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ORIGINAL RESEARCH ARTICLE

Introduction of Biopharmaceuticals in Europe: A Cross-Sectional Study of Early Diffusion Patterns and Data Availability

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Abstract

Background and Objectives Biopharmaceuticals add value in the treatment of many diseases but different health systems in Europe face clinical and economic challenges with introducing them. Joint efforts across Europe are therefore essential to ensure their sustainable and equitable use. However, to date few cross-national comparative studies have assessed their introduction. This study aimed to assess the availability of health authority data and variation in the early diffusion of biopharmaceuticals across Europe.

Methods A cross-sectional study was undertaken to analyze the diffusion of 17 biopharmaceuticals, approved between 2015 and 2019, among European countries between 2015 and 2022. The study assessed data availability, diffusion rates measured as accumulated defined daily doses per 1000 inhabitants, as well as relative rankings between countries during the first 4 years following market authorization.

Results Twenty countries and two regions out of 31 European countries provided data on biopharmaceutical utilization for out-of-hospital care, 15 provided wholesaler data, and 14 provided hospital data. Certain countries and regions contributed data in multiple categories, while six did not provide any data. Diffusion rates were assessed for 17 countries and two regions, which showed appreciable variation, with secukinumab and erenumab being introduced in most countries and follitropin delta and tildrakizumab in the least number of countries. Germany, Austria, and Norway demonstrated the highest early diffusion rates, while Lithuania, Romania, and Latvia had the lowest.

Conclusions This study revealed a substantial variation between European countries and regions in the early diffusion of biopharmaceuticals and the availability of data to monitor their use. The reasons behind these patterns require further investigation to support European countries in optimizing the use of biopharmaceuticals to reach an equitable and cost-effective use of medicines across Europe.

1 Introduction

Many therapeutic innovations are biopharmaceuticals, also referred to as biologics. Their applications include a diverse set of therapeutic areas incorporating oncology, rheumatology, endocrinology, dermatology, infectious diseases, and immunology [1]. Biopharmaceuticals offer a number of advantages over synthetic drugs. Their adaptable nature allows for custom tailoring, typically resulting in appreciable specificity and selectivity. These attributes enable biopharmaceuticals to precisely target specific molecules of interest, potentially reducing certain side effects, and providing

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Key Points

Biopharmaceuticals account for a large proportion of all new medicines, but there are few cross-national comparative studies assessing their introduction in healthcare.

In this study, diffusion rates for the first 4 years on the market were assessed in 17 European countries and two regions for 17 biopharmaceuticals approved between 2015 and 2019. Data were taken from public databases on utilization in ambulatory care and hospitals.

There is substantial variation between European countries and regions in the early diffusion of these 17 biopharmaceuticals and the availability of data to monitor their use. This is a concern if equity is a key consideration among patients across Europe.

more effective therapeutic approaches [1, 2]. In addition, biopharmaceuticals are larger and more complex than traditional small molecules, subjecting them to a unique set of advanced manufacturing techniques, regulations, and intellectual property rights. Biologics also exhibit high molecular instability, rendering them highly sensitive to degradation from pH changes, temperature variations, and excessive agitation. This highlights the demand for specialized storage and handling, contributing to additional expenses and logistical difficulties [3].

These characteristics often lead to higher requested prices compared with traditional medicines [4, 5], which can limit their utilization, particularly in low- and middle-income countries with limited resources [6]. Their biological nature also elevates the risk of eliciting an immune response in patients during administration, which can result in potential immunological adverse events [7] or lead to heightened susceptibility to infections [8, 9]. Furthermore, biological medicines are often administered as an infusion requiring advanced equipment and skilled healthcare professionals, primarily available within specialized care [1, 4]. However, other parenteral administration methods, including subcutaneous injections, have enabled patients to self-administer some biologics, alternatively have them administered in patients' homes by healthcare professionals to lower costs.

Biopharmaceuticals, which address high-risk populations with high unmet medical needs, may be eligible for an accelerated European marketing authorization process. However, rapid market access presents several challenges and has sparked extensive debate within the European Union (EU). A key point of contention is whether all biopharmaceuticals can genuinely be considered innovative and provide adequate therapeutic value [10, 11]. This debate is particularly relevant given their often-high prices, with a range from €10,000 to €30,000 per patient annually, with some treatments costing as much as €500,000 [12]. In certain cases, these therapies offer only limited additional benefits to patients, raising questions about their overall value [10, 13]. Moreover, efficacy data evaluated for accelerated market authorization can be limited, assessed based on surrogate endpoints and/or clinical trials without randomization and adequate control groups [13, 14]; consequently, not robustly estimating the (long-term) treatment benefits [15]. As a result, these evaluations may fail to fully capture the true benefit-risk profile of these innovative therapies. This uncertainty has prompted stakeholders to question their subsequent safety, efficacy, and real-world effectiveness. This is because in some cases, therapies have been found to offer no significant improvement over existing treatments in practice, leading to their withdrawal or severely limited market penetration shortly after introduction [13, 16].

There are additional challenges related to their high prices. As drug expenditure is rising rapidly, outpacing other healthcare expenses, biopharmaceuticals account for a significant portion of this increase. The most critical area is cancer, where global spending on medicines is expected to reach $409 billion by 2028, up from $223 billion in 2023, assisted by the launch of new biological medicines with more than 2000 currently under development [17]. In view of this, payers and health technology assessment agencies are compelled to prioritize and make tough decisions regarding which medicines genuinely offer value for patient care and deliver favorable cost effectiveness, and which do not, to more effectively target scare resources [11, 18]. However to date, such decisions may be hampered by the emotive nature of certain diseases [19–21].

Comparative drug utilization studies may serve as essential tools for advancing healthcare improvements by describing the utilization of medicines and actual clinical practice. These studies support evidence-based policies and practices aimed at fostering efficient, equitable, and safe medication utilization, as well as supporting optimized resource allocation to improve overall health outcomes [22]. The field of comparative drug utilization is expanding, with recent publications further enhancing its role in shaping future policy initiatives [23–26]. However, cross-national comparisons present distinct challenges because of differences in health authority procedures, population demographics, and healthcare systems [27, 28]. Furthermore, the introduction of biopharmaceuticals adds complexity, as they are frequently utilized in hospital settings, where comparable data are scarce and often the number of patients treated is modest [29, 30]. Alongside this, many biopharmaceuticals lack standardized drug utilization metrics, such as the defined daily dose (DDD), which is commonly utilized for medications [31].

