) ranging from 36.9% [n=940] in the UK HIC to 81.1% [n=13,038] in France-LPD. Data from the included geographies showed a comparable gender distribution with an on average marginally higher number of female patients ranging from 46.9% [n=1,196] in UK HIC to 58.6% [n=9,409] in France LPD. Similar to the ambulatory prevalent cohort, hypertension (range: 0.7% [n=294] in the UK-IMRD to 29.0% [n=1,245] in Italy-LPD) was most commonly reported co-morbidity. The proportion of COVID-19 patients who have COVID-19 symptoms recorded ranges from 1.3% in the UK-IMRD [n=511] to 14.3% [n=2,300] in France-LPD. In addition, the proportion of patients receiving glucocorticoids at diagnosis ranged from 0.1% [n=21] in France-LPD to 0.4% in Italy-LPD [n=18] and in Germany-DA [n=133]. While, the proportion of patients receiving any other COVID-19 treatment except glucocorticoids at diagnosis ranged from 2.8% [n=1,155] in UKIMRD to 21.9% [n=939] in Italy-LPD. The proportion of patients receiving both the glucocorticoids and other COVID-19 related treatments at diagnosis varied from 0.1% [n=17] in France-LPD to 0.7% [n=32] in Italy-LPD. However, the majority of patients did not receive any COVID-19 specific treatment at diagnosis (range between 77.0% [n=3,309] in Italy-LPD to 96.7% [n=39,603] in the UK-IMRD).

Four databases contributed information to the **hospital prevalent cohort**: the US-HDMC, Spain-IMASIS, and Serbia-Clinerion and Heliant. France-APHM was excluded as had less than 50 patients in this cohort In the **hospital prevalent cohort**, majority of the patients were adults (18-64 years) ranging from 33.6% [n=38] in Spain-IMASIS to 48.8% [n=6,247] in the US-HCDM. The proportion of female patients ranged from 40.9% [n=453] in Serbia-Clinerion and

Heliant to 47.8% in the US-HCDM [n=6,121] and Spain-IMASIS [n=54]. Hypertension was the most prevalent comorbidity (range: 49.0% [n=542] in Serbia-UCCS to 71.8% [n=9,197] in the US-HCDM) and dyspnoea (ranging from 6.2% [n=69] in Serbia-UCCS to 21.9% [n=2,802] in US-HCDM) was the most reported symptoms. The proportion of COVID-19 patients who have COVID-19 symptoms recorded ranged from 6.2% [n=7] in Spain-IMASIS to 37.0% [n=4,739] in US-HCDM. In addition, the proportion of patients receiving any other COVID-19 treatment except glucocorticoids at diagnosis varied from 14.5% [n=161] in Serbia-UCCS to 32.7% [n=37] in Spain-IMASIS, while the proportion of patients receiving no treatment ranged from 67.3% [n=76] in Spain-IMASIS to 85.5% [n=946] in Serbia-UCCS.

Six databases contributed information to the **hospital naïve cohort**: France-APHM, Germany-Academy hospital, the US-HCDM, Spain-IMASIS, Serbia-Clinerion and Heliant, and Spain-Hospitales. In the **hospital naive cohort,** majority of the COVID-19 patients were adults (range: 34.6% [n=545] in the Germany-Academy hospital to 68.0% [n=9,635] in France-APHM). A similar gender distribution was observed across the included countries, with slightly higher number of male than female patients (ranging from 50.0% [n=2,362] in Spain-IMASIS to 59.8% [n=5,828]) in Serbia-UCCS. The most reported comorbidity was hypertension (ranging from 11.0% [n=1,563] in France-APHM to 48.5% [n=30,156] in US-HCDM), while the most reported symptoms was fever (ranging from 0.0% [n=0] in France-APHM to 12.2% [n=310] in Spain-Hospitales). The number of patients receiving glucocorticoids ranged from 0.2% in France APHM [n=33], Spain IMASIS [n=9], and Serbia-UCCS [n=18] to 1.0% [n=588] in the US-HCDM. In addition, the number of patients receiving glucocorticoids at diagnosis ranged from 0.2% in France-APHM [n=33], Spain-IMASIS [n=9], and Serbia-UCCS [n=18] to 1.0% [n=588] in the US-HCDM. At diagnosis, the number of patients receiving any other COVID-19 treatment except glucocorticoids ranged from 25.4% [n=3,597] in France-APHM to 70.7% [n=1,799] in Spain-Hospitales.

Incidence rates of study adverse events of interest

In **ambulatory prevalent cohort**, the top three adverse events at 90 days comprised of viral infection, LRTI, and hypertension: viral infection (range: 14.1 to 151.2 per 1,000 patient-days in the other COVID-19 treatment group and 2.1 to 46.9 per 1,000 patient-days in no specific COVID-19 treatment group), LRTI (range: 4.3 to 17.8 per 1,000 patient-days in the other COVID-19 treatment group and 0.4 to 4.1 per 1,000 patient-days in no specific COVID-19 treatment group), and hypertension (range: 0 to 2.1 per 1,000 patient-days in the other COVID-19 treatment group and 0 to 2.2 per 1,000 patient-days in no specific COVID-19 treatment group). The meta-analysis showed a pooled incidence rate of 1.05 per 1,000 patient-days for cardiovascular events in other COVID-19 treatments group. The pooled incidence rates of gastritis in other COVID-19 treatments group and no specific COVID-19 treatment group were 0.30 and 0.03 per 1,000 patient-days, respectively.

In the **ambulatory naïve cohort**, the top three adverse events at 90 days comprised of viral infection, LRTI, and hypertension: viral infection (range: 6.9 to 38.3 per 1,000 patient-days for glucocorticoid only group, 1.8 to 117.1 per 1,000 patient-days for other COVID-19 treatments only, 20.3 to 585.4 per 1,000 patient-days for glucocorticoid and other COVID treatments and 0.76 to 36.9 per 1,000 patient-days for no specific COVID-19 treatments group), LRTI (range: 0 to 2.7 per 1,000 patient-days for glucocorticoid only group, 0.5 to 12.7 per 1,000 patient-days for other COVID-19 treatments only, 0 to 41.7 per 1,000 patient-days for glucocorticoid and other COVID treatments and 0.2 to 3.2 per 1,000 patient-days for no specific COVID-19 treatments group), and hypertension (range: 0 per 1,000 patient-days for glucocorticoid only group, 0.7 to 7.8 per 1,000 patient-days for other COVID-19 treatments only, 0 per 1,000 patient-days for glucocorticoid and other COVID treatments and 0 to 1.3 per 1,000 patient-days for no specific COVID-19 treatments group). The pooled incidence rates of hypertension in glucocorticoid only treatment and glucocorticoids and other COVID-19 treatments were 1.50 and 3.76 per 1,000 patient-days, respectively. The pooled incidence rates of cardiovascular events in glucocorticoid only treatment and glucocorticoids and other COVID-19 treatments were 0.08 and 0.85 per 1,000 patient-days, respectively.

In the **hospital prevalent cohort**, the top three reported adverse events at 90 days comprised of viral infection, LRTI, and hypertension: viral infection (ranged from 14.3 to 1921.1 per 1,000 patient-days for other COVID-19 treatments only and 15.6 to 67.8 per 1000 patient days for the no specific COVID-19 treatments group), hypertension (ranged from 24.6 to 109.5 per 1,000 patient-days for other COVID-19 treatments only and 2.8 to 22.3 per 1000 patient days for the no specific COVID-19 treatments group), and LRTI (ranged from 50.1 to 136.9 per 1,000 patient-days for other COVID-19 treatments only and 7.9 to 11.4 per 1000 patient days for the no specific COVID-19 treatments group). The meta-analysis showed a pooled incidence rate of 19.84 per 1,000 patient-days for LRTI in no COVID-19 related treatment group.

In the **hospital naïve cohort**, the top three adverse events at 90 days comprised of viral infection, LRTI, and arrythmia: viral infection (ranged from 0 to 652.2 per 1,000 patient-days for glucocorticoid only group, 0.9 to 1123.9 per 1,000 patient-days for other COVID-19 treatments only, 34.1 to 2228.3 per 1,000 patient-days for glucocorticoid and other COVID treatments and 0.1 to 94.6 per 1,000 patient-days for no specific COVID-19 treatments group), LRTI (ranged from 0 to 206.9 per 1,000 patient-days for glucocorticoid only group, 0 to 194.7 per 1,000 patient-days for other COVID-19 treatments only, 0 to 323.4 per 1,000 patient-days for glucocorticoid and other COVID treatments and 0 to 38.1 per 1,000 patient-days for no specific COVID-19 treatments group), and arrhythmia (ranged from 0 to 20.7 per 1,000 patient-days for glucocorticoid only group, 0 to 36.2 per 1,000 patient-days for other COVID-19 treatments only, 0 to 23.6 per 1,000 patient-days for glucocorticoid and other COVID treatments and 0 to 9.2 per 1,000 patient-days for no specific COVID-19 treatments group). The meta-analysis showed a pooled incidence rate (in decreasing order) in glucocorticoids

only treatments group: 16.42 per 1,000 patient-days for arrythmia, 13.45 per 1,000 patient-days for hyperglycaemia, 9.55 per 1,000 patient-days for sepsis, 8.17 per 1,000 patient-days for cardiovascular events, 7.29 per 1,000 patient-days for bacterial infection, 4.29 per 1,000 patient-days for psychosis, 2.46 per 1,000 patient-days for fungal and 0.43 per 1,000 patient--days for parasitic infection.

Incidence of disease outcomes

In the **ambulatory prevalent cohort,** hospital admission ranged from 0.0 to 6.2 per 1,000 patient-days in the other COVID-19 treatment group and from 0.7 to 7.3 per 1,000 patient-days in no specific COVID-19 treatment group. Death ranged from 0.0 to 571.4 per 1,000 patient-days in the other COVID-19 treatment group and from 0.8 to 6.3 per 1,000 patient-days in no specific COVID-19 treatment group. The pooled incidence rate for VTE was 0.56 per 1,000 patient-days in other COVID-19 treatments only group and 0.14 per 1,000 patient-days in no COVID-19 related treatments group.

In the **ambulatory naïve cohort,** death ranged from 0.0 to 2.2 per 1,000 patient-days in the glucocorticoid only group, from 0.1 to 37.2 per 1,000 patient-days in the other COVID-19 treatment group, from 0.0 to 10.2 per 1,000 patient-days in the glucocorticoid and other COVID treatments and from 0.03 to 3.3 per 1,000 patient-days in the no specific COVID-19 treatment group. The pooled incidence rates for hospitalisation were 1.43 per 1,000 patient-days in glucocorticoids only group and 3.44 per 1,000 patient-days in glucocorticoids and other COVID-19 treatments group. The pooled incidence rate for VTE was 0.24 per 1,000 patient-days in glucocorticoids only group and 0.20 per 1,000 patient-days in glucocorticoids and other COVID-19 treatments group.

No ambulatory setting database reported DIC as outcome.

In the **hospital prevalent cohort**, the pooled incidence rates for VTE were 6.84 per 1,000 patient-days in other COVID-19 treatment only and 1.59 per 1,000 patient-days in no COVID-19 related treatments. Furthermore, the pooled incidence rates for DIC were 0.22 and 0.19 per 1,000 patient-days in other COVID-19 treatment only and in no COVID-19 related treatments, respectively. Death ranged from 11.3 to 76.2 per 1,000 patient-days in the other COVID-19 treatment group and from 15.7 to 103.8 per 1,000 patient-days in no specific COVID-19 treatment group.

In the **hospital naïve cohort**, meta-analysis showed a pooled incidence rate of 2.45 per 1,000 patient-days for VTE in glucocorticoids only group. The pooled incidence rate of DIC ranged from 0.17 per 1,000 patient-days in other COVID-19 treatment only to 0.43 per 1,000 patient-days in glucocorticoid only treatment. Death ranged from 18.5 to 56.7 per 1,000 patient-days in the glucocorticoid only group.

Furthermore, no hospital database reported hospital discharge.

	None of the incidence proportions and rates were formally compared between groups, as this was outside the scope of this study, therefore any comparison should be made with caution.
Discussion and Conclusion	This study provides a good understanding of the utilisation patterns of systemic glucocorticoids in COVID-19 patients in a selection of both ambulatory and hospital settings in Europe and the US. In line with usual clinical practice, more patients are treated with steroids in hospital than in the ambulatory setting, while the dose and the treatment duration are largely in line with recommendations. The patient characteristics are in line with previous studies on COVID-19 patients and might illustrate a higher risk of getting COVID-19 in older patients, male gender (for severe disease) and patients with comorbidities, although no formal comparison was performed. The most common AEs were infection related, which may be due confounding by the COVID-19 diagnosis. Patients in the hospital settings had generally more AEs than those in ambulatory settings. The death rates were higher than reported in other studies, which may be due to inclusion of a population with more severe disease. However, for most part there was a high heterogeneity of results across the different databases, which precluded meta-analyses of many AEs and disease outcomes. The E-CORE project included 6 additional databases than initially envisaged in the technical specification, with a balanced mix of ambulatory and hospital databases. The identified large heterogeneity in COVID disease and management across the countries was an important finding, even though it presented a challenge for the meta-analysis part of the study. To our knowledge this is the first study on COVID-19 treatments in real world setting, based on a considerable number of data sources providing a large number of patients from across different countries. Despite the many databases included, small sample size was still an issue for some rare outcomes. Expanding the network to include further data sources is therefore recommended. We conclude that E-CORE network can be successfully used for studying effects of COVID-19 therapies in an international setting.

Section 4.0 Milestones

Milestone	Planned date	Actual date
Study protocol submitted	20th September 2020	20th September 2020
Approval Study Protocol by EMA	23rd November 2020	23rd November 2020
Registration of protocol in the EU PAS register	October 2020	October 2020
Start of data collection	NA. Data extraction start date is 1st January 2020	NA. Data extraction start date is 1st January 2020
End of data collection	NA. Data extraction end date was 17th July 2021	NA. Data extraction end date was 27th August 2021
Final study report provided to EMA	27th July 2021	27th September 2021

Section 5.0 Rationale and Background

Coronavirus disease 2019 (COVID-19) caused by Severe Acute Respiratory Syndrome Corona virus 2 (SARS-CoV-2) originated in China in December 2019 and was accepted as a global pandemic March 2020. (1) The majority of COVID-19 infections are either asymptomatic or have mild symptoms, however, progression to pneumonia and acute respiratory distress syndrome (ARDS) is reported in 10-20% cases, especially in those of older age or with co-morbidities who are subsequently more likely to be hospitalized and require ventilatory support. (2,3) The infection fatality rate is hard to estimate in view of rapidly changing data, but it is estimated to be between 0.15% and 1%, with substantial heterogeneity by location and across risk groups. (4) Amongst COVID-19 patients admitted to the UK hospitals, the case fatality rate is over 26% overall, and over 37% in patients requiring invasive mechanical ventilation. (5)

According to the current literature, older age and co-morbidities are associated with higher risk of immunologic complications such as macrophage activation syndrome (MAS) and cytokine storm syndrome secondary to, and disproportionate to the severity of Covid-19 infection. (6) In addition, there are recommendations that anti-viral treatment should be combined with appropriate immunosuppressive and immunomodulatory drugs since it is hypothesized that early recognition and appropriate treatment of immunologic complications will decrease the morbidity and mortality in COVID-19 patients. (7) With this regard, IL-6 receptor blockers (tocilizumab, sarilumab) and corticosteroids are now recommended for severe disease whereas ivermectin, hydroxychloroquine and lopinavir/ritonavir are not recommended. For non-severe disease, only supportive treatment is currently recommended. (8)

Several studies have been investigating the potential use of systemic glucocorticoid in COVID-19 patients. RECOVERY, one of the largest randomised clinical trial (RCT) showed a significant reduction of death in COVID-19 patients treated with dexamethasone by 35% in ventilated patients and by 20% amongst patients on supplemental oxygen therapy, however no benefit was observed in mild cases. (9,10) Similarly, the CoDEX RCT showed that the use of dexamethasone plus standard care compared with standard care alone among patients with COVID-19 resulted in a statistically significant increase in the number of ventilator-free days over 28 days (difference, 2.26; 95% CI, 0.2-4.38; P = 0.04) (11). Although other trials are smaller, they also reported mortality 28 days after randomization (12,13) except for one trial at 21 days. (14,15) In addition, a prospective meta-analysis of seven randomized clinical trials confirmed that administration of corticosteroids was associated with lower 28-day all-cause mortality among critically ill patients. (10) Likewise, another systematic review of forty-four RCTs and observational studies covering 20,197 patients showed a significant reduced mortality in the corticosteroid group (OR 0.72 [95%CI: 0.57–0.87]). (16)

Based on the data from RCTs and meta-analyses, the updated WHO guideline on drugs for COVID-19 and recommends corticosteroids for severely ill patients with COVID-19 who are on supplemental oxygen or ventilatory support and does not support its use in non-severe patients. (17) This recommendation is also backed by the UK and the US national recommendations. (18) Nevertheless, research in the use of systemic glucocorticoids among patients with COVID-19 is still needed as there are still some inconsistencies in the literature review. Lu et al. performed a review addressing use of steroids in critically ill COVID-19 patients to explore whether these drugs may reduce mortality, however for patients with severe COVID-19 without ARDS the evidence remained inconsistent. (19) Another systematic review (20) found five studies on the role of steroids for COVID-19 reporting inconsistent

outcomes. Of the five studies (four retrospective studies and one quasi-prospective study) conducted for evaluating the role of glucocorticoids, three studies have shown benefit, while two studies showed no benefit and there was a suggestion of significant harm in critical cases in one sub-study. Even though systemic glucocorticoid steroids are recommended for severely ill patients with COVID-19 who are on supplemental oxygen or ventilatory support, a lot of questions remain unanswered: what is the best substance, dose, (7) timing of administration and what are the side effects of steroids in these patients. (21) Therefore, the current study aims to partially answer some of the remaining questions as detailed in the following sections.

Section 6.0 Research Questions and Objectives

EMA wish to generate real world evidence to describe the utilisation patterns of systemic glucocorticoids in patients with COVID-19 and investigate the risks of adverse outcomes including non-fatal complications and deaths occurring within 90 days following COVID-19 diagnosis[1] in patients treated with systemic glucocorticoids, as observed in ambulatory and hospital inpatient care settings of eight countries (eight European countries and the US) during the first year of the pandemic until latest data availability.

6.1 Primary Objective

To describe utilization of systemic glucocorticoids (e.g., dexamethasone, prednisolone, methylprednisolone or hydrocortisone) for treatment of COVID-19 in two settings: hospitalized (in hospital care) and ambulatory (any care received outside of hospital) within 90 days following COVID-19 diagnosis. The following variables were described:

- Prevalent use or naïve (incident) use of systemic glucocorticoid at date of diagnosis of COVID-19
- Concomitant use of other medications (number and type) and invasive/non-invasive respiratory support during follow up
- Type of systemic glucocorticoid received
- Time to systemic glucocorticoid initiation from COVID-19 diagnosis
- Route of administration
- Systemic glucocorticoid daily dose at initiation (treatment index date), cumulative duration, distribution of duration of use and cumulative dose of systemic glucocorticoid received
- For prevalent users: proximity of previous glucocorticoid use to COVID-19 diagnosis (current use (concomitant on date of COVID-19 diagnosis, very recent use (end date within 30 days before date of COVID-19 diagnosis) or recent use (use ended more than 30 days before date of COVID-19 diagnosis))

6.2 Secondary Objectives

1. To describe **at COVID-19 diagnosis date and at treatment index date** the demographic, health and clinical patient characteristics. The following variables were described:
   - demographics
   - comorbidities (number and type)
   - symptoms (number and type) preceding and/or on the date of diagnosis the diagnosis if captured time from onset of COVID-19 illness symptoms to confirmed diagnosis date.

Some of these characteristics were stratified by setting, glucocorticoid exposure type (naive, prevalent) and subgroups of special interest. (e.g., chronic cardiac and pulmonary disease, diabetes, renal insufficiency, see Section 7.5 Subgroups).

[1] COVID-19 diagnosis is referred to patient either having a diagnosis confirmed (diagCOVID-19) or a laboratory confirmed (labCOVID-19); please refer to section 7.6.7 for further details.

2. To quantify the crude and adjusted (selected confounders tbc) incidence rates and time to onset of adverse events of interest (e.g., infections, hyperglycaemia, hypertension, GI bleeding, composite of cardiovascular events) within **30 and 90 days post treatment index date**, in **various treatment groups**, stratified by setting, glucocorticoid exposure type (naive, prevalent) and subgroups of special interest.
3. To quantify the crude and adjusted incidence rates of mortality and other disease outcomes within **30 and 90 days post treatment index date**, in **various treatment groups**, stratified by setting, glucocorticoid exposure type (naive, prevalent) and subgroups of special interest.
4. To explore the performance of **different coding definitions** for COVID-19 and how they influence the size of the cohort

Section 7.0 Research Methods

7.1 Study Design

This was a descriptive cohort study using secondary data sources (electronic medical records) from 14 databases in nine countries (eight European countries and the US) reflecting either hospital or ambulatory care setting. The study population was comprised of a cohort of diagCOVID-19 or labCOVID-19 patients in the database within the study time period.

Patients were either diagnosed and followed-up in an ambulatory or in an hospital setting (according to the database) and they might be new users or prevalent users of systemic glucocorticoids. Based on these two characteristics, four mutually exclusive cohorts were created overall. Not all cohorts could be constructed in each database. They were used differently depending the objective as mentioned in the analysis section.

Objective 4 was performed in a different cohort that the rest of the objectives, using a random sample from the entire datasets to test the performance of the COVID-19 definitions.

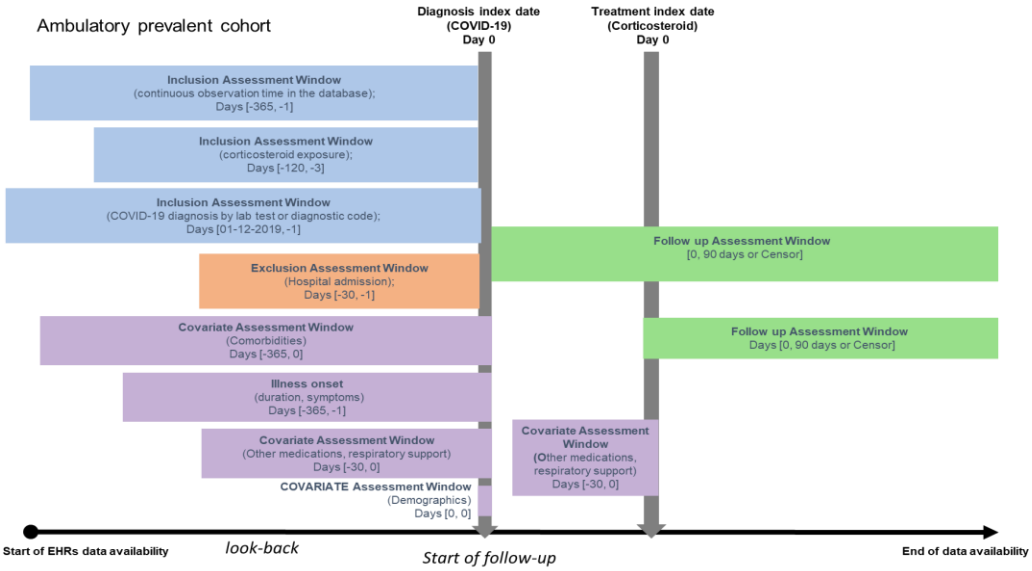
An overview of the study design is provided in

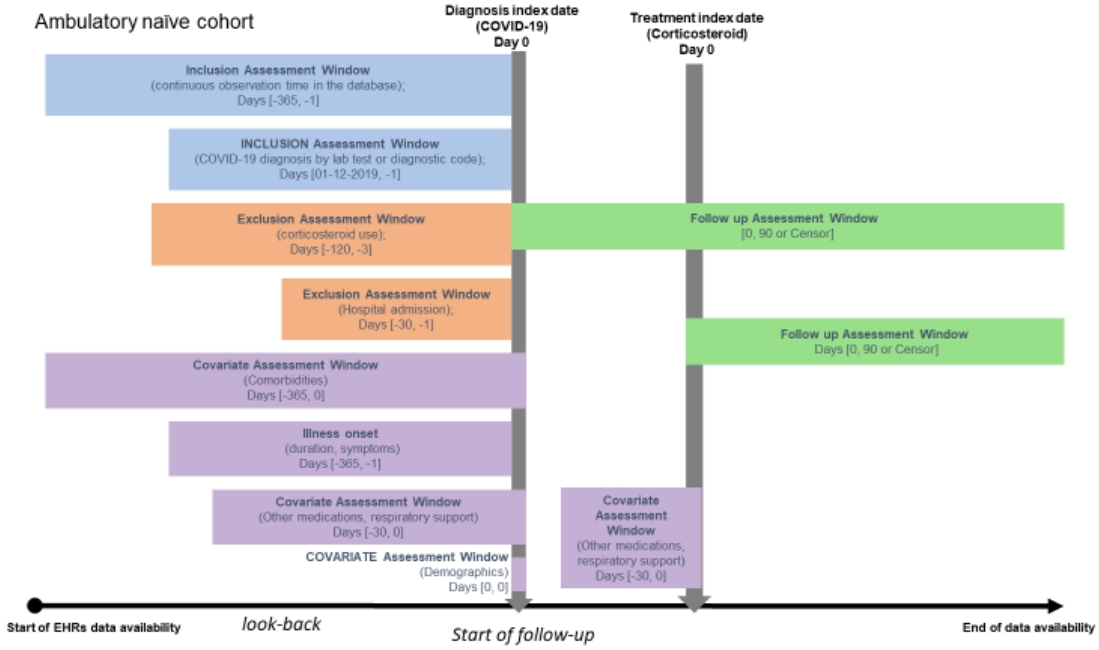
Figure 1 below.

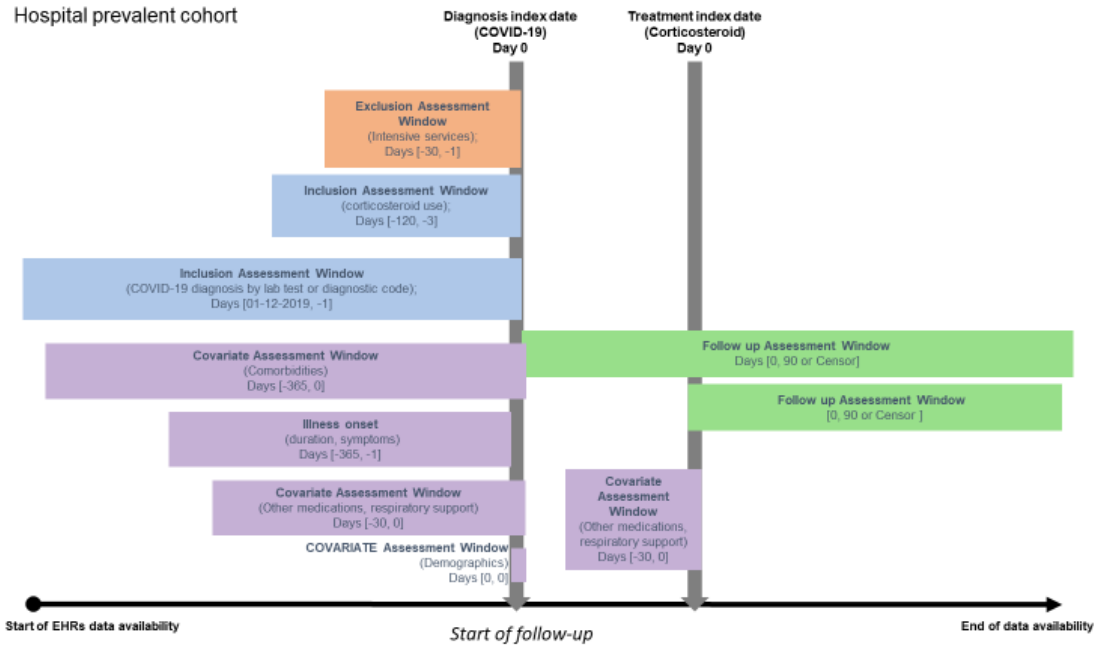
Patients were followed during the study period from COVID-19 diagnosis date to assess the utilization of systemic glucocorticoids specifically indicated for the treatment of COVID-19 and from treatment index date for the occurrence of outcomes of interest.

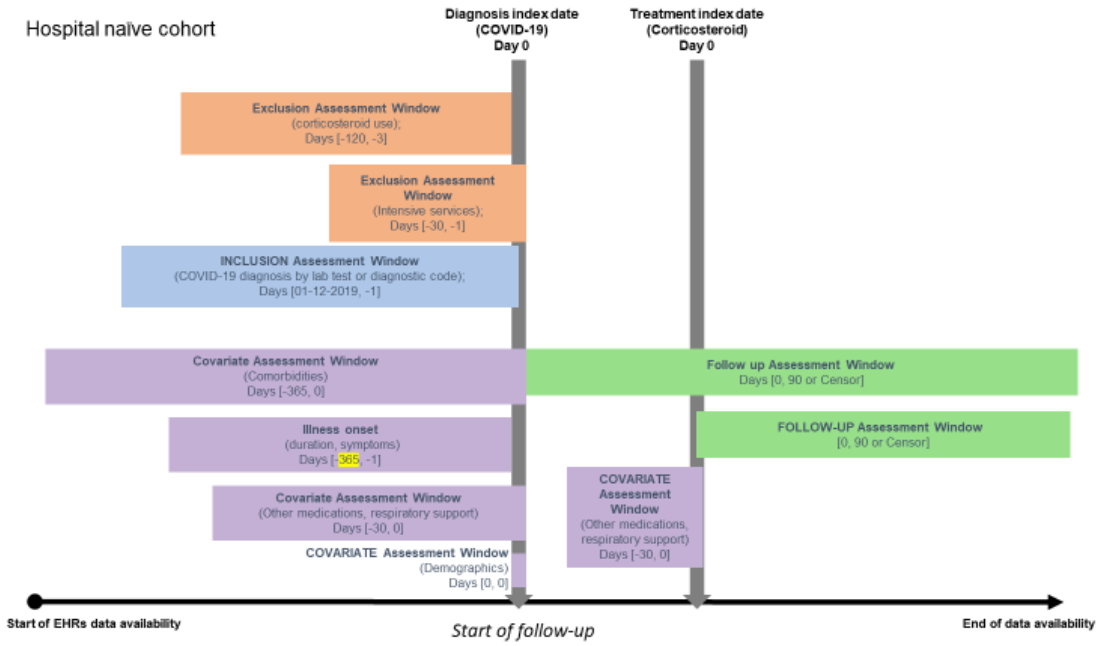
The minimum length of patient history was 365 days for the ambulatory cohorts and 0 days for hospital cohorts.

Figure 1 Study design




Ambulatory naïve cohort
Diagnosis index date (COVID-19) Day 0
Treatment index date (Corticosteroid) Day 0
Inclusion Assessment Window (continuous observation time in the database); Days [-365, -1]
INCLUSION Assessment Window (COVID-19 diagnosis by lab test or diagnostic code); Days [01-12-2019, -1]
Exclusion Assessment Window (corticosteroid use); Days [-120, -3]
Follow up Assessment Window [0, 90 or Censor]
Exclusion Assessment Window (Hospital admission); Days [-30, -1]
Follow up Assessment Window Days [0, 90 or Censor]
Covariate Assessment Window (Comorbidities) Days [-365, 0]
Illness onset (duration, symptoms) Days [-365, -1]
Covariate Assessment Window (Other medications, respiratory support) Days [-30, 0]
Covariate Assessment Window (Other medications, respiratory support) Days [-30, 0]
COVARIATE Assessment Window (Demographics) Days [0, 0]
Start of EHRs data availability
look-back
Start of follow-up
End of data availability


Hospital prevalent cohort
Diagnosis index date (COVID-19) Day 0
Treatment index date (Corticosteroid) Day 0
Exclusion Assessment Window (Intensive services); Days [-30, -1]
Inclusion Assessment Window (corticosteroid use); Days [-120, -3]
Inclusion Assessment Window (COVID-19 diagnosis by lab test or diagnostic code); Days [01-12-2019, -1]
Covariate Assessment Window (Comorbidities) Days [-365, 0]
Follow up Assessment Window Days [0, 90 or Censor]
Follow up Assessment Window [0, 90 or Censor]
Illness onset (duration, symptoms) Days [-365, -1]
Covariate Assessment Window (Other medications, respiratory support) Days [-30, 0]
Covariate Assessment Window (Other medications, respiratory support) Days [-30, 0]
COVARIATE Assessment Window (Demographics) Days [0, 0]
Start of EHRs data availability
Start of follow-up
End of data availability



7.2 Setting

The proposed setting for this study was within eight European countries (Belgium [general practice EHR], Netherlands [general practice EHR], Germany [general practice EHR, hospital EHR], France [general practice and hospital EHR], Italy [general practice EHR], Spain [general practice EHR, two hospital EHR], Serbia [hospital EMR] United Kingdom [general practice EHR]) and the United States [hospital EHR].

The study was conducted using data from multiple real-world data (RWD) sources previously mapped to the OMOP CDM in collaboration with the OHDSI and European Health Data and Evidence Network (EHDEN) initiatives. See Appendix 1 for more details on the included data sources.

Each cohort was defined in a separate setting (either hospital or primary care) based on the data source type and was described accordingly. The follow up took place in the same setting and switch of setting (hospitalization for ambulatory cohorts or discharge for hospital cohorts) during follow up was captured as an outcome.

Table 1 Characteristics of the included databases

Database	Country	Type of data	Size	COVID-19 patients in this study	Actual data lock points [1]
Belgium - LPD	Belgium	Primary care EHR	1.1M	0	December 2020
France - LPD	France	Primary care EHR	7.8M	17,180	June 2020
France - APHM		Hospital data	xxx	14,167	February 2021

Database	Country	Type of data	Size	COVID-19 patients in this study	Actual data lock points [1]
Italy - LPD	Italy	Primary care EHR	2M	4,487	July 2020
Germany - DA	Germany	Primary care EHR	34M	33,837	January 2021
Germany - Academic Hospital		Hospital data	480K	184	June 2021
Netherlands - IPCI	Netherlands	Primary care EHR	2.6M	43,219	February 2021
Spain - SIDIAP	Spain	Primary care EHR	7.8M	118,359	January 2021
Spain - Hospitales		Hospital data	18M	2,543	July 2020
Spain - IMASIS		Hospital data	1.5M	8,491	January 2021
UK - IMRD	United Kingdom	Primary care EHR	15.2	42,241	February 2021
UK - HIC		Primary care EHR	1.5M	2827	July 2021
Serbia - University Clinical Center of Serbia (Clinerion and Heliant, UCCS)	Serbia	Hospital data	400K	9,866	March 2021
US - HCDM	US	Hospital data	98M	127,915	September 2020

[1] Different data lock points across databases would imply that analyses will cover different time periods

7.2.1 Study Time Period

The study period, when index events and outcomes of interest can be observed, started from 1st January 2020 and ended at the latest available date for all the data sources in 2020 (**Table 1**). Before the final extraction and analysis, data was updated as frequently as possible, in collaboration with local data partners. The last data extraction took place on 27th August 2021.

