Study Report

P4-C1-018

DARWIN EU® - Drug Utilisation Study of terbinafine-containing products

28/01/2026

Version 3.0

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Public

CONTENTS

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Study title	DARWIN EU® - Drug Utilisation Study of terbinafine-containing products
Study report version	V3.0
Date	28/01/2026
EUPAS number	EUPAS1000000790
Active substance	• Terbinafine for topical use, WHO ATC code D01AE15 • Terbinafine for systemic use, WHO ATC code D01BA02
Medicinal product	Not applicable.
Research question and objectives	Research question: What are the patterns of use of terbinafine-containing products in Europe, 2015–2024? Study objectives: 1. To calculate the monthly and annual incidence of terbinafine use, overall and stratified by age and sex. 2. To characterise patients at the time of terbinafine treatment initiation in terms of i) demographics, ii) indication for use, iii) comorbidities, iv) other antifungal and antibiotic treatments (6, 3, and 1 month prior to treatment initiation and 6 months following initiation for antifungal treatment), and v) disease code for resistance (6 months before and 6 months after treatment initiation). 3. To report the number of treatment initiations, dose (initial, cumulative), and duration of terbinafine use, overall and stratified by type of dermatophytosis. 4. To explore the treatment pattern following new terbinafine treatment initiation, overall and stratified by type of dermatophytosis, including transitions between topical to systemic and combination therapies.
Countries of study	Croatia, Denmark, Finland, Germany, Spain, the United Kingdom
Authors	Ellen Gerritsen, e.gerritsen@darwin-eu.org Dina Vojinovic, d.vojinovic@darwin-eu.org

LIST OF ABBREVIATIONS

Acronyms/term	Description
ATC	Anatomical Therapeutic Chemical
CC	Coordination Centre
CDM	Common Data Model
CPRD GOLD	Clinical Practice Research Datalink GOLD
DA	Disease Analyzer
DARWIN EU®	Data Analysis and Real-World Interrogation Network
DK-DHR	Danish Data Health Registries
DQD	Data Quality Dashboard
EHR	Electronic Health Records
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EU	European Union
EUPAS	EU Post-Authorisation Studies Register
FinOMOP-THL	Finnish Care Register for Health Care
GDPR	General Data Protection Regulation
GP	General Practitioner
ICD	International Classification of Diseases
IP	Inpatient
IRB	Institutional Review Board
NAJS	Croatian National Public Health Information System
OHDSI	Observational Health Data Sciences and Informatics
OMOP	Observational Medical Outcomes Partnership
OP	Outpatient
OTC	Over-the-counter
RxNorm	Medical prescription normalized
SIDIAP	The Information System for Research in Primary Care
SNOMED	Systematized Nomenclature of Medicine
WHO	World Health Organisation

1. TITLE

DARWIN EU® - Drug Utilisation Study of terbinafine-containing products

2. DESCRIPTION OF THE STUDY TEAM

Study team role	Names	Organisation
Principal Investigator	Ellen Gerritsen Dina Vojinovic	IQVIA
Data Scientist	Gargi Jadhav Akram Mendez	IQVIA
Study Manager	Natasha Yefimenko	Erasmus MC
Data source	**Names**	**Data Partner Organisation***
NAJS	Ivan Pristaš Marko Čavlina Antea Jezidžić Jakov Vuković Anamaria Jurčević Karlo Pintarić	Croatian Institute for Public Health
DK-DHR	Elvira Bräuner Susanne Bruun	Danish Medicines Agency
FinOMOP-THL	Toni Lehtonen Tiina Wahlfors Gustav Klingstedt	Finnish Care Register for Health Care
IQVIA DA Germany	Isabella Kaczmarczyk James Brash	IQVIA
SIDIAP	Anna Palomar Cros Agustina Giuliodori Picco Laura Granés González Irene López Sánchez	Institute for Primary Health Care Research Jordi Gol i Gurina
CPRD GOLD	Antonella Delmestri Marta Pineda Moncusí	University of Oxford

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

3. ABSTRACT

Title

DARWIN EU® - Drug Utilisation Study of terbinafine-containing products

Rationale and background

Terbinafine is an antifungal agent indicated for the treatment of superficial mycoses, with widespread use across Europe in both oral and topical formulations. Monitoring its utilisation is essential to informing regulatory decision-making, particularly in relation to emerging safety concerns, such as antifungal resistance. This study aimed to characterise the incidence and patterns of terbinafine use, describe the clinical profiles of treated patients, and examine treatment pathways.

Research question and objectives

Research questions

What are the patterns of use of terbinafine-containing products in Europe, 2015–2024?

Objectives

The specific objectives of this study were:

1. To calculate the monthly and annual incidence of terbinafine use, overall and stratified by age and sex.
2. To characterise patients at the time of terbinafine treatment initiation in terms of i) demographics, ii) indication for use, iii) comorbidities, iv) other antifungal and antibiotic treatments (6, 3, and 1 month prior to treatment initiation and 6 months following initiation for antifungal treatment), and v) disease code for resistance (6 months before and 6 months after treatment initiation).
3. To report the number of treatment initiations, dose (initial, cumulative), and duration of terbinafine use, overall and stratified by type of dermatophytosis.
4. To explore the treatment pattern following new terbinafine treatment initiation, overall and by type of dermatophytosis, including transitions between topical to systemic and combination therapies.

Methods

Study design

This retrospective cohort study aimed to estimate population-level drug utilisation of terbinafine-containing products (*objective 1*), characterise individuals being treated with terbinafine (*objective 2*), evaluate treatment utilisation at the patient-level by assessing dose and treatment duration (*objective 3*), and describe patient-level treatment patterns (*objective 4*).

Population

For *objective 1*, the study population included all individuals present in the data source during the study period between 1 January 2015 and 31 December 2024 (or latest date available), and with at least 1 year of data visibility prior to the index date. Children <1 year of age were excluded.

New terbinafine user cohort (objectives 2, 3, and 4): All individuals with a first recorded prescription of a terbinafine-containing product during the study period, defined as 1 January 2015 to 31 December 2024 (or latest date available). Eligible individuals had at least 1 year of data visibility prior to the date of treatment initiation and no recorded use of terbinafine in the 180 days preceding treatment initiation. The cohort focused on terbinafine initiators, specifically the initial treatment episode. To ensure sufficient follow-up,

only individuals who initiated terbinafine treatment at least 1 year prior the end of data availability in each data source were included. Children <1 year of age were excluded.

For *objective 3*, an additional cohort included all new terbinafine treatment episodes meeting the washout criteria. Individuals could contribute multiple treatment episodes, provided each was preceded by 180 days washout period.

Variables

Exposure: Terbinafine for topical use (WHO ATC code D01AE15) and terbinafine for systemic use (WHO ATC code D01BA02)

Condition of interest: Dermatophytosis (Tinea infections), such as Tinea corporis (Ringworm of the body), Tinea cruris, Tinea pedis (Athlete's foot), Tinea manuum, Tinea capitis, Tinea barbae, and Tinea unguium (Onychomycosis (nail)), and other fungal infections, such as Cutaneous candidiasis, Sporotrichosis, and Pityriasis versicolor.

Data sources:

Six data sources from six different countries (Croatia, Denmark, Finland, Germany, Spain, and the United Kingdom) were used. They included primary care electronic heath records (EHRs), as well as nationwide registries.

Study size

No sample size was calculated, as this was a drug utilisation study which did not test a specific hypothesis. Based on a preliminary feasibility assessment, the expected number of person counts for terbinafine-containing products in the data sources included in this study ranged from 208,400 (IQVIA DA Germany) to 1,185,000 (DK-DHR).

Statistical analysis

Population-level utilisation of terbinafine-containing products (objective 1): Monthly and annual incidence rates of terbinafine use were estimated as treatment initiations per 1,000 person-years among eligible individuals, overall and stratified by age (≤18, 19–65, ≥66 years) and sex, with 95% Poisson confidence intervals. The analyses were based on Observational Medical Outcomes Partnership Common Data Model (OMOP CDM) mapped data using the *IncidencePrevalence* R package.

Patient-level characterisation and utilisation (objectives 2–4): Demographics (age, sex) were assessed at the first recorded terbinafine prescription (index date). Indication was inferred from diagnosis codes within predefined time windows: i) 180 days before to 7 days after, ii) 90 days before to 7 days after, iii) 30 days before to 7 days after. Comorbidities were evaluated at the index date and within one year prior. Pre-specified antifungal and antibiotic use was assessed 6, 3, and 1 month prior to treatment initiation. Post-initiation antifungal use was evaluated up to 6 months (antibiotics excluded). Resistance codes were assessed 6 months before and 6 months after the index date. Initial and cumulative dose and treatment duration were summarised (minimum, p25, median, p75, maximum). These analyses were conducted using *CohortCharacteristics* and *DrugUtilisation* R packages on OMOP CDM mapped data.

The treatment pattern following the first recorded terbinafine prescription was visualised by Sunburst plots and Sankey diagrams, stratified by type of dermatophytosis, using the *TreatmentPatterns* R package.

Patient-level utilisation (objective 3) for multiple treatment episodes: Number of treatment initiations, initial and cumulative dose, and treatment duration were summarised as above using the *DrugUtilisation* R package.

Results

Incidence of terbinafine use

Across six European data sources 1,230,556 individuals initiated terbinafine treatment between 2015 and 2024. Monthly and annual incidence rates ranged from approximately 1 to over 10 per 1,000 person-years (PYs), with clear seasonal peaks during warmer months and a transient decline in 2020, likely reflecting the COVID-19 pandemic. Incidence was highest in Nordic sources (FinOMOP-THL and DK-DHR) often exceeding 8–10 per 1,000 PYs during peak months. Incidence rates in NAJS ranged between approximately 6 and 8 per 1,000 PYs, between approximately 4 and 6 per 1,000 PYs in SIDIAP and CPRD GOLD, and around 1 per 1,000 PYs in IQVIA DA Germany. Older adults (≥66 years) consistently exhibited the highest incidence rates, followed by adults aged 19–65 years and children/adolescents. Males generally had higher incidence rates than females, except in NAJS, where females predominated.

Characterisation of terbinafine initiators

Among terbinafine initiators, median age ranged from 47 to 57 years, with adults representing the majority and older adults accounting for up to 31%. Dermatophytosis was the most frequent recorded indication, ranging from 12% in SIDIAP to nearly 60% in IQVIA DA Germany. Among subtypes, onychomycosis was consistently the most common. Other dermatophytosis subtypes and other fungal infections were rare. A substantial proportion of individuals had other indication codes, ranging from 21.55% in IQVIA DA Germany to 73.11% in NAJS for the 30-day window.

Treatment initiation, dose, and duration

The median number of terbinafine exposures per patient was one across most data sources, with limited variability, except in SIDIAP (median two exposures) and CPRD GOLD (median one, most patients with one to two exposures). Median treatment duration for the initial episode ranged from 28 days in CPRD GOLD to 41 days in SIDIAP, with maximum durations exceeding 1,000 days in a small subset of patients. Median initial daily dose ranged from 0.04 mg in CPRD GOLD to 250 mg in IQVIA DA Germany. Median cumulative dose was highest in IQVIA DA Germany and FinOMOP-THL (7,000 mg), with wide variability across sources.

Treatment Patterns

Treatment patterns showed that most patients initiated terbinafine as monotherapy, with cutaneous formulations predominating in NAJS, DK-DHR, and SIDIAP, and systemic terbinafine serving as the main first-line treatment in IQVIA DA Germany, FinOMOP-THL, and CPRD GOLD. Prior to initiation, topical antifungal use was relatively common but declined as patients approached the index date, while systemic antifungal use remained consistently low. Post-index, antifungal use increased markedly, driven largely by topical and systemic terbinafine. Although most individuals had only a single terbinafine exposure, a substantial proportion progressed to additional antifungal therapies, following highly heterogeneous treatment pathways with no consistently dominant second-line pattern. When present, transitions typically involved other topical agents among cutaneous initiators and fluconazole or itraconazole among systemic initiators. Stratification by clinical indication showed clear differentiation, with topical monotherapy dominating treatment for superficial tinea infections and systemic terbinafine monotherapy primarily used for onychomycosis, while rarer conditions, such as tinea barbae and tinea capitis, reflected similar systemic-first patterns. No coded evidence of terbinafine resistance was identified during the study period.

Discussion

This multi-country study provides real-world evidence on terbinafine use across six European healthcare systems. Incidence patterns were stable over time, with seasonal peaks reflecting the epidemiology of dermatophyte infections and a temporary decline in 2020 likely related to the COVID-19 pandemic. Treatment practices generally aligned with clinical guidelines, with topical terbinafine used for superficial infections and systemic therapy for onychomycosis. Variability in treatment duration, dosing, and indication

coding across data sources likely reflects differences in prescribing practices and data capture. While most individuals had a single terbinafine exposure, a substantial proportion received additional antifungal therapy and followed heterogeneous subsequent treatment pathways, reflecting the stepwise and individualised management of dermatophyte infections in routine care. No coded evidence of antifungal resistance was identified, although resistance may not be routinely documented. These findings confirm the widespread and appropriate use of terbinafine in Europe and provide valuable evidence to support regulatory decision-making.

4. AMENDMENTS AND UPDATES

Amendment number	Previous approved version of the report	Date	Section of the study report	Amendment or update	Reason
1	-	November 2025	8.5 Study period; 8.2 Follow-up	Exclusion of the latest 6 months of available data in IQVIA DA Germany.	To reduce artefacts in incidence rate estimates caused by methodological aspects to obtain observation period.
2	-	November 2025	8.5 Study period	End of observation period set to end of 2023 in FinOMOP-THL.	Drug prescription data available only until end of 2023.

5. MILESTONES

Study deliverable	Timelines (planned)	Timelines (actual)
Final Study Protocol	October 2025	October 2025
Creation of Analytical code	September/October 2025	October/November 2025
Execution of Analytical Code on the data	November 2025	November 2025
Draft Study Report	28 November 2025	28 November 2025
Final Study Report	December 2025/January 2026	January 2026

6. RATIONALE AND BACKGROUND

Terbinafine is a widely used antifungal drug indicated for the treatment of superficial mycoses, including tinea pedis (athlete's foot), tinea corporis (ringworm), and onychomycosis (fungal nail infections). It works by inhibiting the enzyme squalene epoxidase, which is essential for the synthesis of ergosterol, a critical component of fungal cell membranes. This leads to disruption of membrane integrity, leading to fungal cell death. Terbinafine is available in both oral and topical formulations and is widely prescribed in clinical practice across Europe.[1, 2]

Understanding the real-world utilisation of terbinafine is essential for monitoring prescribing practices, identifying clinical characteristics, and evaluating potential safety concerns. Real-world data can provide valuable insights into treatment patterns, including transitions between topical and systemic therapies, and help identify populations at risk of resistance or treatment failure.[3] These insights will support regulatory activities, including the periodic assessment of benefits and risks, and contribute to a broader understanding of antifungal use in Europe as well as resistance.

This study aimed to describe the incidence and patterns of terbinafine use, characterise the clinical profiles of patients receiving the medication, and explore treatment pathways.

7. RESEARCH QUESTION AND OBJECTIVES

Research question

What are the patterns of use of terbinafine-containing products in Europe, 2015–2024?

Objectives

The specific objectives of this study were:

1. To calculate the monthly and annual incidence of terbinafine use, overall and stratified by age and sex.
2. To characterise patients at the time of terbinafine treatment initiation in terms of i) demographics, ii) indication for use, iii) comorbidities, iv) other antifungal and antibiotic treatments (6, 3, and 1 month prior to treatment initiation and 6 months following initiation for antifungal treatment), and v) disease code for resistance (6 months before and 6 months after treatment initiation).
3. To report the number of treatment initiations, dose (initial, cumulative), and duration of terbinafine use, overall and stratified by type of dermatophytosis.
4. To explore the treatment pattern following new terbinafine treatment initiation, overall and by type of dermatophytosis, including transitions between topical to systemic and combination therapies.

8. RESEARCH METHOD

8.1. Study design

A retrospective cohort study was conducted using routinely collected health data from 6 data sources from 6 countries across Europe and in 5 EU member states. The study included:

- A population-level drug utilisation study conducted to address *objective 1,* estimating the incidence of terbinafine-containing product use in the study population (**Figure 1a**).
- A patient-level characterisation and drug utilisation study conducted to address *objectives 2, 3, and 4,* characterising individuals initiating terbinafine treatment, evaluating treatment utilisation, including dose and duration, and treatment patterns (**Figure 1b**).
- A patient-level drug utilisation study conducted to address *objective 3,* evaluating treatment utilisation of all new terbinafine treatment initiations, including dose and duration (**Figure 1c**).

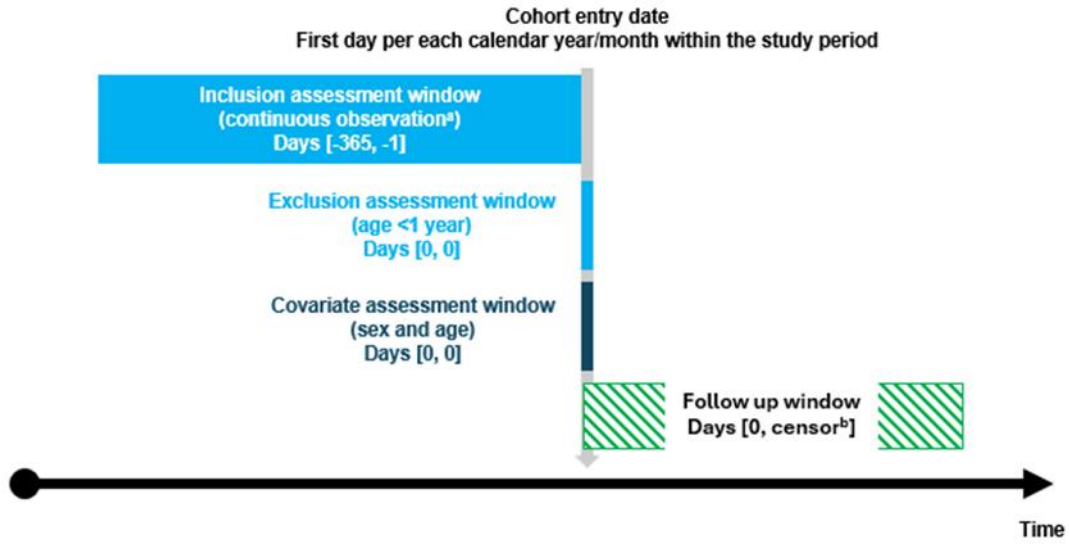


Figure 1a. Graphical depiction of the study design for *objective 1*.

a. Applied to individuals older than one year.
b. Death, loss to follow-up, end of data source availability, end of each calendar year/month (i.e., 31 December), or end of the study period (31/12/2024).

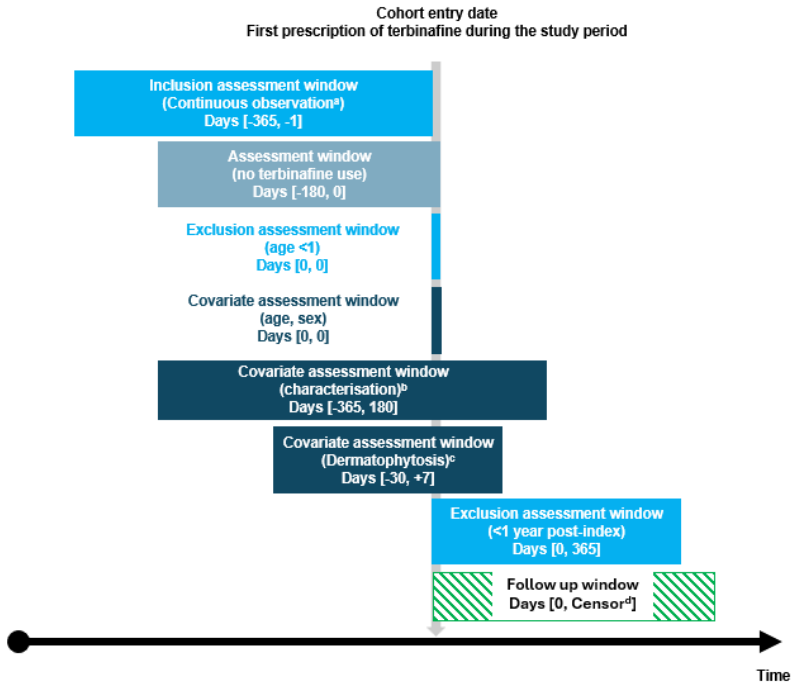


Figure 1b. Graphical depiction of the study design for *objectives 2, 3,* and *4*.

a. Applied to individuals older than one year.
b. Indication of use, comorbidities, fungal and antibiotic treatment prior to and following treatment initiation and resistance to terbinafine (all defined in **section 8.7.1**).
c. Applied to *objectives 2* and *4* and stratification by type of dermatophytosis.
d. Death, loss to follow-up, end of data source availability, or end of the study period (31/12/2024).

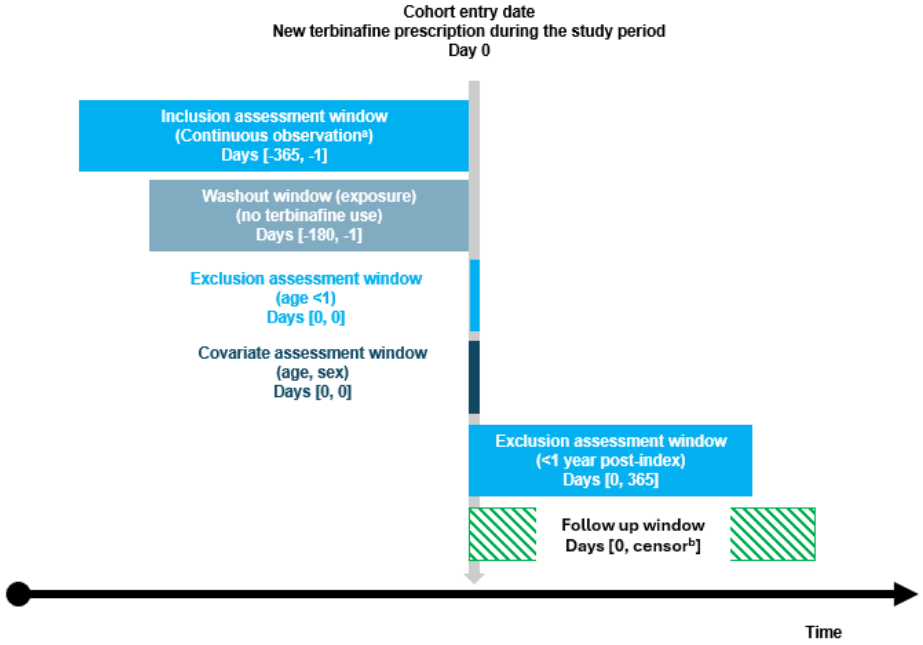


Figure 1c. Graphical depiction of the study design for *objective 3*.

Individuals could contribute multiple terbinafine treatment episodes during the study period. Each episode was defined by a new prescription following a ≥180-day washout period without terbinafine use. The timeline and assessment windows applied to each qualifying episode, anchored to its respective index date.

a. Applied to individuals older than one year.
b. Death, loss to follow-up, end of data source availability, or end of the study period (31/12/2024).

8.2. Follow-up

For calculation of incidence rates of terbinafine-containing product use *(objective 1),* follow-up started on the respective date of the latest of the following: i) study start date 1 January 2015 or ii) date at which individuals have 1 year of prior history. End of follow-up was defined as the earliest of i) loss to follow-up, ii) death, or iii) end of observation period (the latest available data), whichever occurred first.

For patient-level characterisation of terbinafine-containing product users *(objective 2),* estimation of drug utilisation *(objective 3),* and the description of treatment patterns *(objective 4)*, follow-up started on the date of a first recorded terbinafine-containing product prescription between 1 January 2015 and 31 December 2024 (or latest date available). Eligible individuals had at least 1 year of data visibility prior to the index date and no use of terbinafine products in the 180 days preceding treatment initiation. To ensure sufficient follow-up, only individuals who initiated terbinafine treatment at least one year before the end of data availability in each data source were included. Children under 1 year of age were excluded. End of follow-up was defined as the earliest of i) loss to follow-up, ii) death, or iii) end of observation period (the latest available data), whichever occurred first.

Additionally, for estimation of drug utilisation for multiple treatment episodes *(objective 3)*, follow-up started on the date of a new recorded terbinafine-containing product prescription between 1 January 2015 and 31 December 2024 (or latest date available) and corresponded to each new treatment episode. Eligible individuals had at least 1 year of data visibility prior to the index date and met the criteria washout period of 180 days. To ensure sufficient follow-up, only individuals who initiated terbinafine treatment at least one year before the end of data availability in each data source were included. Children under 1 year of age were excluded. End of follow-up was defined as the earliest of i) loss to follow-up, ii) death, or iii) end of observation period (the latest available data), whichever occurred first.

Estimating incidence required an appropriate denominator population and contributed observation time to first be identified. Study participants in the denominator population begun contributing person time at risk as described above in the current section.

An example of entry and exit into the denominator population is shown in **Figure 2**. In this example, person ID 1 already had sufficient prior history before the study start date and the observation period ends after the study end date, so this person contributed time during the complete study period. Person IDs 2 and 4 enter 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.

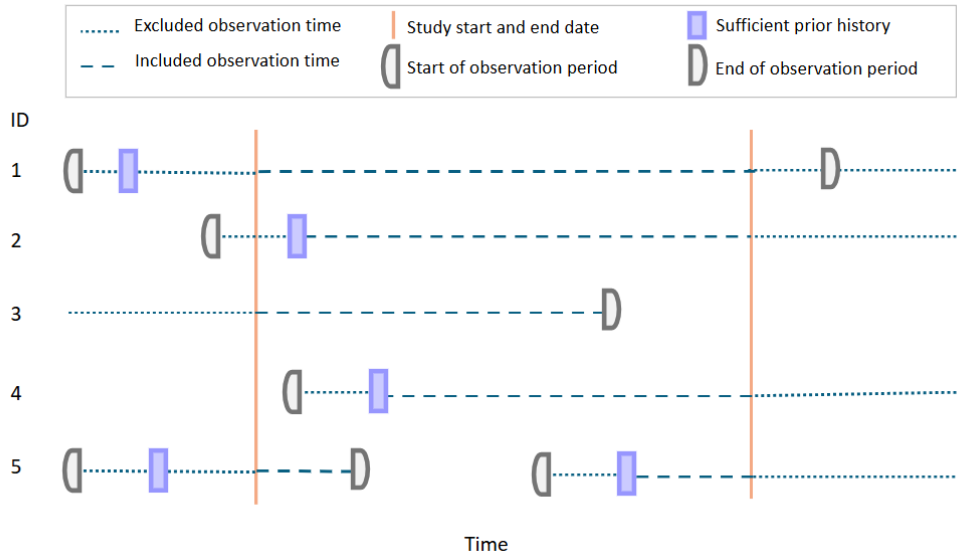


Figure 2. Included observation time for the denominator population.

8.3. Study population with inclusion and exclusion criteria

For calculation of incidence rates of terbinafine-containing product use, the study population included the general population *(objective 1)*.

Inclusion criteria:

- All individuals present in the data source between 1 January 2015 and 31 December 2024 (or latest available date).
- At least 1 year of data visibility prior to the index date.

Exclusion criteria:

- Children aged <1 year at any time during the study period.

For characterisation of terbinafine treatment initiators *(objective 2),* estimation of treatment utilisation *(objective 3),* and description of treatment patterns *(objective 4)*, the study population included individuals with a first recorded prescription of a terbinafine-containing product prescription during the study period.

Inclusion criteria:

- First record of a terbinafine-containing product between 1 January 2015 and 31 December 2024 (or latest available date).
- At least 1 year of data visibility prior to the index date.
- No use of terbinafine products in previous 180 days.

Exclusion criteria:

- Children aged <1 year at the index date.
- Individuals initiating terbinafine treatment <1 year before the end of data availability in the respective data source (to ensure sufficient follow-up).

Additionally, for estimation of treatment utilisation *(objective 3),* multiple treatment episodes were considered.

Inclusion criteria:

- New record of a terbinafine-containing product between 1 January 2015 and 31 December 2024 (or latest available date).
- At least 1 year of data visibility prior to the index date.
- No use of terbinafine products 180 days before each treatment episode.

Exclusion criteria:

- Children aged <1 year at the index date.
- Individuals initiating terbinafine treatment <1 year before the end of data availability in the respective data source (to ensure sufficient follow-up).

8.4. Study setting and data sources

This study was conducted using routinely collected data from 3 registries and 3 primary care data sources in the DARWIN EU® network of data partners from 6 European countries in 5 EU member states. All data were a priori mapped to the Observational Medical Outcomes Partnership Common Data Model (OMOP CDM).

Data sources

1. Croatia: Croatian National Public Health Information System (NAJS)
2. Denmark: Danish Data Health Registries (DK-DHR)
3. Finland: Finnish Care Register for Health Care (FinOMOP-THL)
4. Germany: IQVIA Disease Analyzer Germany (IQVIA DA Germany)
5. Spain: The Information System for Research on Primary Care (SIDIAP)
6. The United Kingdom: Clinical Practice Research Datalink GOLD (CPRD GOLD)

Data Selection

These data sources fulfilled the criteria required in terms of data quality, completeness, timeliness, and representativeness for drug utilisation study while covering different regions of Europe.

When it came 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,[4] which systematically characterised the data and

generated data characteristics such as age distribution, condition prevalence per year, and data density. Data density included information on 1) monthly record counts by data domain (which offers insights into data collection patterns and the start date of each data source), and 2) measurement value distribution (i.e., min, max, quartiles for numeric values per measurement concept and per unit and counts for discrete measurement-value pairs). The latter can be compared against expectations for the data based on predefined standards, historical trends, or known epidemiological patterns to identify potential anomalies or inconsistencies. Additionally, the data quality dashboard (DQD) provided more objective checks on plausibility of data completeness, consistency, and conformity across the data sources.

In terms of relevance, the selection of data sources was based on the availability of data on the selected terbinafine-containing products and dermatophytosis to perform the described analyses. In addition, the data sources were chosen considering their ability to support timely Institutional Review Board (IRB) approvals, thus ensuring alignment with the timeline established by stakeholders for the conduct of this study.

The DARWIN EU® portal, as well as information from the onboarding documents, were used to assess whether data sources have information on terbinafine-containing products and dermatophytosis. Data within the DARWIN EU® portal is maintained up to date by extracting the release dates for each dataset in the network and monitoring when data are out-of-date with the expected refresh cycle (typically quarterly or half-yearly). In addition, it is important to have clear understanding of the time covered by each released data source, as this can vary across different domains. To facilitate this, the C*DMOnboarding* (and *Achilles*) packages [4] contained a 'data density' plot. This plot displayed the number of records per OMOP domain monthly. This allowed getting insights into when data collection started, when new sources of data were added, and until when data was included. In addition, at the time of inviting data partners, they were informed about study objectives and asked whether they could participate in the study.

More general-purpose diagnostic tools, *CohortDiagnostics* [5] and *DrugExposureDiagnostics* [6], have been developed. The *CohortDiagnostics* package provided additional insights into cohort characteristics, record counts, and index event misclassification. The *DrugExposureDiagnostics* package evaluated ingredient-specific attributes and patterns in drug exposure records. Upon finalisation of the study protocol and creation of the disease and drug cohorts of interest by DARWIN EU® Coordination Centre, these packages were executed in each data source by each data partner.

Data source justification and key characteristics

Multiple data sources were included in this study, as they represent registry-based and outpatient general practitioner care databases that provide relevant information on terbinafine exposure and dermatophytosis diagnoses in the general population. Based on preliminary feasibility assessments, the expected number of individuals with terbinafine use ranged from approximately 208,400 (IQVIA DA Germany) to 1,185,000 (DK-DHR), while the number of individuals with dermatophytosis diagnoses ranged from 280,200 (FinOMOP-THL) to over 1,000,000 (IQVIA DA Germany). Data availability and follow-up were sufficient to support the study objectives, with data collection starting years ranging from 1987 (CPRD GOLD) to 2014 (NAJS) and the most recent data ranging from June 2023 (SIDIAP) to February 2025 (NAJS). Median follow-up durations varied across sources, ranging from 116 days (IQVIA DA Germany) to 7,920 days (DK-DHR), ensuring adequate longitudinal coverage. While most data sources aligned with the planned study period (1 January 2015 to 31 December 2024), the actual study period was extended until the last available observation period month in each source, specifically October 2024 for FinOMOP-THL, November 2024 for DK-DHR, and June 2023 for SIDIAP. NAJS was included from January 2017 onwards due to data reliability constraints. IRB approvals were either covered under existing umbrella protocols or expected to be obtained within 1 to 3 months (FinOMOP-THL, SIDIAP), supporting timely execution of the study within the established timelines.