From January 2018 to June 2022, a total of 196 biopharmaceuticals gained marketing authorization in the EU and/or the USA, marking a significant increase compared with approval rates observed between 1995 and 2014, when 50–60 biopharmaceuticals were approved in each 4-year interval [32]. After accounting for recent approvals and the exclusion of withdrawn products, the total number of actively licensed biopharmaceuticals in the EU and USA was 443 by mid-2022 [32]. To the best of our knowledge, there has been no comprehensive pan-European cross-national utilization studies focusing on the market diffusion of typically premium-priced biopharmaceuticals since their launch. This knowledge gap needs timely addressing to enhance understanding of uptake and utilization of these biological drugs and their potential impact in clinical and economical terms. Such a study could help inform future policies on the managed entry of new medicines given increasing expenditure on biopharmaceuticals across Europe, building on earlier collaborative efforts [11, 33].

This study consequently aims to investigate the current availability of health authority data and assess variation in the early diffusion of biopharmaceuticals across Europe. It was initiated by the authors (Ivar Veszelei and Björn Wettermark) and builds on prior experience from cross-national collaborations conducted within the Piperska Group and the European Drug Utilization Research Group (EuroDURG). These scientific networks have, for several decades, carried out comparative studies to promote the rational use of medicines and to support evidence-based policymaking across Europe [34–36]. The findings are intended to contribute to a better understanding of biopharmaceutical utilization in Europe and support ongoing efforts to improve health outcomes through rational and equitable use, particularly in settings with constrained resources.

2 Methods

A cross-sectional design was used to assess the availability of health authority data across Europe and to assess the utilization of biopharmaceuticals introduced between 2015 and 2019, in both hospital and out-of-hospital care.

2.1 Population

A total of 31 countries were considered eligible for inclusion in the study. This comprised the 27 EU member states, as well as four non-EU countries closely aligned with the EU and the European Medicines Agency (EMA), Norway, Iceland, Switzerland, and the UK.

Eligibility criteria included the availability of a contact person with access to relevant data sources and the ability to provide data for the therapies of interest across the study period. Only those countries or regions that submitted data, either from wholesalers or other comparable sources, and which were deemed sufficiently comparable, were included in the final analysis population. For countries without the availability of national data, data were collected for a region within the country.

2.2 Selection of Biopharmaceuticals

The European Public Assessment Reports list served as the initial source for identifying potential pharmaceutical candidates [37]. This list includes all human and veterinary medicine applications submitted to the EMA, both approved and rejected, from 1995 to the present day. Initially, all new chemical entities (substances) that received approval from the EMA for human use within the timeframe of 2015–19 were identified, which resulted in a total of 2050 medicines. The timeframe was chosen to reflect the current influence of biopharmaceuticals in the evolving and highly dynamic market. This timeframe also allowed for a subsequent 4-year observation period to analyze the initial early diffusion patterns of these biopharmaceuticals.

Medicines were subsequently excluded if they:

- Were classified as small molecular drugs, vaccines, advanced therapeutic medicinal products, oncological therapies (Anatomical Therapeutic Chemical [ATC] group L01), biosimilars, or generics [31].
- Were approved under designations including orphan drugs, exceptional circumstances, or accelerated assessments.
- Had no assigned DDD, enabling comparisons of volumes using aggregated data [31].
- Were withdrawn from the market during the follow-up period of 4 years after market approval.

The rationale for excluding vaccines, advanced therapeutic medicinal products, and oncological therapies stems from their preventative administration, individualized patient tailoring, and irregular administration methods, respectively, making it challenging to compare diffusion patterns, especially if there is an absence of approved DDD metrics. Medicines classified as orphan drugs or authorized under, exceptional circumstances and accelerated assessment, were also excluded to reduce random variation caused by low or unequal prevalence of these diseases, particularly in smaller countries. The orphan designation by the EMA indicates a disease prevalence not exceeding five patients per 10,000 inhabitants [38]. Given the small populations of countries including Estonia and Slovenia, estimated disease prevalence remains exceptionally low, with a potential range from just 100 to 1000 patients. Furthermore, withdrawal of therapies by the EMA would only occur in response to significant concerns regarding quality, efficacy, or safety reasons [39].

In such cases, these therapies would no longer be relevant or utilized within European countries closely associated with the EMA. The study focused on the attributes of newly developed biological entities. As a consequence, biosimilars and generics, which are closely based on already approved reference products, were excluded from the analysis.

The final selection comprised 17 biopharmaceuticals across seven distinct ATC groups, reflecting a wide range of therapeutic areas. Detailed information on each therapy, including ATC codes, the calculation of one DDD as per World Health Organization (WHO) methodology [31], and their initially approved indications according to the EMA [37], is provided in the Electronic Supplementary Material (ESM). A chronological overview of the EMA approval dates for these therapies is shown in Fig. 1, based on information extracted from the EMA's European Public Assessment Reports [37]. The highest number of approvals occurred in 2017, with five therapies receiving market authorization, followed by four therapies each in 2015 and 2018, and two therapies in both 2016 and 2019.

Seven of the therapies are classified under the L04AC group, which includes immunosuppressive antibodies primarily indicated for the treatment of plaque psoriasis and rheumatoid arthritis. These therapies will henceforth be referred to as immunosuppressives. Additionally, three therapies, erenumab, galcanezumab, and fremanezumab, belong to the N02CD group, all of which are calcitonin gene-related peptide (CGRP) receptor antagonists. The CGRP therapies are indicated for the preventive treatment of migraines, aiming to reduce both the frequency and severity of migraine attacks. Two further therapies, mepolizumab and benralizumab, are classified under the R03DX group and target interleukin-5 (IL-5). These treatments are indicated for obstructive airway diseases, particularly severe asthma, with the goal of reducing exacerbations and improving lung function in affected patients. Two therapies, evolocumab and alirocumab, classified under the C10AX group, are proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors. These are indicated for the treatment of dyslipidemia, with the primary objective of lowering low-density lipoprotein cholesterol levels and reducing the risk of cardiovascular events. Additionally, three individual therapies are classified under separate ATC groups: the fixed-dose combination (FDC) of insulin glargine and lixisenatide under A10AE, indicated for metabolic disorders associated with type 2 diabetes mellitus; dupilumab under D11AH, which was initially indicated for dermatological conditions such as dermatitis; and follitropin delta, classified under G03GA, a follicle-stimulating hormone aimed at treating infertility by promoting follicular development and ovulation.