7.3 Subjects

7.3.1 Inclusion Criteria

For primary objective and secondary objective 1-3, four cohorts were created based on healthcare setting and type of steroid use. Their eligibility criteria are described below (using Covid-19 catch-all definition Section 7.6.1):

Ambulatory prevalent user

- Have at least 365 days of continuous observation time prior to cohort entry (COVID-19 diagnosis)
- Have a glucocorticoid (oral or parenteral) exposure in the 3 to 120 days prior to diagnosis date (unrelated to COVID-19 diagnosis)
- Have a positive PCR test for SARS-CoV-2 (labCOVID-19) or a confirmed COVID-19 diagnosis (diagCOVID-19)
- Have no hospitalizations in the 30 days prior to or on index

Ambulatory naive user

- Have at least 365 days of continuous observation time prior to cohort entry (COVID-19 diagnosis)
- Have no glucocorticoid (oral or parenteral) exposure in the 3 to 120 days prior to index (unrelated to COVID-19 diagnosis)
- Have a positive PCR test for SARS-CoV-2 (labCOVID-19) or a confirmed COVID-19 diagnosis (diagCOVID-19)
- Have no hospitalizations in the 30 days prior to or on index

Hospital prevalent user

- Have a glucocorticoid (oral or parenteral) exposure in the 120 days prior to index (unrelated to COVID-19 diagnosis)
- Have a positive PCR test for SARS-CoV-2 (labCOVID-19) or a confirmed COVID-19 diagnosis (diagCOVID-19)
- Have no intensive services in the 30 days prior to or on index

Hospitalized naïve user

- Have no prior exposures to glucocorticoids in the 3 to 120 days prior to index
- Have a positive PCR test for SARS-CoV-2 (labCOVID-19) or a confirmed COVID-19 diagnosis (diagCOVID-19)
- Have no intensive services in the 30 days prior to or on index

For objective four, different cohorts are used, please refer to section 7.9.5 for details

7.3.2 Exclusion Criteria

Missing age or sex

7.4 Follow-up

Two index date definitions were applied as appropriate for each objective:

- Diagnosis index date was defined as a positive PCR test for SARS-CoV-2 (labCOVID-19) or a confirmed COVID-19 diagnosis(diagCOVID-19) whichever is the earliest.
- Treatment index date was defined as the start of first systemic glucocorticoid treatment episode specifically for the treatment of COVID-19, irrespective of whether the patient was a prevalent or naïve user.

Follow up for all patients begun from the index date until they experienced the outcome of interest (endpoint, depending on the objective) or until cohort exit (date of censoring). The patients were followed up for maximum 90 days or until censoring occurs, censoring criteria were:

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

The lookback window for evaluating risk factors, medical history is 365 days and was applied only to ambulatory cohorts. Hospital cohorts were allowed to have as little as 0 days lookback period, in order to maximise inclusion.

7.5 Subgroups

The following subgroups were used to stratify the descriptive tables in Primary objective 1 and secondary objective 1-3. These are a mix of contraindications (e.g. heart failure, myocardial infarction, ischaemic stroke, hypertension, diabetes) and underrepresented groups in clinical trials (e.g. renal impairment, hepatic impairment) as well as conditions for which glucocorticoids are indicated (COPD and asthma).

Comorbidities

- Cardiovascular diseases[2] (e.g., hypertension, arrhythmia, valve disorders, stroke, acute myocardial infarction, heart failure)
- Type 2 diabetes mellitus
- Respiratory diseases: asthma, COPD
- Renal impairment
- Hepatic impairment
- Autoimmune diseases (e.g., type 1 diabetes mellitus, rheumatoid arthritis, psoriasis, psoriatic arthritis, multiple sclerosis, systemic lupus erythematosus, Addison's, Graves, Sjogrens, Hashimoto, myasthenia gravis, autoimmune vasculitis, pernicious anaemia, celiac disease, scleroderma, sarcoid, ulcerative colitis, Crohn disease)
- Starting dose of steroids: low dose and high dose (used the cut off defined by WHO)

Speciality of the healthcare practitioner (GPs vs specialists) in databases that record this information

[2] Cardiovascular disease as a subgroup variable has a different definition from the composite cardiovascular event as an adverse event which is focused on acute and severe outcomes.

The subgroups are not mutually exclusive, and patients could contribute to more than one subgroup. The above subgroups were used for descriptive purposes and were not used for statistical comparisons.

7.6 Variables

Each treatment/variable definition was based on standard concepts in the OMOP Standardized Vocabularies. Variables were identified using pre-specified concept sets reviewed by a core team of clinicians, epidemiologists, vocabulary experts, and health data scientists with extensive expertise in the use of the OMOP CDM and the OHDSI tools. Some of the codes used and validated before were reused in this project.

7.6.1 COVID-19 diagnosis

The definitions used for COVID-19 diagnosis depended on the data source, for example, the primary care data sources usually do not contain the laboratory values. All the analyses were run on the main definition while the alternative definitions were used for secondary objective 4 - to explore how COVID-19 is captured across different databases.

1. **Catch-all** (main definition, the most sensitive)

Defined either as the first confirmed diagnosis for COVID-19 **OR** the first SARS-CoV-2 positive PCR test, if both present the earliest date was considered.

Alternative definitions

2. **Diagnosis confirmed (diagCOVID-19)**

Defined as one of the following medical codes for COVID-19 at any time (first occurrence considered) as detailed in Appendix 2.

3. **Laboratory confirmed (labCOVID-19)**

Defined as a record of SARS-CoV-2 positive PCR as performed on nasopharyngeal swabs and/or on respiratory tract secretions and aspirates.

We did not include the testing for the presence of antibodies due to the issue of not knowing the point of infection via antibody testing. If patient has more than one test, first occurrence was considered.

4. **Symptomatic COVID-19**.

At least two distinct symptoms of the following, observed within 14 days of each other.

- Cough
- Dyspnoea
- Fever, unspecified
- Malaise and fatigue
- Myalgia
- Anosmia, Hyposmia or Dysgeusia episodes

5. **Suspected COVID-19**

- Coronavirus as the cause of diseases classified to other chapters
- Coronavirus infection, unspecified site
- Other viral pneumonia
- Acute bronchitis due to other specified organisms

- Unspecified acute lower respiratory infection
- Bronchitis, not specified as acute or chronic
- Adult respiratory distress syndrome
- Other specified respiratory disorders

This classification is aligned with the ICD-10 International coding guidance on COVID-19 disease. (22)

7.6.2 Exposures

The following exposures of interest were captured in this study.

Table 2 Exposures of interest

	Cohort	When is measured
Glucocorticoids used in COVID-19 indication	All	At diagnosis index date and follow-up
Glucocorticoids for pre-existing conditions	Only in prevalent users' cohort	Before diagnosis index date
Other COVID-19 treatments: • antiviral therapy (AV) • antibiotic therapy (AB) • immune-based therapy (IB) • antithrombotic therapy (AT) • anti-hypertensives (AH) • statins (S) • anti-diabetic (AD)	All	At diagnosis index date and during follow-up
Respiratory support	All	At diagnosis index date and during follow-up*

* During follow-up this was considered as an outcome

7.6.2.1 **Glucocorticoids**

Glucocorticoids used in COVID-19 indication

The primary treatment group of interest is based on exposure to systemic glucocorticoids. The following drugs were considered as being used for COVID-19 diagnosis:

- Dexamethasone (H02AB02)
- Prednisone (H02AB07)
- Prednisolone (H02AB06)
- Methylprednisolone (H02AB04)
- Hydrocortisone (H02AB09)

Only glucocorticoids which were investigated in clinical trials (9,23) or are recommended by clinical guidelines were included (24–26) to avoid misclassification of steroids used for other conditions. As indication is not captured in the available databases, a glucocorticoid treatment was considered to have been initiated for COVID-19 treatment if:

For incident users

- The glucocorticoid treatment was initiated between 2 before and 30 days after COVID-19 diagnosis date (23)
- It is one of the five glucocorticoids recommended for COVID-19 as above

For prevalent users

- The glucocorticoid treatment was initiated between 2 before and 30 days after COVID-19 diagnosis date
- It is one of the five glucocorticoids recommended for COVID-19 as above
- The glucocorticoid started after COVID-19 diagnosis differs from the chronically used glucocorticoids OR there is a change in dose compared to the prevalent use, occurred after COVID-19 diagnosis.

Glucocorticoids for pre-existing conditions

For the prevalent users, any steroid in the ATC class H02 glucocorticoids for systemic use was considered. A patient was defined as a systemic glucocorticoids prevalent user if they had at least one prior exposure to systemic[3] glucocorticoids in the 120 days prior to diagnosis index date.

For the description of prevalent users of glucocorticoids, categories of use were created based on proportion of days covered (PDC) during the lookback period. PDC calculation was proposed as the number of days in period covered by prescriptions divided by number of days in the period.

- PDC > 85% as heavy user
- PDC 50-85% as moderate user
- less than 50% PDC as light user

Another categorization of prevalent glucocorticoids user was proposed on how recently in the past the last prescription was observed:

- current use (concomitant on date of COVID-19 diagnosis)
- very recent use (end date within 30 days before date of COVID-19 diagnosis)
- recent use (use ended more than 30 days before date of COVID-19 diagnosis)

7.6.2.2 **Other COVID-19 treatments**

Additional distinct treatment cohorts were created based on use of other drugs that might be used as treatment of COVID-19 according to various guidelines. Patients were considered exposed to other pharmacotherapeutic treatments for COVID-19 if available prescription data was available and if the drugs are in the list below.

a) antiviral therapy (AV)
b) antibiotic therapy (AB)
c) mmune-based therapy (IB)
d) antithrombotic therapy (AT)
e) anti-hypertensives (AH)

[3] Systemic effects of inhaled and topical use of glucocorticoids is considered low and therefore use was not considered for this study

f) statins (S)
g) anti-diabetics (AD)

These treatments were identified and classified through systematic review of CDC treatment guidelines, clinicaltrials.gov, or clinical guidelines, as part of another OHDSI project. (27)

7.6.2.3 Operationalization of exposure metrics

Cumulative duration

For glucocorticoids used in COVID-19 indication

Exposure to a treatment commenced on the date of the first qualifying record, subject to satisfying all inclusion criteria listed in section 7.3.1. Each drug exposure record had a start date and inferred end date, which is either explicitly entered or derived from other available information, such as days' supply or refills. Duration of each episode was calculated as end date minus start date or directly from days' supply variable, whatever available. For each patient, the cumulative duration of use was calculated as the sum of the duration of treatment episodes.

Daily dose

For glucocorticoids used in COVID-19 indication, the prescribed daily dose at initiation of glucocorticoid (treatment index date) was recorded and categorized in low and high dose. The definition of low dose and high dose used the cut off defined by WHO in their prospective meta-analysis from REACT subgroup (10), namely: 15 mg/d of dexamethasone, 400 mg/d of hydrocortisone, and 1 mg/kg/d of methylprednisolone.

The current recommendation is to use 10 mg or dexamethasone for maximum 10 days, administered orally or intravenously. In case glucocorticoids other than dexamethasone were administered, their dose was converted in prednisolone equivalents as described: https://emedicine.medscape.com/article/2172042-overview

Steroids often have adjusted dose regimens such that drug may be slowly increased or decreased over time and short acute treatment episodes are also possible. Such changes in dose over time were not be examined, however total cumulative dose was examined in relation to outcomes of interest (see below).

Cumulative dose

For glucocorticoids used in COVID-19 indication, orally administered, if quantity was available, the formula to calculate the cumulative exposure in mg is described below:

$$Cumulative\ dose_{solid}[mg] = \sum_{all\ exposures} quantity\ \times\ amount\_value\ [mg]$$

If the **quantity was missing**, the number of units per day for solid formulations were extracted. The cumulative exposure in mg can then be calculated using the following formula:

$$Cumulative\ dose_{solid}[mg] = \sum_{exposures} units\ per\ day\ \times\ amount\_value\ [mg] \times duration$$

For intravenous administration (bolus administration), the dose administered each time was counted.

$$Cumulative\ dose\ intravenous\ [mg] = \sum_{all\ exposures} amount\_value\ [mg]$$

Exposure groups for incidence calculation (secondary objective 2 and 3)

For the incidence rates calculation, an on-treatment exposure was considered with mutually exclusive groups to allow calculation of incidence rates.

Each person was classified as belonging to one of the following mutually exclusive exposure groups at treatment index date following COVID-19 diagnosis:

- Use of systemic glucocorticoids without other treatments for COVID-19 (drug and respiratory support)
- Use of systemic glucocorticoids plus other treatments for COVID-19 (drug and respiratory support)
- Only other treatments and respiratory support with no systemic glucocorticoids
- No specific treatments for COVID-19 infection (other concomitant treatments for indications other than for COVID-19 were allowed)

A single prescription was enough to consider the patient as exposed. See section 7.6.2.2 for description of 'other treatment for COVID-19' that were included.

Only the first episode of exposure was considered, patients being censored when they switched to another treatment or when follow up ended. Duration of follow-up for each treatment cohort was summarized and constituted the denominator for calculation of effect estimates. A persistence window of 7 days between drug utilization records for each study drug was allowed considered as continuous exposure for the outcome's assessment.

In case that more than 70% of the patients were censored, a sensitivity approach was applied for objectives 2 and 3 (see Section 7.9.7).

7.6.3 Adverse events

AEs under study were selected on the basis of those events associated with the corticosteroids class with a known pattern of onset that is acute. The list is not intended to be fully inclusive of all known AEs for corticosteroids since this was a POC study and was agreed between study investigators and study funder.

The following acute adverse events were evaluated in the glucocorticoid treated patients and patients treated with alternative therapies:

- Composite cardiovascular events (composite of ischemic stroke, haemorrhagic stroke, heart failure, acute myocardial infarction or sudden cardiac death)
- Hypertension
- Arrhythmia
- Gastritis, gastric ulcer, GI bleed
- Psychosis
- Myopathy
- Hyperglycaemia
- Infections (composite)

- Any bacterial infection
- Any viral infection
- Any fungal infection
- Any parasitic infection

And if numbers allow, within infections, also separately look at:

- Sepsis
- Lower respiratory tract infections
- Herpes zoster
- Cutaneous cellulitis

7.6.4 Disease severity outcomes

Outcomes under study were selected on the basis of those events associated with COVID-19 and with an acute onset. The list is not intended to be fully inclusive of all known outcomes and was agreed between study investigators and study funder.

In ambulatory care cohorts

- Hospital admission
- Venous thromboembolism (VTE)
- Disseminated intravascular coagulation (DIC)
- Death of any cause

In hospitalized cohorts

- Intensive services as an outcome in inpatient cohorts (including mechanical ventilation and Extracorporeal membrane oxygenation (ECMO))
- Discharge from hospital
- Death of any cause
- Venous thromboembolism (VTE)
- Disseminated intravascular coagulation (DIC)

They were all treated as time to event outcomes, see section **Error! Reference source not found.** for details.

7.6.5 Other Variables

Age – measured both as continuous and categorical variable in years. The following categories were created:

- <18
- ≥18 and <65
- ≥ 65 and <75
- ≥75

Sex

- Male
- Female

Index month of diagnosis

Comorbidities: Hypertension**,** Type 2 diabetes mellitus**,** Chronic obstructive pulmonary disease (COPD), Asthma, Ischemic stroke or haemorrhagic stroke, Heart failure**,** Acute myocardial infarction**,** Arrhythmia **,** Venous thromboembolism (VTE), Obesity (using diagnosis codes), Smoker, Alcohol/Drug abuse, Autoimmune conditions, Organ transplantation, Cancer, Dementia, Major psychiatric disorder, Renal impairment, Hepatic impairment.

These were used to describe the cohorts at relevant index dates(s) and some of these were selected as risk factors/confounders for the incidence rates analysis.

Respiratory support

Patients were considered having adjunctive respiratory support if available medical records data were available for the following interventions on or post COVID-19 diagnosis:

- Any type of respiratory support
- Invasive mechanical ventilation (including ECMO)
- ECMO only

If no records were observed, then the patient were considered as receiving no respiratory support.

7.7 Study Size

The number of patients in each of the proposed EU countries was projected to be modest, and it was difficult to confirm and likely to vary between data sources. As the primary objective is a descriptive one, the aim was to observe a sufficient number of patients in order to estimate the frequency of drug utilization measures with an acceptable level of precision. The 95% CI width provides an indication of precisions of the point estimate; the upper and lower limit will provide a range of credible values consistent with observed data.

7.8 Data Management

Data management for this study was conducted using standard IQVIA processes. Further details on the data handling procedure were provided to the EMA in the SAP and/or in the Data Management Plan. The process would take into consideration any data governance imposed on the data source including any plans to handle the data outside of the institution or country of origin. IQVIA will adhere to all local and regional laws on data protection and privacy.

An initial exploratory descriptive analysis was conducted for each country specific cohort post data extraction to provide insight into general patterns, functional form and any outliers of exposure and covariates; this was presented in Report 1.

7.9 Statistical methods

Continuous variables were described using mean, standard deviation, median, first and third quartiles, minimum, and maximum. Categorical variables were described by the number and percentage of patients in each category. The number of patients with missing data for each variable were reported. Confidence intervals (CIs) of 95% were presented for means using a normal approximation and for proportions using a binomial approximation. Only available data was summarized.

In all regression analyses, guidelines for appropriate fitting of any logistic or Cox regression model recommend a minimum of 10 outcome events per term (where term may be any linear covariate, non-

linear predictor, or interaction term). Where sensitivity analyses were conducted, fully adjusted regression analysis were only undertaken if sufficient outcome events were observed. In any scenario where the fully adjusted regression model did not have sufficient events, but where a minimally adjusted regression model including only the exposure, age, and sex in the linear predictor had sufficient events, the minimally adjusted regression model was carried out instead.

Additionally, in all analyses where Cox regression modelling was used, the hazard rate was used to represent the incidence rate.

The results for each country and database were presented separately.

7.9.1 General considerations

From the study population, country specific cohorts were created as detailed in section 7.1. Not all cohorts were possible to be constructed in all databases as they depend on the healthcare setting of the database.

7.9.2 Glucocorticoid prescribing patterns (primary objective)

Prescribing patterns of systemic glucocorticoids for the treatment of COVID-19 were summarized by the four cohorts (section 7.3) and by subgroups of special interest (section 7.5) and the description included time to initiation of glucocorticoid treatment (from COVID-19 diagnosis), duration of treatment, route of administration, daily dose at start, cumulative dose and duration of treatment received post COVID-19 diagnosis.

Frequency of concomitant use of other medications and invasive/non-invasive respiratory support at COVID-19 diagnosis index date and during follow-up will also be presented.

The time to systemic glucocorticoid initiation from COVID-19 diagnosis was modelled as a time-to-event outcome using the Kaplan-Meier (KM) estimator. The patient follow-up from COVID-19 diagnosis date until systemic glucocorticoid treatment index date was included in the KM analysis, with start of systemic glucocorticoid therapy being considered a ‘failure’ event. This KM analysis was stratified by route of systemic glucocorticoid administration (oral vs intravenous). The KM survival function curve (95% CI) and summary statistics of 25th percentile, median, 75th percentile of time to event (in days) were provided when possible to calculate. The survival function within each stratification was compared using log-rank test, where sufficient sample size permits.

A time series graph was used to investigate changes in prescribing patterns over calendar time. Monthly and quarterly incidence steroid incident use was plotted against time from January 2020 until study end. Key dates (such as Recovery trial) were highlighted on this graph to allow differentiation between time periods. A formal before/after analysis was not proposed. Results were stratified per country and per database.

7.9.3 Patient characteristics (secondary objective 1)

Descriptive analysis for systemic glucocorticoid use patterns was carried out and stratified by setting, glucocorticoid exposure type (naive, prevalent) and subgroups of special interest. Data was further stratified by subgroups of special interest.

7.9.4 Estimation of incidence of study adverse events of interest and disease outcomes (secondary objectives 2 and 3)

The crude incidence rate of the individual outcome relevant to each sub-cohort reported during person-time treated for each exposure group was calculated. The crude person-time from relevant index date was calculated for the following groups:

- Use of systemic glucocorticoids without other treatments for COVID-19 (drug and respiratory support)
- Use of systemic glucocorticoids plus other treatments for COVID-19 (drug and respiratory support)
- Only other treatments and respiratory support with no steroids
- No specific treatments for COVID-19 infection (other concomitant treatments were allowed)

Only the earliest eligible treatment was considered, and for patients who switched to another treatment, their follow-up was censored at date of switching. The number and reasons for patients censoring was reported.
We calculated both the incidence proportion and the incidence rate. The numerator for both (risk and rate) was comprised of counts of incident events of interest during the person-time as defined above recorded during each cumulative interval and summed to reflect the cumulative count for the interval.

The crude cumulative incidence rate was calculated according to the formula:
Total number of patients on Rx with first event during cumulative interval of interest x 100
Total person-time at risk (days)

The crude incidence proportion was calculated according to the formula:

Total number of patients on Rx with first event during cumulative interval of interest x 100
Total population at risk at start of study period

For each sub-cohort and type of person-time the numerator for each time frame contained the number of patients for whom an outcome has been recorded in that time frame since the onset of that type of person-time. The crude incidence rate of each outcome within the relevant sub-cohort was expressed as number of cases per 1,000 patient-days at risk.

The cumulative incidence rate was reported at the end of follow-up (30 and 90 days).

The person-time estimation and the calculation of the crude incidence rate for secondary objectives 2 and 3 was similar except for the outcomes being considered in each case. For secondary objective 2, adverse events of interest for glucocorticoids (listed in Section 7.6.3) was the outcome, and for secondary objective 3 mortality and other disease outcomes (Section 7.6.4) were the outcome.

Both stratification and adjustment (for age and sex) were proposed as a method to deal with confounders.

In order to examine risk factors of the outcomes of interest, data was also stratified by subgroups of interest (section 7.5) and stratum-specific crude incidence rates were calculated in each subgroup.

Each of the adverse event incidence rate and incidence proportion were analysed overall and in the following subgroups:

- Cohort
- Comorbidity
- Starting dose of glucocorticoid (for relevant treatment groups)
- Medical history of that specific AEs (yes/no)

The stratification of medical history specific to each AE are detailed in the table below:

Adverse event outcome	Medical history stratification[1]
Composite cardiovascular events	Any of the composite cardiovascular events in 365 days prior to diagnosis index date: yes/no
Hypertension	Hypertension recorded in 365 days prior to diagnosis index date (as per comorbidities): yes/ no
Arrhythmia	Arrhythmia recorded in 365 days prior to diagnosis index date (as per comorbidities): yes/ no
Gastrointestinal events	Gastrointestinal events recorded in 365 days prior to diagnosis index date (as per comorbidities): yes/no
Psychosis	Any major psychiatric disorder (not specifically psychosis) recorded in the 365 days prior to and including diagnosis index date: yes/ no
Myopathy	Myopathy recorded in the 90 days prior to and including diagnosis index date: yes/ no
Hyperglycaemia	Any type 1 or type 2 diabetes (not specifically hyperglycaemia) recorded in the 365 days prior to and including diagnosis index date: yes/ no
Any infection	Any infection recorded in the 90 days prior to and including diagnosis index date: yes/ no
Any bacterial infection	Any bacterial infection recorded in the 90 days prior to and including diagnosis index date: yes/ no
Any viral infection	Any viral infection recorded in the 90 days prior to and including diagnosis index date: yes/ no
Any fungal infection	Any fungal infection recorded in the 90 days prior to and including diagnosis index date: yes/ no
Any parasitic infection	Any parasitic infection recorded in the 90 days prior to and including diagnosis index date: yes/ no

[1] –365 days was used for chronic events and 90 days for acute/recurrent events. This applies only to ambulatory cohorts, while in hospital cohorts, any history is used

Separate Cox regression models were used to estimate adjusted cause-specific hazard rate[4] for each outcome **within** the following four treatment groups:

- Use of systemic glucocorticoids without other treatments for COVID-19 (drug and respiratory support)
- Use of systemic glucocorticoids plus other treatments for COVID-19 (drug and respiratory support)
- Only other treatments and respiratory support with no systemic glucocorticoids
- No specific treatments for COVID-19 infection (other concomitant treatments for indications other than for COVID-19 were allowed)

In addition to stratified analysis, for each of the above four treatment groups, a Cox model that is adjusted for a list of predefined confounders (age and sex) was run.

7.9.5 Explore the performance of different COVID-19 coding definitions (secondary objective 4)

The PheValuator[5] is a tool that can be used to estimate the performance of rule-based coding definitions when validation by clinical adjudication of patient records is not possible. (28) This tool was used to evaluate different COVID-19 definitions as described in section 7.6.1. The method involves three steps:

(1) Developing a probabilistic diagnostic predictive model for a rule-based case definition:

To construct the diagnosis predictive model, a very specific outcome cohort is needed (XSpec), sampled from the total database, where cases have a high certainty to be true positives. This was either a positive laboratory test or a diagnosis of COVID-19 in the 1-7 days prior to the visit[6] (as defined by the 'catch-all' definition). This specific outcome cohort was used to discriminate between positive and negative cases and to both 'train' and test the diagnostic prediction model.

Another cohort, the XSens, or 'noisy negatives' was created and then excluded from the target cohort, in order not to confuse the model. In this study the XSens cohort is a broader cohort of individuals likely to have covid-19 but do not meet the very specific criteria for XSpec and was comprised of either a positive lab test or a diagnosis of COVID-19 at any time prior to the visit OR 2 symptoms in the 14 days prior to the visit

The model was developed in a 'Target Cohort' which consists of a random selection of up to 5000 of the XSpec cohort plus a random selection of up to 5000 of all others in the database excluding those in the XSens cohort. The outcome is then derived based on presence in the XSpec cohort. (see Figure 2)

(2) Determine the probability for everyone in a large group of subjects to be a case.

Once the model was developed, this was applied to a larger study cohort (called the Evaluation cohort, which is a random selection of 2 million subjects from the databases (broader than the study population) from January 2020 onwards - selected to ensure the same prevalence of COVID-19 as defined by the XSpec cohort.

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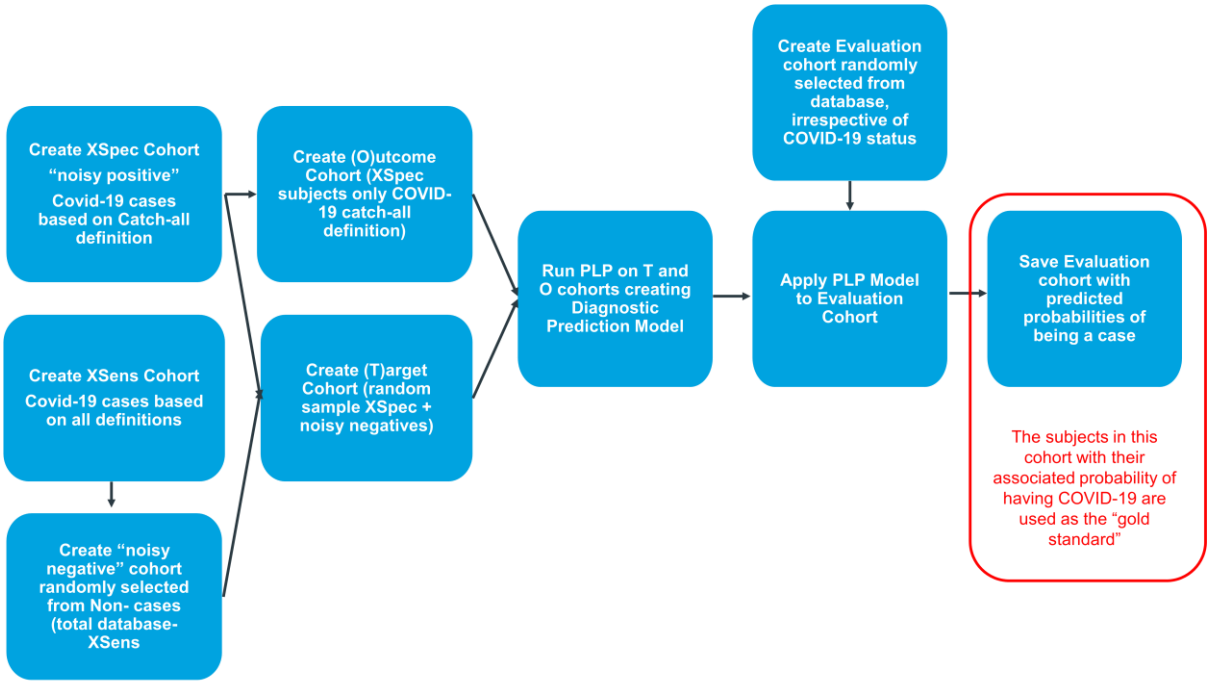
[4] Cause-specific HR were interpreted as instantaneous risk estimates and not as cumulative risk estimates; cumulative risks estimates were subject to competing events https://pubmed.ncbi.nlm.nih.gov/30012114/
[5] The PatientLevelPrediction R package (https://github.com/OHDSI/PatientLevelPrediction) was used to create this model.
[6] Visit refers to a healthcare encounter.

Each subject in the ‘Evaluation cohort’ has a predicted probability of COVID-19 calculated from the prediction model, this is regarded as ‘pseudo gold standard’.

Figure 2 Creation of the evaluation cohort

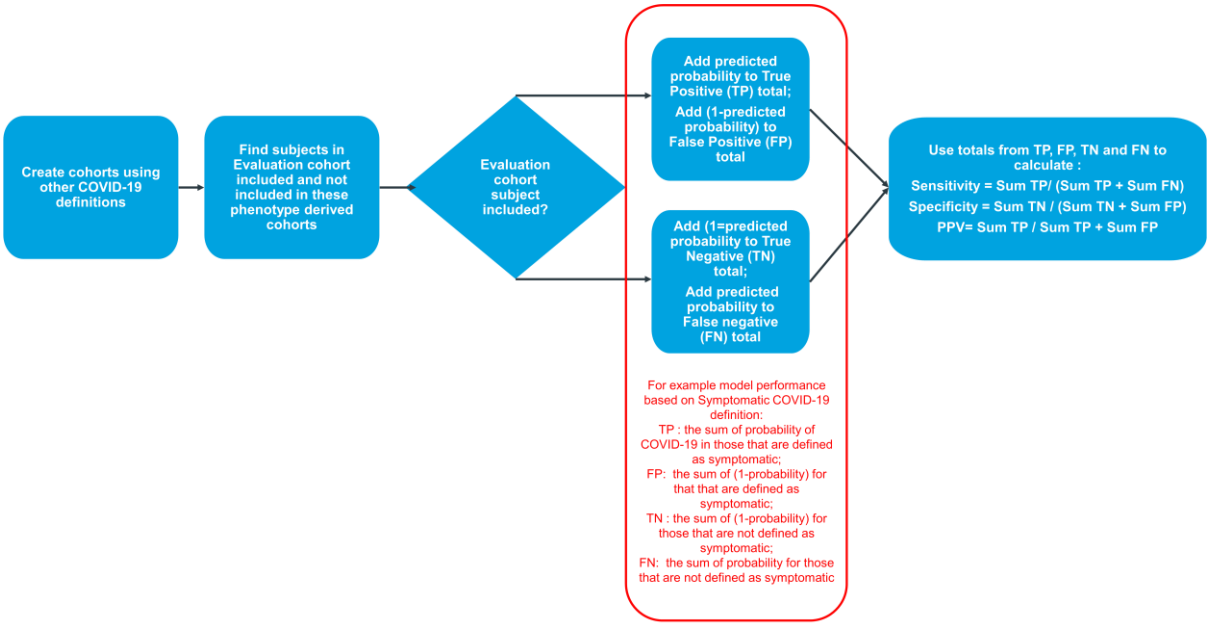


(3) Evaluating the performance of various definitions

Finally, for each definition, one creates a 2x2 confusion matrix of true positives, true negatives, false positives and false negatives. These counts are determined by summing the predicted probabilities (or 1-probability) within those that are defined as Covid-19 (or not) for each definition being evaluated (diagCOVID-19, Symptomatic COVID-19, Suspected COVID-19) against the probabilistic gold standard. Using this informationthe following the performance characteristics of each of the aforementioned case definition was examined:

- Sensitivity defined as True Positives/ (True Positives + False Negatives)
- Specificity defined as True Negatives / (True Negatives + False Positives)
- Positive Predictive Value defined as True Positives/ (True Positives + False Positives)
- Negatives Predictive Value defined as True Negatives / (True Negatives + False Negatives) (see Figure 3)

Figure 3 Evaluation of definition performance



7.9.6 Meta-analysis

All the proposed analyses were conducted for each database separately, with cumulative HR estimates (at 30 days follow-up) for each treatment group of interest combined using the DerSimonian-Lard random effects meta-analysis methods when I2 <=40%. The standard errors associated with the cumulative HRs were used to weight individual database estimates using the inverse variance weighting methods. No meta-analysis was conducted when I2 for a given drug-outcome pair is >40%.

7.9.7 Sensitivity Analyses

For objective 2 and 3, with regards to the reference group for incidence rates:
As a sensitivity analysis, the reference group for incidence rates will be replaced with 'other immunotherapies'.

For prevalent users' cohorts, the definition of remote users:
A sensitivity analysis to exclude those patients for whom short term duration of corticosteroid use (1-14 days) is identified prior to COVID-19 diagnosis.

For objectives 2 and 3, if the number of patients censored due to switching was higher than 70%, a sensitivity analysis was performed, namely an intention to treat approach (ITT), such that after initial exposure is defined to allocate patients to one of the four treatment groups, the denominator was then person-time observed (irrespective of treatment status), rather than person-time treated.

7.10 Quality Control

The study was conducted according to the guidelines for Good Pharmacoepidemiology Practice (GPP) (International Society for Pharmacoepidemiology 2008) and according to the ENCePP code of conduct (European Medicines Agency 2018).

Standard operating procedures or internal process guidance at each collaborating centre should be adhered to for the conduct of the study. These procedures should include rules for secure and confidential data storage, methods to maintain and archive project documents, quality-control procedures for all aspects of the study from protocol development to the reporting of the results. This will include quality control on study methodology, statistical analysis plan, programming, data management and analysis, study results, conclusions and study report.

The study coordinating centre is responsible for the implementation of quality management procedures, supported by the technical support team. Each individual site is responsible for the execution of the study against their CDM, the interpretation of the study results and quality control sign-off. Final quality control is the responsibility of the Principal Investigators and study coordinating centre.

Data quality control is the responsibility of database owners.

OHDSI and EHDEN quality control mechanisms for the CDM was applied. Each data source has to comply to the minimum threshold of the OHDSI recommendations and provide a summary report in form of a Data Quality Dashboard.

The Data Quality Dashboard (DQD) has been developed in the EHDEN project in close collaboration with OHDSI. and are described in high detail in Chapter 15 of The Book of OHDSI (http://book.ohdsi.org/DataQuality.html) and in the publication by Kahn et al., 2016.

In summary, this package runs a series of data quality checks against an OMOP CDM instance (currently supports v5.3.1 and v5.2.2). It systematically runs the checks, evaluates the checks against some pre-specified threshold, and then communicates what was done in a transparent and easily understandable way. The quality checks were organised according to the Kahn Framework, which uses a system of categories and contexts that represent strategies for assessing data quality (Kahn et al., 2016).

