Study Report

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DARWIN EU® - Drug utilisation of salbutamol products for inhalation and therapeutic alternative inhalation products

Authors: M. Amini, K. Verhamme

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Study title	DARWIN EU® - Drug utilisation of salbutamol products for inhalation and therapeutic alternative inhalation products
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Active substance	1. Inhalation drugs as reliever therapy:
	• Salbutamol
	    o Dry powder (dry powder inhalers)
	    o Suspension / solution (metered-dose inhalers)
	    o Liquid solution (nebulised solution)
	• Short acting beta-2 agonists other than salbutamol:
	    o Terbutaline
	    o Fenoterol
	• Short acting anticholinergic drugs:
	    o Ipratropium bromide
	    o Oxitropium bromide
	• Combinations of beta-2 agonists and anticholinergics:
	    o Fenoterol + ipratropium bromide
	    o Salbutamol + ipratropium bromide
	• Formoterol
	• Formoterol + inhaled corticosteroids (ICS):
	    o Formoterol + beclomethasone
	    o Formoterol + budesonide
	• Salbutamol + ICS:
	    o Salbutamol + beclomethasone
	    o Salbutamol + budesonide
	2. Salbutamol administered orally

Medicinal product	n/a
Research question and objectives	What is the real-world use of salbutamol (inhaled formulations)? 1. To describe the overall rates of prescribing inhaled salbutamol (i.e. all drug device types combined) by calendar time (month, year) and by data source. 2. To describe the rates of prescribing inhaled salbutamol by type of device, calendar time (year, month), and by data source. 3. To describe the rates of prescribing other inhaled alternatives and oral salbutamol by calendar time (month, year) and by data source. 4. To describe the distribution of predefined indication of use, sex, and defined age groups for inhaled salbutamol, stratified by device type and years.
Countries of study	United Kingdom, The Netherlands, Spain, Denmark, Germany, Croatia
Author(s)	M. Amini, m.amini@darwin-eu.org K. Verhamme, k.verhamme@darwin-eu.org

TITLE

DARWIN EU® - Drug utilisation of salbutamol products for inhalation and therapeutic alternative inhalation products

1. DESCRIPTION OF STUDY TEAM

Study team role	Names	Organisation
Study Project Manager/Principal Investigator	Marzyeh Amini Katia Verhamme	Erasmus MC
Data Scientist(s)	Cesar Barboza	Erasmus MC
Epidemiologist/ Clinical Domain Expert	Marzyeh Amini Guido van Leeuwen Katia Verhamme	Erasmus MC
Data Partner*	**Names**	**Organisation**
CPRD-GOLD	Antonella Delmestri	University of Oxford
DK-DHR	Claus Møldrup Elvira Bräuner Susanne Bruun Tine Iskov Kopp Cæcilie Brinth Christiansen	Danish Medicines Agency (DKMA)
IMASIS	Miguel-Angel Mayer Maria Angeles Leis Machin Juan Manuel Ramirez Anguita	IMIM and PSMAR
IPCI	Katia Verhamme	Erasmus MC
IQVIA DA	Gargi Jadhav Isabella Kacmarczyl Akram Mendez Dina Vojinovic	IQVIA
NAJS	Jakov Vuković Ivan Pristaš Anamaria Jurčević Marko Čavlina Antea Jezidžić Pero Ivanko	The Croatian National Institute of Public Health
SIDIAP	Talita Duarte-Salles Anna Palomar Agustina Giuliodori Picco Irene López	IDIAPJGol

*Data partners' role is to execute code at their data source, review and approve their results. These people do not have an investigator role.

2. DATA SOURCES

This study used routinely collected health data from 7 data sources in the DARWIN EU® network of data partners from 6 European countries. All data sources were previously mapped to the OMOP CDM.

Data sources

1. Clinical Practice Research Datalink (CPRD-GOLD), United Kingdom
2. Danish Data Health Registries (DK-DHR), Denmark
3. Institute Municipal Assistència Sanitària Information System (IMASIS), Spain
4. Integrated Primary Care Information (IPCI), Netherlands
5. IQVIA Disease Analyzer Germany (IQVIA DA), Germany
6. Croatian National Public Health Information System (NAJS), Croatia
7. The Information System for Research on Primary Care (SIDIAP), Spain

These data sources fulfilled the criteria required for population-level and patient-level drug utilisation while covering different regions of Europe. Detailed information on the selected data sources is described in **Table 1**.

Table 1. Description of data sources used for this study and ability to answer objectives.

Country	Name of Data source	Health Care setting	Type of Data	Active subjects*	End of available data	Ability to answer study objectives
United Kingdom	CPRD-GOLD	Primary care	Electronic Healthcare Records (EHR)	2.92m	12/12/2024	1, 2, 3, and 4
Denmark	DK-DHR	Inpatient hospital care and secondary outpatient care	EHRs, registries, others	5.96m	31/07/2024	1, 2, 3, and 4
Spain	IMASIS	Inpatient hospital care and secondary outpatient care	EHR	149K	31/07/2024	1, 2, 3, and 4
Netherlands	IPCI	Primary care	EHR	1.25m	30/06/2024	1, 2, 3, and 4
Germany	IQVIA DA	Primary care and outpatient secondary care	EHR	4.72m	30/06/2024	1, 2, 3, and 4
Croatia	NAJS	Primary care, outpatient specialist care, and inpatient care	Registries	4.22m[#]	31/12/2024	1, 2, 3, and 4
Spain	SIDIAP	Primary care	EHR	5.95m	30/06/2023	1, 2, 3, and 4

* Active Persons is defined as the maximum number of persons in an observation period, in the last 6 months.

[#] The person table in the NAJS data source also includes deceased individuals and those who were previously insured. All individuals met the definition of "active subjects" by contributing person-time within their respective observation periods.

M= million, CPRD-GOLD= Clinical Practice Research Datalink (CPRD) GOLD; DK-DHR=Danish Data Health Registries; IMASIS=Institute Municipal Assistència Sanitària Information System; IPCI=Integrated Primary Care Information; DA= Disease Analyzer; NAJS=Croatian National Public Health Information System; SIDIAP=The Information System for Research on Primary Care.

3. ABSTRACT

Title

DARWIN EU® – Drug utilisation of salbutamol products for inhalation and therapeutic alternative inhalation products

Rationale and background

Salbutamol is frequently used in patients with asthma and chronic obstructive pulmonary disease (COPD) due to its rapid bronchodilation effects. There has been an increase in demand for salbutamol inhalation products, which cannot be met by the current manufacturing capacity, combined with other manufacturing issues for some of the products. These issues have led to shortages of some salbutamol inhalation products in most EU/EEA countries. Shortages of salbutamol products might impact the management of acute symptoms and require the use of alternative therapies.

The aim of the study was to understand if prescribing of salbutamol inhalation products has been increasing over the last few years in Europe, which could in turn inform prevention of future shortages and mitigation measures. Secondly, to explore how prescribing patterns of therapeutic alternative inhalation products co-vary with prescribing of salbutamol inhalation products, which may indirectly reflect potential consequences of shortages.

Research question and objectives

Research questions

What is the real-world use of salbutamol (mainly focusing on inhaled formulations)?

Objectives

The aim of this study was to determine the real-world use of salbutamol (inhaled formulations).

The specific objectives of this study were:

1. To describe the overall rate of prescribing inhaled salbutamol (i.e. all drug device types combined) by calendar time (month, year) and by data source.
2. To describe the rate of prescribing inhaled salbutamol by device type, calendar time (month, year), by data source.
3. To describe the rates of prescribing other inhaled alternatives and oral salbutamol by calendar time (month, year) and by data source.
4. To describe the distribution of predefined indication of use, sex, defined age groups for inhaled salbutamol, stratified by device types and years.

Methods

Study design

- Population-level cohort study for the calculation of prescription rates (objectives 1, 2, 3)
- Drug user cohort study to describe the indication of use of salbutamol (objective 4).

Study period

Study period was between 01/01/2015 to the end of available data.

Population

The study population included all individuals present in the data sources for objectives 1, 2, 3 and all individuals who received prescriptions for inhaled salbutamol in the study period for objective 4. In these populations, rates of prescribing inhaled salbutamol as well as other inhaled alternatives and the indication for use of inhaled salbutamol were explored. Patients needed to have at least 365 days of data visibility prior to the index date. The index date was the date of each prescribing of salbutamol (regardless of whether incident or prevalent) during the study period.

Variables

Outcomes

Drugs of interest consisted of reliever therapy, namely: (1) salbutamol inhalation products (administrated using the following devices: dry powder inhalers (DPIs), metered dose inhalers (MDIs), nebuliser solution), (2) Short-acting Beta-2 agonists (SABA) other than salbutamol (terbutaline, fenoterol), (3) short acting anticholinergic drugs (ipratropium bromide, oxitropium bromide), (4) fixed combinations of SABA + anticholinergic drug (fenoterol + ipratropium bromide; salbutamol+ ipratropium bromide), (5) formoterol, (6) formoterol + ICS (formoterol + beclomethasone; formoterol+ budesonide), (7) salbutamol+ ICS (salbutamol + beclomethasone; salbutamol + budesonide), (8) oral salbutamol.

Conditions of interest

Asthma, lower respiratory tract infection (LRTI), COPD and emphysema, chronic bronchitis, bronchospasm, and respiratory conditions due to inhalation of chemical agents were considered as indications for salbutamol use.

Other covariates

Sex, age, calendar months and years

Data source

1. Clinical Practice Research Datalink (CPRD-GOLD), United Kingdom
2. Danish Data Health Registries (DK-DHR), Denmark
3. Institute Municipal Assistència Sanitària Information System (IMASIS), Spain
4. Integrated Primary Care Information (IPCI), Netherlands
5. IQVIA Disease Analyzer Germany (IQVIA DA), Germany
6. Croatian National Public Health Information System (NAJS), Croatia
7. The Information System for Research on Primary Care (SIDIAP), Spain

Sample size

No sample size was calculated, as this was an exploratory study. To estimate prescribing rates of drug utilization of inhaled salbutamol products and other inhaled alternative in each data source, we used already collected available data. Thus, the sample size was driven by the availability of patients with the outcome of interest (i.e. salbutamol and other inhaled alternatives prescribing) within each data source.

<u>Statistical analysis</u>

Prescription rate calculation

Monthly and yearly prescription rates of inhaled, oral salbutamol and other inhaled alternatives (either incident or prevalent) per 100,000 person-months (PMs) were estimated, stratified by data source and by device type for salbutamol.

Characterisation of individuals being prescribed salbutamol

Patients were characterised in terms of frequency of predefined indication of inhaled salbutamol prescription around index date (±7 and -365 days of index date), sex, and age (at index-date, categorized) distribution, stratified by type of device and year.

For the calculation, we used Darwin EU® analytical tools, in particular the "*IncidencePrevalence*" R package and the "*DrugUtilization*" R package. Cell suppression was applied as required by data sources to protect individual's privacy meaning that cell counts <5 were masked.

<u>Results</u>

Yearly and monthly prescription rates of salbutamol inhalation products

Between 2015 and 2024, differences in the prescribing pattern of inhaled salbutamol products by device type were observed across European healthcare data sources. MDIs were most prescribed in IPCI, IQVIA DA, NAJS, and SIDIAP, while DPIs were mostly prescribed in CPRD-GOLD and DK-DHR, and nebuliser solution dominated in IMASIS, a hospital data source. In CPRD-GOLD, DPI yearly prescription rates increased steadily and surpassed MDIs, with both exceeding 900/100,000 PMs. In DK-DHR, yearly prescription rates for DPIs and MDIs rose modestly over the years, peaking at 306/100,000 PMs, while nebuliser solutions prescription remained below 11. IMASIS reported a notable rise in nebuliser solution prescriptions, from 203/100,000 PMs in 2015 to 923 in 2024. IPCI maintained a balanced prescription of MDIs and DPIs (ranging from 299 to 433), while IQVIA DA showed an increase in MDI yearly prescriptions from 135/100,000 PMs to 469. NAJS data indicated a decline in MDI prescriptions from 469 to 388, and in SIDIAP MDI prescription peaked at 1,104 before stabilizing around 1,068, with minimal prescription of DPIs. Monthly prescribing trends of salbutamol mirrored yearly trends with regional differences and seasonal peaks in winter. For example, in DK-DHR, DPI prescription increased from 283/100,000 PMs in August 2023 to 333 in December 2023. In SIDIAP, MDIs prescription rates peaked at 1,421 in December 2022, dropping to 600–900 in summer months. IMASIS showed a strong winter trend in nebuliser prescription, rising from 669 in April 2020 to a peak of 1,044 in January 2024. A marked spike in salbutamol prescribing was also seen in March 2020 across several sources (e.g., CPRD-GOLD, DK-DHR, IPCI, IQVIA DA, NAJS), coinciding with the onset of the COVID-19 pandemic.

Yearly and monthly prescription rates of salbutamol (inhaled and oral) compared to inhaled alternatives

Yearly prescription rate results showed that inhaled salbutamol, formoterol combined with ICS, and short-acting anticholinergic were the most frequently prescribed treatments across most data sources, while oral salbutamol, inhaled formoterol alone, and other SABAs (e.g., terbutaline, fenoterol) had much lower prescription. Monthly prescription rate trends of inhaled salbutamol varied across data sources with DK-DHR, IMASIS, and IQVIA DA showing increasing prescription of inhaled salbutamol, SIDIAP and IPCI remained stable, and CPRD-GOLD and NAJS showed a decline in prescription. A sharp peak in March 2020 was observed across multiple sources, likely reflecting increased respiratory treatment at the start of the COVID-19 pandemic. Formoterol + ICS showed consistently high and increasing prescription, especially in DK-DHR, where it surpassed inhaled salbutamol. Short-acting anticholinergic prescription remained high and stable in IMASIS, IPCI, and SIDIAP, but was lower than inhaled salbutamol and formoterol + ICS.

Age, sex, and indication of use of salbutamol inhalation products

From 2015–2024, prescribing patterns for inhaled salbutamol across European data sources varied by age, sex, indication of use, and over years. Adults aged 18–75 primarily used DPIs (3.6–39.9%) and MDIs (2.1–34.0%), with sex distribution generally balanced but showing a slight predominance of females for both device types. In contrast, nebuliser solutions were most often prescribed for children aged 2–11 years (up to 64.5%) and adults over 75 years (up to 50.6%). Asthma was the leading indication across devices (12.8–70.2%), while nebuliser solutions were mainly prescribed for LRTI (up to 87.1%). Over time, the prevalence of some indications among inhaled salbutamol users were increased, with LRTI rising sharply in SIDIAP (28% to 75%), IMASIS (24% to 83%), and NAJS (35% to 84%). Asthma remained stable, around 60% in DK-DHR and peaking at 55% in NAJS. COPD showed steady rates (20–40%) in DK-DHR, IQVIA DA, and NAJS, but stayed below 20% in SIDIAP and IPCI. Bronchospasm increased only in DK-DHR (25-40%), while chronic bronchitis showed modest indication of use in data sources IMASIS, IQVIA DA, NAJS, and SIDIAP, where it ranged from 5% to 30% over time and was infrequent across other sources.

<u>Conclusion</u>

In conclusion, the analysis of prescription rates for inhaled salbutamol and alternatives across European data sources reveals differences in usage patterns across data sources and over years, seasonal variations, and disparities in usage by age, sex, and indications. MDIs were the most prescribed inhalers in IPCI, IQVIA DA, NAJS, and SIDIAP, while DPIs dominated in CPRD-GOLD and DK-DHR, and nebuliser solutions were most prescribed in IMASIS, a hospital data source, especially among young children and the elderly. Asthma was consistently the leading indication for inhaled salbutamol, although prescriptions for LRTI became increasingly common for nebuliser solutions users over time, particularly in IMASIS and SIDIAP. Seasonal peaks in winter were evident across all devices of salbutamol and data sources. Inhaled alternatives, notably formoterol with corticosteroids and short-acting anticholinergics, also showed rising prescription, with patterns that may indirectly reflect the impact of salbutamol availability. These findings underscore the importance of proactive shortage prevention strategies and mitigation efforts to ensure consistent access to essential respiratory treatments, and to better understand how therapeutic alternatives may be leveraged during supply disruptions.

4. LIST OF ABBREVIATIONS

Acronyms/term	Description
CDM	Common Data Model
CC	Coordinating centre
CIPH	Croatian Institute of Public Health
COPD	Chronic Obstructive Pulmonary Disease
COVID-19	Coronavirus Disease 2019
CPRD	Clinical Practice Research Datalink
DARWIN EU®	Data Analysis and Real-World Interrogation Network
DK-DHR	Danish Data Health Registries
DOI	Declaration of Interests
DP	DARWIN-EU Data Partner
DPI	Dry powder inhaler
DQD	Data Quality Dashboard
DRE	Digital Research Environment
DUS	Drug Utilisation Study
EHR	Electronic Health Records
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EU	European Union
GDPR	General Data Protection Regulation
GINA	Global Strategy for Asthma Management and Prevention
GP	General Practitioner
HMA	The Heads of Medicines Agencies
ICD	International Classification of Diseases
ICS	inhaled corticosteroids
ID	Index date
IMASIS	Institut Municipal Assistència Sanitària Information System
IP	Inpatient
IPCI	Integrated Primary Care Information
IQR	Interquartile Range
IQVIA DA	IQVIA Data Analyzer Germany
LRTI	Lower respiratory tract infection
MDI	Metered-dose inhaler
NAJS	Croatian National Public Health Information System
NCA	National Competent Authority
OHDSI	Observational Health Data Sciences and Informatics

OMOP	Observational Medical Outcomes Partnership
OP	Outpatient
PM	Person month
RxNorm	Normalized names for clinical drugs
SABA	Short-acting Beta-2 agonists
SD	Standard Deviation
SIDIAP	The Information System for Research on Primary Care Spain
SNOMED	Systematized Nomenclature of Medicine
UK	United Kingdom
WHO	World Health Organisation
WONCA	World Organization of Family Doctors

5. AMENDMENTS AND UPDATES

None.

6. MILESTONES

Study deliverable	Timelines (planned)	Timelines (actual)
Draft Study Protocol	29 October 2024	29 October 2024
Final Study Protocol	20 November 2024	27 November 2024
Creation of Analytical code	20 November 2024	13 December 2024
Execution of Analytical Code on the Data	2nd December 2024	20 January 2025
Draft Study Report	16 December 2024	30 January 2025
Final Study Report	15 January 2025	25 July 2025

7. RATIONALE AND BACKGROUND

Salbutamol, a short-acting beta-2 agonist, is a critical therapeutic agent used primarily in the management of asthma and chronic obstructive pulmonary disease (COPD). Inhaled salbutamol provides rapid bronchodilation, which explains why salbutamol is used as reliever therapy. Over recent years, the prevalence of asthma and COPD in Europe has increased, partly due to aging populations and worsening air quality. This has led to a corresponding rise in the demand for salbutamol, particularly in urban areas where environmental triggers for respiratory conditions are more common.(1, 2)

Reported supply shortages of salbutamol inhalation products in Europe and other regions, such as the UK, alongside signals of a global increase in demand, highlight the need to explore whether salbutamol utilisation has increased across Europe.(3) Disruptions in the global pharmaceutical supply chain—exacerbated by events like the COVID-19 pandemic—have already highlighted vulnerabilities in the supply and availability of essential medications.(3, 4) Clear evidence of intermittent shortages has already emerged across multiple EU/EEA markets, largely driven by increased demand and manufacturing constraints and issues.(3) A shortage of salbutamol might have significant public health implications, as salbutamol is often used as reliever therapy for acute bronchoconstriction in both asthma and COPD patients.(3, 5) Without adequate supplies, patients may face difficulties managing acute exacerbations, increasing the risk of hospital admissions and morbidity.(6)

Additionally, a salbutamol shortage could create fluctuation effects across the respiratory care market, with increased demand for alternative inhalation therapies, such as other short acting bronchodilators, or a combination of inhaled corticosteroid with a bronchodilation drug.

Understanding current trends in salbutamol usage is therefore critical to inform preparedness, prevention, and mitigation strategies, allowing healthcare systems to anticipate shortages and mitigate the impact on public health.(7)

The aim of the study was to understand salbutamol inhalation products prescribing patterns over the last years in Europe to inform European Regulatory Network shortage preparedness and mitigation strategies. Secondly, to explore how prescribing patterns of therapeutic alternative inhalation products co-vary with prescribing of salbutamol inhalation products, which may indirectly reflect potential consequences of shortages.

8. RESEARCH QUESTION AND OBJECTIVES

Research question

What is the real-world use of salbutamol (inhaled formulations)?

Research objectives

The proposed objectives to be achieved in the study are described in **Table 2**.

Table 2. Primary and secondary research questions and objective.

A. Primary research question and objective.

Objectives 1, 2, and 3:	• To describe the overall rates of prescribing of inhaled salbutamol (i.e. all drug device type combined) by calendar time (month, year) and by data source. • To describe the rates of prescribing of inhaled salbutamol by type of device, calendar time (month, year), and by data source. • To describe the rates of prescribing of other inhaled alternatives and oral salbutamol by calendar time (month, year) and by data source.
Hypothesis:	n/a
Population *(key inclusion-exclusion criteria):*	The study population included all eligible individuals present in the data sources. To be eligible for the study, individuals needed to have at least 365 days of data visibility prior to index date.
Exposure:	None.
Comparator:	None.
Outcome:	1. Inhaled formulations: • Salbutamol o Dry powder (using dry powder inhalers) o Suspension / solution (using metered-dose inhalers) o Liquid solution (using nebuliser solutions) • Short-acting Beta-2 agonists (SABA) other than salbutamol: o Terbutaline o Fenoterol • Short acting anticholinergic drugs: o Ipratropium bromide o Oxitropium bromide • Fixed Combinations of beta-2 agonists and anticholinergics inhaled: o Fenoterol + ipratropium bromide o Salbutamol + ipratropium bromide • Formoterol: • Formoterol + inhaled corticosteroids (ICS): o Formoterol + beclomethasone o Formoterol + budesonide • Salbutamol + ICS:

	○ Salbutamol + beclomethasone ○ Salbutamol + budesonide **2.** Salbutamol administered orally
Time *(when follow up begins and ends)*:	Follow-up started on the latest of the following dates: i) study start date (1st January 2015) or ii) date on which individuals had 365 days of prior history. End of follow-up was defined as loss to follow-up, death, or end of observation period (the latest available data), whichever occurred first.
Setting:	Inpatient and outpatient setting using data from the following 7 data sources: CPRD-GOLD (United Kingdom), DK-DHR (Denmark), IMASIS (Spain), IPCI (Netherlands), IQVIA DA (Germany), NAJS (Croatia), SIDIAP (Spain).
Main measure of effect:	Monthly prescribing rates of inhaled salbutamol, oral salbutamol, and other inhaled alternatives, stratified by device type (i.e. only for inhaled salbutamol) and provided by data source.