2.3 Data Collection

The data collection for this study was primarily organized through data providers from academia and governmental agencies across Europe identified through the Piperska group and EuroDURG [34–36]. A request was sent out to all country representatives identified through these networks and to researchers who previously participated in scientific publications on cross-national comparisons focusing on the rational use of medicines including the introduction of new medicines [40–42]. The goal was to collaborate directly with health authority personnel or academic researchers with experience of drug utilization studies to strengthen the robustness of our findings, rather than relying on data from commercial sources. In cases where the contact was unable to provide data, the request was referred onward, when possible, if no suitable contact

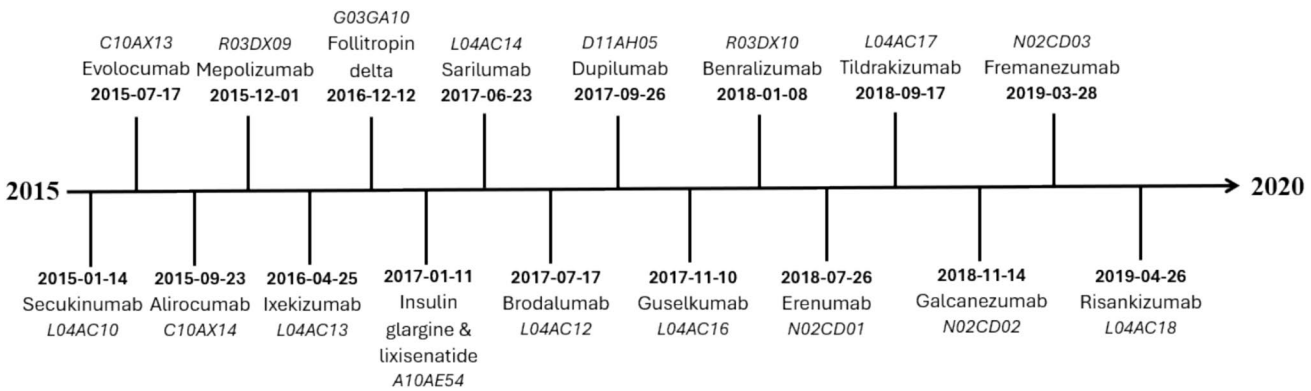

Fig. 1 Timeline of the selected biopharmaceuticals approved by the European Medicines Agency from 2015 to 2020. Anatomical Therapeutic Chemical codes, along with their International Nonproprietary Names; the fixed dose combination of insulin glargine & lixisenatide (A10AE54), evolocumab (C10AX13), alirocumab (C10AX14), dupilumab (D11AH05), follitropin delta (G03GA10), secukinumab (L04AC10), brodalumab (L04AC12), ixekizumab (L04AC13), sarilumab (L04AC14), guselkumab (L04AC16), tildrakizumab (L04AC17), risankizumab (L04AC18), erenumab (N02CD01), galcanezumab (N02CD02), fremanezumab (N02CD03), mepolizumab (R03DX09), benralizumab (R03DX10)

could be identified, the process was terminated. To assess data availability, a standard e-mail was sent to all potential data providers. The e-mail inquired about the metrics used for data quantification, such as DDDs, number of packages, and active ingredients. In cases where data could be translated into DDDs using the WHO methodology for calculating DDD indicators [31], data providers were subsequently sent a template shown in the ESM. They were asked about their capacity to provide national- or regional-level data on biopharmaceuticals, including both in-hospital and out-of-hospital utilization, as well as wholesalers' data, for the period 2015–22.

To reduce country-specific variation and enhance comparability in drug utilization analyses, we classified distribution into three overarching categories of drug delivery to patients. For the purposes of this study, utilization is defined as consumption measured based on either wholesaler's data or dispensations, depending on the data source available. While these categories offer an approximate framework, we acknowledge that healthcare systems, reporting practices, and distribution pathways vary significantly, and the boundaries between the categories occasionally overlap.

- In-hospital utilization refers to medications administered during hospitalizations or dispensed through hospital pharmacies. This category includes medicines managed within hospital settings, or through hospital budgets, whether intended to be administered in inpatient or outpatient settings. Typically, this included just in-patient costs with different organizations involved with funding in-patient and ambulatory care costs, including out-patient costs in a number of European countries, for example, Austria and Germany.
- Out-of-hospital utilization includes medications dispensed through public or community pharmacies, primarily intended for outpatient utilization. This category broadly represents utilization outside institutional hospital settings, encompassing medications utilized in primary care and certain specialized care settings where distribution occurs via non-hospital channels.
- Wholesalers represent aggregated sales data to hospitals and community pharmacies, capturing utilization across both sectors. However, a distinction between the two pathways may not always be possible.

2.4 Data Analysis

Data analysis included an assessment of data availability across the 31 initially considered countries, followed by a comparative evaluation of the accumulated diffusion of biopharmaceuticals within the 17 countries and two regions that made up the final study population. Diffusion was measured using DDDs, a standardized and widely adopted metric, to facilitate the identification of usage trends, cross-country variation, and differences across therapeutic areas. The diffusion of countries was assessed using available data presented in the ESM and represents total use as wholesalers or the sum of out-of-hospital and in-hospital consumption. This approach was applied for all countries except Germany and Austria, which only had out-of-hospital data in this study. Notably, as described above, the distinction into in-hospital and out-hospital medicines is not necessarily consistent across countries because data commonly reflect financing structures rather than realized utilization. Therefore, in-patient medicines may include products that are dispensed in hospitals or through hospital pharmacies for outpatient use or financed through hospital budgets although dispensed and used in outpatient settings [43].

To standardize population figures, and facilitate comparative analysis across countries/regions, utilization data were converted from DDDs to DDDs per 1000 inhabitants, following the WHO methodology for calculating DDD indicators [31]. The population figures were sourced from the European Commission via the Eurostat population database [44]. However, regional data or data from sub-populations were utilized in instances where full national data were unavailable, including population estimates for Scotland obtained from the Office for National Statistics. Catalonia relied on data from the Registre Central de Població Acreditada del Servei Català de Salut, and population data for Germany were sourced from their Federal Health Ministry. The accumulated diffusion was measured over the first 4 years following market authorization by the EMA, henceforth referred as accumulated diffusion. Data were presented in this manner to minimize random annual variation and enable comparisons regardless of how rapidly after market approval the first sales started.

The analysis of utilization across the different therapeutic areas was grouped by the fourth level of the ATC classification system [31]. This approach was chosen to enable a comparative analysis, as some countries/regions may introduce only a limited number of therapies within each ATC group, which could lead to misinterpretations. In the accumulated diffusion graphs, countries/regions were positioned by the extent of their diffusion, with the highest value country presented first. Values below 1 were recorded as < 1, apart from the follitropin delta graph.

The distribution of utilization across different pathways (out-of-hospital and in-hospital) was analyzed in detail for four medication classes, CGRP receptor antagonists, PCSK-9 inhibitors, immunosuppressants, and IL-5 inhibitors. These four classes were selected based on the presence of at least two new biopharmaceutical substances within the class as well as indicated for the treatment of relatively common diseases. Additionally, other aspects contributed to the exclusion of single-entity therapies. Suliqua is a FDC of two

already approved therapies, insulin glargine and lixisenatide, essentially a combination of two previously existing agents. Rekovelle is used within multi-step in vitro fertilization protocols, and dupilumab's subsequent approval for severe asthma complicates the interpretation of its utilization across different indications. This analysis utilized data only from countries/regions, which provided both out-of-hospital and hospital sector data for all these four medication classes.