7.11 Last amendments to the protocol

From version 4.0 to 5.0 (submitted to EMA)				
	Date	**Section of the Protocol**	**Amendment or update**	**Reason**
1	16th March 2021	Inclusion and exclusion criteria	Inclusion criteria for hospital cohort were modified to include patients who have diagnosis mentioned only at discharge (known to be the case for US Hospital database) Also, the window for the prevalent user was specified (3 to 120 days)	From SAP review and cross check
2	16th March 2021	Variables	Heart failure added to the list of cardiovascular diseases	From SAP review and cross check

From version 4.0 to 5.0 (submitted to EMA)			
Date	**Section of the Protocol**	**Amendment or update**	**Reason**
3 16th March 2021	Variables – COVID-19 definition	For the main definition, reference was made to the code lists in the Annex as the mentioned code list was not complete. Two unspecific codes were removed from the suspected COVID definition as were considered too unspecific during feasibility tests. Added the word 'distinct' in the symptomatic definition.	From SAP review and cross check
4 16th March 2021	Variables	Categories of prevalent glucocorticoids exposures changed to current, very recent and recent	After medical QC, alignment the with SAP
5 16th March 2021	Variables	Switch to another glucocorticoid is not considered a censoring event anymore (they are perceived as interchangeable)	After medical QC, alignment with SAP
6 16th March 2021	Variables	VTE contains PE therefore the specification of PE was removed	After medical QC, alignment with SAP
7 16th March 2021	Variables	Renal and hepatic impairment added to the comorbidities list.	After medical QC, alignment with SAP
8 16th March 2021	Data analysis estimation of incidence	PS adjustment was removed since there is no comparison of treatment groups. Multivariable adjustment and stratification were performed instead, directly in the final models, conducted within each treatment group cohort.	SAP review
9 16th March 2021	Data analysis estimation of incidence	For the AE analysis, a stratification by medical history of that specific event was introduced in order to distinguish safety signals from reoccurrence of chronic/previous disease	SAP review
10 16th March 2021	Data analysis estimation of incidence	Adjustment for age and sex mentioned	SAP review

From version 4.0 to 5.0 (submitted to EMA)				
	Date	**Section of the Protocol**	**Amendment or update**	**Reason**
11	16th March 2021	Quality control	Quality control section aligned with E-CORE specifications.	SAP review

After version 5.0 (changes not submitted to EMA)				
Nr.	**Date**	**Section of the Protocol**	**Amendment or update**	**Reason**
1	5th September 2021	Rationale and background	Updated with the newest research published since last version of the protocol	EMA reviewer comment
2	5th September 2021	Study design	Study design amended to correct small errors Number of databases updated	EMA reviewer comment/ more data added
3	5th September 2021	Study period	Study period extended with EMA approval (to include more data sources in the report)	
4	5th September 2021	Setting	Table 1 updated with actual data lock points and additional databases included	More data sources added to the list
5	5th September 2021	Study design	Updated to the minimum length of follow up. The minimum length of patient history was 365 days for the ambulatory cohorts and 0 days for hospital cohorts.	Error corrected
6	5th September 2021	Study design	Clarification regarding objective 4 - Objective 4 was performed in a different cohort that the rest of the objectives, using the entire available data to test the performance of the COVID-19 definitions.	Clarification point added
7	5th September 2021	Inclusion criteria	Diagnosis for COVID-19 during a hospitalisation where the start date of hospitalisation is <30 days before diagnosis or hospitalised within 30 days after diagnosis removed as the setting is dictated	Error corrected

After version 5.0 (changes not submitted to EMA)				
Nr.	**Date**	**Section of the Protocol**	**Amendment or update**	**Reason**
			by the type of database and therefore this is not needed	
8	5th September 2021	Variables	In the symptomatic definition, the following clarification was added 'observed within 14 days of each other.'	Clarification point added
9	5th September 2021	Variables – Adverse events	The mode of selecting the AEs was explained: AEs under study were selected on the basis of those events associated with the corticosteroids class with a known pattern of onset that is acute. The list is not intended to be fully inclusive of all known AEs for corticosteroids since this was a POC study and was agreed between study investigators and study funder.	EMA reviewer comment
10	5th September 2021	Statistical methods - Explore the performance of different COVID-19 coding definitions (secondary objective 4)	The section was heavily amended as the first iteration did not perform well and adjustments were made	Source package was updated and required modification of approach as the original package was tailored to claims data sources. Also the source package was updated to version 2.0 meanwhile and had to be rerun.

Section 8.0 Results

The report was intended to include 14 data sources, however Belgium - LPD had an insufficient number of COVID-19 patients and it was excluded (see Appendix 2). The results section will only refer to the 13 data sources from 8 countries that had a sufficient number of COVID-19 patients and had generated results before the data lock point of 27th August 2021.

The results are presented per objective and within each objective per cohort (ambulatory prevalent; ambulatory naïve; hospitalized prevalent; hospitalized naïve). Within each cohort, data from all countries that contributed with data are summarized. Please note the following restrictions apply:

Data privacy

- Cells which contain counts less than 5, together with the next less frequent category were masked and not reported. Corresponding percentages an incidence rates were masked.
- Cohorts and subgroups with less than 50 patients were masked.

ShinyApp

- As the number of results generated was very high, only the most important results were selected to be presented in this report, to improve the readability. The additional tables, especially the ones relating to subgroups, can be found in the ShinyApp which functions as an Electronic Supplementary material: https://ecorecoviddashboard.shinyapps.io/e-core-shiny-app/

8.1 Overall number of included patients

In the ambulatory prevalent cohort, across the seven databases that contributed information (France-LPD, Italy-LPD, Germany-DA, Netherlands-IPCI, Spain-SIDIAP, UK-IMRD, and UK-HIC), a total of 9,719 patients were included.

In the ambulatory naïve cohort, from the same seven databases, a total of 497,723 patients were included.

In the hospitalised prevalent cohort, across three databases (US-HDMC, Spain-IMASIS, and Serbia-UCCS) a total of 14,026 patients were included.

In the hospitalised naïve cohort, across six databases (US-HCDM, Spain-IMASIS, Serbia-UCCS, France-APHM, Germany-Academic hospital, and Spain-Hospitales) a total of 94,916 patients were included.

8.2 Glucocorticoid prescribing patterns

8.2.1 Ambulatory naïve cohort

Glucocorticoid use in ambulatory naïve cohort was reported in a total of 8,627 COVID-19 patients who were treated with glucocorticoid from France-LPD (n=98), Italy-LPD (n=140), Germany-DA (n=382), Netherlands-IPCI (n=473), Spain-SIDIAP (n=7,053), and UK-IMRD (n=481). The overall incidence of glucocorticoid use in this cohort during the entire period ranged from 0.6% in France-LPD to 3.3% in Italy-LPD.

The top three prescribed glucocorticoids were prednisolone (range: 0.0% (n=0) in Italy-LPD to 92.1% (n=443) in UK-IMRD), prednisone (range: 3.8% (n=18) in Netherlands-IPCI to 68.6% (n=96) in Italy-LPD), and dexamethasone (range: 0.0% (n=0) in France-LPD to 40.3% (n=154) in Germany-DA). Three out of six databases did not report the route of administration but for those that did, only oral administration was reported (95.4% (n=451) in Netherlands-IPCI and 97.4% (n=372) in Germany-DA).

Median time from diagnosis index date to treatment with glucocorticoids ranged from 2.0 days in the Germany-DA to 10.0 days in the Spain-SIDIAP. The median daily dose at treatment initiation ranged from 1.0mg in Italy-LPD to 15.0mg in France-LPD. Furthermore, the median cumulative dose of all glucocorticoids to 90 days across the included countries was between 29.9mg in UK-IMRD to 74.6mg in Germany-DA. The median cumulative duration of all glucocorticoids ranged from 4.0 days in the France-LPD to 25.0 days in Italy-LPD.

The number of patients receiving other COVID-19 treatments[7], irrespective of their glucocorticoid treatment ranged from 14.6% (n=1,030) in Spain-SIDIAP to 42.1% (n=59) in Italy-LPD. No patient received respiratory support in the ambulatory setting.

[7] Other COVID-19 treatments include antiviral therapy, antibiotic therapy, immune-based therapy, antithrombotic therapy, anti-hypertensives, statins, and anti-diabetic drugs

Table 3 Glucocorticoid prescribing patterns

		France-LPD		Italy-LPD		Germany-DA		Netherlands-IPCI		Spain-SIDIAP		UK-IMRD	
		N	%	N	%	N	%	N	%	N	%	N	%
Patients with COVID-19		16071		4298		33200		42030		358632		40943	
Patients receiving glucocorticoids	Yes	98	0.6	140	3.3	382	1.2	473	1.1	7053	2.0	481	1.2
Type of 1st glucocorticoid received	Dexamethasone	0	0.0	**	**	154	40.3	143	30.2	2661	37.7	29	6.0
	Hydrocortisone	*	*	*	*	*	*	**	**	40	0.6	7	1.5
	Methylprednisolone	*	*	33	23.6	14	3.7	*	*	1356	19.2	*	*
	Prednisolone	68	69.4	0	0.0	200	52.4	295	62.4	412	5.8	443	92.1
	Prednisone	21	21.4	96	68.6	**	**	18	3.8	2584	36.6	*	*
Route of administration	Intravenous	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
	Oral	0	0.0	0	0.0	372	97.4	451	95.4	0	0	**	**
	Other/Missing	98	100.0	140	100.0	10	2.6	22	4.7	7053	100.0	*	*
Time to treatment with glucocorticoid	Mean (SD)	9.1 (9.7)		9.5 (9.2)		6.0 (8.1)		6.8 (7.6)		10.9 (8.5)		8.0 (8.6)	
	Median (Q1 - Q3)	6.0 (0.0-16.0)		7.0 (0.0-17.0)		2.0 (0.0-10.0)		4.0 (0.0-10.0)		10.0 (4.0-16.0)		5.0 (0.0-14.0)	
	Min - Max	0.0 - 30.0		0.0 - 30.0		0.0 - 30.0		0.0 - 30.0		0.0 - 30.0		0.0 - 30.0	
	N	98	100.0	140	100.0	382	100.0	473	100.0	7053	100.0	481	100.0

		France-LPD		Italy-LPD		Germany-DA		Netherlands-IPCI		Spain-SIDIAP		UK-IMRD	
		N	%	N	%	N	%	N	%	N	%	N	%
	Missing	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Daily dose (mg) at treatment initiation[a]	Mean (SD)	19.6 (15.2)		2.5 (3.8)		16.5 (61.4)		6.0 (8.2)		17.2 (94.2)		4.3 (1.9)	
	Median (Q1 - Q3)	15.0 (12.0-20.0)		1.0 (1.0-4.0)		4.0 (3.0-7.0)		4.0 (4.0-6.0)		4.0 (3.0-6.0)		4.0 (4.0-4.0)	
	Min - Max	0.0 - 60.0		0.0 - 30.0		0.0 - 800.0		0.0 - 142.0		0.0 - 2731.0		0.0 - 35.0	
	N	**	**	125	89.3	370	96.9	418	88.4	5440	77.1	**	**
	Missing	*	*	15	10.7	12	3.1	55	11.6	1613	22.9	*	*
Cumulative dose (mg) of all glucocorticoids to 90 days[a]	Mean (SD)	56.0 (17.1)		50.1 (54.7)		102.3 (149.3)		63.0 (137.3)		163.6 (570.7)		46.2 (95.0)	
	Median (Q1 - Q3)	59.7 (59.7-59.7)		37.3 (15.1-44.8)		74.6 (30.1-99.3)		31.3 (29.9-59.4)		42.0 (22.4-103.0)		29.9 (22.4-33.6)	
	N	**	**	125	89.3	370	96.9	418	88.4	5389	76.4	**	**
	Missing	*	*	15	10.7	12	3.1	55	11.6	1664	23.6	*	*
Cumulative duration (days) of all glucocorticoids to 90 days	Mean (SD)	7.8 (15.8)		24.7 (19.9)		20.1 (16.2)		11.6 (14.8)		18.2 (22.0)		10.2 (12.2)	
	Median (Q1 - Q3)	4.0 (3.0-5.0)		25.0 (10.0-40.0)		20.0 (10.0-20.0)		7.0 (5.0-10.0)		8.0 (5.0-22.0)		7.0 (5.0-10.0)	
	Min - Max	1.0 - 90.0		1.0 - 90.0		1.0 - 90.0		1.0 - 90.0		1.0 - 90.0		1.0 - 90.0	

		France-LPD		Italy-LPD		Germany-DA		Netherlands-IPCI		Spain-SIDIAP		UK-IMRD	
		N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
	N	98	100.0	**	**	382	100.0	466	98.5	6971	98.8	481	100.0
	Missing	0	0.0	*	*	0	0.0	7	1.5	82	1.2	0	0.0
Other COVID-19 treatments received[b]	No	69	70.4	81	57.9	291	76.2	347	73.4	6023	85.4	401	83.4
	Yes	29	29.6	59	42.1	91	23.8	126	26.6	1030	14.6	80	16.6
Respiratory support	No	98	100.0	140	100.0	382	100.0	473	100.0	7053	100.0	481	100.0

Legend: * and ** - categories with ≤ 5 counts and the next less frequent category were masked; a - In case glucocorticoids other than dexamethasone were administered, their dose was converted in dexamethasone equivalents as described in https://emedicine.medscape.com/article/2172042-overview b - Other COVID-19 treatments include antiviral therapy, antibiotic therapy, immune-based therapy, antithrombotic therapy, anti-hypertensives, statins, and anti-diabetic drugs.
UK-HIC was not included as it included less than 50 patients receiving glucocorticoids.
Daily dose and cumulative dose had very high values for some databases and this has to be investigated as it might be due to different recording of dose. This was reported for Germany-Academic Hospital and Serbia -UCCS.

The description of cohorts by subgroup can be found online in the Electronic Supplementary material.

Changes in prescribing patterns over calendar time

In the ambulatory naïve cohort, monthly incidence of glucocorticoids utilisation in COVID-19 patients was constantly low in most countries. Only four databases have enough data points before and after publication of RECOVERY trial (June 2020), to be able to identify a potential trend in use. From these, in Germany-DA and Spain-SIDIAP it seems that glucocorticoids utilisation had increased after RECOVERY results were published, while in Netherlands-IPCI and UK-IMRD the RECOVERY results publication did not have impact on glucocorticoids utilisation. (see Figure 4)

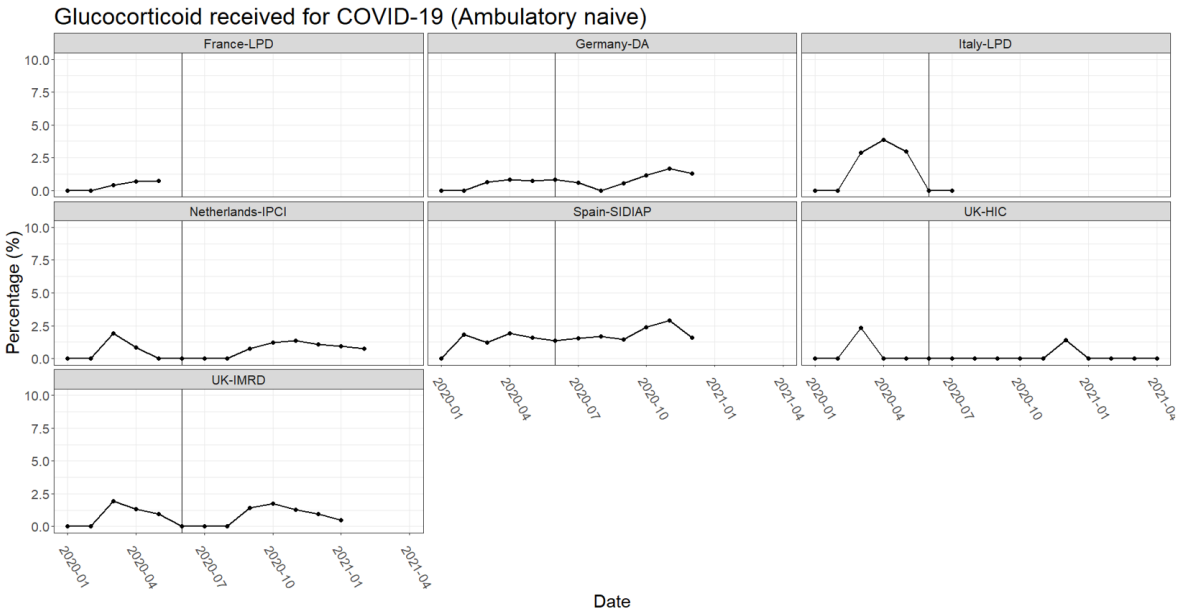


Figure 4 Monthly incidence of use of glucocorticoid per month for the study period

Legend: The vertical line represents the date when RECOVERY results were made public, June 2020

8.2.2 Hospital naïve cohort

Glucocorticoid use in hospital naïve cohort was reported in a total of 30,483 COVID-19 patients from France-APHM (n=339), Germany-Academic Hospital (n=721), Serbia-UCCS (n=4,189), Spain-Hospitales (n=1,119), Spain-IMASIS (n=1,145), and US-HCDM (n=22,970). The incidence of glucocorticoid use in this cohort ranged from 2.4% in France-APHM to 45.6% in Germany-Academic Hospital.

The three most commonly prescribed glucocorticoids were dexamethasone (range: 19.7% (n=220) in Spain-Hospitales to 80.7% (n=582) in Germany-Academic Hospital), methylprednisolone (range: 17.7% (n=60) in France-APHM to 72.5% (n=3,035) in Serbia-UCCS), and hydrocortisone (range: 2.2% (n=495) in US-HCDM to 21.3% (n=74) France-APHM). The route of administration was missing in all databases except Spain-IMASIS where 85.9% (n=984) of the COVID-19 patients received glucocorticoids via intravenous route and 13.3% (n=152) orally.

Median time from diagnosis to treatment with glucocorticoids ranged from 0.0 days in Serbia-UCCS and US-HCDM to 6.0 days in France-APHM. The median daily dose at treatment initiation ranged from 2.0mg in Spain-IMASIS to 22.5mg in France-APHM. Additionally, the median cumulative dose of all glucocorticoids to 90 days across the included countries ranged between 22.5mg in Spain-IMASIS to

135.6mg in Serbia-UCCS. The median cumulative duration of all glucocorticoids to 90 days ranged from 4.0 days in the France-APHM to 10.0 days in Spain-Hospitales.

The number of patients receiving other COVID-19 treatments[8], irrespective of their glucocorticoid treatment ranged from 43.7% (n=148) in France-APHM to 99.5% (n=1,113) in Spain-Hospitales. No patient received respiratory support in the hospital setting.

[8] Other COVID-19 treatments include antiviral therapy, antibiotic therapy, immune-based therapy, antithrombotic therapy, anti-hypertensives, statins, and anti-diabetic drugs

Table 4 Glucocorticoid prescribing patterns

		France-APHM		Germany-Academic Hospital		Serbia-UCCS		Spain-Hospitales		Spain-IMASIS		US-HCDM	
		N	%	N	%	N	%	N	%	N	%	N	%
Patients with COVID-19		14167		1574		9745		2543		4719		62168	
Patients receiving glucocorticoids		339	2.4	721	45.8	4189	43.0	1119	44.0	1145	24.3	22970	36.9
Type of 1st glucocorticoid received	Dexamethasone	193	56.9	582	80.7	**	**	220	19.7	682	59.6	15872	69.1
	Hydrocortisone	74	21.3	*	*	*	*	72	6.4	**	**	495	2.2
	Methylprednisolone	60	17.7	**	**	3035	72.5	772	69.0	327	28.6	5003	21.8
	Prednisolone	0	0.0	0	0.0	0	0.0	*	*	*	*	58	0.3
	Prednisone	12	3.5	0	0.0	622	14.9	*	*	70	6.1	1542	6.7
Route of administration	Intravenous	0	0.0	0	0.0	0	0.0	0	0.0	984	85.9	0	0.0
	Oral	0	0.0	0	0.0	0	0.0	0	0.0	152	13.3	0	0.0
	Other/Missing	339	100.0	721	100.0	4189	100.0	1119	100.0	9	0.8	22970	100.0
Time to treatment with glucocorticoid	Mean (SD)	7.1 (6.3)		2.3 (4.0)		1.9 (4.0)		2.7 (3.1)		3.6 (4.8)		1.9 (4.1)	
	Median (Q1 - Q3)	6.0 (2.0-10.0)		1.0 (0.0-2.0)		0.0 (0.0-2.0)		2.0 (1.0-4.0)		2.0 (1.0-4.0)		0.0 (0.0-1.0)	
	Min - Max	0.0 - 30.0		0.0 - 28.0		0.0 - 30.0		0.0 - 26.0		0.0 - 30.0		0.0 - 30.0	

		France-APHM		Germany-Academic Hospital		Serbia-UCCS		Spain-Hospitales		Spain-IMASIS		US-HCDM	
		N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
	N	339	100.0	721	100.0	4189	100.0	1119	0.0	1145	100.0	22970	100.0
	Missing	0	0.0	0	0.0	0	0.0	0	100.0	0	0.0	0	0.0
Daily dose (mg) at treatment initiation[a]	Mean (SD)	25.9 (27.9)		NA (NA)		493.3 (8014.5)		NA (NA)		4.5 (5.4)		11.1 (17.6)	
	Median (Q1 - Q3)	22.5 (8.8-31.5)		NA (NA-NA)		15.0 (8.0-24.0)		NA (NA-NA)		2.0 (2.0-4.3)		8.0 (5.0-13.0)	
	Min - Max	1.0 - 200.0		NA		0.0 - 377358.0		NA		1.0 - 19.0		0.0 - 907.0	
	N	68	20.1	0	0.0	3476	83.0	0	0.0	12	1.1	21343	92.9
	Missing	271	79.9	721	100.0	713	17.0	1119	100.0	1133	98.9	1627	7.1
Cumulative dose (mg) of all glucocorticoids to 90 days[a]	Mean (SD)	144.8 (203.4)		NA (NA)		2640.9 (25426.6)		NA (NA)		40.4 (52.7)		79.2 (155.2)	
	Median (Q1 - Q3)	50.0 (23.4-217.9)		NA (NA-NA)		135.6 (60.4-264.0)		NA (NA-NA)		22.5 (6.8-35.0)		34.0 (13.0-82.0)	
	N	64	18.9	0	0.0	3462	82.7	0	0.0	11	1.0	21323	92.8
	Missing	275	81.1	721	100.0	727	17.4	1119	100.0	1134	99.0	1647	7.2

		France-APHM		Germany-Academic Hospital		Serbia-UCCS		Spain-Hospitales		Spain-IMASIS		US-HCDM	
		N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Cumulative duration (days) of all glucocorticoids to 90 days	Mean (SD)	6.47 (7.3)		7.6 (6.0)		10.7 (7.6)		17.7 (21.5)		12.8 (16.7)		6.7 (6.4)	
	Median (Q1 - Q3)	4.0 (1.0-9.0)		7.0 (3.0-10.0)		9.0 (6.0-14.0)		10.0 (4.0-21.0)		7.0 (1.0-16.0)		5.0 (3.0-9.0)	
	Min - Max	1.0 - 36.0		1.0 - 47.0		1.0 - 80.0		1.0 - 90.0		1.0 - 90.0		1.0 - 90.0	
	N	298	87.9	709	98.3	4189	100.0	1094	97.8	**	**	22376	97.4
	Missing	41	12.1	12	1.7	0	0.0	25	2.2	*	*	594	2.6
Other COVID-19 treatments received[b]	No	191	56.3	66	9.2	568	13.6	6	0.5	186	16.2	2869	12.5
	Yes	148	43.7	655	90.8	3621	86.4	1113	99.5	959	83.8	20101	87.5
Respiratory support	No	339	100.0	721	100.0	4189	100.0	1119	100.0	1145	100.0	22970	100.0

Legend: * and ** - categories with ≤ 5 counts and the next less frequent category were masked; a - In case glucocorticoids other than dexamethasone were administered, their dose was converted in prednisolone equivalents as described in https://emedicine.medscape.com/article/2172042-overview b - Other COVID-19 treatments include antiviral therapy, antibiotic therapy, immune-based therapy, antithrombotic therapy, anti-hypertensives, statins, and anti-diabetic drugs

Daily dose and cumulative dose had very high values for some databases and this has to be investigated as it might be due to different recording of dose. This was reported for Germany-Academic Hospital and Serbia -UCCS.

The description of cohorts by subgroup can be found online in the Electronic supplementary material

Changes in prescribing patterns over calendar time

In the hospital naïve cohort, the monthly proportion of glucocorticoid utilisation in COVID-19 patients seems to have increased after the publication of RECOVERY trial (June 2020) in the France-APHM, Spain-IMASIS, Serbia UCCS and US-HCDM. However, in Spain-IMASIS, it seems to have subsequently dropped after October 2020. No trend testing was performed. (see **Figure 5**)

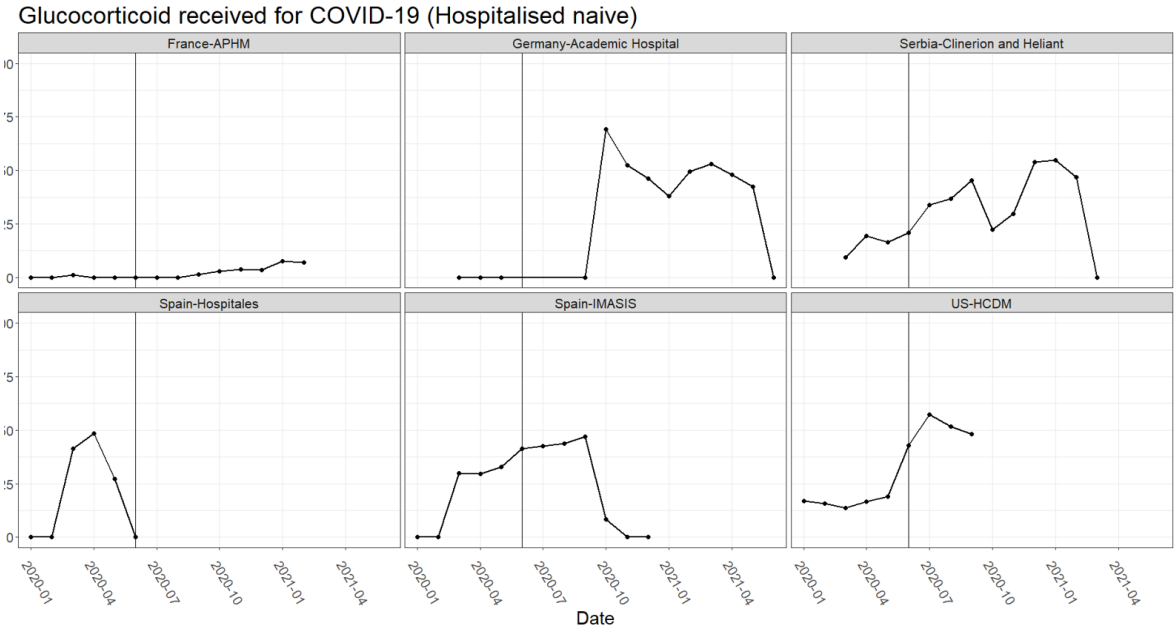


Figure 5 Monthly incidence of use of glucocorticoid per month for the study period

Legend: The vertical line represents the date when RECOVERY results were made public, June 2020

8.2.3 Ambulatory prevalent and hospital prevalent cohorts

Based on available data there was no suggestion of repurposing chronic steroid treatment for Covid-19. It was outside the scope of the study to describe patients who used glucocorticoids for other indications than COVID-19.] Due to this, the recency of use and the PDC variables were not described.

8.3 Patient characteristics

8.3.1 Ambulatory Prevalent Cohort

Seven databases contributed information to the ambulatory -prevalent cohort, France-LPD, Italy-LPD, Germany-DA, Netherlands-IPCI, Spain-SIDIAP, UK-IMRD, and UK-HIC (**In the** ambulatory prevalent cohort, patients who had a glucocorticoid (oral or parenteral) exposure in the 3 to 120 days prior to diagnosis date (unrelated to COVID-19 diagnosis) were included. Across the seven databases studied, a total of 9,719 patients met the study pre-defined inclusion and exclusion criteria. The number of patients identified with COVID-19 in the ambulatory prevalent cohort was 1,109 in France-LPD, 189 in Italy-LPD, 637 in Germany-DA, 991 in the Netherland-IPCI, 5,266 in Spain-SIDIAP, 1,249 in the UK-IMRD, and 278 in UK-HIC.

The median (IQR) age at COVID-19 diagnosis ranged from 49.0 (37.0-58.0) years in France-LPD to 76.0 (63.0-83.0) years in the UK-HIC. The majority of patients were adults (18-65 years) ranging from 44.7% (n=443) in the Netherlands-IPCI to 81.9% (n=908) in France-LPD except the UK-HIC where 55.8% (n=155) of the patients were older adults (75+ years). The number of children diagnosed with COVID-19 was less than 5% of the population. A similar gender distribution was observed across the included geographies with a higher proportion of female patients (range: 51.1% [n=142] in UK-HIC to 67.4% [n=747] in France-LPD). The median time from symptoms to diagnosis (when symptoms were reported) varied from 0.0 days in Germany-DA, Italy-LPD, France-LPD, and UK-HIC to 3.0 days in the Netherland-IPCI and UK-IMRD.

Hypertension (ranging from 1.8% [n=22] in the UK-IMRD to 46.0% [n=87] in Italy-LPD) was found to be most commonly occurring co-morbidity followed by COPD (ranging from 3.6% [n=40] in France-LPD to 30.9% [n=86] in UK-HIC), and asthma (ranging from 2.4% [n=127] in Spain-SIDIAP to 15.5% [n=172] in France-LPD).

The proportion of patients with one or more COVID-19 symptom varied from 4.8% (n=9) in Italy-LPD to 21.6% (n=60) in the UK-HIC. The three most common symptoms were cough (ranging from 3.2% [n=6] in Italy-LPD to 12.1% [n=134] in France-LPD), fever (ranging from 0.0% [n=0] in Italy-LPD to 7.2% [n=20] in UKHIC), and dyspnoea (ranging from 0.0% [n=0] in Italy-LPD to 11.2% [n=31] in UKHIC.

At diagnosis, the proportion of patients receiving any other COVID-19 treatment except glucocorticoids varied from 5.8% (n=16) in UK-HIC to 23.8% (n=45) in Italy-LPD. Furthermore, at diagnosis, -no patients were receiving glucocorticoid only or glucocorticoid and other COVID-19 treatment across all the included databases.

Table 5).

In the ambulatory prevalent cohort, patients who had a glucocorticoid (oral or parenteral) exposure in the 3 to 120 days prior to diagnosis date (unrelated to COVID-19 diagnosis) were included. Across the seven databases studied, a total of 9,719 patients met the study pre-defined inclusion and exclusion criteria. The number of patients identified with COVID-19 in the ambulatory prevalent cohort was 1,109 in France-LPD, 189 in Italy-LPD, 637 in Germany-DA, 991 in the Netherland-IPCI, 5,266 in Spain-SIDIAP, 1,249 in the UK-IMRD, and 278 in UK-HIC.

The median (IQR) age at COVID-19 diagnosis ranged from 49.0 (37.0-58.0) years in France-LPD to 76.0 (63.0-83.0) years in the UK-HIC. The majority of patients were adults (18-65 years) ranging from 44.7% (n=443) in the Netherlands-IPCI to 81.9% (n=908) in France-LPD except the UK-HIC where 55.8% (n=155) of the patients were older adults (75+ years). The number of children diagnosed with COVID-19 was less than 5% of the population. A similar gender distribution was observed across the included geographies with a higher proportion of female patients (range: 51.1% [n=142] in UK-HIC to 67.4% [n=747] in France-LPD). The median time from symptoms to diagnosis (when symptoms were reported) varied from 0.0 days in Germany-DA, Italy-LPD, France-LPD, and UK-HIC to 3.0 days in the Netherland-IPCI and UK-IMRD.

Hypertension (ranging from 1.8% [n=22] in the UK-IMRD to 46.0% [n=87] in Italy-LPD) was found to be most commonly occurring co-morbidity followed by COPD (ranging from 3.6% [n=40] in France-LPD to 30.9% [n=86] in UK-HIC), and asthma (ranging from 2.4% [n=127] in Spain-SIDIAP to 15.5% [n=172] in France-LPD).

The proportion of patients with one or more COVID-19 symptom varied from 4.8% (n=9) in Italy-LPD to 21.6% (n=60) in the UK-HIC. The three most common symptoms were cough (ranging from 3.2% [n=6] in Italy-LPD to 12.1% [n=134] in France-LPD), fever (ranging from 0.0% [n=0] in Italy-LPD to 7.2% [n=20] in UKHIC), and dyspnoea (ranging from 0.0% [n=0] in Italy-LPD to 11.2% [n=31] in UKHIC.

At diagnosis, the proportion of patients receiving any other COVID-19 treatment except glucocorticoids[9] varied from 5.8% (n=16) in UK-HIC to 23.8% (n=45) in Italy-LPD. Furthermore, at diagnosis, -no patients were receiving glucocorticoid only or glucocorticoid and other COVID-19 treatment across all the included databases.

[9] Other COVID-19 treatments include antiviral therapy, antibiotic therapy, immune-based therapy, antithrombotic therapy, anti-hypertensives, statins, and anti-diabetic drugs

Table 5 Patient demographics and baseline characteristics for ambulatory prevalent cohort

	France-LPD		Italy-LPD		Germany-DA		Netherlands-IPCI		Spain-SIDIAP		UK-IMRD		UK-HIC	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Patients with COVID-19	**1109**	**100%**	**189**	**100%**	**637**	**100%**	**991**	**100%**	**5266**	**100%**	**1249**	**100%**	**278**	**100.0%**
Age (years) - continuous														
Mean (SD)	47.6 (16.5)		63.7 (16.7)		59.1 (19.7)		65.6 (16.4)		62.2 (21.1)		62.8 (19.5)		71.5 (16.5)	
Median (Q1-Q3)	49.0 (37.0-58.0)		65.0 (52.0-78.0)		59.0 (47.0-76.0)		67.0 (55.0-78.5)		63.0 (47.0-80.0)		64.0 (52.0-78.0)		76.0 (63.0-83.0)	
Min-Max	2.0-97.0		5.0-95.0		3.0-96.0		5.0-101.0		2.0-106.0		1.0-103.0		5.0-99.0	
N	1109	100.0 %	189	100.0 %	637	100.0 %	991	100.0%	5266	100.0 %	1249	100.0 %	278	100.0%
Missing	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%
Age (years) - categorical														
<18	43	3.9%	*	*	13	2.0%	*	*	130	2.5%	33	2.6%	*	*
18-64	908	81.9%	93	49.2%	382	60.0%	443	44.7%	2616	49.7%	602	48.2%	71	25.5%
65-74	104	9.4%	*	*	77	12.1%	*	*	729	13.8%	203	16.3%	49	17.6%
75+	54	4.9%	59	31.2%	165	25.9%	329	33.2%	1791	34.0%	411	32.9%	155	55.8%
Sex														
Female	747	67.4%	112	59.3%	367	57.6%	586	59.1%	3274	62.2%	760	60.9%	142	51.1%
Male	361	32.6%	58	30.7%	269	42.2%	405	40.9%	1992	37.8%	489	39.2%	136	48.9%
Comorbidities														
Hypertension	170	15.3%	87	46.0%	166	26.1%	185	18.7%	229	4.4%	22	1.8%	45	16.2%
Type-2 diabetes mellitus	48	4.3%	15	7.9%	82	12.9%	157	15.8%	152	2.9%	41	3.3%	38	13.7%
Chronic obstructive pulmonary disease	40	3.6%	24	12.7%	76	11.9%	106	10.7%	276	5.2%	137	11.0%	86	30.9%
Asthma	172	15.5%	26	13.8%	65	10.2%	88	8.9%	127	2.4%	124	9.9%	30	10.8%
Chronic kidney disease	9	0.8%	19	10.1%	53	8.3%	*	*	121	2.3%	65	5.2%	56	20.1%
Stroke	11	1.0%	11	5.8%	49	7.7%	80	8.1%	291	5.5%	36	2.9%	41	14.8%
Arrythmia	23	2.1%	22	11.6%	58	9.1%	60	6.1%	158	3.0%	34	2.7%	48	17.3%
Venous thromboembolism	8	0.7%	10	5.3%	15	2.4%	20	2.0%	81	1.5%	26	2.1%	21	7.6%
Obesity	7	0.6%	*	*	25	3.9%	9	0.9%	68	1.3%	7	0.6%	*	*

	France-LPD		Italy-LPD		Germany-DA		Netherlands-IPCI		Spain-SIDIAP		UK-IMRD		UK-HIC	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Patients with COVID-19	**1109**	**100%**	**189**	**100%**	**637**	**100%**	**991**	**100%**	**5266**	**100%**	**1249**	**100%**	**278**	**100.0%**
Current smoker	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%
Alcohol or drug abuse	15	1.4%	*	*	11	1.7%	16	1.6%	45	0.9%	0	0.0%	13	4.7%
Autoimmune conditions	69	6.2%	39	20.6%	106	16.6%	69	7.0%	180	3.4%	55	4.4%	34	12.2%
Organ transplant	*	*	0	0.0%	*	*	0	0.0%	47	0.9%	*	*	11	4.0%
Cancer	18	1.6%	38	20.1%	33	5.2%	88	8.9%	357	6.8%	39	3.1%	38	13.7%
Dementia	0	0.0%	*	*	26	4.1%	16	1.6%	46	0.9%	15	1.2%	13	4.7%
Major psychiatric disorder	*	*	*	*	41	6.4%	*	*	105	2.0%	*	*	*	*
Symptoms														
Fever episodes	72	6.5%	0	0.0%	11	1.7%	34	3.4%	330	6.3%	*	*	20	7.2%
Cough	134	12.1%	6	3.2%	22	3.5%	55	5.6%	211	4.0%	43	3.4%	33	11.9%
Myalgia	*	*	0	0.0%	*	*	0	0.0%	*	*	*	*	*	*
Malaise or fatigue	40	3.6%	*	*	11	1.7%	19	1.9%	46	0.9%	10	0.8%	*	*
Dyspnoea	22	2.0%	0	0.0%	8	1.3%	37	3.7%	250	4.8%	48	3.8%	31	11.2%
Anosmia, hyposmia and dysgeusia episodes	19	1.7%	*	*	9	1.4%	*	*	41	0.8%	*	*	*	*
Number of symptoms														
0	894	80.6%	180	95.2%	584	91.7%	850	85.8%	4530	86.0%	1153	92.3%	218	78.4%
1	152	13.7%	9	4.8%	46	7.2%	135	13.6%	616	11.7%	87	7.0%	37	13.3%
2	51	4.6%	0	0.0%	*	*	6	0.6%	98	1.9%	*	*	17	6.1%
3	*	*	0	0.0%	*	*	0	0.0%	*	*	0	0.0%	*	*
4	*	*	0	0.0%	0	0.0%	0	0.0%	*	*	*	*	*	*
Time from symptoms to diagnosis														
Mean (SD)	3.3 (4.7)		2.6 (4.6)		2.4 (3.8)		4.6 (4.4)		2.1 (3.3)		4.0 (3.9)		0.4 (1.6)	
Median (Q1-Q3)	0.0 (0.0-7.0)		0.0 (0.0-4.0)		0.0 (0.0-4.0)		3.0 (1.0-7.0)		1.0 (0.0-3.0)		3.0 (0.0-6.3)		0.0 (0.0-0.0)	
Min-Max	0.0-14.0		0.0-14.0		0.0-14.0		0.0-14.0		0.0-14.0		0.0-14.0		0.0- 9.0	
N	215	19.4%	9	4.8%	53	8.3%	141	14.2%	736	14.0%	96	7.7%	60	21.6%
Missing	894	80.6%	180	95.2%	584	91.7%	850	85.8%	4530	86.0%	1153	92.3%	218	78.4%

	France-LPD		Italy-LPD		Germany-DA		Netherlands-IPCI		Spain-SIDIAP		UK-IMRD		UK-HIC	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Patients with COVID-19	**1109**	**100%**	**189**	**100%**	**637**	**100%**	**991**	**100%**	**5266**	**100%**	**1249**	**100%**	**278**	**100.0%**
Treatment received at diagnosis (days)														
Glucocorticoid only	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%
Other COVID-19 treatments only[a]	146	13.2%	45	23.8%	53	8.3%	95	9.6%	428	8.1%	77	6.2%	16	5.8%
Glucocorticoid and other COVID-19 treatments	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%
No specific COVID-19 treatments	963	86.8%	144	76.2%	584	91.7%	896	90.4%	4838	91.9%	1172	93.8%	262	94.2%
Switched to different treatment before treatment ends[b]	40	3.6%	25	13.2%	88	13.8%	190	19.2%	562	10.7%	286	22.9%	59	21.2%

* and **- categories with ≤ 5 counts and the next less frequent category were masked

[a] - Other COVID-19 treatments include antiviral therapy, antibiotic therapy, immune-based therapy, antithrombotic therapy, anti-hypertensives, statins, and anti-diabetic drugs

b – This variable quantifies the number of patients censored due to switching

Note: No database reported speciality data

8.3.2 Ambulatory Naïve cohort

Seven databases contributed information to the ambulatory naive cohort, France-LPD, Italy-LPD, Germany-DA, Netherlands-IPCI, Spain-SIDIAP, UK-IMRD, and UK-HIC (**Table 6**).