B. Secondary research question and objective.

Objective 4:	To describe characteristics of individuals treated with inhaled salbutamol in terms of indication of use, sex, and age, stratified by device type and year, and provided by data source.
Hypothesis:	n/a
Population *(key inclusion-exclusion criteria)*:	The study population included all individuals prescribed inhaled salbutamol in the period between 01/01/2015 to the end of available data. To infer the treatment indications, windows of ±7 days and -365 days of the index date were used.
Exposure:	None.
Comparator:	None.
Outcome:	Inhaled salbutamol administrated using • DPIs • MDIs • Nebuliser solution
Time *(when follow up begins and ends)*:	Characteristics were described at the start date of each prescription (i.e. index date) for inhaled salbutamol. To assess the indication of use, a window of ±7 days and -365 days around the index date was explored.
A Setting:	Inpatient and outpatient setting using data from the following 7 data sources: CPRD-GOLD (United Kingdom), DK-DHR (Denmark), IMASIS (Spain), IPCI (Netherlands), IQVIA DA (Germany), NAJS (Croatia), SIDIAP (Spain).
Main measures:	The descriptive characteristics were measured as counts and proportions for binary categorical variables, and as mean/median with interquartile range (IQR) for continuous variables.

9. RESEARCH METHODS

9.1. Study type and study design

The study types with related study designs are described in the

Table 3 below, and were selected from the Complete Catalogue of Standard Data Analyses.(8)

A cohort study was conducted using routinely collected health data from 7 data sources. The study was comprised of two consecutive parts:

- A population-level cohort study was conducted to address objectives 1 ,2, 3; to assess the yearly/monthly prescription rates of medication with inhaled salbutamol, oral salbutamol, and other inhaled alternatives, stratified by device type for inhaled salbutamol and provided by data source.
- A patient-level characterisation study was used to address objective 4; to describe characteristics of individuals treated with inhaled salbutamol in terms of indication of use, sex, and age categories, stratified by device type and years and provided by data source.

Table 3. Description of potential study types and related study designs.

Study type	Study design	Study classification
Population-Level DUS	Population level cohort	Off the shelf
Patient-Level DUS	Drug user cohort	Off the shelf

9.2. Study setting and data sources

This study used routinely collected health data from 7 data sources in the DARWIN EU® network of data partners from 6 European countries. All data sources were previously mapped to the OMOP CDM.

Data sources

1. Clinical Practice Research Datalink (CPRD-GOLD), United Kingdom
2. Danish Data Health Registries (DK-DHR), Denmark
3. Institute Municipal Assistència Sanitària Information System (IMASIS), Spain
4. Integrated Primary Care Information (IPCI), Netherlands
5. IQVIA Disease Analyzer Germany (IQVIA DA), Germany
6. Croatian National Public Health Information System (NAJS), Croatia
7. The Information System for Research on Primary Care (SIDIAP), Spain

These data sources fulfilled the criteria required for population-level and patient-level drug utilisation while covering different regions of Europe.

When it comes to assessing the reliability of data sources, the data partners were asked to describe their internal data quality process on the source data as part of the DARWIN EU® onboarding procedure. To further ensure data quality, we utilised the *Achilles* tool, which systematically characterises the data and generates data characteristics such as age distribution, condition prevalence per year, data density, and measurement value distribution, which can be compared against expectations for the data. Additionally, the data quality dashboard (DQD) provides more objective checks on plausibility consistently across the data sources.

In terms of relevance, the selection of data sources was based on the availability of data on the selected drugs of interest and the possibility to generate results promptly. The DARWIN EU® portal, as well as information from the onboarding documents, were used to assess whether data sources have information on use of salbutamol or other inhaled alternatives. Data within the DARWIN EU® portal was maintained up to date by extracting the release dates for each dataset in the network and monitoring when data were out-of-date with the expected refresh cycle (typically quarterly or half-yearly). In addition, it is important to have a clear understanding of the time covered by each data source release, as this can vary across different domains. To facilitate this, the C*DMOnboarding* (and *Achilles*) packages contain a 'data density' plot. This plot displays the number of records per OMOP domain monthly. This allows getting insights into when data collection started, when new sources of data were added, and until when data was included. In addition, at time of inviting data partners (DPs), they were informed about study objectives and asked whether they could participate in the study.

Detailed information on data sources is described in **Table 1**.

Clinical Practice Research Datalink GOLD, United Kingdom (University of Oxford)

The Clinical Practice Research Datalink (CPRD) GOLD is a database of anonymised electronic health records (EHR) from General Practitioner (GP) clinics in the UK that use the Vision® software system for their management.(9) The source population encompasses 98% of the UK, registered with GPs responsible for non-emergency care and referrals. Participating GPs provide CPRD EHR for all registered patients who did not specifically request to opt out of data sharing. Covering 4.6% of the current UK population, GOLD includes 4.9% of contributing GP practices, providing comprehensive information within its defined source population. GOLD contains data from all four UK constituent countries, and the current regional distribution of its GP practices is 5.7% in England, 55.6% in Scotland, 28.4% in Wales, and 10.2% in Northern Ireland (May 2022).

GOLD data include patient's demographic, biological measurements, clinical symptoms and diagnoses, referrals to specialist/hospital and their outcome, laboratory tests/results, and prescribed medications. GOLD has been assessed and found broadly representative of the UK general population in terms of age, gender, and ethnicity.(9) GOLD has been widely used internationally for observational research to produce nearly 3,000 peer-reviewed publications, making GOLD the most influential UK clinical database so far(10-12).

Danish Data Health Registries (DK-DHR), Denmark

Danish health data is collected, stored, and managed in national health registers at the Danish Health Data Authority, and covers the entire population, which makes it possible to study the development of diseases and their treatment over time. There are no gaps in terms of gender, age, and geography in Danish health data due to mandatory reporting on all patients from cradle to grave, in all hospitals and medical clinics. Personal identification numbers enable linking of data across registers, so it captures data on all Danes throughout their lives, regardless of whether they have moved around the country. High data quality due to standardisation, digitisation, and documentation means that Danish health data is not based on interpretation. The Danish Health Data Authority is responsible for the national health registers and for maintaining and developing standards and classifications in the Danish healthcare system. Legislation ensures balance between personal data protection and use. The current data release includes data on the entire Danish population of 5.9 million persons from 1995. It includes data from the following registries: The central Person Registry, The National Patient Registry, The Register of Outpatient Prescription Retrievals, The National Cancer Register, The Cause of Death registry, and Coronavirus disease 2019 test and vaccination Registries.

The Institute Municipal Assistència Sanitària Information System (IMASIS), Spain

The Institute Municipal Assistència Sanitària Information System (IMASIS) is the Electronic Health Record (EHR) system of Parc de Salut Mar Barcelona (PSMar), which is a complete healthcare services organisation. Currently, this information system includes and shares the clinical information of two general hospitals (Hospital del Mar and Hospital de l'Esperança), one mental health care centre (Centre Dr. Emili Mira), and one social-healthcare centre (Centre Fòrum), including emergency room settings, that are offering specific and different services in the Barcelona city area (Spain). At present, IMASIS includes clinical information from around 1 million patients with at least one diagnosis and who have used the services of this healthcare system since 1990, and from different settings such as admissions, outpatients, emergency room, and major ambulatory surgery. The diagnoses are coded using The International Classification of Diseases ICD-9-CM and ICD-10-CM. The average follow-up period per patient in years is 6.37 (SD±6.82). IMASIS-2 is the anonymized relational database of IMASIS which is used for mapping to OMOP, including additional sources of information such as the Tumours Registry.

The Integrated Primary Care Information (IPCI), the Netherlands

The Integrated Primary Care Information (IPCI) database is a longitudinal observational database containing routinely collected data extracted from computer-based patient records of a selected group of general practitioners (GPs) across the Netherlands.(13) IPCI was started in 1992 by the department of Medical Informatics of the Erasmus University Medical Center in Rotterdam. The current database includes patient records from 2006 on, when the size of the database started to increase significantly. The demographic composition of the IPCI population mirrors that of the general Dutch population in terms of age and sex. Although the geographical spread is limited, GP practices are located in urban and non-urban areas.

Patient-level data includes demographic information, patient's complaints and symptoms, diagnoses, laboratory test results, lifestyle factors, and correspondence with secondary care, such as referral and discharge letters. For complaints, symptoms, and diagnoses, Dutch GPs use International Classification of Primary Care (ICPC-1) coding, an international standard developed and updated by the World Organization of Family Doctors' (WONCA) International Classification Committee.

IPCI data quality has been previously documented, and IPCI has proved valuable for epidemiological studies.(14-18) In terms of quality control, extensive quality control steps are performed prior to each data release. These include comparison of patient characteristics between practices and checks to identify abnormal temporal data patterns in practices. Additional checks include over 200 indicators related to population characteristics (e.g. reliability of birth and mortality rates) and medical data (e.g. availability of durations of prescriptions, completeness of laboratory results, availability of hospital letters and prescriptions, proportion of patients with blood pressure measurement, etc.)(13) Based on this information, two quality scores have been created. Practices with low scores have been excluded.

IQVIA Disease Analyser (DA), Germany

IQVIA Disease Analyzer (DA) Germany is a database of de-identified electronic medical records from specialized and general primary practices (GP) in Germany since 1992. This dataset encompasses approximately 3% of all outpatient practices within Germany, ensuring a substantial representation of the national healthcare landscape.(19, 20) The sampling methods used for practice selection, taking into account physician's demographics, specialty focus, community size category, and federal state location, was instrumental in constructing a database that accurately mirrors the diverse spectrum of healthcare providers in the country.(19, 20) Consequently, data within the IQVIA DA Germany database has been demonstrated to be representative of general and specialised practices throughout Germany.

The database contains demographics records, basic medical data, disease diagnosis according to International Classification of Diseases, 10th revision (ICD-10), and prescription records.(20) While the database partly records information on deaths and procedures, it currently does not support linkage with external data sources and therefore information on mortality is incomplete. Routine updates are conducted at regular intervals. The quality of data is assessed based on several criteria, including completeness of information and correctness (e.g. linkage between diagnosis and prescriptions). IQVIA DA Germany is suitable for pharmacoepidemiologic and pharmacoeconomic studies as previously demonstrated.(20-22)

National Public Health Information System (NAJS), Croatia

The National Public Health Information System (Nacionalni javnozdravstveni informacijski sustav - NAJS) is an organised system of information services by the Croatian Institute of Public Health (CIPH). This database was established in 1998, with nationwide coverage, representing approximately 5.4 million inhabitants. Settings covered include public primary, secondary/outpatient, and inpatient care. Data is retrieved primarily from EHR and holds information on demographics, inpatient and outpatient visits, conditions and procedures, drugs (outpatient and inpatient prescriptions), measurements, and inpatient and outpatient dates of death. NAJS provides linkage between medical and public health data collected and stored in health registries and other health data collections, including cancer registry, mortality, work injuries, occupational diseases, communicable and non-communicable diseases, health events, disabilities, psychosis and suicide, diabetes, drug abuse, and others. Data is being collected from 2015 in Central electronic health information system in Croatia, and from 2017 in National public health information system. The CDM population comprises all publicly insured persons residing in Croatia starting in 2017.

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

The Information System for Research in Primary Care (SIDIAP) is a dynamic database of pseudo-anonymized electronic health records of the primary care patient population in Catalonia, Spain.(23) It contains data of approximately 80% of the Catalan population registered in over 280 primary care practices throughout Catalonia since 2005.

The database contains data recorded in primary care centres on a daily basis. Additionally, it integrates data from external sources, including biomarkers data from laboratories and records of drug prescription and dispensation. The dataset covers demographics, all-cause mortality, disease diagnoses classified under the International Classification of Diseases 10th revision (ICD-10), prescription and dispensation records of drugs, results of laboratory tests, socio-economic indicators, vaccination records, lifestyle information, parent–child linkage, and various clinical parameters. Additional data from other data sources such as hospital discharges, mental health centres, or specific disease registries can be obtained through diverse linkages. The demographic composition within SIDIAP closely mirrors that of the broader Catalan population, encompassing a representative spectrum of geographic distribution, age, and sex proportions. The database is updated every 6 months.

SIDIAP data quality has been previously documented, and SIDIAP has proved valuable for epidemiological studies.(21, 24-31) In terms of data integrity and reliability, SIDIAP has been subject to rigorous evaluation. Quality checks have been implemented including central identification of duplicate patient ID and visual inspection for temporal patterns in the registry of a certain variable. Furthermore, the data undergoes assessment for availability (longitudinally and reliability), plausibility (range checks and unusual values), and consistency using visualization tools. Specifically, for biochemistry data, consistency for measurements taken in different laboratories is assessed, and unit conversion is undertaken when needed.

9.3. Study period

The study period was from 1st January 2015 to the most recent data available for each contributing data sources (see **Table 1**).

9.4. Follow-up

For the population-level analysis, follow-up was started on the respective date of the latest of the following: i) study start date (1st January 2015) or ii) date on which individuals had 365 days of prior history (not for children < 1 year of age). End of follow-up was defined as loss to follow-up, death, or end of observation period (the latest available data), whichever occurred first.

For the patient-level analysis, the follow-up began and was limited to the index date, which is the date the patient received each prescription for salbutamol inhalation products. There is no extended observation period beyond this date. The follow-up ended on the index date itself, as the study is structured as a cross-sectional snapshot rather than a longitudinal observation.

Operational definition of index date and other primary time anchors are described in **Table 4**.

Table 4. Operational definition of time 0 (index date) and other primary time anchors.

Study population name(s)	Time Anchor Description (e.g. time 0)	Number of entries	Type of entry	Washout window	Care Setting[1]	Code Type[2]	Diagnosis position	Incident with respect to...	Measurement characteristics/ validation	Source of algorithm
Objectives 1,2, and 3 - - all patients from the data source eligible for the study	Date of the start of study period with sufficient prior data availability.	Multiple entries	The first date of eligibility of patients	n/a	OP & IP	n/a	n/a	n/a	n/a	n/a
Objective 4 – all patients from the data source eligible for the study and being prescribed inhaled salbutamol	Each date during follow-up on which an individual was prescribed inhaled salbutamol (irrespective whether incident or prevalent use).	Multiple entries	Prescription	n/a	OP & IP	RxNorm	n/a	n/a	n/a	n/a

[1] IP = inpatient, OP = outpatient, n/a = not applicable
[2] The type(s) of clinical codes that were used to define the time 0 (or another primary anchor) criterion.

Prescribing rate estimation first required identifying an appropriate denominator population and determining the corresponding observation time. Study participants in the denominator population were contributing person time at risk, as described above in section **Follow-up**.

An example of entry and exit into the denominator population is shown in **Figure 1**. In this example, person ID 1 already had sufficient prior history before the study start date and the observation period ended after the study end date, so this person contributed during the entire study period. Person IDs 2 and 4 entered the study only when they had sufficient prior history. Person ID 3 left when exiting the data source (the end of the observation period). Lastly, person ID 5 had two observation periods in the data source. The first period contributed time from study start until end of observation period, the second started contributing time again once sufficient prior history was reached and exited at study end date.

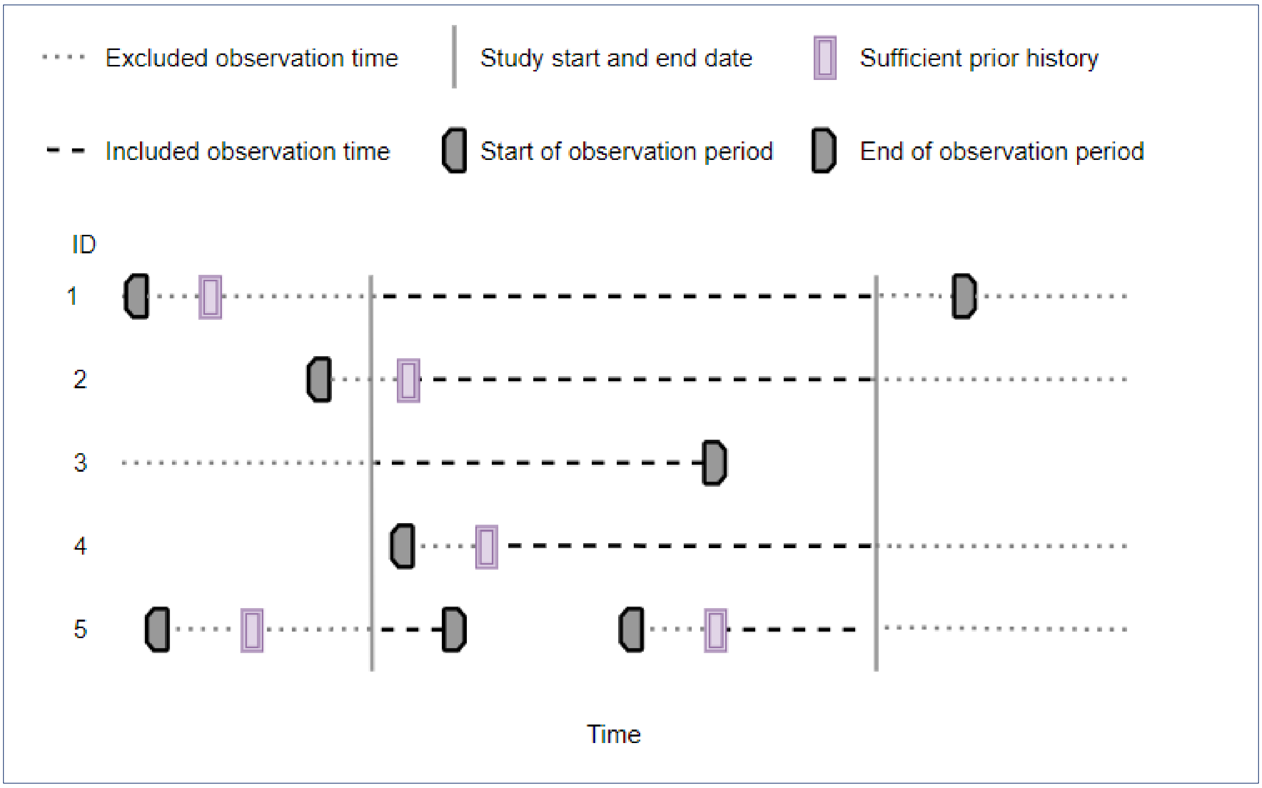

Figure 1. Included observation time for the denominator population.

9.5. Study population with inclusion and exclusion criteria

9.5.1. Population-level utilisation of selected medicinal products

The study cohort included all individuals registered in the data source between 1st January 2015 and the most recently available data, with at least 365 days of data visibility prior to becoming eligible for study inclusion. This requirement of at least 365 days of prior data history was not applied to children <1 year of age. Applying at least 365 days prior data history ensures more stable denominators (i.e. one knows the patient has been registered with the data collecting medical practice for some time) and allows for better characterization of the patients, for instance regarding the indication of use.

Patients were excluded if they did not have sufficient data availability prior to study start.

9.5.2. Patient-level utilisation of selected medicinal products

The study cohort included all users of inhaled salbutamol in the period between 1st January 2015 and with at least 365 days of data visibility prior to the first prescription of salbutamol since study start. This requirement of at least 365 days of prior data history was not applied to children <1 year of age.

At least 365 days data history is needed to accurately identify the indication for use (e.g. asthma, COPD), as these are determined from diagnostic codes recorded in the year before prescribing. Without this information, there is a risk of incorrectly assigning the reason for the prescription.

The operational definitions of the inclusion and exclusion criteria are presented by means of **Table 5** and **Table 6**, respectively.

Table 5. Operational definitions of inclusion criteria.

Criterion	Details	Order of application[2]	Assessment window	Care Settings[1]	Code Type	Diagnosis position	Applied to study populations:	Measurement characteristics/ validation	Source for algorithm
Prior data source history with an observation period between 2015 and the most recent available data	Individual has to have a minimum of one year observation in the data source (except for children <1 year of age), and this should overlap (at least partially) with the study period	After	[-365, -1]	IP & OP	n/a	n/a	All individuals within selected data sources	n/a	n/a

[1] IP = inpatient, OP = outpatient, n/a = not applicable
[2] Order of application specified whether the eligibility criterion was applied before or after selection of the study entry date. For example, selecting "before" means that all possible study entry dates were identified, and then one or more was chosen. In contrast, selecting "after" means that the first possible study entry date was chosen, followed by the application of the inclusion and/or exclusion criteria. If the patient did not meet the criterion, then the patient dropped out.

Table 6. Operational definitions of exclusion criteria.

Criterion	Details	Order of application	Assessment window	Care Settings[1]	Code Type	Diagnosis position	Applied to study populations:	Measurement characteristics/ validation	Source for algorithm
n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a

9.6. Variables

9.6.1. Exposure/s

None.

9.6.2. Outcome/s

For this study, outcomes of interest were prescription records of inhaled salbutamol, other inhaled alternatives, and oral salbutamol:

- Salbutamol inhalation products
    - Dry powder (using DPIs)
    - Suspension/solution/ (using MDIs)
    - Liquid solution (using nebulised solutions)
- SABA other than salbutamol:
    - Terbutaline
    - Fenoterol
- Short acting anticholinergic drugs:
    - Ipratropium bromide
    - Oxitropium bromide
- Combinations of beta-2 agonists and anticholinergics:
    - Fenoterol + ipratropium bromide
    - Salbutamol + ipratropium bromide
- Formoterol
- Formoterol and ICS:
    - Formoterol + beclomethasone
    - Formoterol + budesonide
- Salbutamol and ICS:
    - Salbutamol + beclomethasone
    - Salbutamol + budesonide
- Salbutamol administered orally:
    - Oral salbutamol

The concept/code lists used for the identification of outcomes are described in **Appendix I, Table S1**. These were refined during the study execution following the DARWIN EU® phenotyping standard processes, which involve the review of code lists by clinical experts, and the review of phenotypes after their execution in the participating data sources.

The main salbutamol cohorts of interest consisted of inhaled salbutamol prescribed as monotherapy. Fixed combination of beta-2 agonists and anticholinergics were identified using a cohort defined based on concept IDs referring to either fixed-dose combination products or use of the individual components prescribed on the same day (named as loose combination therapy). The same approach was applied to other combinations of Formoterol + ICS and Salbutamol + ICS as inhaled alternatives. Since a fixed-dose combination of salbutamol + ICS is not yet broadly authorised in the European Union,(32, 33) the method of defining loose combination therapy may result in overlap with the salbutamol cohorts.

9.6.3. Other covariates, including confounders, effect modifiers, and other variables

The device type used for inhaled salbutamol was assessed at the time of each prescription. The following pharmaceutical device types were used for stratification for population-level prescribing rates analyses (objective 2) and patient-level descriptive analyses (objective 4):

- Inhalation via DPIs
- Inhalation via MDIs
- Inhalation via nebuliser solution

Other covariates in the patient-level utilisation study (objective 4) included:

- Sex: male or female
- Age: described as continuous and by age category at index date. Age categories were the following:
    - 0 to 23 months
    - 2 to 11 years
    - 12 to 17 years
    - 18 to 45 years
    - 46 to 65 years
    - 66 to 75 years
    - > 75 years
- Conditions considered as indication for inhaled salbutamol use were assessed within ±7 days and -365 days of the index date (i.e. date of each prescribing of inhaled salbutamol during the study period). These indications were identified based on the presence of disease codes. The list of concepts for prespecified conditions of interest (by standard SNOMED code) are described in **Appendix I, Table S2**.