A scoring system was implemented to provide a rank for the whole study population regarding their overall biopharmaceutical diffusion for these therapies. Each country was assigned a score that ranged from 1 to 19, reflecting its relative accumulated diffusion across each therapeutic area. The country with the highest diffusion in each graph received the lowest score, while the country with the lowest diffusion received the highest. If two or more countries/regions had identical values, they were given equal scores. The overall rank was determined by summing their scores across all seven therapeutic areas, where a lower total score indicated higher biopharmaceutical diffusion.

3 Results

3.1 Data Availability

The availability and completeness of diffusion data varied among the 31 European countries initially considered. Of the countries assessed, two European countries (Portugal and Bulgaria) lacked data for the periods of 2015–18 and 2015–17, respectively, and were therefore excluded from further analysis of utilization. Additionally, six countries (Austria, France, Germany, Hungary, Republic of Ireland, and the Netherlands) had no hospital data available. Four of these countries (France, Hungary, Republic of Ireland, and the Netherlands) were subsequently excluded from further analysis because of the limited coverage of the therapies of interest, which hindered their suitability for comparison. In contrast, Austria and Germany were retained, as their data, despite limitations, provided valuable insights into diffusion patterns within their populations. In both countries, it can be assumed that out-of-hospital utilization accounts for the majority of pharmaceutical use [45, 46]. Six countries were also excluded through a lack of suitable data (Grece, Cyprus, Luxembourg, Malta, Poland, and Switzerland).

The final study population, as illustrated in Fig. 2, comprised 17 countries, Austria, Belgium, Croatia, Czech Republic, Denmark, Estonia, Finland, Germany, Iceland, Italy, Latvia, Lithuania, Norway, Romania, Slovakia, Slovenia, and Sweden. In addition, two regions, namely Catalonia to reflect Spain and Scotland to reflect the UK, were included in the absence of national-level data. This

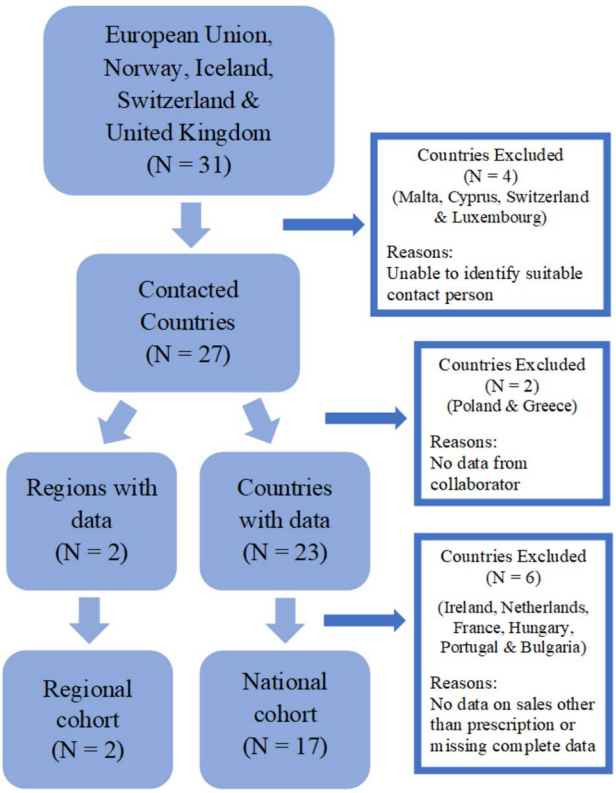

Fig. 2 Overview of the final study population derived from the initially considered countries, resulting in 17 national and 2 regional cohorts with adequately comparable diffusion data

regional approach is consistent with previous pan-European drug utilization studies [23, 47].

Some countries/regions contributed data across multiple diffusion categories. In total for this study, 22 countries/regions provided biopharmaceutical diffusion data for out-of-hospital utilization, 15 countries/regions provided wholesaler data, and 14 countries/regions provided data for hospital care.

However, Slovenia's hospital care utilization was limited to only mepolizumab and benralizumab, as these were the only therapies covered in their dataset. Germany's diffusion data were confined to individuals insured by public health funds, which represents approximately 90% of the total population. The ESM provides the specific data sources each country/region utilized for this study. Availability across the three categories, out-of-hospital, hospital, and wholesalers, is shown in Fig. 3.

3.2 Total Diffusion Rankings

An overview of the overall diffusion presented as early diffusion rankings is detailed in Table 1. It illustrates the relative diffusion of biopharmaceuticals across the various therapeutic areas within the entire study population.

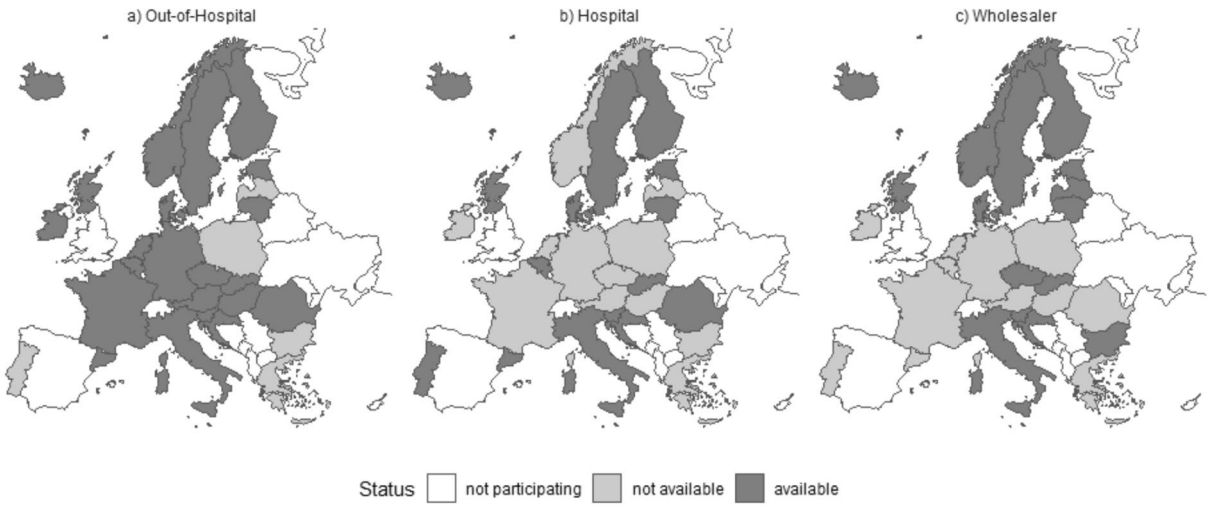

Fig. 3 Availability of health authority data on **a** out-of-hospital, **b** hospital, and **c** wholesaler of biopharmaceuticals for this study over the initial 4 years post-market authorization. The shade of color represents availability. A darker shade indicates the availability of data at the specified level, while a lighter shade represents data that are limited to one of the other levels. Uncolored countries/regions were unable to provide any data