Information on the data sources planned for use in this study is provided in **Table 1** and **ANNEX I**.

Table 1. Data sources justification and key characteristics.

Country	Data source acronym	Type of data	Terbinafine users (n)[a]	Dermatophytosis diagnosis (n)[b]	Data collection start year	Source release date	Last observation period	Follow-up duration (days), median (IQR)[c]	IRB approval
Croatia	NAJS	Registry	224,400	456,200	2014 (from 2017 reliable IDs)	08/02/2025	01/2025	3,640 (3,110 –3,740)	Umbrella protocol
Denmark	DK-DHR	Registry	1,185,000	324,000	1995	18/01/2025	11/2024	7,920 (2,610–10,900)	Umbrella protocol
Finland	FinOMOP-THL	Registry	472,800	280,200	2011	01/10/2024	10/2024	5,020 (4,030–5,020)	1-3 months
Germany	IQVIA DA Germany	Outpatient General Practitioner and Specialist Care	208,400	1,024,600	1989	31/12/2024	12/2024	116 (0–1,610)	Not needed
Spain	SIDIAP	Outpatient General Practitioner Care	269,800	629,200	2006	30/06/2023	06/2023	5,670 (2,220–6,390)	1-3 months
UK	CPRD GOLD	Outpatient General Practitioner Care	724,400	736,400	1987	01/01/2025	12/2024	2,150 (727–4,930)	Umbrella protocol

NAJS = Croatian National Public Health Information System; DK-DHR = Danish Data Health Registries; FinOMOP-THL = Finnish Care Register for Health Care; IQVIA DA Germany = IQVIA Disease Analyzer Germany; SIDIAP = The Information System for Research on Primary Care; CPRD GOLD = Clinical Practice Research Datalink GOLD.

[a] = person counts at drug era (as generated from drug era, this also includes the descendant person-counts of terbinafine at the clinical drug level (drug exposure table)).

[b] = descendant person counts for dermatophytosis.

[c] = median follow-up of the first observation period.

8.5. Study period

The study period was from 1 January 2015 to 31 December 2024, or the most recent data available for each contributing data source.

It should be noted for several data sources that the availability of the accurate data deviated from the start or end date of the study period. Detailed information about the study period per data partner can be found in **Section 8.4.**

8.6. Variables

8.6.1. Exposure

The primary exposure was defined as a prescription or dispensing record of the drug terbinafine, representing the new recorded prescription in the study period with no prior terbinafine use in the 180 days prior to the index date. For o*bjectives 2*, *3,* and *4*, only the first terbinafine initiation per individual during the study period was considered as the index treatment. For *objective 3,* an additional cohort included all new treatment episodes during the study period were included.

To define treatment episodes, sequential prescriptions were grouped into drug eras, allowing a maximum gap of 30 days between the end of one prescription and the start of the next.

The final concept sets used for the identification of exposures are described in **ANNEX III**. These codes were refined during the study execution following the DARWIN EU® phenotyping standard processes, which involved the review of code lists and the review of phenotypes after their execution in the participating data sources.

8.6.2. Outcome

The outcomes were as follows:

- Incidence rate of terbinafine use *(objective 1)*
- Characterisation of terbinafine initiators *(objective 2)*
- Initial and cumulative dose, and duration of first terbinafine treatment initiation *(objective 3)*
- Number of treatment initiations, initial and cumulative dose, and duration of all terbinafine treatment initiations *(objective 3)*
- Treatment patterns following first terbinafine treatment initiation during the study period *(objective 4)*

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

The covariates for calculation of incidence rates of terbinafine-containing product use *(objective 1)* were as follows:

- Calendar year
- Calendar month
- Age groups (overall, ≤18 years, 19–65 years, ≥66 years)
- Sex (overall, males, females)

The variables for characterisation of terbinafine users *(objective 2)* were as follows:

- Indication of use: Pre-specified conditions were used as a proxies to assess the indication for terbinafine use, including both authorised and non-authorised indications. Primary assessment

window was 30 days prior to the index date to 7 days after [-30, +7]. Additional sensitivity windows were 90 days prior to the index date to 7 days after [-90, +7] and 180 days prior to the index date to 7 days after [-180, +7].

  - Dermatophytosis (Tinea infections) including:
    - Tinea corporis (Ringworm of the body)
    - Tinea cruris (Jock itch)
    - Tinea pedis (Athlete's foot)
    - Tinea manuum (Hand ringworm)
    - Tinea capitis (Scalp ringworm)
    - Tinea barbae (Beard ringworm)
    - Tinea unguium (Onychomycosis (nail))
  - Other fungal infections including:
    - Cutaneous candidiasis
    - Sporotrichosis
    - Pityriasis versicolor
  - Other
  - Missing
- Comorbidities: The top 10 most frequent diagnostic codes (comorbidities) were identified through large-scale characterisation. These were assessed at the index date [0, 0] and 1 year prior to the index date [-365, 0].
- Antifungal and antibiotic treatment: Exposure to antifungal and antibiotic medications were evaluated 6, 3, and 1 month prior to treatment initiation and for antifungal treatments, up to 6 months post-initiation.
  - Antifungals for topical use (WHO ATC D01A)
  - Antifungals for systemic use (WHO ATC D01B)
  - Antibiotics for topical use (WHO ATC D06A)
  - Antibacterials for systemic use (WHO ATC J01)
- Resistance: Diagnostic codes indicating resistance were assessed 6 months before and 6 months after treatment initiation.

The variables for stratification by type of dermatophytosis in drug utilisation (assessment window was 30 days prior to the index date to 7 days after [-30, +7]) *(objective 3)*:

- Superficial Tinea infections (tinea pedis, tinea manuum, tinea corporis)
- Hair Follicle-involving Tinea infections (tinea capitis, tinea barbae)
- Onychomycosis

The variables for treatment patterns following first terbinafine treatment initiations during the study period (*objective 4*) were as follows:

- Treatment:
    - Antifungal drugs, other
        - Ciclopirox (cutaneous)
        - Methylrosaniline (cutaneous)
        - Terbinafine (cutaneous)
        - Terbinafine (systemic)
    - Antimycotic antibiotics
        - Griseofulvin (systemic)
    - Corticosteroids, combination preparations cutaneous
        - Miconazole/hydrocortisone (cutaneous)
    - Combination preparations
        - Benzoic acid/salicylic acid (cutaneous)
    - Imidazoles, cutaneous
        - Clotrimazole (cutaneous)
        - Ketoconazole (cutaneous)
        - Miconazole (cutaneous)
        - Sulconazole (cutaneous)
    - Triazoles
        - Fluconazole (systemic)
        - Itraconazole (systemic)

Types of dermatophytosis, for stratification by indication:

- Superficial Tinea infections (tinea pedis, tinea manuum, tinea corporis)
- Hair follicle-involving Tinea infections (tinea capitis, tinea barbae)
- Onychomycosis

The final concept sets used for the identification of covariates are described in **ANNEX III**. These codes were refined during the study execution following the DARWIN EU® phenotyping standard processes, which involved the review of code lists and the review of phenotypes after their execution in the participating data sources.

8.7. Study size

No sample size has been calculated, as this was a drug utilisation study with a descriptive design and no formal hypothesis testing. The study relied on existing routinely collected data to estimate incidence rates of terbinafine-containing product use and to describe treatment patterns. Thus, the sample size was driven by the availability of data for eligible individuals within the included data sources.

8.8. Data transformation

All analyses were conducted separately for each data source, and were carried out in a federated manner, allowing analyses to be run locally without sharing patient-level data.

Before sharing the study package, test runs of the analytics were performed on a subset of the data sources and quality control checks were performed. After all the tests passed (**ANNEX II**), the final package was released in a 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 default aggregated results. They then made available to the Principal Investigators and study team in secure online repository (Data Transfer Zone). The study results of all data sources were checked, after which they were made available to the team, and the Study Dissemination Phase started. All results were locked and timestamped for reproducibility and transparency.

8.9. Statistical methods

8.9.1. Statistical model specification and assumptions of the analytical approach considered

R-packages

The incidence of terbinafine-containing product use *(objective 1)* was estimated based on OMOP CDM mapped data using the *IncidencePrevalence* R package, developed by DARWIN EU® (https://darwin-eu.github.io/IncidencePrevalence/). Patient-level characterisation of terbinafine initiators and treatment utilisation *(objectives 2* and *3)* were assessed using *CohortCharacteristics* and *DrugUtilisation* R packages (https://github.com/darwin-eu/DrugUtilisation), while patient-level characterisation of treatment patterns *(objective 4)* were described using *TreatmentPatterns* (https://github.com/darwin-eu-dev/TreatmentPatterns).

Incidence rate estimation of terbinafine use *(objective 1)*

Monthly and annual incidence rates of terbinafine use were calculated as the number of treatment initiations after 180 days of no use of terbinafine-containing product per 1,000 person-years, among individuals fulfilling the inclusion and exclusion criteria. Individuals who enter the denominator population contributed time at risk from cohort entry until the earliest of the following: initiation of terbinafine treatment during the study period, death, loss to follow-up (defined as the date of last contact), or end of the study period. Participants who did not initiate terbinafine treatment during the study period are administratively censored at the end of follow-up.

An illustration of the calculation of incidence of selected pre-specified medication of interest is shown below in **Figure 3**. Patient ID 1 and ID 4 contributed time at risk up to the point at which they become incident users of selected pre-specified medication of interest. Patient ID 2 and ID 5 were not seen to use pre-specified medication of interest and so contributed time at risk but no incident outcomes. Meanwhile, patient ID 3 first contributed time at risk starting at the day when the washout period of a previous exposure, before study start, had ended, and ended when the next exposure of pre-specified medication of interest started. A second period of time at risk again started after the washout period. For person ID 4, only the first and third exposures of pre-specified medication of interest counted as incident use, while the second exposure started within the washout period of the first exposure. The time between start of the first exposure until the washout period after the second exposure was not considered as time at risk.

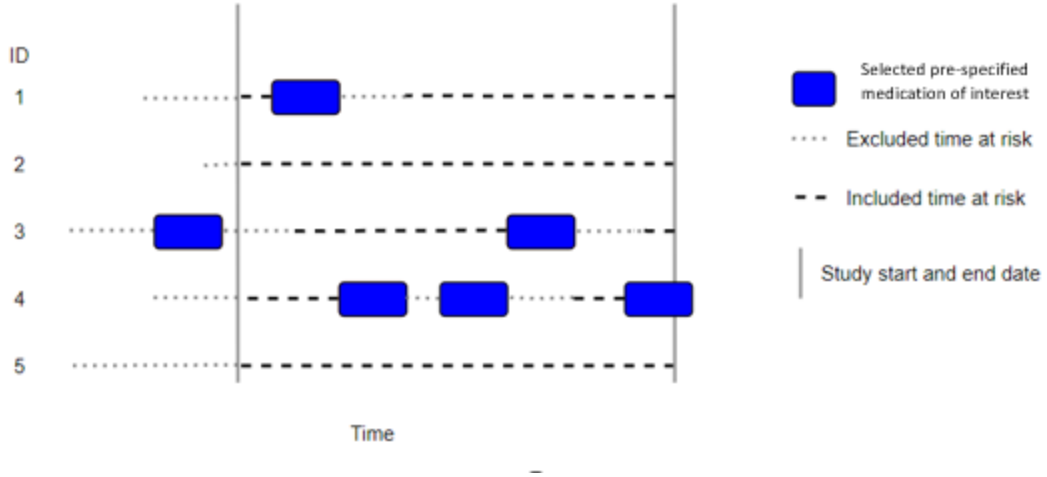


Figure 3. Incidence example.

Drug exposure calculations

Drug eras were defined as follows: exposure started at the date of a new prescription of terbinafine containing product during the study period after a washout of 180 days. For each prescription, the estimated duration of use was retrieved from the drug exposure table in the CDM, using the start and end date of the exposure. Subsequent prescriptions were combined into continuous exposed episodes (drug eras) using the following specifications: two drug eras were merged into one continuous drug era if the distance in days between end of the first era and start of the second era was ≤30 days. The time between the two joined eras was considered as exposed by the first era as shown in **Figure 4**, first row.

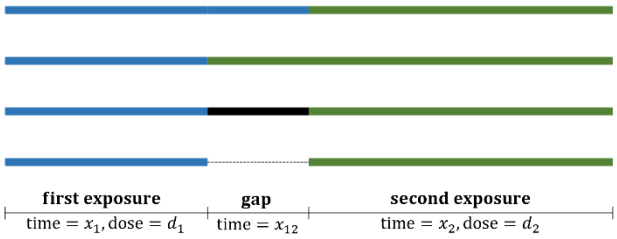
Gap era joint mode	Schematics	Dose in between	Cumulative dose	Cumulative time
"first"		d_1	$d_1 \cdot (x_1 + x_{12}) + d_2 \cdot x_2$	$x_1 + x_{12} + x_2$
"second"		d_2	$d_1 \cdot x_1 + d_2 \cdot (x_2 + x_{12})$	$x_1 + x_{12} + x_2$
"zero"		0	$d_1 \cdot x_1 + d_2 \cdot x_2$	$x_1 + x_{12} + x_2$
"join"		NA	$d_1 \cdot x_1 + d_2 \cdot x_2$	$x_1 + x_2$

Figure 4. Gap era joint mode.

If two exposures overlap, the overlap time was considered exposed to the first exposure (**Figure 5**). No time was added at the end of the combined drug era to account for the overlap. If two exposures started at the same date, the overlapping period was considered exposed to both.

Overlap mode	Schematics	Dose overlap
"first"		d_1
"second"		d_2
"both"		$d_1 + d_2$
"maximum"		$\max(d_1, d_2)$

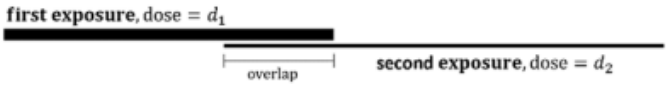


Figure 5. Gap era overlap mode.

New terbinafine user cohort *(objectives 2, 3, 4)*

Initial terbinafine users were selected based on the first recorded prescription of a terbinafine-containing products during the study period. Eligible individuals had at least 1 year of data visibility prior to the date of treatment initiation and no recorded use of terbinafine in the 180 days preceding treatment initiation. Repeated treatment episodes were excluded. To ensure sufficient follow-up, only individuals who initiated terbinafine treatment at least 1 year prior the end of data availability in each data source were included. Children <1 year of age were excluded. The new terbinafine user cohort study was used to characterise patient-level drug utilisation in terms of indication, comorbidities, antifungal and antibiotic treatment, resistance, evaluate treatment by assessing dose and duration of terbinafine use, and describe treatment patterns.

New terbinafine treatment episode cohort *(objective 3)*

New users were selected based on their new terbinafine-containing product prescription during the study period after a washout of 180 days. The cohort included all new terbinafine treatment episodes meeting the washout criteria. For each patient, at least one year of data visibility was required prior to becoming eligible for study inclusion. The new terbinafine treatment episode cohort study was used to characterise patient-level drug utilisation in terms of dose and duration.

Treatment duration *(objective 3)*

Treatment duration was calculated separately for first treatment episode and for multiple treatment episodes of the medication of interest during the study period (provided the episode meets the washout criteria). Treatment duration was summarised providing the minimum, quartiles, and maximum duration of treatment episodes. For data sources where duration cannot be calculated due to e.g., missing information on quantity or dosing, treatment duration was not provided.

Treatment patterns (*objective 4*)

The number and percentage of patients receiving each of the pre-specified treatment options, as well as treatment combinations, were described in the study population of new terbinafine users (*objective 4*). Additionally, Sunburst plots and Sankey diagrams were used to visualise treatment patterns and sequences over time per data source. Sankey diagrams were censored at end of follow-up as described in **Section 8.2**.

To construct treatment pathways, various parameters were defined in the *TreatmentPatterns* package (**Figure 6**).

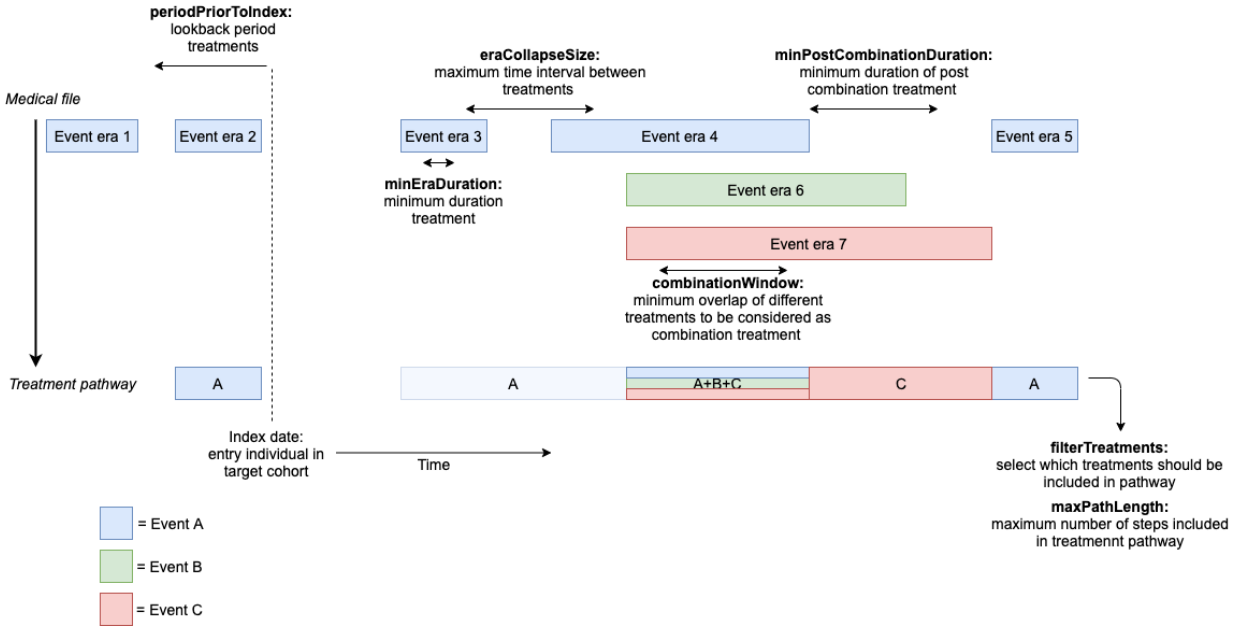


Figure 6. Parameters in *TreatmentPatterns* package.

The parameters outlined in this study are described in **Table 2**.

Table 2. List of pathway settings with description and expected input.

Individual pathway settings		
periodPriorToIndex	The period (number of days) prior to the index date of the target cohort from which treatments should be included	0
minEraDuration	Minimum time an event era should last to be included in the analysis	1
eraCollapseSize	Maximum gap within two eras of the same event cohort which would still allow the eras to be collapsed into one era	30 days
combinationWindow	Time that two event eras need to overlap to be considered a combination treatment	7 days
minPostCombinationDuration	Minimum time that an event era before or after a generated combination treatment should last to be included in the pathway as a separate treatment	7 days
filterTreatments	Select which treatments should be included in pathway: first time occurrences of treatments ('First'), remove sequential repeated treatments ('Changes'), all treatments ('All')	Changes
maxPathLength	Maximum number of treatments included in pathway	5
Aggregate pathway settings		
minCellCount	Minimum number of persons with a specific treatment pathway for the pathway to be included in analysis	5
minCellMethod	Select to completely remove / sequentially adjust (by removing last step as often as necessary) treatment pathways below minCellCount	Adjust
groupCombinations	Select to group all non-fixed combinations in one category 'other' in the sunburst plot	TRUE
addNoPaths	Select to include untreated persons without treatment pathway in the sunburst plot	TRUE

8.9.2. Missing values

We assumed that the absence of a prescription record in the data source means that the person did not receive the respective treatment. Similarly, for assessment of comorbidities, we assumed that the absence of a recorded diagnostic code for a given condition means that that condition was not present or not recorded in the context of routine clinical care.

8.9.3. Sensitivity analysis

Not applicable.

8.10. Deviations from the protocol

Deviation number	Protocol version	Date	Section of study protocol	Deviation	Reason
1	V2.0	November 2025	8.5. Study period; 8.2 Follow-up	Exclusion of the latest 6 months of available data in IQVIA DA Germany.	To reduce artefacts in incidence rate estimates caused by methodological aspects to obtain observation period.
2	V2.0	November 2025	8.5 Study period	End of observation period set to end of 2023 in FinOMOP-THL.	Drug prescription data available only until end of 2023.

9. RESULTS

The full set of results for this study is available through an interactive web-application ShinyApp at EUPAS1000000790.

9.1. Incidence of terbinafine use

9.1.1. Participants

A total of 48,055,763 individuals met all inclusion criteria and was retained in the final study population (NAJS: 4,633,339; DK-DHR: 6,665,161; FinOMOP-THL: 6,174,938; IQVIA DA Germany: 16,003,483; SIDIAP: 7,013,687; CPRD GOLD: 7,565,155).

Table 3. Attrition of participants based on all relevant inclusion criteria, presented by data source.

Criteria	NAJS (n)*	DK-DHR (n)*	FinOMOP-THL (n)*	IQVIA DA Germany (n)*	SIDIAP (n)*	CPRD GOLD (n)*
Individuals in the data source	4,853,340	8,593,356	6,618,745	45,156,504	8,553,325	17,539,783
Non-missing year of birth	4,853,340	8,593,356	6,618,745	45,156,504	8,553,325	17,539,783
Non-missing sex	4,853,340	8,593,356	6,618,208	45,128,169	8,553,325	17,539,783
Meeting age eligibility criteria	4,821,090	8,543,853	6,539,364	45,096,581	8,553,325	17,511,209
Observation period within the study period	4,689,509	6,939,981	6,256,987	33,656,486	7,266,665	8,297,503
At least one year data visibility prior to the index date	4,633,506	6,665,663	6,175,086	16,007,451	7,013,975	7,567,225
Eligible observation time available**	4,633,506	6,665,504	6,175,084	16,007,451	7,013,975	7,567,225
Apply washout criteria of 180 days	4,633,339	6,665,161	6,174,938	16,003,483	7,013,687	7,565,155
Contribution of at least 1 day of observation	4,633,339	6,665,161	6,174,938	16,003,483	7,013,687	7,565,155

NAJS = Croatian National Public Health Information System, DK-DHR = Danish Data Health Registries, FinOMOP-THL = Finnish Care Register for Health Care, IQVIA DA Germany = IQVIA Disease Analyzer Germany, SIDIAP = Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària, CPRD GOLD = Clinical Practice Research Datalink GOLD.
*n = number of individuals, ** = The criterion ensures that, after applying all preceding requirements (age eligibility, alignment of the observation period with the study period, and prior data visibility), individuals still contribute >0 days of observable follow-up within the study period.

9.1.2. Incidence estimates

Monthly incidence rates of terbinafine use showed distinct trends across six data sources from 2015 to 2024 (**Figure 7**). Incidence rates ranged approximately from 1 to over 10 per 1,000 person-years (PYs) and demonstrated seasonal pattern with peaks occurring annually during the warmer months. FinOMOP-THL and DK-DHR reported the highest incidence rates, often exceeding 8–10 per 1,000 PYs during peak months. Incidence rates in NAJS ranged between approximately 6 and 8 per 1,000 PYs, between approximately 4 and 6 per 1,000 PYs in SIDIAP and CPRD GOLD, while IQVIA DA Germany reported incidence rates of approximately 1 per 1,000 PYs, with a slight increase toward 2024. Overall, trends across data sources remained stable over time despite seasonal variability, with a slight decline observed across most data sources in 2020, likely reflecting the COVID-19 pandemic.

Similarly, annual incidence rates of terbinafine use were highest in FinOMOP-THL and DK-DHR (**Figure 8**). In FinOMOP-THL, the incidence rate was 9 per 1,000 PYs in 2015, peaked at 10 per 1,000 PYs in 2018, declined to approximately 9 per 1,000 PYs in 2020 and then gradual increased reaching 10 per 1,000 PYs in 2024. In DK-DHR, annual incidence rates ranged from 9 per 1,000 PYs in 2015, decreased to 7 per 1,000 PYs in 2020 and stabilised around 8 per 1,000 PYs by 2023. The apparent decline in 2024 reflects partial data availability of prescription data in 2024, as described in **Section 10.2**. In NAJS, incidence rates were 8 per 1,000 PYs in 2017 and remained stable until 2019, followed by a decline to 6 per 1,000 PYs in 2020 and a subsequent increase to 8 per 1,000 PYs by 2024. In CPRD GOLD, annual incidence rates ranged from 7 per 1,000 PYs in 2015 to 6 per 1,000 PYs in 2019, followed by a dip to 4 per 1,000 PYs in 2020 and a gradual increase to 7 per 1,000 PYs in 2024. Annual incidence rates in SIDIAP were approximately 3 per 1,000 PYs in 2015, gradually increased to 5 per 1,000 PYs in 2019, followed by a decline to 3 per 1,000 PYs in 2020 and subsequent increase to 7 per 1,000 PYs in 2023. The lowest annual incidence rates were observed in IQVIA DA Germany, with estimates around 1 per 1,000 PYs throughout most of the study period, increasing slightly to 3 per 1,000 PYs in 2024, which might be related to the artefactual decrease in the denominator, as described in **Section 10.2**.

Age-stratified analyses (**Figure 9** and **Figure 10**) demonstrated a consistent age-related gradient across all six European data sources. Older adults (≥66 years) exhibited the highest incidence rates throughout the study period, followed by adults aged 19–65 years, and children and adolescents (1–18 years). FinOMOP-THL and DK-DHR showed the highest monthly incidence estimates, often 8–16 per 1,000 PYs for older adults during peak months. NAJS reported incidence estimates similar or below these values, followed by CPRD GOLD and SIDIAP. IQVIA DA Germany consistently reported the lowest estimates throughout. Seasonal variation was evident in most sources, with peaks during warmer months, although overall monthly trends remained stable over time apart from a transient decline in 2020. Annual incidence rates mirrored these patterns (**Figure 10**), with the incidence rates in older adults ranging from approximately 8 to 13 per 1,000 PYs in FinOMOP-THL and DK-DHR, 8 to 11 per 1,000 PYs in NAJS, 6 to 9 per 1,000 PYs in CPRD GOLD, 4 to 7 per 1,000 PYs in SIDIAP, and around 1 per 1,000 PYs in IQVIA DA Germany. Adults aged 19–65 years showed incidence rates generally between 6 and 10 per 1,000 PYs in FinOMOP-THL, DK-DHR and NAJS, and lower in CPRD GOLD, SIDIAP, and IQVIA DA Germany. Children and adolescents consistently had the lowest incidence, typically 2–5 per 1,000 PYs across most data sources. Annual trends were stable overall, with a temporary decline in 2020 and recovery thereafter.

Sex-stratified analyses (**Figure 11** and **Figure 12**) revealed higher monthly and annual incidence rates among males compared to females in most data sources, including DK-DHR, FinOMOP-THL, IQVIA DA Germany, and CPRD GOLD. In contrast, NAJS consistently showed slightly higher incidence among females, while SIDIAP exhibited negligible sex-related differences.

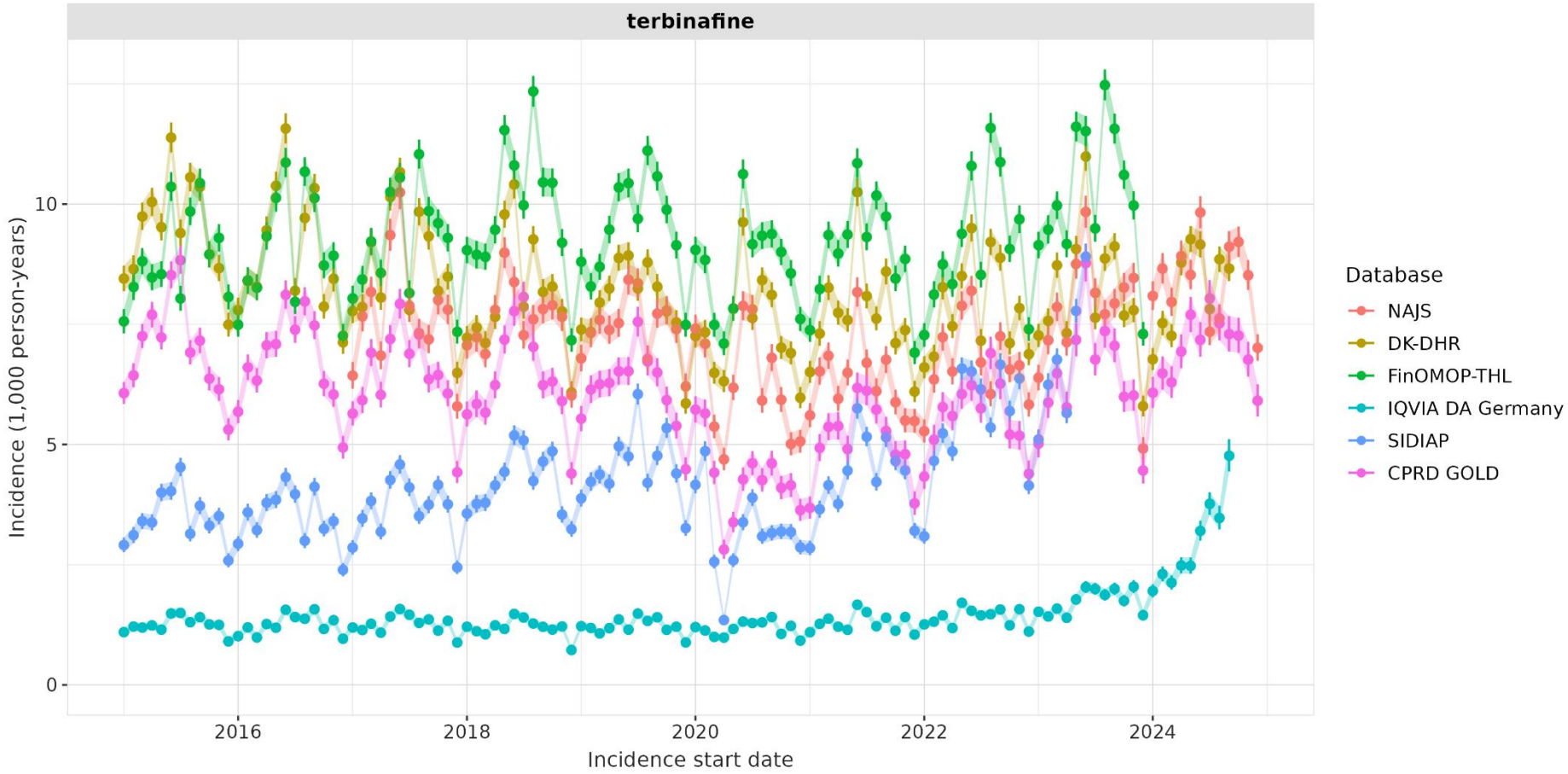


Figure 7. Monthly incidence of terbinafine use across six European data sources (2015–2024).

NAJS = Croatian National Public Health Information System, DK-DHR = Danish Data Health Registries, FinOMOP-THL = Finnish Care Register for Health Care, IQVIA DA Germany = IQVIA Disease Analyzer Germany, SIDIAP = Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària, CPRD GOLD = Clinical Practice Research Datalink GOLD.