  Conditions of interest:

    - Asthma
    - LRTI
    - COPD with or without emphysema
    - Chronic bronchitis
    - Bronchospasm
    - Respiratory conditions due to inhalation of chemical agents
    - Other conditions: If there is a record of any condition other than those mentioned above, the individual will be considered as having another indication.

The operational definition of the covariates is described in the **Table 7**.

Table 7. Operational definitions of covariates.

Characteristic	Details	Type of variable	Assessment window	Care Settings[1]	Code Type	Diagnosis Position[2]	Applied to study populations	Measurement characteristics/ validation	Source for algorithm
Type of device for inhaled salbutamol	Pharmaceutical device types for inhaled salbutamol, including DPIs, MDIs, and nebuliser solution	Categorical	At time of index date	IP & OP	n/a	n/a	Inhaled salbutamol users	n/a	n/a
Demographics	Distribution of sex and age (continuous and by age category) at index date	Binary, continuous	At time of index date	IP & OP	n/a	n/a	Inhaled salbutamol users	n/a	n/a
Indication of use	Prespecified indications of interest within the window of ± 7 days and -365 days of the index date	Binary	[-7, +7] or [-365, -1] of index date	IP & OP	SNOMED	n/a	Inhaled salbutamol users	n/a	n/a

[1] IP = inpatient, OP = outpatient, n/a = not applicable

9.7. Study size

No sample size was calculated, as this was an exploratory study. To estimate prescribing rates of drug utilization of inhaled salbutamol products and other inhaled alternative in each data source, we used already collected available data. Thus, the sample size was driven by the availability of patients with outcome of interest within each data source.

9.8. Data transformation

Analyses were conducted separately for each data source. Before study initiation, test runs of the analytics were performed on a subset of the data sources and quality control checks were performed. Once all the tests were passed (see section 11 Quality Control), the final study code package was released in the version-controlled Study Repository for execution against all the participating data sources.

The data partners locally executed the analytics against the OMOP CDM in R Studio and reviewed and approved the—by default—aggregated results.

The study results of all data sources were checked, after which they were made available to the team, and the dissemination phase started. All results were locked and timestamped for reproducibility and transparency.

9.9. Statistical methods

9.9.1. Patient privacy protection

Cell suppression was applied as required by data sources to protect individual's privacy. Cell counts <5 was masked.

9.9.2. Main summary measures

Results were presented as monthly prescribing rates of inhaled salbutamol, oral salbutamol, and other inhaled alternatives, stratified by device types (i.e. only for inhaled salbutamol) and provided by data source. The descriptive characteristics included counts and proportions for binary categorical variables, as well as mean/median with interquartile range (IQR) for continuous variables.

9.9.3. Main statistical methods

The analysis included calculation of population-based prescription rates, as well as characterisation of individuals at time of each prescribing of inhaled salbutamol during the study period. The type of analysis by study type is presented in **Table 8**.

Table 8. Description of study types and types of analysis.

Study type	Study classification	Type of analysis
Population-Level DUS	Off-the-shelf	• Population-based prescription rates of use of a drug
Patient-Level DUS	Off-the-shelf	• Age distribution (counts and proportions by age category) • Sex distribution (counts and proportion of females/males) • Indications distributions (counts and proportions)

<u>R-packages</u>

The prescription rates were calculated based on OMOP CDM mapped data using the "*IncidencePrevalence*" R package, developed by DARWIN EU®.(34)

Population-level drug utilization study

Prescription rates calculations were conducted separately for salbutamol and other inhaled alternatives.

<u>Prescription rates calculations</u>

Monthly prescription rates for use of inhaled salbutamol, other inhaled alternatives, and use of oral salbutamol were calculated as the number of prescriptions issued within the month per 100,000 person-months (PMs) of the population at risk of getting exposed. A person-month was defined as a unit of time representing one individual being at risk or under observation for one month. The use of person-months provided more precise and timely estimates, particularly when tracking short-term changes, seasonal patterns, or sudden shifts in prescribing behaviour.

Time at risk of subjects who died was censored at the time of death. Similarly, time at risk of subjects who were lost to follow-up was censored at the time of loss to follow-up (last contact). Subjects with data until the end of the study period with or without experiencing outcome was administratively censored at the end of the study period. Prescription rates were reported together with 95% Poisson confidence intervals.

An illustration of the calculation of prescription rates of medication use of inhaled salbutamol, oral salbutamol, and other inhaled alternatives is shown below in **Figure 2**. For the numerator, all prescriptions within the respective calendar month were counted. For all patients, follow up time was time within the study period.

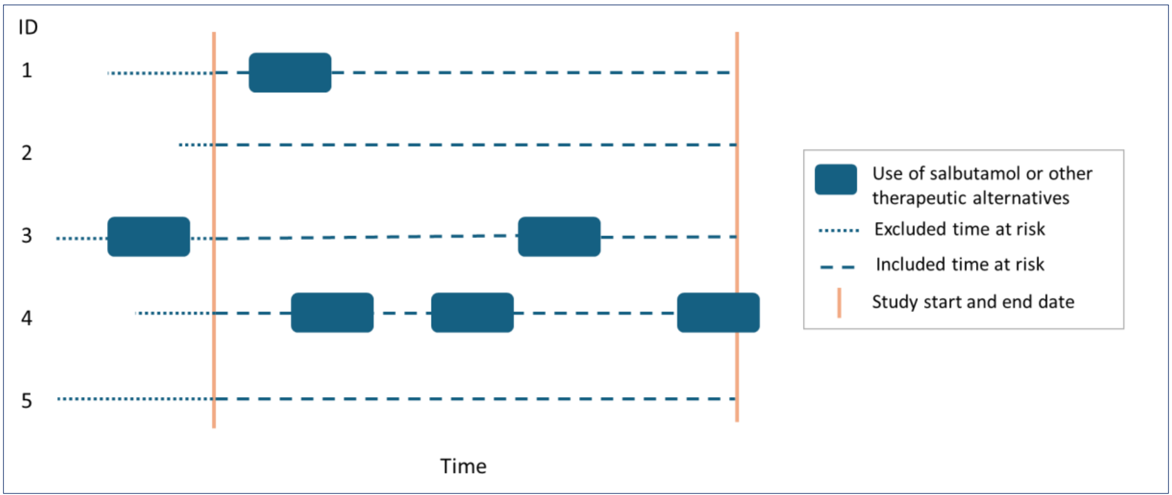

Figure 2. Person time at risk example

Patient-level drug utilization study

Characteristics at time of each prescribing (irrespective whether incident or prevalent) of inhaled salbutamol during the study period were described.

Characteristics include age, sex, and indication of use. Indication of use was assessed within ± 7 days and -365 days of the index date. The indications of use were not mutually exclusive, as there might be more than one indication of use for one individual, especially when assessed within a year prior to the index date, and the predefined indication of use not only consisted of conditions but also symptoms (i.e. bronchospasm).

Characteristics were provided by type of device for salbutamol inhalation (DPIs, metered-dose inhalers, nebuliser solution) at index date. The index date was the date of each prescription, meaning that each individual may have multiple index dates.

9.9.4. Missing values

For the drug utilisation studies we assumed that the absence of a prescription record indicated that the person did not receive the respective drug. For indications, we assumed that the absence of a record of the respective condition of interest meant that salbutamol was not prescribed for that indication.

9.9.5. Sensitivity analysis

There were no sensitivity analyses in this study.

9.9.6. Deviation from the protocol analysis plan

In the protocol, we planned to report monthly prescribing data by healthcare setting (inpatient vs. outpatient). This was not done, because most data sources only include prescriptions from one setting. For example, IMASIS only cover inpatient care. Although a few sources, like NAJS, include both settings, there were not enough data to make meaningful comparisons. Instead, results were shown by data source.

We also included some extra results not planned in the protocol. Specifically, we showed the distribution of indications by year. This ad-hoc analysis was added because it provided useful insights into changes of proportion of indication of use over time.

It was originally planned to classify prescriptions as 'salbutamol formulation unknown' if they were only mapped at the ingredient level. In practice, salbutamol was mapped at the clinical class level in all data sources, except SIDIAP, where MDIs were initially mapped at the ingredient level. This issue was identified during the analysis, and custom codes were applied in SIDIAP to correctly classify MDIs.

In addition, the analysis planned to assess the characteristics at the time of each inhaled salbutamol prescription during the study period. There was an exception in IQVIA DA Germany, where the number of records referred to drug eras rather than individual prescriptions.

10. DATA MANAGEMENT

10.1. Data management

All data sources have previously mapped their data to the OMOP common data model. This enabled the use of standardised analytics and using DARWIN EU® tools across the network, since the structure of the data and the terminology system was harmonised. The OMOP CDM was developed and maintained by the Observational Health Data Sciences and Informatics (OHDSI) initiative and is described in detail on the wiki page of the CDM: https://ohdsi.github.io/CommonDataModel and in The Book of OHDSI: http://book.ohdsi.org

The analytic code for this study was written in R and used standardized analytics wherever possible. Each data partner executed the study code against their data source containing patient-level data, and then returned the results (csv files), which only contained aggregated data. The results from each of the contributing data sites were then combined in tables and figures for the study report.

10.2. Data storage and protection

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

All data sources used in this study were already used for pharmaco-epidemiological research and have a well-developed mechanism to ensure that European and local regulations dealing with ethical use of the data and adequate privacy control were adhered to. In agreement with these regulations, rather than combining person level data and performing only a central analysis, local analyses were run, which generate non-identifiable aggregate summary results.

11. QUALITY CONTROL

General database quality control

A number of open-source quality control mechanisms for the OMOP CDM have been developed (see Chapter 15 of The Book of OHDSI http://book.ohdsi.org/DataQuality.html). In particular, all data partners ran the OHDSI Data Quality Dashboard tool (https://github.com/OHDSI/DataQualityDashboard). This tool provides numerous checks relating to the conformance, completeness, and plausibility of the mapped data. Conformance focuses on checks that describe the compliance of the representation of data against internal or external formatting, relational, or computational definitions. Completeness in the sense of data quality is solely focused on quantifying missingness, or the absence of data, while plausibility seeks to determine the believability or truthfulness of data values. Each of these categories has one or more subcategories and are evaluated in two contexts: validation and verification. Validation relates to how well data align with external benchmarks with expectations derived from known true standards, while verification relates to how well data conform to local knowledge, metadata descriptions, and system assumptions.

Study specific quality control

The SNOMED codes of the conditions and outcomes of interest and RxNorm of ingredients were derived from ATLAS. The codes were then reviewed by two clinical epidemiologists to consider their relevance and accuracy. In addition, the "*CohortDiagnostics*" (https://ohdsi.github.io/CohortDiagnostics/) and "*DrugExposureDiagnostics*" (https://cran.r-project.org/web/packages/DrugExposureDiagnostics/index.html) R packages were run. The *CohortDiagnostics* package provides additional insights into cohort characteristics, record counts and index event misclassification. The *DrugExposureDiagnostics* package evaluates ingredient-specific attributes and patterns in drug exposure records.

12. RESULTS

The full set of results for this study is available through an interactive web-application "ShinyApp" at https://data.darwin-eu.org/EUPAS1000000403/.

12.1. Prescription rates of three inhaler device types for salbutamol administration

Yearly prescription rates of inhaled salbutamol

Differences in prescribing rates were observed between salbutamol formulations (i.e., administrated via DPIs, MDIs, and solution nebulisers) across multiple European healthcare data sources over 2015–2024 (**Appendix II, Figure S1 and Table S1**). MDIs were the most frequently prescribed in IPCI, IQVIA DA, NAJS, and SIDIAP; DPIs were more commonly used in CPRD-GOLD and DK-DHR, while nebuliser solutions were predominantly prescribed in IMASIS, which is a hospital data source.

In CPRD-GOLD, both DPIs and MDIs were prescribed at high rates relative to the other data sources, exceeding 1,000 prescriptions per 100,000 PMs in most study years, while nebuliser solutions prescribing remained consistently low. There was a slow increase in DPI prescribing and a slow decrease in MDI prescribing over the study period.

In DK-DHR, prescription rates showed modest increases for both DPIs and MDIs, peaking at 306/100,000 PMs in 2023. The prescription rate for nebuliser solutions stayed below 11.

In contrast, IMASIS shows a significant increase in nebuliser solution prescriptions. The increase of prescription rates was barely noticeable between 2015 and 2019 but then rose markedly starting from 233/100,000 PMs in 2019 to 923 in 2024. Prescription rates for MDIs remained below 31 throughout the period and there was no recorded DPI prescribing.

In IPCI, prescription rates for DPIs and MDIs were relatively balanced, ranging between 300 and 500/100,000 PMs, whereas nebuliser solution prescription rates remained low, fluctuating between 29 to 72.

In IQVIA DA, NAJS, and SIDIAP MDIs was the most prescribed salbutamol form. In IQVIA DA, a gradual upward trend was observed from 2015 to 2023, followed by a sharp and sustained increase in prescriptions from mid-2023 onward. Prescription rates rose steadily from 135/100,000 PMs in 2015 to 469 in 2024. NAJS showed a slow decline in prescription rates from 469/100,000 PMs in 2015 to 388 in 2024. In SIDIAP, prescribing rates peaked at 1,104 in 2015, dipped towards 2020, then rebounded to 1,068 in 2023. Prescription rates of DPIs and nebuliser solutions remained low in all three data sources, throughout the study period. (**Appendix II, Figure S1 and Table S1**).

Monthly prescription rates of inhaled salbutamol

Monthly prescribing patterns of salbutamol were in line with what was reported for yearly trends, showing differences in prescribing across European regions and notable seasonal trends with higher use during winter (**Figures 3-9** and **Appendix II, Tables S2- S8**).

Salbutamol prescribing over time showed mixed preference in CPRD-GOLD. A clear shift in preference of prescription from MDIs to DPIs was seen over time. In March 2016, MDIs were prescribed at 1,328/100,000 PMs compared to 1,270 for DPIs. In December 2024, DPIs prescription had increased to 1,455, surpassing MDIs at 1,212 (**Figure 3** and **Appendix II, Table S2**).

In the DK-DHR data, prescribing rates were the highest for salbutamol DPIs, with clear seasonal variation. DPI prescription rose to 332/100,000 PMs and 333 in December 2022 and 2023, compared to 285 and 283 in August of the same years. MDIs showed moderate but steady growth over time, from 244/100,000 PMs in December 2016 to 322 in December 2023, also reflecting winter peaks and summer dips (e.g., 222 in July 2024). In contrast, prescribing of nebuliser solutions was low (<10/100,000 PMs), with minimal seasonal fluctuation (**Figure 4** and **Appendix II, Table S3**).

In the IMASIS data, after a constant prescribing pattern, with winter peaks, between 2015 and 2020, salbutamol nebuliser solution prescribing rose significantly from 669/100,000 PMs in April 2020 to 883 in December 2023, peaking at 1,044 in January 2024. In contrast, MDIs stayed consistently low, e.g. 22/100,000 PMs and 33 in December 2022 and 2023, respectively. No prescribing of DPI was recorded (**Figure 5** and **Appendix II, Table S4**).

In IPCI, MDIs and DPIs were equally prescribed, but from August 2017 on, prescribing of MDIs became predominant, with rates ranging from 376/100,000 PMs in September 2017 to 472 in December 2023, whereas DPI prescription rates kept the same trend (**Figure 6** and **Appendix II, Table S5**).

In the IQVIA DA dataset, there was a steady increase in the prescription rates of MDIs for salbutamol over the years. For instance, MDIs prescription rates rose constantly from 147/100,000 PMs in January 2015 to 218 in January 2020 to 266 in January 2023. Prescribing of salbutamol administered via nebuliser solutions was much lower; with rates of 34/100,000 PMs (December 2021) and 79 (December 2022). Prescription of salbutamol via DPIs was the lowest, with rates between 3-35/100,000 PMs, where the highest rate was in June 2024.

Furthermore, in the NAJS data, mainly salbutamol administered via MDIs with prescribing rates gradually decreasing until 2021 and then showing a slight increase thereafter, alongside clear seasonal trends. For example, MDIs prescription rates increased in December 2022 to 474/100,000 PMs and December 2023 to

350. In contrast, rates were lower during summer months—for instance, in August 2022 and 2023 they were 307/100,000 PMs and 314, respectively. Prescribing of salbutamol via nebuliser solutions was lower than MDIs but also displayed strong seasonal trends. Prescribing of salbutamol via DPIs was rare.

In the SIDIAP data source, mainly salbutamol administered via MDIs with prescription rates remaining relatively constant (though slightly declining) before 2020. Seasonal variation was also stable. For example, prescription rates were rising from 1,051/100,000 PMs in December 2021 to 1,421 in December 2022, and 1,272 in January 2023, while dropping to around 600–900 in summer months. However, there was a noticeable dip in 2020 and 2021, after which the previous trend resumed. Salbutamol prescribed via DPIs and nebuliser solutions consistently showed very low prescription rates across all months, typically below 1 for DPIs and ranging between 5 and 21 for nebuliser solutions (**Figures 7-9** and **Appendix II, Tables S6-S8**).

In CPRD-GOLD, DK-DHR, IPCI, IQVIA DA, and NAJS high prescription of salbutamol was observed in March 2020, coinciding with the initial wave of COVID-19. For example, in CPRD-GOLD, DPIs prescription rates surged to 2,271/100,000 PMs and MDIs rates to 1,938, nearly doubling from levels in January 2019. In SIDIAP, there is no peak around the start of COVID-19 before the dip, which was different from other data-sources.

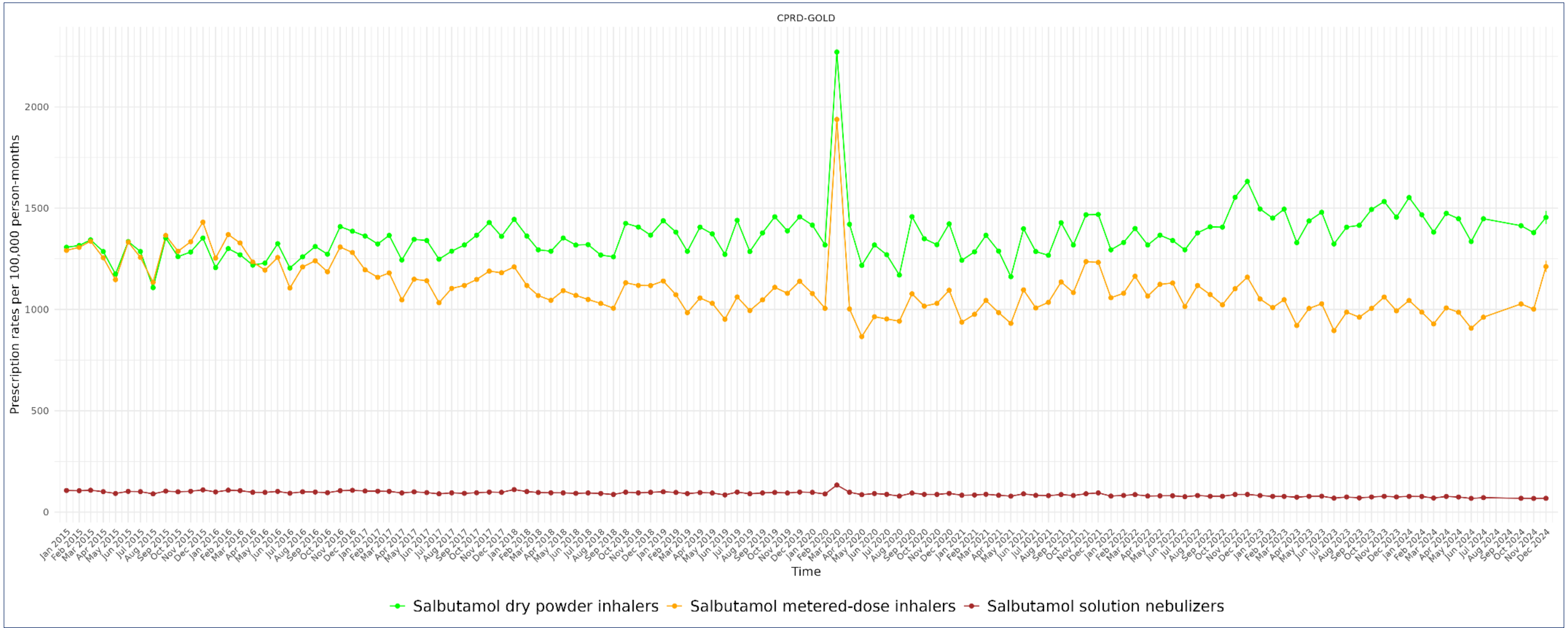

Figure 3. Monthly prescribing rates of inhaled salbutamol by device type—including dry powder inhalers, metered-dose inhalers, and nebuliser solution—in the CPRD-GOLD data source.

CPRD=Clinical Practice Research Datalink.

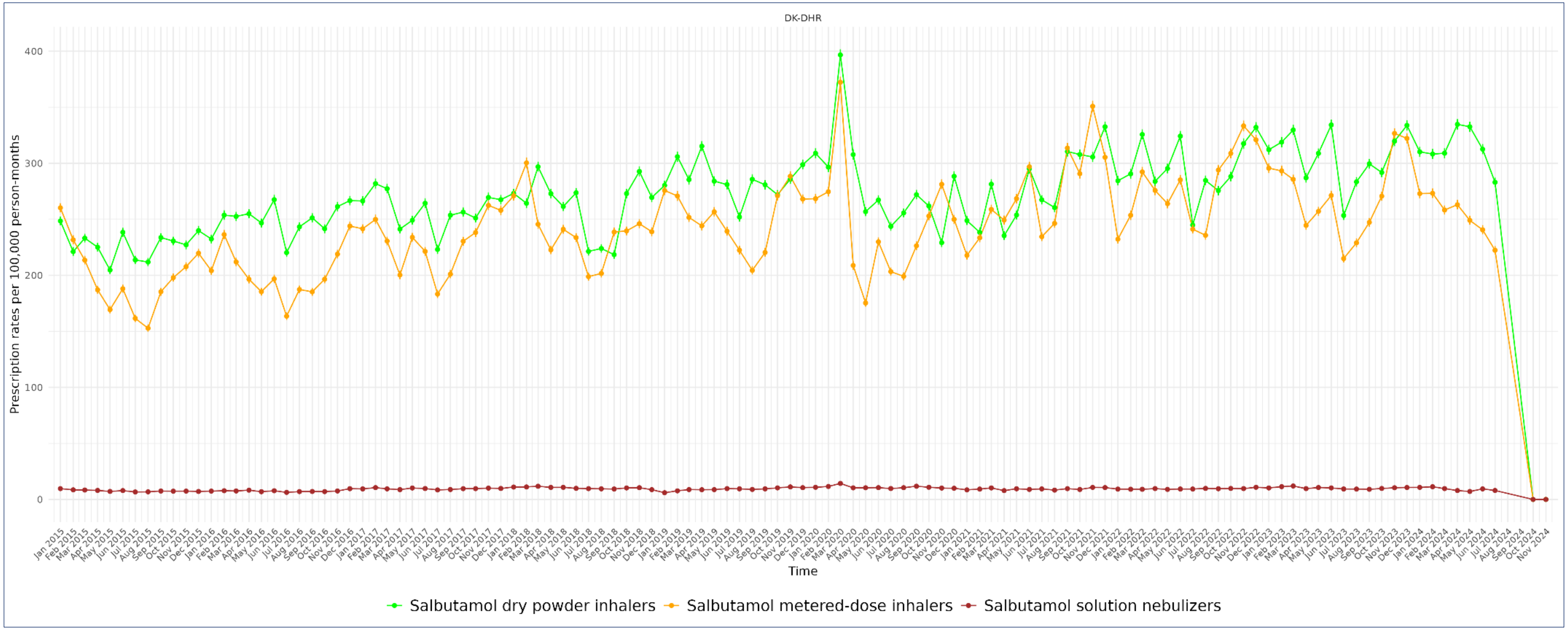

Figure 4. Monthly prescribing rates of inhaled salbutamol by device type—including dry powder inhalers, metered-dose inhalers, and nebuliser solution—in the DK-DHR data source.