Table 1 Diffusion rankings for each therapy group, given by mechanism of action or active ingredients, and the overall study population

Country/ region	Overall Rank	*Insulin glargine & Lixisenatide*	*PCSK9-inhibitors*	*Dupilumab*	*Follitropin delta*	*Immunosuppressives*	*CGRP-antagonists*	*IL-5-targeting therapies*
Germany	***1*** (35)	10	4	1	7	2	7	4
Austria	***2*** (37)	14	1	2	11	3	4	2
Norway	***3*** (44)	11	2	7	2	12	1	9
Sweden	***4*** (45)	4	8	5	11	7	3	7
Iceland	***4*** (45)	13	6	9	1	8	5	3
Denmark	***6*** (49)	15	3	3	3	10	10	5
Belgium	***7*** (53)	8	5	11	11	4	13	1
Italy	***8*** (59)	6	10	4	8	11	14	6
Slovenia	***9*** (66)	12	11	13	11	1	8	10
Finland	***10*** (67)	16	13	8	11	5	2	12
Catalonia	***10*** (67)	17	7	14	4	6	11	8
Czech Republic	***12*** (76)	3	14	10	9	13	9	18
Scotland	***13*** (82)	17	12	6	11	9	16	11
Estonia	***14*** (85)	2	15	12	11	14	17	14
Croatia	***15*** (88)	9	16	16	5	15	12	15
Slovakia	***16*** (94)	5	9	17	11	18	15	19
Lithuania	***17*** (98)	17	18	15	10	19	6	13
Romania	***18*** (99)	7	17	18	6	16	19	16
Latvia	***19*** (101)	1	18	19	11	17	18	17

Ranks are determined by their accumulated early diffusion; lowest rank indicates highest diffusion. The overall rank is determined by the total accumulated score from all seven groups. The accumulated score is shown in the overall rank parentheses

CGRP calcitonin gene-related peptide, *IL-5* interleukin-5, *PCSK9* proprotein convertase subtilisin/kexin type 9

Germany and Austria exhibited the highest overall diffusion rates and were ranked 1 and 2, respectively. Norway, Sweden, Iceland, and Denmark similarly demonstrated high diffusion rates, with Norway leading this group. Finland, the last remaining Northern country, positioned itself in the middle of the rankings. Belgium closely followed the rank of the first four Nordic countries. A small gap separates Belgium from Italy, which ranks eighth with higher diffusion than the average study population. In contrast, Catalonia was ranked in the middle, while Scotland was ranked 13th with lower diffusion rates. Croatia was ranked among the five countries with the lowest diffusion. All central and Eastern European countries, with the exception of Slovenia, displayed low diffusion rates and were consequently ranked below the average rank. The lowest rankings were observed in Slovakia, Lithuania, Romania, and Latvia.

3.3 Diffusion in the Different Therapeutic Areas

Further analysis in terms of the uptake rates for the 17 individual substances, rather than the overall total, revealed a large variation between countries and regions. The main findings are summarized below, with detailed figures for each therapeutic area and all countries/regions provided in the ESM.

The Southern European countries and regions Italy and Catalonia, along with Scotland and Croatia, showed varied diffusion rates in the respective therapeutic groups. In contrast, three Western European countries, Austria, Belgium, and Germany, displayed high or medium diffusion rates across all therapy groups, apart from the FDC of insulin glargine and lixisenatide, as well as follitropin delta. Notable is that in these categories, comparable European countries, by their respective ranking, exhibited inconsistent diffusion patterns.

The highest uptake of the FDC of insulin glargine and lixisenatide was observed in central and Eastern European countries including Latvia, Estonia, and the Czech Republic, with diffusion rates two to three times higher than those of the next closest countries/regions. In contrast, other Central and Eastern European countries, including Lithuania and Slovenia, along with several other countries, demonstrated minimal or no diffusion of this combination.

This trend was, however, not observed in other groups including follitropin delta, where most central and Eastern European countries exhibited minimal or zero diffusion. Instead, three Northern European countries, Iceland, Norway, and Denmark, displayed the highest diffusion rates. However, Sweden and Finland had no diffusion of follitropin delta but aligned closely with the other Northern European countries in most of the other therapeutic groups. The pattern of high diffusion in the Northern region is most notable in the CGRP group, in which they account for the majority of the diffusion observed.

For the remaining therapy groups, the PCSK9 inhibitors, IL-5 treatments, dupilumab, and the immunosuppressants, there was a consistent trend of lower diffusion in most central and Eastern European countries and higher diffusion in Western and Northern European countries. Slovenia, however, showed varying diffusion rates depending on the therapeutic group. While Slovenia's diffusion was below average in certain groups, it exhibited the highest diffusion of immunosuppressants among all European countries and regions.

In examining the early diffusion of specific therapies, tildrakizumab demonstrated the lowest level of diffusion, with 12 countries or regions showing no uptake. Following this, follitropin delta had nine countries/regions without any diffusion during the studied period. In contrast, secukinumab and erenumab exhibited the highest diffusion rates, with all countries showing an uptake. For the remaining therapies, the diffusion was widespread, with only one or two countries or regions lacking diffusion on average.

3.4 Distribution Between Out-of-Hospital and Hospital Diffusion

To further investigate the comprehensive diffusion data, Fig. 4 illustrates the distribution of diffusion across four medical classes through the different pathways, out-of-hospital and hospital.

The majority of utilization for the CGRP receptor antagonists occurred through out-of-hospital utilization in nine out of 13 countries/regions. A similar trend was observed for PCSK-9 inhibitors, with eight out of 13 countries/regions reporting major diffusion through out-of-hospital utilization. For immunosuppressant antibodies, 7 out of 13 countries/regions also saw the majority of utilization through out-of-hospital utilization. In contrast, for monoclonal antibodies targeting IL-5, hospital utilization was the predominant pathway in 10 out of 13 countries/regions.

Our data revealed that utilization across all medication classes occurred primarily or exclusively through the hospital sector in Catalonia, Denmark, Scotland, and Italy. In contrast, out of hospital was the dominant pathway for all medication classes in Romania and Slovakia. In Belgium, Iceland, Finland, and Sweden, out of hospital was predominant for three medication classes, with the hospital sector being more prominent only for IL-5 treatments. Croatia, Estonia, and Lithuania exhibited a mixed pattern of diffusion, with the dominant pathway varying between different therapy groups.