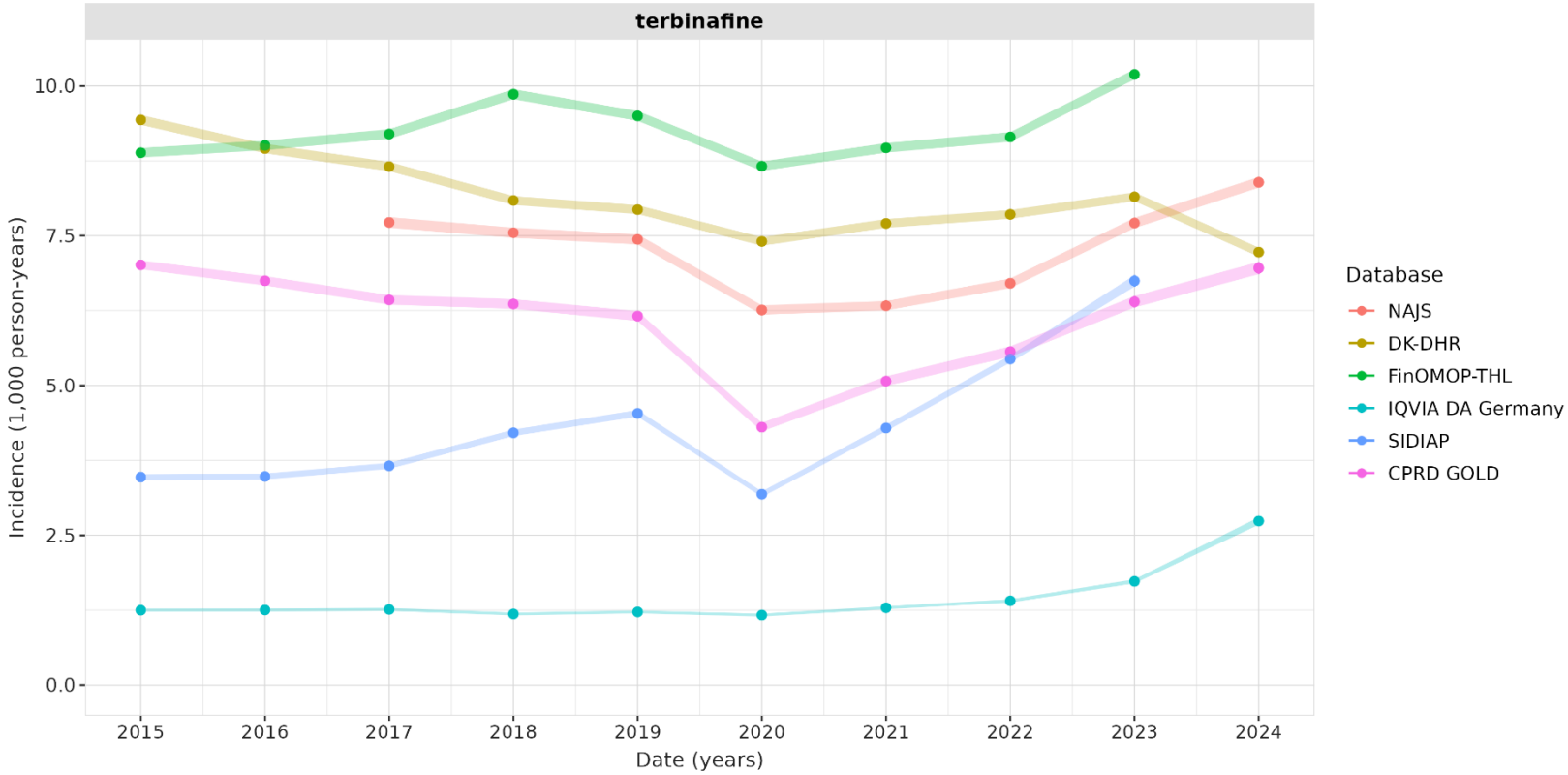


Figure 8. Annual incidence of terbinafine use across six European data sources (2015–2024).

NAJS = Croatian National Public Health Information System, DK-DHR = Danish Data Health Registries, FinOMOP-THL = Finnish Care Register for Health Care, IQVIA DA Germany = IQVIA Disease Analyzer Germany, SIDIAP = Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària, CPRD GOLD = Clinical Practice Research Datalink GOLD.

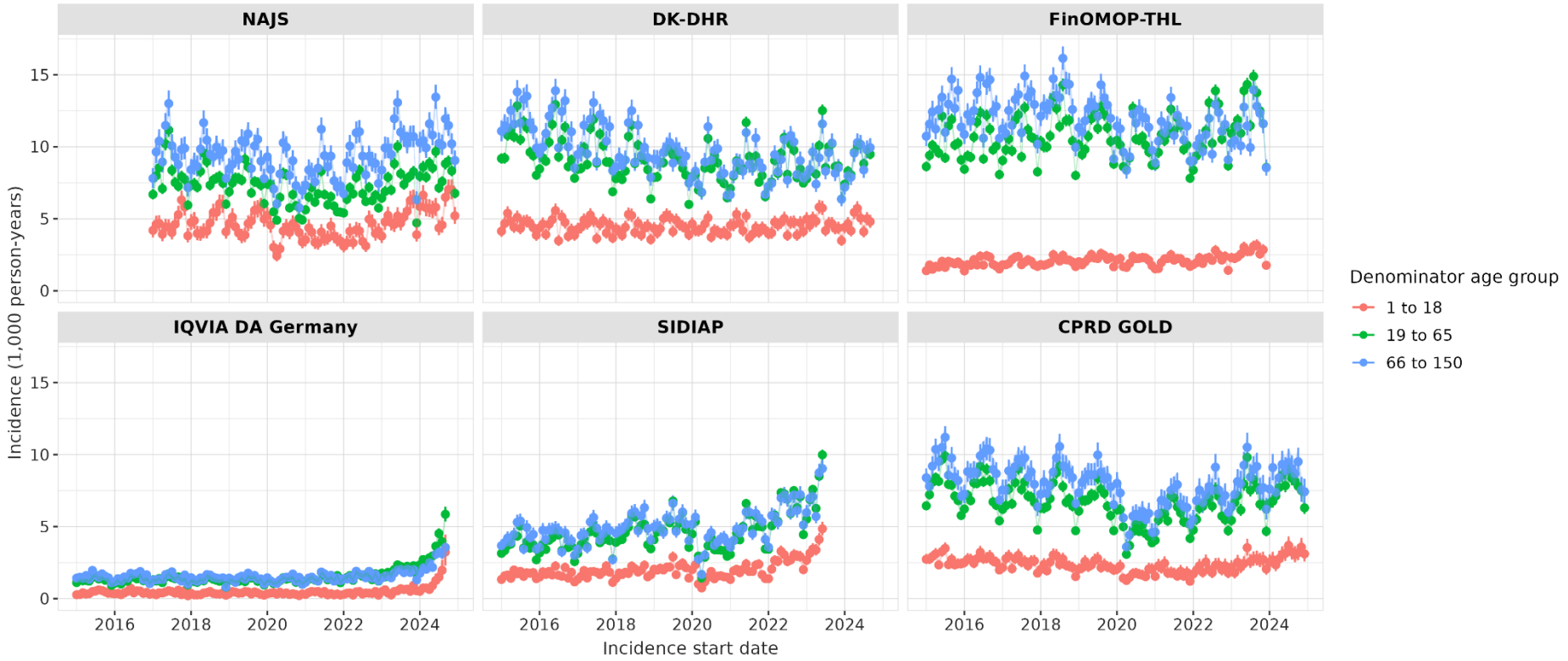


Figure 9. Monthly incidence of terbinafine use by age across six European data sources (2015–2024).

NAJS = Croatian National Public Health Information System, DK-DHR = Danish Data Health Registries, FinOMOP-THL = Finnish Care Register for Health Care, IQVIA DA Germany = IQVIA Disease Analyzer Germany, SIDIAP = Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària, CPRD GOLD = Clinical Practice Research Datalink GOLD.

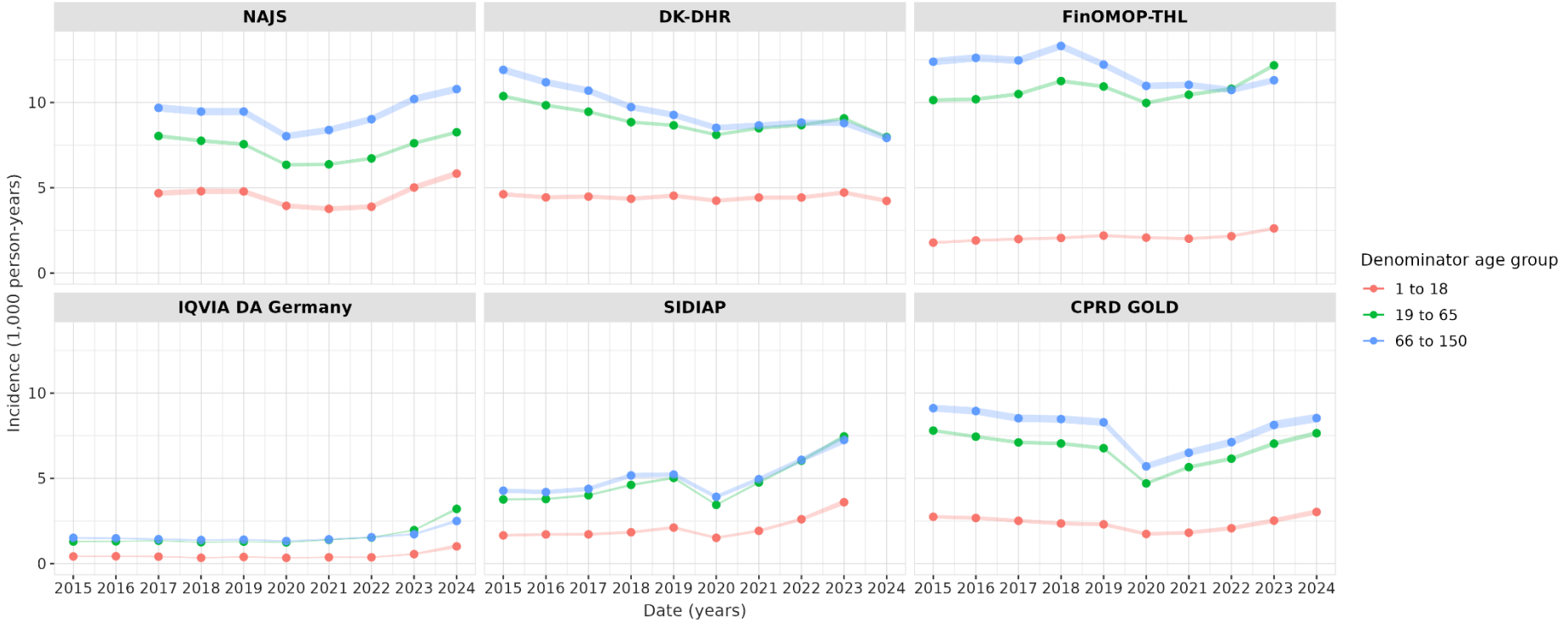


Figure 10. Annual incidence of terbinafine use by age across six European data sources (2015–2024).

NAJS = Croatian National Public Health Information System, DK-DHR = Danish Data Health Registries, FinOMOP-THL = Finnish Care Register for Health Care, IQVIA DA Germany = IQVIA Disease Analyzer Germany, SIDIAP = Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària, CPRD GOLD = Clinical Practice Research Datalink GOLD.

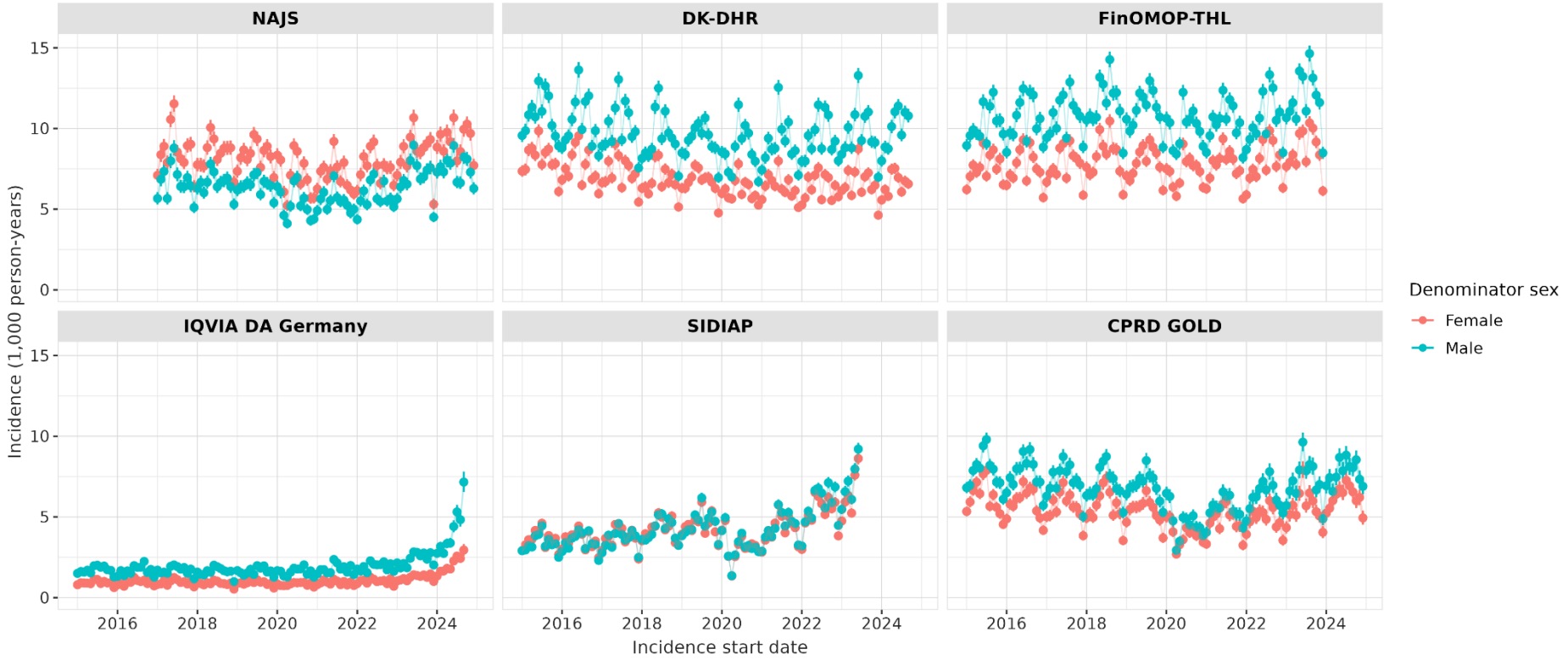


Figure 11. Monthly incidence of terbinafine use by sex across six European data sources (2015–2024).

NAJS = Croatian National Public Health Information System, DK-DHR = Danish Data Health Registries, FinOMOP-THL = Finnish Care Register for Health Care, IQVIA DA Germany = IQVIA Disease Analyzer Germany, SIDIAP = Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària, CPRD GOLD = Clinical Practice Research Datalink GOLD.

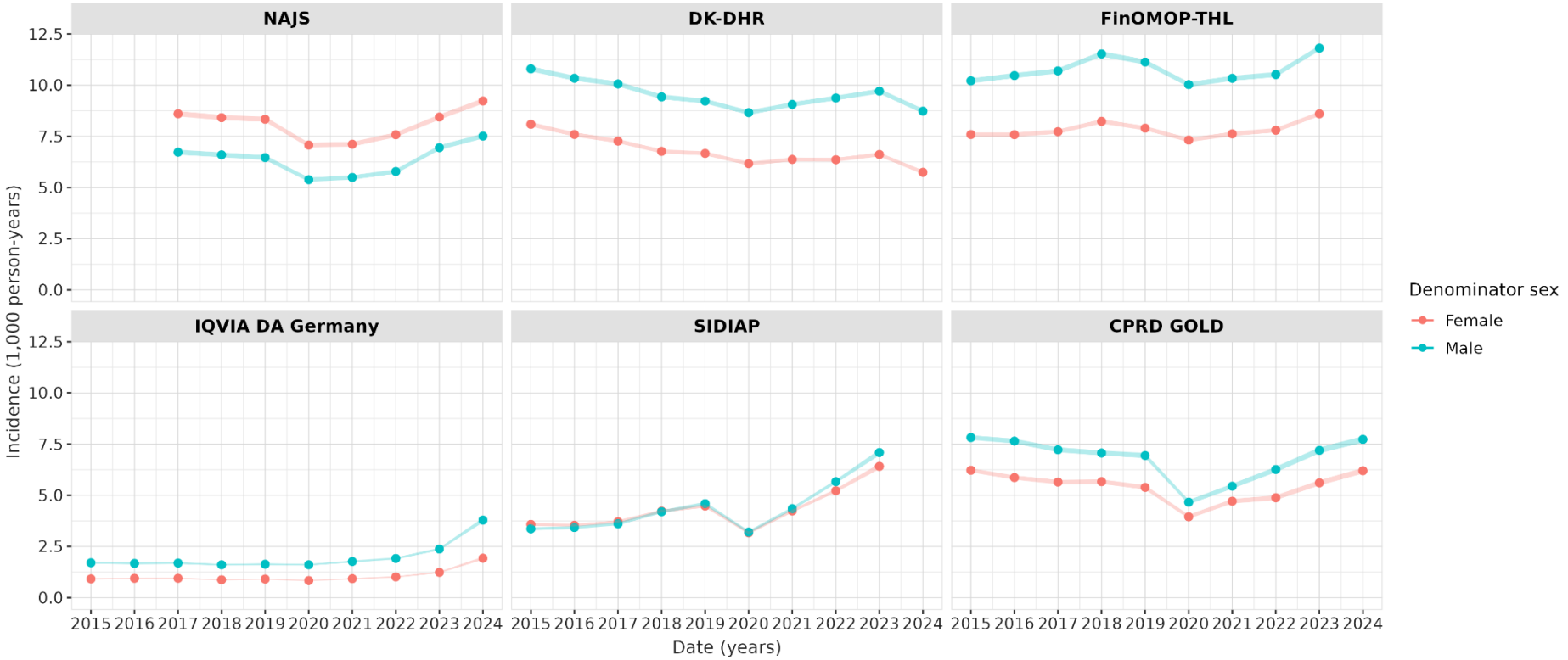


Figure 12. Annual incidence of terbinafine use by sex across six European data sources (2015–2024).

NAJS = Croatian National Public Health Information System, DK-DHR = Danish Data Health Registries, FinOMOP-THL = Finnish Care Register for Health Care, IQVIA DA Germany = IQVIA Disease Analyzer Germany, SIDIAP = Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària, CPRD GOLD = Clinical Practice Research Datalink GOLD.

9.2. Characterisation of terbinafine initiators

9.2.1. Participants

A total of 1,230,556 individuals met all inclusion criteria and were retained in the final study population of terbinafine initiators (NAJS: 156,916; DK-DHR: 350,877; FinOMOP-THL: 336,449; IQVIA DA Germany: 70,753; SIDIAP: 146,994; CPRD GOLD: 168,567). DK-DHR and FinOMOP-THL contributed the largest proportion of individuals initiating terbinafine, accounting for 28.51% and 27.34%, respectively.

Table 3. Attrition of participants based on terbinafine initiator prescription and relevant inclusion criteria, presented by data source.

Criteria	NAJS (n)*	DK-DHR (n)*	FinOMOP-THL (n)*	IQVIA DA Germany (n)*	SIDIAP (n)*	CPRD GOLD (n)*
Initial qualifying events (terbinafine prescription)	224,323	1,184,997	472,760	205,830	316,603	727,074
Collapse records separated by 30 or less days	224,323	1,184,997	472,760	205,830	316,603	727,074
No use of terbinafine products in previous 180 days	224,323	1,184,997	472,760	205,830	316,603	727,074
At least 1 year of data visibility prior to the index date	206,342	1,138,338	465,746	119,394	293,369	650,274
Record of terbinafine containing product between 2015-01-01 to 2024-12-31 (or latest available)	181,190	377,963	377,808	78,547	176,393	182,526
First prescription	181,190	377,960	377,808	78,547	176,393	182,526
Follow-up censored at death	156,916	350,877	336,449	70,753	146,994	168,567
Follow up to latest available data	156,916	350,877	336,449	70,753	146,994	168,567

NAJS = Croatian National Public Health Information System, DK-DHR = Danish Data Health Registries, FinOMOP-THL = Finnish Care Register for Health Care, IQVIA DA Germany = IQVIA Disease Analyzer Germany, SIDIAP = Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària, CPRD GOLD = Clinical Practice Research Datalink GOLD.
*n = number of individuals.

9.2.2. Demographic characteristics

The median age of terbinafine initiators varied across data sources, ranging from 47 years in DK-DHR and SIDIAP to 57 years in IQVIA DA Germany (**Table 4**). Across all data sources, the majority of participants were adults aged 19 to 65 years, representing approximately 63% in NAJS and up to 70% in SIDIAP. Older adults (≥66 years) accounted for 21% in SIDIAP and up to 31% in IQVIA DA Germany, whereas children and adolescents (1–18 years) comprised between 4% in IQVIA DA Germany to 13% in NAJS.

Sex distribution varied by data source. Overall, males predominated in most data sources, with proportions ranging from 55% in CPRD GOLD to 58% in IQVIA DA Germany. In contrast, females were more frequent in NAJS (58%) and slightly more common in SIDIAP (51%).

Table 4. Demographic characteristics of terbinafine initiators across six European data sources (2015–2024).

Variable name	CDM name					
	NAJS	DK-DHR	FinOMOP-THL	IQVIA DA Germany	SIDIAP	CPRD GOLD
Number of subjects	156,916	350,877	336,449	70,753	146,994	168,567
Age (years), median [q25–q75]	50 [31–65]	47 [29–63]	53 [38–67]	57 [43–69]	47 [33–63]	50 [34–64]
Age (years), range (min–max)	1 to 102	1 to 108	1 to 106	1 to 98	1 to 105	1 to 106
Age group, n (%)						
• 1 to 18	20,418 (13.01%)	43,159 (12.30%)	15,624 (4.64%)	2,733 (3.86%)	13,316 (9.06%)	13,998 (8.30%)
• 19 to 65	99,412 (63.35%)	231,334 (65.93%)	230,471 (68.50%)	45,857 (64.81%)	102,424 (69.68%)	115,046 (68.25%)
• ≥66	37,086 (23.63%)	76,384 (21.77%)	90,354 (26.86%)	22,163 (31.32%)	31,254 (21.26%)	39,523 (23.45%)
Sex, n (%)						
• Female	90,987 (57.98%)	150,960 (43.02%)	144,989 (43.09%)	30,029 (42.44%)	74,775 (50.87%)	76,341 (45.29%)
• Male	65,929 (42.02%)	199,917 (56.98%)	191,449 (56.90%)	40,691 (57.51%)	72,219 (49.13%)	92,226 (54.71%)
• None	–	–	11 (0.00%)	33 (0.05%)	–	–

NAJS = Croatian National Public Health Information System, DK-DHR = Danish Data Health Registries, FinOMOP-THL = Finnish Care Register for Health Care, IQVIA DA Germany = IQVIA Disease Analyzer Germany, SIDIAP = Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària, CPRD GOLD = Clinical Practice Research Datalink GOLD.
*n = number of individuals, q25–q75 = 25th and 75th percentiles (interquartile range), min–max = minimum and maximum observed values.

9.2.3. Indication of use

Across all data sources, dermatophytosis (tinea infections) was the most frequently observed diagnosis code recorded within the predefined time window (30 days before to 7 days after treatment initiation), although prevalence varied substantially between data sources (**Table 5**). Dermatophytosis accounted for 12.31% in SIDIAP and up to 59.49% in IQVIA DA Germany, with intermediate proportions in other data sources (e.g., 24.22% in NAJS, 40.61% in DK-DHR, 18.75% in FinOMOP-THL, and 23.30% in CPRD GOLD). Among specific subtypes, tinea unguium (onychomycosis) was consistently the most common, representing 13.41% of initiators in NAJS, 22.57% of initiators in DK-DHR, 8.83% in FinOMOP-THL, 47.41% in IQVIA DA Germany, 5.17% in SIDIAP, and 15.28% in CPRD GOLD. Other subtypes, such as tinea pedis and tinea corporis, were less frequent but present across all sources. Tinea barbae and tinea capitis were recorded only in DK-DHR and CPRD GOLD in a very small number of individuals.

Indications for other fungal infections (e.g., cutaneous candidiasis, pityriasis versicolor) were rare, generally below 3% in all data sources. Sporotrichosis was reported in fewer than five cases per data source, except for NAJS, where 13 cases were identified.

A substantial proportion of terbinafine initiators had other indication codes, defined as diagnosis codes that do not correspond to any condition in the pre-specified list of indications for terbinafine use, within the specified time windows, ranging from 21.55% in IQVIA DA Germany to 73.11% in NAJS for the 30-day window. Additionally, some sources recorded no indication codes for a large share of terbinafine initiators (e.g., 45.14% in FinOMOP-THL and 57.21% in SIDIAP).

Patterns were broadly consistent in the sensitivity analyses of indication using longer time windows (90-day and 180-day) (**Table 5**). As the window widened, dermatophytosis prevalence increased slightly, accompanied by corresponding decreases in the proportion of unknown or missing indications.

Table 5. Indication of terbinafine use based on proxy diagnostic codes within predefined time windows across six European data sources.

Indication	CDM name					
	NAJS	DK-DHR	FinOMOP-THL	IQVIA DA Germany	SIDIAP	CPRD GOLD
Indication from 30 days before to 7 days after the index date						
Dermatophytosis (Tinea infections), n (%)	37,998 (24.22%)	142,483 (40.61%)	63,077 (18.75%)	42,092 (59.49%)	18,097 (12.31%)	39,278 (23.30%)
• Tinea barbae, n (%)	0 (0.00%)	10 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	6 (0.00%)
• Tinea capitis, n (%)	0 (0.00%)	1,418 (0.40%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	408 (0.24%)
• Tinea corporis, n (%)	6,761 (4.31%)	246 (0.07%)	4,573 (1.36%)	3,131 (4.43%)	4,483 (3.05%)	1,554 (0.92%)
• Tinea cruris, n (%)	796 (0.51%)	62 (0.02%)	6,479 (1.93%)	495 (0.70%)	1,602 (1.09%)	2,134 (1.27%)
• Tinea manuums, n (%)	1,208 (0.77%)	27 (0.01%)	767 (0.23%)	524 (0.74%)	19 (0.01%)	71 (0.04%)
• Tinea pedis, n (%)	9,160 (5.84%)	63,502 (18.10%)	24,587 (7.31%)	8,868 (12.53%)	5,158 (3.51%)	9,743 (5.78%)
• Tinea unguium, n (%)	21,039 (13.41%)	79,183 (22.57%)	29,693 (8.83%)	33,545 (47.41%)	7,594 (5.17%)	25,752 (15.28%)
Other fungal infections, n (%)	4,276 (2.73%)	32 (0.01%)	1,264 (0.38%)	568 (0.80%)	1,949 (1.33%)	2,082 (1.24%)
• Cutaneous candidiasis, n (%)	0 (0.00%)	0 (0.00%)	59 (0.02%)	0 (0.00%)	0 (0.00%)	828 (0.49%)
• Sporotrichosis, n (%)	13 (0.01%)	0 (0.00%)	0 (0.00%)	<5	0 (0.00%)	<5
• Pityriasis versicolor, n (%)	4,263 (2.72%)	32 (0.01%)	1,205 (0.36%)	567 (0.80%)	1,949 (1.33%)	1,254 (0.74%)
Other*, n (%)	114,720 (73.11%)	197,726 (56.35%)	120,382 (35.78%)	15,246 (21.55%)	42,905 (29.19%)	64,552 (38.29%)
None**, n (%)	88 (0.06%)	10,642 (3.03%)	151,875 (45.14%)	13,050 (18.44%)	84,098 (57.21%)	62,813 (37.26%)
Indication from 90 days before to 7 days after the index date						
Dermatophytosis (Tinea infections) , n (%)	38,598 (24.60%)	142,918 (40.73%)	65,417 (19.44%)	44,464 (62.84%)	20,789 (14.14%)	41,875 (24.84%)
• Tinea barbae, n (%)	0 (0.00%)	10 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	7 (0.00%)
• Tinea capitis, n (%)	0 (0.00%)	1,422 (0.41%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	435 (0.26%)
• Tinea corporis, n (%)	6,881 (4.39%)	253 (0.07%)	4,657 (1.38%)	3,332 (4.71%)	4,824 (3.28%)	1,630 (0.97%)
• Tinea cruris, n (%)	814 (0.52%)	65 (0.02%)	6,627 (1.97%)	556 (0.79%)	1,800 (1.22%)	2,264 (1.34%)

Indication	CDM name					
	NAJS	DK-DHR	FinOMOP-THL	IQVIA DA Germany	SIDIAP	CPRD GOLD
• Tinea manuums, n (%)	1,246 (0.79%)	27 (0.01%)	783 (0.23%)	575 (0.81%)	19 (0.01%)	73 (0.04%)
• Tinea pedis, n (%)	9,320 (5.94%)	63,660 (18.14%)	25,178 (7.48%)	9,637 (13.62%)	5,602 (3.81%)	10,096 (5.99%)
• Tinea unguium, n (%)	21,528 (13.72%)	79,586 (22.68%)	31,447 (9.35%)	35,670 (50.41%)	9,413 (6.40%)	27,886 (16.54%)
Other fungal infections, n (%)	4,359 (2.78%)	33 (0.01%)	1,356 (0.40%)	639 (0.90%)	2,130 (1.45%)	2,295 (1.36%)
• Cutaneous candidiasis, n (%)	0 (0.00%)	0 (0.00%)	76 (0.02%)	0 (0.00%)	0 (0.00%)	957 (0.57%)
• Sporotrichosis, n (%)	13 (0.01%)	0 (0.00%)	0 (0.00%)	<5	0 (0.00%)	<5
• Pityriasis versicolor, n (%)	4,346 (2.77%)	33 (0.01%)	1,280 (0.38%)	638 (0.90%)	2,130 (1.45%)	1,338 (0.79%)
Other*, n (%)	114,121 (72.73%)	200,600 (57.17%)	147,453 (43.83%)	16,446 (23.24%)	66,044 (44.93%)	79,000 (46.87%)
None**, n (%)	43 (0.03%)	7,332 (2.09%)	122,411 (36.38%)	9,467 (13.38%)	58,108 (39.53%)	45,613 (27.06%)
Indication from 180 days before to 7 days after the index date						
Dermatophytosis (Tinea infections) , n (%)	39,102 (24.92%)	143,355 (40.86%)	66,232 (19.69%)	45,687 (64.57%)	22,961 (15.62%)	42,902 (25.45%)
• Tinea barbae, n (%)	0 (0.00%)	10 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	7 (0.00%)
• Tinea capitis, n (%)	0 (0.00%)	1,424 (0.41%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	449 (0.27%)
• Tinea corporis, n (%)	6,996 (4.46%)	260 (0.07%)	4,704 (1.40%)	3,470 (4.90%)	5,011 (3.41%)	1,683 (1.00%)
• Tinea cruris, n (%)	829 (0.53%)	65 (0.02%)	6,726 (2.00%)	617 (0.87%)	1,971 (1.34%)	2,372 (1.41%)
• Tinea manuums, n (%)	1,268 (0.81%)	28 (0.01%)	792 (0.24%)	599 (0.85%)	20 (0.01%)	77 (0.05%)
• Tinea pedis, n (%)	9,440 (6.02%)	63,789 (18.18%)	25,411 (7.55%)	10,147 (14.34%)	5,990 (4.07%)	10,329 (6.13%)
• Tinea unguium, n (%)	21,921 (13.97%)	80,028 (22.81%)	31,992 (9.51%)	36,765 (51.96%)	10,972 (7.46%)	28,616 (16.98%)
Other fungal infections, n (%)	4,442 (2.83%)	36 (0.01%)	1,428 (0.42%)	710 (1.00%)	2,281 (1.55%)	2,530 (1.50%)
• Cutaneous candidiasis, n (%)	0 (0.00%)	0 (0.00%)	93 (0.03%)	0 (0.00%)	0 (0.00%)	1,128 (0.67%)
• Sporotrichosis, n (%)	13 (0.01%)	0 (0.00%)	0 (0.00%)	<5	0 (0.00%)	<5
• Pityriasis versicolor, n (%)	4,429 (2.82%)	36 (0.01%)	1,335 (0.40%)	709 (1.00%)	2,281 (1.55%)	1,403 (0.83%)

Indication	CDM name					
	NAJS	DK-DHR	FinOMOP-THL	IQVIA DA Germany	SIDIAP	CPRD GOLD
Other*, n (%)	113,600 (72.40%)	202,124 (57.61%)	167,779 (49.87%)	17,313 (24.47%)	84,462 (57.46%)	90,249 (53.54%)
None**, n (%)	22 (0.01%)	5,369 (1.53%)	101,225 (30.09%)	7,360 (10.40%)	37,391 (25.44%)	33,159 (19.67%)

NAJS = Croatian National Public Health Information System, DK-DHR = Danish Data Health Registries, FinOMOP-THL = Finnish Care Register for Health Care, IQVIA DA Germany = IQVIA Disease Analyzer Germany, SIDIAP = Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària, CPRD GOLD = Clinical Practice Research Datalink GOLD, n (%) = number of individuals and corresponding proportion of cohort.
*Unknown = a record of a condition that is not included in the pre-specified list.
**None = no recorded condition in the pre-specified list or a clinical table.