Note: The sharp drop in prescribing at the end of 2024 likely reflects a data lag or incompleteness due to the end of the follow-up period, where data are missing and prescription counts are based on small numerators, leading to an artificial decline to zero.
DK-DHR=Danish Data Health Registries.

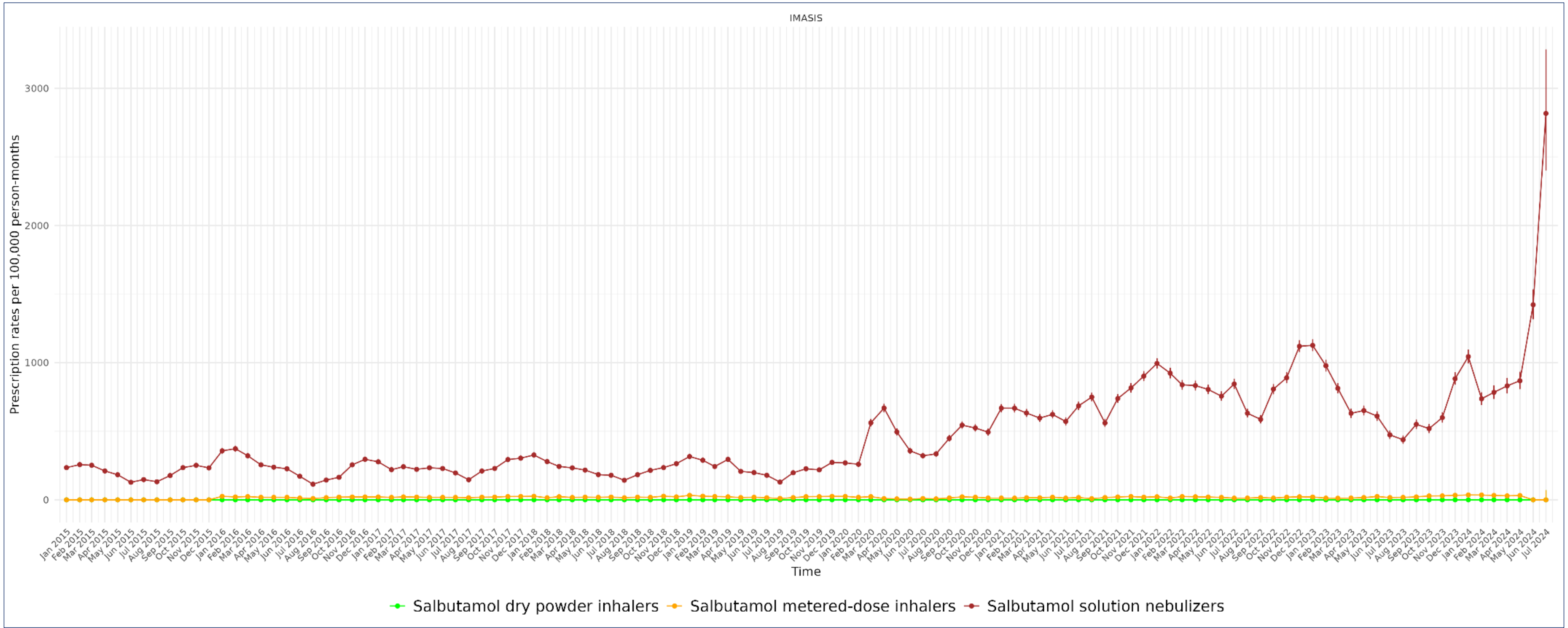

Figure 5. Monthly prescribing rates of inhaled salbutamol by device type—including dry powder inhalers, metered-dose inhalers, and nebuliser solution—in the IMASIS data source.

Note: The sharp increase at the end of study period may reflect an artificial rise due to a sudden drop in person-months, possibly related to data cut-off, which inflates the rate despite stable or declining prescription counts.
IMASIS=Institute Municipal Assistència Sanitària Information System.

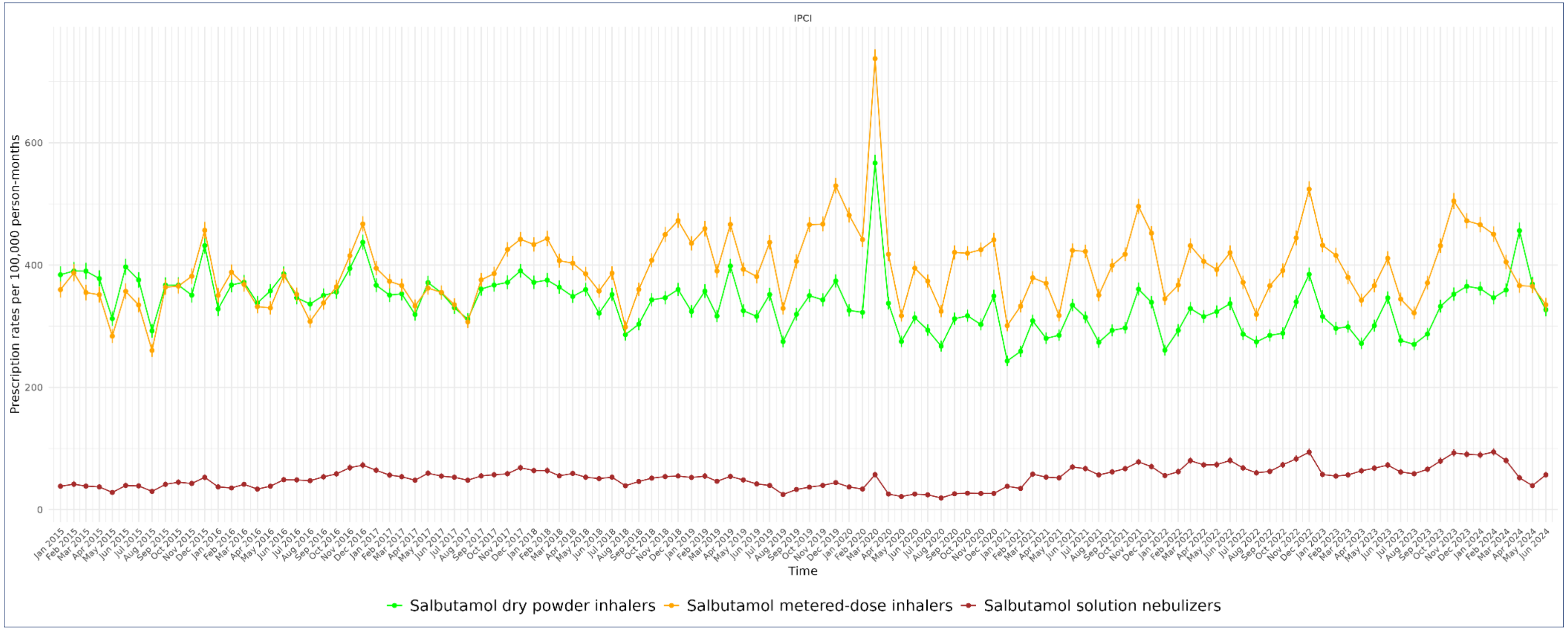

Figure 6. Monthly prescribing rates of inhaled salbutamol by device type—including dry powder inhalers, metered-dose inhalers, and nebuliser solution—in the IPCI data source.

IPCI=Integrated Primary Care Information.

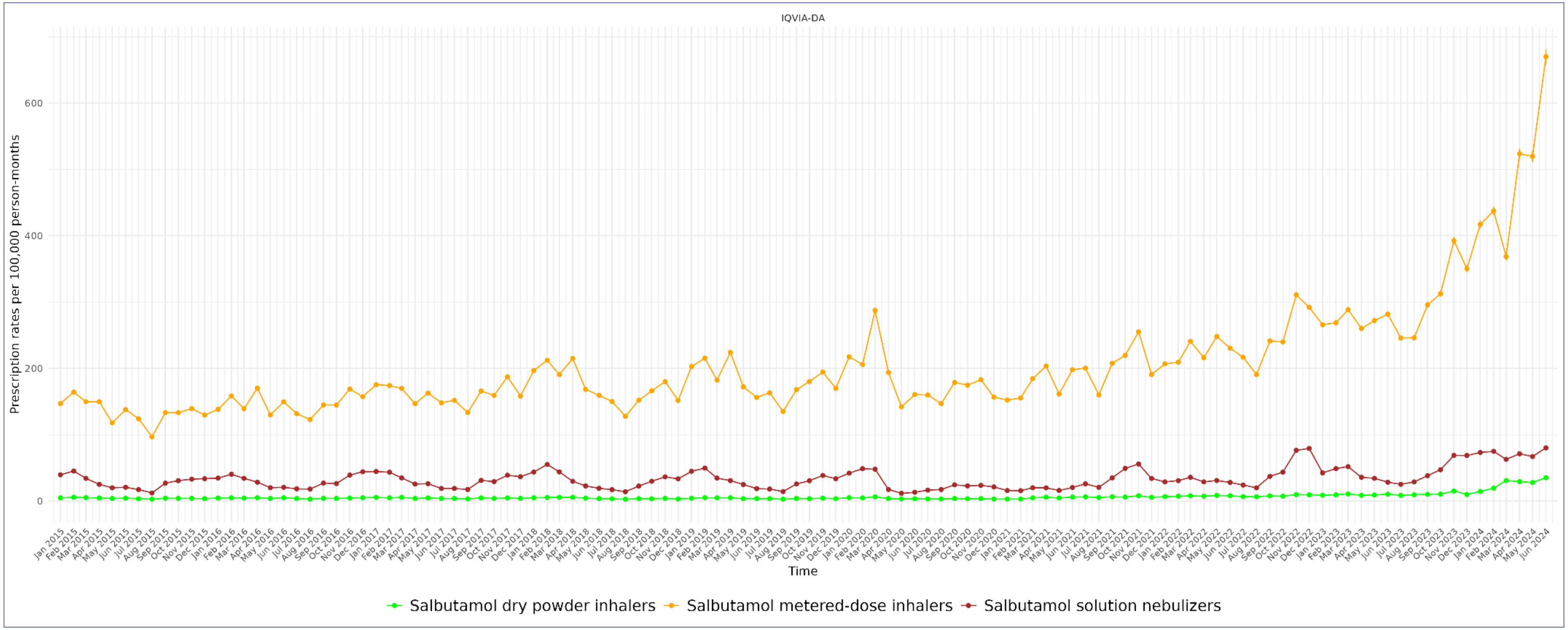

Figure 7. Monthly prescribing rates of inhaled salbutamol by device type—including dry powder inhalers, metered-dose inhalers, and nebuliser solution—in the IQVIA DA Germany data source.

Note: The sharp increase at the end of study period may reflect an artificial rise due to a sudden drop in person-months, possibly related to data cut-off, which inflates the rate despite stable or declining prescription counts.
DA= Disease Analyzer.

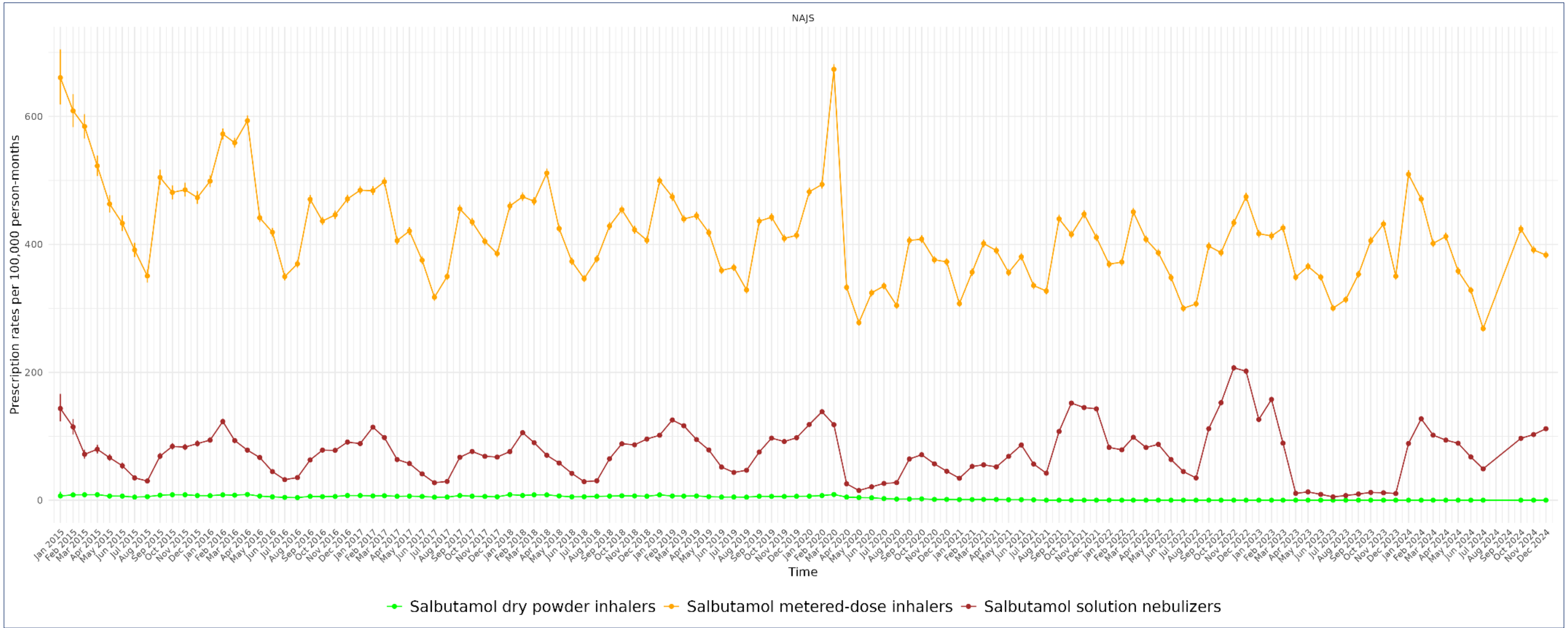

Figure 8. Monthly prescribing rates of inhaled salbutamol by device type—including dry powder inhalers, metered-dose inhalers, and nebuliser solution—in the NAJS data source.

NAJS=Croatian National Public Health Information System.

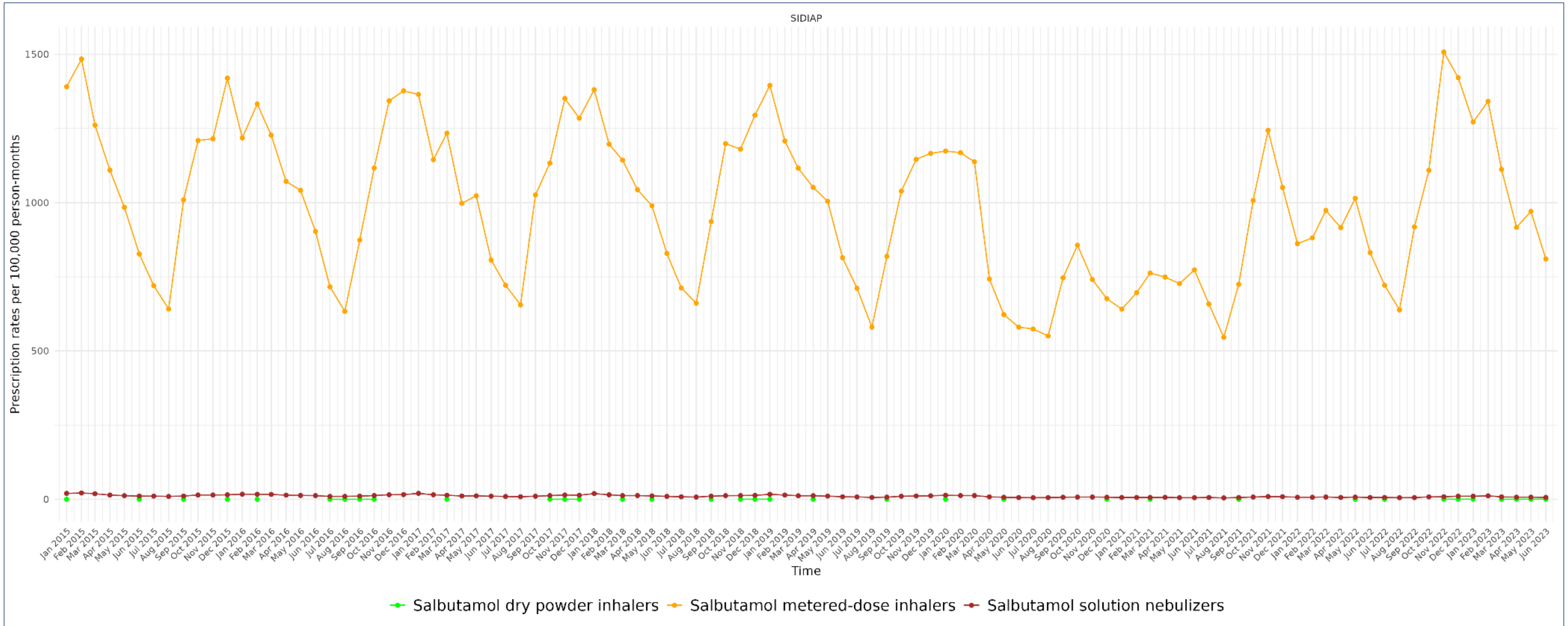

Figure 9. Monthly prescribing rates of inhaled salbutamol by device type—including dry powder inhalers, metered-dose inhalers, and nebuliser solution—in the SIDIAP data source.

SIDIAP=The Information System for Research on Primary Care.

12.2. Prescription rates of salbutamol products and inhaled alternatives

Yearly prescription rates of salbutamol products and inhaled alternatives

The results of yearly prescribing rates of inhaled salbutamol (i.e. administrated via DPIs, MDIs, and solution nebuliser devices), oral salbutamol, and inhaled alternatives are presented in **Appendix II, Figure S2 and Table S9**. Across most data sources, *salbutamol inhalation* and *formoterol + ICS* (i.e. formoterol + beclomethasone and formoterol + budesonide) were the most prescribed bronchodilators, whereas prescribing of *oral salbutamol*, *formoterol inhalation*, and *SABA inhalation other than salbutamol* (i.e. terbutaline and fenoterol) was much lower.

The prescribing of salbutamol inhalation showed varying trends across data sources. In DK-DHR, IMASIS, and IQVIA DA an upward trend was observed over years, suggesting a growing reliance on inhaled salbutamol in these regions over time. In contrast, prescribing patterns in SIDIAP and IPCI remained relatively steady. Meanwhile, CPRD-GOLD and NAJS showed trends that were overall stable.

In CPRD-GOLD, *salbutamol inhalation* consistently recorded the highest usage rates, ranging between 2,163/100,000 PMs in 2015 to 1,901 in 2024. This was followed by *formoterol + ICS*, which increased from 421 in 2015 to 797 in 2022. Although the rates for *salbutamol + ICS* (i.e. salbutamol + beclomethasone and salbutamol + budesonide) (loose or fixed combinations) declined from 564/100,000 PMs in 2015 to 426 in 2024, it remained higher than other respiratory medications. Prescribing of oral salbutamol was very low (<5/100,000 PMs) (**Appendix II, Figure S2 and Table S9**).

In DK-DHR, *formoterol + ICS* was the most frequently prescribed bronchodilator and prescribing increased over time (513/100,000 PMs in 2015 to 640 in 2023). The second most prescribed drug was *salbutamol inhalation*, which increased from 399 to 541 in the same period from 2015 to 2023.

In IMASIS, which is a hospital data source, mainly *short acting anticholinergic* drugs (i.e. ipratropium bromide and oxitropium bromide) were prescribed, with a significant rise from 589/100,000 PMs in 2015 to 2,937 in 2024. Prescription rates of *formoterol + ICS* also surged, reaching 1,868 in 2024. This was followed by *salbutamol inhalation* which showed an increase in rates from 203 in 2015 to 930 in 2024.

Similarly, in IPCI and IQVIA DA, mainly *salbutamol inhalation* and *formoterol combined with ICS* were prescribed. (**Appendix II, Figure S2 and Table S9**).

In the NAJS data source, the most prescribed medication was *salbutamol inhalation*, starting at 524/100,000 PMs in 2015 and declined to 459 in 2024, though with some fluctuation. *Formoterol + ICS* was also widely used, with prescription rates fluctuating between 259/100,000 PMs and 352 over years.

In SIDIAP, the most prescribed medications were also *salbutamol inhalation,* with rates between 1,112 in 2015 and 1,073 in 2023, followed by *short acting anticholinergic inhalation* (rates from 631/100,000 PMs in 2015 to 997 in 2023) and *formoterol + ICS* (249 in 2015 to 1,076 in 2023) (**Appendix II, Figure S2 and Table S9**).

Monthly prescription rates of salbutamol products and inhaled alternatives

Monthly prescription rates for inhaled salbutamol, oral salbutamol, and inhaled alternatives showed seasonal variation, typically peaking during winter months and decreasing during summer, across multiple European healthcare data sources from 2015 to 2024 (**Figures 10-16 and Tables S10-S16**). For example, *salbutamol inhalation* as the most commonly prescribed reliever has been recorded in most data sources with higher prescription rates in December 2021 (2,113/100,000 PMs in CPRD-GOLD, 596 in DK-DHR, 801 in IPCI) compared to lower rates in August 2021 (1,804/100,000 PMs in CPRD-GOLD, 471 in DK-DHR, and 630 in IPCI). Similarly, the prescription rates for *formoterol with inhaled corticosteroids*—the second most prescribed reliever in most data sources—were generally lower in summer than in winter period (e.g. prescription rates increased from 669/100,000 PMs in August 2019 to 728 in December 2019 in CPRD-GOLD, from 526 to 540 in DK-DHR, from 389 to 508 in IPCI, and from 131 to 142 in IQVIA DA. A comparable seasonal trend was observed in IMASIS, where prescriptions for *short acting anticholinergic inhalation* rose from 1,333/100,000 PMs in August 2023 to 2,489 in December 2023, with another example being 539/100,000 PMs in August 2022 increasing to 1,244 in December 2022 in SIDIAP (**Figures 10-16 and Tables S10-S16**).

Monthly prescribing rates of inhaled salbutamol showed heterogeneous patterns across data sources. An upward trend was evident in DK-DHR, IMASIS, and IQVIA DA, while SIDIAP and IPCI displayed relatively stable prescribing. In contrast, CPRD-GOLD and NAJS showed a gradual decline. A distinct peak around March 2020 was observed in data sources CPRD-GOLD, DK-DHR, IPCI, IQVIA DA, and NAJS coinciding with the early phase of the COVID-19 pandemic.