Patients in ambulatory naïve cohort had no glucocorticoid (oral or parenteral) exposure in the 3 to 120 days prior to index (unrelated to COVID-19 diagnosis). This cohort included data from the seven databases, comprising a total of 497,723 patients. The number of patients available in background populations were as follows: 16,071 in France-LPD, 4,298 in Italy-LPD, 33,200 in Germany-DA, 42,030 in the Netherlands-IPCI, 358,632 in Spain-SIDIAP, 40,943 in the UK-IMRD, and 2,549 in the UKHIC.

The median (IQR) age of the COVID-19 patients among the included cohorts from different countries ranged from 43.0 (28.0-57.0) years in the UK-IMRD to 71.0 (56.0-83.0) years in the UK-HIC. Majority of the patients were adults (18-65 years) ranging from 36.9% [n=940] in the UK-HIC to 81.1% [n=13,038] in France-LPD. The number of children diagnosed with COVID-19 was less than 10% of the population Data from the included geographies showed a comparable gender distribution with a higher number of female patients ranging from 46.9% [n=1,196] in UK-HIC to 58.6% [n=9,409] in France-LPD. The median time from symptoms to diagnosis varied from 0 days in Italy-LPD, France-LPD, and UK-HIC to 2.0 days in the Netherland-IPCI.

The three most prevalent comorbidities in all COVID-19 patients were hypertension (range: 0.7% [n=294] in the UK-IMRD to 29.0% [n=1,245] in Italy-LPD) followed by T2DM (range: 1.0% [n=3,733] in Spain-SIDIAP to 15.9% [n=406] in UK-HIC), and CKD (range: 0.7% [n=2,459] in Spain-SIDIAP to 18.3% [n=466] in UK-HIC).

The proportion of COVID-19 patients who had COVID-19 symptoms recorded ranged from 1.3% in the UK-IMRD [n=511] to 14.3% [n=2,300] in France-LPD. Cough (0.8% [n=318] in the UK-IMRD to 11.1% [n=283] in UKHIC), fever (range: 0.0% [n=0] in Italy-LPD to 8.8% [n=223] in the UK-HIC, and dyspnoea (range: 0.0% [n=0] in Italy-LPD to 9.2% [n=235] in UK-HIC) were the most commonly occurring symptoms.

The proportion of patients receiving glucocorticoids at diagnosis ranged from 0.1% [n=21] in France-LPD to 0.4% in Italy-LPD [n=18] and in Germany-DA [n=133]. At diagnosis, the proportion of patients receiving any other COVID-19 treatment except glucocorticoids ranged from 2.8% [n=1,155] in UKIMRD to 21.9% [n=939] in Italy-LPD. Moreover, the proportion of patients receiving both the glucocorticoids and other COVID-19 related treatments at diagnosis varied from 0.1% [n=17] in France-LPD to 0.7% [n=32] in Italy-LPD. However, at diagnosis, the majority of patients did not receive any COVID-19 specific treatment (range between 77.0% [n=3,309] in Italy-LPD to 96.7% [n=39,603] in the UKIMRD).

Table 6 Patient demographics and baseline characteristics for ambulatory naïve cohort

	France-LPD		Italy-LPD		Germany-DA		Netherlands-IPCI		Spain-SIDIAP		UK-IMRD		UK-HIC	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Patients with COVID-19	**16071**	**100.0%**	**4298**	**100.0%**	**33200**	**100.0%**	**42030**	**100.0%**	**358632**	**100.0%**	**40943**	**100.0%**	**2549**	**100.0%**
Age (years)-continuous														
Mean (SD)	46.8 (17.4)		55.4 (17.7)		45.2 (20.7)		45.6 (19.7)		45.2 (21.7)		44.0 (20.4)		67.6 (19.4)	
Median (Q1-Q3)	47.0 (34.0-58.0)		55.0 (44.0-68.0)		45.0 (29.0-59.0)		47.0 (29.0-59.0)		45.0 (29.0-59.0)		43.0 (28.0-57.0)		71.0 (56.0-83.0)	
Min-Max	1.0-118.0		5.0-102.0		1.0-100.0		1.0-103.0		1.0-112.0		1.0-106.0		0.0-105.0	
N	16071	100.0%	4298	100.0%	33200	100.0%	42030	100.0%	358632	100.0%	40943	100.0%	2549	100.0%
Missing	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%
Age (years)-categorical														
<18	652	4.1%	29	0.7%	2775	8.4%	3483	8.3%	38813	10.8%	3912	9.6%	44	1.7%
18-64	13038	81.1%	2980	69.3%	25059	75.5%	31431	74.8%	254553	71.0%	30831	75.3%	940	36.9%
65-74	1454	9.1%	591	13.8%	2191	6.6%	3777	9.0%	25572	7.1%	2788	6.8%	481	18.9%
75+	927	5.8%	698	16.2%	3175	9.6%	3339	7.9%	39694	11.1%	3412	8.3%	1084	42.5%
Sex														
Female	9409	58.6%	2243	52.2%	18057	54.4%	23310	55.5%	196660	54.8%	22624	55.3%	1196	46.9%
Male	6620	41.2%	1534	35.7%	15059	45.4%	18720	44.5%	161972	45.2%	18319	44.7%	1353	53.1%
Comorbidities														
Hypertension	2258	14.1%	1245	29.0%	4502	13.6%	2500	6.0%	7409	2.1%	294	0.7%	383	15.0%
Type-2 diabetes mellitus	909	5.7%	348	8.1%	1774	5.3%	2135	5.1%	3733	1.0%	459	1.1%	406	15.9%
Chronic obstructive pulmonary disease	163	1.0%	127	3.0%	866	2.6%	372	0.9%	1967	0.6%	147	0.4%	180	7.1%
Asthma	805	5.0%	222	5.2%	1244	3.8%	988	2.4%	2323	0.7%	654	1.6%	136	5.3%
Chronic kidney disease	138	0.9%	103	2.4%	794	2.4%	*	*	2459	0.7%	369	0.9%	466	18.3%
Stroke	153	1.0%	119	2.8%	923	2.8%	639	1.5%	3609	1.0%	246	0.6%	284	11.1%
Arrythmia	294	1.8%	288	6.7%	1255	3.8%	546	1.3%	3199	0.9%	301	0.7%	325	12.8%
Venous thromboembolism	111	0.7%	42	1.0%	295	0.9%	214	0.5%	1043	0.3%	150	0.4%	57	2.2%

	France-LPD		Italy-LPD		Germany-DA		Netherlands-IPCI		Spain-SIDIAP		UK-IMRD		UK-HIC	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Patients with COVID-19	**16071**	**100.0%**	**4298**	**100.0%**	**33200**	**100.0%**	**42030**	**100.0%**	**358632**	**100.0%**	**40943**	**100.0%**	**2549**	**100.0%**
Obesity	59	0.4%	64	1.5%	830	2.5%	333	0.8%	3618	1.0%	135	0.3%	40	1.6%
Current smoker	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%
Alcohol or drug abuse	143	0.9%	25	0.6%	374	1.1%	415	1.0%	2007	0.6%	49	0.1%	78	3.1%
Autoimmune conditions	533	3.3%	257	6.0%	1040	3.1%	731	1.7%	2121	0.6%	289	0.7%	116	4.6%
Organ transplant	*	*	0	0.0%	12	0.04%	0	0.0%	73	0.0%	*	*	8	0.3%
Cancer	221	1.4%	318	7.4%	642	1.9%	844	2.0%	2950	0.8%	241	0.6%	192	7.5%
Dementia	29	0.2%	57	1.3%	490	1.5%	183	0.4%	1166	0.3%	168	0.4%	199	7.8%
Major psychiatric disorder	69	0.4%	55	1.3%	1442	4.3%	98	0.2%	3216	0.9%	41	0.1%	32	1.3%
Symptoms														
Fever episodes	1255	7.8%	0	0.0%	632	1.9%	480	1.1%	22143	6.2%	49	0.1%	223	8.8%
Cough	1687	10.5%	98	2.3%	914	2.8%	542	1.3%	11830	3.3%	318	0.8%	283	11.1%
Myalgia	89	0.6%	*	*	45	0.1%	33	0.1%	237	0.1%	31	0.1%	24	0.9%
Malaise or fatigue	854	5.3%	30	0.7%	368	1.1%	263	0.6%	2945	0.8%	90	0.2%	60	2.4%
Dyspnoea	279	1.7%	0	0.0%	251	0.8%	288	0.7%	7684	2.1%	188	0.5%	235	9.2%
Anosmia, hyposmia and dysgeusia episodes	388	2.4%	10	0.2%	836	2.5%	31	0.1%	3946	1.1%	17	0.0%	15	0.6%
Number of symptoms														
0	12803	79.7%	4160	96.8%	30560	92.1%	40468	96.3%	318161	88.7%	40359	98.6%	2026	79.5%
1	2300	14.3%	134	3.1%	2282	6.9%	1490	3.6%	33650	9.4%	511	1.3%	263	10.3%
2	702	4.4%	*	*	312	0.9%	*	*	5493	1.5%	45	0.1%	208	8.2%
3	219	1.4%	0	0.0%	*	*	*	*	1165	0.3%	*	*	*	*
4	*	*	0	0.0%	*	*	0	0.0%	*	*	6	0.0%	*	*
5	*	*	0	0.0%	0	0.0%	0	0.0%	*	*	*	*	0	0.0%
Time from symptoms to diagnosis (days)														
Mean (SD)	2.55 (4.27)		2.82 (4.12)		1.86 (2.86)		3.38 (3.93)		1.77 (2.71)		2.99 (3.97)		0.2 (1.4)	
Median (Q1-Q3)	0.00 (0.00-4.00)		0.00 (0.00-5.75)		1.00 (0.00-3.00)		2.00 (0.00-6.00)		1 (0.00-2.00)		1.00 (0.00-5.00)		0.0 (0.0-0.0)	
Min-Max	0.00 - 14.00		0.00 - 14.00		0.00 - 14.00		0.00 - 14.00		0.00 - 14.00		0.00 - 14.00		0.0-14.0	

	France-LPD		Italy-LPD		Germany-DA		Netherlands-IPCI		Spain-SIDIAP		UK-IMRD		UK-HIC	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Patients with COVID-19	**16071**	**100.0%**	**4298**	**100.0%**	**33200**	**100.0%**	**42030**	**100.0%**	**358632**	**100.0%**	**40943**	**100.0%**	**2549**	**100.0%**
N	3268	20.3%	138	3.2%	2640	8.0%	1562	3.7%	40471	11.3%	584	1.4%	523	20.5%
Missing	12803	79.7%	4160	96.8%	30560	92.1%	40468	96.3%	318161	88.7%	40359	98.6%	2026	79.5%
Treatment received at diagnosis														
Glucocorticoid only	21	0.1%	18	0.4%	133	0.4%	96	0.2%	936	0.3%	118	0.3%	*	*
Other COVID-19 treatments only[a]	2270	14.1%	939	21.9%	1733	5.2%	1531	3.6%	15466	4.3%	1155	2.8%	120	4.7%
Glucocorticoid and other COVID-19 treatments	17	0.1%	32	0.7%	72	0.2%	82	0.2%	562	0.2%	67	0.2%	*	*
No specific COVID-19 treatments	13763	85.6%	3309	77.0%	31262	94.2%	40321	95.9%	341668	95.3%	39603	96.7%	2423	95.1%
Specialty														
GP	*	*	137	3.2%	321	1.0%	NR	NR	2586	0.7%	464	1.1%	NR	NR
Specialist	*	*	NR	NR	61	0.2%	466	1.1%	4385	1.2%	17	0.0%	NR	NR
Switched to different treatment before end of current treatment[b]	66	0.4%	103	2.4%	237	0.7%	340	0.8%	5817	1.6%	339	0.8%	17	0.7%

* and **- categories with ≤ 5 counts and the next less frequent category were masked

[a] - Other COVID-19 treatments include antiviral therapy, antibiotic therapy, immune-based therapy, antithrombotic therapy, anti-hypertensives, statins, and anti-diabetic drugs

b- This variable quantifies the number of patients censored due to switching

Abbreviations: GP, general physician; NR, not reported; SD, standard deviation

8.3.3 Hospital Prevalent cohort

Three databases contributed information to the hospital prevalent cohort: the US-HDMC, Spain-IMASIS, and Serbia-UCCS. France-APHM- was excluded as had less than 50 patients in this cohort (**Table 7**).

In the hospital prevalent cohort, patients who had a glucocorticoid (oral or parenteral) exposure in the 120 days prior to diagnosis date (unrelated to COVID-19 diagnosis) were included. A total of 14,026 patients met the study pre-defined inclusion and exclusion criteria. The number of patients diagnosed with COVID-19 in the hospital prevalent cohort was 113 in Spain-IMASIS, 1,107 in Serbia-UCCS, and 12,806 in the US-HCDM.

The median (IQR) age ranged from 64.0 (51.0-74.0) years in the US-HCDM to 74.0 (59.0-81.0) years in Spain-IMASIS. Majority of the patients were adults (18-64 years) ranging from 33.6% [n=38] in Spain-IMASIS to 48.8% [n=6,247] in the US-HCDM. No children with COVID-19 were recorded in this cohort, except for US HCDM, 2.4% (n=309). The proportion of female patients ranged from 40.9% [n=453] in Serbia-UCCS to 47.8% in the US-HCDM [n=6,121] and Spain-IMASIS [n=54].

The most prevalent comorbidities were hypertension (range: 49.0% [n=542] in Serbia-UCCS to 71.8% [n=9,197] in the US-HCDM), CKD (range: 8.4% [n=93] in Serbia-UCCS to 46.0% [n=52] in Spain-IMASIS), and T2DM (range: 17.8% [n=197] in Serbia-UCCS to 46.6% [n=5,964] in US-HCDM).

The proportion of COVID-19 patients who had COVID-19 symptoms recorded ranges from 6.2% [n=7] in Spain-IMASIS to 37.0% [n=4,739] in USHCDM. With regards to COVID-19 symptoms, the median time from symptoms to COVID-19 diagnosis ranged from 0 days in Spain-IMASIS to 6.0 days in the US-HCDM and Serbia-UCCS.

Most frequently occurring symptoms in hospitalised prevalent cohort of COVID-19 patients comprised of dyspnoea (ranging from 6.2% [n=69] in Serbia-UCCS to 21.9% [n=2,802] in USHCDM, fever (ranging from 8.3% [n=1,058] in US-HCDM to 18.0% [n=199]) in Serbia-UCCS), and cough (ranging from 0.0% [n=0] in Spain-IMASIS to 4.8% [n=616] in USHCDM).

At diagnosis, the proportion of patients receiving any other COVID-19 treatment except glucocorticoids varied from 14.5% [n=161] in Serbia-UCCS to 32.7% [n=37] in Spain-IMASIS, while the proportion of patients receiving no treatment ranged from 67.3% [n=76] in Spain-IMASIS to 85.5% [n=946] in Serbia-UCCS.

Table 7 Patient demographics and baseline characteristics for hospital prevalent cohort

	France-APHM		Serbia-UCCS		Spain-IMASIS		US-HCDM	
	N	%	N	%	N	%	N	%
Patients with COVID-19	**35**	**100.0%**	**1107**	**100.0%**	**113**	**100.0%**	**12806**	**100.0%**
Age (years) - continuous								
Mean (SD)	59.5 (23.5)		64.5 (15.0)		69.4 (16.1)		60.9 (17.8)	
Median (Q1-Q3)	68.0 (58.5-74.0)		67.0 (56.0-75.0)		74.0 (59.0-81.0)		64.0 (51.0-74.0)	
Min-Max	1.00 - 84.00		5.00 - 98.00		5.00 - 102.00		0.00 - 85.00	
N	35	100.0%	1107	100.0%	113	100.0%	12806	100.0%
Missing	0	0.0%	0	0.0%	0	0.0%	0	0.0%
Age (years) - categorical								
<18	*	*	NR	NR	NR	NR	309	2.4%
18-64	11	31.4%	479	43.3%	38	33.6%	6247	48.8%
65-74	14	40.0%	344	31.1%	21	18.6%	3115	24.3%
75+	*	*	284	25.7%	54	47.8%	3135	24.5%
Sex								
Female	14	40.0%	453	40.9%	54	47.8%	6121	47.8%
Male	21	60.0%	654	59.1%	59	52.2%	6671	52.1%
Comorbidities								
Hypertension	11	31.4%	542	49.0%	72	63.7%	9197	71.8%
Type-2 diabetes mellitus	0	0.0%	197	17.8%	37	32.7%	5964	46.6%
Chronic obstructive pulmonary disease	0	0.0%	118	10.7%	40	35.4%	2890	22.6%
Asthma	0	0.0%	69	6.2%	11	9.7%	1801	14.1%
Chronic kidney disease	*	*	93	8.4%	52	46.0%	5661	44.2%
Stroke	0	0.0%	112	10.1%	42	37.2%	3949	30.8%
Arrythmia	0	0.0%	152	13.7%	42	37.2%	4041	31.6%
Venous thromboembolism	0	0.0%	64	5.8%	6	5.3%	1014	7.9%
Obesity	0	0.0%	27	2.4%	17	15.0%	4487	35.0%
Current smoker	0	0.0%	0	0.0%	0	0.0%	0	0.0%
Alcohol or drug abuse	0	0.0%	*	*	18	15.9%	1954	15.3%
Autoimmune conditions	0	0.0%	135	12.2%	22	19.5%	1266	9.9%
Organ transplant	0	0.0%	15	1.4%	10	8.9%	442	3.5%
Cancer	0	0.0%	226	20.4%	31	27.4%	1751	13.7%
Dementia	0	0.0%	18	1.6%	9	8.0%	1257	9.8%

	France-APHM		Serbia-UCCS		Spain-IMASIS		US-HCDM	
	N	%	N	%	N	%	N	%
Patients with COVID-19	**35**	**100.0%**	**1107**	**100.0%**	**113**	**100.0%**	**12806**	**100.0%**
Major psychiatric disorder	*	*	21	1.9%	16	14.2%	2500	19.5%
Symptoms								
Fever episodes	0	0.0%	199	18.0%	*	*	1058	8.3%
Cough	*	*	11	1.0%	0	0.0%	616	4.8%
Myalgia	0	0.0%	0	0.0%	*	*	55	0.4%
Malaise or fatigue	0	0.0%	*	*	*	*	682	5.3%
Dyspnoea	0	0.0%	69	6.2%	*	*	2802	21.9%
Anosmia, hyposmia and dysgeusia episodes	0	0.0%	0	0.0%	0	0.0%	64	0.5%
Number of symptoms								
0	*	*	861	77.8%	106	93.8%	8067	63.0%
1	*	*	211	19.1%	7	6.2%	4314	33.7%
2	0	0.0%	*	*	0	0.0%	330	2.6%
3	0	0.0%	*	*	0	0.0%	78	0.6%
4	0	0.0%	0	0.0%	0	0.0%	*	*
5	0	0.0%	0	0.0%	0	0.0%	*	*
Time from symptoms to diagnosis (days)								
Total	35	100.0%	1107	100.0%	113	100.0%	12806	100.0%
Mean (SD)	0.50 (0.71)		5.67 (3.96)		2.00 (5.29)		6.74 (3.99)	
Median (Q1-Q3)	0.50 (0.25-0.75)		6.00 (3.00-8.00)		0 (0.00-0.00)		6.00 (4.00-10.00)	
Min-Max	0.00 - 10.00		0.00 - 14.00		0.00 - 14.00		0.00 - 14.00	
N	*	*	246	22.2%	7	6.2%	4739	37.0%
Missing	33	94.3%	861	77.8%	106	93.8%	8067	63.0%
Treatment received at diagnosis								
Glucocorticoid only	0	0.0%	0	0.0%	0	0.0%	0	0.0%
Other COVID-19 treatments only[a]	*	*	161	14.5%	37	32.7%	3257	25.4%
Glucocorticoid and other COVID-19 treatments	0	0.0%	0	0.0%	0	0.0%	0	0.0%
No specific COVID-19 treatments	*	*	946	85.5%	76	67.3%	9549	74.6%
Switched to different treatment before end of current treatment [b]	13	37.1%	882	79.7%	61	54.0%	8944	69.8%

* and **- categories with ≤ 5 counts and the next less frequent category were masked

[a] - Other COVID-19 treatments include antiviral therapy, antibiotic therapy, immune-based therapy, antithrombotic therapy, anti-hypertensives, statins, and anti-diabetic drugs

b- This variable quantifies the number of patients censored due to switching
Note: No database reported speciality data

8.3.4 Hospital Naïve Cohort

Six databases contributed information to the hospital naïve cohort: France-APHM, Germany-Academy hospital, the US-HCDM, Spain-IMASIS, Serbia-UCCS, and Spain-Hospitales (Table 8).

Patients in hospital naïve cohort had no prior exposures to glucocorticoids in the 3 to 120 days prior to index (unrelated to COVID-19 diagnosis). Across the countries studied, a total of 94,916 patients met the study inclusion and exclusion criteria. The number of patients identified in different databases were 14,167 in France-APHM, 1,574 in Germany Academy-hospital, 62,168 in the US-HCDM, 4,719 in Spain-IMASIS, 9,745 in Serbia-UCCS, and 2,543 in Spain-Hospitales.

The median (IQR) age was broadly similar across the countries, ranging from 53.0 (35.0-68.0) years in France-APHM to 71.0 (58.0-81.0) years in Spain-Hospitales. Majority of the COVID-19 patients were adults (range: 34.6% [n=545] in the Germany-Academy hospital to 68.0% [n=9,635] in France-APHM). The number of children diagnosed with COVID-19 was less than 4% of the population. A similar gender distribution was observed across the included countries, with slightly higher number of male patients (ranging from 50.0% [n=2,362] in Spain-IMASIS to 59.8% [n=5,828]) in Serbia-UCCS.

The most prevalent comorbidities were: hypertension (ranging from 11.0% [n=1,563] in France-APHM to 48.5% [n=30,156] in US-HCDM), T2DM (ranging from 0.0% [n=0] in France-APHM to 30.2% [n=18,768] in the US-HCDM) and CKD (ranging from 0.7% [n=104] in France-APHM to 25.0% [n=15,541] in the US-HCDM). Furthermore, fever (ranging from 0.0% [n=0] in France-APHM to 12.2% [n=310] in Spain-Hospitales) was the most commonly reported symptom followed by dyspnoea (ranging from 0.0% [n=0] in France-APHM to 14.7% [n=232] in Germany-Academy hospital) and malaise or fatigue (ranging from 0.0% [n=0] in France-APHM to 7.1% [n=112 in Germany-Academy hospital]). Median time from symptoms to diagnosis ranged from 0 days in Spain-IMASIS and France-APHM to 3.0 days in the US-HCDM.

At diagnosis, the number of patients receiving glucocorticoids ranged from 0.2% in France-APHM [n=33], Spain-IMASIS [n=9], and Serbia-UCCS [n=18] to 1.0% [n=588] in the US-HCDM. At diagnosis, the number of patients receiving any other COVID-19 treatment except glucocorticoids ranged from 25.4% [n=3,597] in France-APHM to 70.7% [n=1,799] in Spain-Hospitales. However, at diagnosis, most patients were not receiving any COVID-19 specific treatment.

Table 8 Patient demographics and baseline characteristics for hospital naïve cohort

	France-APHM		Germany-Academic hospital		Serbia-UCCS		Spain-IMASIS		US-HCDM		Spain-Hospitales	
	N	%	N	%	N	%	N	%	N	%	N	%
Patients with COVID-19	**14167**	**100%**	**1574**	**100%**	**9745**	**100%**	**4719**	**100%**	**62168**	**100%**	**2543**	**100%**
Age (years) - continuous												
Mean (SD)	52.2 (20.9)		67.5 (18.6)		61.3 (17.1)		58.68 (20.26)		57.47 (19.70)		68.90 (16.73)	
Median (Q1-Q3)	53.0 (35.0-68.0)		70.0 (58.0-81.0)		63.0 (51.0-72.0)		59.0 (44.0-75.0)		61.0 (46.0-73.0)		71.0 (58.0-81.0)	
Min-Max	0.00 - 104.00		0.00 - 102.00		1.00 - 725.00		1.00 - 101.00		0.00 - 85.00		1.00 - 107.00	
N	14166	100.0%	1574	100.0%	9745	100.0%	4719	100.0%	62168	100.0%	2543	100.0%
Missing	*	*	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%
Age (years) - categorical												
<18	389	2.8%	42	2.7%	7	0.1%	84	1.8%	2124	3.4%	14	0.6%
18-64	9635	68.0%	545	34.6%	5124	52.6%	2700	57.2%	33913	54.6%	933	36.7%
65-74	1820	12.9%	344	21.9%	2640	27.1%	689	14.6%	12677	20.4%	554	21.8%
75+	2322	16.4%	643	40.9%	1974	20.3%	1246	26.4%	13454	21.6%	1042	41.0%
Sex												
Female	7049	49.8%	650	41.3%	3917	40.2%	2358	50.0%	30638	49.3%	1049	41.3%
Male	7117	50.2%	924	58.7%	5828	59.8%	2361	50.0%	31472	50.6%	1494	58.8%
Comorbidities												
Hypertension	1563	11.0%	299	19.0%	2466	25.3%	1322	28.0%	30156	48.5%	1139	44.8%
Type-2 diabetes mellitus	0	0.0%	177	11.3%	962	9.9%	614	13.0%	18768	30.2%	428	16.8%
Chronic obstructive pulmonary disease	0	0.0%	40	2.5%	215	2.2%	233	4.9%	5251	8.5%	181	7.1%
Asthma	*	*	18	1.1%	251	2.6%	179	3.8%	4433	7.1%	120	4.7%
Chronic kidney disease	104	0.7%	147	9.3%	441	4.5%	565	12.0%	15541	25.0%	323	12.7%
Stroke	0	0.0%	159	10.1%	526	5.4%	319	6.8%	10097	16.2%	138	5.4%
Arrythmia	0	0.0%	136	8.6%	601	6.2%	469	9.9%	10039	16.2%	401	15.8%
Venous thromboembolism	0	0.0%	64	4.1%	179	1.8%	100	2.1%	2055	3.3%	151	5.9%
Obesity	*	*	40	2.5%	140	1.4%	282	6.0%	11379	18.3%	149	5.9%
Current smoker	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%
Alcohol or drug abuse	0	0.0%	22	1.4%	*	*	394	8.4%	6340	10.2%	119	4.7%
Autoimmune conditions	19	0.1%	66	4.2%	508	5.2%	164	3.5%	3016	4.9%	121	4.8%

	France-APHM		Germany-Academic hospital		Serbia-UCCS		Spain-IMASIS		US-HCDM		Spain-Hospitales	
	N	%	N	%	N	%	N	%	N	%	N	%
Patients with COVID-19	**14167**	**100%**	**1574**	**100%**	**9745**	**100%**	**4719**	**100%**	**62168**	**100%**	**2543**	**100%**
Organ transplant	0	0.0%	38	2.4%	14	0.1%	40	0.9%	460	0.7%	*	*
Cancer	78	0.6%	151	9.6%	464	4.8%	517	11.0%	4950	8.0%	286	11.3%
Dementia	83	0.6%	72	4.6%	90	0.9%	125	2.7%	5695	9.2%	108	4.3%
Major psychiatric disorder	19	0.1%	23	1.5%	83	0.9%	228	4.8%	8330	13.4%	128	5.0%
Symptoms												
Fever episodes	0	0.0%	78	5.0%	940	9.7%	117	2.5%	5397	8.7%	310	12.2%
Cough	1073	7.6%	6	0.4%	78	0.8%	95	2.0%	3873	6.2%	6	0.2%
Myalgia	0	0.0%	0	0.0%	*	*	27	0.6%	576	0.9%	*	*
Malaise or fatigue	0	0.0%	112	7.1%	47	0.5%	61	1.3%	2595	4.2%	17	0.7%
Dyspnoea	0	0.0%	232	14.7%	312	3.2%	43	0.9%	7627	12.3%	8	0.3%
Anosmia, hyposmia and dysgeusia episodes	0	0.0%			*	*	108	2.3%	239	0.4%	*	*
Number of symptoms												
0	13094	92.4%	1148	72.9%	8515	87.4%	4389	93.0%	45456	73.1%	2201	86.6%
1	1073	7.6%	*	*	1090	11.2%	234	5.0%	14146	22.8%	*	*
2	0	0.0%	*	*	129	1.3%	76	1.6%	1762	2.8%	*	*
3	0	0.0%	0	0.0%	11	0.1%	16	0.3%	603	1.0%	0	0.0%
4	0	0.0%	0	0.0%	0	0.0%	*	*	178	0.3%	0	0.0%
5	0	0.0%	0	0.0%	0	0.0%	*	*	*	*	0	0.0%
6	0	0.0%	0	0.0%	0	0.0%	0	0.0%	*	*	0	0.0%
Time from symptoms to diagnosis (days)												
Mean (SD)	0.54 (1.42)		1.49 (2.37)		2.56 (3.25)		0.47 (1.96)		3.78 (3.83)		0.00 (0.00)	
Median (Q1 - Q3)	0 (0.0-1.0)		1.0 (0.0-2.0)		1.0 (0.0-4.0)		0.0 (0.0-0.0)		3.0 (0.0-6.0)		0.00 (0.0-0.0)	
Min-Max	0.00 - 14.00		0.00 - 14.00		0.00 - 14.00		0.00 - 14.00		0.00 - 14.00		0.00 - 5.00	
N	1073	7.6%	426	27.1%	1230	12.6%	330	7.0%	16712	26.9%	342	13.5%
Missing	13094	92.4%	1148	72.9%	8515	87.4%	4389	93.0%	45456	73.1%	2201	86.6%
Treatment received at diagnosis												
Glucocorticoid only	33	0.2%	13	0.8%	18	0.2%	9	0.2%	588	1.0%	*	*
Other COVID-19 treatments only[a]	3597	25.4%	608	38.6%	2497	25.6%	1462	31.0%	28981	46.6%	1799	70.7%

	France-APHM		Germany-Academic hospital		Serbia-UCCS		Spain-IMASIS		US-HCDM		Spain-Hospitales	
	N	%	N	%	N	%	N	%	N	%	N	%
Patients with COVID-19	**14167**	**100%**	**1574**	**100%**	**9745**	**100%**	**4719**	**100%**	**62168**	**100%**	**2543**	**100%**
Glucocorticoid and other COVID-19 treatments	59	0.4%	549	34.9%	3193	32.8%	654	13.9%	17729	28.5%	701	27.6%
No specific COVID-19 treatments	10478	74.0%	404	25.7%	4037	41.4%	2594	55.0%	14870	23.9%	*	*
Specialty												
GP	NR	NR	NR	NR	*	*	NR	NR	45	0.1%	NR	NR
Not set	NR	NR	NR	NR	3897	40.0%	NR	NR	12	0.0%	NR	NR
Specialist	298	2.1%	709	45.0%	*	*	1140	24.2%	22319	35.9%	1094	43.0%
Switched to different treatment before end of current treatment [b]	233	1.6%	463	29.4%	1427	14.6%	821	17.4%	10495	16.9%	807	31.7%

* and **- categories with ≤ 5 counts and the next less frequent category were masked

[a] - Other COVID-19 treatments include antiviral therapy, antibiotic therapy, immune-based therapy, antithrombotic therapy, anti-hypertensives, statins, and anti-diabetic drugs

b- This variable quantifies the number of patients censored due to switching

Abbreviations : NR, not reported

8.4 Incidence of study adverse events of interest

This is analysis focuses on investigating a preselected list of AEs that were considered clinically relevant at the time of protocol writing, see Section 8.6.3. Not all AEs occurring during treatment are captured.

For each of the adverse events, crude incidence rate and incidence proportion over the entire time period and post treatment index date were calculated by cohort, overall and in each treatment group. Please note that these are dynamic cohorts for which the follow-up is variable. The results were stratified by medical history of that specific AEs (yes/no). The other two stratifications mentioned in the protocol, by comorbidity and by starting dose of glucocorticoid are presented in the Supplementary material.

The adjusted events rates are not presented in the report as in many cases the model did not converge due to small numbers. The adjusted rates can be found in the Electronic Supplementary material.