9.2.4. Comorbidities

At the index date, the top 10 most frequent comorbidities predominantly reflected fungal infections and related dermatological conditions (**Table 6**). Dermatophytosis and superficial mycoses were among the most frequent diagnoses in NAJS (20.46% and 18.17%, respectively) and DK-DHR (39.28% and 13.33%, respectively), whereas onychomycosis due to dermatophyte was the leading condition in IQVIA DA Germany (43.75%) and also common in FinOMOP-THL (7.90%), SIDIAP (1.97%), and CPRD GOLD (9.27%). Essential hypertension appeared among the top comorbidities in NAJS (11.39%), FinOMOP-THL (1.97%), and IQVIA DA Germany (2.44%) indicating the presence of chronic conditions alongside fungal infections. Type 2 diabetes mellitus was frequently reported in NAJS (3.20%) and FinOMOP-THL (0.94%). Other frequent diagnoses included inflammatory dermatoses, eczema, and pain-related codes, with variability across data sources.

One year prior to the index date, the comorbidity profile shifted toward chronic and systemic conditions (**Table 6**). Essential hypertension was the most common diagnosis in NAJS (36.81%), FinOMOP-THL (10.49%), and IQVIA DA Germany (9.83%), while DK-DHR showed high prevalence of mycosis (40.99%) and pain-related codes (30.37%). Respiratory infections (e.g., acute upper respiratory infection, common cold) and musculoskeletal conditions (e.g., pain in spine, joint pain) were frequently observed across several sources. Type 2 diabetes mellitus appeared among the top 10 comorbidities in multiple data sources, particularly FinOMOP-THL (6.40%). Across data sources, diagnoses related to dermatophytosis and onychomycosis remained among the most frequently recorded comorbidities in the year prior to treatment initiation, although their relative ranking varied by setting. Dermatophytosis-related codes were still highly prevalent and appeared at higher proportions compared with the index date, consistent with the chronic and often recurrent nature of these infections.

Table 6. Top 10 most frequent comorbidities among terbinafine initiators in pre-specified windows across six European data sources.

NAJS	n (%)	DK-DHR	n (%)	FinOMOP-THL	n (%)	IQVIA DA Germany	n (%)	SIDIAP	n (%)	CPRD GOLD	n (%)
Index date											
Dermatophytosis	32,112 (20.46%)	Mycosis	137,827 (39.28%)	Onychomycosis due to dermatophyte	26,583 (7.90%)	Onychomycosis due to dermatophyte	30,955 (43.75%)	Onychomycosis due to dermatophyte	2,901 (1.97%)	Onychomycosis	15,621 (9.27%)
Superficial mycosis	28,516 (18.17%)	Onychomycosis	78,456 (22.36%)	Tinea pedis	23,010 (6.84%)	Tinea pedis	8,041 (11.36%)	Mycosis	2,133 (1.45%)	Eruption	10,881 (6.46%)
Onychomycosis due to dermatophyte	20,204 (12.88%)	Tinea pedis	63,165 (18.00%)	Essential hypertension	6,629 (1.97%)	Melanocytic nevus	2,924 (4.13%)	Tinea pedis	2,055 (1.40%)	Tinea pedis	9,242 (5.48%)
Inflammatory dermatosis	18,909 (12.05%)	Dermatophytosis	46,766 (13.33%)	Dermatophytosis	6,599 (1.96%)	Tinea corporis	2,849 (4.03%)	Tinea corporis	1,569 (1.07%)	Onychomycosis due to dermatophyte	6,860 (4.07%)
Essential hypertension	17,866 (11.39%)	Eczema	15,608 (4.45%)	Tinea cruris	6,150 (1.83%)	Dermatophytosis	2,469 (3.49%)	Dermatophytosis	1,358 (0.92%)	Dermal mycosis	6,031 (3.58%)
Mycosis	14,145 (9.01%)	Pain	13,471 (3.84%)	Inflammatory dermatosis	5,140 (1.53%)	Mycosis	2,418 (3.42%)	Pityriasis versicolor	858 (0.58%)	Dermatophytosis	5,732 (3.40%)
Candidiasis	10,939 (6.97%)	Dermal mycosis	10,476 (2.99%)	Tinea corporis	4,249 (1.26%)	Inflammatory dermatosis	1,837 (2.60%)	-	-	Tinea cruris	1,971 (1.17%)
Tinea pedis	8,888 (5.66%)	Disorder of skin	5,699 (1.62%)	Pain in limb	4,213 (1.25%)	Essential hypertension	1,729 (2.44%)	-	-	Skin lesion	1,473 (0.87%)
Tinea corporis	6,455 (4.11%)	Hypercholesterolemia	4,572 (1.30%)	Erysipelas	3,569 (1.06%)	Superficial mycosis	1,684 (2.38%)	-	-	Tinea corporis	1,419 (0.84%)
Type 2 diabetes mellitus	5,023 (3.20%)	Hypertensive disorder	3,637 (1.04%)	Type 2 diabetes mellitus	3,159 (0.94%)	Dystrophia unguium	1,331 (1.88%)	-	-	Pityriasis versicolor	1,147 (0.68%)
1 year prior to the index date											

NAJS	n (%)	DK-DHR	n (%)	FinOMOP-THL	n (%)	IQVIA DA Germany	n (%)	SIDIAP	n (%)	CPRD GOLD	n (%)
Essential hypertension	57,766 (36.81%)	Mycosis	143,816 (40.99%)	Essential hypertension	35,308 (10.49%)	Essential hypertension	6,956 (9.83%)	Common cold	14,255 (9.70%)	Onychomycosis	21,031 (12.48%)
Inflammatory dermatosis	36,736 (23.41%)	Pain	106,564 (30.37%)	Onychomycosis due to dermatophyte	32,358 (9.62%)	Melanocytic nevus	6,583 (9.30%)	Onychomycosis due to dermatophyte	10,185 (6.93%)	Eruption	20,723 (12.29%)
Dermatophytosis	35,423 (22.57%)	Onychomycosis	80,364 (22.90%)	Pain in limb	27,562 (8.19%)	Inflammatory dermatosis	5,369 (7.59%)	Traumatic or non-traumatic injury	9,283 (6.32%)	Cough	12,873 (7.64%)
Pain in spine	31,659 (20.18%)	Eczema	67,883 (19.35%)	Tinea pedis	25,501 (7.58%)	Illness	4,671 (6.60%)	Urinary tract infectious disease	8,030 (5.46%)	Tinea pedis	10,829 (6.42%)
Superficial mycosis	31,181 (19.87%)	Tinea pedis	64,058 (18.26%)	Acute upper respiratory infection	24,485 (7.28%)	Onychomycosis due to dermatophyte	37,911 (53.58%)	Inflammatory dermatosis	7,938 (5.40%)	Onychomycosis due to dermatophyte	9,189 (5.45%)
Onychomycosis due to dermatophyte	22,527 (14.36%)	Dermatophytosis	47,487 (13.53%)	Type 2 diabetes mellitus	21,521 (6.40%)	Acute upper respiratory infection	4,015 (5.67%)	Low back pain	7,928 (5.39%)	Dermal mycosis	8,459 (5.02%)
Dental caries	20,787 (13.25%)	Hypercholesterolemia	41,945 (11.95%)	Joint pain	20,700 (6.15%)	Tinea corporis	3,612 (5.11%)	Mycosis	6,366 (4.33%)	Dermatophytosis	7,413 (4.40%)
Cystitis	19,521 (12.44%)	Dermal mycosis	34,280 (9.77%)	Open wound	15,759 (4.68%)	Dermatophytosis	3,472 (4.91%)	Acute pharyngitis	6,069 (4.13%)	Asthma not limiting activities	6,382 (3.79%)
Acute upper respiratory infection	17,800 (11.34%)	Disorder of skin	30,879 (8.80%)	Low back pain	14,712 (4.37%)	Dystrophia unguium	3,420 (4.83%)	Abdominal pain	5,851 (3.98%)	Asthma not disturbing sleep	6,375 (3.78%)
Conjunctivitis	17,506 (11.16%)	Esophageal reflux finding	30,227 (8.61%)	Atrial arrhythmia	13,665 (4.06%)	Mycosis	3,133 (4.43%)	Gastrointestinal infection	5,206 (3.54%)	Pain of knee region	5,714 (3.39%)

NAJS = Croatian National Public Health Information System, DK-DHR = Danish Data Health Registries, FinOMOP-THL = Finnish Care Register for Health Care, IQVIA DA Germany = IQVIA Disease Analyzer Germany, SIDIAP = Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària, CPRD GOLD = Clinical Practice Research Datalink GOLD, n (%) = number of individuals and corresponding proportion of cohort.

9.2.5. Disease resistance

No records of disease codes associated with resistance were identified in any of the six European data sources during the pre-specified time window of 6 months before and 6 months after terbinafine treatment initiation.

9.3. Treatment initiations, dose, and treatment duration

The median number of terbinafine exposures was one across most data sources (most individuals had a single exposure). Exceptions were observed in SIDIAP, where the median number of terbinafine exposures was two and most individuals had two to three exposures, and in CPRD GOLD, where the median remained one, but most individuals had one to two exposures (**Table 7**).

Median treatment duration (days exposed) for the initial treatment episode ranged from 28 days (IQR: 15–79) in CPRD GOLD, 30 days (IQR: 30–98) in DK-DHR and 30 days (IQR: 28–71) in IQVIA DA Germany, to 41 days (IQR: 31–74) in SIDIAP. The overall range was broad, with maximum duration exceeding 1,000 days in several data sources, reflecting either a small subset of individuals undergoing prolonged or repeated therapy due to other conditions or recording artefacts.

Initial daily dose and cumulative dose estimates for the initial episode varied substantially across data sources. The median initial daily dose was 250 mg in IQVIA DA Germany but was lower or highly variable in other sources (e.g., 10 mg in DK-DHR, 19.09 mg in SIDIAP, and 0.04 mg in CPRD GOLD). The median cumulative dose was highest in IQVIA DA Germany (7,000 mg), with wide variability across all data sources.

When stratified by indication (**Table 8**), similar patterns were observed. For superficial tinea infections, the median number of exposures was one, with median duration of initial treatment episodes ranging from 15 days (IQR: 7–28) in CPRD GOLD to 31 days (IQR: 31–40) in SIDIAP. Median initial daily dose ranged from 0.02 mg in CPRD GOLD to 250 mg in IQVIA DA Germany. For onychomycosis, treatment duration and initial daily dose were higher, with median durations ranging between 42 days (IQR: 28–85) in IQVIA DA Germany to 98 days (IQR: 98–98) in DK-DHR, and initial doses of approximately 250 mg in DK-DHR, IQVIA DA Germany, SIDIAP, and CPRD GOLD. Results for tinea infections of hair-bearing areas were limited, however available estimates indicated median treatment duration of 28 days (DK-DHR, CPRD GOLD) and median initial daily dose of 250 mg in both data sources.

When considering multiple treatment episodes, results were comparable to those observed for the initial episode only (**Table S1** and **Table S2** in **ANNEX IV**).

Table 7. Number of prescriptions, treatment duration, and dose (initial and cumulative) in terbinafine treatment initiators (initial episode), overall, by data source.

Variable name	Estimate name	NAJS	DK-DHR	FinOMOP-THL	IQVIA DA Germany	SIDIAP	CPRD GOLD
Number of subjects	N	156,916	350,877	336,449	70,753	146,994	168,567
Number of exposures	Median (q25–q75)	1 (1–1)	1 (1–1)	1 (1–1)	1 (1–1)	2 (2–3)	1 (1–2)
	Range (min–max)	1–97	1–118	1–124	1–46	1–78	1–243
Days exposed	Median (q25 - q75)	-	30 (30–98)	-	30 (28–71)	41 (31–74)	28 (15–79)
	Range (min–max)	1–1,497	1–2,301	-	1–1,944	1–2,983	1–2,427
Initial daily dose, milligram*	Median (q25 - q75)	0.00 (0.00–0.00)	10.00 (5.00–250.00)	-	250.00 (71.43–250.00)	19.09 (9.68–242.19)	0.04 (0.02–250.00)
	Range (min–max)	0.00–816.67	0.00–2,450.00	-	0.33–2,333.33	0.00–22,252.75	0.00–75,250.00
Cumulative dose, milligram*	Median (q25 - q75)	0.01 (0.01–0.02)	300.00 (150.00–24,500.00)	-	7,000.00 (3,500.00–10,500.00)	600.00 (280.00–10,000.00)	1.50 (0.30–20,500.00)
	Range (min–max)	0.00–220,500.00	0.00–738,500.00	-	9.99–458,500.00	0.00–2,331,000.00	0.00–2,107,000.00

NAJS = Croatian National Public Health Information System, DK-DHR = Danish Data Health Registries, FinOMOP-THL = Finnish Care Register for Health Care, IQVIA DA Germany = IQVIA Disease Analyzer Germany, SIDIAP = Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària, CPRD GOLD = Clinical Practice Research Datalink GOLD.
N = number of individuals, q25–q75 = 25th and 75th percentiles (interquartile range), min–max = minimum and maximum observed values.
* = There is heterogeneity in dose, as both topical and oral products were included.

Table 8. Number of prescriptions, treatment duration, and dose (initial and cumulative) in terbinafine treatment initiators (initial episode), stratified by indication, by data source.

Variable name	Estimate name	NAJS	DK-DHR	FinOMOP-THL	IQVIA DA Germany	SIDIAP	CPRD GOLD
Superficial tinea infections							
Number of subjects	N	16,993	63,762	29,652	12,188	11,395	11,36
Number of exposures	Median (q25–q75)	1 (1–1)	1 (1–1)	1 (1–1)	1 (1–1)	2 (2–2)	1 (1–1)
	Range (min–max)	1–97	1–19	1–100	1–38	1–70	1–27
Days exposed	Median (q25–q75)	–	30 (30–30)	–	30 (28–54)	31 (31–40)	15 (7–28)
	Range (min–max)	–	1–1,153	–	1-1,622	1–2,556	1–983
Cumulative dose, milligram*	Median (q25–q75)	0.01 (0.01–0.02)	150.00 (150.00–300.00)	–	7,000.00 (300.00–10,500.00)	300.00 (100.00–4,281.19)	0.30 (0.30–0.60)
	Range (min–max)	0–126,000.14	0–280,000.00	–	9.99–399,000.00	0–282,260.00	0.01–189,000.00
Initial daily dose, milligram*	Median (q25–q75)	0.00 (0.00–0.00)	5.00 (5.00–10.00)	–	250.00 (10.00–250.00)	18.67 (8.75–233.33)	0.02 (0.02–0.04)
	Range (min–max)	0–700.00	0–1,049.07	–	0.33–1,005.00	0–3,266.67	0–13,500.00
Onychomycosis							
Number of subjects	N	21,039	79,183	29,693	33,545	12,086	25,752
Number of exposures	Median (q25–q75)	1 (1–2)	1 (1–1)	1 (1–1)	1 (1–2)	2 (2–4)	2 (1–3)
	Range (min–max)	1–97	1–59	1–43	1–43	1–46	1–158

Variable name	Estimate name	NAJS	DK-DHR	FinOMOP-THL	IQVIA DA Germany	SIDIAP	CPRD GOLD
Days exposed	Median (q25–q75)	–	98 (98–98)	–	42 (28–85)	86 (43–118)	84 (49–154)
	Range (min–max)	–	2–2,301	–	2–1,875	1–2,649	1–2,427
Cumulative dose, milligram*	Median (q25–q75)	0.01 (0.01–3,500.02)	24,500.00 (24,500.00–24,500.00)	–	8,750.00 (7,000.00–10,650.00)	15,000.00 (7,000.00–22,500.00)	21,000.00 (14,000.00–38,250.00)
	Range (min–max)	0–220,500.00	0–539,000.00	–	9.99–451,500.00	0–661,500.00	0–763,000.00
Initial daily dose, milligram*	Median (q25–q75)	0.00 (0.00–116.67)	250.00 (250.00–250.00)	–	250.00 (250.00–250.00)	245.90 (235.29–247.25)	250.00 (250.00–250.00)
	Range (min–max)	0–816.67	0–1,633.33	–	0.33–2,333.33	0–6,758.62	0–25,500.00
Tinea infections of hair bearing areas							
Number of subjects	N	–	1,427	–	–	–	414
Number exposures	Median (q25–q75)	–	1 (1–1)	–	–	–	1 (1–1)
	Range (min–max)	–	1–6	–	–	–	1–8
Days exposed	Median (q25–q75)	–	28 (28–86)	–	–	–	28 (15–28)
	Range (min–max)	–	1–313	–	–	–	1–393
Cumulative dose, milligram*	Median (q25–q75)	–	7,000.00 (3,934.00–14,868.00)	–	–	–	3,500.00 (0.60–7,000.00)
	Range (min–max)	–	0–73,500.00	–	–	–	0.15–49,000.00
Initial daily dose, milligram*	Median (q25–q75)	–	250.00 (250.00–281.00)	–	–	–	250.00 (0.04–250.00)

Variable name	Estimate name	NAJS	DK-DHR	FinOMOP-THL	IQVIA DA Germany	SIDIAP	CPRD GOLD
	Range (min–max)	–	0–562.00	–	–	–	0.01–2,000.02

NAJS = Croatian National Public Health Information System, DK-DHR = Danish Data Health Registries, FinOMOP-THL = Finnish Care Register for Health Care, IQVIA DA Germany = IQVIA Disease Analyzer Germany, SIDIAP = Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària, CPRD GOLD = Clinical Practice Research Datalink GOLD.
N = number of individuals, q25–q75 = 25th and 75th percentiles (interquartile range), min–max = minimum and maximum observed values.
* = There is heterogeneity in dose, as both topical and oral products were included.

9.4. Treatment patterns

In the 180-, 90-, and 30-day windows prior to terbinafine initiation, exposure to antifungal agents was observed but declined as the index date approached (**Table 9**). Topical antifungals were most frequent in the 180-day window, up to 17.72% in CPRD GOLD and 16.69% in SIDIAP, decreasing to 9.16% and 10.68%, respectively, at 30 days prior to terbinafine initiation. The most commonly used topical agents included clotrimazole, ciclopirox, and miconazole, with notable variability across data sources. For example, within the 180-day window prior to terbinafine initiation, clotrimazole use ranged from 0.22% in CPRD GOLD and 1.66% in IQVIA DA Germany to 8.45% in NAJS, with no clotrimazole users identified in FinOMOP-THL. Ciclopirox use was observed in IQVIA DA Germany (4.71%) and SIDIAP (6.58%), while miconazole use ranged from 0.18% in FinOMOP-THL to 4.09% in NAJS. Systemic antifungal use prior to initiation was consistently low (<3% across all windows), primarily involving fluconazole and itraconazole. Antibiotic use was common in the pre-index period, particularly systemic antibiotics, which reached 47.7% in NAJS within the 180-day window.

In the 180-day post-index period, antifungal exposure increased substantially compared with the pre-index windows, reflecting treatment initiated at the index date and subsequent follow-up therapies. Topical antifungal use ranged widely across data sources, from 21.32% in FinOMOP-THL to 95.21% in NAJS, with topical terbinafine recorded as the predominant agent in most settings. Systemic antifungal use after initiation was also frequent, ranging from 18.88% in NAJS to 84.54% in IQVIA DA Germany, with systemic terbinafine representing the majority of post-index systemic treatments. Use of alternative systemic agents, including fluconazole and itraconazole, remained low overall but was observed across most data sources.

The majority of patients initiated treatment with terbinafine as monotherapy, either cutaneous or systemic, with notable variation across data sources (**Figures 13–18**). Cutaneous terbinafine was the predominant first-line treatment in NAJS (77.87%), DK-DHR (50.23%), and SIDIAP (49.29%), while systemic terbinafine accounted for the majority of first-line exposure in IQVIA DA Germany (70.45%), FinOMOP-THL (54.93%), and CPRD GOLD (50.70%). Combination therapy, defined as the concurrent use of terbinafine with other antifungal agents, was observed in a minority of patients as the first-line. The most frequent combinations involved topical terbinafine administered alongside other topical antifungals, such as clotrimazole, ciclopirox, miconazole, or amorolfine. Systemic terbinafine was combined with topical antifungals, such as cutaneous terbinafine, clotrimazole, miconazole, amorolfine, or ciclopirox.

Across all data sources, a substantial proportion of individuals followed pathways from initial terbinafine use to second-line or subsequent antifungal therapies (**Figures 13–18**). Although these later treatment pathways were numerous, each individual pathway occurred at a low frequency. As a result, the overall proportion of individuals progressing beyond initial terbinafine therapy was substantial, but the specific pathways taken were highly heterogeneous, with no single second-line pathway consistently observed across data sources. In NAJS, the most common pathways originating from cutaneous terbinafine involved cutaneous antifungals, most frequently clotrimazole (8.12%), miconazole (3.41%), and amorolfine (0.83%). In DK-DHR, individuals initiating cutaneous terbinafine most commonly followed pathways to cutaneous miconazole/hydrocortisone (5.23%), ketoconazole (2.21%), and miconazole (1.45%). Among systemic terbinafine initiators, the pathways most frequently led to cutaneous miconazole/hydrocortisone (2.81%) and ketoconazole (1.59%). In FinOMOP-THL, among systemic terbinafine initiators, the most frequent systemic-to-systemic pathways were to fluconazole (2.00%) and itraconazole (1.14%). Pathways from cutaneous terbinafine to systemic terbinafine occurred in 1.12% of the included individuals. In IQVIA DA Germany, pathways originating from systemic terbinafine initiation most commonly led to cutaneous

ciclopirox (1.85%) and clotrimazole (0.96%), as well as systemic alternatives fluconazole (1.36%) and itraconazole (0.96%). In SIDIAP, the pathways from cutaneous terbinafine frequently proceeded to cutaneous clotrimazole (2.41%), ciclopirox (2.04%), and ketoconazole (1.75%). Among systemic terbinafine initiators, the most common pathway led to cutaneous ciclopirox (1.74%). In CPRD GOLD, the most common pathways from cutaneous terbinafine were to miconazole/hydrocortisone (2.09%) and to cutaneous clotrimazole (1.34%). For systemic terbinafine initiators, pathways most often led to miconazole/hydrocortisone (1.46%), cutaneous amorolfine (1.38%), and cutaneous clotrimazole (1.00%). A small subset of individuals followed more complex multi-step pathways consistent with additional lines of therapy, although these later pathways were highly heterogeneous and each occurred at very low frequency.

Treatment patterns stratified by clinical indication demonstrated distinct differences across groups (**Figures S1–S14** in **ANNEX V**). For superficial tinea infections, the majority of individuals received topical antifungal monotherapy, most commonly cutaneous terbinafine or clotrimazole, as first-line therapy. In contrast, systemic terbinafine monotherapy was the main first-line treatment for onychomycosis. Pathways involving combination and sequential antifungal therapies were observed in a substantial proportion of individuals initiating terbinafine across all indications. The diversity of observed pathways varied by data source, reflecting differences in clinical practice. Tinea barbae and tinea capitis were rarely observed as indications, and when present, treatment patterns resembled those for onychomycosis, with systemic terbinafine monotherapy or combinations with cutaneous products being most common. Comprehensive details of treatment pathways by indication are provided in the supplementary Sunburst plots and are available for further exploration in the interactive Shiny application (EUPAS1000000790).

Sankey plots are also available in the ShinyApp.

Table 9. Antifungal and antibiotic treatment in pre-specified intervals around the index date (terbinafine initiation) across six European data sources.

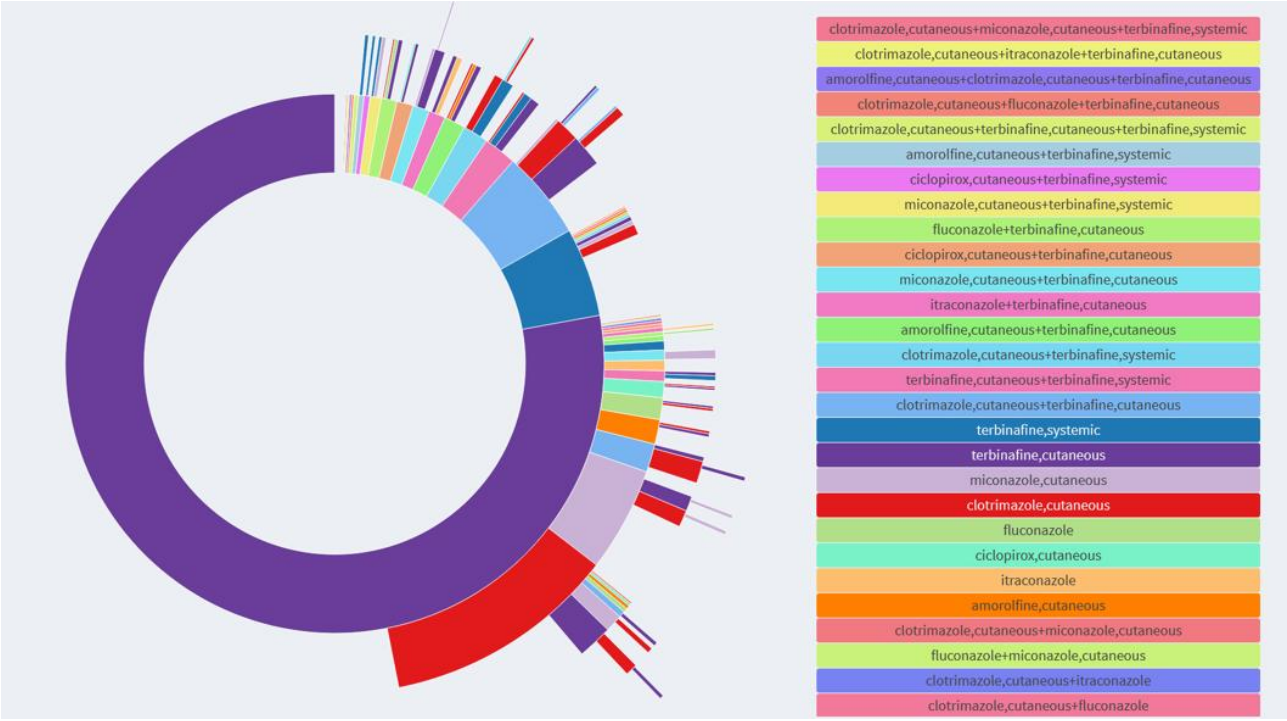
Variable name	CDM					
	NAJS	DK-DHR	FinOMOP-THL	IQVIA DA Germany	SIDIAP	CPRD GOLD
Number of subjects	156,916	350,877	336,449	70,753	146,994	168,567
180 days prior index date						
antifungals topical, n (%)	20,671 (13.17%)	36,788 (10.48%)	1,103 (0.33%)	5,378 (7.60%)	24,536 (16.69%)	29,862 (17.72%)
• amorolfine, n (%)	1,497 (0.95%)	1,116 (0.32%)	0 (0.00%)	823 (1.16%)	3,739 (2.54%)	4,000 (2.37%)
• benzoic acid salicylic acid	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
• ciclopirox, n (%)	1,218 (0.78%)	0 (0.00%)	0 (0.00%)	3,330 (4.71%)	9,670 (6.58%)	0 (0.00%)
• clotrimazole, n (%)	13,265 (8.45%)	779 (0.22%)	0 (0.00%)	1,176 (1.66%)	5,337 (3.63%)	8,957 (5.31%)
• ketoconazole, n (%)	176 (0.11%)	8,583 (2.45%)	93 (0.03%)	64 (0.09%)	5,094 (3.47%)	4,328 (2.57%)
• methylrosaniline, n (%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
• miconazole/hydrocortisone, n (%)	0 (0.00%)	22,043 (6.28%)	440 (0.13%)	0 (0.00%)	102 (0.07%)	13,172 (7.81%)
• miconazole, n (%)	6,420 (4.09%)	7,434 (2.12%)	619 (0.18%)	359 (0.51%)	3,518 (2.39%)	3,821 (2.27%)
• sulconazole, n (%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
antifungals systemic, n (%)	3,108 (1.98%)	8,159 (2.33%)	6,375 (1.89%)	1,398 (1.98%)	4,919 (3.35%)	4,388 (2.60%)
• fluconazole, n (%)	1,788 (1.14%)	7,300 (2.08%)	4,645 (1.38%)	741 (1.05%)	2,768 (1.88%)	3,472 (2.06%)
• griseofulvin, n (%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	6 (0.01%)	<5	63 (0.04%)
• itraconazole, n (%)	1,374 (0.88%)	945 (0.27%)	1,827 (0.54%)	668 (0.94%)	2,269 (1.54%)	929 (0.55%)
antibiotics topical, n (%)	12,525 (7.98%)	330 (0.09%)	0 (0.00%)	250 (0.35%)	3,245 (2.21%)	304 (0.18%)
antibiotics systemic, n (%)	74,791 (47.66%)	97,530 (27.80%)	102,152 (30.36%)	6,797 (9.61%)	42,118 (28.65%)	53,771 (31.90%)
90 days prior index date						
antifungals topical, n (%)	15,920 (10.15%)	28,012 (7.98%)	790 (0.23%)	4,066 (5.75%)	20,084 (13.66%)	23,044 (13.67%)

Variable name	CDM					
	NAJS	DK-DHR	FinOMOP-THL	IQVIA DA Germany	SIDIAP	CPRD GOLD
• amorolfine, n (%)	1,024 (0.65%)	717 (0.20%)	0 (0.00%)	530 (0.75%)	2,967 (2.02%)	2,700 (1.60%)
• benzoic acid salicylic acid, n (%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
• ciclopirox, n (%)	937 (0.60%)	0 (0.00%)	0 (0.00%)	2,568 (3.63%)	7,994 (5.44%)	0 (0.00%)
• clotrimazole, n (%)	10,205 (6.50%)	528 (0.15%)	0 (0.00%)	902 (1.27%)	4,106 (2.79%)	6,381 (3.79%)
• ketoconazole, n (%)	126 (0.08%)	6,343 (1.81%)	75 (0.02%)	35 (0.05%)	4,191 (2.85%)	3,715 (2.20%)
• methylrosaniline, n (%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
• miconazole/hydrocortisone, n (%)	0 (0.00%)	16,670 (4.75%)	301 (0.09%)	0 (0.00%)	76 (0.05%)	9,999 (5.93%)
• miconazole, n (%)	4,763 (3.04%)	5,736 (1.63%)	442 (0.13%)	287 (0.41%)	2,655 (1.81%)	2,961 (1.76%)
• sulconazole, n (%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
antifungals systemic, n (%)	2,333 (1.49%)	5,342 (1.52%)	4,329 (1.29%)	1,065 (1.51%)	3,648 (2.48%)	3,143 (1.86%)
• fluconazole, n (%)	1,305 (0.83%)	4,748 (1.35%)	3,065 (0.91%)	592 (0.84%)	2,053 (1.40%)	2,452 (1.45%)
• griseofulvin, n (%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	5 (0.01%)	<5	56 (0.03%)
• itraconazole, n (%)	1,053 (0.67%)	630 (0.18%)	1,314 (0.39%)	474 (0.67%)	1,661 (1.13%)	680 (0.40%)
antibiotics topical, n (%)	8,708 (5.55%)	213 (0.06%)	0 (0.00%)	171 (0.24%)	2,140 (1.46%)	175 (0.10%)
antibiotics systemic, n (%)	54,245 (34.57%)	65,640 (18.71%)	71,031 (21.11%)	4,374 (6.18%)	28,389 (19.31%)	37,011 (21.96%)
30 days prior index date						
antifungals topical, n (%)	10,989 (7.00%)	19,513 (5.56%)	533 (0.16%)	2,523 (3.57%)	15,705 (10.68%)	15,441 (9.16%)
• amorolfine, n (%)	573 (0.37%)	440 (0.13%)	0 (0.00%)	249 (0.35%)	2,423 (1.65%)	1,656 (0.98%)
• benzoic acid salicylic acid, n (%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
• ciclopirox, n (%)	618 (0.39%)	0 (0.00%)	0 (0.00%)	1,638 (2.32%)	6,474 (4.40%)	0 (0.00%)
• clotrimazole, n (%)	7,028 (4.48%)	327 (0.09%)	0 (0.00%)	548 (0.77%)	2,760 (1.88%)	3,847 (2.28%)