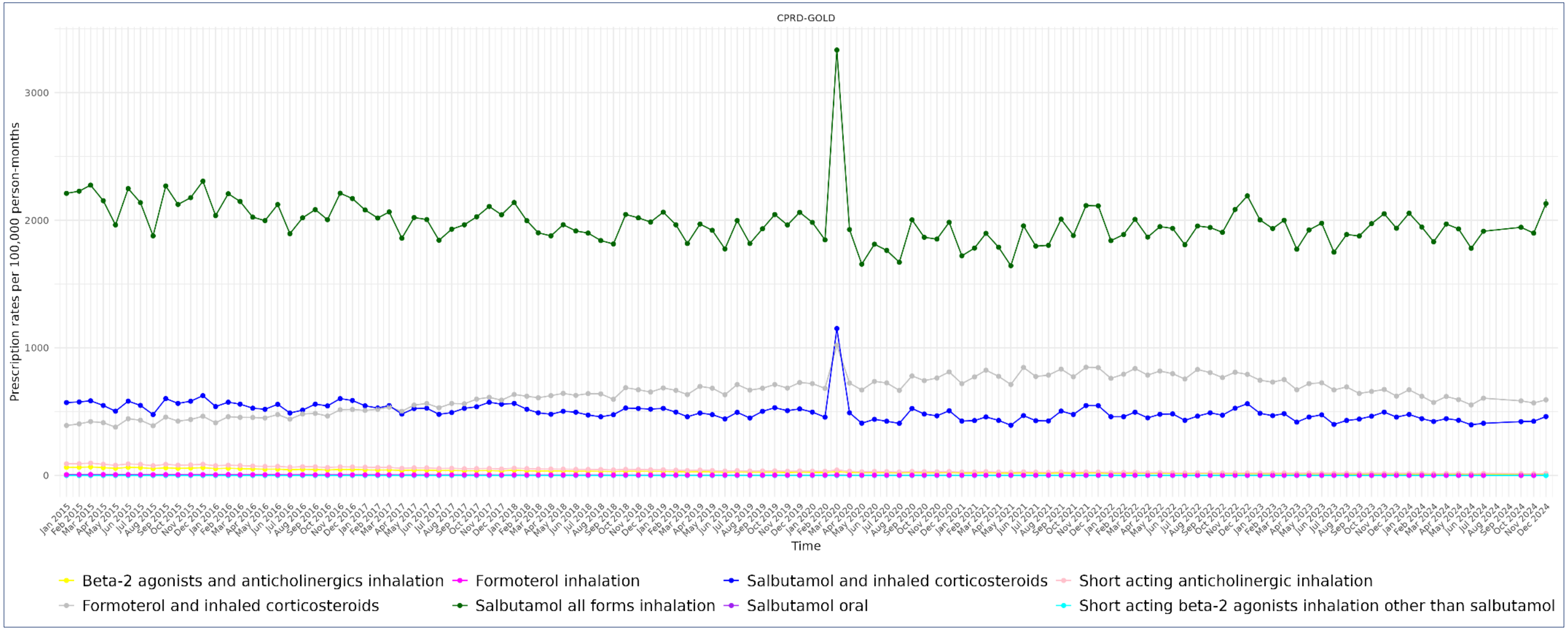

Figure 10. Monthly prescribing rates for i. all forms inhaled salbutamol products (using dry powder inhalers, metered-dose inhalers, and solution nebuliser), ii. SABA other than salbutamol (terbutaline and fenoterol), iii. short acting anticholinergic drugs (ipratropium bromide and oxitropium bromide), iv. combination of beta-2 agonists and anticholinergics (fenoterol + ipratropium bromide and salbutamol + ipratropium bromide), v. formoterol, vi. formoterol + inhaled corticosteroids (formoterol + beclomethasone and formoterol + budesonide), vii. salbutamol + inhaled corticosteroids (salbutamol + beclomethasone and salbutamol + budesonide), viii. oral salbutamol in the CPRD-GOLD data source.

Note: Short acting beta-2 agonists inhalation other than salbutamol were not prescribed in the CPRD-GOLD data source.
CPRD=Clinical Practice Research Datalink.

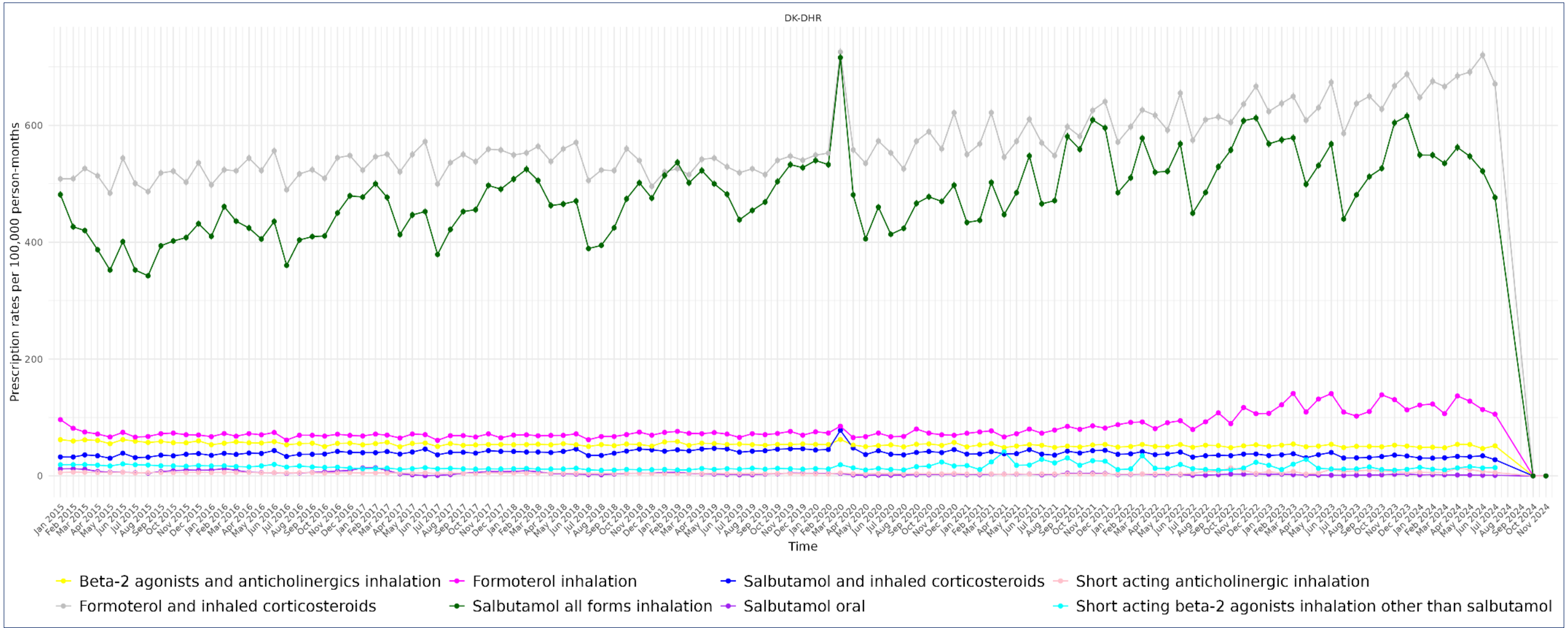

Figure 11. Monthly prescribing rates for i. all forms inhaled salbutamol products (using dry powder inhalers, metered-dose inhalers, and solution nebuliser), ii. SABA other than salbutamol (terbutaline and fenoterol), iii. short acting anticholinergic drugs (ipratropium bromide and oxitropium bromide), iv. combination of beta-2 agonists and anticholinergics (fenoterol + ipratropium bromide and salbutamol + ipratropium bromide), v. formoterol, vi. formoterol + inhaled corticosteroids (formoterol + beclomethasone and formoterol + budesonide), vii. salbutamol + inhaled corticosteroids (salbutamol + beclomethasone and salbutamol + budesonide), viii. oral salbutamol in the DK-DHR data source.

Note: Salbutamol oral and short-acting anticholinergic inhalation lines overlap at near zero prescription rates (purple and pale pink lines).
Note: The sharp drop in prescribing at the end of 2024 likely reflects a data lag or incompleteness due to the end of the follow-up period, where data are missing and prescription counts are based on small numerators, leading to an artificial decline to zero.
DK-DHR=Danish Data Health Registries.

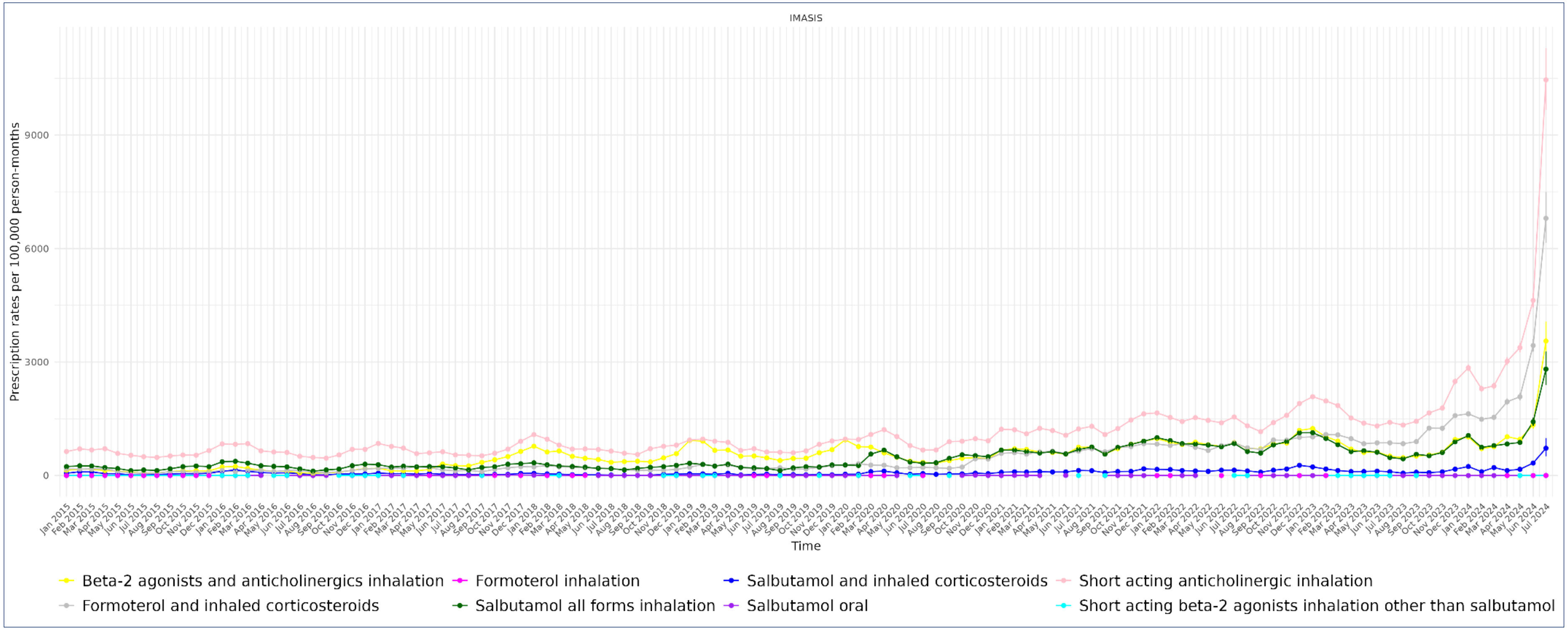

Figure 12. Monthly prescribing rates for i. all forms inhaled salbutamol products (using dry powder inhalers, metered-dose inhalers, and solution nebuliser), ii. SABA other than salbutamol (terbutaline and fenoterol), iii. short acting anticholinergic drugs (ipratropium bromide and oxitropium bromide), iv. combination of beta-2 agonists and anticholinergics (fenoterol + ipratropium bromide and salbutamol + ipratropium bromide), v. formoterol, vi. formoterol + inhaled corticosteroids (formoterol + beclomethasone and formoterol + budesonide), vii. salbutamol + inhaled corticosteroids (salbutamol + beclomethasone and salbutamol + budesonide), viii. oral salbutamol in the IMASIS data source.

Note: Salbutamol oral, formoterol inhalation, and SABA other than salbutamol overlap at near zero prescription rates (purple, pink, and blue lines).
Note: The very high prescription rates observed toward the end of the period are likely an artifact, potentially driven by a sharp decrease in person-time denominators, leading to increased rate estimates.
IMASIS=Institut Municipal Assistència Sanitària Information System

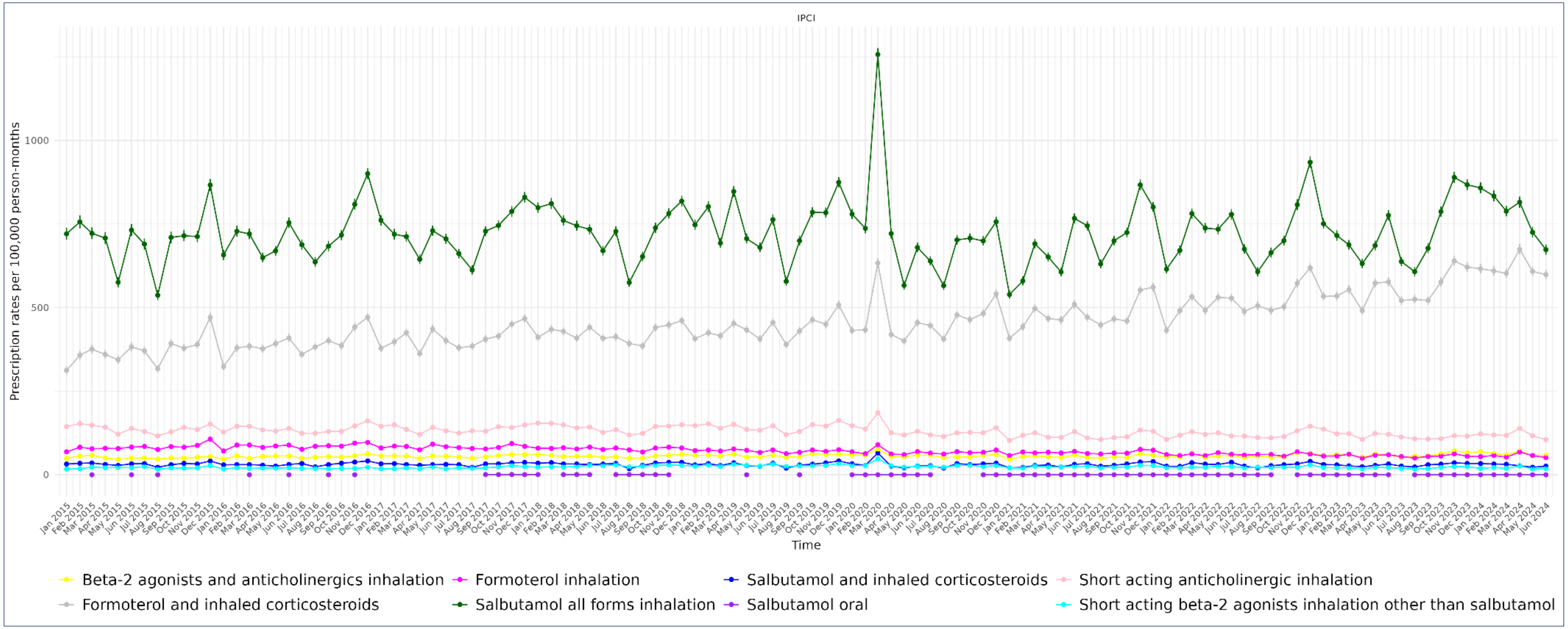

Figure 13. Monthly prescribing rates for i. all forms inhaled salbutamol products (using dry powder inhalers, metered-dose inhalers, and solution nebuliser), ii. SABA other than salbutamol (terbutaline and fenoterol), iii. short acting anticholinergic drugs (ipratropium bromide and oxitropium bromide), iv. combination of beta-2 agonists and anticholinergics (fenoterol + ipratropium bromide and salbutamol + ipratropium bromide), v. formoterol, vi. formoterol + inhaled corticosteroids (formoterol + beclomethasone and formoterol + budesonide), vii. salbutamol + inhaled corticosteroids (salbutamol + beclomethasone and salbutamol + budesonide), viii. oral salbutamol in the IPCI data source.

IPCI=Integrated Primary Care Information.

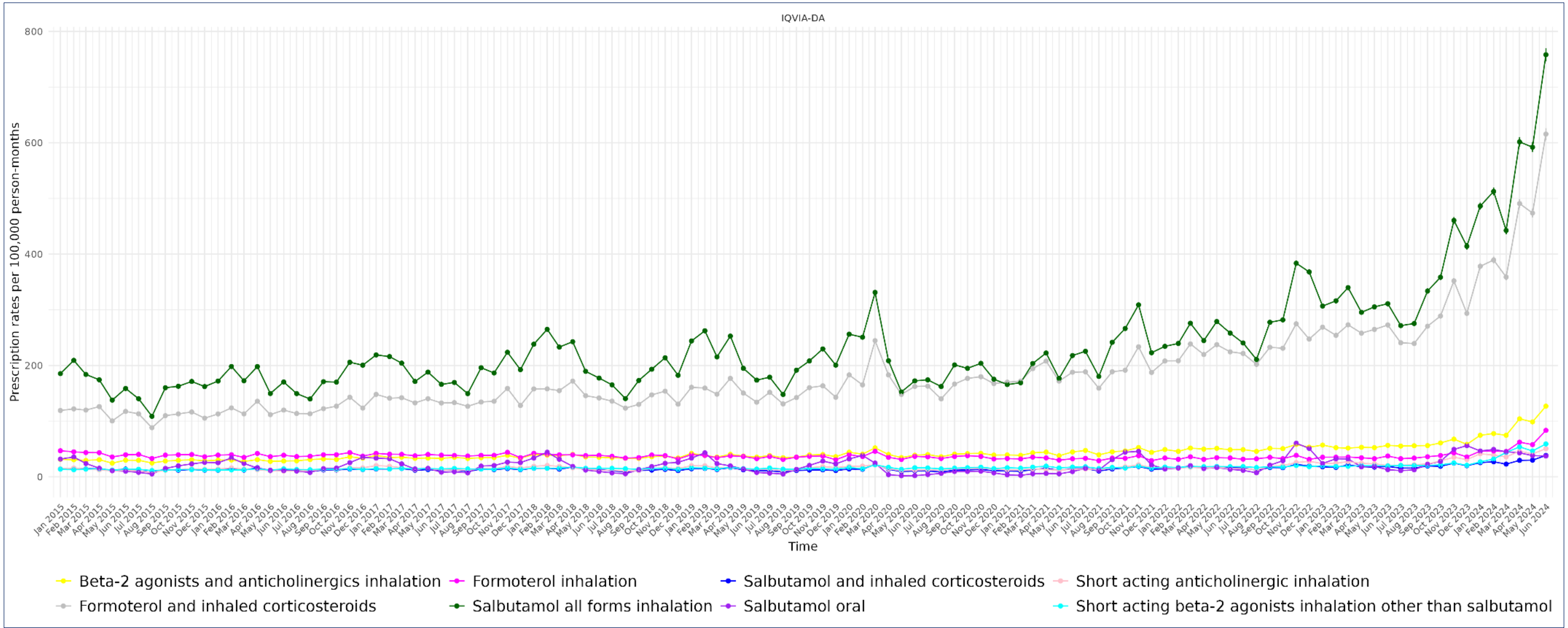

Figure 14. Monthly prescribing rates for i. all forms inhaled salbutamol products (using dry powder inhalers, metered-dose inhalers, and solution nebuliser), ii. SABA other than salbutamol (terbutaline and fenoterol), iii. short acting anticholinergic drugs (ipratropium bromide and oxitropium bromide), iv. combination of beta-2 agonists and anticholinergics (fenoterol + ipratropium bromide and salbutamol + ipratropium bromide), v. formoterol, vi. formoterol + inhaled corticosteroids (formoterol + beclomethasone and formoterol + budesonide), vii. salbutamol + inhaled corticosteroids (salbutamol + beclomethasone and salbutamol + budesonide), viii. oral salbutamol in the IQVIA DA Germany data source.

Note: SABA and SABA other than salbutamol overlap at near zero prescription rates (pale pink and blue lines).
Note: The sharp increase at the end of study period may reflect an artificial rise due to a sudden drop in person-months, possibly related to data cut-off, which inflates the rate despite stable or declining prescription counts.
DA= Disease analyser.

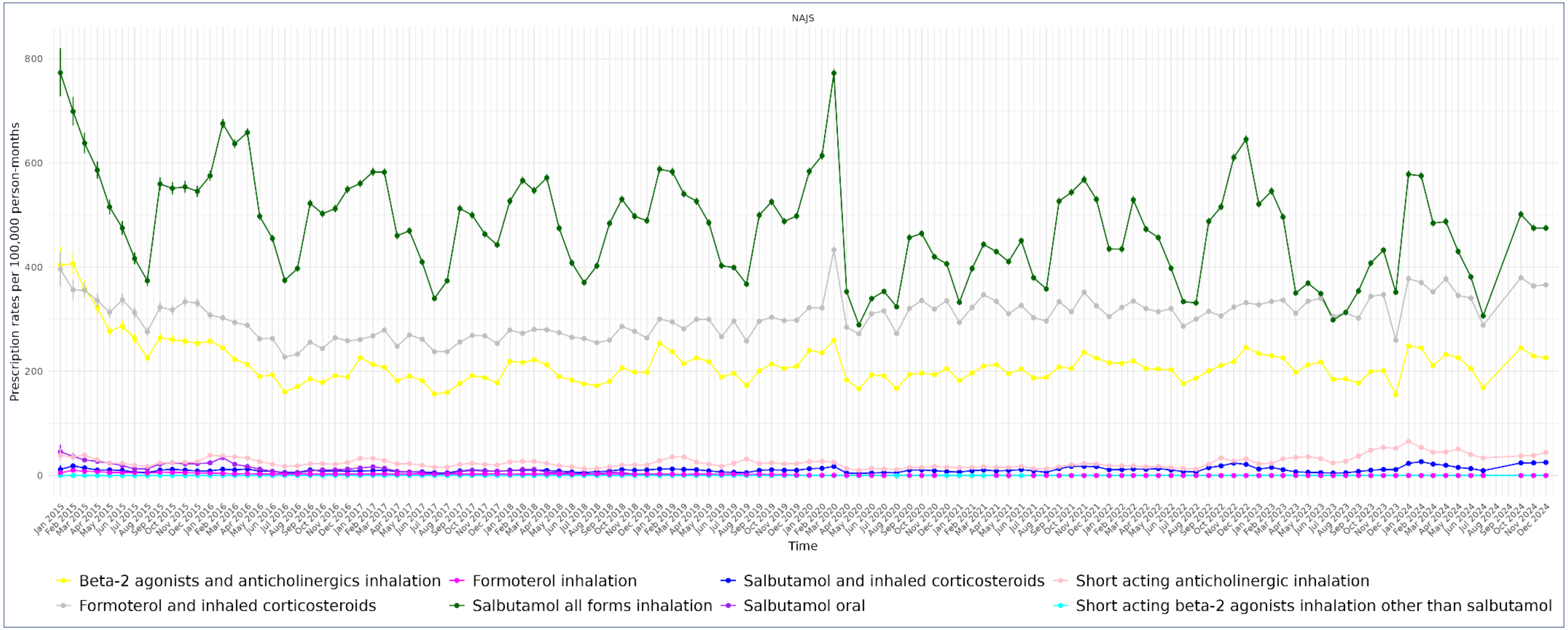

Figure 15. Monthly prescribing rates for i. all forms inhaled salbutamol products (using dry powder inhalers, metered-dose inhalers, and solution nebuliser), ii. SABA other than salbutamol (terbutaline and fenoterol), iii. short acting anticholinergic drugs (ipratropium bromide and oxitropium bromide), iv. combination of beta-2 agonists and anticholinergics (fenoterol + ipratropium bromide and salbutamol + ipratropium bromide), v. formoterol, vi. formoterol + inhaled corticosteroids (formoterol + beclomethasone and formoterol + budesonide), vii. salbutamol + inhaled corticosteroids (salbutamol + beclomethasone and salbutamol + budesonide), viii. oral salbutamol in the NAJS data source. Salbutamol oral, salbutamol and inhaled corticosteroids, and formoterol inhalation have overlap at near zero prescription rates.