8.4.1 Overall overview of AEs

Infection (composite) was reported in 12 out of 13 both ambulatory and hospital setting, ranging from 0.93% (n=132) in France APHM to 79.86 (n=1257) in Germany- Academic Hospital.

Viral infection was reported in 12 out of 13 databases both ambulatory and hospital setting, ranging from 0.68% (n=132) in France APHM to 78.8 (n=1241) in Germany- Academic Hospital.

LRTI was reported in 12 out of 13 databases, both ambulatory and hospital setting, ranging from 0.21%(n=30) in France APHM to 59.1 (n=5761) in Serbia -Clinerion and Heliant.

Hypertension was reported in 12 out of 13 databases, both ambulatory and hospital setting, ranging from 2.12 (n=21) in Netherlands IPCI to 28.5%(n=448) in Germany- Academic Hospital.

Arrhythmia was reported 12 out of 13 databases, both ambulatory and hospital setting, ranging from 0.15%(n=526) in Spain-SIDIAP to 24.8 (n=28) in Spain-IMASIS.

Cardiovascular events were reported in 11 out of 13 databases, both ambulatory and hospital setting, ranging from 0.1%(n=36) in IMRD UK to 12.8 (n=202) in Germany- Academic Hospital

Bacterial infection was reported 12 out of 13 databases, ranging from 0.1%(n=38) in IMRD UK to 15.6% (n=245) in Germany- Academic Hospital.

Fungal infection was reported 12 out of 13 databases, both ambulatory and hospital setting, ranging from 0.1% (n=6) in Serbia -Clinerion and Heliant to 2.2% (n=35) in Germany- Academic Hospital.

Sepsis was reported in 8 out of 13 databases, both ambulatory and hospital setting, ranging from 0.01%(n=52) in Spain SIDIAP to 7.1 (n=111) in Germany- Academic Hospital.

Gastritis was reported in four was reported 8 out of 13 databases, ranging from 0.02%(n=62) in Spain SIDIAP to 1.3 (n=20) in Germany- Academic Hospital.

Psychosis was reported in 6 out of 13 databases, ranging from 0.02%(n=54) in Spain SIDIAP to 1.5 (n=953) in US–HCDM.

Myopathy was reported in 6 out of 13 databases, ranging from 0.2%(n=98) in US–HCDM to 0.4 (n=6) in Germany-Hospital.

Hyperglycaemia was reported in 8 out of 13 databases, ranging from 0.03% (n=11) in IMRD UK to 0.4 (n=6) 6.3 (n=3882) in Germany-Hospital.

Parasitic infection, was reported in 9 out of 13 databases, ranging from 0.03% (n=110) in Spain SIDIAP to 0.1 (n=27) in Germany DA

Herpes was reported in 7 out of 13 databases, ranging from 0.03% (n=93) in Spain SIDIAP to 0.3 (n=13) in Italy LPD.

Cutaneous cellulitis was reported in 7 out of 13 databases, being masked in all of them except from Germany DA 0.1% (n=16).

Spain-Hospitales did not capture any event except arrhythmia.

8.4.2 Ambulatory prevalent cohort

From all the AEs studied the following were reported in at least one database for any of the treatment group: infection, viral infection, LRTI, hypertension, arrhythmia, cardiovascular events, bacterial infection, fungal infection, sepsis and gastritis.

The following AEs were not reported (or all values were masked) in any of the ambulatory prevalent cohorts: psychosis, myopathy, hyperglycaemia, parasitic infection, herpes and cutaneous cellulitis.

Crude incidence proportions at 30 days

Infection (composite) was reported in six databases, ranging from 2.6% to 68.9% in the other COVID-19 treatment group and from 7.2% to 69.4% in no specific COVID-19 treatment group. (see Figure 8).

Viral infection was reported in six databases, ranging from 27.5% (n=91) to 68.9% (n=31) in the other COVID-19 treatment group and from 6.9% (n=81)to 69.4% (n=100) in no specific COVID-19 treatment group.

LRTI was reported in six databases, ranging from 4.8% (n=7) to 22.2% (n=10) in the other COVID-19 treatment group and from 1.8% (n=21) to 16.7% (n=24) in no specific COVID-19 treatment group.

Hypertension was reported in five databases, ranging from 0% to 4.2% (n=24) in the other COVID-19 treatment group and from 2.2% (n=20) to 9.7% (n=14) in no specific COVID-19 treatment group.

Arrhythmia was reported in six databases, ranging from masked values in the other COVID-19 treatment group and from 0.5% (n=19) to masked values in no specific COVID-19 treatment group.

Cardiovascular events were reported in five databases, ranging from 0% to 0.3% (n=7) in the other COVID-19 treatment group and from 0.9% (n=42) to 1.23% (n=11) in no specific COVID-19 treatment group.

Fungal infection was reported in six databases, ranging from 0% to masked values in the other COVID-19 treatment group and from masked values to 0.9% (n=9) in no specific COVID-19 treatment group.

Sepsis was reported in four databases, ranging from 0% to masked values in the other COVID-19 treatment group and 0% to masked values in no specific COVID-19 treatment group.

Bacterial infection was reported in six databases ranging from 0% to masked value in the other COVID-19 treatment group and 0% to masked values in no specific COVID-19 treatment group.

Gastritis was reported in four databases ranging from 0% to masked values in the other COVID-19 treatment group and 0% in no specific COVID-19 treatment group.

When data were stratified by past medical history, the incidence of AEs became very low in those without prior medical history, suggestive of medical history as an effect modifier (see Figure 6).

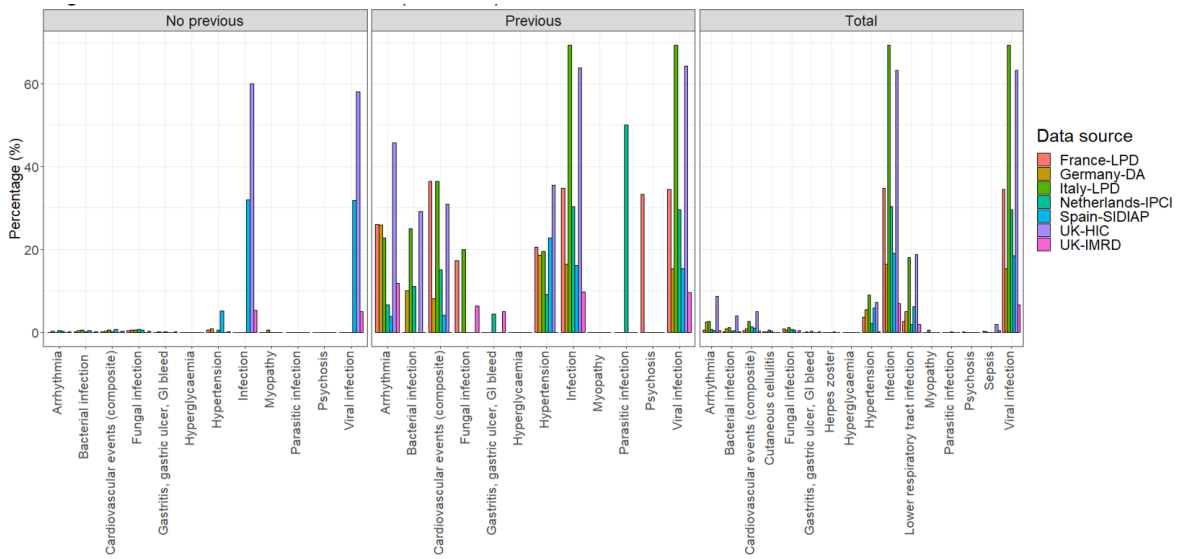


Figure 6 Proportion experiencing adverse event by 30 days in the ambulatory prevalent cohort

Crude incidence proportions at 90 days

The same pattern is observed at 90 days as for 30 days, just the proportions were slightly higher. *(see* Figure 7*)*

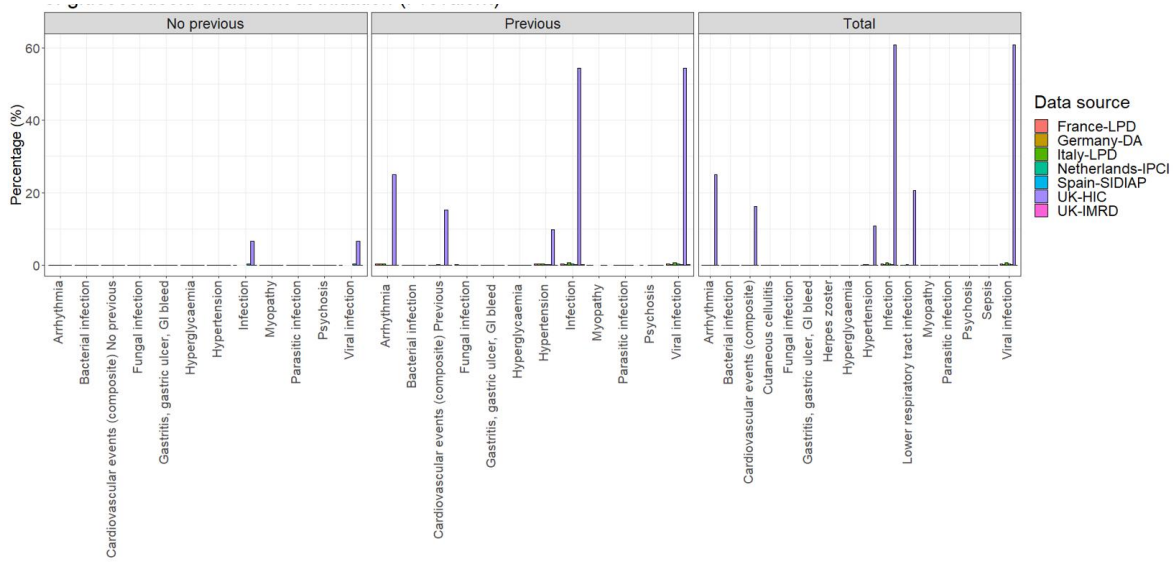


Figure 7 Proportion experiencing adverse event by 90 days in the ambulatory prevalent cohort

Crude incidence rates at 30 days

Infection (composite) ranged from 31.9 to 213 per 1,000 patient-days in the other COVID-19 treatment group and from 4.1 to 104.7 per 1,000 patient-days in no specific COVID-19 treatment group.

Viral infection ranged from 31.3 to 213.8 per 1,000 patient-days in the other COVID-19 treatment group and from 3.9 to 104.7 per 1,000 patient-days in no specific COVID-19 treatment group.

LRTI ranged from 6.9 to 26.3 per 1,000 patient-days in the other COVID-19 treatment group and from 0.7 to 7.7 per 1,000 patient-days in no specific COVID-19 treatment group.

Hypertension ranged from 0 to 3.6 per 1,000 patient-days in the other COVID-19 treatment group and 1.1 to 4.1 per 1,000 patient-days in no specific COVID-19 treatment group.

Arrhythmia ranged from 0 per 1,000 patient-days in the other COVID-19 treatment group and from 0.2 to 0.9 per 1,000 patient-days in no specific COVID-19 treatment group.

Cardiovascular ranged from 0 to masked values per 1,000 patient-days in the other COVID-19 treatment group and 0.4 to 0.6 per 1,000 patient-days in no specific COVID-19 treatment group.

Fungal infection ranged from 0 to masked values per 1,000 patient-days in the other COVID-19 treatment group and 0.2 to 0.5 per 1,000 patient-days in no specific COVID-19 treatment group.

Sepsis was 0 to masked values per 1,000 patient-days in both the other COVID-19 treatment group and in no specific COVID-19 treatment group. (see Figure 8)

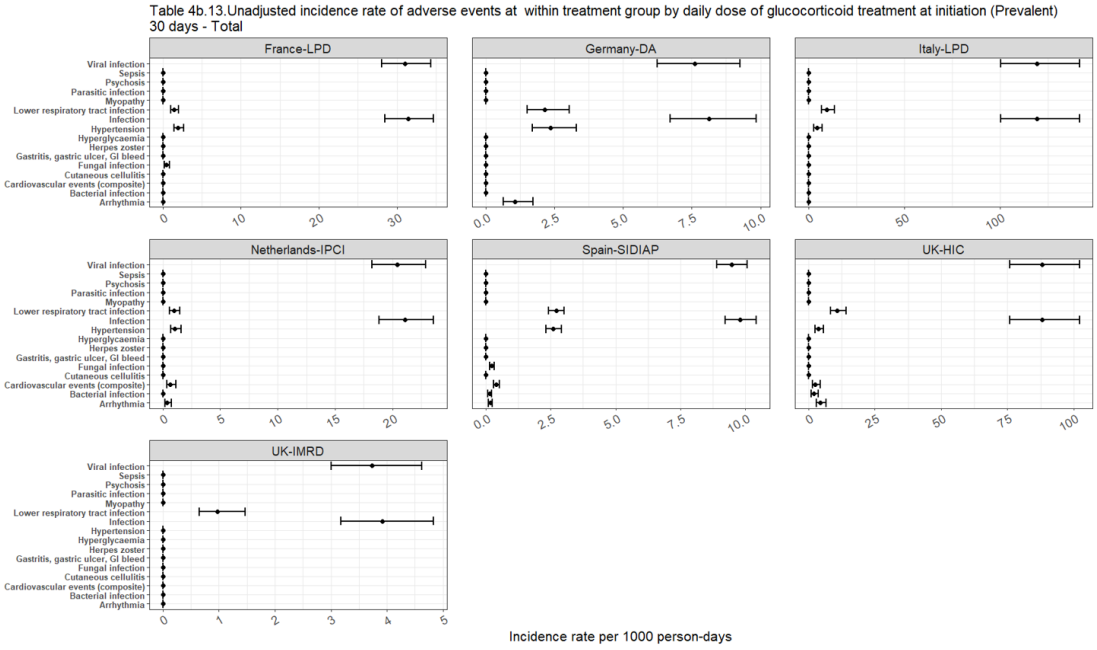


Figure 8 Crude incidence rates of AEs at 30 days in the Ambulatory prevalent cohort

Crude incidence rates at 90 days

Infection (composite) ranged from 14.1 to 151.2 per 1,000 patient-days in the other COVID-19 treatment group and from 2.3 to 46.9 per 1,000 patient-days in no specific COVID-19 treatment group.

Viral infection ranged from 14.1 to 151.2 per 1,000 patient-days in the other COVID-19 treatment group and from 2.1 to 46.9 per 1,000 patient-days in no specific COVID-19 treatment group.

LRTI ranged from 4.3 to 17.8 per 1,000 patient-days in the other COVID-19 treatment group and from 0.4 to 4.1 per 1,000 patient-days in no specific COVID-19 treatment group.

Hypertension ranged from 0 to 2.1 per 1,000 patient-days in the other COVID-19 treatment group and 0 to 2.2 per 1,000 patient-days in no specific COVID-19 treatment group.

Arrhythmia ranged from 0 per 1,000 patient-days in the COVID-19 treatment group and from 0.1 to 0.9 per 1,000 patient-days in no specific COVID-19 treatment group.

Cardiovascular events ranged from 0 per 1,000 patient-days in the other COVID-19 treatment group and 0.2 to 0.7 per 1,000 patient-days in no specific COVID-19 treatment group.

Fungal infection ranged from 0 per 1,000 patient-days in the other COVID-19 treatment group and 0.2 to 0.3 per 1,000 patient-days in no specific COVID-19 treatment group.

Sepsis ranged from 0 to masked values per 1,000 patient-days in the other COVID-19 treatment group and 0 to 0.1 per 1,000 patient-days in no specific COVID-19 treatment group.

Notably the rate was lowest/highest 30 days after starting treatment suggesting most /fewer cases occurred immediately after starting treatment.

Time to onset of adverse events

Over the period of interest, it was not possible to estimate the median and IQR of time to event for most of the reported AEs. The ones which reached the median time to event or at least the 25th percentile were:

- Hypertension in Italy LPD with a median time to event of 39 days in the Other COVID-19 treatments only.
- Infection (composite) and viral infection in Italy LPD with a median of 0 days in both treatment groups.

See Electronic Supplementary Material for the KM plots for each event.

Meta-analysis of adverse events in ambulatory prevalent cohort

Please note the following rules were applied when meta-analysing results.

- Several databases report no or only a small number of events in the treatment groups. Only events that are reported in at least one database are introduced in the meta-analysis.
- Most treatment groups/outcome combinations show high levels of heterogeneity between studies. Meta-analysis was not conducted for adverse events with high heterogeneity (I2>40%).
- When low events were masked, they were assigned the value of 1 event, in order to be included in the meta-analysis
- The cumulative hazard is estimated from the Cox-proportional hazards model and requires a minimum of ten events per variable included. It is recommended that in survival analysis at least 10-20% of the cohort be event-free and uncensored at the end of the follow-up period for robust inference. (29,30) Given the low number of events, there were few outcome treatment group combinations where the cumulative hazard could be estimated and pooled across databases; therefore, we have instead pooled the crude incidence rates at 30 days.

In ambulatory prevalent cohort meta-analysis was performed only for AEs reported in at least one database: cardiovascular events, arrythmia, gastritis, psychosis, myopathy, hyperglycaemia, bacterial infection, fungal infection, parasitic infection, sepsis, herpes, and cutaneous cellulitis. Meta-analysis was not conducted for adverse events with high heterogeneity (I^2>40%).

The meta-analysis showed a pooled incidence rate of 1.05 per 1,000 patient-days for cardiovascular events in other COVID-19 treatments group and 0.26 per 1,000 patient-days for arrythmia in other COVID-19 treatments group. The pooled incidence rates of gastritis in other COVID-19 treatments group and no specific COVID-19 treatment group were 0.30 and 0.03 per 1,000 patient-days, respectively. The pooled incidence rates of bacterial infection in other COVID-19 treatments group and no specific COVID-19 treatment group were 0.15 and 0.12 per 1,000 patient-days, respectively. The pooled incidence rate of sepsis in other COVID-19 treatments group and no specific COVID-19 treatment group were 0.15 and 0.12 per 1,000 patient-days, respectively. The data for other COVID-19 treatments group showed no adverse events of psychosis, myopathy, hyperglycaemia, parasitic infection, herpes, and cutaneous cellulitis.

The forest plots for the meta-analysis are presented in the Electronic Supplementary material.

Table 9 shows the pooled incidence rate of adverse events in COVID-19 patients for ambulatory prevalent cohort. The forest plots for the meta-analysis are presented in the Electronic Supplementary material.

Table 9 Pooled incidence rates of adverse events in ambulatory prevalent cohort

	Other COVID treatments Only					No COVID related treatments				
	Databases					Databases				
Outcome	**N**	**0 AE**	**<5 AE**	**>5 AE**	**Pooled IR (95% CI) (per 1,000 person-days)**	**N**	**0 AE**	**<5 AE**	**>5 AE**	**Pooled IR (95% CI) (per 1,000 person-days)**
Cardiovascular events	6	2	4	1	1.05 (95% CI 0.57-1.93)	6	0	4	2	NA*
Hypertension	6	1	4	1	NA*	6	0	1	5	NA*
Arrythmia	6	2	4	0	0.26 (95% CI 0.09-0.69)	6	0	4	2	NA*
Gastritis	6	5	1	0	0.3 (95% CI 0.06-1.47)	6	2	4	0	0.03 (95% CI 0.01-0.09)
Psychosis	6	6	0	0	NR^	6	4	2	0	0.02 (95% CI 0.00-0.06)
Myopathy	6	6	0	0	NR^	6	4	2	0	0.02 (95% CI 0.00-0.16)
Hyperglycaemia	6	6	0	0	NR^	6	5	1	0	0.01 (95% CI 0.00-0.04)
Infection composite	6	0	2	4	NA*	6	0	0	6	NA*
Bacterial infection	6	5	1	0	0.15 (95% CI 0.03-0.72)	6	0	4	1	0.12 (95% CI 0.08-0.19)
Viral infection	6	0	2	4	NA*	6	0	0	6	NA*
Fungal infection	6	4	2	0	0.43 (95% CI 0.12-1.51)	6	0	4	2	NA*
Parasitic infection	6	6	0	0	NR^	6	4	2	0	0.02 (95% CI 0.01-0.06)
Sepsis	6	5	1	0	0.39 (95% CI 0.08-1.93)	6	2	4	0	0.03 (95% CI 0.01-0.08)
LRTI	6	0	3	3	NA*	6	0	0	6	NA*
Herpes	6	6	0	0	NR^	6	5	1	0	0.01 (95% CI 0.00-0.04)
Cutaneous cellulitis	6	6	0	0	NR^	6	4	2	0	0.07 (95% CI 0.03-0.19)

*No pooled result I-squared > 40%
^No database reported an event
Note: Due to lengthy ethical procedures, the HIC data was received late and therefore could not be included in the meta-analysis
Abbreviations: AE, adverse events; IR, incidence rate; LRTI, lower respiratory tract infection; NA, not applicable; NR, not reported

8.4.3 Ambulatory naive cohort

From all the AEs studied the following were reported in at least one database for any of the treatment group: infection, viral infection, LRTI, hypertension, arrhythmia, cardiovascular events, bacterial infection, fungal infection and sepsis.

The following AEs were reported only in the no specific COVID-19 treatments group: gastritis, psychosis, parasitic infection, herpes, and cutaneous cellulitis.

The following AEs were not reported in any of the ambulatory naïve cohorts treatment arms: myopathy.

Incidence proportions at 30 days

Infection was reported in six databases, ranging from 10.1% to 33.1% for glucocorticoid only group, 6.4% to 69.9% for other COVID-19 treatments only, 20.1% to 57.3% for glucocorticoid and other COVID treatments and 3.5 to 61.5% for no specific COVID-19 treatments group.

Viral infection was reported in six databases, ranging from 10.1% to 33.3% for glucocorticoid only group, 6.1 to 69.7% for other COVID-19 treatments only, 19.4 to 57.3% for glucocorticoid and other COVID treatments and 3.3% to 61.4% for no specific COVID-19 treatments group.

LRTI was reported in six databases, ranging from 0% to 7.5% in for glucocorticoid only group, 4.1% to 18.7% for other COVID-19 treatments only, 0% to 28.1% for glucocorticoid and other COVID treatments and 0% to 28.1% for no specific COVID-19 treatments group.

Hypertension was reported in six databases, ranging from 0% for glucocorticoid only group, 2.4% to 9.1% for other COVID-19 treatments only, 0% for glucocorticoid and other COVID treatments and 0.1% to 8.9% for no specific COVID-19 treatments group.

Arrhythmia was reported in six databases, ranging from 0% for glucocorticoid only group, 0.3 to 3.7% for other COVID-19 treatments only, 0% for glucocorticoid and other COVID treatments and 0.2% to 2.1% for no specific COVID-19 treatments group.

Cardiovascular events were reported in five databases, ranging from 0% for glucocorticoid only group, 0.5% to 1.3% for other COVID-19 treatments only, 0% for glucocorticoid and other COVID treatments and 0.2% to 0.8% for no specific COVID-19 treatments group.

Fungal infection was reported in six databases, ranging from 0% for glucocorticoid only group, 0.3 to 0.5% for other COVID-19 treatments only, 0% for glucocorticoid and other COVID treatments and 0.1% to 0.6% for no specific COVID-19 treatments group.

Bacterial infection was reported in six databases, ranging from 0% to masked values for glucocorticoid only group, 0.2% to 0.8% for other COVID-19 treatments only, 0% to masked values for glucocorticoid and other COVID treatments and 0.2% to 0.5% for no specific COVID-19 treatments group.

The following AEs were reported only in no specific COVID-19 treatments group: gastritis (range:0 to 0.2%), herpes zoster (range: from 0 to masked values), cutaneous cellulitis (range: from 0 to masked values), parasitic infection (range: from 0 to masked values) and psychosis (range: from 0 to masked values). (see Figure 9).

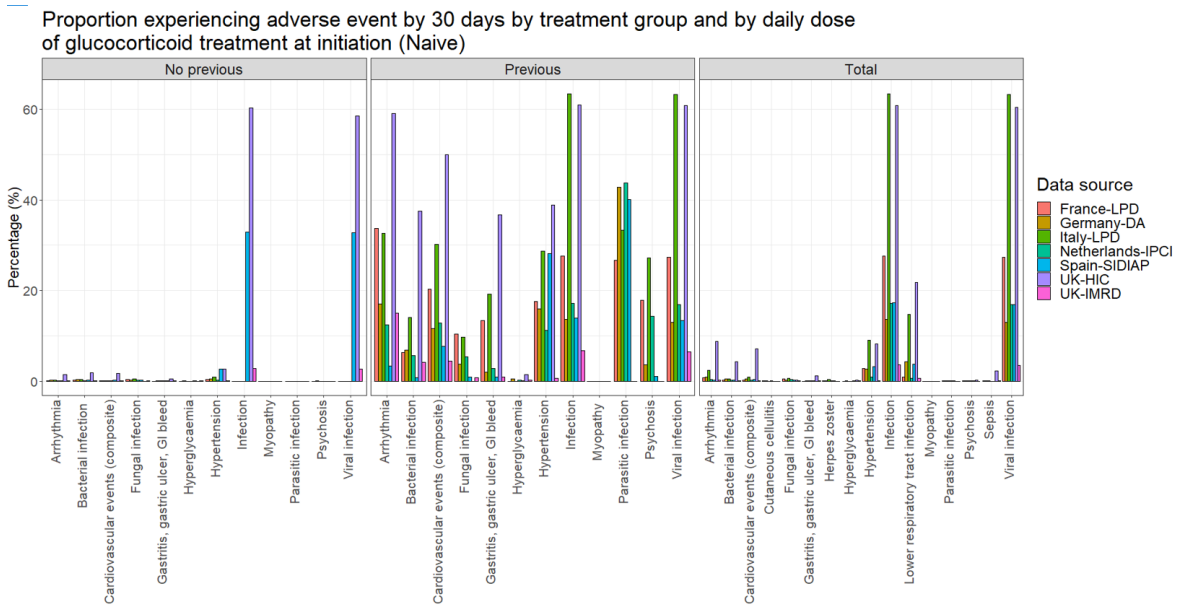


Figure 9 Proportion experiencing adverse event by 30 days in the Ambulatory Naïve cohort

When data were stratified by past medical history, the incidence of AEs became very low in those without prior medical history, suggestive of medical history as an effect modifier (see Figure 6). The frequency of AEs was much higher in patients that had that event in medical history.

Incidence proportions at 90 days

The same pattern is observed at 90 days as for 30 days, just the proportions were slightly higher. *(see* Figure 10*)*

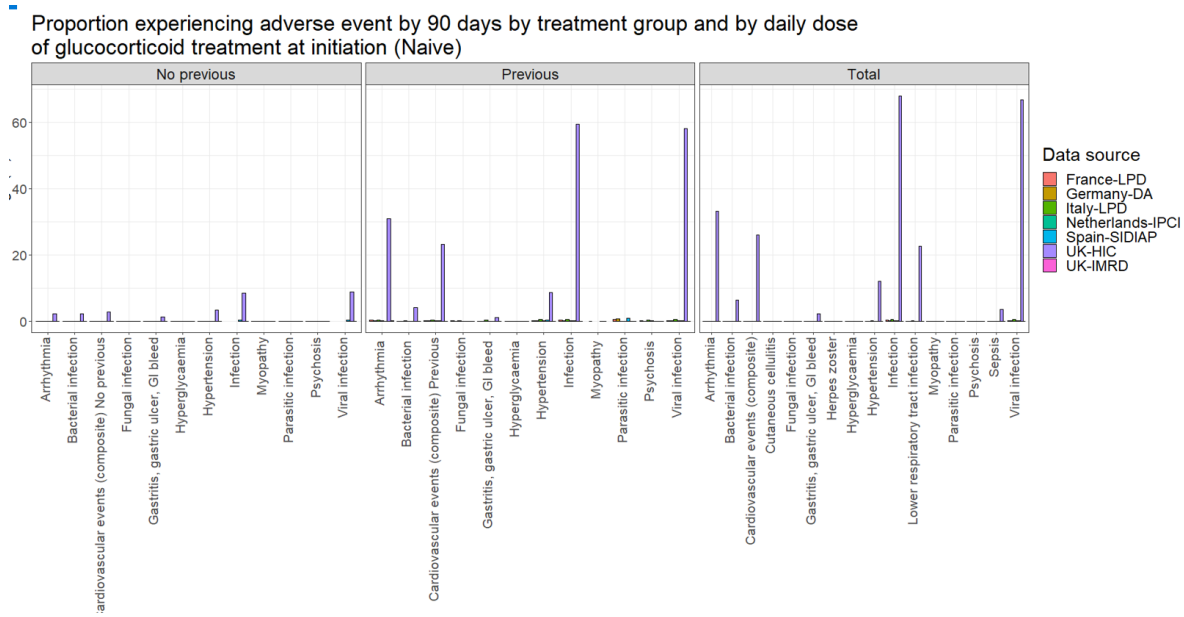


Figure 10 Proportion experiencing adverse event by 90 days in the Ambulatory Naïve cohort

Crude Incidence rates at 30 days

Infection ranged from 6.9 to 43.3 per 1,000 patient-days for glucocorticoid only group, 3.5 to 214.3 per 1,000 patient-days for other COVID-19 treatments only, 38.9 to 585.4 per 1,000 patient-days for glucocorticoid and other COVID treatments and 1.5 to 90.6 per 1,000 patient-days for no specific COVID-19 treatments group.

Viral infection ranged from 6.9 to 43.3 per 1,000 patient-days for glucocorticoid only group, 3.2 to 210.1 per 1,000 patient-days for other COVID-19 treatments only, 20.3 to 585.4 per 1,000 patient-days for glucocorticoid and other COVID treatments and 7.5 to 90.4 per 1,000 patient-days for no specific COVID-19 treatments group.

LRTI ranged from 0 to 2.7 per 1,000 patient-days for glucocorticoid only group, 1.1 to 20.2 per 1,000 patient-days for other COVID-19 treatments only, 0 to 41.7 per 1,000 patient-days for glucocorticoid and other COVID treatments and 0.2 to 6.5 per 1,000 patient-days for no specific COVID-19 treatments group.

Hypertension ranged from 0 per 1,000 patient-days for glucocorticoid only group, 1.3 to 9.3 per 1,000 patient-days for other COVID-19 treatments only, 0 per 1,000 patient-days for glucocorticoid and other COVID treatments and 0 to 4.1 per 1,000 patient-days for no specific COVID-19 treatments group.

Arrhythmia ranged from 0 per 1,000 patient-days for glucocorticoid only group, 0.2 to 3.5 per 1,000 patient-days for other COVID-19 treatments only, 0 per 1,000 patient-days for glucocorticoid and other COVID treatments and 0.1 to 0.9 per 1,000 patient-days for no specific COVID-19 treatments group.

Cardiovascular ranged from 0 per 1,000 patient-days for glucocorticoid only group, 0.3 to 1.2 per 1,000 patient-days for other COVID-19 treatments only, 0 per 1,000 patient-days for glucocorticoid and other COVID treatments and 0 to 0.4 per 1,000 patient-days for no specific COVID-19 treatments group.

Fungal infection ranged from 0 per 1,000 patient-days for glucocorticoid only group, 0.1 to 0.3 per 1,000 patient-days for other COVID-19 treatments only, 0 per 1,000 patient-days for glucocorticoid and other COVID treatments and 0 to 0.3 per 1,000 patient-days for no specific COVID-19 treatments group.

Bacterial infection ranged from 0 per 1,000 patient-days for glucocorticoid only group, 0.2 to 0.6 per 1,000 patient-days for other COVID-19 treatments only, 0 per 1,000 patient-days for glucocorticoid and other COVID treatments and 0 to 0.2 per 1,000 patient-days for no specific COVID-19 treatments group.

Herpes zoster, gastritis, cutaneous cellulitis, parasitic infection and psychosis were reported only in no specific COVID-19 treatments group, with a rate of less than 0.1 per 1,000 patient-days.

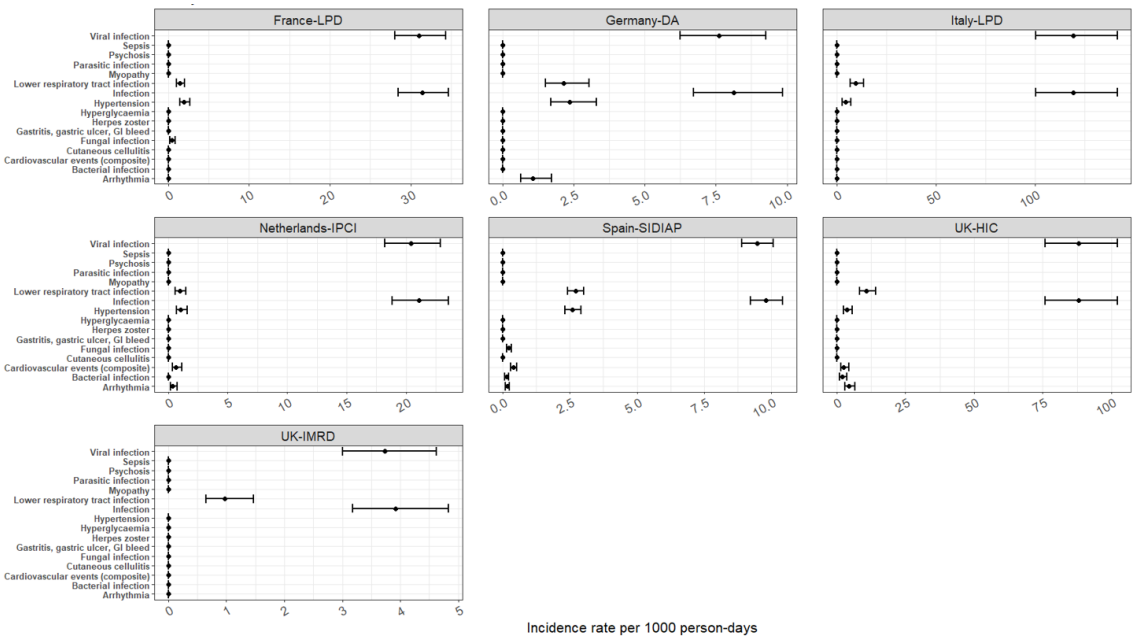


Figure 11 Crude incidence rates of AEs at 30 days in the Ambulatory Naïve cohort

Crude Incidence rates at 90 days

Infection ranged from 6.9 to 38.3 per 1,000 patient-days for glucocorticoid only group, 3.5 to 121.3 per 1,000 patient-days for other COVID-19 treatments only, 21.5 to 585.4 per 1,000 patient-days for glucocorticoid and other COVID treatments and 0.8 to 37.2 per 1,000 patient-days for no specific COVID-19 treatments group.

Viral infection ranged from 6.9 to 38.3 per 1,000 patient-days for glucocorticoid only group, 1.8 to 117.1 per 1,000 patient-days for other COVID-19 treatments only, 20.3 to 585.4 per 1,000 patient-days for glucocorticoid and other COVID treatments and 0.76 to 36.9 per 1,000 patient-days for no specific COVID-19 treatments group.

LRTI ranged from 0 to 2.7 per 1,000 patient-days for glucocorticoid only group, 0.5 to 12.7 per 1,000 patient-days for other COVID-19 treatments only, 0 to 41.7 per 1,000 patient-days for glucocorticoid and other COVID treatments and 0.2 to 3.2 per 1,000 patient-days for no specific COVID-19 treatments group.

Hypertension ranged from 0 per 1,000 patient-days for glucocorticoid only group, 0.7 to 7.8 per 1,000 patient-days for other COVID-19 treatments only, 0 per 1,000 patient-days for glucocorticoid and other COVID treatments and 0 to 1.3 per 1,000 patient-days for no specific COVID-19 treatments group.

Arrhythmia ranged from 0 per 1,000 patient-days for glucocorticoid only group, 0.2 to 2.3 per 1,000 patient-days for other COVID-19 treatments only, 0 per 1,000 patient-days for glucocorticoid and other COVID treatments and 0.1 to 0.6 per 1,000 patient-days for no specific COVID-19 treatments group.