Variable name	CDM					
	NAJS	DK-DHR	FinOMOP-THL	IQVIA DA Germany	SIDIAP	CPRD GOLD
• ketoconazole, n (%)	99 (0.06%)	4,115 (1.17%)	50 (0.01%)	17 (0.02%)	3,270 (2.22%)	3,097 (1.84%)
• methylrosaniline, n (%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
• miconazole/hydrocortisone, n (%)	0 (0.00%)	11,476 (3.27%)	197 (0.06%)	0 (0.00%)	52 (0.04%)	6,161 (3.65%)
• miconazole, n (%)	3,253 (2.07%)	4,160 (1.19%)	305 (0.09%)	218 (0.31%)	1,891 (1.29%)	1,977 (1.17%)
• sulconazole, n (%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
antifungals systemic, n (%)	1,535 (0.98%)	2,685 (0.77%)	2,698 (0.80%)	562 (0.79%)	2,473 (1.68%)	1,938 (1.15%)
• fluconazole, n (%)	873 (0.56%)	2,345 (0.67%)	1,854 (0.55%)	367 (0.52%)	1,397 (0.95%)	1,488 (0.88%)
• griseofulvin, n (%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	<5	<5	38 (0.02%)
• itraconazole, n (%)	670 (0.43%)	347 (0.10%)	869 (0.26%)	193 (0.27%)	1,101 (0.75%)	421 (0.25%)
antibiotics topical, n (%)	5,478 (3.49%)	121 (0.03%)	0 (0.00%)	108 (0.15%)	1,245 (0.85%)	80 (0.05%)
antibiotics systemic, n (%)	33,840 (21.57%)	36,975 (10.54%)	44,337 (13.18%)	2,314 (3.27%)	15,486 (10.54%)	20,291 (12.04%)
180 days post index date						
antifungals topical, n (%)	149,404 (95.21%)	216,953 (61.83%)	71,718 (21.32%)	25,115 (35.50%)	111,989 (76.20%)	101,603 (60.28%)
• amorolfine, n (%)	5,573 (3.55%)	7,482 (2.13%)	0 (0.00%)	3,092 (4.37%)	7,267 (4.94%)	5,596 (3.32%)
• benzoic acid salicylic acid, n (%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
• ciclopirox, n (%)	5,118 (3.26%)	0 (0.00%)	0 (0.00%)	9,151 (12.93%)	17,249 (11.74%)	0 (0.00%)
• clotrimazole, n (%)	23,097 (14.72%)	1,071 (0.31%)	0 (0.00%)	2,637 (3.73%)	7,069 (4.81%)	7,358 (4.37%)
• ketoconazole, n (%)	144 (0.09%)	17,114 (4.88%)	201 (0.06%)	121 (0.17%)	10,410 (7.08%)	7,352 (4.36%)
• methylrosaniline, n (%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
• miconazole/hydrocortisone, n (%)	0 (0.00%)	27,871 (7.94%)	893 (0.27%)	0 (0.00%)	308 (0.21%)	11,401 (6.76%)
• miconazole, n (%)	8,506 (5.42%)	8,377 (2.39%)	1,155 (0.34%)	712 (1.01%)	5,392 (3.67%)	3,399 (2.02%)

Variable name	CDM					
	NAJS	DK-DHR	FinOMOP-THL	IQVIA DA Germany	SIDIAP	CPRD GOLD
• sulconazole, n (%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
• terbinafine, n (%)	142,133 (90.58%)	193,542 (55.16%)	69,965 (20.80%)	11,625 (16.43%)	88,914 (60.50%)	88,773 (52.67%)
antifungals systemic, n (%)	29,627 (18.88%)	169,808 (48.40%)	221,868 (65.94%)	59,815 (84.54%)	72,374 (49.25%)	88,061 (52.25%)
• fluconazole, n (%)	4,571 (2.91%)	9,044 (2.58%)	7,165 (2.13%)	984 (1.39%)	5,509 (3.75%)	4,497 (2.67%)
• griseofulvin, n (%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	9 (0.01%)	<5	149 (0.09%)
• itraconazole, n (%)	4,558 (2.90%)	2,464 (0.70%)	5,640 (1.68%)	722 (1.02%)	5,069 (3.45%)	2,157 (1.28%)
• terbinafine, n (%)	21,955 (13.99%)	162,815 (46.40%)	215,998 (64.20%)	59,663 (84.33%)	65,924 (44.86%)	83,979 (49.83%)

NAJS = Croatian National Public Health Information System, DK-DHR = Danish Data Health Registries, FinOMOP-THL = Finnish Care Register for Health Care, IQVIA DA Germany = IQVIA Disease Analyzer Germany, SIDIAP = Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària, CPRD GOLD = Clinical Practice Research Datalink GOLD.
*n = number of individuals.



a) Top 10 drug combinations

Id	Line	Drug combinations	Percentage	Frequency
1	1	terbinafine,cutaneous	77.87%	110,434
2	1	terbinafine,systemic	5.34%	7,571
3	1	clotrimazole,cutaneous+terbinafine,cutaneous	5.30%	7,516
4	1	terbinafine,cutaneous+terbinafine,systemic	1.97%	2,792
5	1	amorolfine,cutaneous+terbinafine,cutaneous	1.28%	1,818
6	1	ciclopirox,cutaneous+terbinafine,cutaneous	0.98%	1,396
7	1	clotrimazole,cutaneous+terbinafine,systemic	1.53%	2,169
8	1	fluconazole+terbinafine,cutaneous	0.93%	1,323
9	1	itraconazole+terbinafine,cutaneous	1.01%	1,429
10	1	miconazole,cutaneous+terbinafine,cutaneous	1.00%	1,419

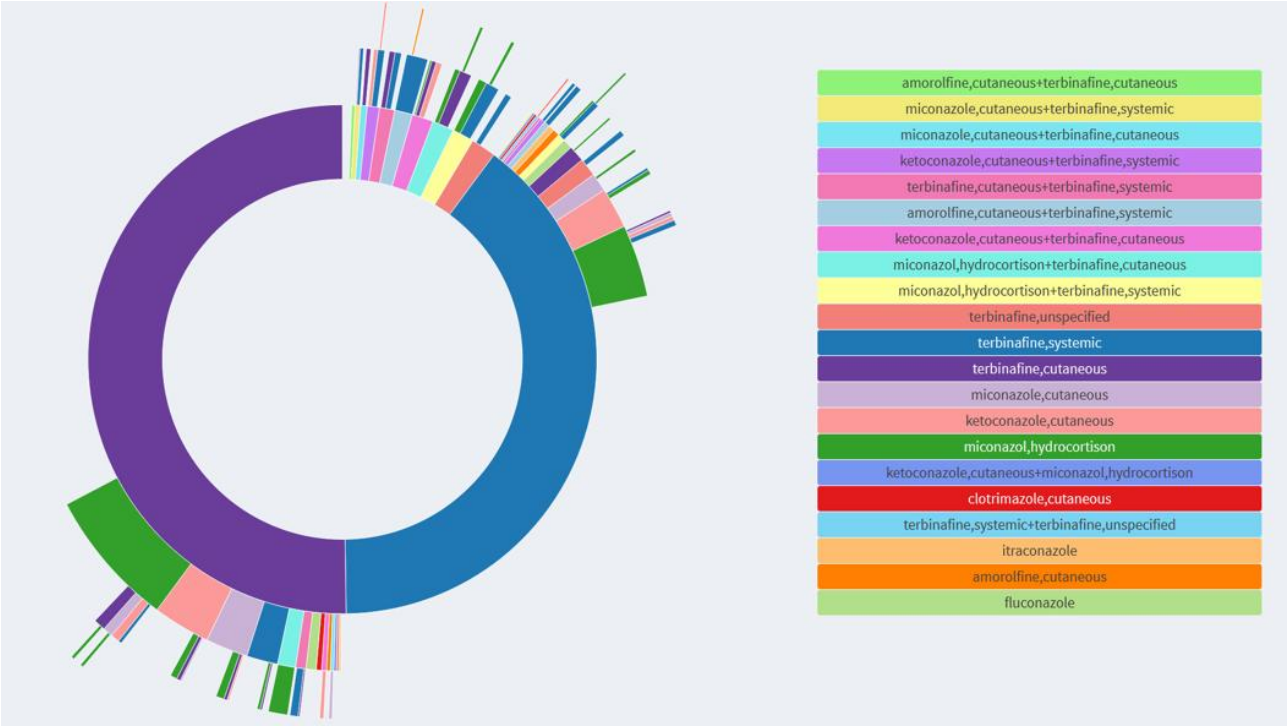
b) Top 10 treatment pathways

Id	Treatment pathway	Percentage	Frequency
1	terbinafine,cutaneous	53.11%	75,318
2	terbinafine,cutaneous-clotrimazole,cutaneous	8.12%	11,514
3	terbinafine,systemic	3.54%	5,022
4	terbinafine,cutaneous-miconazole,cutaneous	3.41%	4,837
5	clotrimazole,cutaneous+terbinafine,cutaneous	2.17%	3,071
6	clotrimazole,cutaneous+terbinafine,cutaneous-terbinafine,cutaneous	0.94%	1,337
7	terbinafine,cutaneous+terbinafine,systemic	0.87%	1,235
8	terbinafine,cutaneous-amorolfine,cutaneous	0.83%	1,184

Id	Treatment pathway	Percentage	Frequency
9	clotrimazole,cutaneous+terbinafine,cutaneous-clotrimazole,cutaneous	0.8%	1,134
10	terbinafine,cutaneous-clotrimazole,cutaneous-terbinafine,cutaneous	0.8%	1,134

Figure 13. Sunburst plot of treatment pathways following terbinafine initiation in NAJS.

The sunburst plot visualises treatment sequences: the inner circle represents first-line treatments and outer segments represent subsequent lines of therapy. Segment size is proportional to the number of individuals in each pathway. Colours correspond to specific treatments, as shown in the legend. The accompanying tables provides detailed counts and percentages for top 10 drug combinations in first-line (a) and top 10 treatment pathways (b). The complete set of drug combinations (a) and treatment pathways (b) is available in the ShinyApp at EUPAS1000000790. "Line" refers to the position in the treatment sequence (e.g., first-line, second-line). Percentage column represents the proportion of the study cohort initiating that drug/drug combination (a) or treatment pathway (b) and frequency column shows the number of individuals on drug/drug combination (a) or following each pathway (b). Treatment pathways (b) were derived using an algorithm that groups prescriptions into treatment episodes based on predefined input parameters. The "+" symbol in a pathway indicates concurrent prescriptions considered part of the same treatment episode (combination therapy), while the "–" symbol represents a switch from one regimen to another. NAJS = Croatian National Public Health Information System.



a) Top 10 drug combinations

Id	Line	Drug combinations	Percentage	Frequency
1	1	terbinafine,cutaneous	50.23%	167,935
2	1	terbinafine,systemic	39.61%	132,434
3	1	terbinafine,unspecified	1.58%	5,298
4	1	amorolfine,cutaneous+terbinafine,systemic	1.14%	3,812
5	1	ketoconazole,cutaneous+terbinafine,cutaneous	1.35%	4,511
6	1	miconazol,hydrocortison+terbinafine,systemic	1.39%	4,662
7	1	miconazol,hydrocortison+terbinafine,cutaneous	1.38%	4,603
8	1	terbinafine,cutaneous+terbinafine,systemic	0.97%	3,244
9	1	ketoconazole,cutaneous+terbinafine,systemic	0.77%	2,570
10	1	miconazole,cutaneous+terbinafine,cutaneous	0.41%	1,386

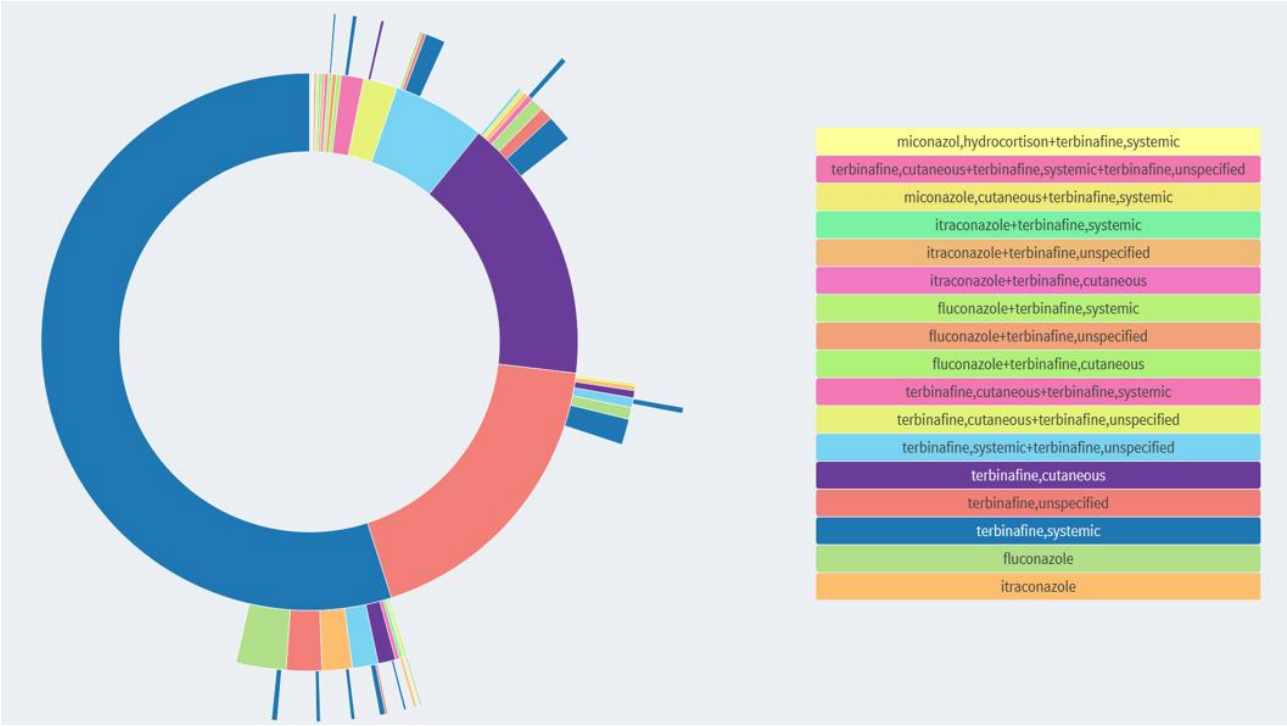
b) Top 10 treatment pathways

Id	Treatment pathway	Percentage	Frequency
1	terbinafine,cutaneous	32.70%	109,327
2	terbinafine,systemic	28.03%	93,689
3	terbinafine,cutaneous-miconazol,hydrocortison	5.23%	17,489
4	terbinafine,systemic-miconazol,hydrocortison	2.81%	9,398
5	terbinafine,cutaneous-ketoconazole,cutaneous	2.21%	7,380
6	terbinafine,systemic-ketoconazole,cutaneous	1.59%	5,329
7	terbinafine,cutaneous-miconazole,cutaneous	1.45%	4,834

Id	Treatment pathway	Percentage	Frequency
8	terbinafine,cutaneous-terbinafine,systemic	1.15%	3,833
9	terbinafine,unspecified	1.03%	3,450
10	amorolfine,cutaneous+terbinafine,systemic-terbinafine,systemic	0.78%	2,596

Figure 14. Sunburst plot of treatment pathways following terbinafine initiation in DK-DHR.

The sunburst plot visualises treatment sequences: the inner circle represents first-line treatments and outer segments represent subsequent lines of therapy. Segment size is proportional to the number of individuals in each pathway. Colours correspond to specific treatments, as shown in the legend. The accompanying tables provides detailed counts and percentages for top 10 drug combinations in first-line (a) and top 10 treatment pathways (b). The complete set of drug combinations (a) and treatment pathways (b) is available in the ShinyApp at EUPAS1000000790. "Line" refers to the position in the treatment sequence (e.g., first-line, second-line). Percentage column represents the proportion of the study cohort initiating that drug/drug combination (a) or treatment pathway (b) and frequency column shows the number of individuals on drug/drug combination (a) or following each pathway (b). Treatment pathways (b) were derived using an algorithm that groups prescriptions into treatment episodes based on predefined input parameters. The "+" symbol in a pathway indicates concurrent prescriptions considered part of the same treatment episode (combination therapy), while the "–" symbol represents a switch from one regimen to another. DK-DHR = Danish Data Health Registries.



a) Top 10 drug combinations

Id	Line	Drug combinations	Percentage	Frequency
1	1	terbinafine,systemic	54.93%	182,073
2	1	terbinafine,unspecified	18.20%	60,334
3	1	terbinafine,cutaneous	16.02%	53,099
4	1	terbinafine,systemic+terbinafine,unspecified	5.56%	18,443
5	1	terbinafine,cutaneous+terbinafine,unspecified	2.04%	6,763
6	1	terbinafine,cutaneous+terbinafine,systemic	1.35%	4,470
7	1	fluconazole+terbinafine,cutaneous	0.28%	924
8	1	fluconazole+terbinafine,unspecified	0.26%	864
9	1	itraconazole+terbinafine,cutaneous	0.21%	697
10	1	itraconazole+terbinafine,unspecified	0.20%	652

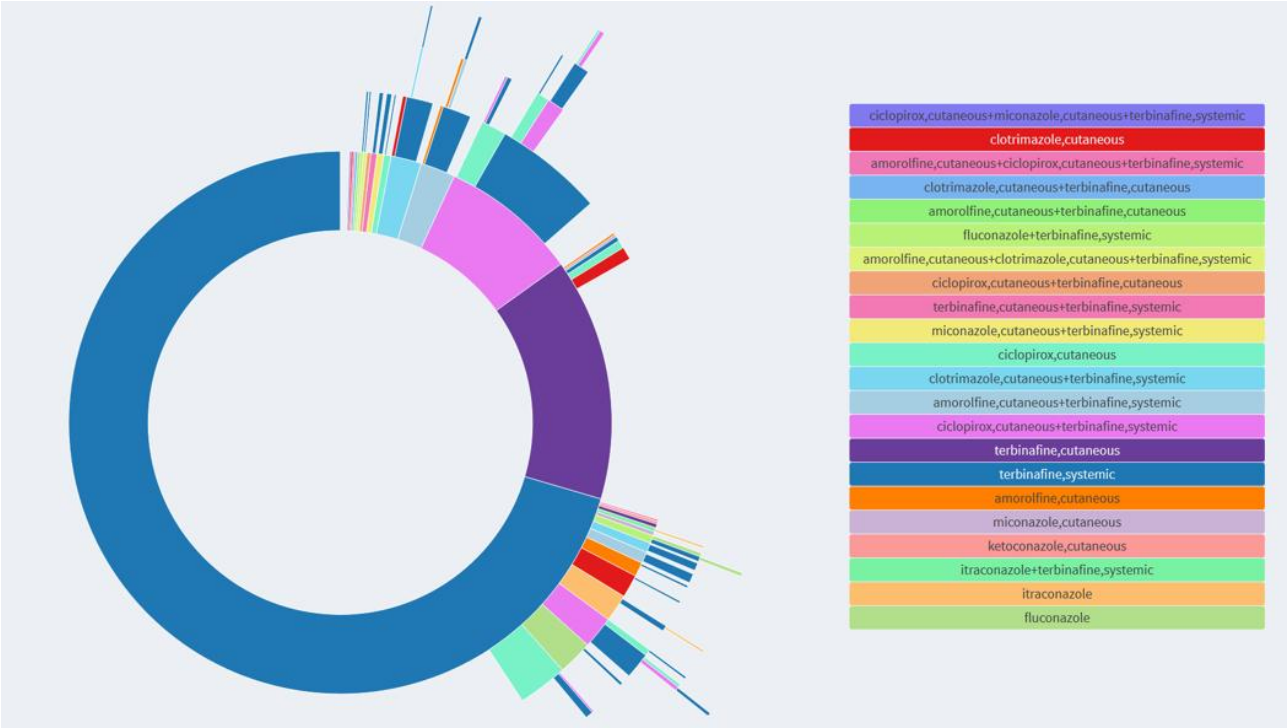
b) Top 10 treatment pathways

Id	Treatment pathway	Percentage	Frequency
1	terbinafine,systemic	46.40%	153,815
2	terbinafine,unspecified	15.01%	49,767
3	terbinafine,cutaneous	12.45%	41,255
4	terbinafine,systemic+terbinafine,unspecified	4.10%	13,584
5	terbinafine,systemic-fluconazole	2.00%	6,619
6	terbinafine,cutaneous+terbinafine,unspecified	1.64%	5,439
7	terbinafine,systemic-terbinafine,unspecified	1.42%	4,723
8	terbinafine,systemic-itraconazole	1.14%	3,779

Id	Treatment pathway	Percentage	Frequency
9	terbinafine,cutaneous-terbinafine,systemic	1.12%	3,725
10	terbinafine,unspecified-terbinafine,systemic	1.09%	3,629

Figure 15. Sunburst plot of treatment pathways following terbinafine initiation in FinOMOP-THL.

The sunburst plot visualises treatment sequences: the inner circle represents first-line treatments and outer segments represent subsequent lines of therapy. Segment size is proportional to the number of individuals in each pathway. Colours correspond to specific treatments, as shown in the legend. The accompanying tables provides detailed counts and percentages for top 10 drug combinations in first-line (a) and top 10 treatment pathways (b). The complete set of drug combinations (a) and treatment pathways (b) is available in the ShinyApp at EUPAS1000000790. "Line" refers to the position in the treatment sequence (e.g., first-line, second-line). Percentage column represents the proportion of the study cohort initiating that drug/drug combination (a) or treatment pathway (b) and frequency column shows the number of individuals on drug/drug combination (a) or following each pathway (b). Treatment pathways (b) were derived using an algorithm that groups prescriptions into treatment episodes based on predefined input parameters. The "+" symbol in a pathway indicates concurrent prescriptions considered part of the same treatment episode (combination therapy), while the "–" symbol represents a switch from one regimen to another. FinOMOP-THL = Finnish Care Register for Health Care.



a) Top 10 drug combinations

Id	Line	Drug combinations	Percentage	Frequency
1	1	terbinafine,systemic	70.45%	46,566
2	1	terbinafine,cutaneous	14.46%	9,558
3	1	ciclopirox,cutaneous+terbinafine,systemic	8.19%	5,413
4	1	amorolfine,cutaneous+terbinafine,systemic	2.07%	1,371
5	1	clotrimazole,cutaneous+terbinafine,systemic	1.82%	1,205
6	1	ciclopirox,cutaneous	0.42%	280
7	1	miconazole,cutaneous+terbinafine,systemic	0.40%	267
8	1	terbinafine,cutaneous+terbinafine,systemic	0.36%	240
9	1	ciclopirox,cutaneous+terbinafine,cutaneous	0.24%	158
10	1	amorolfine,cutaneous+terbinafine,cutaneous	0.16%	106

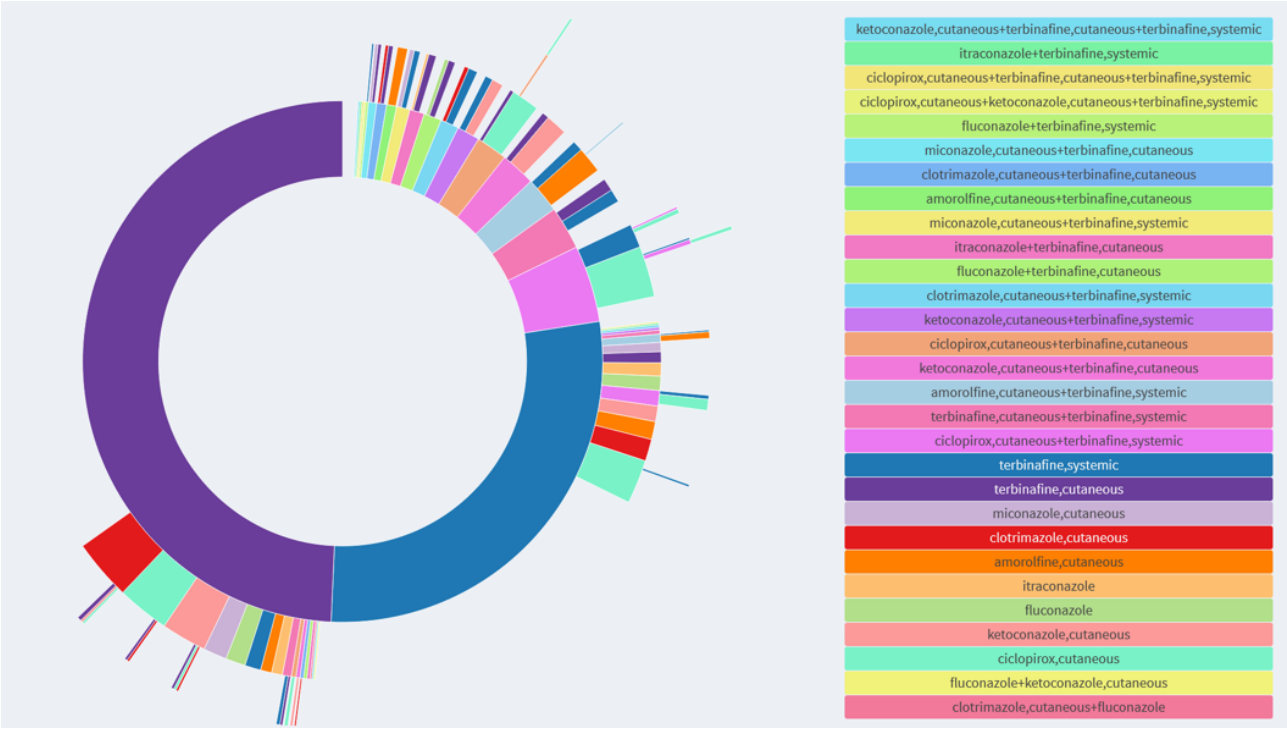
b) Top 10 treatment pathways

Id	Treatment pathway	Percentage	Frequency
1	terbinafine,systemic	59.21%	39,137
2	terbinafine,cutaneous	12.74%	8,420
3	ciclopirox,cutaneous+terbinafine,systemic-terbinafine,systemic	3.70%	2,444
4	terbinafine,systemic-ciclopirox,cutaneous	1.85%	1,220
5	ciclopirox,cutaneous+terbinafine,systemic	1.54%	1,017
6	terbinafine,systemic-fluconazole	1.36%	901
7	amorolfine,cutaneous+terbinafine,systemic-terbinafine,systemic	1.03%	681

Id	Treatment pathway	Percentage	Frequency
8	clotrimazole,cutaneous+terbinafine,systemic-terbinafine,systemic	1.02%	675
9	terbinafine,systemic-clotrimazole,cutaneous	0.96%	635
10	terbinafine,systemic-itraconazole	0.96%	635

Figure 16. Sunburst plot of treatment pathways following terbinafine initiation in IQVIA DA Germany.

The sunburst plot visualises treatment sequences: the inner circle represents first-line treatments and outer segments represent subsequent lines of therapy. Segment size is proportional to the number of individuals in each pathway. Colours correspond to specific treatments, as shown in the legend. The accompanying tables provides detailed counts and percentages for top 10 drug combinations in first-line (a) and top 10 treatment pathways (b). The complete set of drug combinations (a) and treatment pathways (b) is available in the ShinyApp at EUPAS1000000790. "Line" refers to the position in the treatment sequence (e.g., first-line, second-line). Percentage column represents the proportion of the study cohort initiating that drug/drug combination (a) or treatment pathway (b) and frequency column shows the number of individuals on drug/drug combination (a) or following each pathway (b). Treatment pathways (b) were derived using an algorithm that groups prescriptions into treatment episodes based on predefined input parameters. The "+" symbol in a pathway indicates concurrent prescriptions considered part of the same treatment episode (combination therapy), while the "–" symbol represents a switch from one regimen to another. IQVIA DA Germany = IQVIA Disease Analyzer Germany.



a) Top 10 drug combinations

Id	Line	Drug combinations	Percentage	Frequency
1	1	terbinafine,cutaneous	49.29%	63,010
2	1	terbinafine,systemic	28.17%	36,014
3	1	ciclopirox,cutaneous+terbinafine,systemic	4.76%	6,083
4	1	terbinafine,cutaneous+terbinafine,systemic	2.69%	3,437
5	1	ciclopirox,cutaneous+terbinafine,cutaneous	1.95%	2,488
6	1	amorolfine,cutaneous+terbinafine,systemic	2.22%	2,843
7	1	ketoconazole,cutaneous+terbinafine,cutaneous	2.17%	2,772
8	1	ketoconazole,cutaneous+terbinafine,systemic	1.42%	1,821
9	1	fluconazole+terbinafine,cutaneous	1.10%	1,412
10	1	amorolfine,cutaneous+terbinafine,cutaneous	0.62%	796

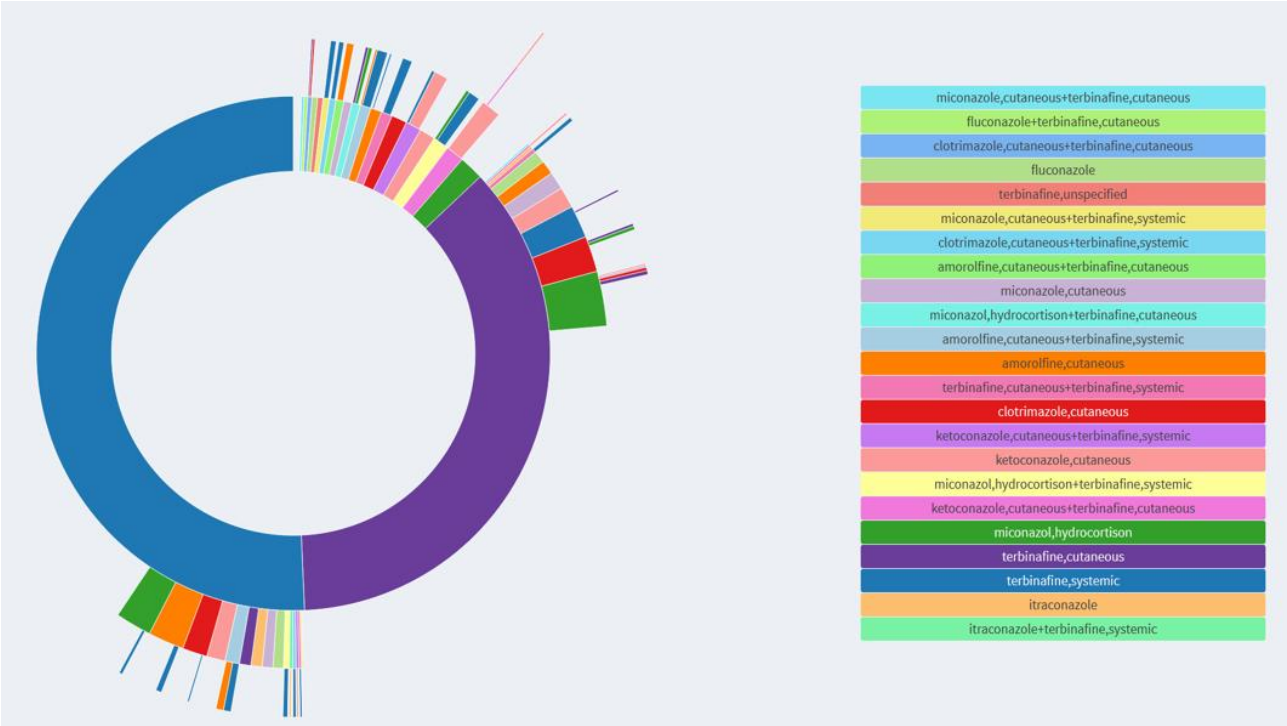
b) Top 10 treatment pathways

Id	Treatment pathway	Percentage	Frequency
1	terbinafine,cutaneous	34.80%	44,490
2	terbinafine,systemic	18.44%	23,575
3	terbinafine,cutaneous-clotrimazole,cutaneous	2.41%	3,078
4	terbinafine,cutaneous-ciclopirox,cutaneous	2.04%	2,608
5	ciclopirox,cutaneous+terbinafine,systemic-ciclopirox,cutaneous	1.91%	2,437
6	terbinafine,cutaneous-ketoconazole,cutaneous	1.75%	2,232
7	terbinafine,systemic-ciclopirox,cutaneous	1.74%	2,226

Id	Treatment pathway	Percentage	Frequency
8	terbinafine,cutaneous+terbinafine,systemic	1.13%	1,444
9	ciclopirox,cutaneous+terbinafine,cutaneous-ciclopirox,cutaneous	0.99%	1,266
10	amorolfine,cutaneous+terbinafine,systemic-amorolfine,cutaneous	0.96%	1,224

Figure 17. Sunburst plot of treatment pathways following terbinafine initiation in SIDIAP.