Note: SABA inhalation other than salbutamol and formoterol inhalation were not prescribed in the NAJS data source.
NAJS=Croatian National Public Health Information System

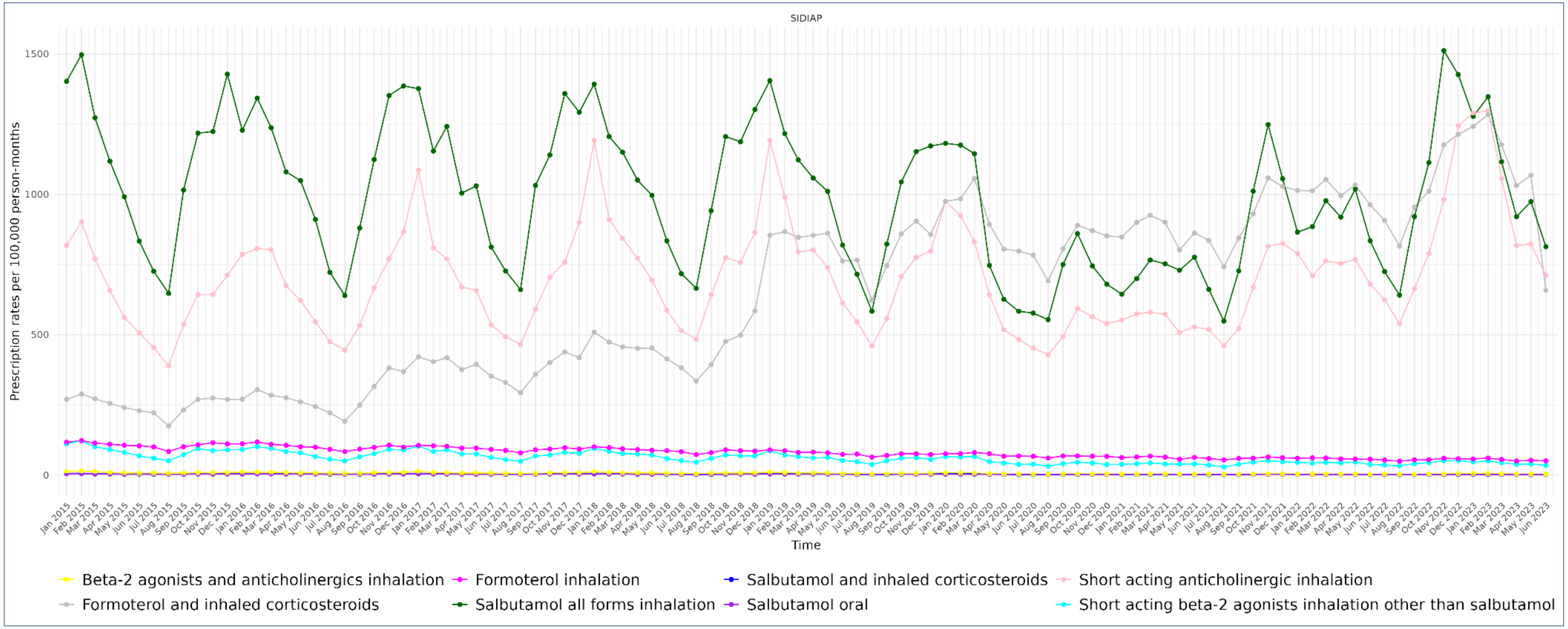

Figure 16. Monthly prescribing rates for i. all forms inhaled salbutamol products (using dry powder inhalers, metered-dose inhalers, and solution nebuliser), ii. SABA other than salbutamol (terbutaline and fenoterol), iii. short acting anticholinergic drugs (ipratropium bromide and oxitropium bromide), iv. combination of beta-2 agonists and anticholinergics (fenoterol + ipratropium bromide and salbutamol + ipratropium bromide), v. formoterol, vi. formoterol + inhaled corticosteroids (formoterol + beclomethasone and formoterol + budesonide), vii. salbutamol + inhaled corticosteroids (salbutamol + beclomethasone and salbutamol + budesonide), viii. oral salbutamol in the SIDIAP data source.

Note: Salbutamol oral, salbutamol and inhaled corticosteroids, and beta-2 agonists and anticholinergics inhalation overlap at near zero prescription rates (purple, dark blue, and yellow).
SIDIAP=The Information System for Research on Primary Care

12.3. Distribution of age group, sex, and predefined indication of use for inhaled salbutamol, by device type

Table 9 presents the prescription of inhaled salbutamol by type of device (DPIs, MDIs, and nebuliser solution) across different age groups, sexes, and indications of use in the CPRD-GOLD, DK-DHR, IMASIS, IPCI, IQVIA DA, NAJS, and SIDIAP data sources.

Age and sex distribution among individuals prescribed inhaled salbutamol during the study period

The distribution of age and sex varied across the three types of inhaled salbutamol delivery devices. For DPI prescriptions, the proportion of elderly individuals (over 75 years) ranged from 6.9% to 27.3%, while it ranged from 10.7% to 20.0% for MDI prescriptions. In both DPI and MDI groups, the most common age groups were middle-aged and older adults (18–75 years). In contrast, among individuals prescribed salbutamol via nebuliser solution, the proportion of children aged 2–11 years varied widely across data sources, from 1.0% to 64.5%, with the highest proportion observed in Croatian NAJS. The proportion of elderly individuals (over 75 years) in the nebuliser solutions users group ranged from 4.4% to 50.6%, with the highest proportion observed in SIDIAP. (**Table 9**).

Sex distribution across the three types of inhaled salbutamol devices showed relatively balanced prescription between males and females, with a slight predominance of female users overall. For DPIs, the proportion of female users ranged from 48.2% to 57.9% across data sources, while male users accounted for 42.1% to 51.9%. In the case of MDIs, females represented between 44.6% and 56.5% of users, and males between 43.5% and 55.4%. Nebuliser solutions had a slightly higher representation of male users in some data sources (e.g. IMASIS, IQVIA DA, and NAJS), with proportions ranging from 41.8% to 57.9%, whereas females ranged from 42.1% to 58.2% (**Table 9**).

Indication of use distribution among individuals prescribed inhaled salbutamol during the study period

The distribution of indication of use (assessed at ±7 days of index date) varied considerably across the three types of devices. Overall, asthma and LRTI were the most frequently recorded reason for prescribing salbutamol across all inhaled device types, though with varying proportions. Asthma was reported as indication of use in 12.8% to 70.2% of all prescriptions for inhaled salbutamol across data sources. Notably, in SIDIAP, the prevalence of an asthma diagnosis around the index date was considerably lower than that of LRTI (12.8% vs. 55.2%).

A disease code of LRTI was frequently recorded around the date of salbutamol prescribing, especially for nebuliser solutions, with proportions ranging from 25.3% to 87.1%. For salbutamol inhalation users, these ranged between 22.5% to 67.6%.

Recording of COPD among salbutamol inhalation users varied, with ranges of 6.7% to 34.9%.

Chronic bronchitis was recorded less frequently among all salbutamol inhalation users (1.0% to 24.6%). Bronchospasm indication was not recorded for salbutamol inhalation in some data sources (IPCI, IQVIA DA, and NAJS) and in other data sources, it was recorded with varying frequencies ranging from 0.1% (CPRD-GOLD) to 50.0% (DK-DHR).

Prescription of salbutamol for reasons of respiratory conditions due to chemical agents was rare across all devices and all data sources, never exceeding 0.2% (**Table 9**).

Similar findings were observed when the indication of use was assessed during the window of -365 to -1 days prior to the index date (**Appendix II, Table S17**).

Distribution of Indication of use among individuals prescribed inhaled salbutamol by calendar year

To explore changes in indication of use over time, the indication of use was assessed per calendar year. **Figure 17** displays the trends in distribution of predefined indications for use of inhaled salbutamol within window of ±7 days of index date of each prescription from 2015 to 2024 across data sources. More details of results stratified by device types are presented in **Appendix II, Figures S3-S8**.

Over the years, the proportion of individuals with a recording of a disease code of interest (i.e. indication of use) for inhaled salbutamol increased. For instance, in SIDIAP, LRTI rose from 28% in 2015 to over 75% by 2024, and in IMASIS, from 24% to 83% over the same period. NAJS showed a similar upward trend, with LRTI increasing from 35% to 84%. Asthma remained relatively stable or showed mild fluctuations over time in most data sources. For example, in DK-DHR, asthma consistently accounted for around 60% of salbutamol prescriptions, while in NAJS it peaked around 55% in 2020, before slightly declining in 2024. In IPCI, asthma increased from 17% in 2015 to 41% in 2021, then plateaued (**Figure 17**).

COPD showed a more stable trend, particularly in DK-DHR, IQVIA DA, and NAJS, ranging from 20% to 40% throughout the study period. However, in SIDIAP and IPCI, COPD proportions remained relatively low (typically under 20%) and did not show substantial variation. The recording of bronchospasm increased in DK-DHR, rising from 30% to 60%, and in IMASIS from 5% to 17%, while remaining low or nearly absent in other data sources. Similarly, chronic bronchitis was a less frequently recorded indication overall, with modest representation in some data sources, such as IMASIS, IQVIA DA, NAJS, and SIDIAP, where it ranged from 5% to 30% over time. In most other databases, its presence remained minimal or near zero throughout the study period (**Figure 17**).

Table 9. The distribution of predefined indications for use (±7 of index date), age, and sex at the time of each inhaled salbutamol prescription during the study period stratified by device types across data sources CPRD-GOLD, DK-DHR, IMASIS, IPCI, IQVIA DA, NAJS, and SIDIAP.

		Data Sources Name						
		CPRD-Gold	DK-DHR	IMASIS	IPCI	IQVIA DA	NAJS	SIDIAP
Variable name	**Variable level**	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Cohort name	Salbutamol all forms inhalation							
Number of subjects*	N	1,165,050	819,014	19,574	220,301	1,077,628	541,020	1,107,498
Number of records**	N	14,218,794	3,617,411	132,049	1,029,194	3,415,131	2,330,382	7,395,845
Age group	0-23 months	53,022 (0.37)	143,052 (3.95)	1,762 (1.33)	14,394 (1.40)	161,689 (4.73)	81,540 (3.50)	255,530 (3.46)
	2-11 years	916,654 (6.45)	416,145 (11.50)	6,067 (4.59)	98,044 (9.53)	708,991 (20.76)	453,673 (19.47)	1,291,458 (17.46)
	12-17 years	517,543 (3.64)	134,864 (3.73)	697 (0.53)	54,072 (5.25)	205,442 (6.02)	143,456 (6.16)	296,460 (4.01)
	18-45 years	3,115,005 (21.91)	584,566 (16.16)	7,121 (5.39)	261,430 (25.40)	683,354 (20.01)	486,869 (20.89)	1,464,954 (19.81)
	46-65 years	4,795,751 (33.73)	974,271 (26.93)	36,696 (27.79)	342,962 (33.32)	891,388 (26.10)	535,545 (22.98)	1,853,897 (25.07)
	66-75 years	2,608,208 (18.34)	683,435 (18.89)	24,768 (18.76)	148,078 (14.39)	419,235 (12.28)	331,547 (14.23)	1,057,879 (14.30)
	>75 years	2,212,611 (15.56)	681,078 (18.83)	54,938 (41.60)	110,214 (10.71)	345,032 (10.10)	297,752 (12.78)	1,175,667 (15.90)
Sex	Female	7,776,072 (54.69)	2,010,495 (55.58)	57,158 (43.29)	579,554 (56.31)	1,701,313 (49.82)	1,131,877 (48.57)	3,813,315 (51.56)
	Male	6,442,722 (45.31)	1,606,916 (44.42)	74,891 (56.71)	449,640 (43.69)	1,712,479 (50.14)	1,198,505 (51.43)	3,582,530 (48.44)
Indication of use (±7 of index date)	Asthma	2,631,371 (18.51)	2,540,124 (70.22)	24,350 (18.44)	357,977 (34.78)	813,561 (23.82)	1,285,958 (55.18)	943,782 (12.76)
	Lower Respiratory Tract Infection	3,847,421 (27.06)	1,545,320 (42.72)	89,235 (67.58)	312,783 (30.39)	767,530 (22.47)	1,536,582 (65.94)	4,081,254 (55.18)
	COPD	2,504,765 (17.62)	1,261,983 (34.89)	59,125 (44.78)	166,091 (16.14)	697,174 (20.41)	787,617 (33.80)	493,341 (6.67)

		Data Sources Name						
		CPRD-Gold	DK-DHR	IMASIS	IPCI	IQVIA DA	NAJS	SIDIAP
		N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Variable name	Variable level							
	Chronic Bronchitis	128,325 (0.90)	150,793 (4.17)	14,527 (11.00)	21,427 (2.08)	420,947 (12.33)	574,296 (24.64)	1,323,330 (17.89)
	Bronchospasm	13,737 (0.10)	1,802,288 (49.82)	12,997 (9.84)	0 (0.00)	0 (0.00)	0 (0.00)	304,194 (4.11)
	Respiratory condition due to chemical agents	153 (0.00)	363 (0.01)	178 (0.13)	0 (0.00)	447 (0.01)	1,252 (0.05)	4,791 (0.06)
	Other conditions#	-	126,200 (3.49)	21,456 (16.25)	391,757 (38.06)	1,879,674 (55.04)	65,508 (2.81)	2,485,570 (33.61)
Cohort name	**Salbutamol dry powder inhalers**							
Number of subjects*	N	658,729	478,960	-	95,548	43,765	6,539	214
Number of records**	N	7,754,082	1,945,179	-	443,143	105,702	14,541	297
Age group	0-23 months	24,064 (0.31)	50 (0.00)	-	92 (0.02)	15 (0.01)	23 (0.16)	<5 (<5)
	2-11 years	446,531 (5.76)	81,316 (4.18)	-	4,391 (0.99)	13,633 (12.90)	530 (3.64)	37 (12.46)
	12-17 years	274,981 (3.55)	100,636 (5.17)	-	20,286 (4.58)	16,324 (15.44)	1,161 (7.98)	28 (9.43)
	18-45 years	1,635,271 (21.09)	409,354 (21.04)	-	149,402 (33.71)	23,998 (22.70)	3,225 (22.18)	41 (13.80)
	46-65 years	2,612,695 (33.69)	608,632 (31.29)	-	176,974 (39.94)	28,296 (26.77)	4,249 (29.22)	51 (17.17)
	66-75 years	1,488,275 (19.19)	401,159 (20.62)	-	61,330 (13.84)	13,268 (12.55)	2,562 (17.62)	56 (18.86)
	>75 years	1,272,265 (16.41)	344,032 (17.69)	-	30,668 (6.92)	10,168 (9.62)	2,791 (19.19)	81 (27.27)
Sex	Female	4,269,918 (55.07)	1,126,096 (57.89)	-	248,851 (56.16)	55,356 (52.37)	7,930 (54.54)	143 (48.15)
	Male	3,484,164 (44.93)	819,083 (42.11)	-	194,292 (43.84)	50,321 (47.61)	6,611 (45.46)	154 (51.85)
Indication of use (±7 of index date)	Asthma	1,583,427 (20.42)	1,355,722 (69.70)	-	162,834 (36.75)	24,884 (23.54)	7,353 (50.57)	29 (9.76)

Variable name	Variable level	CPRD-Gold N (%)	DK-DHR N (%)	IMASIS N (%)	IPCI N (%)	IQVIA DA N (%)	NAJS N (%)	SIDIAP N (%)
		Data Sources Name						
	Lower Respiratory Tract Infection	2,421,247 (31.23)	760,048 (39.07)	-	119,903 (27.06)	15,360 (14.53)	8,406 (57.81)	214 (72.05)
	COPD	1,456,783 (18.79)	653,656 (33.60)	-	55,299 (12.48)	14,086 (13.33)	5,467 (37.60)	47 (15.82)
	Chronic Bronchitis	78,141 (1.01)	61,060 (3.14)	-	6,779 (1.53)	7,784 (7.36)	3,131 (21.53)	56 (18.86)
	Bronchospasm	6,804 (0.09)	908,658 (46.71)	-	0 (0.00)	0 (0.00)	0 (0.00)	12 (4.04)
	Respiratory condition due to chemical agents	26 (0.00)	184 (0.01)	-	0 (0.00)	15 (0.01)	24 (0.17)	0 (0.00)
	Other conditions#	-	66,430 (3.42)	-	178,890 (40.37)	68,674 (64.97)	698 (4.80)	61 (20.54)
Cohort name	**Salbutamol metered-dose inhalers**							
Number of subjects*	N	654,852	450,012	3,304	136,046	885,991	454,420	1,102,586
Number of records**	N	6,277,656	1,704,556	5,079	526,931	2,780,581	1,993,973	7,345,286
Age group	0-23 months	28,795 (0.46)	142,162 (8.34)	45 (0.89)	12,558 (2.38)	68,559 (2.47)	30,592 (1.53)	254,665 (3.47)
	2-11 years	468,927 (7.47)	334,704 (19.64)	866 (17.05)	82,683 (15.69)	400,512 (14.40)	241,668 (12.12)	1,286,078 (17.51)
	12-17 years	244,306 (3.89)	34,866 (2.05)	469 (9.23)	30,551 (5.80)	170,372 (6.13)	130,286 (6.53)	295,132 (4.02)
	18-45 years	1,471,260 (23.44)	179,216 (10.51)	865 (17.03)	102,014 (19.36)	640,552 (23.04)	474,258 (23.78)	1,461,604 (19.90)
	46-65 years	2,132,165 (33.96)	379,947 (22.29)	1,378 (27.13)	148,891 (28.26)	827,261 (29.75)	519,673 (26.06)	1,848,286 (25.16)
	66-75 years	1,058,662 (16.86)	292,110 (17.14)	705 (13.88)	78,463 (14.89)	376,554 (13.54)	315,989 (15.85)	1,051,456 (14.31)
	>75 years	873,541 (13.92)	341,551 (20.04)	751 (14.79)	71,771 (13.62)	296,771 (10.67)	281,507 (14.12)	1,148,065 (15.63)
Sex	Female	3,398,691 (54.14)	903,636 (53.01)	2,266 (44.62)	297,734 (56.50)	1,419,962 (51.07)	988,322 (49.57)	3,786,067 (51.54)

		Data Sources Name						
		CPRD-Gold N (%)	DK-DHR N (%)	IMASIS N (%)	IPCI N (%)	IQVIA DA N (%)	NAJS N (%)	SIDIAP N (%)
Variable name	Variable level							
	Male	2,878,965 (45.86)	800,920 (46.99)	2,813 (55.38)	229,197 (43.50)	1,359,522 (48.89)	1,005,651 (50.43)	3,559,219 (48.46)
Indication of use (±7 of index date)	Asthma	1,022,872 (16.29)	1,211,615 (71.08)	1,347 (26.52)	179,515 (34.07)	731,357 (26.30)	1,199,367 (60.15)	939,756 (12.79)
	Lower Respiratory Tract Infection	1,327,178 (21.14)	798,017 (46.82)	2,461 (48.45)	173,460 (32.92)	618,873 (22.26)	1,246,352 (62.51)	4,049,980 (55.14)
	COPD	954,725 (15.21)	627,337 (36.80)	1,193 (23.49)	101,926 (19.34)	589,636 (21.21)	727,809 (36.50)	488,033 (6.64)
	Chronic Bronchitis	47,416 (0.76)	90,123 (5.29)	355 (6.99)	13,572 (2.58)	348,702 (12.54)	482,090 (24.18)	1,313,450 (17.88)
	Bronchospasm	6,208 (0.10)	914,372 (53.64)	536 (10.55)	0 (0.00)	0 (0.00)	0 (0.00)	301,923 (4.11)
	Respiratory condition due to chemical agents	127 (0.00)	178 (0.01)	<5 (<5)	0 (0.00)	353 (0.01)	1,168 (0.06)	4,746 (0.06)
	Other conditions[#]	-	59,816 (3.51)	1,602 (31.54)	187,044 (35.50)	1,473,150 (52.98)	51,841 (2.60)	2,470,078 (33.63)
Cohort name	**Salbutamol nebuliser solution**							
Number of subjects*	N	35,119	11,898	19,124	23,132	249,840	129,312	13,868
Number of records**	N	395,538	61,929	130,674	67,144	593,919	334,716	61,300
Age group	0-23 months	278 (0.07)	1,193 (1.93)	1,748 (1.34)	1,853 (2.76)	95,262 (16.04)	51,309 (15.33)	1,090 (1.78)
	2-11 years	3,502 (0.89)	4,194 (6.77)	5,990 (4.58)	11,685 (17.40)	308,898 (52.01)	215,869 (64.49)	6,872 (11.21)
	12-17 years	1,315 (0.33)	1,451 (2.34)	679 (0.52)	4,006 (5.97)	22,550 (3.80)	13,829 (4.13)	1,647 (2.69)
	18-45 years	22,596 (5.71)	4,015 (6.48)	6,835 (5.23)	12,153 (18.10)	25,309 (4.26)	11,480 (3.43)	4,375 (7.14)
	46-65 years	125,079 (31.62)	11,400 (18.41)	36,233 (27.73)	19,713 (29.36)	51,306 (8.64)	13,269 (3.96)	7,824 (12.76)

		Data Sources Name						
		CPRD-Gold N (%)	DK-DHR N (%)	IMASIS N (%)	IPCI N (%)	IQVIA DA N (%)	NAJS N (%)	SIDIAP N (%)
Variable name	Variable level							
	66-75 years	125,400 (31.70)	16,218 (26.19)	24,537 (18.78)	9,236 (13.76)	41,611 (7.01)	14,395 (4.30)	8,480 (13.83)
	>75 years	117,368 (29.67)	23,458 (37.88)	54,652 (41.82)	8,498 (12.66)	48,983 (8.25)	14,565 (4.35)	31,012 (50.59)
Sex	Female	230,055 (58.16)	34,813 (56.21)	56,499 (43.24)	37,785 (56.27)	255,660 (43.05)	141,035 (42.14)	32,129 (52.41)
	Male	165,483 (41.84)	27,116 (43.79)	74,175 (56.76)	29,359 (43.73)	338,017 (56.91)	193,681 (57.86)	29,171 (47.59)
Indication of use (±7 of index date)	Asthma	60,618 (15.33)	49,343 (79.68)	24,072 (18.42)	19,147 (28.52)	74,353 (12.52)	87,839 (26.24)	5,507 (8.98)
	Lower Respiratory Tract Infections	201,171 (50.86)	51,624 (83.36)	88,443 (67.68)	21,962 (32.71)	150,481 (25.34)	291,474 (87.08)	37,763 (61.60)
	COPD	199,227 (50.37)	47,147 (76.13)	58,711 (44.93)	10,440 (15.55)	116,146 (19.56)	58,925 (17.60)	6,585 (10.74)
	Chronic Bronchitis	6,057 (1.53)	9,303 (15.02)	14,404 (11.02)	1,302 (1.94)	74,257 (12.50)	93,324 (27.88)	11,760 (19.18)
	Bronchospasm	1,325 (0.33)	48,044 (77.58)	12,863 (9.84)	0 (0.00)	0 (0.00)	0 (0.00)	2,929 (4.78)
	Respiratory condition due to chemical agents	0 (0.00)	<5 (<5)	178 (0.14)	0 (0.00)	92 (0.02)	66 (0.02)	48 (0.08)
	Other conditions[#]	-	328 (0.53)	21,119 (16.16)	28,242 (42.06)	369,053 (62.14)	13,089 (3.91)	18,853 (30.76)

NC=No count; COPD=Chronic Obstructive Pulmonary Disease; CPRD=Clinical Practice Research Datalink; DK-DHR=Danish Data Health Registries; IMASIS=Institute Municipal Assistència Sanitària Information System; IPCI=Integrated Primary Care Information; DA=Disease Analyzer; NAJS=Croatian National Public Health Information System; SIDIAP=The Information System for Research on Primary Care

* Number of subjects = Total number of individuals who were prescribed drug during the study period

** Number of records = Total number of drug prescriptions issued during the study period. The total number of records by device type may be higher than the number of "salbutamol all form inhalation" records, as patients can receive multiple device types on the same day. For IQVIA DA Germany, the number of records refer to number of drug eras and not number of prescriptions.