Cardiovascular ranged from 0 per 1,000 patient-days for glucocorticoid only group, 0.3 to 1.2 per 1,000 patient-days for other COVID-19 treatments only, 0 per 1,000 patient-days for glucocorticoid and other COVID treatments and 0 to 0.4 per 1,000 patient-days for no specific COVID-19 treatments group.

Fungal infection ranged from 0 per 1,000 patient-days for glucocorticoid only group, 0.1 to 0.3 per 1,000 patient-days for other COVID-19 treatments only, 0 per 1,000 patient-days for glucocorticoid and other COVID treatments and 0 to 0.3 per 1,000 patient-days for no specific COVID-19 treatments group.

Bacterial infection ranged from 0 per 1,000 patient-days for glucocorticoid only group, 0.2 to 0.6 per 1,000 patient-days for other COVID-19 treatments only, 0 per 1,000 patient-days for glucocorticoid and other COVID treatments and 0 to 0.2 per 1,000 patient-days for no specific COVID-19 treatments group.

Herpes zoster, gastritis, cutaneous cellulitis, parasitic infection and psychosis were reported only in no specific COVID-19 treatments group, with a rate of less than 0.1 per 1,000 patient-days.

Notably the rate was lowest/highest 30 days after starting treatment suggesting most /fewer cases occurred immediately after starting treatment.

Time to onset of adverse events

Over the period of interest, the frequency of events was lower than 25% therefore it was not possible to estimate the median and IQR of time to event for most of the reported AEs. The ones which reached the median time to event or at least the 25th percentile were infection (composite) and viral infection in LPD Italy in the glucocorticoid only group which had a median time to event of 34 days, while in the other treatment groups is 0 days.

Additionally, the length of follow-up is short in some treatment groups where in several cases there are very few or no individuals continuing follow-up after 30 days, as illustrated in the table below:

Database	Median cumulative duration of glucocorticoids to 90 days
DA Germany	20 days
LPD France	4 days
LPD Italy	25 days
UK IMRD	7 days
Spain - SIDIAP	8 days
Netherlands - IPCI	7 days

See Electronic Supplementary Material for the KM plots for each event.

Meta-analysis

In ambulatory naïve cohort meta-analysis was performed only for AEs reported in at least one database: cardiovascular events, hypertension, arrythmia, gastritis, psychosis, myopathy, hyperglycaemia, bacterial infection, fungal infection, parasitic infection, sepsis, herpes, and cutaneous cellulitis. Meta-analysis was not conducted for adverse events with high heterogeneity (I^2>40%).

The pooled incidence rates of hypertension in glucocorticoid only treatment and glucocorticoids and other COVID-19 treatments were 1.50 and 3.76 per 1,000 patient-days, respectively. The pooled incidence rates of cardiovascular events in glucocorticoid only treatment and glucocorticoids and other COVID-19 treatments were 0.08 and 0.85 per 1,000 patient-days, respectively.

The pooled incidence rate of hyperglycaemia ranged from 0.05 per 1,000 patient-days in other COVID-19 treatment only to 0.20 per 1,000 patient-days in glucocorticoid and other COVID-19 treatments. The pooled incidence rate of fungal infections varied from 0.08 per 1,000 patient-days in glucocorticoids only to 0.75 per 1,000 patient-days in glucocorticoid and other COVID-19 treatments.

The meta-analysis showed a pooled incidence rate of 0.08 per 1,000 patient-days for cardiovascular events, bacterial infection, fungal infection, and sepsis in glucocorticoids only group.

Table **10** shows the pooled incidence of adverse events in ambulatory naïve COVID-19 patients. The forest plots for the meta-analysis are presented in the Electronic Supplementary material.

Table 10 Pooled incidence rates of adverse events in ambulatory naïve cohort

	Glucocorticoid Only					Other COVID treatments Only					Glucocorticoid and other COVID treatments					No COVID related treatments				
	Databases					Databases					Databases					Databases				
Outcome	**N**	**0 AE**	**<5 AE**	**>5 AE**	**Pooled IR (95% CI) (per 1,000 person-days)**	**N**	**0 AE**	**<5 AE**	**>5 AE**	**Pooled IR (95% CI) (per 1,000 person-days)**	**N**	**0 AE**	**<5 AE**	**>5 AE**	**Pooled IR (95% CI) (per 1,000 person-days)**	**N**	**0 AE**	**<5 AE**	**>5 AE**	**Pooled IR (95% CI) (per 1,000 person-days)**
Cardiovascular events	6	5	1	0	0.08 (95% CI 0.02-0.39)	6	0	1	5	NA*	6	3	3	0	0.85 (95% CI 0.26-2.83)	6	0	0	6	NA*
Hypertension	6	2	3	1	1.50 (95% CI 1.01-2.24)	6	0	1	5	NA*	6	3	2	1	3.76 (95% CI 2.55-5.55)	6	0	0	6	NA*
Arrythmia	6	3	3	0	0.25 (95% CI 0.09-0.74)	6	0	0	6	NA*	6	1	5	0	NA*	6	0	0	6	NA*
Gastritis	6	6	0	0	NR^	6	1	5	0	0.02 (95% CI 0.01-0.04)	6	6	0	0	NA*	6	0	2	4	NA*
Psychosis	6	6	0	0	NR^	6	2	4	0	0.01 (95% CI 0.00-0.05)	6	6	0	0	NA*	6	0	3	3	NA*
Myopathy	6	6	0	0	NR^	6	6	0	0	0.00 (95% CI 0.00-0.04)	6	6	0	0	NA*	6	3	3	0	0.00 (95% CI 0.00-0.00)
Hyperglycaemia	6	4	2	0	0.15 (95% CI 0.04-0.52)	6	4	1	1	0.05 (95% CI 0.03-0.09)	6	5	1	0	0.2 (95% CI 0.04-0.98)	6	2	1	3	NA*
Infection Composite	6	0	1	5	NA*	6	0	0	6	NA*	6	0	1	5	NA*	6	0	0	6	NA*
Bacterial infection	6	5	1	0	0.08 (95% CI 0.02-0.39)	6	0	2	4	NA*	6	2	4	0	0.86 (95% CI 0.33-2.25)	6	0	0	6	NA*
Viral infection	6	0	1	5	NA*	6	0	0	6	NA*	6	0	1	5	NA*	6	0	0	6	NA*
Fungal infection	6	5	1	0	0.08 (95% CI 0.02-0.39)	6	0	3	3	0.18 (95% CI 0.12-0.28)	6	5	1	0	0.75 (95% CI 0.15-3.73)	6	0	0	6	NA*
Parasitic infection	6	6	0	0	NR^	6	4	2	0	0.03 (95% CI 0.01-0.11)	6	5	1	0	0.2 (95% CI 0.04-0.98)	6	1	2	3	NA*
Sepsis	6	5	1	0	0.08 (95% CI 0.02-0.39)	6	2	3	1	0.03 (95% CI 0.01-0.06)	6	6	0	0	NR^	6	0	4	2	NA*
LRTI	6	1	2	3	NA*	6	0	0	6	NA*	6	1	1	4	NA*	6	0	0	6	NA*
Herpes	6	6	0	0	NR^	6	1	5	0	0.02 (95% CI 0.01-0.05)	6	6	0	0	NR^	6	0	2	4	NA*

	Glucocorticoid Only					Other COVID treatments Only					Glucocorticoid and other COVID treatments					No COVID related treatments				
	Databases					Databases					Databases					Databases				
Outcome	**N**	**0 AE**	**<5 AE**	**>5 AE**	**Pooled IR (95% CI) (per 1,000 person-days)**	**N**	**0 AE**	**<5 AE**	**>5 AE**	**Pooled IR (95% CI) (per 1,000 person-days)**	**N**	**0 AE**	**<5 AE**	**>5 AE**	**Pooled IR (95% CI) (per 1,000 person-days)**	**N**	**0 AE**	**<5 AE**	**>5 AE**	**Pooled IR (95% CI) (per 1,000 person-days)**
Cutaneous cellulitis	6	6	0	0	NR^	6	5	1	0	0.00 (95% CI 0.00-0.02)	6	5	1	0	0.59 (95% CI 0.12-2.94)	6	1	3	2	NA*

*No pooled result I-squared > 40%
^No database report an event
Note: Due to lengthy ethical procedures, the HIC data was received late and therefore could not be included in the meta-analysis
Abbreviations: AE, adverse events; IR, incidence rate; LRTI, lower respiratory tract infection; NA, not applicable; NR, not reported

8.4.4 Hospital prevalent cohort

From all the AEs studied the following were reported in at least one hospitalized prevalent cohort for any of the treatment group: infection, viral infection, LRTI, hypertension, arrhythmia, cardiovascular events, bacterial infection, fungal infection and sepsis, gastritis, psychosis, myopathy, hyperglycaemia.

The following AEs were not reported in any of the hospital prevalent cohorts: parasitic infection, herpes and cutaneous cellulitis.

Incidence proportions at 30 days

Infection was reported in databases, ranging from 21.1% to 45.9% in the other COVID-19 treatment group and from 9.9% to 21.1% in no specific COVID-19 treatment group.

Viral infection was reported in databases, ranging from 18.9 to 45.3 % in the other COVID-19 treatment group and from 7.4 to 18.4% in no specific COVID-19 treatment group.

Hypertension was reported in four databases, ranging from 18% to 27% in the other COVID-19 treatment group and from 1.4% to 25% in no specific COVID-19 treatment group.

LRTI was reported in databases, ranging from 10.7% to 24.8% in the other COVID-19 treatment group and from 1.7% to 11.8% in no specific COVID-19 treatment group.

Arrhythmia was reported in databases, ranging from 9.9% to 24.4% in the other COVID-19 treatment group and from 0.7% to 27.6% in no specific COVID-19 treatment group.

Cardiovascular events were reported in databases, ranging from 5.6% to 10.8% in the other COVID-19 treatment group and from 0.9% to 7.9% in no specific COVID-19 treatment group.

Bacterial infection was reported in three databases ranging from 3.3% to 5.4% in the other COVID-19 treatment group and from 0.5% to 3.9% in no specific COVID-19 treatment group.

Sepsis was reported in three databases, ranging from 0.6% to 3.9% in the other COVID-19 treatment group and 0.5% in no specific COVID-19 treatment group.

Hyperglycaemia was reported in two databases, being 2.8% in the other COVID-19 treatment group and 0.4% in no specific COVID-19 treatment group.

Psychosis was reported in two databases, being 1.1% in the other COVID-19 treatment group and 0.2% in no specific COVID-19 treatment group.

Myopathy was reported in US Hospital database only, being 0.9% in the other COVID-19 treatment group and masked in the no specific COVID-19 treatment group.

Fungal infection was reported in three databases, ranging from 0.7% to 1.2% in the other COVID-19 treatment group and from 0.1% to 1.3% in no specific COVID-19 treatment group.

Gastritis was reported in two databases, being 0.3% in the other COVID-19 treatment group and 0.1% in no specific COVID-19 treatment group.

When data were stratified by past medical history, the incidence of AEs became very low in those without prior medical history, suggestive of medical history as an effect modifier (see Figure 12). The frequency of AEs was much higher in patients that had that event in medical history.

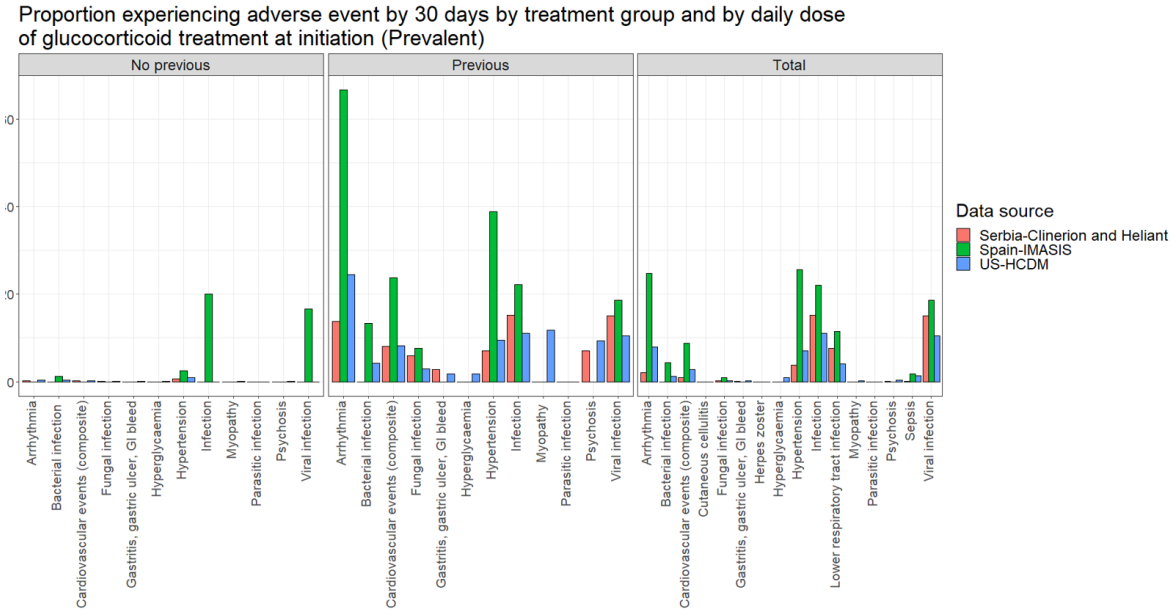


Figure 12 Proportion experiencing adverse event by 30 days in the Hospitalized Prevalent Cohort

Incidence proportions at 90 days

The same pattern is observed at 90 days as for 30 days, just the proportions are slightly higher. (see Figure 13*)*

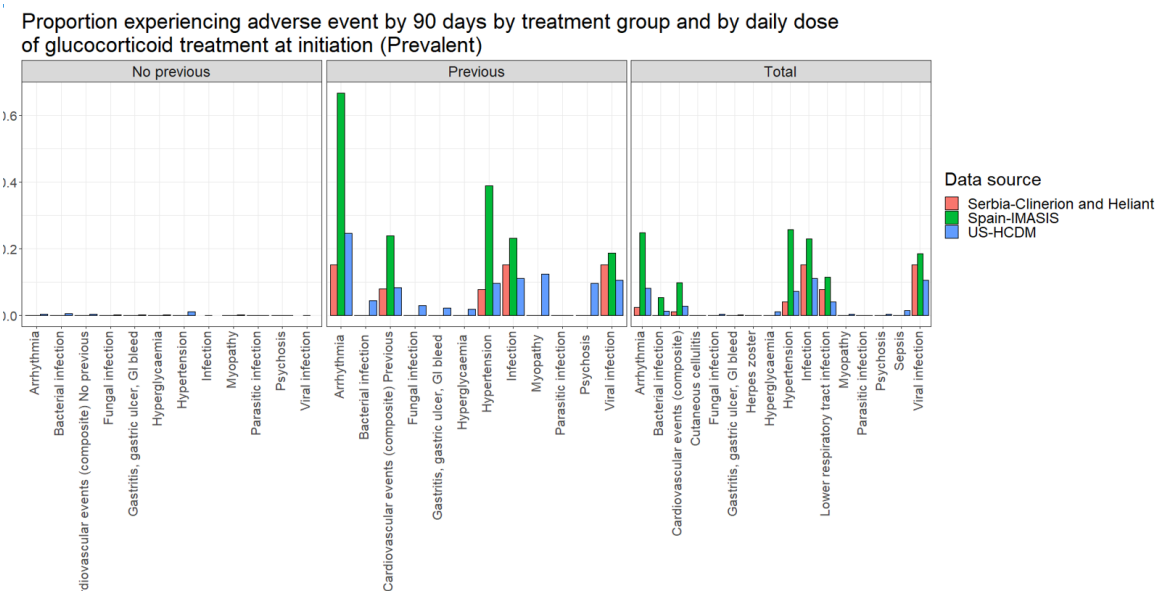


Figure 13 Proportion experiencing adverse event by 90 days in the Hospitalized Prevalent Cohort

Crude Incidence rates at 30 days

Hypertension ranged from 37.4 to 177.6 per 1,000 patient-days for other COVID-19 treatments only and 0.6 to 71.0 per 1000 patient days for the no specific COVID-19 treatments group.

Infection ranged from 30.8 to 1947.4 per 1,000 patient-days for other COVID-19 treatments only and 36.6 to 160.1 per 1000 patient days for the no specific COVID-19 treatments group.

Viral infection ranged from 270.1 to 1921.1 per 1,000 patient-days for other COVID-19 treatments only and 30.0 to 144.1 per 1000 patient days for the no specific COVID-19 treatments group.

Arrhythmia ranged from 25.1 to 162.8 per 1,000 patient-days for other COVID-19 treatments only and 2.6 to 48.6 per 1000 patient days for the no specific COVID-19 treatments group.

LRTI ranged from 75.4 to 136.9 per 1,000 patient-days for other COVID-19 treatments only and 14.5 to 20.9 per 1000 patient days for the no specific COVID-19 treatments group.

Cardiovascular events ranged from 20.1 to 53.7 per 1,000 patient-days for other COVID-19 treatments only and 9.6 per 1000 patient days for the no specific COVID-19 treatments group.

Bacterial infection ranged from 19.0 per 1,000 patient-days for other COVID-19 treatments only and 5.1 per 1000 patient days for the no specific COVID-19 treatments group.

Sepsis ranged from 23.9 per 1,000 patient-days for other COVID-19 treatments only and 5.8 per 1000 patient days for the no specific COVID-19 treatments group.

Hyperglycaemia ranged from 15.8 per 1,000 patient-days for other COVID-19 treatments only and 3.7 per 1000 patient days for the no specific COVID-19 treatments group.

Psychosis ranged from 5.9 per 1,000 patient-days for other COVID-19 treatments only and 2.1 per 1000 patient days for the no specific COVID-19 treatments group.

Fungal infection ranged from 4.0 per 1,000 patient-days for other COVID-19 treatments only and 0.8 per 1000 patient days for the no specific COVID-19 treatments group.

Gastritis ranged from 1.3 per 1,000 patient-days for other COVID-19 treatments only and 1.4 per 1000 patient days for the no specific COVID-19 treatments group.

Myopathy was reported for other COVID-19 treatments only with a value of 5.4 per 1,000 patient-days.

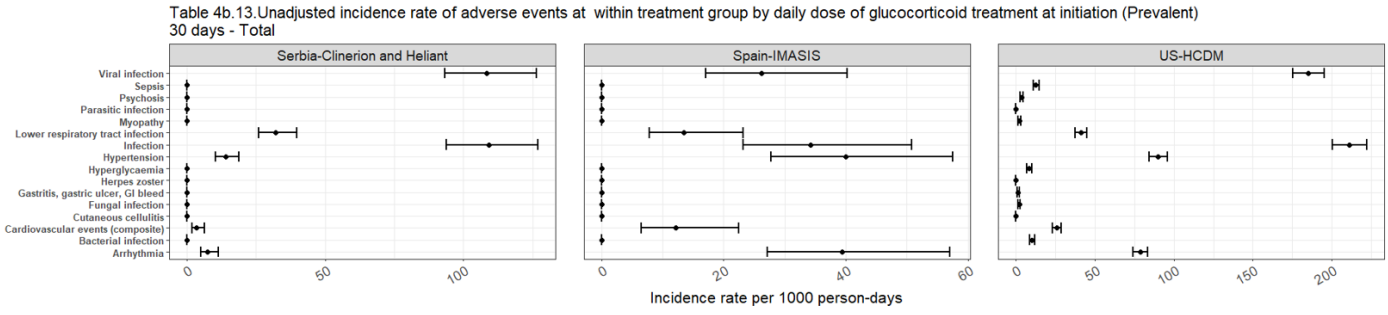


Figure 14 Crude incidence rates of AEs at 30 days in the Hospitalized prevalent cohort

Crude Incidence rates at 90 days

Hypertension ranged from 24.6 to 109.5 per 1,000 patient-days for other COVID-19 treatments only and 2.8 to 22.3 per 1000 patient days for the no specific COVID-19 treatments group.

Infection ranged from 20.7 to 1947.4 per 1,000 patient-days for other COVID-19 treatments only and 20.2 to 76.9 per 1000 patient days for the no specific COVID-19 treatments group.

Viral infection ranged from 14.3 to 1921.1 per 1,000 patient-days for other COVID-19 treatments only and 15.6 to 67.8 per 1000 patient days for the no specific COVID-19 treatments group.

Arrhythmia ranged from 17.4 to 109.0 per 1,000 patient-days for other COVID-19 treatments only and 1.6 to 25.5 per 1000 patient days for the no specific COVID-19 treatments group.

LRTI ranged from 50.1 to 136.9 per 1,000 patient-days for other COVID-19 treatments only and 7.9 to 11.4 per 1000 patient days for the no specific COVID-19 treatments group.

Cardiovascular events ranged from 20.1 to 36.3 per 1,000 patient-days for other COVID-19 treatments only and 5.3 to 7.1 per 1000 patient days for the no specific COVID-19 treatments group.

Bacterial infection ranged from 13.8 per 1,000 patient-days for other COVID-19 treatments only and 3.1 per 1000 patient days for the no specific COVID-19 treatments group.

Sepsis ranged from 16.9 per 1,000 patient-days for other COVID-19 treatments only and 3.4 per 1000 patient days for the no specific COVID-19 treatments group.

Hyperglycaemia ranged from 11.1 per 1,000 patient-days for other COVID-19 treatments only and 2.1 per 1000 patient days for the no specific COVID-19 treatments group.

Psychosis ranged from 4.2 per 1,000 patient-days for other COVID-19 treatments only and 1.1 per 1000 patient days for the no specific COVID-19 treatments group.

Myopathy was reported as 3.9 per 1,000 patient-days for other COVID-19 treatments only.

Fungal infection ranged from 3.4 per 1,000 patient-days for other COVID-19 treatments only and 0.5 per 1000 patient days for the no specific COVID-19 treatments group.

Gastritis ranged from 0.9 per 1,000 patient-days for other COVID-19 treatments only and 0.9 per 1000 patient days for the no specific COVID-19 treatments group.

Notably the rate was lowest/highest 30 days after starting treatment suggesting most /fewer cases occurred immediately after starting treatment.

Time to onset of adverse events

Over the period of interest, the frequency of events was lower than 25% , therefore it was not possible to estimate the median and IQR of time to event for most of the reported AEs. The ones which reached the median time to event or at least the 25th percentile were:

- Infection (composite) and viral infection in LPD Italy in the glucocorticoid only group had a median time to event of 34 days, while in the other treatment groups is 0 days.
- Hypertension had a median time to event between 13 and 18 days in Other COVID-19 treatments only
- LRTI had a median time to event between 12 and 34 days in Other COVID-19 treatments only

See Electronic Supplementary Material for the KM plots for each event.

Meta-analysis

In hospitalised prevalent cohort meta-analysis was performed only for AEs reported in at least one database: gastritis, psychosis, myopathy, hyperglycaemia, bacterial infection, fungal infection, LRTI, and cutaneous cellulitis. Meta-analysis was not conducted for adverse events with high heterogeneity (I^2>40%).

The meta-analysis showed a pooled incidence rate in no COVID-19 related treatment group and other COVID-19 treatments only group: hyperglycaemia (ranged from 1.23 per 1,000 patient-days in no COVID-19 related treatment group to 6.99 per 1,000 patient-days in other COVID-19 treatments only group), psychosis (ranged from 1.16 per 1,000 patient-days in no COVID-19 related treatment group to 5.84 per 1,000 patient-days in other COVID-19 treatments only group), myopathy (ranged from 0.10 per 1,000 patient-days in no COVID-19 related treatment group to 5.35 per 1,000 patient-days in other COVID-19 treatments only group), fungal infection (ranged from 0.82 per 1,000 patient-days in no COVID-19 related treatment group to 3.87 per 1,000 patient-days in other COVID-19 treatments only group), and gastritis (ranged from 1.22 per 1,000 patient-days in no COVID-19 related treatment group to 1.28 per 1,000 patient-days in other COVID-19 treatments only group).

The meta-analysis showed a pooled incidence rate of 0.40 per 1,000 patient-days for cutaneous cellulitis in no COVID-19 related treatment group. However, no database reported event of cutaneous cellulitis in other COVID-19 treatment only group. The meta-analysis showed a pooled incidence rate of 19.84 per 1,000 patient-days for LRTI in no COVID-19 related treatment group. However, no database reported event of LRTI in other COVID-19 treatment only group. The meta-analysis showed a pooled incidence rate of 2.98 per 1,000 patient-days for bacterial infection in no COVID-19 related treatment group. However, no database reported event of bacterial infection in other COVID-19 treatment only group. Moreover, no databases reported events of parasitic infection and herpes in other COVID-19 treatments only and no COVID-19 related treatment group.

Meta-analysis was not conducted for cardiovascular events, hypertension, arrythmia, infection composite, viral infection, and sepsis due to high heterogeneity (I^2>40%).

Table 11 shows the pooled incidence rate of adverse events in the hospital prevalent cohort. The forest plots for the meta-analysis are presented in the Supplementary material .

Table 11 Pooled incidence rates of adverse events in hospitalised prevalent cohort

	Other COVID treatments Only					No COVID related treatments				
		Databases					Databases			
Outcome	Total	0 AE	<5 AE	>5 AE	Pooled IR (95% CI) (per 1,000 person-days)	Total	0 AE	<5 AE	>5 AE	Pooled IR (95% CI) (per 1,000 person-days)
Cardiovascular events	4	1	1	2	NA*	4	1	2	1	NA*
Hypertension	4	1	0	3	NA*	4	1	0	3	NA*
Arrythmia	4	1	0	3	NA*	4	1	0	3	NA*
Gastritis	4	3	0	1	1.28 (95% CI 0.65-2.54)	4	2	1	1	1.22 (95% CI 0.72-2.05)
Psychosis	4	3	0	1	5.84 (95% CI 4.20-8.12)	4	2	1	1	1.16 (95% CI 0.37-3.64)
Myopathy	4	3	0	1	5.35 (95% CI 3.79-7.55)	4	3	1	0	0.1 (95% CI 0.02-0.58)
Hyperglycaemia	4	3	0	1	6.99 (95% CI 1.05-46.81)	4	3	0	1	1.23 (95% CI 0.14-10.55)
Infection composite	4	1	0	3	NA*	4	0	1	3	NA*
Bacterial infection	4	2	1	1	NA*	4	1	2	1	2.98 (95% CI 1.11-8.04)
Viral infection	4	1	0	3	NA*	4	1	0	3	NA*
Fungal infection	4	2	1	0	3.87 (95% CI 2.62-5.73)	4	1	2	1	0.82 (95% CI 0.44-1.52)
Parasitic infection	4	4	0	0	NR^	4	4	0	0	NR^
Sepsis	4	2	1	1	NA*	4	2	1	1	NA*
LRTI	4	1	1	2	NA*	4	1	0	3	19.84 (95% CI 16.64-23.66)
Herpes	4	4	0	0	NR^	4	4	0	0	NR^
Cutaneous cellulitis	4	4	0	0	NR^	4	3	1	0	0.40 (95% CI 0.04-4.43)

*No pooled result I-squared > 40%
^No database report an event
Note: Due to lengthy ethical procedures, the HIC data was received late and therefore could not be included in the meta-analysis
Abbreviations: AE, adverse events; IR, incidence rate; LRTI, lower respiratory tract infection; NA, not applicable; NR, not reported; N, number

8.4.5 Hospital naïve cohort

All the AEs studied were reported in at least one database for any of the treatment groups.

Incidence proportions at 30 days

Infection was reported in five databases, ranging from 0% to 83.3% for glucocorticoid only group, 0.5% to 76.6% for other COVID-19 treatments only, 27.6% to 97.2% for glucocorticoid and other COVID treatments and 1.1 to 75.5% for no specific COVID-19 treatments group.

Viral infection was reported in five databases, ranging from 0% to 83.3% for glucocorticoid only group, 0.3% to 75.2% for other COVID-19 treatments only, 25.4% to 94.1% for glucocorticoid and other COVID treatments and 0.8 to 74.0% for no specific COVID-19 treatments group.

LRTI was reported in five databases, ranging from 0% to 76.9% in for glucocorticoid only group, 21.5% to 45.9% for other COVID-19 treatments only, 0 to 85.7% for glucocorticoid and other COVID treatments and 0% to 46.2% for no specific COVID-19 treatments group.

Hypertension was reported in five databases, ranging from 30.1% for glucocorticoid only group, 6.5% to 29.1% for other COVID-19 treatments only, 21.1 to 35.0 for glucocorticoid and other COVID treatments and 6.2% to 30.9% for no specific COVID-19 treatments group.

Arrhythmia was reported in five databases, ranging from 0% to 12.2% for glucocorticoid only group, 11.0% to 15.3% for other COVID-19 treatments only, 0% to 14.6% for glucocorticoid and other COVID treatments and 0% to 17.6% for no specific COVID-19 treatments group.

Cardiovascular events were reported in five databases, ranging from 0% to 5.1% for glucocorticoid only group, 0 to 11.8% for other COVID-19 treatments only, 0% to 12.4% for glucocorticoid and other COVID treatments and 0.2% to 14.8% for no specific COVID-19 treatments group.

Bacterial infection was reported in five databases, ranging from 0% to 4.6% for glucocorticoid only group, 1.8 to 14.8% for other COVID-19 treatments only, 0% to 13.1% for glucocorticoid and other COVID treatments and 0.2% to 20.3% for no specific COVID-19 treatments group.

Sepsis was reported in five databases, ranging from 0% to 5.8% for glucocorticoid only group, 0 to 5.2% for other COVID-19 treatments only, 0% to 8.1% for glucocorticoid and other COVID treatments and 0% to 19.3% for no specific COVID-19 treatments group.

Hyperglycaemia was reported in five databases, ranging from 0% to 8.2% for glucocorticoid only group, 0 to 4.0% for other COVID-19 treatments only, 0% to 10.8% for glucocorticoid and other COVID treatments and 0% to 5.0% for no specific COVID-19 treatments group.

Psychosis was reported in four databases, ranging from 0% to 2.7 for glucocorticoid only group, 0.36 to 1.6% for other COVID-19 treatments only, 0% to 0.9% for glucocorticoid and other COVID treatments and 0.1% to 1.9% for no specific COVID-19 treatments group.

Myopathy was reported only in one database (US Hospital) being 0% for glucocorticoid only group, 0.15 % for other COVID-19 treatments only, 0.12% for glucocorticoid and other COVID treatments and 0.22% for no specific COVID-19 treatments group.

Fungal infection was reported in five databases, ranging from 0% to 1.4% for glucocorticoid only group, 0.4 to 1.3% for other COVID-19 treatments only, 0% to 1.6% for glucocorticoid and other COVID treatments and 0.1% to 3.9% for no specific COVID-19 treatments group.

Gastritis was reported in four databases, ranging from 0% for glucocorticoid only group, 0 to 1.8% for other COVID-19 treatments only, 0% to 0.8% for glucocorticoid and other COVID treatments and 0% to 1.5% for no specific COVID-19 treatments group.

Herpes zoster and parasitic infection were reported only in no specific COVID-19 treatments group, range from 0 to <0.1%.

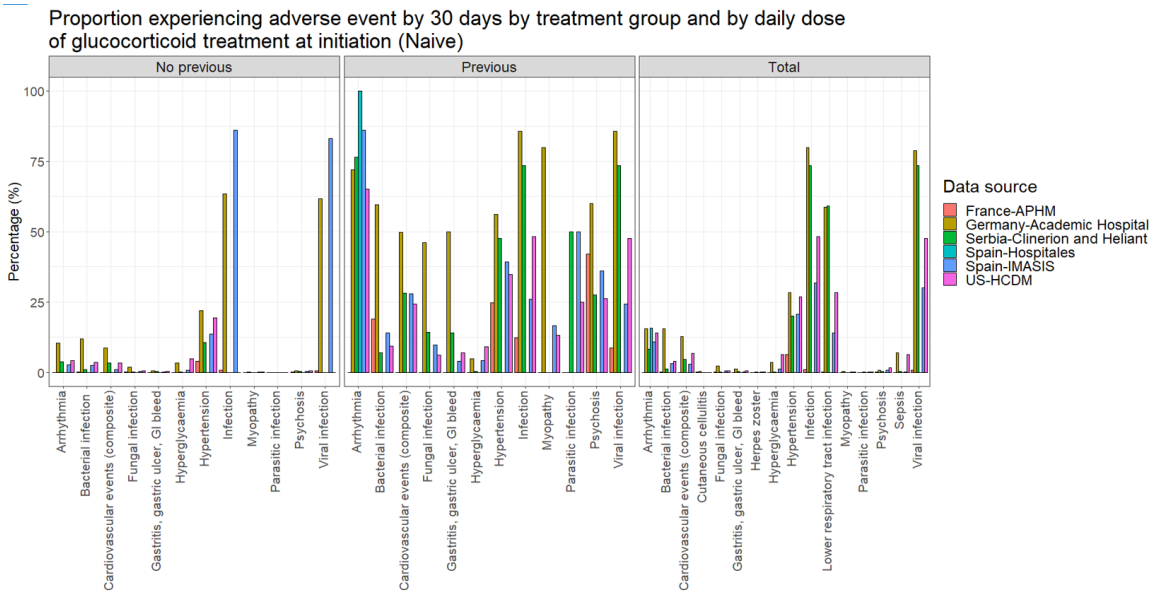


Figure 15 Proportion experiencing adverse event by 30 days in the Hospitalized Naïve Cohort

Incidence proportions at 90 days

The same pattern is observed at 90 days as for 30 days, just the proportions were slightly higher.

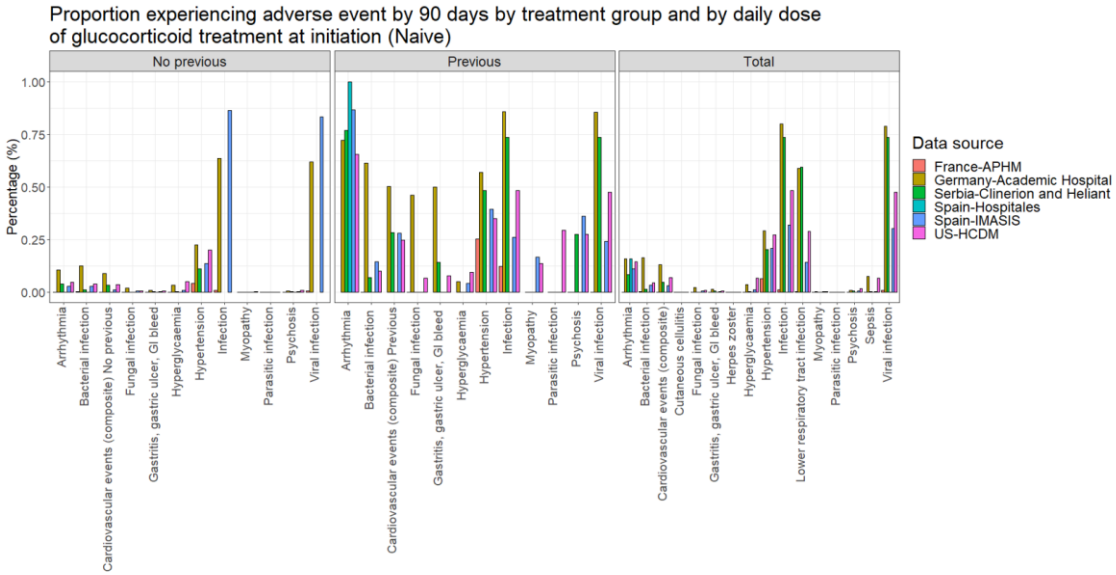


Figure 16 Proportion experiencing adverse event by 90 days in the Hospitalized Naïve Cohort

Crude Incidence rates at 30 days

Infection ranged from 0 to 652.2 for glucocorticoid only group, 2.2 to 1504.9 per 1,000 patient-days for other COVID-19 treatments only, 39.4 to 2277.8 per 1,000 patient-days for glucocorticoid and other COVID treatments and 0.5 to 201.2 per 1,000 patient-days for no specific COVID-19 treatments group.