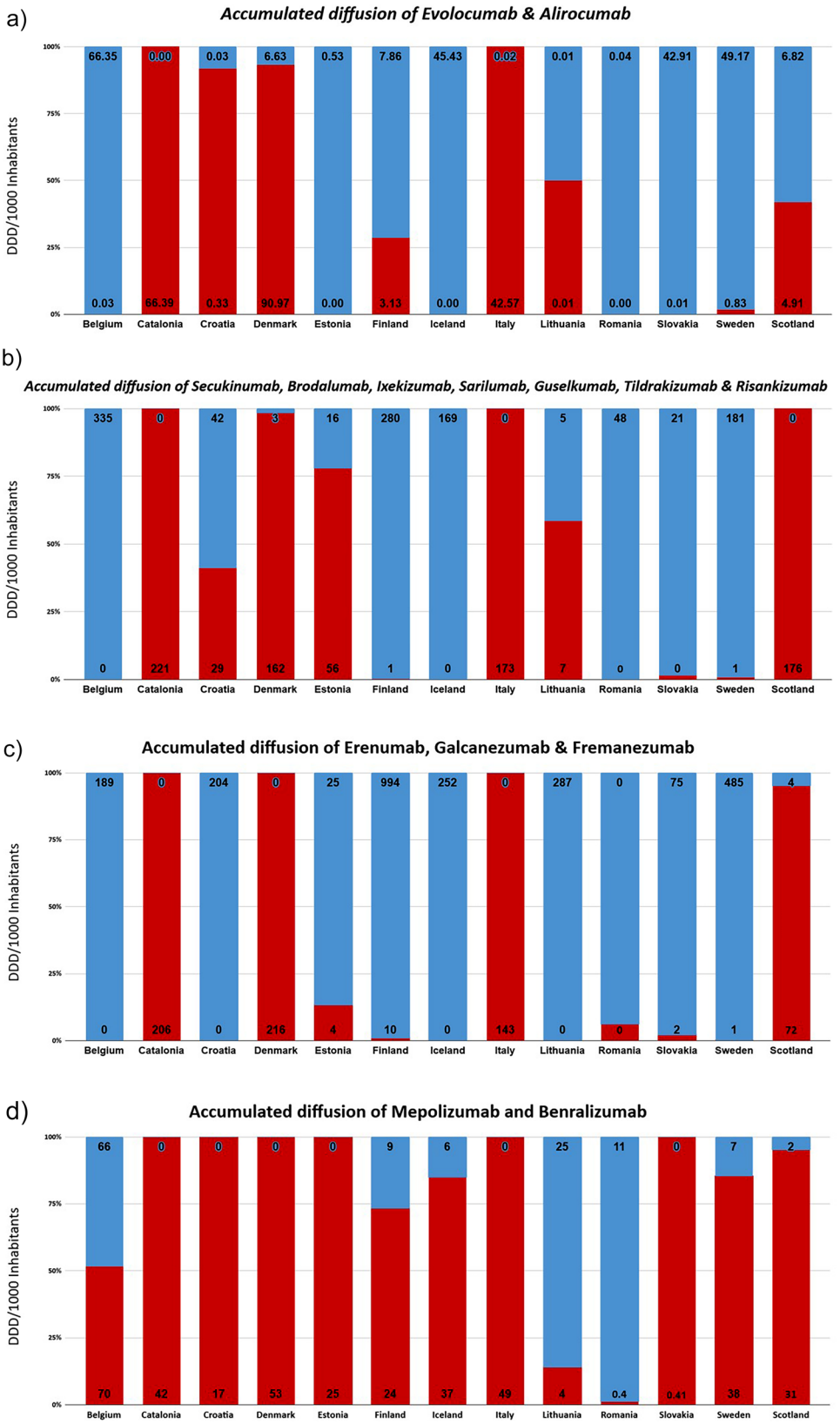

Fig. 4 Distribution of out-of-hospital and hospital utilization across the selected countries and regions for **a** proprotein convertase subtilisin/kexin type 9 inhibitors, **b** all immunosuppressant antibodies, **c** the calcitonin gene-related peptide receptor antagonists, and **d** the interleukin-5 targeting therapies. Out-of-hospital utilization is represented in blue, while hospital utilization is shown in red. The accumulated diffusion numbers in defined daily doses per 1000 inhabitants for out-of-hospital utilization are displayed at the top of each bar, and for hospital utilization at the bottom of each bar

4 Discussion

This study is, to the best of our knowledge, the first to investigate the market diffusion of a large number of different premium-priced biopharmaceuticals across Europe using health authority data. By incorporating real-world drug utilization data from 17 European countries and two regions, it reveals variability in the early diffusion of biopharmaceuticals across these nations and regions. The highest rate of biopharmaceuticals diffusion was observed in Germany and Austria, followed by several Northern European countries. The slowest uptake was seen among Central and Eastern European countries including Lithuania, Romania, and Latvia. Additionally, the study highlighted substantial challenges in acquiring data from health authorities, and the considerable differences in the data that was provided for monitoring drug utilization across the included countries/regions.

4.1 Determinants of Early Biopharmaceutical Diffusion

Previous literature has consistently found differences across European countries in the use and uptake patterns of novel and premium priced medicines, including biopharmaceutical products, orphan medicines, and oncology products. The differences are likely attributed to several interlinking and interacting reasons. Countries with a large market size and strong economies tend to exhibit rapid uptake and high utilization patterns [6, 48–52]. Countries with a lower gross domestic product and a smaller market size may in turn heavily restrict access through coverage decisions or reimbursement criteria because of budgetary reasons; alternatively, other barriers to access may limit their uptake [52–54]. Small markets may also lack attractiveness because of low profits in relation to entry costs attributed to regulatory processes and labeling requirements, and in the case of rare diseases, differences may be related to prevalence rates with smaller countries either having a rapid or a slow uptake [48, 55].

Restrained markets can also set lower pharmaceutical prices and thus experience delays in pricing applications to avoid price erosion in markets where reference pricing is based on the lowest available price [56, 57]. In such restrained settings, the use of biosimilars following loss of market exclusivity offers an increasing potential to improve access to biopharmaceuticals and promote more equitable use in countries with limited healthcare budgets [6, 58]. Cross-national comparisons are limited in this field. However, they are increasingly being undertaken and show similar results as for branded biopharmaceuticals, i.e., that there is a large variation between countries in their utilization [24, 58, 59]. This is attributable to a large variation in factors including specific measures taken to stimulate the utilization of biosimilars [59, 60].

Other important determinants for differences in early diffusion across countries that have similar macroeconomic features include regulatory and health technology assessment processes, payment models, distribution channels as well as pricing and reimbursement [56, 61]. The duration and outcomes of pricing and reimbursement processes vary significantly across countries [61, 62]. For example, some countries seem to place a higher emphasis on budget control, whereas others prioritize the potential benefits of new medicine [48, 50, 51, 63, 64]. As all new products are not equal in their value, a medicine's therapeutic importance is a likely contributor [50]. Furthermore, some health systems may approve new treatments rapidly but impose strict usage conditions, such as limiting access to patients unresponsive to conventional therapies or to subgroups with demonstrated higher benefits. Others may delay decisions because of prolonged evaluations, yet ultimately provide broader access [57, 65, 66]. These divergent approaches influence both the timing of reimbursement decisions and the inclusiveness of access to novel therapies across populations [49, 54, 64, 67–69].