The sunburst plot visualises treatment sequences: the inner circle represents first-line treatments and outer segments represent subsequent lines of therapy. Segment size is proportional to the number of individuals in each pathway. Colours correspond to specific treatments, as shown in the legend. The accompanying tables provides detailed counts and percentages for top 10 drug combinations in first-line (a) and top 10 treatment pathways (b). The complete set of drug combinations (a) and treatment pathways (b) is available in the ShinyApp at EUPAS1000000790. "Line" refers to the position in the treatment sequence (e.g., first-line, second-line). Percentage column represents the proportion of the study cohort initiating that drug/drug combination (a) or treatment pathway (b) and frequency column shows the number of individuals on drug/drug combination (a) or following each pathway (b). Treatment pathways (b) were derived using an algorithm that groups prescriptions into treatment episodes based on predefined input parameters. The "+" symbol in a pathway indicates concurrent prescriptions considered part of the same treatment episode (combination therapy), while the "–" symbol represents a switch from one regimen to another. SIDIAP = Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària.



a) Top 10 drug combinations

Id	Line	Drug combinations	Percentage	Frequency
1	1	terbinafine,systemic	50.70%	71,126
2	1	terbinafine,cutaneous	36.34%	50,988
3	1	miconazol,hydrocortison	1.55%	2,171
4	1	ketoconazole,cutaneous	1.00%	1,398
5	1	clotrimazole,cutaneous	0.98%	1,377
6	1	ketoconazole,cutaneous+terbinafine,cutaneous	1.15%	1,618
7	1	ketoconazole,cutaneous+terbinafine,systemic	0.98%	1,380
8	1	amorolfine,cutaneous	0.69%	974
9	1	miconazol,hydrocortison+terbinafine,systemic	1.02%	1,431
10	1	amorolfine,cutaneous+terbinafine,systemic	0.68%	953

b) Top 10 treatment pathways

Id	Treatment pathway	Percentage	Frequency
1	terbinafine,systemic	40.58%	56,938
2	terbinafine,cutaneous	25.69%	36,042
3	terbinafine,cutaneous-miconazol,hydrocortison	2.09%	2,938
4	terbinafine,systemic-miconazol,hydrocortison	1.46%	2,049
5	terbinafine,systemic-amorolfine,cutaneous	1.38%	1,935
6	terbinafine,cutaneous-clotrimazole,cutaneous	1.34%	1,876
7	terbinafine,cutaneous-terbinafine,systemic	1.31%	1,843

Id	Treatment pathway	Percentage	Frequency
8	miconazol,hydrocortison	1.22%	1,717
9	terbinafine,systemic-clotrimazole,cutaneous	1.00%	1,400
10	terbinafine,cutaneous-ketoconazole,cutaneous	0.85%	1,186

Figure 18. Sunburst plot of treatment pathways following terbinafine initiation in CPRD GOLD.

The sunburst plot visualises treatment sequences: the inner circle represents first-line treatments and outer segments represent subsequent lines of therapy. Segment size is proportional to the number of individuals in each pathway. Colours correspond to specific treatments, as shown in the legend. The accompanying tables provides detailed counts and percentages for top 10 drug combinations in first-line (a) and top 10 treatment pathways (b). The complete set of drug combinations (a) and treatment pathways (b) is available in the ShinyApp at EUPAS1000000790. "Line" refers to the position in the treatment sequence (e.g., first-line, second-line). Percentage column represents the proportion of the study cohort initiating that drug/drug combination (a) or treatment pathway (b) and frequency column shows the number of individuals on drug/drug combination (a) or following each pathway (b). Treatment pathways (b) were derived using an algorithm that groups prescriptions into treatment episodes based on predefined input parameters. The "+" symbol in a pathway indicates concurrent prescriptions considered part of the same treatment episode (combination therapy), while the "–" symbol represents a switch from one regimen to another. CPRD GOLD = Clinical Practice Research Datalink GOLD.

10. DISCUSSION

10.1. Key results

Incidence of terbinafine use

Incidence rates of terbinafine use ranged from approximately 1 to more than 10 per 1,000 PYs, with clear seasonal peaks occurring during the warmer months. The highest incidence rates were observed in FinOMOP-THL and DK-DHR, frequently exceeding 8 to 10 per 1,000 PYs during peak months. Incidence rates in NAJS ranged between approximately 6 and 8 per 1,000 PYs, between approximately 4 to 6 per 1,000 PY in SIDIAP and CPRD GOLD, while IQVIA DA Germany consistently reported the lowest incidence rates, around 1 per 1,000 PYs, with a slight increase toward the end of the study period which might be related to the artefactual decrease in the denominator as described in **Section 10.2**. Overall, trends across data sources remained stable over time despite seasonal variability, with a transient decline observed in 2020, likely reflecting the impact of the COVID-19 pandemic.

Age-stratified analyses demonstrated a consistent gradient across all data sources, with older adults (≥66 years) exhibiting the highest incidence rates throughout the study period, followed by adults aged 19 to 65 years and children and adolescents aged 1 to 18 years. Sex-stratified analyses revealed higher incidence rates among males compared to females in most data sources, including DK-DHR, FinOMOP-THL, IQVIA DA Germany, and CPRD GOLD, whereas NAJS showed slightly higher incidence among females and SIDIAP exhibited negligible sex-related differences.

Characterisation of terbinafine users

Characterisation of terbinafine initiators included 1,230,556 individuals across all data sources. Median age varied from 47 years in DK-DHR and SIDIAP to 57 years in IQVIA DA Germany. Adults aged 19 to 65 years represented the majority of initiators up to 70%, while older adults accounted for up to 31% and children and adolescents for up to 13%, depending on the data source. Males predominated in most sources, with proportions ranging from 55% to 58%, except in NAJS, where females were more frequent, and SIDIAP, where females were slightly more common.

Dermatophytosis was the most commonly recorded diagnostic code for terbinafine use within the predefined time window, although prevalence varied substantially between data sources, ranging from 12% in SIDIAP to nearly 60% in IQVIA DA Germany. Among specific subtypes, onychomycosis (tinea unguium) was consistently the most common, representing up to 47% of initiators in IQVIA DA Germany. Other fungal infections were rare, generally below 3% in all data sources. A substantial proportion of initiators had unknown or missing indication codes, with variability across sources. Patterns were broadly consistent in the sensitivity analysis using longer time windows.

Comorbidity profiles at the index date were dominated by fungal infections and dermatological conditions, alongside chronic conditions such as essential hypertension and type 2 diabetes mellitus. One year prior to initiation, comorbidities shifted toward systemic conditions, including cardiovascular and musculoskeletal disorders. Dermatophytosis and onychomycosis diagnoses remained among the most common comorbidities in the year before treatment initiation, with dermatophytosis-related codes persisting at high proportions, consistent with the chronic and recurrent nature of these infections. No records of disease codes associated with terbinafine resistance were identified in any of the six European data sources during the pre-specified time window.

Treatment initiation, dose, and treatment duration

Across all data sources, most individuals received a single treatment episode with terbinafine. Exceptions were observed in SIDIAP, where the median was two exposures and most individuals had two to three episodes, and in CPRD GOLD, where the median remained one, but most individuals had one to two

exposures. Median treatment duration for the initial episode ranged from 28 days in CPRD GOLD, 30 days in DK-DHR and IQVIA DA Germany, to 41 days in SIDIAP.

Initial daily dose and cumulative dose estimates for the initial episode varied substantially across data sources. The median initial daily dose was 250 mg in IQVIA DA Germany, 10 mg in DK-DHR, 19.09 mg in SIDIAP, and 0.04 mg in CPRD GOLD. Median cumulative dose was highest in IQVIA DA Germany and FinOMOP-THL (7,000 mg), with wide variability across all sources. When stratified by indication, similar patterns were observed. For superficial tinea infections, the median duration ranged from 15 days in CPRD GOLD to 31 days in SIDIAP. For onychomycosis, treatment duration and cumulative dose were higher, with median durations ranging from 42 days in IQVIA DA Germany to 98 days in DK-DHR. Results for tinea infections of hair-bearing areas were limited but showed comparable trends. When considering multiple treatment episodes, findings were broadly consistent with those observed for the initial episode only.

Treatment patterns

Topical antifungals were most frequent in the 180-day window before initiation, with prevalence up to 17.7% in CPRD GOLD and 16.7% in SIDIAP, decreasing to approximately 9–11% at 30 days prior to terbinafine initiation. Commonly used topical agents included clotrimazole, ciclopirox, and miconazole, with notable variability across data sources. Systemic antifungal use prior to initiation was consistently low (<3% across all windows), primarily involving fluconazole and itraconazole. In the 180-day post-index window, antifungal use increased markedly, with topical and systemic terbinafine constituting the majority of post-index treatments across data sources.

The majority of patients initiated treatment with terbinafine as monotherapy, either cutaneous or systemic. Cutaneous terbinafine was the predominant first-line therapy in NAJS, DK-DHR, and SIDIAP, whereas systemic terbinafine accounted for most first-line exposure in IQVIA DA Germany, FinOMOP-THL, and CPRD GOLD. Combination therapy was observed in a minority of patients as the first line, most often involving topical terbinafine combined with other topical antifungals, such as clotrimazole, ciclopirox, or miconazole. A substantial proportion of individuals progressed from initial terbinafine to second-line of treatment across all data sources, although each specific pathway occurred at low frequency. The overall pattern was highly heterogeneous, with no single treatment pathway consistently observed. These pathways most often involved transitions to other topical antifungals for cutaneous terbinafine initiators and to fluconazole or itraconazole for systemic initiators, with notable variation by data source.

Treatment patterns stratified by clinical indication demonstrated distinct differences. For superficial tinea infections, topical antifungal monotherapy, most commonly cutaneous terbinafine or clotrimazole, was the predominant first-line therapy. In contrast, systemic terbinafine monotherapy was the main first-line treatment for onychomycosis. Tinea barbae and tinea capitis were rarely observed but treatment patterns resembled those for onychomycosis, with systemic terbinafine monotherapy or combinations with cutaneous products being most common.

10.2. Strengths and limitations of the research methods

Strengths

This study leveraged a large, diverse set of real-world data sources across multiple European countries, including registry-based and outpatient general practitioner care databases. The inclusion of six data sources, spanning Croatia, Denmark, Finland, Germany, Spain, and the United Kingdom, ensured broad geographic coverage. The longitudinal nature of data sources supported the assessment of treatment patterns over time. Additionally, the use of the OMOP CDM facilitated standardised data structuring, variable harmonisation, consistent cohort definitions, and analysis across data sources.

Limitations

This study was informed by routinely collected health care data from six European countries, which introduces several important considerations that may influence the interpretation of the findings. The findings reflect only the populations captured within these data sources and may not be generalisable to other countries or healthcare systems.

The observation period in IQVIA DA Germany is defined by the patient's last recorded healthcare encounter. This methodology impacts the individuals considered at risk (i.e., the individuals included in the denominator population) during the latest months of data, where healthy and/or non-frequent users of the healthcare system were not considered active. Consequently, the denominator used to calculate incidence rates of terbinafine in the population artefactually decreased whilst the incident users remained, increasing the incidence rates. To mitigate this, the incidence rate estimates for the last 6-months of available data were excluded. However, incidence estimates for 2024 may still be affected by this artefact.

Electronic health records are primarily designed for clinical purposes rather than research, and as such, may contain incomplete, inconsistent, or variably recorded information. Therefore, the documentation of comorbidities, necessary for patient-level characterisation, may vary across data sources. The actual clinical indication for prescribing terbinafine was not directly recorded in the data sources. Instead, proxy measures, based on diagnosis codes around the time of treatment initiation, were used. Consequently, the estimation of potential indications may be incomplete or imprecise as this might not be recorded in all patients.

The identification of tinea barbae and tinea capitis as specific indications for terbinafine use was limited by coding constraints. In International Classification of Diseases 10th revision (ICD-10), these conditions are represented by a single code (B35.0), which was mapped to the broader SNOMED concept of dermatophytosis during the ETL process in several data sources. This mapping approach reduced granularity and prevented precise differentiation of these subtypes across multiple data sources. As a result, stratified analyses for tinea barbae and tinea capitis could not be reliably performed, and findings for these indications should be interpreted with caution.

Some data sources may face challenges in reliably determining treatment duration due to documentation gaps. End-of-treatment dates were not consistently available, and when direct observation was not possible, imputation methods using fixed duration assumptions (aligned with OMOP CDM conventions) were applied during the ETL process. While this promoted consistency across sources, it may not fully captured true treatment variability and should be interpreted with caution. FinOMOP-THL and NAJS lack information on treatment duration and were therefore excluded from treatment duration-related analysis. FinOMOP-THL also lacks reliable information on dose and was therefore excluded from dose-related analysis. Additionally, dose heterogeneity should be noted, as data sources included both topical and oral products, which differ in formulation characteristics and resulted in variability in dose recording and comparability across sources.

A recorded prescription did not guarantee that the medication was dispensed or consumed. Therefore, assumptions of actual drug use have been made.

For DK-DHR, prescription data were only available until 30 September 2024. Consequently, monthly estimates for the remainder of the year are missing and the annual estimate is based on partial data capture and should be interpreted with caution.

Terbinafine is available over-the-counter (OTC). Since the study relied on healthcare databases and exclusively on individuals who seek medical care and received a recorded prescription, individuals with mild or self-managed dermatophytosis who opt for OTC terbinafine treatments were not captured, which may lead to underestimation of overall use, particularly for topical formulations. Terbinafine is available OTC in several countries included in this study. In Croatia, only the nail lacquer formulation is available OTC, while

tablets, gels, and creams require a prescription. In Denmark, topical terbinafine creams and ointments are generally not prescribed and are available OTC. In the United Kingdom, terbinafine creams, gels, sprays, and liquid solutions are available OTC, whereas oral tablets require a prescription. In Finland, terbinafine creams are available OTC, while systemic formulations require a prescription. In Germany, topical terbinafine products are not prescription-bound and can be purchased OTC, whereas systemic terbinafine requires a prescription. In Spain, terbinafine is primarily prescribed and reimbursed through the national health system; while some topical creams may be available OTC, they represent only a small proportion of overall use. According to the Spanish Agency of Medicines, only two OTC products containing terbinafine were available during the study period (one withdrawn in 2021), both topical and indicated solely for tinea pedis.

Disease resistance could not be assessed directly in this study because no specific codes for antifungal resistance were identified in any of the six European data sources during the predefined observation window. In many cases, suspected resistance may be managed by switching to an alternative antifungal agent rather than recording a resistance diagnosis. For example, clinicians may transition patients to another drug when treatment response is inadequate. Additionally, coding limitations exist in certain countries; for instance, Denmark does not implement ICD-10 U84 codes for antimicrobial resistance in its SKS classification, and resistance data are maintained in a separate registry (MiBA), which was not accessible for this study. These factors should be considered when interpreting the absence of resistance-related codes in the study findings.

10.3. Interpretation

This multi-country study provides real-world evidence on terbinafine use across six European healthcare systems. Incidence rates of terbinafine were broadly stable over time, with clear seasonal peaks during warmer months, reflecting the epidemiology of dermatophyte infections. The transient decline in 2020 likely corresponds to reduced healthcare utilisation during the COVID-19 pandemic. Higher incidence among older adults and males aligns with known risk factors for fungal infections, supporting the validity of these findings.

The characterisation of terbinafine initiators indicates demographic patterns consistent with clinical expectations, with adults comprising the majority of users and onychomycosis being the most common indication. However, the substantial proportion of missing or other indication codes across data sources underscores the need for cautious interpretation of indication-specific results.

The majority of patients initiated treatment with terbinafine as monotherapy, either cutaneous or systemic, with notable variation across data sources. Cutaneous terbinafine dominated first-line treatment in NAJS, DK-DHR, and SIDIAP, while systemic terbinafine was the predominant initial treatment in IQVIA DA Germany, FinOMOP-THL, and CPRD GOLD. Initiation patterns and dosing were broadly consistent with clinical guidelines, with topical terbinafine used mostly for superficial infections and systemic therapy for nail infections. Although median treatment durations and dose estimates varied across data sources, these differences likely reflect variations in prescribing practices, product availability, and data capture methods rather than true clinical divergence.

A substantial proportion of patients progressed to additional antifungal treatments after terbinafine initiation, indicating that second- and, less commonly, third-line and subsequent therapeutic adjustments form a routine part of real-world management. These treatments were highly heterogeneous, with each individual pathway occurring at low frequency and no consistent second-line regimen emerging across data sources. Among individuals initiating cutaneous terbinafine, pathways most commonly involved transitions to other topical antifungals such as clotrimazole, ciclopirox, miconazole, ketoconazole, or amorolfine. These topical-to-topical transitions are clinically coherent and may reflect adjustments in formulation, potency, or active ingredient to optimise symptom control or address slow resolution of superficial lesions.

Among those initiating systemic terbinafine, treatment pathways more often incorporated the transition to topical agents rather than alternative systemic therapies. True systemic-to-systemic transitions, to agents such as fluconazole or itraconazole, were relatively uncommon and did not converge on a consistent alternative across countries. This low and scattered use of systemic alternatives supports the inference that second-line systemic therapy is not routinely required. Instances in which systemic alternatives were used likely reflect individual clinical circumstances such as tolerability concerns, uncertainty in the causative organism, or atypical disease course.

A small proportion of patients exhibited more complex multi-step pathways suggestive of third-line therapy. These were highly heterogeneous and included a wide array of topical agents and occasional systemic alternatives. The absence of any clear clustering of these later pathways suggests that such cases represent either particularly persistent infections, recurrent episodes, or variability in individual prescribing practices.

Disease resistance could not be assessed directly in this study because no specific codes for antifungal resistance were identified in any of the six European data sources. This does not necessarily indicate the absence of resistance, as such information is rarely captured in structured fields and may not be routinely coded in clinical practice. In many cases, suspected resistance may be managed by switching to an alternative antifungal agent rather than recording a resistance diagnosis. For example, clinicians may transition patients from terbinafine to fluconazole, itraconazole, or other systemic or topical antifungals when treatment response is inadequate. Additionally, coding limitations exist in certain countries. These factors should be considered when interpreting the absence of resistance-related codes in the study findings.

10.4. Generalisability

While our study comprised data from 6 data sources across Europe, and covered primary care and registries, findings from this study are not to be generalised to other countries or data sources but only reflect the situation in the specific region and setting covered by the respective database.

11. CONCLUSION

This multi-country study provides comprehensive real-world evidence on terbinafine use across six European healthcare systems. Incidence rates were stable over time, with clear seasonal peaks reflecting the epidemiology of dermatophyte infections and a transient decline in 2020 likely associated with the COVID-19 pandemic. Treatment patterns generally aligned with clinical guidelines, with topical terbinafine used for superficial infections and systemic therapy for onychomycosis. Median treatment durations and doses were broadly consistent with recommended regimens, although variability across data sources suggested differences in prescribing practices, product availability, and data capture rather than true divergence in clinical care.

A substantial proportion of patients continued with additional antifungal treatment after terbinafine initiation, reflecting the heterogeneous and often stepwise management of dermatophyte infections in routine practice. Although each individual treatment pathway occurred at low frequency, their overall presence underscores the diversity of real-world clinical decision-making and possibly the need for individualised treatment in certain cases. No coded evidence of terbinafine resistance was identified; however, resistance may not be routinely documented as a clinical code and is often managed through therapeutic adjustments rather than diagnostic coding. Overall, these findings provide robust real-world evidence to inform regulatory assessment of terbinafine use in Europe.

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13. ANNEXES

ANNEX I. Description of data sources

Croatian 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. 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 Electronic Health Records (EHRs) 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. The CDM population comprises all publicly insured persons residing in Croatia starting in 2015. NAJS will provide data from 2017 onwards only, as prior data might include information on duplicated patients.

Danish Data Health Registries (DK-DHR), Denmark

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 and age in Danish health data due to mandatory reporting on all patients from birth to death, in all hospitals and medical clinics. Personal identification numbers enable linking of data across registers, capturing data on all individuals from birth or entry into the country until death or emigration, regardless of whether they have moved around the country. The high quality of Danish health data is attributed to standardisation, digitisation, and comprehensive documentation, which together enhance accuracy, consistency, and reliability, minimising potential for interpretation errors. 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 Pharmaceutical Sales, The National Cancer Register, The Cause of Death registry, the Laboratory Database (including coronavirus disease 2019 test results), and the Vaccination Registry (including COVID-19 vaccinations).

Finnish Care Register for Health Care (FinOMOP-THL), Finland

This database covers both public and private, primary, and specialised inpatient and outpatient health care encounters in Finland starting from 2011. The entire public sector and private inpatient encounters have been included since 2011, while private outpatient encounters, including occupational care, are included since 2020. The main content of the THL CDM is The Finnish Care Register for Health Care, which is a continuation of the former Hospital Discharge Register, which originally gathered data on patients discharged from hospitals. The Care Register has comprehensive data on the use of services and service users from Finnish public inpatient and outpatient primary and specialised care nationwide. Since 1998, the register has covered both public outpatient and inpatient specialised care and private inpatient care (TerveysHilmo). From 2011 the register has covered public primary care (AvoHilmo). From 2020 the register has covered private outpatient care and occupational care. In addition, the CDM also contains the vaccination data from the Finnish National Vaccination Register, the vaccination data from the Finnish National Vaccination Register, and COVID-19 test results from the Finnish National Infectious Diseases Register, which is maintained by THL. The CDM includes all the above-mentioned data sources and is limited to observation periods commencing after 1/1/2011. The National Population is used to form the

base population. This ensures up-to-date location (municipality of residence) of patients and complete death occurrences (although not the cause of death). Using the complete population as a basis for the person table also facilitates calculations on a population level, e.g., incidence rates. The current CDM population comprises all persons having been alive and residing in Finland since the beginning of 2011.

IQVIA Disease Analyzer Germany (IQVIA DA Germany), Germany

IQVIA Disease Analyzer (DA) Germany is a database of de-identified electronic medical records from specialised and primary general practitioner (GP) in Germany since 1992.[7] This dataset encompasses approximately 3% of all outpatient practices within Germany, ensuring a substantial representation of the national healthcare landscape. The sampling methods used for practice selection, taking into account physician's demographics, specialty focus, community size category and federal state location, were instrumental in constructing a database that accurately mirrors the diverse spectrum of healthcare providers in the country. Consequently, data within 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 diagnoses according to the International Classification of Diseases, 10th revision (ICD-10), and prescription records. 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. Data quality is assessed based on several criteria, including completeness of information and correctness (e.g., linkage between diagnosis and prescriptions).

No registration or approval is required for drug utilisation studies. As previously demonstrated, IQVIA DA Germany is suitable for pharmacoepidemiologic and pharmacoeconomic studies.[8, 9]

The Information System for Research on Primary Care (SIDIAP), Spain

The Information System for Research in Primary Care (SIDIAP) is a clinical database of anonymized patient records in Catalonia, Spain.[10] The Spanish public healthcare system covers more than 98% of the population, and more than two thirds of the Catalan population see their GP at least once a year. The computerisation of the primary care patient records of the Catalan Health Institute (CHI) was complete in 2005. SIDIAP was designed to provide a valid and reliable database of information from clinical records of patients registered in primary care centres for use in biomedical research. SIDIAP contains data of anonymized patients' healthcare records for nearly six million people (approximately 80% of the Catalan population) registered in 287 primary care practices throughout Catalonia since 2006. It includes data collected by health professionals during routine visits in primary care, including anthropometric measurements, clinical diagnoses (International Classification of Diseases 10th revision ICD-10), laboratory tests, prescribed and dispensed drugs, hospital referrals, demographic, and lifestyle information. It was previously shown that SIDIAP population is highly representative of the entire Catalan region in terms of geographic, age, and sex distributions. The high quality of these data has been previously documented, and SIDIAP has been successfully applied to epidemiological studies of key exposures and outcomes.[11] Quality checks to identify duplicate patient IDs are performed centrally at each SIDIAP database update. Checks for logical values and data harmonisation are performed. For biochemistry data, consistency for measurements taken in different laboratories is assessed, and unit conversion is undertaken when needed.

Clinical Practice Research Datalink GOLD (CPRD GOLD), The United Kingdom

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.[12] The source population is 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. GOLD contains data from all four UK constituent countries, and the current

regional distribution of its GP practices is 0.89% in England, 61.13% in Scotland,26.41% in Wales, and 11.57% in Northern Ireland (January 2025).[13]

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. GPs receive information about patient contacts with secondary care, but this information must be manually entered into the patient record and therefore, may be incomplete. GOLD has been assessed and found broadly representative of the UK general population in terms of age and sex.[12] 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.[14-16]

In terms of quality checks, the integrity, structure, and format of the data is reviewed. Collection-level validation ensures integrity by checking that data received from practices contain only expected data files and ensures that all data elements are of the correct type, length, and format. Duplicate records are identified and removed. Transformation-level validation checks for referential integrity between records ensure that there are no orphan records included in the database (for example, that all event records link to a patient), while research-quality-level validation covers the actual content of the data. CPRD provides a patient-level data quality metric in the form of a binary 'acceptability' flag. This is based on recording and internal consistency of key variables including date of birth, practice registration date and transfer out date.

ANNEX II. Additional information

DATA MANAGEMENT

All data sources have previously mapped their data to the OMOP common data model. This enables the use of standardised analytics and using DARWIN EU® tools across the network since the structure of the data and the terminology system is 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 standardised analytics wherever possible. Each data partner executed the study code against their data source containing patient-level data and then return the results (csv files) which will only contain aggregated data. The results from each of the contributing data sites were then be combined in tables and figures for the study report.

Data storage and protection

For this study, participants from various EU member states processed personal data from individuals which was collected in 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 are adhered to. In agreement with these regulations, rather than combining person level data and performing only a central analysis, local analyses were ran, which generate non-identifiable aggregate summary results.

The output files are stored in the DARWIN EU® Remote Research Environment (RRE). These output files did not contain any data that allow identification of subjects included in the study. The RRE implements further security measures to ensure a high level of stored data protection to comply with the local implementation of the General Data Protection Regulation (GDPR) (EU) 679/20161 in the various member states.

QUALITY CONTROL

General data source 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, it is expected that data partners will have run the OHDSI *DataQualityDashboard* tool (https://github.com/OHDSI/DataQualityDashboard). This tool provided 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

When defining cohorts for indications, a systematic search of possible codes for inclusion were identified using *CodelistGenerator* R package (https://github.com/darwin-eu/CodelistGenerator). This software allowed the user to define a search strategy and using this will then query the vocabulary tables of the

OMOP common data model so as to find potentially relevant codes. In addition, the *CohortDiagnostics* R package (https://github.com/OHDSI/CohortDiagnostics) was run if needed to assess the use of different codes across the data sources contributing to the study and identify any codes potentially omitted in error.

The study code was based on R packages to (1) estimate Incidence, (2) characterise participants and drug utilisation, and 3) describe Treatment Patterns using the OMOP common data model. These packages included numerous automated unit tests to ensure the validity of the codes, alongside software peer review and user testing. The R package was made publicly available via GitHub.

ANNEX III. Operational and reporting considerations

Table S1. List of medicines definitions.