Viral infection ranged from 0 to 652.2 for glucocorticoid only group, 1.3 to 1473.6 per 1,000 patient-days for other COVID-19 treatments only, 36.0 to 2241.6 per 1,000 patient-days for glucocorticoid and other COVID treatments and 0.3 to 184.5 per 1,000 patient-days for no specific COVID-19 treatments group.

LRTI ranged from 0 to 206.9 per 1,000 patient-days for glucocorticoid only group, 0.8 to 208.2 per 1,000 patient-days for other COVID-19 treatments only, 0 to 323.4 per 1,000 patient-days for glucocorticoid and other COVID treatments and 0.1 to 69.7 per 1,000 patient-days for no specific COVID-19 treatments group.

Hypertension ranged from 68.5 per 1,000 patient-days for glucocorticoid only group, 31.6 to 95.4 per 1,000 patient-days for other COVID-19 treatments only, 26.4 to 65.5 per 1,000 patient-days for glucocorticoid and other COVID treatments and 2.8 to 36.7 per 1,000 patient-days for no specific COVID-19 treatments group.

Arrhythmia ranged from 0 to 20.6 per 1,000 patient-days for glucocorticoid only group, 0 to 49.5 per 1,000 patient-days for other COVID-19 treatments only, 0 to 23.7 per 1,000 patient-days for glucocorticoid and other COVID treatments and 0 to 15.3 per 1,000 patient-days for no specific COVID-19 treatments group.

Cardiovascular events ranged from 0 to 8.4 per 1,000 patient-days for glucocorticoid only group, 0 to 18.2 per 1,000 patient-days for other COVID-19 treatments only, 0 to 18.9 per 1,000 patient-days for glucocorticoid and other COVID treatments and 0 to 12.2 per 1,000 patient-days for no specific COVID-19 treatments group.

Fungal infection ranged from 0 to 2.2 per 1,000 patient-days for glucocorticoid only group, 0.8 to 1.8 per 1,000 patient-days for other COVID-19 treatments only, 0 to 2.3 per 1,000 patient-days for glucocorticoid and other COVID treatments and 0 to 3.1 per 1,000 patient-days for no specific COVID-19 treatments group.

Bacterial infection ranged from 0 to 7.5 per 1,000 patient-days for glucocorticoid only group, 3.8 to 23.7 per 1,000 patient-days for other COVID-19 treatments only, 0 to 20.0 per 1,000 patient-days for glucocorticoid and other COVID treatments and 0.1 to 17.3 per 1,000 patient-days for no specific COVID-19 treatments group.

Gastritis ranged from 0 per 1,000 patient-days for glucocorticoid only group, 0 to 2.5 per 1,000 patient-days for other COVID-19 treatments only, 0 to 0.6 per 1,000 patient-days for glucocorticoid and other COVID treatments and 0 to 0.8 per 1,000 patient-days for no specific COVID-19 treatments group.

Psychosis ranged from 0 to 4.5 per 1,000 patient-days for glucocorticoid only group, 0 to 5.5 per 1,000 patient-days for other COVID-19 treatments only, 0 to 1.6 per 1,000 patient-days for glucocorticoid and other COVID treatments and 0 to 1.8 per 1,000 patient-days for no specific COVID-19 treatments group.

Myopathy ranged from 0 per 1,000 patient-days for glucocorticoid only group, 0 to 0.5 per 1,000 patient-days for other COVID-19 treatments only, 0 to 0.2 per 1,000 patient-days for glucocorticoid and other COVID treatments and 0 to 0.2 per 1,000 patient-days for no specific COVID-19 treatments group

Herpes zoster ranged from 0 per 1,000 patient-days for glucocorticoid only group, 0 to 0.1 per 1,000 patient-days for other COVID-19 treatments only, 0 per 1,000 patient-days for glucocorticoid and other COVID treatments and 0 to 0.1 per 1,000 patient-days for no specific COVID-19 treatments group.

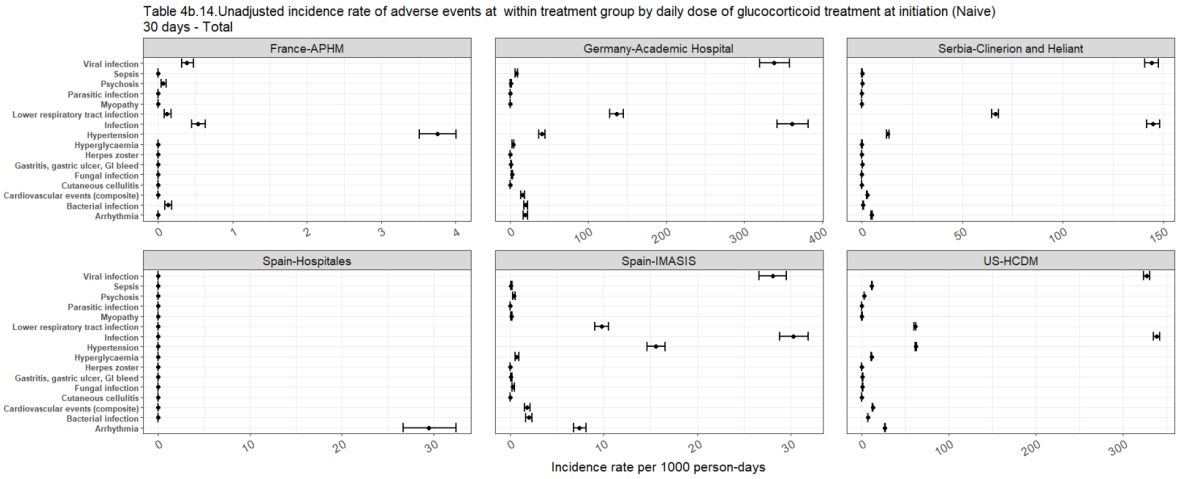


Figure 17 Crude incidence rates of AEs at 30 days in the Hospitalized Naïve cohort

Crude Incidence rates at 90 days

Infection ranged from 0 to 652.2 for glucocorticoid only group, 1.6 to 1142.7 per 1,000 patient-days for other COVID-19 treatments only, 37.7 to 2264.1 per 1,000 patient-days for glucocorticoid and other COVID treatments and 0.2 to 107.8 per 1,000 patient-days for no specific COVID-19 treatments group.

Viral infection ranged from 0 to 652.2 for glucocorticoid only group, 0.9 to 1123.9 per 1,000 patient-days for other COVID-19 treatments only, 34.1 to 2228.3 per 1,000 patient-days for glucocorticoid and other COVID treatments and 0.1 to 94.6 per 1,000 patient-days for no specific COVID-19 treatments group.

LRTI ranged from 0 to 206.9 per 1,000 patient-days for glucocorticoid only group, 0 to 194.7 per 1,000 patient-days for other COVID-19 treatments only, 0 to 323.4 per 1,000 patient-days for glucocorticoid and other COVID treatments and 0 to 38.1 per 1,000 patient-days for no specific COVID-19 treatments group.

Hypertension ranged from 68.5 per 1,000 patient-days for glucocorticoid only group, 21.8 to 67.8 per 1,000 patient-days for other COVID-19 treatments only, 25.2 to 64.8 per 1,000 patient-days for glucocorticoid and other COVID treatments and 1.5 to 22.8 per 1,000 patient-days for no specific COVID-19 treatments group.

Arrhythmia ranged from 0 to 20.7 per 1,000 patient-days for glucocorticoid only group, 0 to 36.2 per 1,000 patient-days for other COVID-19 treatments only, 0 to 23.6 per 1,000 patient-days for glucocorticoid and other COVID treatments and 0 to 9.2 per 1,000 patient-days for no specific COVID-19 treatments group.

Cardiovascular events ranged from 0 to 8.4 per 1,000 patient-days for glucocorticoid only group, 0 to 17.4 per 1,000 patient-days for other COVID-19 treatments only, 0 to 18.9 per 1,000 patient-days for glucocorticoid and other COVID treatments and 0 to 7.5 per 1,000 patient-days for no specific COVID-19 treatments group.

Fungal infection ranged from 0 to 2.2 per 1,000 patient-days for glucocorticoid only group, 0.6 to 1.6 per 1,000 patient-days for other COVID-19 treatments only, 0 to 1.6 per 1,000 patient-days for glucocorticoid and other COVID treatments and 0.1 to 1.8 per 1,000 patient-days for no specific COVID-19 treatments group.

Bacterial infection ranged from 0 to 7.4 per 1,000 patient-days for glucocorticoid only group, 3.8 to 23.7 per 1,000 patient-days for other COVID-19 treatments only, 0 to 19.9 per 1,000 patient-days for glucocorticoid and other COVID treatments and 0.1 to 11.8 per 1,000 patient-days for no specific COVID-19 treatments group.

Gastritis ranged from 0 per 1,000 patient-days for glucocorticoid only group, 0 to 2.5 per 1,000 patient-days for other COVID-19 treatments only, 0 to 0.7 per 1,000 patient-days for glucocorticoid and other COVID treatments and 0 to 0.8 per 1,000 patient-days for no specific COVID-19 treatments group.

Psychosis ranged from 0 to 4.4 per 1,000 patient-days for glucocorticoid only group, 0.7 to 4.1 per 1,000 patient-days for other COVID-19 treatments only, 0 to 1.6 per 1,000 patient-days for glucocorticoid and other COVID treatments and 0 to 1.2 per 1,000 patient-days for no specific COVID-19 treatments group.

Myopathy ranged from 0 per 1,000 patient-days for glucocorticoid only group, 0 to 0.5 per 1,000 patient-days for other COVID-19 treatments only, 0 to 0.3 per 1,000 patient-days for glucocorticoid and other COVID treatments and 0 to 0.2 per 1,000 patient-days for no specific COVID-19 treatments group

Herpes zoster ranged from 0 per 1,000 patient-days for glucocorticoid only group, 0 to 0.1 per 1,000 patient-days for other COVID-19 treatments only, 0 per 1,000 patient-days for glucocorticoid and other COVID treatments and 0 to 0.1 per 1,000 patient-days for no specific COVID-19 treatments group.

Time to event

Over the period of interest, it was not possible to estimate the median and IQR of time to event for most of the reported outcomes. The ones which reached the median time to event or at least the 25th percentile were:

- Arrhythmia with a median time to event between 19 and 29 days in three databases in the glucocorticoid only group and 39 days in the Glucocorticoid and other COVID-19 treatments group.
- Hyperglycaemia with a median time to event between 29 and 32 days in three databases in the glucocorticoid only group and 39 days in the glucocorticoid and other COVID-19 treatments group.
- Infection (composite) had a median time to event of zero in three databases and across all groups and 47 days in one database and the untreated group.
- Viral infection had a median time to event of zero in three databases and across all groups
- Sepsis had a median time to event between 17 and 49 days across three databases.

- LRTI had a median time to event between 0 and 10 days in the Glucocorticoid only group, 0 and 8 days in the Glucocorticoid and other COVID-19 treatments, 5 and 10 days in the Other COVID-19 treatments only and 11 days in the No specific COVID-19 treatments.

See Electronic Supplementary Material for the KM plots for each event.

Very few or no individuals continuing follow-up to 30 days, this is illustrated by the short duration of use of glucocorticoids.

Database	Median cumulative duration of glucocorticoids to 90 days
Spain - IMASIS	7 days
US - HDMC	5 days
Serbia – Clinerion and Heliant	9 days
France APHM	4 days
Germany - Academic hospital	7 days
Spain - Hospitales	10 days

Meta-analysis

In hospital naïve cohort meta-analysis was performed only for AEs reported in at least one database: cardiovascular events, arrhythmia, gastritis, psychosis, myopathy, hyperglycaemia, bacterial infection, fungal infection, parasitic infection, sepsis, herpes, and cutaneous cellulitis. Meta-analysis was not conducted for adverse events with high heterogeneity (I^2>40%).

The meta-analysis showed a pooled incidence rate (in decreasing order) in glucocorticoids only treatments group: 16.42 per 1,000 patient-days for arrythmia, 13.45 per 1,000 patient-days for hyperglycaemia, 9.55 per 1,000 patient-days for sepsis, 8.17 per 1,000 patient-days for cardiovascular events, 7.29 per 1,000 patient-days for bacterial infection, 4.29 per 1,000 patient-days for psychosis, 2.46 per 1,000 patient-days for fungal and 0.43 per 1,000 patient--days for parasitic infection.

The pooled incidence rate of parasitic infection ranged from 0.02 per 1,000 patient-days in glucocorticoid and other COVID-19 treatments only group to 0.43 per 1,000 patient-days in glucocorticoid only treatment group. Moreover, the pooled incidence rate of herpes varied from 0.03 per 1,000 patient-days in no COVID-19 related treatment and glucocorticoids and other COVID-19 treatment group to 0.13 per 1,000 patient-days in other COVID-19 treatments group. However, no database reported herpes in glucocorticoids only treatment group. The meta-analysis showed a pooled incidence rate of 0.07 per 1,000 patient-days for cutaneious cellulitis in other COVID-19 treatments group and glucocorticoid and other COVID-19 treatments. However, no database reported cutaneous cellulitis in glucocorticoids only treatment group.

Table 12 shows the pooled incidence of adverse events in hospital naïve COVID-19 patients. The forest plots for the meta-analysis are presented in the Supplementary material

Table 12 Pooled incidence rates of adverse events in hospital naïve cohort

	Glucocorticoid Only					Other COVID treatments Only					Glucocorticoid and other COVID treatments					No COVID related treatments				
	Databases					Databases					Databases					Databases				
Outcome	**Total**	**0 AE**	**<5 AE**	**>5 AE**	**Pooled IR (95% CI) (per 1,000 person-days)**	**Total**	**0 AE**	**<5 AE**	**>5 AE**	**Pooled IR (95% CI) (per 1,000 person-days)**	**Total**	**0 AE**	**<5 AE**	**>5 AE**	**Pooled IR (95% CI) (per 1,000 person-days)**	**Total**	**0 AE**	**<5 AE**	**>5 AE**	**Pooled IR (95% CI) (per 1,000 person-days)**
Cardiovascular events	6	3	2	1	8.17 (95% CI 5.78-11.53)	6	2	0	4	NA*	6	2	0	4	NA*	6	2	0	4	NA*
Hypertension	6	1	4	1	NA*	6	1	0	5	NA*	6	1	1	4	NA*	6	1	0	5	NA*
Arrythmia	6	1	4	1	16.42 (95% CI 7.74-34.85)	6	1	0	5	NA*	6	1	0	5	NA*	6	1	1	4	NA*
Gastritis	6	5	1	0	3.10 (95% CI 0.63-15.37)	6	2	1	3	NA*	6	3	1	2	0.60 (95% CI 0.49-0.74)	6	2	2	2	NA*
Psychosis	6	5	0	1	4.29 (95% CI 2.65-6.96)	6	1	2	3	NA*	6	2	2	2	NA*	6	1	1	4	NA*
Myopathy	6	6	0	0	NR^	6	3	2	1	0.19 (95% CI 0.06-0.62)	6	3	2	1	0.20 (95% CI 0.14-0.30)	6	3	2	1	NA*
Hyperglycaemia	6	5	0	1	13.45 (95% CI 10.15-17.82)	6	3	0	3	NA*	6	2	0	4	NA*	6	2	1	3	NA*
Infection composite	6	2	1	3	NA*	6	1	0	5	NA*	6	1	1	4	NA*	6	1	0	5	NA*
Bacterial infection	6	4	1	1	7.29 (95% CI 5.05-10.54)	6	1	1	4	NA*	6	2	0	4	NA*	6	1	0	5	NA*
Viral infection	6	2	1	3	NA*	6	1	0	5	NA*	6	1	1	4	NA*	6	1	0	5	NA*
Fungal infection	6	4	1	1	2.46 (95% CI 1.30-4.66)	6	1	2	3	NA*	6	2	2	2	NA*	6	2	1	3	NA*
Parasitic infection	6	5	1	0	0.43 (95CI 0.09-2.13)	6	3	3	0	0.04 (95%CI 0.01-0.11)	6	3	3	0	0.02 (95% CI 0.00-0.06)	6	3	2	1	0.03 (95% CI 0.01-0.07)
Sepsis	6	4	1	1	9.55 (95% CI 6.87-13.28)	6	2	1	3	NA*	6	3	0	3	NA*	6	2	1	3	NA*
LRTI	6	2	1	3	NA*	6	1	0	5	NA*	6	2	0	4	NA*	6	1	0	5	NA*
Herpes	6	6	0	0	NR^	6	3	2	1	0.13 (95% CI 0.08-0.21)	6	3	3	0	0.03 (95% CI 0.01-0.09)	6	3	2	1	0.03 (95% CI 0.01-0.09)
Cutaneous cellulitis	6	6	0	0	NR^	6	5	1	0	0.07 (95% CI 0.01-0.33)	6	5	1	0	0.07 (95% CI 0.01-0.44)	6	4	2	0	NA*

*No pooled result I-squared > 40%
^No database report an event
Note: Due to lengthy ethical procedures, the HIC data was received late and therefore could not be included in the meta-analysis
Abbreviations: AE, adverse events; IR, incidence rate; LRTI, lower respiratory tract infection; NA, not applicable; NR, not reported; N, number of databases

8.5 Incidence of disease outcomes

Each of the disease outcome incidence rate and proportion were calculated in each cohort, both at 30 and 90 days. The other two stratifications, by comorbidity and by starting dose of glucocorticoid are presented in the Supplementary material.

No patients in the prevalent cohorts seemed to have their chronic glucocorticoid treatment repurposed for COVID-19, therefore, in both ambulatory and hospitalised prevalent cohorts, there was no patient considered in the group “glucocorticoid only” and “glucocorticoid and other COVID-19 treatments”. For that reason, disease outcomes are not described in these treatment groups.

8.5.1 Ambulatory prevalent cohort

DIC was not reported as an outcome in any of the databases.

Incidence proportions at 30 days

Hospital admission was reported in four databases, ranging from 0.0% (n=0) to 11.4% (n=49) in the other COVID-19 treatment group and from 1.7% (n=15) to 20.2% (n=53) in the no specific COVID-19 treatment group.

VTE was reported in seven databases, ranging from 0.0% (n=0) to masked in the other COVID-19 treatment group and from 0.4% (n=19) to 4.6% (n=12) in the no specific COVID-19 treatment group.

Death was reported in six databases, ranging from 0.0% (n=0) to 50.0% (n=8) in the other COVID-19 treatment group and from 6.3% (n=57) to 25.6% (n=67) in the no specific COVID-19 treatment group.

Incidence proportions at 90 days

Hospital admission was reported in four databases, ranging from 0.0% (n=0) to 14.5% (n=62) in the other COVID-19 treatment group and from 3.2% (n=29) to 39.7% (n=104) in the no specific COVID-19 treatment group.

VTE was reported in seven databases, ranging from 0.0% (n=0) to masked in the other COVID-19 treatment group and from 0.6% (n=29) to 4.6% (n=12) in the no specific COVID-19 treatment group.

Death was reported in six databases, ranging from 0.0% (n=0) to 50.0% (n=8) in the other COVID-19 treatment group and from 4.9% (n=7) to 34.0% (n=89) in the no specific COVID-19 treatment group.

Incidence rates at 30 days

Hospital admission was reported in four databases, ranging from 0.0 to 8.9 per 1,000 patient-days in the other COVID-19 treatment group and from 0.8 to 9.3 per 1,000 patient-days in no specific COVID-19 treatment group.

VTE was reported in seven databases, ranging from 0.0 to masked in the other COVID-19 treatment group and from 0.2 to 2.2 per 1,000 patient-days in no specific COVID-19 treatment group.

Death was reported in six databases, ranging from 0.0 to 571.4 per 1,000 patient-days in the other COVID-19 treatment group and from 3.1 to 11.7 per 1,000 patient-days in no specific COVID-19 treatment group.

Incidence rates at 90 days

Hospital admission was reported in four databases, ranging from 0.0 to 6.2 per 1,000 patient-days in the other COVID-19 treatment group and from 0.7 to 7.3 per 1,000 patient-days in no specific COVID-19 treatment group.

VTE was reported in seven databases, ranging from 0.0 to masked in the other COVID-19 treatment group and from 0.1 to 0.9 per 1,000 patient-days in no specific COVID-19 treatment group.

Death was reported in six databases, ranging from 0.0 to 571.4 per 1,000 patient-days in the other COVID-19 treatment group and from 0.8 to 6.3 per 1,000 patient-days in no specific COVID-19 treatment group.

Time to event

Over the period of interest, the frequency of events was lower than 25% therefore it was not possible to estimate the median and IQR of time to event for most of the reported AEs. The ones which reached the median time to event or at least the 25th percentile was hospital admission with a 25th percentile of 60 days in one database only.

Meta-analysis

In ambulatory prevalent cohort meta-analysis was performed only for VTE. The pooled incidence rate for VTE was 0.56 per 1,000 patient-days in other COVID-19 treatments only group and 0.14 per 1,000 patient-days in no COVID-19 related treatments group. Meta-analysis was not conducted for death and hospitalisation due to high heterogeneity (I^2>40%).

Table 13 shows the pooled incidence of disease outcomes amongst ambulatory prevalent COVID-19 patients. The forest plots for the meta-analysis are presented in the Supplementary material.

Table 13 Pooled incidence rates of disease outcomes in ambulatory prevalent cohort

	Other COVID treatments Only					No COVID related treatments				
		Databases					Databases			
Outcome	**N**	**0 Disease Outcomes**	**<5 Disease Outcomes**	**>5 Disease Outcomes**	**Pooled IR (95% CI)**	**N**	**0 Disease Outcomes**	**<5 Disease Outcomes**	**>5 Disease Outcomes**	**Pooled IR (95% CI)**
Death	5	1	2	2	NA*	5	0	2	3	NA*
Hospitalisation	5	3	1	1	NA*	5	2	1	2	NA*
VTE/PTE	6	3	3	0	0.56 (95% CI 0.19-1.66)	6	0	5	1	0.14 (95% CI 0.09-0.2)
DIC	6	6	0	0	NR^	6	6	0	0	NR^

*No pooled result I-squared > 40%
^No database reported an event
Note: Due to lengthy ethical procedures, the HIC data was received late and therefore could not be included in the meta-analysis
Abbreviations: AE, adverse events; DIC, disseminated intravascular coagulation; IR, incidence rate; NA, not applicable; NR, not reported; PTE, pulmonary thromboembolism; VTE, venous thromboembolism

8.5.2 Ambulatory naïve cohort

DIC was not reported as an outcome in any of the databases, except for UK-HIC where it was masked.

Incidence proportions at 30 days

Hospital admission was reported in four databases, ranging from 0.0% (n=0) to 2.5% (n=23) in the glucocorticoid only group, from 0.6% (n=7) to 50.0% (n=60) in the other COVID-19 treatment group, from 0.0% (n=0) to 3.9% (n=22) in the glucocorticoid and other COVID treatments and from 0.1% (n=59) to 7.4% (n=180) in the no specific COVID-19 treatment group.

VTE was reported in seven databases, ranging from 0.0% (n=0) to masked in the glucocorticoid only group, from 0.1% (n=21) to 0.9% (n=14) in the other COVID-19 treatment group, from 0.0% (n=0) to masked in the glucocorticoid and other COVID treatments and from 0.1% (n=362) to 2.1% (n=50) in the no specific COVID-19 treatment group.

Death was reported in six databases, ranging from 0.0% (n=0) to 4.3% (n=40) in the glucocorticoid only group, from 1.0% (n=11) to 29.2% (n=35) in the other COVID-19 treatment group, from 0.0% (n=0) to 14.8% (n=83) in the glucocorticoid and other COVID treatments and from 0.0% (n=0) to 16.3% (n=395) in the no specific COVID-19 treatment group.

Incidence proportions at 90 days

Hospital admission was reported in four databases, ranging from 0.0% (n=0) to 3.0% (n=28) in the glucocorticoid only group, from 0.6% (n=7) to 52.5% (n=63) in the other COVID-19 treatment group, from 0.0% (n=0) to 5.0% (n=28) in the glucocorticoid and other COVID-19 treatments and from 0.2% (n=78) to 43.8% (n=1062) in the no specific COVID-19 treatment group.

VTE was reported in seven databases, ranging from 0.0% (n=0) to masked in the glucocorticoid only group, from 0.2% (n=31) to 1.0% (n=15) in the other COVID-19 treatment group, from 0.0% (n=0) to masked in the glucocorticoid and other COVID-19 treatments and from 0.2% (n=74) to 2.5% (n=60) in the no specific COVID-19 treatment group.

Death was reported in six databases, ranging from 0.0% (n=0) to 4.8% (n=45) in the glucocorticoid only group, from 0.3% (n=6) to 29.2% (n=35) in the other COVID-19 treatment group, from 0.0% (n=0) to 14.9% (n=84) in the glucocorticoid and other COVID treatments and from 0.1% (n=43) to 25.0% (n=605) in the no specific COVID-19 treatment group.

Incidence rates at 30 days

Hospital admission was reported in four databases, ranging from 0.0 to 1.5 per 1,000 patient-days in the glucocorticoid only group, from 0.3 to 145.3 per 1,000 patient-days in the other COVID-19 treatment group, from 0.0 to 3.7 per 1,000 patient-days in the glucocorticoid and other COVID treatments and from 0.1 to 2.8 per 1,000 patient-days in the no specific COVID-19 treatment group.

VTE was reported in seven databases, ranging from 0.0 to masked in the glucocorticoid only group, from 0.1 to 0.5 per 1,000 patient-days in the other COVID-19 treatment group, from 0.0 to masked in the glucocorticoid and other COVID treatments and from 0.04 to 0.8 per 1,000 patient-days in the no specific COVID-19 treatment group.

Death was reported in six databases, ranging from 0.0 to 2.7 in the glucocorticoid only group, from 0.5 to 84.7 per 1,000 patient-days in the other COVID-19 treatment group, from 0.0 to 14.3 per 1,000

patient-days in the glucocorticoid and other COVID treatments and from 0.02 to 6.1 per 1,000 patient-days in the no specific COVID-19 treatment group.

Incidence rates at 90 days

Hospital admission was reported in four databases, ranging from 0.0 to 1.3 per 1,000 patient-days in the glucocorticoid only group, from 0.2 to 67.0 per 1,000 patient-days in the other COVID-19 treatment group, from 0.0 to 3.4 per 1,000 patient-days in the glucocorticoid and other COVID treatments and from 0.04 to 5.8 per 1,000 patient-days in the no specific COVID-19 treatment group.

VTE was reported in seven databases, ranging from 0.0 to masked in the glucocorticoid only group, from 0.1 to 0.2 per 1,000 patient-days in the other COVID-19 treatment group, from 0.0 to masked in the glucocorticoid and other COVID treatments and from 0.03 to 0.3 per 1,000 patient-days in the no specific COVID-19 treatment group.

Death was reported in six databases, ranging from 0.0 to 2.2 per 1,000 patient-days in the glucocorticoid only group, from 0.1 to 37.2 per 1,000 patient-days in the other COVID-19 treatment group, from 0.0 to 10.2 per 1,000 patient-days in the glucocorticoid and other COVID treatments and from 0.03 to 3.3 per 1,000 patient-days in the no specific COVID-19 treatment group.

Time to event

Over the period of interest, the frequency of events was lower than 25% therefore it was not possible to estimate the median and IQR of time to event for any of the reported outcomes.

Meta-analysis

In ambulatory naïve cohort meta-analysis was performed only for VTE and hospitalisation. The pooled incidence rates for hospitalisation were 1.43 per 1,000 patient-days in glucocorticoids only group and 3.44 per 1,000 patient-days in glucocorticoids and other COVID-19 treatments group. The pooled incidence rate for VTE was 0.24 per 1,000 patient-days in glucocorticoids only group and 0.20 per 1,000 patient-days in glucocorticoids and other COVID-19 treatments group. Death data from different cohorts were not pooled due to high heterogeneity (I^2>40%). Furthermore, no databases reported DIC.

Table 14 shows the pooled incidence of disease outcomes in ambulatory naïve COVID-19 patients. The forest plots for the meta-analysis are presented in the Supplementary material.

Table 14 Pooled incidence rates of disease outcomes in ambulatory naïve cohort

	Glucocorticoid Only					Other COVID treatments Only				
	Databases					Databases				
Outcome	N	0 Disease Outcomes	<5 Disease Outcomes	>5 Disease Outcomes	Pooled IR (95% CI)	N	0 Disease Outcomes	<5 Disease Outcomes	>5 Disease Outcomes	Pooled IR (95% CI)
Death	5	1	3	1	NA*	5	0	1	4	NA*
Hospitalisation	5	3	1	1	1.43 (95% CI 0.96-2.13)	5	2	0	3	NA*
VTE/PTE	6	3	3	0	0.24 (95% CI 0.08-0.70)	6	1	5	0	NA*
DIC	6	6	0	0	NR^	6	6	0	0	NR^

	Glucocorticoid and other COVID treatments					No COVID related treatments				
	Databases					Databases				
Outcome	N	0 Disease Outcomes	<5 Disease Outcomes	>5 Disease Outcomes	Pooled IR (95% CI)	N	0 Disease Outcomes	<5 Disease Outcomes	>5 Disease Outcomes	Pooled IR (95% CI)
Death	5	2	2	1	NA*	5	0	0	5	NA*
Hospitalisation	5	3	1	1	3.44 (95% CI 2.29-5.16)	5	2	0	3	NA*
VTE/PTE	6	5	1	0	0.2 (95% CI 0.04-0.98)	6	0	0	6	NA*
DIC	6	6	0	0	NR^	6	6	0	0	NR^

*No pooled result I-squared > 40%
^No database reported an event
Note: Due to lengthy ethical procedures, the HIC data was received late and therefore could not be included in the meta-analysis
Abbreviations: AE, adverse events; DIC, disseminated intravascular coagulation; IR, incidence rate; NA, not applicable; NR, not reported; PTE, pulmonary thromboembolism; VTE, venous thromboembolism; N, number of databases

8.5.3 Hospital prevalent cohort

Germany-Academic Hospital and Spain-Hospitales had no observation for the hospital prevalent cohort and France-APHM had less than 50 patients in this cohort. Therefore, those databases are not described here.

Hospital discharge was not reported as an outcome in any of the database.

Incidence proportions at 30 days

DIC was reported in two databases, ranging from 0.0% (n=0) to masked in the other COVID-19 treatment group and masked in the no specific COVID-19 treatment group.

VTE was reported in three databases, ranging from masked to 1.6% (n=51) in the other COVID-19 treatment group and from masked to 0.2% (n=20) in the no specific COVID-19 treatment group.

Death was reported in three databases, ranging from 11.2% (n=18) to 20.1% (n=565) in the other COVID-19 treatment group and from 17.7% (n=167) to 23.7% (n=18) in the no specific COVID-19 treatment group.

Incidence proportions at 90 days

DIC was reported in two databases, ranging from 0.0% (n=0) to masked in the other COVID-19 treatment group and masked in the no specific COVID-19 treatment group.

VTE was reported in three databases, ranging from masked to 1.6% (n=51) in the other COVID-19 treatment group and from 0.2% (n=23) to 0.7% (n=7) in the no specific COVID-19 treatment group.

Death was reported in three databases, ranging from 11.2% (n=18) to 20.1% (n=656) in the other COVID-19 treatment group and from 18.2% (n=172) to 23.7% (n=18) in the no specific COVID-19 treatment group.

Incidence rates at 30 days

DIC was reported in two databases, ranging from 0.0 to masked in the other COVID-19 treatment group and masked in the no specific COVID-19 treatment group.

VTE was reported in three databases, ranging from masked to 8.6 per 1,000 patient-days in the other COVID-19 treatment group and from masked to 2.1 per 1,000 patient-days in no specific COVID-19 treatment group.

Death was reported in three databases, ranging from 36.2 to 107.5 per 1,000 patient-days in the other COVID-19 treatment group and from 28.8 to 212.2 per 1,000 patient-days in no specific COVID-19 treatment group.

Incidence rates at 90 days

DIC was reported in two databases, ranging from 0.0 to masked in the other COVID-19 treatment group and masked in the no specific COVID-19 treatment group.

VTE was reported in three databases, ranging from masked to 6.0 per 1,000 patient-days in the other COVID-19 treatment group and from 1.1 to 1.2 per 1,000 patient-days in no specific COVID-19 treatment group.

Death was reported in three databases, ranging from 11.3 to 76.2 per 1,000 patient-days in the other COVID-19 treatment group and from 15.7 to 103.8 per 1,000 patient-days in no specific COVID-19 treatment group.

Time to event

Over the period of interest, the frequency of events was lower than 25% so it was not possible to estimate the median and IQR of time to event for most of the reported outcomes. The ones which reached the median time to event or at least the 25th percentile were:

- Death with a 25th percentile between 6 and 47 days in the Other treatment groups and between 4 and 90 days in the untreated group.
- Intensive care with a 25th percentile of 24 days in one database.

Meta-analysis

In hospital prevalent cohort meta-analysis was performed only for VTE and DIC. The pooled incidence rates for VTE were 6.84 per 1,000 patient-days in other COVID-19 treatment only and 1.59 per 1,000 patient-days in no COVID-19 related treatments. Furthermore, the pooled incidence rates for DIC were 0.22 and 0.19 per 1,000 patient-days in other COVID-19 treatment only and in no COVID-19 related treatments, respectively. Death from different cohorts were not pooled due to high heterogeneity (I^2>40%). Furthermore, no databases reported hospital discharge.

Table 15 shows the pooled incidence of disease outcomes in hospitalised prevalent COVID-19 patients. The forest plots for the meta-analysis are presented in the Supplementary material

Table 15 Pooled incidence rates of disease outcomes in hospital prevalent cohort

	Other COVID treatments Only					No COVID related treatments				
	Databases					Databases				
Outcome	**N**	**0 Disease Outcomes**	**<5 Disease Outcomes**	**>5 Disease Outcomes**	**Pooled IR (95% CI)**	**N**	**0 Disease Outcomes**	**<5 Disease Outcomes**	**>5 Disease Outcomes**	**Pooled IR (95% CI)**
Death	4	1	1	2	NA*	4	1	0	3	NA*
Hospital discharge	4	4	0	0	NR^	4	4	0	0	NR^
VTE PTE	4	1	2	1	6.84 (95% CI 3.79-12.35)	4	1	2	1	1.59 (95% CI 0.75-3.37)
DIC	4	3	1	0	0.22 (95% CI 0.04-1.24)	4	2	2	0	0.19 (95% CI 0.05-0.72)
Intensive care	4	2	0	2	NA*	4	2	0	2	NA*

*No pooled result I-squared > 40%
^No database reported an event
Note: Due to lengthy ethical procedures, the HIC data was received late and therefore could not be included in the meta-analysis
Abbreviations: AE, adverse events; DIC, disseminated intravascular coagulation; IR, incidence rate; NA, not applicable; NR, not reported; PTE, pulmonary thromboembolism; VTE, venous thromboembolism; N, number of databases

8.5.4 Hospital naïve cohort

Hospital discharge was not reported as an outcome in any of the databases.

Incidence proportions at 30 days

DIC was reported in four databases, ranging from 0.0% (n=0) to masked in the glucocorticoid only group, from 0.0% (n=0) to 0.06% (n=16) in the other COVID-19 treatment group, from 0.0% (n=0) to 0.8% (n=24) in the glucocorticoid and other COVID treatments and from 0.0% (n=0) to 0.1% (n=15) in the no specific COVID-19 treatment group.

VTE was reported in four databases, ranging from 0.0% (n=0) to 1.4% (n=8) in the glucocorticoid only group, from 0.8% (n=12) to 9.0% (n=55) in the other COVID-19 treatment group, from 1.4% (n=9) to 9.8% (n=54) in the glucocorticoid and other COVID treatments and from 0.5% (n=13) to 17.3% (n=70) in the no specific COVID-19 treatment group.

Death was reported in six databases, ranging from 11.6% (n=68) to 53.8% (n=7) in the glucocorticoid only group, from 2.6% (n=94) to 24.0% (n=146) in the other COVID-19 treatment group, from 14.2% (n=93) to 28.1% (n=154) in the glucocorticoid and other COVID treatments and from 1.5% (n=40) to 29.5% (n=119) in the no specific COVID-19 treatment group.