Furthermore, differences in interpretations of evidence and cultural factors are also among the hypothesized explanations for variation in uptake. The perceived clinical value and necessity of new therapies among key medical specialists, who frequently influence the development of clinical guidelines and prescribing norms, can play a crucial role [70, 71]. Variability in key specialist perspectives, both between and within countries, shaped by national and local diagnostic practices, clinical traditions, the influence of pharmaceutical companies, and differing levels of experience with specific patient populations, may contribute to divergent patterns in the adoption and use of biopharmaceuticals [72–74].

While the current study was not designed to formally assess associations between diffusion rates and macro-level determinants, the observed patterns broadly align with previous findings indicating a higher uptake of biopharmaceuticals in countries with greater economic resources. In particular, countries such as Germany, Austria, Norway, Denmark, Sweden, Belgium, and Iceland, characterized by higher gross domestic product and health expenditure per capita, as reported in the World Development Indicators database, appear at the top of the ranking. In contrast, countries with comparatively lower economic resources, including Romania, Latvia, Slovakia, Lithuania, and Croatia, tend to show a more limited uptake. These observations support the concept that a macroeconomic context plays a role in facilitating an earlier or broader adoption of biopharmaceutical therapies. One notable outlier is Scotland, which ranks comparatively low in this study despite being part of the UK,

a country with a relatively high gross domestic product. As the data reflect only the Scottish context with a potentially more constrained health budget or different policy environment relative to the rest of the UK, this may still align with the broader interpretation.

Regardless of the countries or health system circumstances, collective efforts are essential within the European context to address the rising costs and associated of novel biopharmaceuticals [75]. Ongoing initiatives include the European Pharmaceutical Strategy [76] and European Network for Health Technology Assessment [77]. They aim to tackle challenges by establishing effective and sustainable structures, providing timely and transparent information to help reduce inequities and harmonize market access timelines across countries [76, 77]. Studies such as this one help in this process by highlighting appreciable differences in utilization rates of new biopharmaceutical medicines between European countries, which need to be explored further to provide future guidance.

4.2 Diffusion of Biologics Across European Healthcare Systems

The early diffusion rankings revealed considerable disparities among countries and regions in their adoption of new biopharmaceuticals. The highest-ranking countries displayed nearly three times the diffusion rate versus the lowest-ranking countries, indicating a substantial variation in early biopharmaceutical access and usage across the study population. The comparatively lower utilization of new biopharmaceuticals among Central and Eastern European countries is similar to previous studies including the tumor necrosis factor-α inhibitors for rheumatoid arthritis and Crohn's disease [78, 79] as well as the lipid-lowering PCSK9 inhibitors [26].

While the overall ranking provided a concise summary of total diffusion, further analysis of the accumulated diffusion graphs revealed that the observed patterns of high or low uptake were not consistent across all therapeutic areas. Instead, several countries and regions exhibited high adoption in certain therapeutic areas while showing a low uptake in others. This finding aligns with previous cross-national comparisons [56, 80], and reflects the complex range of determinants influencing the uptake of new medicines [81–84].

For the FDC of insulin, as well as follitropin and tildrakizumab, only a limited number of countries demonstrated a substantial uptake, whereas most healthcare systems showed relatively modest diffusion. In contrast, IL-5 targeting therapies and immunosuppressive antibodies displayed a more uniformly distributed uptake across countries, with fewer instances of significantly elevated use and a more gradual tapering pattern. Dupilumab and the PCSK-9 inhibitors displayed similar diffusion patterns to the evenly distributed substances. However, uptake was observed in fewer countries and among those with higher usage, there was a steeper decline in diffusion compared with other therapies. Finally, for the CGRP receptor antagonists, two countries stood out with notably greater use, while the remainder exhibited lower and relatively constant levels of diffusion. It is important to note that these graphs are not presented on a uniform numerical scale, hence, absolute levels of use should be interpreted with caution.

Overall, high or low rates of diffusion do not necessarily reflect the performance of a healthcare system. Some medicines may fail to meet patients' needs effectively, particularly when their cost outweighs their clinical efficacy and demand side measures, along with pressure from patient populations, which appreciably vary between European countries affecting their uptake [85]. Increased use of such medicines can place substantial burdens on healthcare systems without delivering proportional benefits, thereby undermining overall healthcare performance [19]. In addition, they may counteract existing priority areas for investment in new and established medicines. The analytical framework of "pharmaceuticalization" conceptualizes the growing economic, societal, and political importance of medicines and the pharmaceutical industry. It is often associated with negative connotations, such as media mediation and the use of medicines for enhancement rather than treatment [86]. This highlights the need for critical assessment of whether all new treatments are necessary, advocating for caution in the adoption of new medications.

4.3 Barriers and Opportunities in Accessing Utilization Data

The lack of harmonized data on pharmaceutical utilization across countries and regions has hindered comparisons of the diffusion and uptake of novel pharmaceuticals. Previous cross-national studies have relied on comprehensive commercial data, reporting both hospital and out-of-hospital diffusion [26, 30, 78]. However, commercial data are costly to obtain, making it inaccessible for many researchers. To transparently conduct research on drug utilization, data that are readily available without significant costs must be accessible, which is why commercial data were excluded from this study. The development of the new European Health Data Space Regulation represents an important initiative to facilitate access to key health data. The European Health Data Space Regulation aims to assist individuals in accessing, controlling, and sharing their health data, while also enabling the secondary use of such health data across borders within EU member states. The European Health Data

Space Regulation therefore has the potential to support more equitable and transparent research on pharmaceutical utilization by improving access for non-commercial and academic researchers [87].

Aggregated health authority data on drug utilization were available from many European countries and regions. However, consistent with previous research [28, 30], the greatest challenge in accessing data was observed in the hospital setting. This is particularly concerning as many biopharmaceuticals are administered parenterally and are often introduced in hospital settings before potentially transitioning to out-of-hospital settings. Thus, the absence of hospital data severely limited the full scope of biopharmaceutical utilization in certain healthcare systems including France, Hungary, Republic of Ireland, and the Netherlands, to the extent that they could not be included in the analysis because of the uncertainty. However, Germany and Austria, which had only out-of-hospital data for this study, still provided valuable insights into utilization patterns within their healthcare systems, as implied by their rankings.