[#] Other conditions= Conditions other than asthma, LRTI, COPD, chronic bronchitis, bronchospasm, and respiratory condition due to chemical agents for which salbutamol was prescribed. The results on other conditions are missing for CPRD-GOLD due to a technical issue encountered while running the study codes.

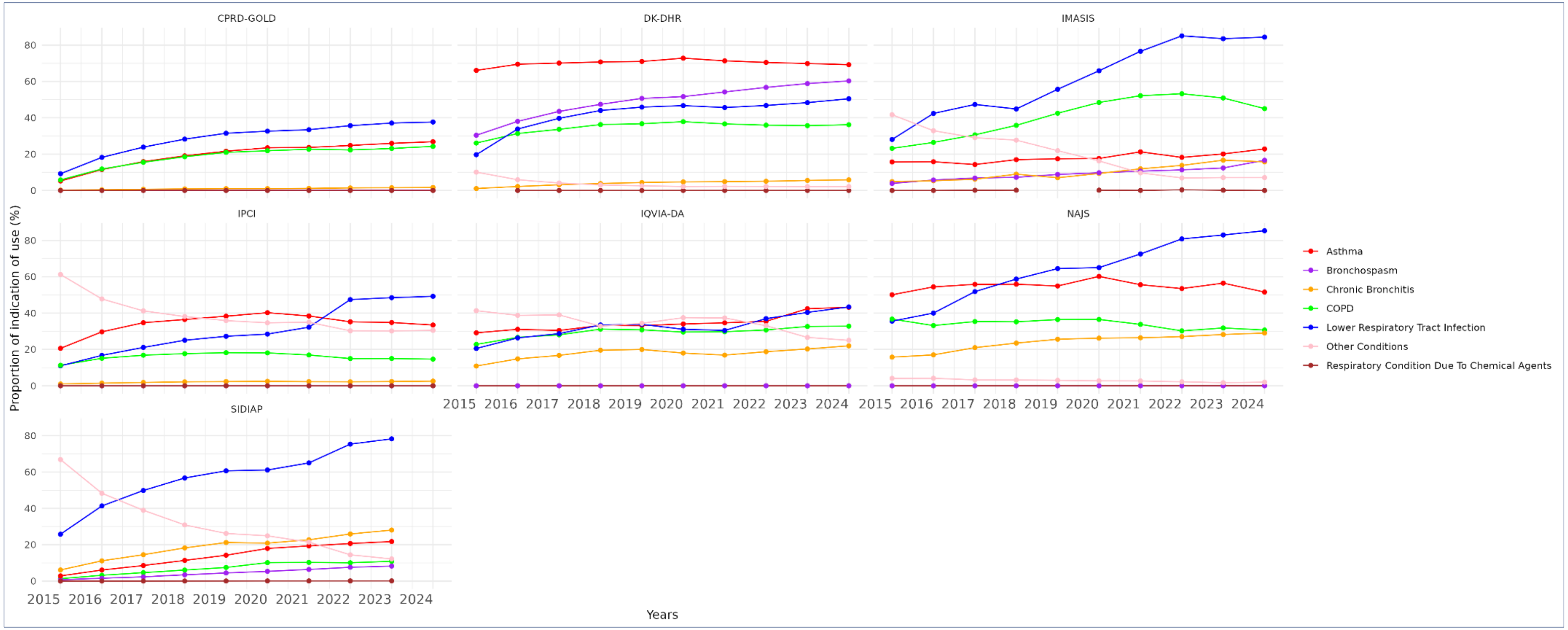

Figure 17. Trends in indications of use for prescribed inhaled salbutamol over years (2015–2024) across data sources CPRD-GOLD, DK-DHR, IMASIS, IPCI, IQVIA DA, NAJS, and SIDIAP.

COPD=Chronic Obstructive Pulmonary Disease; CPRD=Clinical Practice Research Datalink; DK-DHR=Danish Data Health Registries; IMASIS=Institut Municipal Assistència Sanitària Information System; IPCI=Integrated Primary Care Information; DA=Disease Analyzer; NAJS=Croatian National Public Health Information System; SIDIAP=The Information System for Research on Primary Care.

13. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

Adverse events/adverse reactions were not collected or analysed as part of this evaluation. The nature of this non-interventional evaluation, through the use of secondary data, does not fulfil the criteria for reporting adverse events, according to module VI, VI.C.1.2.1.2 of the Good Pharmacovigilance Practices (https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/guideline-good-pharmacovigilance-practices-gvp-module-vi-collection-management-submission-reports_en.pdf).

Only in case of prospective data collection, there is a need to describe the procedures for the collection, management, and reporting of individual cases of adverse events/adverse reactions.

14. DISCUSSION

14.1. Key results

Yearly and monthly prescription rates of inhaled salbutamol products

Across multiple European healthcare data sources from 2015–2024, significant differences were observed in yearly salbutamol prescribing patterns by device type. MDIs were the most prescribed type in IPCI, IQVIA DA, NAJS, and SIDIAP, while DPIs were prescribed more in CPRD-GOLD and DK-DHR, and nebuliser solutions dominated in IMASIS. In CPRD-GOLD, DPIs prescription rates increased over time to surpass MDIs by 2017, both exceeding 976 prescriptions/100,000 PMs. DK-DHR showed moderate increases in DPIs and MDIs prescribing peaking at 306, with nebuliser solutions remaining below 11. In IMASIS we saw a rise in nebuliser solutions prescription from 203/100,000 PMs to 923. IPCI maintained relatively balanced in MDIs and DPIs prescription (299–433), while IQVIA DA prescriptions of MDIs increased from 190/100,000 PMs in 2021 to 469 in 2024. NAJS showed a slow decline in MDIs prescription from 469 to 388, and SIDIAP MDI prescribing peaked at 1,104, before settling at rate 1,068, with minimal DPIs prescription and moderate nebuliser solutions usage.

Monthly prescribing trends aligned with yearly patterns, showing regional differences and strong seasonal peaks in winter months and lower prescription in summer. For instance, in DK-DHR, DPI prescription rose to 332/100,000 PMs and 333 in December 2022 and 2023, compared to 285 and 283 in August of the same years. In the SIDIAP data source, mainly salbutamol administered via MDIs was prescribed with clear seasonal peaks, rising from 1,051/100,000 PMs in December 2021 to 1,421 in December 2022, and 1,272 in January 2023, while dropping to around 600–900 in summer months. In the IMASIS data source, salbutamol nebuliser solution prescriptions rose significantly from 669/100,000 PMs in April 2020 to 883 in December 2023, peaking at 1,044 in January 2024, and with a clear seasonal trend.

A sharp spike in salbutamol prescription occurred in March 2020, corresponding to the onset of the COVID-19 pandemic, across data sources CPRD-GOLD, DK-DHR, IPCI, IQVIA DA, and NAJS.

Yearly and monthly prescription rates of salbutamol products and inhaled alternatives

The results of yearly prescribing rates of inhaled salbutamol, oral salbutamol, and inhaled alternatives showed that across most data sources, *salbutamol inhalation* and *formoterol + ICS* (i.e. formoterol + beclomethasone and formoterol + budesonide) were the most prescribed medications, whereas prescribing of *oral salbutamol*, *formoterol inhalation*, and *SABA inhalation other than salbutamol* (i.e. terbutaline and fenoterol) was much lower.

Monthly prescribing rates of inhaled salbutamol showed heterogeneous patterns across data sources. An upward trend was evident in DK-DHR, IMASIS, and IQVIA DA, while SIDIAP and IPCI displayed relatively stable prescribing. In contrast, CPRD-GOLD and NAJS showed a gradual decline. A distinct peak around

March 2020 was observed in data sources CPRD-GOLD, DK-DHR, IPCI, IQVIA DA, and NAJS, reflecting the early phase of the COVID-19 pandemic.

Over the years, prescribing of formoterol combined + ICS was high across multiple data sources, including DK-DHR, IPCI, IQVIA DA, NAJS, and SIDIAP, with a general increase observed over time. However, the rates were lower than those for inhaled salbutamol, except in DK-DHR where formoterol + ICS prescriptions exceeded salbutamol. High prescription of short-acting anticholinergics was also evident in IMASIS, IPCI, and SIDIAP, with a relatively stable prescribing trend observed over the years. Notable spikes in the prescription of salbutamol alternatives were observed in March 2020, coinciding with the onset of the COVID-19 pandemic, across data sources including CPRD-GOLD, DK-DHR, IPCI, IQVIA DA, and NAJS.

Distribution of age, sex, and indication of use among individual prescribed inhaled salbutamol products

The distribution of age, sex, and indication of use among patients prescribed inhaled salbutamol via DPIs, MDIs, and nebuliser solutions varied across multiple European data sources in the study period 2015 to 2024. Individuals aged 18–75 were more frequently used DPIs (13.8–34.0%) and MDIs (10.5–24.0%). In contrast, salbutamol prescribed as nebuliser solutions was mainly used in the youngest (2–11 years, up to 64.5%) and oldest (>75 years, up to 50.6%) age groups, particularly in SIDIAP. Across all three types of inhaled salbutamol devices, prescription was relatively balanced between sexes, with a slight overall predominance of female users. Female representation ranged from 48.2% to 57.9% for DPIs, 44.6% to 56.5% for MDIs, and 42.1% to 58.2% for nebuliser solutions, though some data sources (e.g., IMASIS, IQVIA DA, and NAJS) showed higher male use for nebulisers (up to 57.9%).

Asthma was the most frequently recorded indication for inhaled salbutamol in many data sources (up to 70.2%), though with considerable variation across devices and settings. LRTI was the predominant indication for nebuliser solution prescription, reaching up to 87.17%. COPD, chronic bronchitis, and bronchospasm were less frequently recorded around the salbutamol prescribing date across different devices. Over the years, the number of individuals with a condition of interest recorded around the salbutamol prescription data increased. Recording of LRTI increased from 28% to over 75% in SIDIAP, 24% to 83% in IMASIS, and 35% to 84% in NAJS. Recording of asthma remained stable, accounting for around 60% in DK-DHR and peaking at 55% in NAJS. In IPCI, asthma as indication of use increased from 17% in 2015 to 41% in 2021. COPD ranged between 20% and 40% in DK-DHR, IQVIA DA, and NAJS, but stayed below 20% in SIDIAP and IPCI. Chronic bronchitis was infrequent overall, with 5%–30% in some sources (e.g. IMASIS, IQVIA DA, NAJS, and SIDIAP) and minimal in others. Bronchospasm recording rose in DK-DHR (30% to 60%) and IMASIS (5% to 17%) but stayed low in other data sources.

14.2. Strengths and limitations of the research methods

For this study, we had access to a large number of data sources with long follow-up, allowing us to explore the use/prescribing of salbutamol and alternative drugs over time and within different relevant strata. Furthermore, as information on formulation was available in all databases—but not necessarily for all prescriptions—the study allowed us to explore prescribing by device type.

Some considerations should be noted. Initially, we also aimed to describe prescription rates by health-care setting (inpatient vs. outpatient prescribing), but the lack of granularity on setting posed a limitation.

For this study, several indications of interest were predefined. Not all these indications might be recorded in all data sources (some data sources have less granular source coding), nor recorded at time of salbutamol prescribing. It is also important to note that the indications are not automatically linked to the prescriptions. In some data sources, we noticed a high prevalence of “other conditions”, which included diagnoses not specifically defined in this study. This likely reflects differences in coding systems and practices, where physicians may record symptom-based rather than disease-specific diagnoses, as well as variations in coding granularity. Moreover, validation of recorded diagnoses through individual patient health record review was not performed and does not fall in the scope of off-the-shelf studies.

Another limitation of the study is the restricted data availability in 2024, which limits our ability to fully assess prescription patterns during a period when critical salbutamol shortages were reported. For example, in Germany, the first shortage occurred in July 2023(35), and the situation had worsened by December 2023.(36) Most of data sources, except CPRD-GOLD and NAJS, had earlier cut-off dates (June/July 2024), and in some cases (DK-DHR, IMASIS, IQVIA DA), the final month of data may be less reliable due to incomplete capture. The sharp upward prescribing trends observed in IMASIS and IQVIA DA Germany, as well as the sharp downward trend in DK-DHR, may therefore be artefactual; however, since these changes in prescribing trends begin prior to the last months of data, they are likely at least partially real. This should be considered when interpreting trends near the end of the study period.

While OMOP provides mapping to established vocabularies like SNOMED, inaccuracies or gaps in these mappings can occur, impacting the accuracy and completeness of data analysis in different data sources. Indeed, local coding systems may use different standards or different levels of granularity. For example, the local coding system, which serves as the basis for mappings, may have fewer specific codes for certain medications or medical conditions. For IQVIA DA, as an example, drug source codes for MDIs are not supported by the OHDSI vocabulary and thus lack corresponding OMOP concepts. Similarly, in SIDIAP, MDIs are mapped to the salbutamol ingredient concept only, meaning that information on MDI use was lost during the process of mapping. However, as information of formulation was important, these issues were addressed using custom codes tailored to these specific data sources.

Finally, indication of use was described as one of the characteristics at time of salbutamol prescribing, however, prescription rates were explored in the overall population and not in subgroups of patients with asthma, COPD, LRTI etc. While comparing prescribing patterns between patients with asthma and those with other respiratory conditions (e.g., COPD) could be clinically informative, this was beyond the specific objectives of the study.

Finally, the results estimated from this study only reflect the populations from the included data sources and might not automatically be translated to other data sources/countries. Moreover, electronic health records, as used for this study, are collected for clinical purposes rather than primarily for research use.

14.3. Interpretation

The analysis of salbutamol prescribing trends across European healthcare data sources from 2015 to 2024 showed regional, temporal, and demographic differences. MDIs remained the dominant device type in several data sources (i.e., IPCI, IQVIA DA, NAJS, and SIDIAP), while DPIs were more prescribed in CPRD-GOLD and DK-DHR, and nebulized solutions were predominantly prescribed in IMASIS, a hospital-based source. These differences reflect the interplay of national prescribing guidelines, healthcare setting, reimbursement criteria, and possibly differences in environmental policies aimed at reducing carbon footprints.(37, 38)

In outpatient settings, DPIs and MDIs are the most prescribed forms.(39, 40) In our study, most data sources, with the exception of the Spanish IMASIS data source, represented outpatient settings with higher prescription rates for DPIs and MDIs. These types of inhalers are widely prescribed in outpatient care because they help patients manage their conditions on their own, reducing the need for regular doctor visits or hospital stays. DPIs are popular because they are easy to use, especially for patients who find it hard to coordinate their breathing with using MDIs, and they are more environmentally friendly. Some regions, like the UK and Denmark, showed a consistent trend toward higher DPIs prescription over MDIs, aligning with broader European initiatives encouraging low-carbon inhalers.(41) However, MDIs are still commonly prescribed because they are affordable and widely available in the market, as was evident in IPCI, IQVIA DA, NAJS, and SIDIAP data sources, and they are easier to use in patients who struggle to generate a minimum inspiratory flow rate.(40) In hospital settings, nebulized salbutamol remains essential for treating acute respiratory conditions(42), as observed with higher prescribing rates for nebuliser solutions in the IMASIS data source from Spain. Nebuliser solutions are particularly effective for delivering consistent, high doses in patients with severe asthma or COPD exacerbations, where handheld inhalers may be less effective. Hospital protocols often recommend nebulized therapies to ensure optimal bronchodilation in critically ill patients.(43, 44) The trends observed in this analysis align with the broader shift toward environmentally sustainable inhaler options and personalized care in respiratory medicine.

We noticed differences between data sources about the type of administration (MDIs vs. DPIs). For example, in SIDIAP, mainly salbutamol via MDIs was prescribed. Similarly, in NAJS, mainly MDI was prescribed, as salbutamol via DPI was only included in the reimbursement list for a short period of time. These variations highlight how local prescribing practices and reimbursement policies can influence the observed patterns of medication use.

Higher prescribing rates of salbutamol in CPRD-GOLD, compared to other data sources, likely reflect widespread overuse of SABA products among asthma patients in the UK. Studies have reported that nearly half of UK asthma patients overuse reliever inhalers like salbutamol, often substituting them for appropriate asthma maintenance therapy.(45) This behaviour not only worsens asthma control, but also inflates prescription volumes.

In this study, the observed seasonal peaks in salbutamol prescribing during the winter months align with environmental and clinical factors known to exacerbate respiratory conditions. Increased humidity levels, combined with a higher prevalence of viral respiratory infections, such as influenza and respiratory syncytial virus, are recognized triggers for exacerbations of asthma and COPD during colder periods. In addition, decreased indoor humidity due to heating in winter may further contribute to respiratory infections and consequent bronchoconstriction.(46) These seasonal dynamics were consistently observed across all regions studied, further explaining the recurrent winter surges in demand for bronchodilators like salbutamol.(47, 48) Moreover, the sharp peak in salbutamol prescriptions observed in March 2020 across most data sources (except SIDIAP) corresponds to the onset of the first wave of the COVID-19 pandemic. During this time, a noticeable but temporary surge in salbutamol was likely driven by heightened respiratory symptoms, increased anxiety among patients, and precautionary prescribing by healthcare providers, including initial stockpiling behaviours.(49, 50) For instance, a study in British Columbia reported a significant stockpiling of 19.3% in overall prescriptions dispensed during the week of the pandemic declaration, followed by an immediate decrease of 2.4% in overall dispensations.(51) Concerns over respiratory distress and difficulties accessing healthcare services during lockdowns may have further driven patients and clinicians to prioritize the availability of fast-acting relievers like salbutamol as a precautionary measure.

Regarding alternative respiratory therapies, formoterol combined with ICS consistently ranked among the most prescribed medications, reflecting evolving asthma management strategies that emphasize maintenance and reliever therapy approaches.(2) Short-acting anticholinergics were particularly prevalent in the hospital data source of IMASIS, suggesting higher treatment intensity among hospitalized patients with acute respiratory illnesses. Conversely, oral salbutamol and SABA other than salbutamol showed very low prescription rates. Low prescription of oral salbutamol is consistent with literature indicating a shift toward inhaled formulations, due to their superior efficacy and safety profiles.(52) The low prescription of oral salbutamol across sources reflects clinical guidelines discouraging systemic therapies, except in specific cases where inhaled options are unavailable or impractical.(53)

In our results, we noticed that the prescription rates for salbutamol and related inhalation therapies in Germany were relatively stable until mid-2023 but showed a sharp increase from late 2023, peaking in early 2024. This aligns with reported shortages of salbutamol-containing medicines, first noted in July 2023 and officially declared critical in December 2023.(35, 36) According to the German National Competent Authority (NCA), these shortages likely triggered stockpiling, precautionary prescribing, and therapeutic switching, reflected in rising prescriptions of formoterol + ICS and other alternatives.(36) These patterns highlight how medicine shortages can significantly impact prescribing behaviour, potentially exacerbating supply constraints through stockpiling and overprescribing. The data underline the importance of timely shortage reporting and coordinated response strategies to mitigate cascading effects on the healthcare system.(54) Moreover, salbutamol is included in the Union list of critical medicines, specific list established by the EU to support coordinated action across Member States. This list enables EMA, the Heads of Medicines Agencies (HMA), and the European Commission (55) to work together to take proactive measures to prevent shortages. The Union list comprises human medicines whose continued supply is considered a priority within the EU. Salbutamol has been included since the first version of the list was released in December 2023. Inclusion in the list triggers a review of the medicine's supply chain to identify potential vulnerabilities that may be addressed through regulatory actions (as outlined in the proposed New Pharmaceutical Legislation) or potential industrial measures (as described in the proposed Critical Medicines Act) at Union level. (56)

In patients with asthma, high prescription of salbutamol (either via MDIs, DPIs or nebulisers) without concomitant use of ICS as reliever therapy is a concern. Regular utilization of SABA, even for a duration as short as one to two weeks, can lead to detrimental effects such as beta-receptor downregulation, diminished broncho-protection, and rebound hyper-responsiveness. Increased SABA usage correlates with adverse clinical outcomes; dispensing three or more SABA inhalers annually is linked with a heightened risk of exacerbations, while dispensing twelve or more SABA inhalers annually significantly elevates the risk of mortality. For this reason, the Global Strategy for Asthma Management and Prevention (GINA) guidelines began recommending an as-needed combination of low dose ICS-formoterol as a first choice, or the use of SABA in combination with ICS as reliever therapy.(57, 58) In our study, we observed an increase in prescription of formoterol + ICS in DK-DHR, IPCI, IQVIA DA, NAJS, and SIDIAP, which might reflect the implementation of these guidelines.