Substance Name	Concept name	Class	ATC code	Concept ID	Include descendants
Terbinafine, cutaneous	terbinafine Topical Spray	Other antifungals for topical use	D01AE15	40102776	Yes
Terbinafine, cutaneous	terbinafine Topical Solution	Other antifungals for topical use	D01AE15	40102773	Yes
Terbinafine, cutaneous	terbinafine Topical Ointment	Other antifungals for topical use	D01AE15	42480974	Yes
Terbinafine, cutaneous	terbinafine Topical Gel	Other antifungals for topical use	D01AE15	40102772	Yes
Terbinafine, cutaneous	terbinafine Topical Cream	Other antifungals for topical use	D01AE15	40102767	Yes
Terbinafine, cutaneous	terbinafine Medicated Shampoo	Other antifungals for topical use	D01AE15	41298140	Yes
Terbinafine, systemic	terbinafine Oral Tablet	Antifungals for systemic use	D01BA02	40102776	Yes
Terbinafine, systemic	terbinafine Oral Suspension	Antifungals for systemic use	D01BA02	40102773	Yes
Terbinafine, systemic	terbinafine Oral Solution	Antifungals for systemic use	D01BA02	42480974	Yes
Terbinafine, systemic	terbinafine Oral Granules	Antifungals for systemic use	D01BA02	40102772	Yes
Terbinafine, systemic	terbinafine Oral Capsule	Antifungals for systemic use	D01BA02	40102767	Yes
Terbinafine, systemic	terbinafine Injectable Solution	Antifungals for systemic use	D01BA02	41298140	Yes
Terbinafine, unspecified	terbinafine	Antifungals	-	1741309	-
Ciclopirox, cutaneous	ciclopirox Topical Spray	Other antifungals for topical use	D01AE14	40823556	Yes
Ciclopirox, cutaneous	ciclopirox Topical Solution	Other antifungals for topical use	D01AE14	40095484	Yes
Ciclopirox, cutaneous	ciclopirox Topical Powder	Other antifungals for topical use	D01AE14	40095483	Yes
Ciclopirox, cutaneous	ciclopirox Topical Ointment	Other antifungals for topical use	D01AE14	35850522	Yes
Ciclopirox, cutaneous	ciclopirox Topical Lotion	Other antifungals for topical use	D01AE14	40095480	Yes
Ciclopirox, cutaneous	ciclopirox Topical Gel	Other antifungals for topical use	D01AE14	40095478	Yes
Ciclopirox, cutaneous	ciclopirox Topical Cream	Other antifungals for topical use	D01AE14	40095476	Yes
Ciclopirox, cutaneous	ciclopirox Medicated Shampoo	Other antifungals for topical use	D01AE14	40095474	Yes

Substance Name	Concept name	Class	ATC code	Concept ID	Include descendants
Methylrosaniline, cutaneous	gentian violet Topical Solution	Other antifungals for topical use	D01AE02	40043539	Yes
Methylrosaniline, cutaneous	Gentian Violet Topical Powder	Other antifungals for topical use	D01AE02	40729169	Yes
Methylrosaniline, cutaneous	Gentian Violet Topical Ointment	Other antifungals for topical use	D01AE02	21122641	Yes
Methylrosaniline, cutaneous	Gentian Violet Topical Cream	Other antifungals for topical use	D01AE02	36407278	Yes
Methylrosaniline, cutaneous	Gentian Violet Paint	Other antifungals for topical use	D01AE02	43296086	Yes
Methylrosaniline, cutaneous	Gentian Violet Medicated Shampoo	Other antifungals for topical use	D01AE02	41174108	Yes
Griseofulvin, systemic	griseofulvin Oral Tablet	Antifungals for systemic use	D01BA01	40043314	Yes
Griseofulvin, systemic	griseofulvin Oral Suspension	Antifungals for systemic use	D01BA01	40043312	Yes
Griseofulvin, systemic	Griseofulvin Oral Solution	Antifungals for systemic use	D01BA01	40730661	Yes
Griseofulvin, systemic	griseofulvin Oral Capsule	Antifungals for systemic use	D01BA01	40043310	Yes
Miconazole/hydrocortisone, cutaneous	hydrocortisone / miconazole Topical Ointment	Antifungals for topical use	-	40046785	Yes
Miconazole/hydrocortisone, cutaneous	hydrocortisone / miconazole Topical Gel	Antifungals for topical use	-	40046784	Yes
Miconazole/hydrocortisone, cutaneous	hydrocortisone / miconazole Topical Cream	Antifungals for topical use	-	40046783	Yes
Benzoic acid/salicylic acid, cutaneous	benzoate / salicylic acid Topical Ointment	Antifungals for topical use	-	40173701	Yes
Benzoic acid/salicylic acid, cutaneous	benzoate / salicylic acid Topical Cream	Antifungals for topical use	-	40173700	Yes
Clotrimazole cutaneous	clotrimazole Topical Spray	Antifungals for topical use	D01AC01	40026955	Yes
Clotrimazole cutaneous	clotrimazole Topical Solution	Antifungals for topical use	D01AC01	40026949	Yes
Clotrimazole cutaneous	clotrimazole Topical Powder	Antifungals for topical use	D01AC01	40026943	Yes
Clotrimazole cutaneous	clotrimazole Topical Ointment	Antifungals for topical use	D01AC01	40026942	Yes
Clotrimazole cutaneous	clotrimazole Topical Oil	Antifungals for topical use	D01AC01	43525358	Yes
Clotrimazole cutaneous	clotrimazole Topical Lotion	Antifungals for topical use	D01AC01	40026940	Yes

Substance Name	Concept name	Class	ATC code	Concept ID	Include descendants
Clotrimazole cutaneous	clotrimazole Topical Gel	Antifungals for topical use	D01AC01	40026939	Yes
Clotrimazole cutaneous	clotrimazole Topical Foam	Antifungals for topical use	D01AC01	42800644	Yes
Clotrimazole cutaneous	clotrimazole Topical Cream	Antifungals for topical use	D01AC01	40026931	Yes
Clotrimazole cutaneous	Clotrimazole Medicated Shampoo	Antifungals for topical use	D01AC01	40986551	Yes
Clotrimazole cutaneous	clotrimazole Medicated Bar Soap	Antifungals for topical use	D01AC01	40026926	Yes
Ketoconazole cutaneous	Ketoconazole Topical Spray	Antifungals for topical use	D01AC08	35153468	Yes
Ketoconazole cutaneous	ketoconazole Topical Solution	Antifungals for topical use	D01AC08	42800872	Yes
Ketoconazole cutaneous	ketoconazole Topical Powder	Antifungals for topical use	D01AC08	40048402	Yes
Ketoconazole cutaneous	ketoconazole Topical Ointment	Antifungals for topical use	D01AC08	1735074	Yes
Ketoconazole cutaneous	ketoconazole Topical Lotion	Antifungals for topical use	D01AC08	40048401	Yes
Ketoconazole cutaneous	ketoconazole Topical Gel	Antifungals for topical use	D01AC08	40048400	Yes
Ketoconazole cutaneous	ketoconazole Topical Foam	Antifungals for topical use	D01AC08	40142112	Yes
Ketoconazole cutaneous	ketoconazole Topical Cream	Antifungals for topical use	D01AC08	40048398	Yes
Ketoconazole cutaneous	ketoconazole Medicated Shampoo	Antifungals for topical use	D01AC08	40048392	Yes
Miconazole cutaneous	miconazole Topical Spray	Antifungals for topical use	D01AC02	40063842	Yes
Miconazole cutaneous	miconazole Topical Solution	Antifungals for topical use	D01AC02	40063839	Yes
Miconazole cutaneous	miconazole Topical Powder	Antifungals for topical use	D01AC02	40063828	Yes
Miconazole cutaneous	miconazole Topical Ointment	Antifungals for topical use	D01AC02	40063826	Yes
Miconazole cutaneous	miconazole Topical Lotion	Antifungals for topical use	D01AC02	40063824	Yes
Miconazole cutaneous	miconazole Topical Gel	Antifungals for topical use	D01AC02	40063823	Yes
Miconazole cutaneous	miconazole Topical Cream	Antifungals for topical use	D01AC02	40063807	Yes
Miconazole cutaneous	miconazole Medicated Shampoo	Antifungals for topical use	D01AC02	40063798	Yes

Substance Name	Concept name	Class	ATC code	Concept ID	Include descendants
Sulconazole cutaneaous	sulconazole Topical Spray	Antifungals for topical use	D01AC09	35850744	Yes
Sulconazole cutaneaous	sulconazole Topical Solution	Antifungals for topical use	D01AC09	40101501	Yes
Sulconazole cutaneaous	sulconazole Topical Ointment	Antifungals for topical use	D01AC09	42479827	Yes
Sulconazole cutaneaous	sulconazole Topical Cream	Antifungals for topical use	D01AC09	40101499	Yes
Fluconazole systemic	Fluconazole Prefilled Syringe	Antimycotics for systemic use	J02AC01	36879859	Yes
Fluconazole systemic	Fluconazole Powder for Oral Suspension	Antimycotics for systemic use	J02AC01	43210013	Yes
Fluconazole systemic	Fluconazole Powder for Oral Solution	Antimycotics for systemic use	J02AC01	36880830	Yes
Fluconazole systemic	fluconazole Oral Tablet	Antimycotics for systemic use	J02AC01	40040690	Yes
Fluconazole systemic	fluconazole Oral Suspension	Antimycotics for systemic use	J02AC01	40040688	Yes
Fluconazole systemic	fluconazole Oral Solution	Antimycotics for systemic use	J02AC01	40147994	Yes
Fluconazole systemic	Fluconazole Oral Powder	Antimycotics for systemic use	J02AC01	44042900	Yes
Fluconazole systemic	fluconazole Oral Granules	Antimycotics for systemic use	J02AC01	35859765	Yes
Fluconazole systemic	fluconazole Oral Capsule	Antimycotics for systemic use	J02AC01	40040685	Yes
Fluconazole systemic	Fluconazole Intravenous Solution	Antimycotics for systemic use	J02AC01	36783797	Yes
Fluconazole systemic	fluconazole Injection	Antimycotics for systemic use	J02AC01	35605308	Yes
Fluconazole systemic	fluconazole Injectable Solution	Antimycotics for systemic use	J02AC01	40040683	Yes
Amorolfine cutaneous	amorolfine Topical Solution	Other antifungals for topical use	D01AE16	40009170	Yes
Amorolfine cutaneous	Amorolfine Topical Ointment	Other antifungals for topical use	D01AE16	42479648	Yes
Amorolfine cutaneous	amorolfine Topical Cream	Other antifungals for topical use	D01AE16	40009168	Yes
Amorolfine cutaneous	Amorolfine Medicated Pad	Other antifungals for topical use	D01AE16	43287420	Yes
Amorolfine cutaneous	Amorolfine Medicated Nail Polish	Other antifungals for topical use	D01AE16	43146764	Yes
Amorolfine cutaneous	Amorolfine Medicated nail lacquer	Other antifungals for topical use	D01AE16	21123760	Yes

Substance Name	Concept name	Class	ATC code	Concept ID	Include descendants
Amorolfine cutaneous	Amorolfine Medicated nail lacquer	Other antifungals for topical use	D01AE16	42952300	Yes
Itraconazole systemic	itraconazole Oral Tablet	Antimycotics for systemic use	J02AC02	40052921	Yes
Itraconazole systemic	itraconazole Oral Suspension	Antimycotics for systemic use	J02AC02	40052919	Yes
Itraconazole systemic	itraconazole Oral Solution	Antimycotics for systemic use	J02AC02	40052917	Yes
Itraconazole systemic	itraconazole Oral Granules	Antimycotics for systemic use	J02AC02	35862428	Yes
Itraconazole systemic	itraconazole Oral Capsule	Antimycotics for systemic use	J02AC02	40052914	Yes
Itraconazole systemic	Itraconazole Injection	Antimycotics for systemic use	J02AC02	42480885	Yes
Itraconazole systemic	itraconazole Injectable Solution	Antimycotics for systemic use	J02AC02	40052913	Yes
Itraconazole systemic	Itraconazole Delayed Release Oral Capsule	Antimycotics for systemic use	J02AC02	41017384	Yes
Terbinafine	terbinafine	Antifungals	-	1741309	Yes

Antifungals for systemic use comprised the following active substance concept ids: terbinafine (systemic), itraconazole (systemic), griseofulvin (systemic), and fluconazole (systemic), as listed in **Table S1**.

Antifungals for topical use included following concepts: terbinafine (cutaneous), sulconazole (cutaneous), miconazole (cutaneous), ketoconazole (cutaneous), hydrocortisone/miconazole (cutaneous), methylrosaniline (cutaneous), clotrimazole (cutaneous), ciclopirox (cutaneous), benzoate/salicylic acid (cutaneous), and amorolfine (cutaneous).

Antibiotics for systemic use were defined according to the ATC classification J01 – Antibacterials for Systemic use, covering all major pharmacological classes (e.g., penicillins, cephalosporins, macrolides, fluoroquinolones, tetracyclines, aminoglycosides, and others). Ingredient-level concept IDs corresponding to systemic administration were included, while concepts not relevant to systemic use (such as topical formulations or other routes) were excluded.

Antibiotics for topical use were defined according to the ATC classification D06A – Antibiotics for Topical Use, which includes all major pharmacological classes indicated for cutaneous administration. Ingredient-level concept IDs corresponding to topical formulations were included, while concepts not relevant to topical use (such as systemic formulations or other routes) were excluded.

Table S2. List of conditions definitions.

Phenotype	Concept name	Concept id	Exclude concept id	Include descendants	Vocabulary
Dermatophytosis	Tinea corporis	4224968	-	Yes	SNOMED
Dermatophytosis	Tinea cruris	4160328	-	Yes	SNOMED
Dermatophytosis	Tinea pedis	133141	-	Yes	SNOMED
Dermatophytosis	Tinea manus	80946	-	Yes	SNOMED
Dermatophytosis	Onychomycose	4215978	-	Yes	SNOMED
Dermatophytosis	Tinea capitis	4182398	-	Yes	SNOMED
Dermatophytosis	Tinea barbae	4163426	-	Yes	SNOMED
Superficial tinea infections	Tinea corporis, Tinea pedis, Tinea manus	133141, 80946, 4224968	-	Yes	SNOMED
Tinea infections of hair bearing areas	Tinea capitis, Tinea barbae and tinea capitis, Tinea barbae	4182398, 45552218, 4163426	-	Yes	SNOMED, ICD10
Other fungal infections	Mucocutaneous candidiasis	4104522	-	Yes	SNOMED
Other fungal infections	Sporotrichosis	434859	-	Yes	SNOMED
Other fungal infections	Pityriasis versicolor	134870	-	Yes	SNOMED

Table S3. List of resistance codes.

Phenotype	Concept name	Concept id	Exclude concept id	Include descendants
Resistance	Resistance to antineoplastic drug	36715097	Yes	-
Resistance	Infection resistant to antifungal drug	37394535	-	Yes
Resistance	Increased drug resistance	4320040	Yes	-
Resistance	Erythropoietin resistance in anemia of chronic kidney disease	40478891	Yes	-
Resistance	Drug resistance to insulin	4168924	Yes	-
Resistance	Drug resistance to corticoids	4320041	Yes	-
Resistance	Drug resistance to antiviral agent	37017450	Yes	-
Resistance	Drug resistance to antiretroviral therapy	4137371	Yes	-
Resistance	Drug resistance to antibacterial agent	37017452	Yes	-
Resistance	Drug resistance to anti-seizure medication	37167166	Yes	-
Resistance	Drug resistance	4150981	-	Yes
Resistance	Decreased drug resistance	4318124	Yes	-

ANNEX IV: Supplementary Tables

Table S1. Number of prescriptions, treatment duration, and dose (initial and cumulative) across multiple treatment episodes, overall, by data source.

Variable name	Estimate name	CDM					
		NAJS	DK-DHR	FinOMOP-THL	IQVIA DA Germany	SIDIAP	CPRD GOLD
Number of subjects	N	156,916	350,877	336,449	70,753	146,994	168,567
Number of records	N	197,860	409,266	396,912	81,601	164,423	196,299
Number of exposures	Median (q25–q75)	1 (1–1)	1 (1–1)	1 (1–1)	1 (1–1)	2 (2–3)	1 (1–2)
	Range (min–max)	1–97	1–118	1–124	1–46	1–78	1–243
Days exposed	Median (q25–q75)	–	30 (30–98)	–	30 (28–69)	41 (31–77)	28 (15–78)
	Range (min–max)	–	1–2,301	–	1–1,944	1–2,983	1–2,427
Initial daily dose, milligram*	Median (q25–q75)	0.00 (0.00–0.00)	10.00 (5.00–250.00)	–	250.00 (71.43–250.00)	19.09 (9.68–242.67)	0.04 (0.02–250.00)
	Range (min–max)	0–816.67	0–2,450.00	–	0.33–2,333.33	0–22,252.75	0–75,250.00
Cumulative dose, milligram*	Median (q25–q75)	0.01 (0.01–0.02)	300.00 (150.00–24,500.00)	–	7,000.00 (3,500.00–10,500.00)	600.00 (280.00–10,500.00)	1.20 (0.30–15,000.00)
	Range (min–max)	0–231,000.00	0–738,500.00	–	9.99–458,500.00	0–2,331,000.00	0–2,107,000.00

NAJS = Croatian National Public Health Information System, DK-DHR = Danish Data Health Registries, FinOMOP-THL = Finnish Care Register for Health Care, IQVIA DA Germany = IQVIA Disease Analyzer Germany, SIDIAP = Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària, CPRD GOLD = Clinical Practice Research Datalink GOLD.
N = number of individuals, q25–q75 = 25th and 75th percentiles (interquartile range), min–max = minimum and maximum observed values.
* = There is heterogeneity in dose, as both topical and oral products were included.

Table S2. Number of prescriptions, treatment duration, and dose (initial and cumulative) across multiple treatment episodes, stratified by indication, by data source.

Variable name	Estimate name	NAJS	DK-DHR	FinOMOP-THL	IQVIA DA Germany	SIDIAP	CPRD GOLD
Superficial tinea infections							
Number of subjects	N	21,340	74,384	34,529	13,055	12,640	12,539
Number of records	N	17,918	67,721	33,626	12,636	12,274	12,058
Number of exposures	Median (q25–q75)	1 (1–1)	1 (1–1)	1 (1–1)	1 (1–1)	2 (2–2)	1 (1–1)
	Range (min–max)	1–97	1–19	1–100	1–38	1–70	1–27
Days exposed	Median (q25–q75)	–	30 (30–30)	–	30 (28–51)	31 (31–41)	15 (7–28)
	Range (min–max)	–	1–1,153	–	1-1,622	1–2,556	1–983
Cumulative dose, milligram*	Median (q25–q75)	0.01 (0.01–0.02)	300.00 (150.00–450.00)	–	7,000.00 (300.00–10,500.00)	300.00 (100.00–4,750)	0.30 (0.30–0.60)
	Range (min–max)	0–126,000.14	0–280,000.00	–	9.99–399,000.00	0–282,260.00	0.01–189,000.00
Initial daily dose, milligram*	Median (q25–q75)	0.00 (0.00–0.00)	5.00 (5.00–10.00)	–	250.00 (10.00–250.00)	18.67 (9.09 - 233.33)	0.02 (0.02–0.04)
	Range (min–max)	0–700.00	0–1,049.07	–	0.33–1,005.00	0–3,266.67	0–13,500.00
Onychomycosis							
Number of subjects	N	26,716	96,843	36,386	37,958	13,453	28,675
Number of records	N	22,343	87,526	35,138	34,459	12,742	27,338
Number of exposures	Median (q25–q75)	1 (1–2)	1 (1–1)	1 (1–1)	1 (1–2)	2 (2–4)	2 (1–3)

Variable name	Estimate name	NAJS	DK-DHR	FinOMOP-THL	IQVIA DA Germany	SIDIAP	CPRD GOLD
	Range (min–max)	1–97	1–59	1–43	1–43	1–46	1–158
Days exposed	Median (q25–q75)	–	98 (98–98)	–	42 (28–84.00)	86 (43–117)	84 (49–152)
	Range (min–max)	–	2–2,301	–	2–1,875	1–2,649	1–2,427
Cumulative dose milligram*	Median (q25–q75)	0.01 (0.01–3,500.02)	24,500.00 (24,500.00–24,500.00)	–	7,000.00 (7,000.00–10,650.00)	15,000.00 (6,500.00–22,500.00)	21,000.00 (14,000.00–35,000.00)
	Range (min–max)	0–231,000.00	0–539,000.00	–	9.99–451,500.00	0–661,500.00	0–763,000.00
Initial daily dose milligram*	Median (q25–q75)	0.00 (0.00–116.67)	250.00 (250.00–250.00)	–	250.00 (250.00–250.00)	245.90 (233.33–247.25)	250.00 (250.00–250.00)
	Range (min–max)	0–816.67	0–1,633.33	–	0.33–2,333.33	0–6,758.62	0–25,500.00
Tinea infections of hair bearing areas							
Number of subjects	N	–	1,553	–	–	–	439
Number of records	N	–	1,528	–	–	–	431
Number of exposures	Median (q25–q75)	–	1 (1–1)	–	–	–	1 (1–1)
	Range (min–max)	–	1–6	–	–	–	1–8
Days exposed	Median (q25–q75)	–	28 (28–98)	–	–	–	28 (15–28)
	Range (min–max)	–	1–313	–	–	–	1–393
Cumulative dose, milligram*	Median (q25–q75)	–	7,000.00 (3,934.00–15,736.00)	–	–	–	3,500.00 (0.60–7,000.00)

Variable name	Estimate name	NAJS	DK-DHR	FinOMOP-THL	IQVIA DA Germany	SIDIAP	CPRD GOLD
	Range (min–max)	–	0–73,500.00	–	–	–	0.15–49,000.00
Initial daily dose, milligram*	Median (q25–q75)	–	250.00 (250.00–281.00)	–	–	–	250.00 (0.04–250.00)
	Range (min–max)	–	0–562.00	–	–	–	0.01–2,000.02

NAJS = Croatian National Public Health Information System, DK-DHR = Danish Data Health Registries, FinOMOP-THL = Finnish Care Register for Health Care, IQVIA DA Germany = IQVIA Disease Analyzer Germany, SIDIAP = Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària, CPRD GOLD = Clinical Practice Research Datalink GOLD.
N = number of individuals, q25–q75 = 25th and 75th percentiles (interquartile range), min–max = minimum and maximum observed values.
* = There is heterogeneity in dose, as both topical and oral products were included.

ANNEX V: Supplementary Figures

Note: Due to the large number and complexity of unique treatment pathways identified in the stratified analyses, only the sunburst plots are presented in the supplementary figures. Detailed tables of pathway frequencies and additional descriptive statistics are available in the interactive Shiny application at EUPAS1000000790. Readers are encouraged to consult the ShinyApp for comprehensive information on all observed treatment sequences.

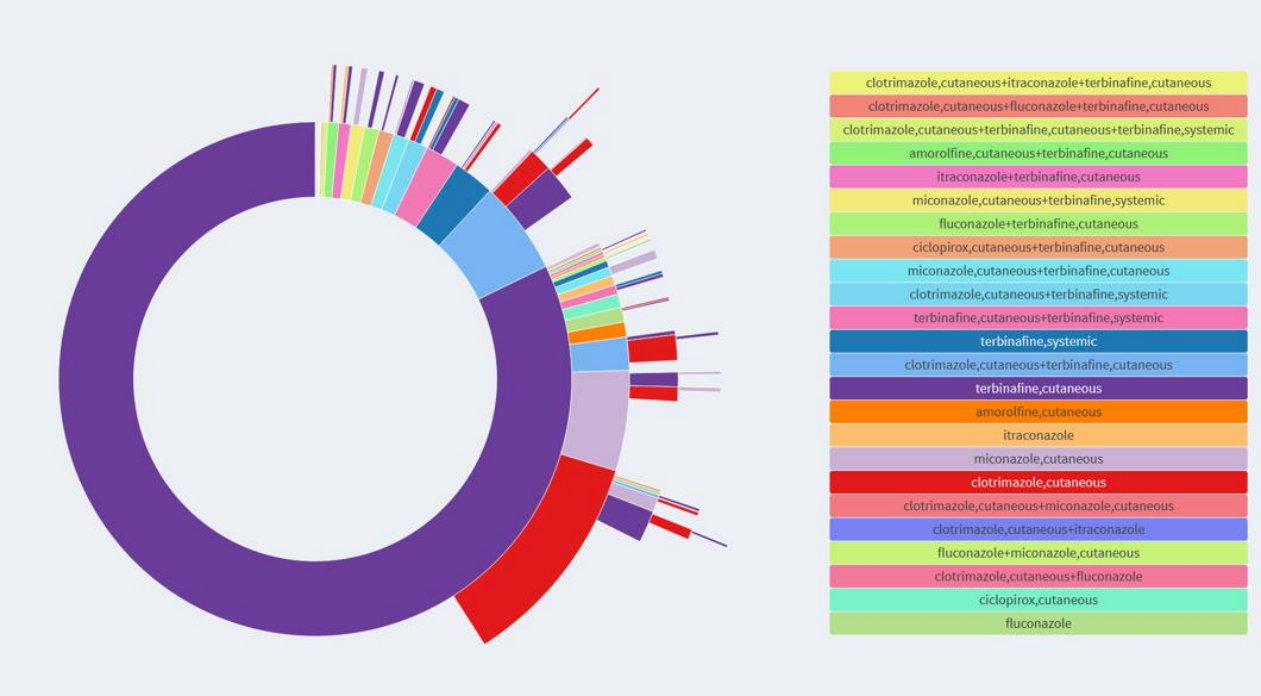

Figure S1. Sunburst plot of treatment patterns among individuals with superficial tinea infection in NAJS.

NAJS = Croatian National Public Health Information System.

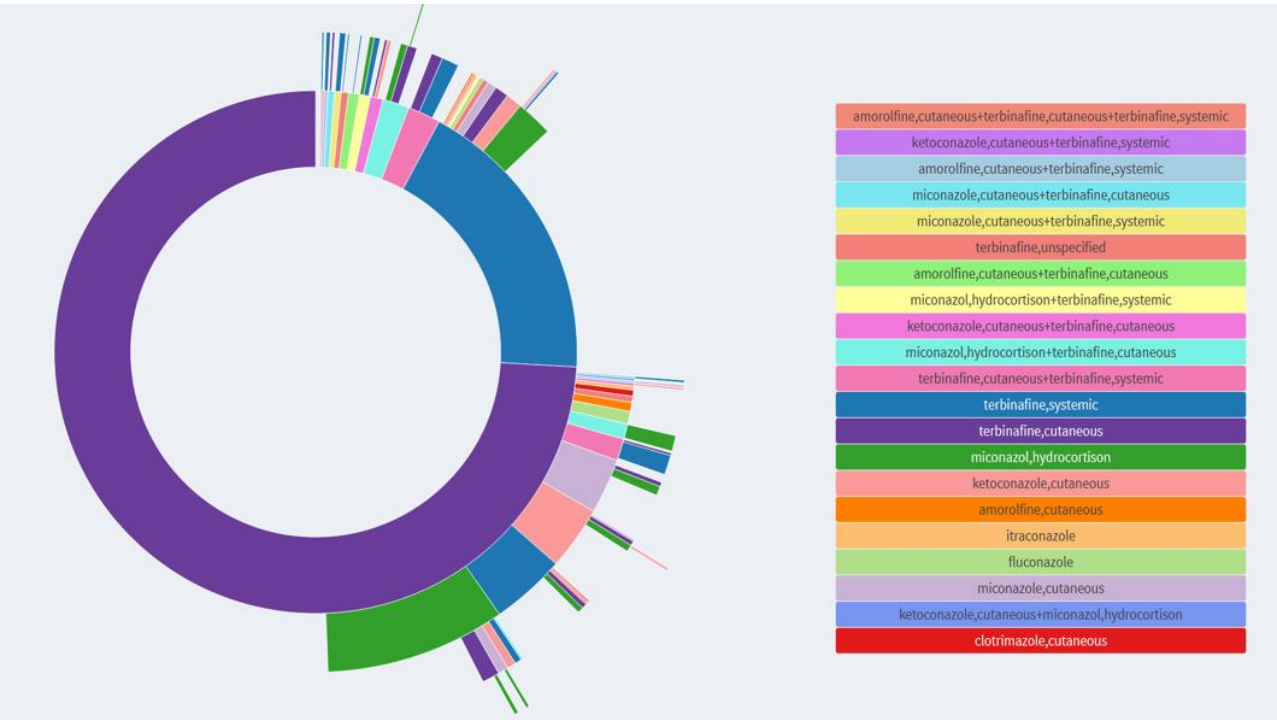

Figure S2. Sunburst plot of treatment patterns among individuals with superficial tinea infection in DK-DHR.

DK-DHR = Danish Data Health Registries.

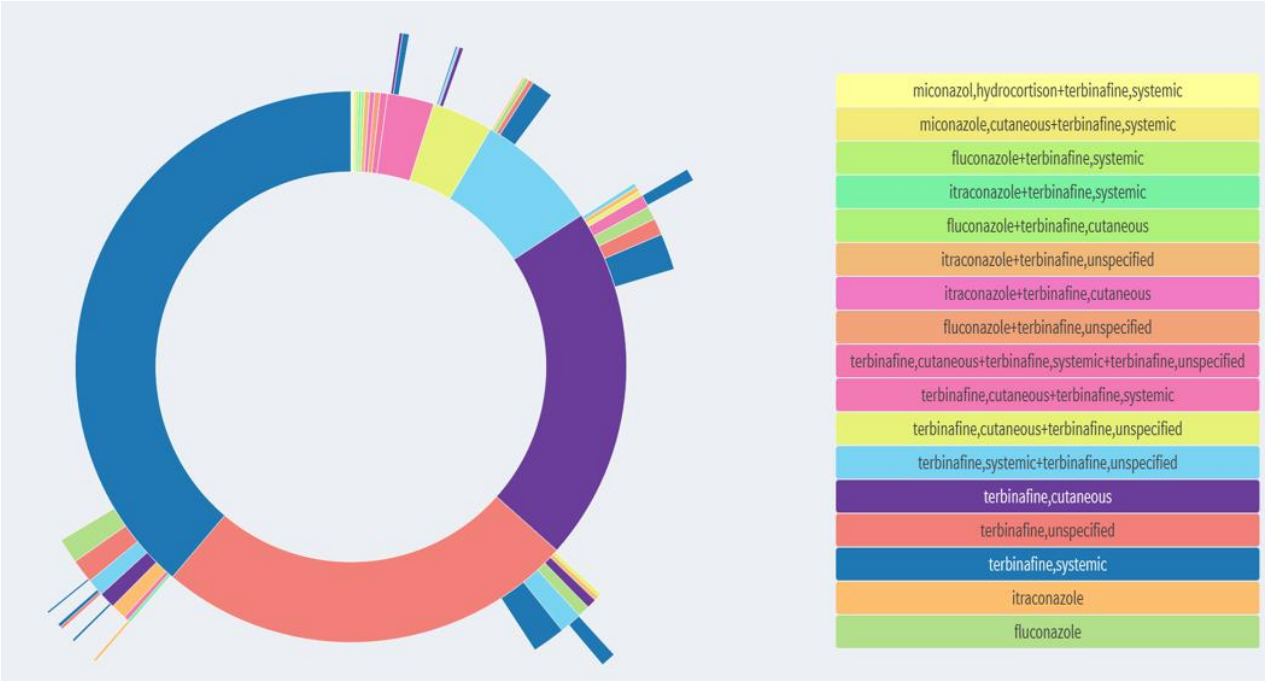

Figure S3. Sunburst plot of treatment patterns among individuals with superficial tinea infection in FinOMOP-THL.

FinOMOP-THL = Finnish Care Register for Health Care.

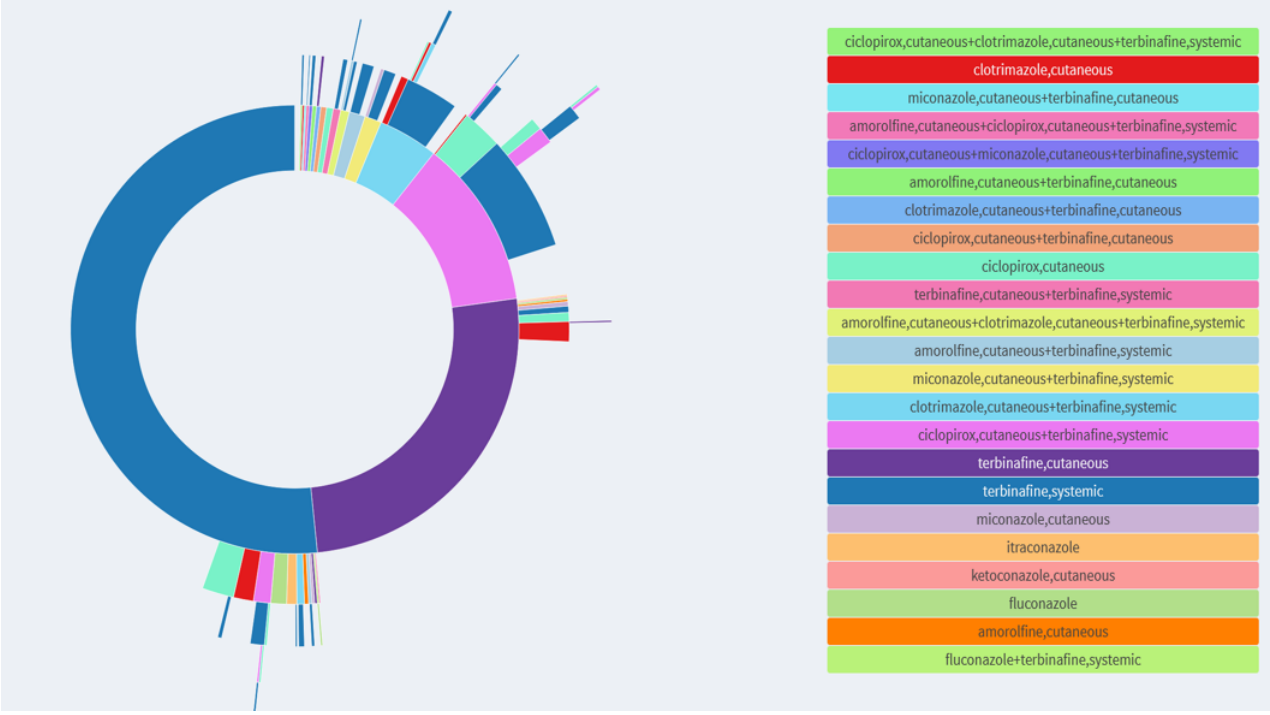

Figure S4. Sunburst plot of treatment patterns among individuals with superficial tinea infection in IQVIA DA Germany.

IQVIA DA Germany = IQVIA Disease Analyzer Germany.