The ongoing global digital transformation, characterized by rapid technological advancements, has significantly expanded the capacity to collect and utilize healthcare data [88–90]. It is anticipated that this trend will continue, enhancing data collection and reporting for biopharmaceuticals. This would enable future studies to incorporate both out-of-hospital and hospital data, offering a more comprehensive view of biopharmaceutical utilization across healthcare settings. Consistent with the crucial need to obtain readily available and transparent data without the significant costs associated with commercial sources, this would enable more inclusive and equitable research, promoting a better understanding of drug utilization across diverse healthcare systems.

4.4 Distribution Preferences for Biopharmaceuticals

In recent years, many countries and regions have introduced funding models aimed at bridging the gap between hospital and outpatient sectors. These models are designed to prevent cost shifting of high-cost medications between sectors or payers, while also enabling countries and regions to benefit from public procurement arrangements [91, 92]. As such countries and regions differ widely in how they structure their systems, policies, and procedures regarding hospital versus out-of-hospital pharmaceuticals [43].

In our study, major variation in the distribution of pharmaceutical utilization between hospital and out-of-hospital pathways were observed across both medication classes and countries/regions. Countries and regions such as Catalonia, Denmark, Italy, and Scotland demonstrated a preference for hospital-based utilization, which aligns with earlier data on sales distribution [93]. In contrast, countries including Belgium, Finland, Iceland, and Sweden, which exhibited a majority of out-of-hospital utilization for three of the therapy classes, showed a shift toward hospital utilization for the severe asthma therapies. By contrast, Croatia, Estonia, and Lithuania exhibited a varied assortment of different pathways, revealing diverse distribution preferences of therapies.

The differences in distribution between out-of-hospital and hospital settings should be interpreted with caution, as they are often shaped by country-specific financing arrangements and reimbursement policies. It is also intensified by inconsistent classification systems and overlapping categories. Accurately understanding pathways patterns thus requires detailed national knowledge to uncover underlying factors and provide a reliable basis for interpretation.

4.5 Strengths and Limitations

The significance of this project lies in its extensive reach, including data from most European countries, a noteworthy achievement given the complexities of establishing large-scale cross-national comparisons. Through a descriptive approach, the study shed light on specific challenges and their implications for conducting comparisons of the early introduction of biopharmaceuticals. Additionally, the findings highlighted variations in early diffusion rates between different therapeutic areas. Other strengths relate to the use of the ATC-DDD system, recommended by the WHO for drug utilization studies [31], and the active participation of researchers and data holders from all countries/regions, enabling validation of findings.

We acknowledge, however, that there are some limitations. The main challenge was related to obtaining comparable data and identifying relevant collaborators in each country. As such, the data availability for this study may not fully reflect clinical practice across all countries. For instance, differences exist between European countries in how they define, fund, and organize in-hospital and out-of-hospital use within their healthcare systems, which can lead to inconsistencies and confusion. This motivated us to categorize the data accordingly, to reduce country-specific variation and enhance comparability. However, this approach may itself introduce some degree of misclassification or oversimplification.

Another issue was related to the available data provided and capturing the full extent of biopharmaceutical utilization, especially in countries/regions that could only provide out-of-hospital data. A further challenge of the study is attributed to its focus on the initial 4 years after market approval. Focusing solely on this period might not capture the entire picture, as diffusion patterns may change over time. Visualizing data with annual trends could offer

more nuanced insights, revealing variations and potential changes over time. This is particularly relevant considering the dynamic nature and constant changes occurring within the European countries or regions.

We also acknowledge a challenge associated with using DDDs as a measure of utilization, as it resulted in the exclusion of some rapidly growing therapeutic areas for biopharmaceutical drugs, including orphan drugs and oncology. It is important to recognize the significance of these areas, as they may exhibit greater variation in access and use across European countries or regions than the therapies included in this study [94, 95]. Conducting further research in these areas could offer valuable insights into the equity of biopharmaceutical introduction in less explored but increasingly important therapeutic domains. The continued development of DDD measures for therapies in areas where they are currently lacking would help improve comparability and facilitate future research on biopharmaceutical utilization in these fields. Additionally, using DDDs per 1000 inhabitants over a 4-year period, allowed us to focus on longer term uptake patterns without being influenced by short-term fluctuations or cross-national inconsistencies in introductory approaches and utilization reporting. However, it may limit comparability to other studies and obscure shorter-term variations.

5 Conclusions

This study aimed to investigate the early diffusion of new biopharmaceuticals across European countries. The research highlighted the challenges of varying data availability from non-commercial sources, complicating the cross-national comparison of biopharmaceutical diffusion. However, by illustrating overall diffusion, therapy-specific diffusion, and distribution across hospital and out-of-hospital pathways, the study revealed considerable variability both between European countries and among therapeutic areas. These findings highlight the importance of strengthened collaboration between European countries to support the sustainable, cost-effective, and equitable introduction of biopharmaceuticals. They also underscore the need for more harmonized data collection and reporting to better understand the disparities in biopharmaceutical diffusion across Europe. In conclusion, we hope the insights from this research will inspire further studies and, ultimately, contribute to improved access to biopharmaceuticals and a more equitable healthcare landscape across Europe.

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Declarations

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Conflict of interest Agnese Cangini, Gisbert W. Selke, Irene Langner, Katri Aaltonen, Ott Laius, Thais de Pando, and Tomáš Tesař are affiliated with organizations involved in payer decision making and the reimbursement of medicines, although they may not be directly engaged in such activities. Juraj Slabý and Leena Saastamoinen are affiliated with organizations involved in health technology assessment in advisory or expert roles. Ivar Veszelei, Brian Godman, Kristina Garuolienė, Amanj Kurdi, António Teixeira Rodrigues, Caridad Pontes, Carla Torre, Carlotta Lunghi, Edel Burton, Elita Poplavska, Freyja Jónsdóttir, Guenka Petrova, Irina Iaru, Irina Odnoletkova, Katarina Gvozdanović, Ria Benkö, Silvija Žiogaitė, Stuart McTaggart, Tanja Mueller, Zornitsa Mitkova, and Björn Wettermark have no conflicts of interest related to payer or health technology assessment agencies.

Ethics approval This is an observational study using only national-level aggregated data and thus ethical approval was not required.

Consent to participate As only national-level aggregated data were used, patient consent to participate was not required.

Consent for publication Not applicable.

Availability of data and material All data of this study are available from the corresponding author upon reasonable request.

Code availability Not applicable.

Author contributions Ivar Veszelei and Björn Wettermark were responsible for the study's conception. All authors participated in designing the study, with Ivar Veszelei taking on overall management responsibilities, including organizing meetings, managing documentation, and facilitating clear communication among the team. Data management, collection, and analysis was performed by Ivar Veszelei. The first draft of the manuscript was written by Björn Wettermark based on a prior master thesis written by Ivar Veszelei, under supervision of BW. All authors reviewed various versions of the manuscript, provided feedback, and approved the final version.

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