Age and indication-specific trends showed expected patterns: nebuliser solutions were mainly prescribed in paediatric and geriatric populations, likely due to coordination difficulties with handheld inhalers. (44) These findings highlight vulnerable groups who may struggle to switch to alternatives like dry-powder inhalers in the event of shortages of other formulations. Female predominance in salbutamol prescriptions across most data sources suggest that women may experience more severe asthma symptoms or report them more frequently, influencing higher prescription rates.(59) Our findings also show the dominance of asthma, LRTI, and COPD as the leading indications for salbutamol use, mirroring the established roles of SABA in the treatment of acute respiratory conditions.(57)

In summary, given the increasing reliance on inhaled salbutamol, particularly during winter surges and pandemic periods, there are growing concerns about supply chain vulnerabilities. Historical episodes during the COVID-19 pandemic have already demonstrated how sudden spikes in demand can precipitate regional shortages of inhalers.(54, 60) Persistent high usage, combined with environmental initiatives phasing down MDIs, may pressure manufacturers to adapt production lines, leading to transitional gaps in availability. Additionally, market concentration of inhaler manufacturers may reduce flexibility in scaling up production during crisis periods; however, regulators often mitigate such risks by granting temporary exemptions, applying regulatory flexibilities, expediting evaluations, and facilitating the entry of additional generic competitors into national markets.(61) The sharp seasonal surges and the growing elderly population, who have higher respiratory disease burdens, suggest that proactive monitoring of prescription trends and ensuring diversified and resilient supply chains are crucial to mitigating potential shortages. In patients with asthma, potential shortages might be less of a concern, as there are better alternatives than salbutamol for reliever therapy. However, also in patients with asthma, salbutamol nebulization is a key treatment for asthma exacerbations, particularly severe ones in the emergency department setting.(2, 57)

14.4. Generalisability

This study included data from seven data sources across six different European countries (United Kingdom, Denmark, Croatia, Germany, the Netherlands, and Spain), covering both primary and secondary healthcare data. These data sources capture different aspects of the healthcare pathway and offer broad population coverage, particularly the large primary care data sources.

While these results may be considered largely representative of prescription rates of inhaled salbutamol and alternative therapies, results should not be completely generalised to the entire Europe or regions outside of Europe. In addition, variations in population characteristics, such as age distribution, prevalence of respiratory conditions, socioeconomic factors, and healthcare access, as well as differences in national guidelines for diagnosis and treatment, availability, or authorisation of products, and prescribing practices may lead to significant disparities between countries. Additionally, regional variations in healthcare infrastructure, physician preferences, medication supply, and market dynamics further emphasize the need for caution when extrapolating these findings to broader populations.

15. CONCLUSION

In conclusion, the analysis of prescription rates for salbutamol and inhaled alternatives across European data sources highlights different usage patterns across data sources and over years, seasonal variations, and disparities by age, sex, and indications. Salbutamol administered via MDIs were the most frequently prescribed in IPCI, IQVIA DA, NAJS, and SIDIAP, while DPIs were preferred in CPRD-GOLD and DK-DHR, and nebuliser solutions dominated in IMASIS, particularly among young children and elderly populations. Asthma was consistently the leading indication for inhaled salbutamol use across all devices, though prescriptions linked to LRTI became increasingly common for nebuliser solutions over time, especially in IMASIS and SIDIAP. Seasonal variations were evident, with winter peaks in prescribing across all device types and data sources.

Inhaled alternatives, notably formoterol with corticosteroids and short-acting anticholinergics also showed rising prescription, with patterns that may indirectly reflect the impact of salbutamol availability. These findings underscore the importance of proactive shortage prevention strategies and mitigation efforts to ensure consistent access to essential respiratory treatments, and to better understand how therapeutic alternatives may be leveraged during supply disruptions.

16. REFERENCES

1. Gibson G, Loddenkemper R, Sibille Y, Lundbäck B. The European Lung White Book. Respiratory Health and Disease in Europe. Sheffield, European Respiratory Society, 2013.

2. GINA. Global Strategy for Asthma Management Prevention (update 2025). https://ginasthma.org/2025-gina-strategy-report/. 2025.

3. EMA. Shortage of salbutamol inhalation products. Last update 19 December 2024 2024.

4. EMA. Medicine shortages in the EU: causes and solutions. Last updated: 30-09-2022. 2022.

5. Holland AE, Spathis A, Marsaa K, Bausewein C, Ahmadi Z, Burge AT, et al. European Respiratory Society clinical practice guideline on symptom management for adults with serious respiratory illness. Eur Respir J. 2024;63(6).

6. Labaki WW, Han MK. Chronic respiratory diseases: a global view. The Lancet Respiratory Medicine. 2020;8(6):531-3.

7. Matera MG, Page CP, Calzetta L, Rogliani P, Cazzola M. Pharmacology and Therapeutics of Bronchodilators Revisited. Pharmacol Rev. 2020;72(1):218-52.

8. EU D. Catalogue of Standard Data Analyses. https://www.darwin-eu.org/index.php/methods/standardised-analytics.

9. Herrett E, Gallagher AM, Bhaskaran K, Forbes H, Mathur R, van Staa T, et al. Data Resource Profile: Clinical Practice Research Datalink (CPRD). Int J Epidemiol. 2015;44(3):827-36.

10. Carey IM, Nirmalananthan N, Harris T, DeWilde S, Chaudhry UAR, Limb E, et al. Prevalence of co-morbidity and history of recent infection in patients with neuromuscular disease: A cross-sectional analysis of United Kingdom primary care data. PLoS One. 2023;18(3):e0282513.

11. Fahmi A, Wong D, Walker L, Buchan I, Pirmohamed M, Sharma A, et al. Combinations of medicines in patients with polypharmacy aged 65-100 in primary care: Large variability in risks of adverse drug related and emergency hospital admissions. PLoS One. 2023;18(2):e0281466.

12. Wigglesworth S, Neligan A, Dickson JM, Pullen A, Yelland E, Anjuman T, et al. The incidence and prevalence of epilepsy in the United Kingdom 2013-2018: A retrospective cohort study of UK primary care data. Seizure. 2023;105:37-42.

13. de Ridder MAJ, de Wilde M, de Ben C, Leyba AR, Mosseveld BMT, Verhamme KMC, et al. Data Resource Profile: The Integrated Primary Care Information (IPCI) database, The Netherlands. Int J Epidemiol. 2022;51(6):e314-e23.

14. Ali MS, Berencsi K, Marinier K, Deltour N, Perez-Guthann S, Pedersen L, et al. Comparative cardiovascular safety of strontium ranelate and bisphosphonates: a multi-database study in 5 EU countries by the EU-ADR Alliance. Osteoporos Int. 2020;31(12):2425-38.

15. Baan EJ, van den Akker ELT, Engelkes M, de Rijke YB, de Jongste JC, Sturkenboom M, et al. Hair cortisol and inhaled corticosteroid use in asthmatic children. Pediatr Pulmonol. 2020;55(2):316-21.

16. Berencsi K, Sami A, Ali MS, Marinier K, Deltour N, Perez-Gutthann S, et al. Impact of risk minimisation measures on the use of strontium ranelate in Europe: a multi-national cohort study in 5 EU countries by the EU-ADR Alliance. Osteoporos Int. 2020;31(4):721-55.

17. Engelkes M, Baan EJ, de Ridder MAJ, Svensson E, Prieto-Alhambra D, Lapi F, et al. Incidence, risk factors and re-exacerbation rate of severe asthma exacerbations in a multinational, multidatabase pediatric cohort study. Pediatr Allergy Immunol. 2020;31(5):496-505.

18. James G, Collin E, Lawrance M, Mueller A, Podhorna J, Zaremba-Pechmann L, et al. Treatment pathway analysis of newly diagnosed dementia patients in four electronic health record databases in Europe. Soc Psychiatry Psychiatr Epidemiol. 2021;56(3):409-16.

19. Rathmann W, Bongaerts B, Carius HJ, Kruppert S, Kostev K. Basic characteristics and representativeness of the German Disease Analyzer database Int J Clin Pharmacol Ther. 2018;56(10):459-66.

20. Zappacosta S, Cascarano A, Konrad M, Tanislav C, Kostev K. Association between COVID-19 and subsequent vascular events in primary care patients in Germany. Public Health. 2022;213:107-13.

21. Ly NF, Flach C, Lysen TS, Markov E, van Ballegooijen H, Rijnbeek P, et al. Impact of European Union Label Changes for Fluoroquinolone-Containing Medicinal Products for Systemic and Inhalation Use: Post-Referral Prescribing Trends. Drug Saf. 2023;46(4):405-16.

22. Tanislav C, Rosenbauer J, Zingel R, Kostev K. No increased incidence of venous thrombosis or pulmonary embolism after SARS-CoV-2 vaccination in Germany. Public Health. 2022;207:14-8.

23. Recalde M, Rodríguez C, Burn E, Far M, García D, Carrere-Molina J, et al. Data Resource Profile: The Information System for Research in Primary Care (SIDIAP). Int J Epidemiol. 2022;51(6):e324-e36.

24. Braeye T, Emborg HD, Llorente-García A, Huerta C, Martín-Merino E, Duarte-Salles T, et al. Age-specific vaccination coverage estimates for influenza, human papillomavirus and measles containing vaccines from seven population-based healthcare databases from four EU countries - The ADVANCE project. Vaccine. 2020;38(16):3243-54.

25. Burn E, Tebé C, Fernandez-Bertolin S, Aragon M, Recalde M, Roel E, et al. The natural history of symptomatic COVID-19 during the first wave in Catalonia. Nat Commun. 2021;12(1):777.

26. Lane JC, Butler KL, Poveda-Marina JL, Martinez-Laguna D, Reyes C, de Bont J, et al. Preschool Obesity Is Associated With an Increased Risk of Childhood Fracture: A Longitudinal Cohort Study of 466,997 Children and Up to 11 Years of Follow-up in Catalonia, Spain. J Bone Miner Res. 2020;35(6):1022-30.

27. Monteagudo M, Nuñez A, Solntseva I, Dhalwani N, Booth A, Barrecheguren M, et al. Treatment Pathways Before and After Triple Therapy in COPD: A Population-based Study in Primary Care in Spain. Arch Bronconeumol (Engl Ed). 2021;57(3):205-13.

28. Ortega Y, Aragonès E, Piñol JL, Basora J, Araujo A, Cabré JJ. Impact of depression and/or anxiety on the presentation of cardiovascular events in a cohort with metabolic syndrome. StreX project: Five years of follow-up. Prim Care Diabetes. 2018;12(2):163-71.

29. Ramos R, Comas-Cufí M, Martí-Lluch R, Balló E, Ponjoan A, Alves-Cabratosa L, et al. Statins for primary prevention of cardiovascular events and mortality in old and very old adults with and without type 2 diabetes: retrospective cohort study. Bmj. 2018;362:k3359.

30. Recalde M, Davila-Batista V, Díaz Y, Leitzmann M, Romieu I, Freisling H, et al. Body mass index and waist circumference in relation to the risk of 26 types of cancer: a prospective cohort study of 3.5 million adults in Spain. BMC Med. 2021;19(1):10.

31. Troncoso-Mariño A, López-Jiménez T, Roso-Llorach A, Villén N, Amado-Guirado E, Guisado-Clavero M, et al. Medication-related problems in older people in Catalonia: A real-world data study. Pharmacoepidemiol Drug Saf. 2021;30(2):220-8.

32. European Medicines Agency. (2025). Union Product Database. Retrieved October 2025, from https://www.ema.europa.eu/en/medicines.

33. AstraZeneca. Airsupra (PT027) approved in the US for asthma. Press release, 10 Jan 2023. Available from: https://www.astrazeneca.com/media-centre/press-releases/2023/airsupra-pt027-approved-in-the-us-for-asthma.html.

34. Raventós B, Català M, Du M, Guo Y, Black A, Inberg G, et al. IncidencePrevalence: An R package to calculate population-level incidence rates and prevalence using the OMOP common data model. Pharmacoepidemiology and Drug Safety. 2024;33(1):e5717.

35. ABDA. 27/23 Information from the manufacturers: Information letter on Sultanol (Salbutamol) metered-dose aerosol: Supply shortage expected to last at least until the end of 2023. https://www.abda.de/fuer-apotheker/arzneimittelkommission/amk-nachrichten/detail/27-23-information-der-hersteller-informationsschreiben-zu-sultanol-salbutamol-dosier-aerosol-lieferengpass-mindestens-bis-voraussichtlich-ende-2023/. July 2023.

36. (BfArM) BfAuM. Bekanntmachung eines Versorgungsmangels nach § 79 Abs. 5 AMG: Salbutamolhaltige Arzneimittel zur pulmonalen Anwendung. Bonn: BfArM; 15 Dec 2023. Available from: https://www.bfarm.de/SharedDocs/Downloads/DE/Arzneimittel/Zulassung/amInformationen/Lieferengpaesse/Bekanntmachung_79_5_amg_salbutamol.pdf. 2023.

37. Wilkinson AJK, Braggins R, Steinbach I, Smith J. Costs of switching to low global warming potential inhalers. An economic and carbon footprint analysis of NHS prescription data in England. BMJ Open. 2019;9(10):e028763.

38. Janson C, Henderson R, Löfdahl M, Hedberg M, Sharma R, Wilkinson AJK. Carbon footprint impact of the choice of inhalers for asthma and COPD. Thorax. 2020;75(1):82.

39. van Beerendonk I, Mesters I, Mudde AN, Tan TD. Assessment of the inhalation technique in outpatients with asthma or chronic obstructive pulmonary disease using a metered-dose inhaler or dry powder device. J Asthma. 1998;35(3):273-9.

40. Steiropoulos P, Bakakos P, Hatziagorou E, Katsaounou P, Loukides S, Papaioannou AI, et al. The present and future of inhalation therapy for the management of obstructive airway diseases: Emphasis on pressurized metered-dose inhalers. Pneumon. 2021;34(4):1-13.

41. Woodcock A, Beeh KM, Sagara H, Aumônier S, Addo-Yobo E, Khan J, et al. The environmental impact of inhaled therapy: making informed treatment choices. Eur Respir J. 2022;60(1).

42. Dhand R, Dolovich M, Chipps B, Myers TR, Restrepo R, Farrar JR. The role of nebulized therapy in the management of COPD: evidence and recommendations. Copd. 2012;9(1):58-72.

43. Arora P, Kumar L, Vohra V, Sarin R, Jaiswal A, Puri MM, et al. Evaluating the technique of using inhalation device in COPD and Bronchial Asthma patients. Respiratory Medicine. 2014;108(7):992-8.

44. Expert consensus on nebulization therapy in pre-hospital and in-hospital emergency care. Ann Transl Med. 2019;7(18):487.

45. Robinson J. Half of asthma patients in the UK overusing SABAs, study finds. The Pharmaceutical Journal. 2021.

46. Romaszko-Wojtowicz A, Dragańska E, Doboszyńska A, Glińska-Lewczuk K. Impact of seasonal biometeorological conditions and particulate matter on asthma and COPD hospital admissions. Scientific Reports. 2025;15(1):450.

47. Johnston NW, Sears MR. Exacerbations of Asthma: Seasonal patterns of asthma exacerbations: CRC Press; 2007.

48. Ko FW, Chan KP, Hui DS, Goddard JR, Shaw JG, Reid DW, et al. Acute exacerbation of COPD. Respirology. 2016;21(7):1152-65.

49. Bloom CI, Wong E, Hickman K, Elkin S. Influence of the first wave of COVID-19 on asthma inhaler prescriptions. NPJ Prim Care Respir Med. 2021;31(1):45.

50. Robinson J. Salbutamol inhaler prescribing jumped 60% at start of COVID-19 pandemic. . the Pharmaceutical Jouranl. 2020.

51. Zeitouny S, McGrail K, Tadrous M, Wong ST, Cheng L, Law M. Impact of the COVID-19 pandemic on prescription drug use and costs in British Columbia: a retrospective interrupted time series study. BMJ Open. 2024;14(1):e070031.

52. Marques L, Vale N. Unraveling the Impact of Salbutamol Polytherapy: Clinically Relevant Drug Interactions. Future Pharmacology [Internet]. 2023; 3(1):[296-316 pp.].

53. Craig S, Tuszynski M, Armstrong D. It is time to stop prescribing oral salbutamol. Australian Journal for General Practitioners. 2016;45:245-7.

54. van Boven JFM, Yorgancioglu A, Roche N, Usmani OS. Ensuring availability of respiratory medicines in times of European drug shortages. Eur Respir J. 2024;64(5).

55. EMA. Union list of critical medicines. Reference Number: EMA/536385/2024. 2024.

56. Commission. E. Staff Working Document on the Critical Medicines Alliance and pharmaceutical legislation. . 2025.

57. GINA. 2023 GINA Report, Global Strategy for Asthma Management and Prevention. Accessed at: https://ginasthma.org/2023-gina-main-report/. 2023.

58. Dubin S, Patak P, Jung D. Update on Asthma Management Guidelines. Mo Med. 2024;121(5):364-7.

59. Yung JA, Fuseini H, Newcomb DC. Hormones, sex, and asthma. Ann Allergy Asthma Immunol. 2018;120(5):488-94.

60. Ow NL, Sadek Attalla S, Davies G, Griffiths CJ, De Simoni A. Experiences and behaviours of patients with asthma requesting prescriptions from primary care during medication shortages linked to the COVID-19 lockdown: insights from a qualitative analysis of a UK asthma online community. BJGP Open. 2022;6(4):BJGPO.2021.0222.

61. EMA. Good practices for industry for the prevention of human medicinal product shortages. 28 February 2023, EMA/760980/2022. 2023.

17. ANNEXES

Appendix I: List of the concept definitions of medicines and conditions are provided below in the **Table S1** and **Table S2**.

The definitions of the concepts for the medicines of interest are provided in **Table S1**.

Table S1. List of medicines definitions.

Substance Name	Concept name	Concept ID including descendants	Vocabulary
Salbutamol	Albuterol	1154343	RxNorm
	Albuterol inhalation solution	1356108	RxNorm
	Albuterol inhalation powder	1356111	RxNorm
	Albuterol metered dose inhaler Albuterol inhalation suspension	40142703 2070100	RxNorm
	Albuterol dry powder inhaler	46234463	RxNorm
Terbutaline	Terbutaline	1236744	RxNorm
	Terbutaline dry powder inhaler	42481922	RxNorm
	Terbutaline inhalation powder	36813480	RxNorm
	Terbutaline inhalation solution	36812414	RxNorm
	Terbutaline metered dose inhaler	1356244	RxNorm
Fenoterol	Fenoterol	19053979	RxNorm
	Fenoterol dry powder inhaler	40861768	RxNorm
	Fenoterol inhalant powder	40727839	RxNorm
	Fenoterol inhalation solution	35150375	RxNorm
	Fenoterol metered dose inhaler	44081619	RxNorm
Ipratropium bromide	Ipratropium	1112921	RxNorm
	Ipratropium dry powder inhaler	42483253	RxNorm
	Ipratropium gas for Inhalation	44081549	RxNorm
	Ipratropium inhalation powder	36811485	RxNorm
	Ipratropium inhalation solution	1356213	RxNorm
	Ipratropium metered dose inhaler	40143214	RxNorm
Oxitropium bromide	Oxitropium	19018882	RxNorm
	Oxitropium dry powder inhaler	40861610	RxNorm
	Oxitropium inhalation powder	36810762	RxNorm
	Oxitropium inhalation solution	35147090	RxNorm
Fenoterol + ipratropium bromide	Fenoterol/ ipratropium dry powder inhaler	43134418	RxNorm
	Fenoterol / ipratropium inhalant powder	40727834	RxNorm
	Fenoterol / ipratropium inhalation solution	36811735	RxNorm
	Albuterol / ipratropium inhalant powder	40727741	RxNorm

Salbutamol + ipratropium bromide	Albuterol / ipratropium inhalation solution	1356123	RxNorm
	Albuterol / ipratropium inhalation spray	37499261	RxNorm
	Albuterol / ipratropium metered-dose inhaler	2072019	RxNorm
Formoterol	Formoterol	1196677	RxNorm
	Formoterol dry powder inhaler	42480849	RxNorm
	Formoterol inhalation powder	1356191	RxNorm
	Formoterol inhalation solution	1356187	RxNorm
	Formoterol metered dose inhaler	44107471	RxNorm
Formoterol + beclomethasone	Beclomethasone / formoterol dry powder inhaler	21158944	RxNorm
	Beclomethasone / formoterol inhalant powder	36894458	RxNorm
	Beclomethasone / formoterol inhalant solution	21090035	RxNorm
Formoterol + budesonide	Budesonide / formoterol dry powder inhaler	42479684	RxNorm
	Budesonide / formoterol inhalation Powder	35133500	RxNorm
	Budesonide / formoterol inhalation solution	783228	RxNorm
	Budesonide / formoterol inhalation suspension	2069097	RxNorm
	Budesonide / formoterol metered dose inhaler	40142910	RxNorm
Salbutamol + beclomethasone	Albuterol / beclomethasone dry powder inhaler	42483138	RxNorm
	Albuterol / beclomethasone inhalation powder	36812530	RxNorm
	Albuterol / beclomethasone Inhalation Solution	36965394	RxNorm
Beclomethasone	Beclomethasone	115572	RxNorm
Budesonide	Budesonide	939259	RxNorm
	Budesonide inhalant	43291282	RxNorm
	Budesonide metered dose inhaler	44120754	RxNorm
	Budesonide dry powder inhaler	40142920	RxNorm
	Budesonide inhalation powder	1356143	RxNorm
	Budesonide inhalation solution	35135829	RxNorm
	Budesonide inhalation suspension	1356140	RxNorm
Oral salbutamol	Albuterol extended-release oral capsule	40006960	RxNorm
	Albuterol extended-release oral tablet	40006962	RxNorm
	Albuterol oral capsule	41079955	RxNorm

	Albuterol oral solution	40104188	RxNorm
	Albuterol oral suspension	1235090	RxNorm
	Albuterol oral tablet	40006997	RxNorm
	Albuterol powder for oral suspension	35154239	RxNorm

For inhaled salbutamol and its alternatives, all concept IDs not related to the inhaled formulation were excluded.

The definitions of condition concept names and concept IDs are provided in **Table S2**.

Table S2. List of conditions definitions.

Phenotype	Concept name	Concept id (including descendants)	Exclude concept id	Vocabulary
Asthma	Asthma	317009	-	SNOMED
COPD and Emphysema	Chronic obstructive lung disease	255573	-	SNOMED
Respiratory conditions due to inhalation of chemical substances	Respiratory condition caused by chemical fumes and vapors Respiratory condition caused by chemical fumes Chronic respiratory condition caused by chemical fumes	3655120 3655118 3655114	-	SNOMED
Chronic bronchitis	Chronic bronchitis	256451	4049964, 4035960, 260139, 3661405, 37017852, 7206139, 4112677, 4112521, 4197404, 4243199, 4048517, 4148242, 4052542, 4110483, 4110485, 40481763, 4137525, 46270376, 4112355, 4170141, 4110023, 4208807, 4208810, 4110481, 4051332, 42536540, 4112359, 4112358, 4112357, 4110484, 4112015, 4121456, 4148204, 4052543, 37206138, 6269701, 4270139	SNOMED
Lower respiratory tract infection	Lower respiratory tract infection Pneumonia Influenza COVID-19 Bronchiolitis Acute chronic bronchitis	4175297 255848 4266367 37311061 4165112 260139	-	SNOMED
Bronchospasm	Bronchospasm	256717	-	SNOMED

Appendix II: Supplementary figures and tables of results are attached to this report.