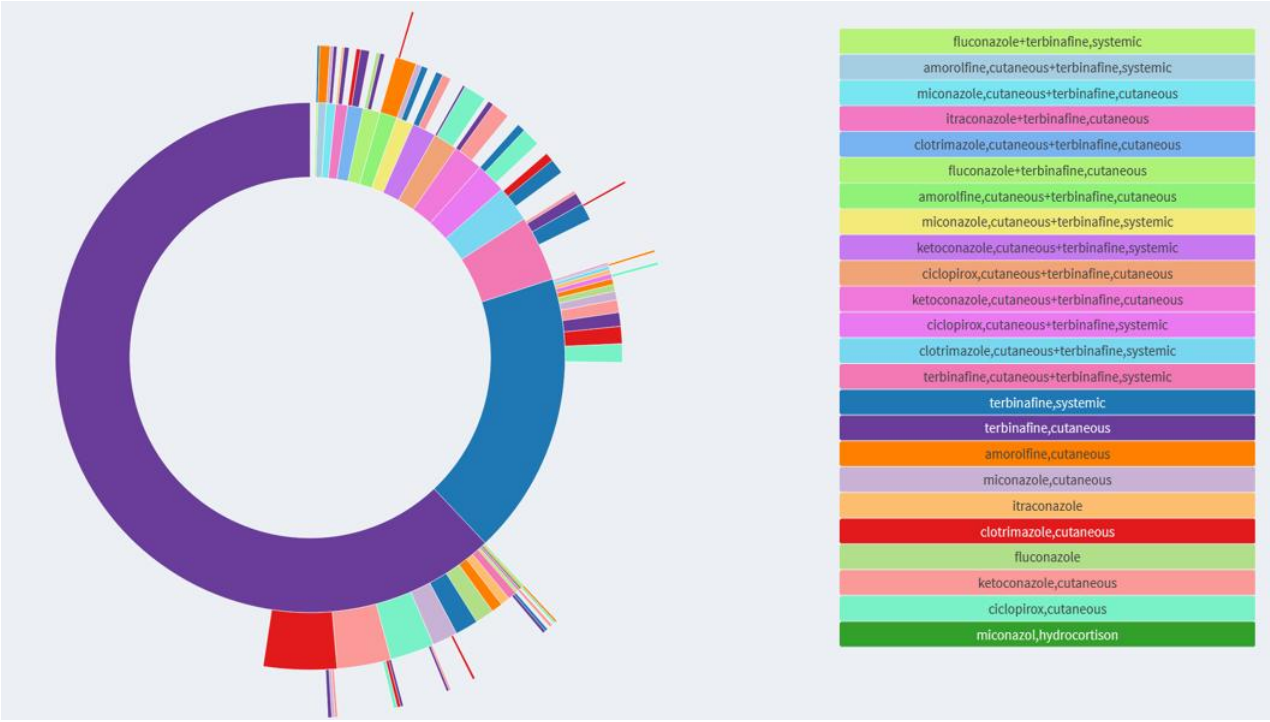

Figure S5. Sunburst plot of treatment patterns among individuals with superficial tinea infection in SIDAP.

SIDIAP = Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària.

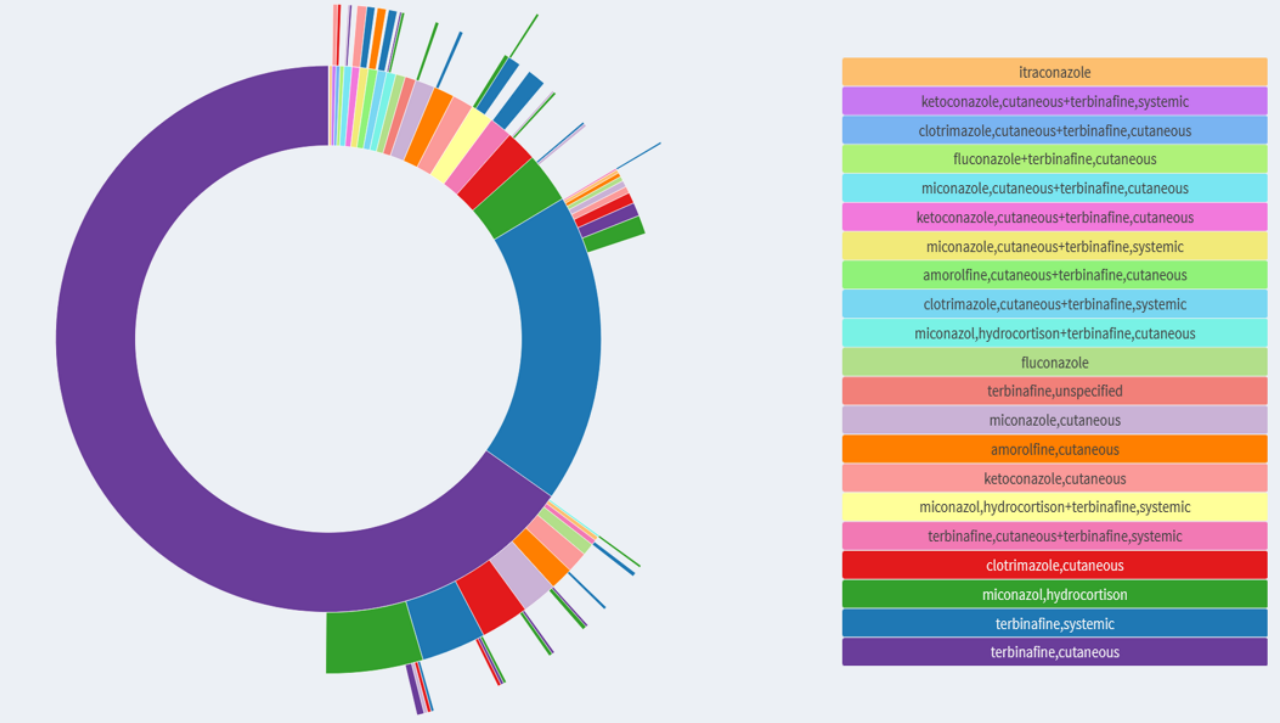

Figure S6. Sunburst plot of treatment patterns among individuals with superficial tinea infection in CPRD GOLD.

CPRD GOLD = Clinical Practice Research Datalink GOLD.

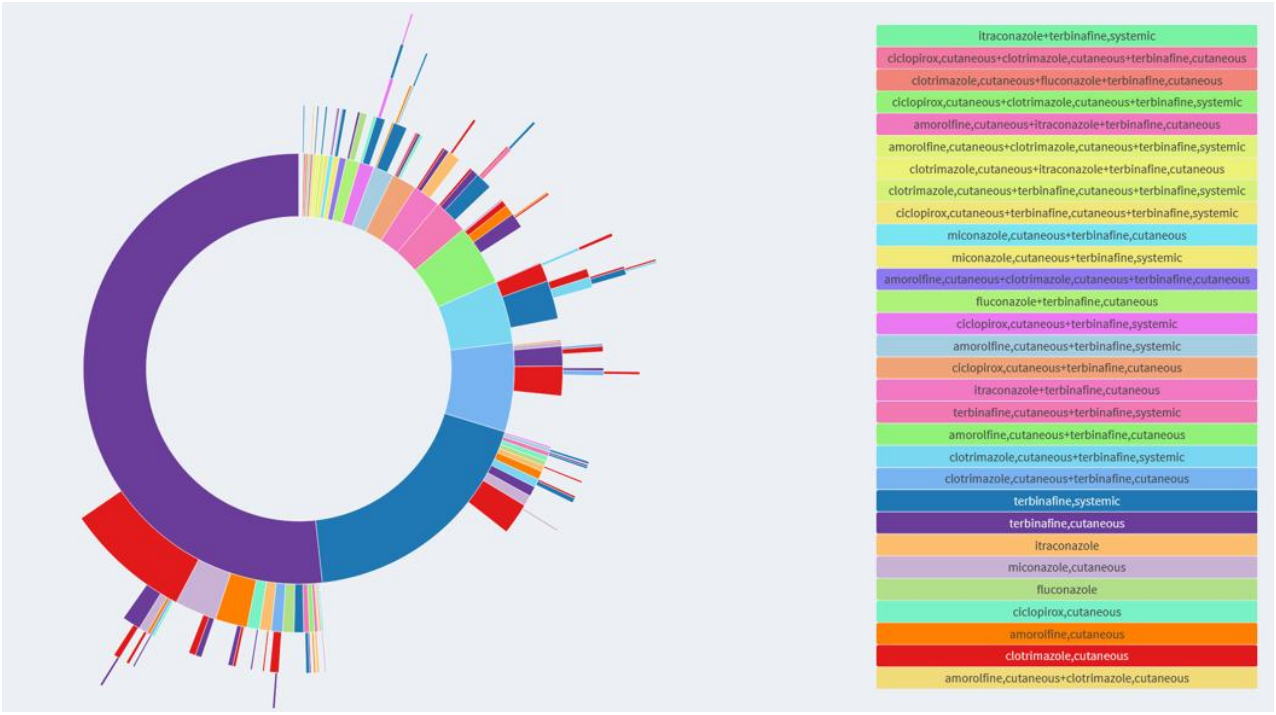

Figure S7. Sunburst plot of treatment patterns among individuals with onychomycosis in NAJS.

NAJS = Croatian National Public Health Information System.

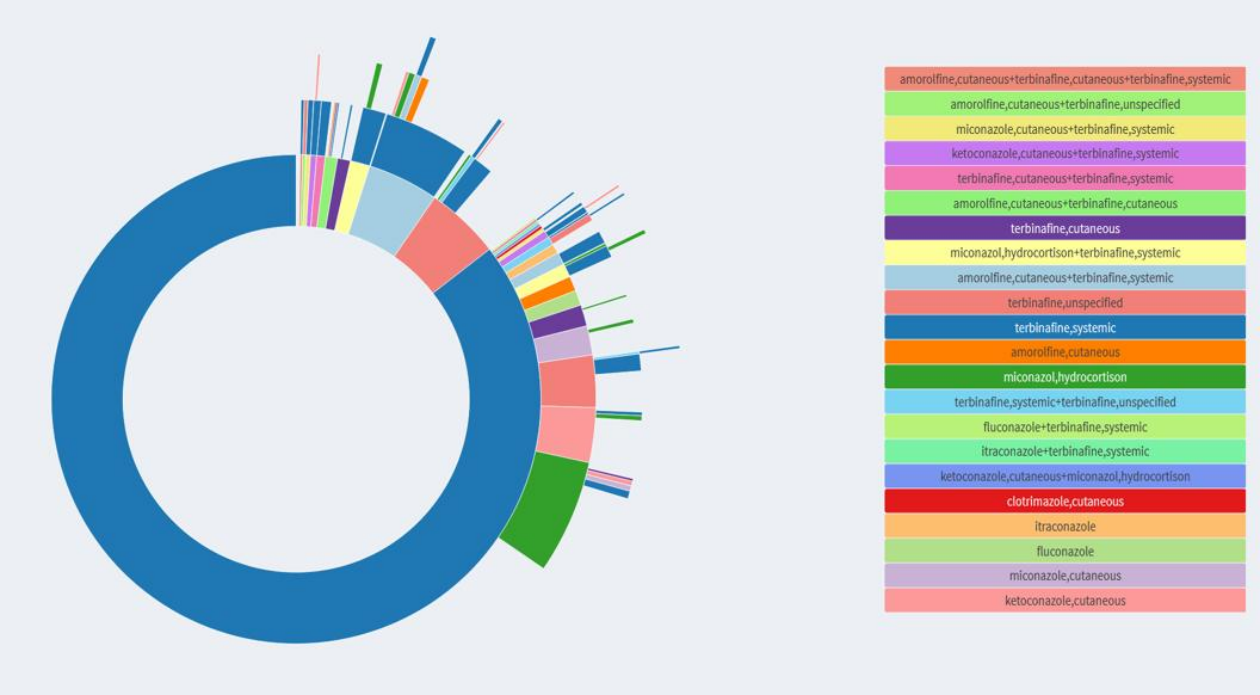

Figure S8. Sunburst plot of treatment patterns among individuals with onychomycosis in DK-DHR.

DK-DHR = Danish Data Health Registries.

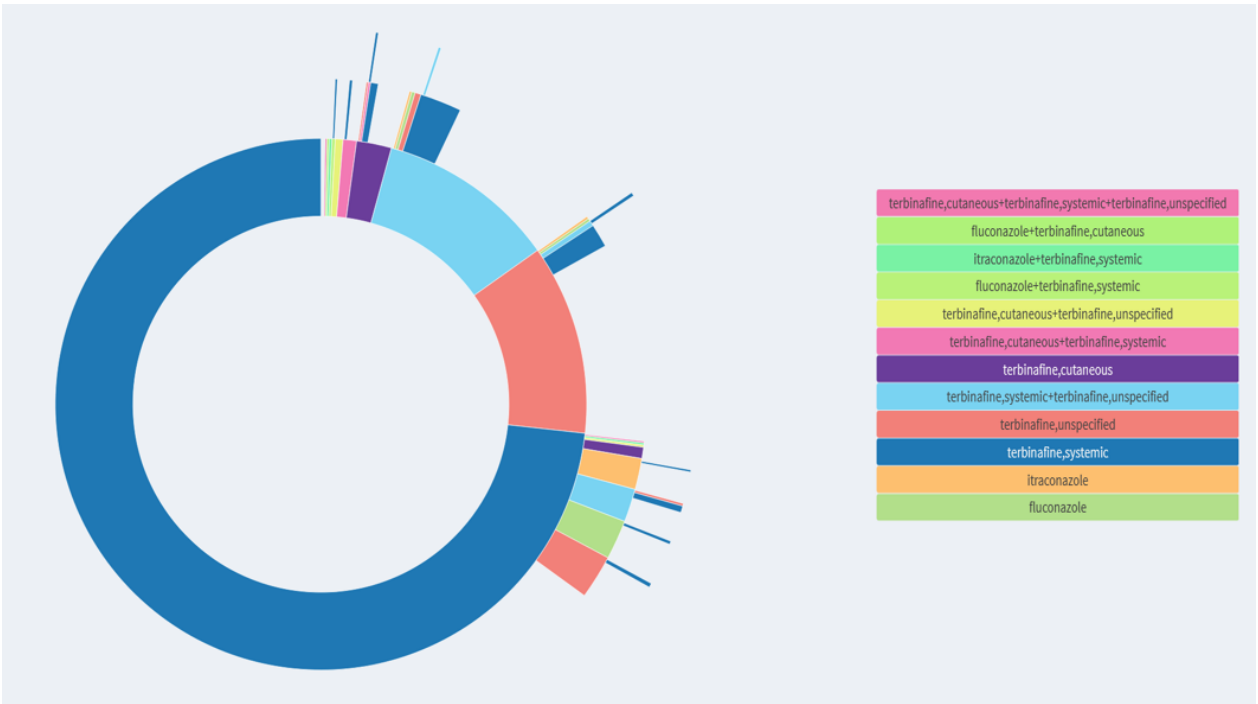

Figure S9. Sunburst plot of treatment patterns among individuals with onychomycosis in FinOMOP-THL.

FinOMOP-THL = Finnish Care Register for Health Care.

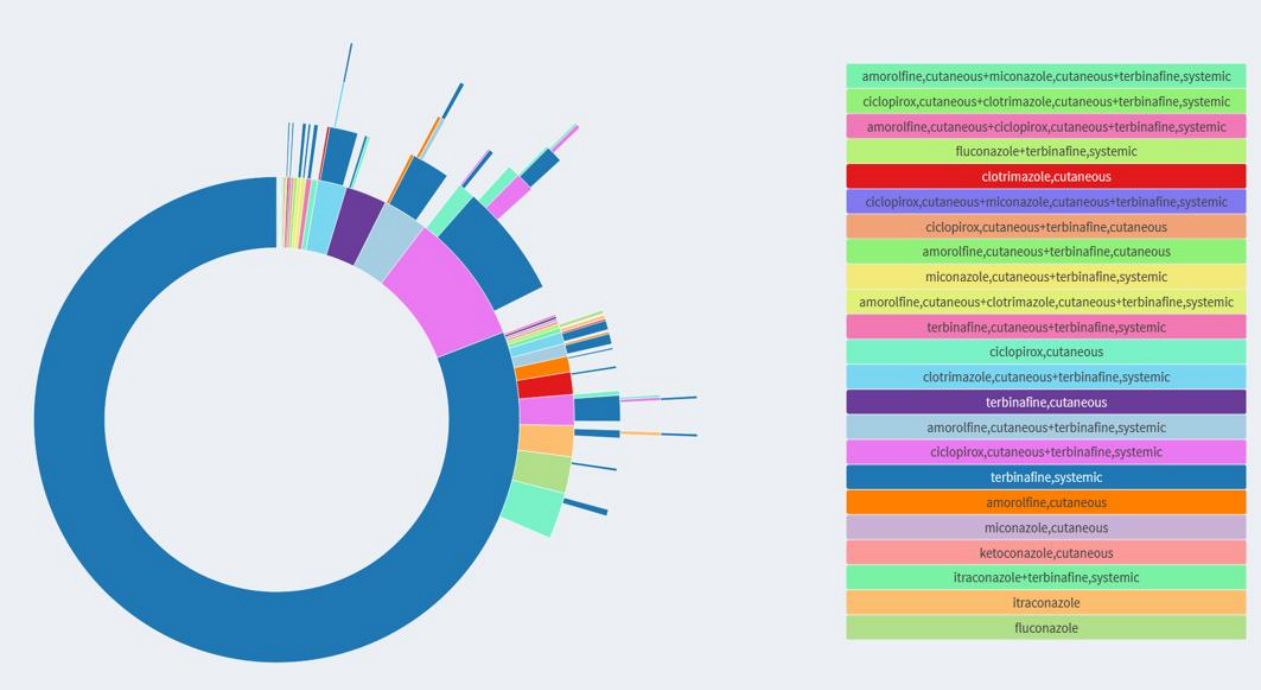

Figure S10. Sunburst plot of treatment patterns among individuals with onychomycosis in IQVIA DA Germany.

IQVIA DA Germany = IQVIA Disease Analyzer Germany.

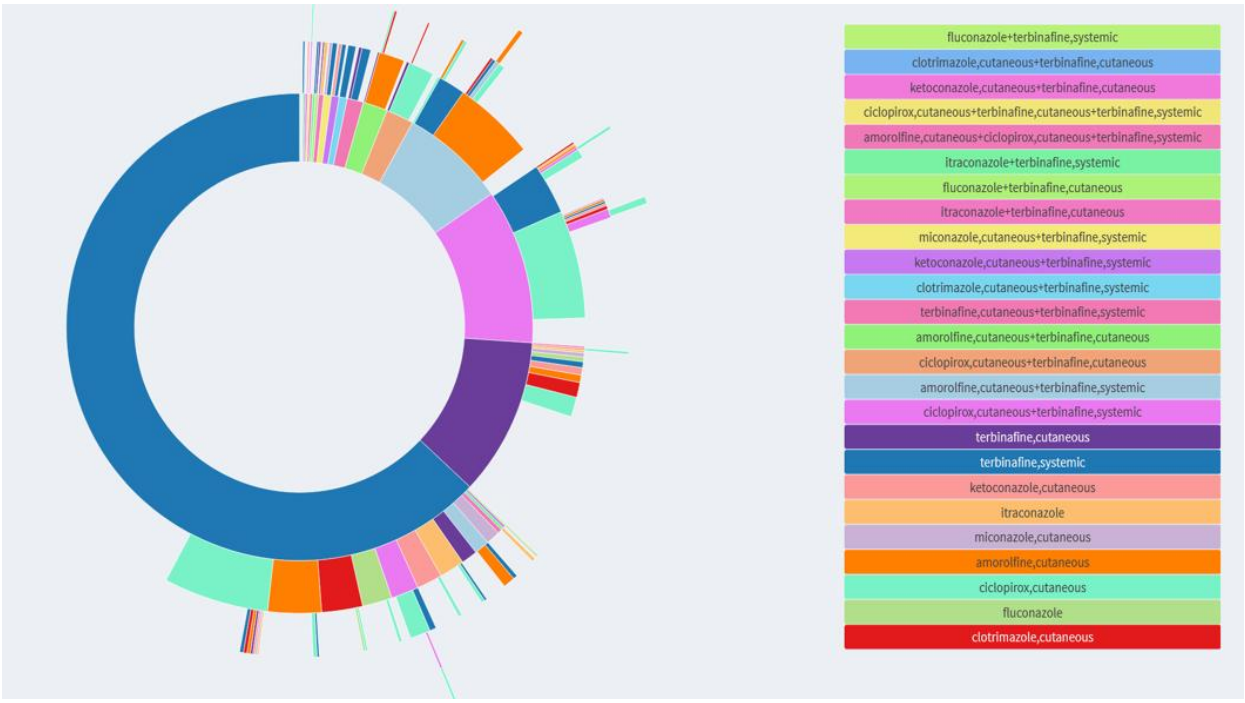

Figure S11. Sunburst plot of treatment patterns among individuals with onychomycosis in SIDIAP.

SIDIAP = Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària.

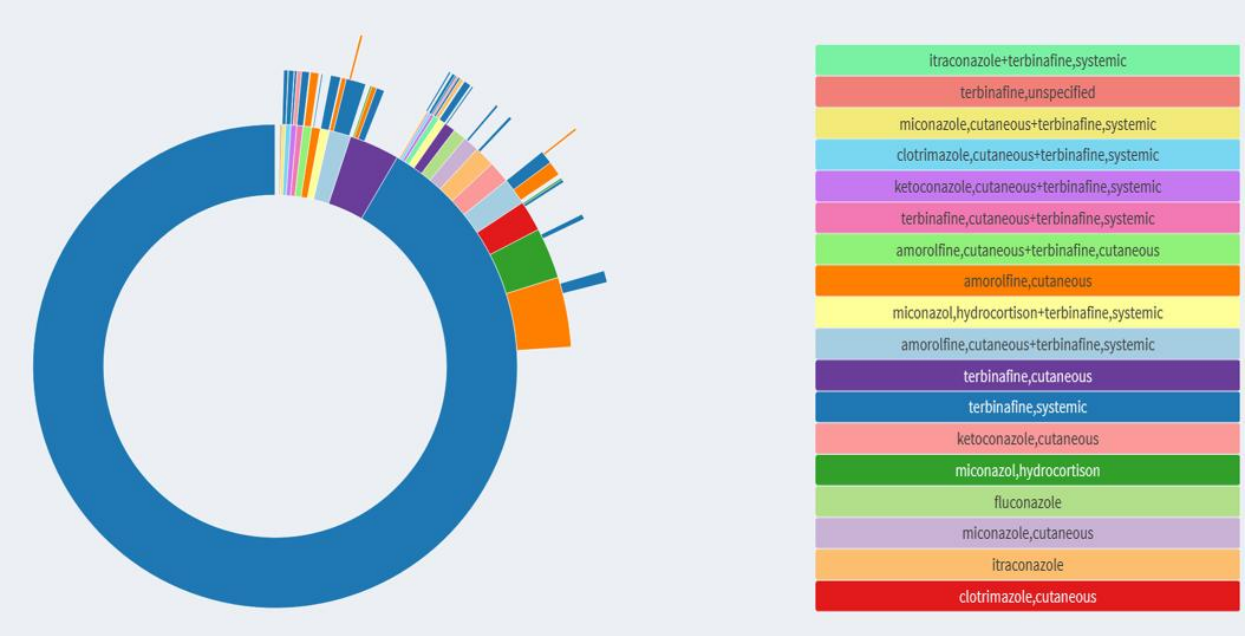

Figure S12. Sunburst plot of treatment patterns among individuals with onychomycosis in CPRD GOLD.

CPRD GOLD = Clinical Practice Research Datalink GOLD.

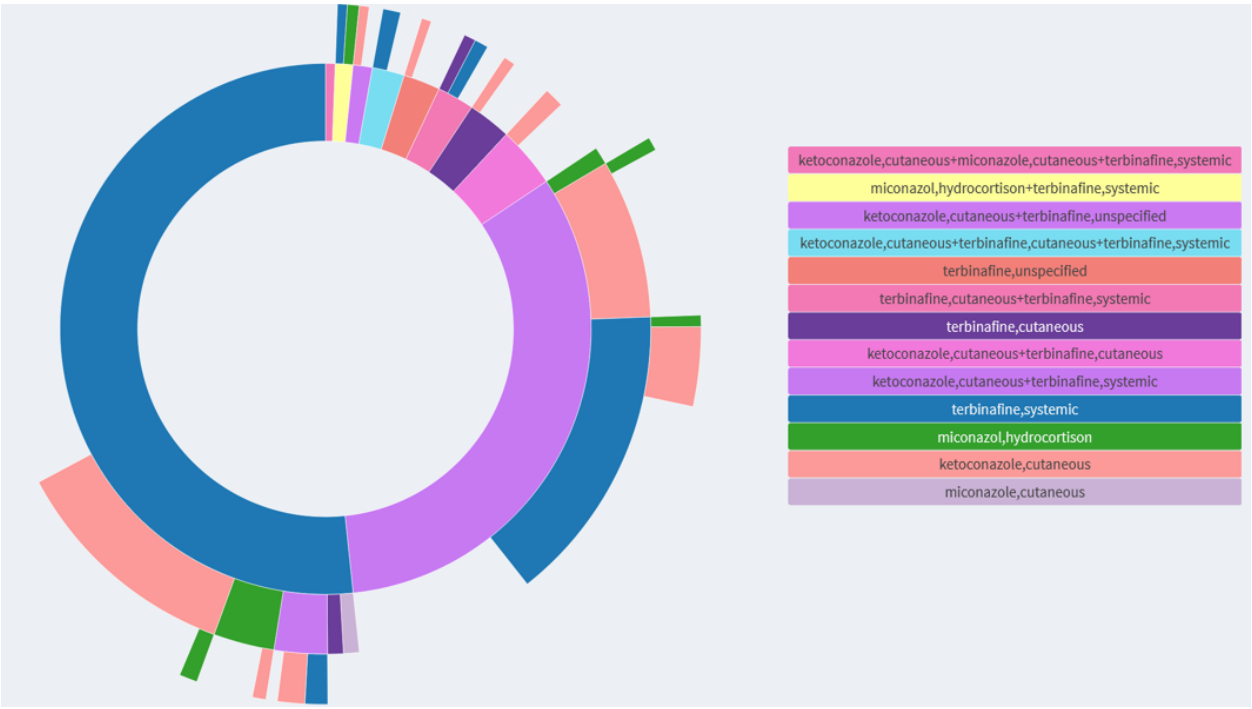

Figure S13. Sunburst plot of treatment patterns among individuals with hair follicle-involving tinea infections in DK-DHR.

DK-DHR = Danish Data Health Registries.

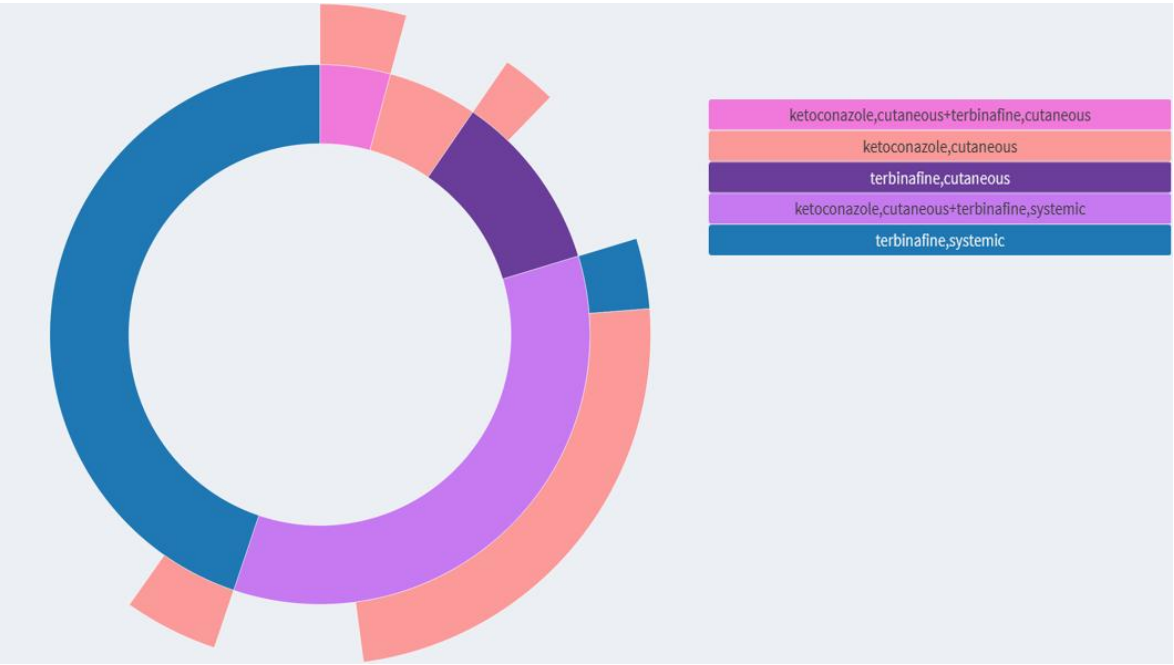

Figure S14. Sunburst plot of treatment patterns among individuals with hair follicle-involving tinea infections in CPRD GOLD.

CPRD GOLD = Clinical Practice Research Datalink GOLD.

ANNEX V: Glossary

Additional definitions are available in the EMA Glossary of terms https://www.ema.europa.eu/en/about-us/glossaries.

Aggregated Data

Data collected and combined from multiple sources to generate summary information, typically anonymised.

Benefit-Risk Assessment

Evaluation of the positive therapeutic effects of a medicine compared to its risks (e.g., side effects).

Common Data Model (CDM)

A standardized data structure that enables data from multiple sources to be harmonized, making analysis consistent and reproducible. DARWIN EU® utilises the OMOP CDM maintained by the OHDSI community.

Complex Studies (C3)

Studies requiring the development or customisation of specific study designs, protocols, and Statistical Analysis Plans (SAPs), with extensive collection or extraction of data. Examples include etiological studies measuring the strength and determinants of an association between an exposure and the occurrence of a health outcome in a defined population considering sources of bias, potential confounding factors, and effect modifiers.

Coordination Centre (CC)

The central hub responsible for managing and overseeing the activities within DARWIN EU®. It is based at Erasmus University Medical Centre in Rotterdam, the Netherlands.

Data Access

The process of obtaining permission to use specific datasets for regulatory or scientific studies.

Data Quality Framework

A set of standards and procedures to ensure accuracy, completeness, timeliness, and consistency of data used in DARWIN EU®.

Data Source

A database or repository of structured health-related data, such as electronic health records (EHRs), insurance claims, or registries.

DARWIN EU®

The European Medicines Agency's (EMA) federated network of real-world data sources designed to generate evidence to support regulatory decision-making.

EMA (European Medicines Agency)

The regulatory body responsible for the evaluation and supervision of medicinal products in the EU, overseeing DARWIN EU®.

Evidence Generation

The process of analysing real-world data to produce scientific information that can inform healthcare or regulatory decisions.

Federated Network

A data infrastructure where data remain at their original location but can be analysed in a harmonised way across multiple partners using a common model and tools.

GDPR (General Data Protection Regulation)

The EU regulation governing the protection of personal data and privacy, crucial to how DARWIN EU® handles health data.

Health Technology Assessment (HTA)

A systematic evaluation of properties and impacts of health technology, often using DARWIN EU® data to support assessments.

Metadata

Descriptive information about a data source (e.g., its content, quality, and structure), essential for identifying relevant databases in DARWIN EU® studies.

Off-the-Shelf Studies (OTS)

Studies for which a standard protocol per study/analysis type and standardised analytics may be developed and applied or adapted, typically relating to a descriptive research question. This includes studies on disease epidemiology, for example, the estimation of the prevalence or incidence of health outcomes in defined time periods and population groups, or drug utilisation studies at the population or patient level.

OHDSI (Observational Health Data Sciences and Informatics)

An open-science collaborative community that develops tools and standards (including the OMOP CDM) to enable large-scale analytics of observational health data. OHDSI provides the technical and scientific foundation for DARWIN EU®'s analytical ecosystem.

Patient-Level Data

Data related to individuals, de-identified, used for longitudinal or detailed analyses.

OMOP (Observational Medical Outcomes Partnership)

A common data model (CDM) that standardises the structure and content of observational healthcare data, enabling systematic analysis across disparate datasets. DARWIN EU® uses the OMOP CDM to ensure interoperability and consistency in real-world evidence generation.

Real-World Data (RWD)

Data relating to individual health status or healthcare delivery that is collected from routine clinical practice rather than from randomised controlled trials.

Real-World Evidence (RWE)

Clinical evidence derived from the analysis of RWD, used to inform decisions by regulators, payers, or clinicians.

Regulatory Decision-Making

The process by which authorities like EMA assess data to authorise, monitor, or modify the use of medicines in the EU.

Routine Repeated Studies (RR)

Studies that are either Off-the-Shelf or Complex studies repeated on a regular basis, following the same protocol and study code, but with updated data and/or different data partners.

Study Protocol

A detailed plan describing how a specific real-world study will be conducted, including objectives, design, data sources, and analyses.

Very Complex Studies (C4)

Studies which cannot rely only on electronic health care databases, or which would require complex methodological work, for example, due to the occurrence of events that cannot be defined by existing diagnosis codes, including events that do not yet have a diagnosis code, where it may be necessary to combine a diagnosis code with other data such as results of laboratory investigations. These studies might require the collection of data prospectively, or the inclusion of new (not previously onboarded) data sources.