Incidence proportions at 90 days

DIC was reported in four databases, ranging from 0.0% (n=0) to masked in the glucocorticoid only group, from 0.0% (n=0) to 0.1% (n=17) in the other COVID-19 treatment group, from 0.0% (n=0) to 0.8% (n=24) in the glucocorticoid and other COVID treatments and from 0.0% (n=0) to 0.1% (n=19) in the no specific COVID-19 treatment group.

VTE was reported in four databases, ranging from 0.0% (n=0) to 1.4% (n=8) in the glucocorticoid only group, from 0.8% (n=12) to 9.0% (n=55) in the other COVID-19 treatment group, from 1.4% (n=9) to 9.8% (n=54) in the glucocorticoid and other COVID treatments and from 0.5% (n=13) to 17.8% (n=72) in the no specific COVID-19 treatment group.

Death was reported in six databases, ranging from 11.6% (n=68) to 61.5% (n=8) in the glucocorticoid only group, from 2.6% (n=94) to 24.2% (n=147) in the other COVID-19 treatment group, from 14.7% (n=96) to 28.1% (n=154) in the glucocorticoid and other COVID treatments and from 1.9% (n=194) to 31.9% (n=129) in the no specific COVID-19 treatment group.

Incidence rates at 30 days

DIC was reported in four databases, ranging from 0.0 to masked in the glucocorticoid only group, from 0.0 to 0.2 per 1,000 patient-days in the other COVID-19 treatment group, from 0.0 to 0.5 per 1,000 patient-days in the glucocorticoid and other COVID treatments and from 0.0 to 0.1 per 1,000 patient-days in the no specific COVID-19 treatment group.

VTE was reported in four databases, ranging from 0.0 to 2.2 per 1,000 patient-days in the glucocorticoid only group, from 0.9 to 13.1 per 1,000 patient-days in the other COVID-19 treatment group, from 1.4 to 14.8 per 1,000 patient-days in the glucocorticoid and other COVID treatments and from 0.2 to 15.0 per 1,000 patient-days in the no specific COVID-19 treatment group.

Death was reported in six databases, ranging from 18.7 to 51.9 per 1,000 patient-days in the glucocorticoid only group, from 8.1 to 36.7 per 1,000 patient-days in the other COVID-19 treatment

group, from 12.2 to 39.8 per 1,000 patient-days in the glucocorticoid and other COVID treatments and from 0.7 to 90.1 per 1,000 patient-days in the no specific COVID-19 treatment group.

Incidence rates at 90 days

DIC was reported in four databases, ranging from 0.0 to masked in the glucocorticoid only group, from 0.0 to 0.1 per 1,000 patient-days in the other COVID-19 treatment group, from 0.0 to 0.5 per 1,000 patient-days in the glucocorticoid and other COVID treatments and from 0.0 to 0.1 per 1,000 patient-days in the no specific COVID-19 treatment group.

VTE was reported in four databases, ranging from 0.0 to 2.2 per 1,000 patient-days in the glucocorticoid only group, from 0.7 to 12.0 per 1,000 patient-days in the other COVID-19 treatment group, from 1.3 to 14.7 per 1,000 patient-days in the glucocorticoid and other COVID treatments and from 0.1 to 9.3 per 1,000 patient-days in the no specific COVID-19 treatment group.

Death was reported in six databases, ranging from 18.5 to 56.7 per 1,000 patient-days in the glucocorticoid only group, from 6.1 to 30.1 per 1,000 patient-days in the other COVID-19 treatment group, from 12.6 to 39.5 per 1,000 patient-days in the glucocorticoid and other COVID treatments and from 0.3 to 90.1 per 1,000 patient-days in the no specific COVID-19 treatment group.

Time to event

Over the period of interest, the frequency of events was lower than 25% so it was not possible to estimate the median and IQR of time to event for most of the reported outcomes. The ones which reached the median time to event or at least the 25th percentile were:

Intensive care had a median between 35 and 72 days in the Glucocorticoid and other COVID-19 treatments group and 69 days in the Other COVID-19 treatments only.

Death had a median between 15 and 26 days in the glucocorticoid only group 16 and 24 days in the Glucocorticoid and other COVID-19 treatments and 90 days in the No specific COVID-19 treatments.

Meta-analysis

In hospital naïve cohort meta-analysis was performed only for VTE, DIC, and intensive case. Meta-analysis showed a pooled incidence rate of 2.45 per 1,000 patient-days for VTE and 2.68 per 1,000 patient-days for intensive care in glucocorticoids only group. The pooled incidence rate of DIC ranged from 0.17 per 1,000 patient-days in other COVID-19 treatment only to 0.43 per 1,000 patient-days in glucocorticoid only treatment. Furthermore, no database reported hospital discharge.

Table 16 shows the pooled incidence of disease outcomes in hospitalised naïve COVID-19 patients. The forest plots for the meta-analysis are presented in the Supplementary material

Table 16 Pooled incidence rates of disease outcomes in hospital naïve cohort

	Glucocorticoid Only					Other COVID treatments Only				
	Databases					Databases				
Outcome	N	0 Disease Outcomes	<5 Disease Outcomes	>5 Disease Outcomes	Pooled IR (95% CI)	N	0 Disease Outcomes	<5 Disease Outcomes	>5 Disease Outcomes	Pooled IR (95% CI)
Death	6	0	4	2	NA*	6	0	0	6	NA*
Hospital discharge	6	6	0	0	NR^	6	6	0	0	NR^
VTE/PTE	6	4	1	1	2.45 (95% CI 1.29-4.64)	6	2	0	4	NA*
DIC	6	5	1	0	0.43 (95% CI 0.09-2.13)	6	3	2	1	0.17 (95%CI 0.11-0.26)
Intensive Care	6	3	2	1	2.68 (95% CI 1.50-4.80)	6	3	0	3	NA*

	Glucocorticoid and other COVID treatments					No COVID related treatments				
	Databases					Databases				
Outcome	N	0 Disease Outcomes	<5 Disease Outcomes	>5 Disease Outcomes	Pooled IR (95% CI)	N	0 Disease Outcomes	<5 Disease Outcomes	>5 Disease Outcomes	Pooled IR (95% CI)
Death	6	0	1	5	NA*	6	0	0	6	NA*
Hospital discharge	6	6	0	0	NR^	6	6	0	0	NR^
VTE/PTE	6	2	0	4	NA*	6	2	0	4	NA*
DIC	6	3	1	2	0.34 (95% CI 0.23-0.51)	6	3	2	1	NA*
Intensive Care	6	3	1	2	NA*	6	3	0	3	NA*

*No pooled result I-squared > 40%
^No database reported an event
Note: Due to lengthy ethical procedures, the HIC data was received late and therefore could not be included in the meta-analysis
Abbreviations: AE, adverse events; DIC, disseminated intravascular coagulation; IR, incidence rate; NA, not applicable; NR, not reported; PTE, pulmonary thromboembolism; VTE, venous thromboembolism; N, number of databases

8.6 Explore the performance of different COVID-19 definitions (secondary objective 4)

The different definitions of COVID-19 were compared to the predicted probabilities calculated from applying the predictive model to a random sample of all individuals with a record in the database during the study period (Evaluation cohort). The performance was explored in nine databases (see Table 19).

The results indicated that sensitivity for each definition was low and specificity was high. The definition based on a diagnosis of COVID-19 showed the best sensitivity (range 0.05 to 0.92) followed by suspected COVID-19 definition (0.02 to 0.12) and finally symptomatic definition (0.003 to 0.1).

The specificity was again best for the diagnosis of COVID-19 (>0.95 in all databases), followed by symptomatic definition (0.98-0.99) and suspected COVID-19 definition (0.96-0.99).

Not all definitions were presented in all databases, especially the laboratory confirmed definition which was missing in all tested databases.

There is a high heterogeneity among databases, with US performing the best for all definitions and UK IMRD having the lowest performance, across all definitions.

Table 17 Evaluation of alternative definitions of COVID-19 against catch-all definition using PheValuator

	COVID definition	Sensitivity	PPV	Specificity	NPV
France - LPD	Diagnosis Confirmed	0.49 (0.48 - 0.49)	0.95 (0.95- 0.95)	0.99 (0.99 - 0.99)	0.98 (0.98 - 0.98)
	Symptomatic	0.03 (0.03 - 0.03)	0.11 (0.11 - 0.12)	0.99 (0.99 - 0.99)	0.97 (0.97 - 0.97)
	Suspected	0.06 (0.06 - 0.07)	0.05 (0.05 - 0.05)	0.96 (0.96 - 0.96)	0.97 (0.97 - 0.97)
Germany - DA	Diagnosis Confirmed	0.23 (0.25 - 0.26)	0.63 (0.62 - 0.64)	0.99 (0.99 - 0.99)	0.99 (0.99 - 0.99)
	Symptomatic	0.02 (0.01 - 0.02)	0.06 (0.05 - 0.06)	0.97 (0.99 - 0.99)	0.99 (0.99 - 0.99)
	Suspected	0.17 (0.16 - 0.17)	0.04 (0.04 - 0.05)	0.96 (0.96 - 0.96)	0.99 (0.99 - 0.99)
Italy - LPD	Diagnosis Confirmed	0.57 (0.55 - 0.58)	0.80 (0.78 - 0.81)	0.99 (0.99 - 0.99)	0.99 (0.99 - 0.99)
	Symptomatic	0.00 (0.00 - 0.00)	0.02 (0.01 - 0.03)	0.99 (0.99 - 0.99)	0.99 (0.99 - 0.99)
	Suspected	0.18 (0.17 - 0.19)	0.03 (0.02 - 0.03)	0.96 (0.96 - 0.96)	0.99 (0.99 - 0.99)
UK - IMRD	Diagnosis Confirmed	0.05 (0.05 - 0.06)	0.17 (0.16 - 0.19)	0.99 (0.99 - 0.99)	0.99 (0.99 - 0.99)
	Symptomatic	0.00 (0.00 - 0.00)	0.02 (0.01 - 0.02)	0.99 (0.99 - 0.99)	0.99 (0.99 - 0.99)
	Suspected	0.00 (0.00 - 0.00)	0.01 (0.01 - 0.01)	0.99 (0.99 - 0.99)	0.99 (0.99 - 0.99)
US - HDMC	Diagnosis Confirmed	0.66 (0.65 - 0.66)	0.86 (0.85 - 0.86)	0.99 (0.99 - 0.99)	0.99 (0.99 - 0.99)
	Symptomatic	0.12 (0.12 - 0.13)	0.07 (0.06 - 0.07)	0.98 (0.98 - 0.98)	0.99 (0.99 - 0.99)
	Suspected	0.16 (0.15 - 0.16)	0.11 (0.11 - 0.12)	0.98 (0.98 - 0.98)	0.99 (0.99 - 0.99)
UK HIC	Diagnosis confirmed	0.92 (0.90 - 0.93)	0.79 (0.77 - 0.81)	0.99 (0.99 - 0.99)	0.99 (0.99 - 0.99)
	Symptomatic	0.14 (0.12 - 0.15)	0.62 (0.57 - 0.67)	0.99 (0.99 - 0.99)	0.99 (0.99 - 0.99)
	Suspected	NA	NA	NA	NA
France APHM	Diagnosis confirmed	0.89 (0.88 - 0.89)	0.82 (0.81 - 0.83)	0.99 (0.98 - 0.99)	0.99 (0.99 - 0.99)
Spain IMASIS	Diagnosis confirmed	0.58 (0.57 - 0.59)	0.74 (0.72 - 0.75)	0.98 (0.98 - 0.98)	0.97 (0.97 - 0.97)
	Symptomatic	0.01 (0.01 - 0.02)	0.73 (0.62 - 0.82)	1.00 (0.99 - 1.00)	0.93 (0.93 - 0.93)
IPCI	Diagnosis confirmed	0.316 (0.31 - 0.32)	0.884 (0.87 - 0.88)	0.998 (0.99 - 0.99)	0.973(0.97 - 0.97)
	Symptomatic	0.00 (0.00 - 0.00)	0.06 (0.05 - 0.07)	0.99 (0.99 - 0.99)	0.96 (0.96 - 0.96)

8.7 Sensitivity analysis

All the results from the sensitivity analyses will be provided in the Supplementary material, after the first version of this report is submitted.

Section 9.0 Discussion

The aim of this proof of concept study was to establish if the newly created E-CORE network can be used to investigate effectiveness and safety of COVID-19 treatments. As a test study it was decided to describe the utilisation patterns of systemic glucocorticoids in patients with COVID-19 and investigate the risks of adverse outcomes occurring within 90 days of COVID-19 diagnosis as observed in ambulatory and hospital care settings of eight countries (seven European countries and the US).

9.1 Key Results and Interpretation

9.1.1 Descriptive characteristics of the included cohorts

In this study, there were 7,560 ambulatory prevalent patients (nine countries), 324,938 ambulatory naïve patients (nine countries), 10,452 hospital prevalent patients (six countries) and 62,929 hospital naïve patients (seven countries).

Across all databases, the majority of patients were adults, with the hospital cohorts having a slightly older population that the ambulatory cohorts (range across all databases 64.0-74.0 vs 49.0-76.0 years in the prevalent cohort and 53.0-71.0 vs 43.0-71.0 in the naïve cohort). The number of children diagnosed with COVID-19 was very small, less than 5% of the included population. The hospital prevalent cohorts did not contain children at all except US-HCDM database.

The percentage of women was slightly higher in the ambulatory prevalent cohorts (range across all databases 51.1% -67.4%) than in the hospital prevalent cohorts (40.9%- 47.8%), while the naïve cohorts have similar percentages for both ambulatory 46.9%-58.6% and the hospital cohorts (50.0%-59.8%)

With regards to comorbidities, the most frequent in the ambulatory prevalent cohorts were hypertension, COPD and T2DM. For hospitalized cohorts, these were: hypertension, T2DM and CKD. In general, comorbidities were more frequent among hospitalized patients. Our findings are similar to the DACCOVID study, conducted in Denmark on both hospitalized and ambulatory patients which found that the most frequent co-morbidities among hospitalized COVID-19 cases were hypertension (55%), COPD (22%), ischaemic heart disease (19%) and diabetes (19%). (31) Our results are also similar to the Charybdis study which included 4,537,153 individuals with a clinical COVID-19 diagnosis or positive test, 886,193 hospitalized with COVID-19, and 113,627 hospitalized with COVID-19 requiring intensive services from United States, Europe and Asia. The Charybdis study found similar prevalent comorbidities to our study with "*type 2 diabetes mellitus, hypertension, chronic kidney disease […] chronic obstructive pulmonary disease (COPD), and asthma was higher in the hospitalised cohort as compared to the diagnosed*". (32)

The recording of COVID-19 symptoms was variable between cohorts (and databases); between 1-37% of patients having one or more symptoms. Cough, dyspnoea, and fever were the most frequent symptoms in both the ambulatory and hospital cohorts, this finding being aligned with Charybdis study.(32) The under-recording of symptoms is acknowledged in other studies investigating COVID-19 in electronic medical records (32) and is an expected result. In our study, the data partners confirmed

that in their databases, symptoms, especially mild ones, are unlikely to be coded, with upcoding using a diagnostic code if there is an existing diagnosis that can be used[10].

9.1.2 Utilization of systemic glucocorticoids for treatment of COVID-19 in the hospital and ambulatory setting

The study did not identify any prevalent users treated with corticosteroids specifically for COVID-19. In electronic medical records that do not capture indication, it is hard to disentangle if a glucocorticoid treatment for a chronic indication was repurposed for COVID-19 treatment. Our algorithm based on change of the type of steroid and change in dose relies on how well the data on indication and dose is captured in those databases, therefore the switch from chronic treatment to COVID-19 treatment might have been missed. It is also likely that the physician decided not to alter the baseline treatment of such patients.

The percentage of patients treated with steroids was lower in the ambulatory setting (8,627 COVID-19 patients (1.7%) ranging from 0.6% to 3.3% across all databases) vs hospital setting (30,483 COVID-19 patients (32.1%), ranging from 2.4% to 45.6% across all databases).This finding is aligned with the recommendation to use steroids in severe cases only. (8) The proportion of hospital patients treated with glucocorticoids was lower than what was reported in other studies: 46.7% in one Spanish hospital (33) and 40.5% in another study on nine Italian hospitals. (34) However the value depends on the time of measurement, the use being lower in the initial stages of the pandemic. Also, exposure to glucocorticoids in hospital setting might have been underrepresented in our study as glucocorticoids might be captured only as ward stock and not as individual patient prescriptions and dispensations.

The treatment duration of corticosteroids was short, ranging from 4.0 to 25.0 days in ambulatory setting and 4.0 days to 10.0 days in hospital setting, aligned with the guidelines that suggest a treatment duration of up to 10 days. (18)

The number of patients receiving other COVID-19 treatment was higher in the hospital setting (ranging from 43.7% to 99.5%) than in the ambulatory setting (ranging from 0.6% to 3.3%). there were no records of patients receiving respiratory support neither in the ambulatory nor the hospital setting, and this might be because especially the non-invasive respiratory support is rarely coded in electronic medical records.

RECOVERY trial results publication seems to have impacted the use of steroids in hospital (increase), but no clear impact in the ambulatory setting. The trend was not formally tested.

9.1.3 Adverse events of interest in various COVID-19 treatment groups

Of the selected AEs identified for evaluation in this POC study, the most frequent AEs, reported in over 10% of the patients in any cohort and at least one treatment group were infection (composite), viral infection, LRTI and hypertension; this finding being constant across databases and both at 30- and 90-days follow-up. The least frequent AEs, reported in less than 1% in any cohort and any treatment group were: myopathy, parasitic infection, herpes zoster and cutaneous cellulitis.

[10] Personal communication from database custodians during Database Holders meeting on 8th September 2021

The AE profile differed in the ambulatory vs hospital cohorts. Overall hospital cohorts had higher frequency of AEs but also some AEs such as psychosis, myopathy, hyperglycaemia, parasitic infection, herpes and cutaneous cellulitis appeared predominantly in the hospital cohorts.

The majority of patients had a follow up consistently lower than 30 days, mainly associated with censoring due to end of treatment. Accordingly, all of the 90 day AE rates were lower or equal to the 30 day AE rates.

The frequency of all AEs decreased substantially to almost zero when restricting to people with no medical history of the event, suggesting strong confounding by prior medical history of the AE of interest.

In the naïve cohorts, higher rates appear in the 'other COVID-19 treatments only' or 'glucocorticoid and other COVID-19 treatments' groups suggesting patients that require multiple COVID treatments may have a higher burden of subsequent AEs than those that require only steroid treatment. The results were not formally compared across treatments taking into account factors such as disease severity therefore caution should be applied when interpreting these results.

9.1.4 Disease outcomes of interest in various COVID-19 treatment groups

In **ambulatory prevalent cohort,** hospital admission ranged from 0.0 to 6.2 per 1,000 patient-days in the other COVID-19 treatment group and from 0.7 to 7.3 per 1,000 patient-days in no specific COVID-19 treatment group. Death ranged from 0.0 to 571.4 per 1,000 patient-days in the other COVID-19 treatment group and from 0.8 to 6.3 per 1,000 patient-days in no specific COVID-19 treatment group. The pooled incidence rate for VTE was 0.56 per 1,000 patient-days in other COVID-19 treatments only group and 0.14 per 1,000 patient-days in no COVID-19 related treatments group.

In **ambulatory naïve cohort,** death ranged from 0.0 to 2.2 per 1,000 patient-days in the glucocorticoid only group, from 0.1 to 37.2 per 1,000 patient-days in the other COVID-19 treatment group, from 0.0 to 10.2 per 1,000 patient-days in the glucocorticoid and other COVID treatments and from 0.03 to 3.3 per 1,000 patient-days in the no specific COVID-19 treatment group. The pooled incidence rates for hospitalisation were 1.43 per 1,000 patient-days in glucocorticoids only group and 3.44 per 1,000 patient-days in glucocorticoids and other COVID-19 treatments group. The pooled incidence rate for VTE was 0.24 per 1,000 patient-days in glucocorticoids only group and 0.20 per 1,000 patient-days in glucocorticoids and other COVID-19 treatments group. No ambulatory setting database reported DIC as outcome.

In the **hospital prevalent cohort**, the pooled incidence rates for VTE were 6.84 per 1,000 patient-days in other COVID-19 treatment only and 1.59 per 1,000 patient-days in no COVID-19 related treatments. Furthermore, the pooled incidence rates for DIC were 0.22 and 0.19 per 1,000 patient-days in other COVID-19 treatment only and in no COVID-19 related treatments, respectively. Death ranged from 11.3 to 76.2 per 1,000 patient-days in the other COVID-19 treatment group and from 15.7 to 103.8 per 1,000 patient-days in no specific COVID-19 treatment group.

In the **hospital naïve cohort**, meta-analysis showed a pooled incidence rate of 2.45 per 1,000 patient-days for VTE in glucocorticoids only group. The pooled incidence rate of DIC ranged from 0.17 per 1,000 patient-days in other COVID-19 treatment only to 0.43 per 1,000 patient-days in glucocorticoid only treatment. Death ranged from 18.5 to 56.7 per 1,000 patient-days in the glucocorticoid only group.

Death as an outcome ranged from 0% to 50.0% in the ambulatory cohort and from 11% to 53.8% in the hospital cohorts. The COVID-19 cases fatality rate was reported in other studies to be 1.4-15% but this includes asymptomatic patients therefore cannot be directly comparted with our study. (35) Two hospital studies reported a mortality proportion of 5.5% at 30 days in a Danish Hospital and 15.1% in a Spanish hospital.(31,33) A recent observation study performed in England showed an unadjusted survival at 30 days was lowest in late March in both high dependency unit (71.6% survival) and ICU (58.0% survival) compared to June (92.7% in high dependency unit and 80.4% in ICU). (36) In some databases, our results show a much higher incidence of death which is likely due to an inclusion of more severe cases.

The proportion of subjects in the ambulatory cohort that were hospitalised were between 0 to 20.2% in the prevalent ambulatory cohort and 0 to 50% in the naïve ambulatory cohort; this being possibly highest in the 'other COVID-19 treatment group'. In a recent study conducted in Milan, 22% of the 36,834 subjects with a positive test result for COVID-19 were hospitalized or admitted to an emergency department with a COVID-19 diagnosis, which is in line with our results (37).

Within the hospital cohorts, no records of hospital discharge were captured (see section 9.2 Strengths and limitations)

9.1.5 The performance of different coding definitions for COVID-19

The gold standard tool to identify COVID-19 disease is the positive result of PCR test for SARS-CoV-2. This is, however, not available in many databases, being recorded only in one database out of 13 (Spain-SIDIAP) in the present study.

Alternative COVID-19 definitions were explored and compared with the results from the predictive algorithm. The diagnosis-based definition (ICD-10 codes, as advised by WHO) had the best performance.

Both suspected and symptomatic definitions have a very low sensitivity and the specificity decreases as well compared to the diagnosis-based definition.

In March 2020 the emergency ICD-10 codes for COVID-19 were introduced by WHO and it appears that their use is rather high (few COVID-19 patients appear to be coded with alternative codes).

The reason behind low performance of symptomatic definition is very likely to be the low prevalence of symptoms recorded in patients with COVD-19, as observed in all the investigated databases.

9.1 Strengths and Limitations

Strengths

The size and diversity of the available data within the E-CORE network enable unprecedented insights into the real-world usage and effect of corticosteroid use as COVID-19 treatment in different countries and regions. Furthermore, the large, diverse sample size allows also for the identification of specific COVID-19 populations of interest that can be targeted for future research in treatments for COVID-19.

Limitations

This study was descriptive in nature, therefore no statistical comparisons with hypothesis testing were attempted. The observed differences in corticosteroid use and effects between groups (e.g. ambulatory vs hospital and corticosteroid treated vs other treatments) should not be interpreted as causal effects

or even proven associations, as underlying group differences that can confound results are not taken into account.

Missing information and heterogeneity are perhaps the biggest limitations for such a study, leading to potential misclassification. Examples of some such observed shortcomings are listed below:

Patient characteristics

- Comorbidities were lower than expected in some databases (e.g., Spain SIDIAP and UK IMRD), probably due to the restricted lookback window to one year. The minimum length of patient history was 365 days for the ambulatory cohorts and 0 days for hospital cohorts. This might have induced left censoring in the ambulatory cohorts, at the same time improving data completeness. In hospital data, medical history which is not recorded at admission was lost.
- Smoking was not captured in any of the databases, and it was a known limitation.
- Specialty of heath care provider is poorly recorded in all databases

Exposures

- Corticosteroid use for COVID-19 was not captured in prevalent cohorts
- Respiratory support was never captured and although it was expected that minimally invasive respiratory support (via mask) is unlikely to be coded, the invasive respiratory support was expected to appear in this population.

Outcomes

- Hospital discharge was not captured as an outcome and it was later confirmed by data partners that no specific code is used for this and the end of visit is considered to be the discharge event.
- It is known that mortality information (vital status) is under-reported in DA Germany, LPD France and LPD Italy, therefore the estimates from these countries are underestimates of the true mortality rates.

A potential limitation of any network study using a multitude of data sources from across different geographies, environments and systems is the potentially limited comparability of the study variables, in particular records of medical events. The Common Data Model greatly improves comparability but cannot fully account for all differences in data provenance. Heterogeneity of results across databases prevented pooling of many estimates and therefore the power of a combined data analysis could not be fully utilised.
The calculated incidences of uncommon, rare or very rare AEs could not be included in the output because of patient identifiability concerns related to small numbers. Hence, the selective exclusion of low values for some but not all databases yields a distorted picture of the true average AE incidences across the different data sources and might lead to overestimation of IRs.

9.2 Generalizability

The study has good generalisability considering the wide range of databases included.

However, for most part there is a high heterogeneity among databases (and countries), which precluded meta-analysis of many AEs and outcomes investigated. There are several sources of heterogeneity, including differences in the treatment, the treated population, database related heterogeneity or methodological heterogeneity. There is also a variability in disease severity, with milder/less

symptomatic cases more likely presenting in outpatient and primary care EHR, and more severe ones in hospital databases. In this study, as we employed a CDM and common analytics, the database and methods related heterogeneity should be minimised. Heterogeneity in observational studies is a well research problem, and not completely solved by the use of a CDM. Madigan et al suggest that 20%–40% of observational database studies can swing from statistically significant in 1 direction to the opposite direction depending on the choice of database, despite holding study design constant. (38)

Section 10.0 Conclusions

This was a federated network study in 14 data sources from 9 countries (Europe and US) from ambulatory and hospital setting set up as a proof of concept study for testing of the E-CORE network.

This study provides a good understanding of the utilisation patterns of systemic glucocorticoids in COVID-19 patients both in ambulatory and hospital settings in Europe and the US. In line with clinical practice, more patients are treated with steroids in hospital than in the ambulatory setting, while the dose and the treatment duration are largely in line with recommendations.

The most common AEs were infection related, suggesting confounding by indication. Patients in hospital cohorts had generally more AEs than those in ambulatory setting.

The E-CORE included 6 more databases than initially envisaged in the technical specification, with a balanced mix of ambulatory and hospital databases. The main challenges were the high heterogeneity and low number of patients for some rare outcomes.

We conclude that E-CORE network can be successfully used identifying cohorts of Covid-19 patients and for studying effects of COVID-19 therapies in an international setting.

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Appendix 1 Data Sources

Belgium

Longitudinal Patient Database (LPD) Belgium

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

France

Longitudinal Patient Database (LPD) France

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

APHM (France)

The AP-HM is a public university hospital system with 4 hospitals, 3,400 beds and more than 12,000 health care professionals. The AP-HM is one the largest health centers in France (after Paris and Lyon). For adults and children, the AP-HM provides hospital care services going from primary care to cutting-edge treatments of complex and rare pathologies. Approximately 300,000 hospitalizations are recorded every year at the APHM, involving approximately 210,000 patients. The information system includes multiple data sources with electronic medical record (Axigate, Cimaise), treatment prescription and deliverance (Pharma), oncology treatment (Chimio), Biology, imaging, Research (Redcap for cohorts), PMSI (Programme de Médicalisation des Systèmes d'Information, french DRG). The PMSI is the French medico-administrative database for all hospitalizations based on diagnosis related-groups (DRG) that can be grouped into diagnostic categories. All the stays are coded using the International Classification of Disease (ICD-10th version). The data are collected and stored for more than 10 years (depending on the sources. We made the choice to take data from 2013 which is when reliable EHR data starts to be really dense) with more than 1 billion data elements. From all these data sources we have already developed several ETLs (using JAVA) to concentrate the different relevant databases into a database we have called IATROS. It is on this unified database that that white rabbit tool has been run, giving the fields in appendix 1. This database is a PostgreSQL one that for now contains information from Axigate, biology, pharmacy prescription and Cora (economic evaluation). In these databases, COVID-19 are identified in France either through lab test results (positive PCR-RT test) or through CIM10 condition codes (rules established by national ATIH). The information that is still not present in this merged database is psychiatry (Cimaise) and clinical research (Redcap).

Italy

Longitudinal Patient Database (LPD) Italy

LPD Italy is comprised of anonymised patient records collected from software used by GPs during an office visit to document patients' clinical records. Data coverage includes over 2M patient records with at least one visit and 119.5M prescription orders across 900 GP practices. Dates of service include from 2004 through present. Observation time is defined by the first and last consultation dates. Drugs are captured as prescription records with product, quantity, dosing directions, strength, indication and date of consultation.

Germany

Disease Analyser (DA) Germany

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

Technical University Hospital Carl Gustav Carus Academic Hospital (Germany)

The University Hospital Academic Hospital with its 20 clinics, four institutes and ten interdisciplinary centres is the city's largest hospital and the only hospital of maximal care in East Saxony. Each year, 67,900 patients receive state-of-the-art medical treatment. With 1,300 in-patient beds and 95 out-patient facilities we offer the whole range of medical service to highest quality standards, treating an average of 60,000 patients per year. Within the hospital there are centres of competence for the treatment of cancer, vascular disease and many more to meet the requirements of an interdisciplinary approach.

UK

IQVIA Medical Research Data (IMRD) UK

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

Health Informatics Centre (Scotland)

The Health Informatics Centre (HIC) is a long-standing Trusted Research Environment (TRE) on behalf of Scottish Government. HIC maintains a clinical data repository of eHealth data covering approximately

20% of the Scottish population. Information includes up to date prescribing and hospitalisation data, diagnoses and interventions, lab tests and deaths. Some of the core datasets provide a continuous record extending back approximately 30 years. The eHealth repository combines routine collected datasets for the Tayside and Fife population and Tayside, with local speciality research, and clinical datasets. All HIC's clinical datasets are fully indexed and electronically linkable.

Spain

Information System for Research in Primary Care (SIDIAP), IDIAP Jordi Gol (Spain)

SIDIAP is collected from EHR records of patients receiving primary care delivered through Primary Care Teams (PCT), consisting of GPs, nurses and non-clinical staff. The Catalan Health Institute manages 286 out of 370 such PCT with a coverage of 5.6M patients, out of 7.8M people in the Catalan population (74%). The database started to collect data in 2006. The mean follow-up is 10 years. The observation period for a patient can be the start of the database (2006), or when a person is assigned to a Catalan Health Institute primary care centre. Date of exit can be when a person is transferred-out to a primary care centre that does not pertain to the Catalan Health Institute, or date of death, or date of end of follow-up in the database. Drug information is available from prescriptions and from dispensing records in pharmacies. Drugs not prescribed in the GP setting might be underreported; and disease diagnoses made at specialist care settings are not included. Studies using SIDIAP data require previous approval by both a Scientific and an Ethics Committee.

Hospital de Madrid (HM) Hospitales (Spain)

Hospital de Madrid (HM) Hospitales data are made available through partnership with SIDIAP. The HM Hospitales database covers in-patient care delivered across a network of private hospitals in Spain. HM Hospitales covers more than 17M patients, out of whom a subset will be catalogued and followed for acute care delivered for suspected COVID-19 onset. This database covers more than 2300 confirmed COVID-19 cases and all in-patient hospital care, including the data of admission, conditions, procedures and medicines dispensed in hospital, date of discharge, and date of known death or date of end of follow-up in the database. Studies using HM Hospitales data require review and approval from data custodians at SIDIAP authorised to execute observational network analyses. The number of newly diagnosed patients in each database per month since the outbreak of COVID-19 can be derived from the databases.

Parc Salut Mar Barcelona (includes Hospital del Mar and Hospital de l'Esperança) (Spain)

The IMASIS information system is the Electronic Health Record (EHR) system of the Parc Salut Mar Barcelona, which is a complete healthcare services organization. Currently, this information system includes the clinical information of two general hospitals (Hospital del Mar and Hospital de l'Esperança), one mental health care center and one social-healthcare center in the Barcelona city area (Spain). IMASIS includes clinical information from patients who have used the services of this healthcare system since 1989 and from different healthcare settings such as admissions, outpatients, emergency room and major ambulatory surgery with a mean of 6.37 years of patient follow-up. The database contains hospital-based information on approximately 1.5 million patients and around 1 million of them have at least one diagnosis coded using The International Classification of Diseases ICD-9-CM or the ICD-10-CM. IMASIS-2 is the relational model database containing anonymized patient information from IMASIS used for research purposes.

The Netherlands

Integrated Primary Care Information (IPCI), The Netherlands

The IPCI is a longitudinal observational database containing routinely collected data from EHR records of patients registered with GPs throughout the Netherlands. The current database includes patient records from 2006 on, when the size of the database started to increase significantly. In 2016, IPCI was certified as Regional Data Center. Since 2019 the data is also standardized to the OMOP CDM, enabling collaborative research in a large network of databases within the OHDSI. The database currently (January 1, 2021) contains 2.5 million patients records with a median follow-up duration of 4.7 year. The number of active patients is 1.4 million, which comprises 8.1% of the Dutch population of 17 million. The age distribution of the patients in IPCI is a good representation of the National age distribution as shown in the image on the right. Patient data in the GP records include demographic information, patient complaints and symptoms, diagnoses, lab results, lifestyle factors, referral notes from consultants, and hospital admissions. The medical records of a patient contain all medical information from primary care and part of that from secondary care such as referral and discharge letter. Approval needs to be obtained for each study from the Governance Board.

Serbia

Clinerion and Heliant

The data owner is the University Clinical Center of Serbia and the hospital information system in use at this university is Heliant Health. Heliant Health will be used for this study, which is a leading software provider within Serbia. Heliant Health information system is a web application that supports all kinds of interactions between the patients and their healthcare professionals within an institution. Approximately 200 healthcare institutions are included and within the electronic medical records, diagnoses are coding using the ICD-10 coding system. Clinerion and Heliant's proprietary technologies comply with international patient privacy and data security regulations. Both Clinerion and Heliant are in charge of OMOP'ing the data for this study.

US

Hospital Charge Data Master (United States)

Anonymized patient level data are sourced from hospital charge data masters (CDM) and collected from resource management software within short-term, acute-care and non-federal hospitals. Hospital charge masters are not a true EHR. It is an in-patient specific view of all things that are ordered in a hospital, captured for revenue purposes. The data covers over 86 million patients with 530 million medical events. The database contains the quantity of administered drugs including prescription and over-the-counter medicines, vaccines and large-molecule biologic therapies.

Appendix 2 Operational status at data lock point

	Databases	Status of results	Reason for absence from the report
1	LPD Belgium	Received fully but excluded	Insufficient number of patients with COVID-19 (less than 50 patients in any of the cohorts) therefore this database was excluded from the results
2	LPD France	Received fully	
3	LPD Italy	Received fully	
4	DA Germany	Received fully	
5	IMRD UK	Received fully	
6	Hospital Charge Data Master US	Received fully	
7	SIDIAP	Received fully	
8	HM Hospitales	Received fully	
9	IPCI	Received fully	
10	Serbia Clinerion and Heliant	Received fully	
11	Health Informatics Centre	Received fully	Not included in the meta-analysis due to later receipt of results. Included in the rest of the report.
12	APHM France	Received fully	
13	IMASIS	Received fully	
14	Academic Hospital Germany	Received fully	