LOGEX

In partnership with ivm

International Comparison Biologics Uptake 2023

Severe asthma

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The ICMU Severe Asthma report has been sponsored through funding by Astra-Zeneca. AstraZeneca had no input or editorial control over the final content of the report. AstraZeneca, along with other industry experts, were approached for medicine indication split estimates for use within LOGEX's calculations in Part B of the report, which was reactively provided with no compulsion to use these data.

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Executive summary

To this day, asthma remains a chronic disease, affecting in excess of 262 million people globally in 2019 (1). Being a common disease, asthma has a substantial impact on individuals and healthcare services. Severe asthma, which has many definitions, can be thought of as one extreme end in the spectrum of the disease. Despite severe asthma being estimated to make up only 5 percent of overall asthma burden, it accounts for 50 percent of the economic expenditure of asthma (2).

In asthma the overuse of short-acting beta agonists (SABAs) is a common occurrence and can signify undertreatment with maintenance therapies (3). In severe asthma, chronic use of oral corticosteroid is similarly widespread, with one UK study citing 51 percent of severe asthma patients being on maintenance oral corticosteroid treatment (4). Patients often suffer from frequent and distressing hospital attendances due to high exacerbation rates. Mortality rates are high. More recently, novel treatments in the form of biologics have entered the market and have shown efficacy for severe asthma management. A recent systematic review demonstrated that biologics can reduce severe asthma exacerbations by 51 percent (5). This is further backed by patients surveyed in 2020 by Asthma and Lung UK, they found that 64 percent of severe asthma patients on biologics experienced reduced symptoms and 43 percent of these patients experienced reduced hospital admissions (6). Additionally a recent ABPI publication highlighted that increased uptake of biologics in severe asthma could lead to an increase in the quality of life for patients (measured in QALYs) and a productivity boost of £9.6 billion to the UK economy (7). Although prescribing is shifting from oral corticosteroids to biologics, wide variations across countries exist in terms of the speed and scale of this shift.

The disproportionate economic cost and burden of severe asthma in relation to asthma, and the shift in usage of biologics makes understanding the changing picture of biologics uptake even more important. This provides a significant opportunity for LOGEX, with financial sponsorship of AstraZeneca, to deliver tangible insights on the extent to which biologics are being used in different European countries. IVM (Instituut Verantwoord Medicijngebruik) supported LOGEX in data collection and analysis.

A previous 2021 report – International Comparison Medicines Uptake was developed for NHS (National Health Service) England and focussed on five high health gain areas of importance for England. It delivered a standard, repeatable, and scalable methodology to carry out robust international comparisons on the uptake of medicines, using publicly available data sources. In this follow-up 2023 report, we deliver an in-depth report of uptake patterns of biologics among patients with severe asthma in European countries, based on that same methodology. As most included countries were already assessed in the first report for the NHS, the current report provides a measure of the increase in the uptake of biologics in all countries. Furthermore, in this report, the relatively new biologic drug dupilumab, has also been taken into account.

We believe an uptake tracking measurement provides a unique and important window of insight, as the measurement can be used to study how countries adhere to the international treatment guidelines. It also provides the opportunity to evaluate the effects of access policies and reimbursement decisions for patients. All countries, regardless of rank, can still improve their services for asthma patients.

Biologics have a complex set of prescription criteria in severe asthma affecting reimbursement and this varies across countries and continents (7). Currently, it is unclear how many patients with severe asthma are eligible for biologics, nor it is known how many patients are able to be reimbursed. This report demonstrates that countries across Europe have varying uptake of asthma biologics ranging from as low as 5% to as high as 60%. Germany has a relatively high biologics uptake in the severe asthma population, while the biologics uptake for severe asthma in England and Finland is lagging behind substantially compared to the other countries. Notably these countries demonstrate that where uptake is high or low, so too is the change over time; Germany and Sweden show a higher relative increase in uptake between 2019 and 2021 for the severe asthma population, whilst England and Finland do not.

Ranking of the included countries based on their asthma biologics uptake in the severe asthma population using the mean uptake. Please note: an accurate ranking for countries with confidence intervals cannot be made and they should be viewed as ranked groups.

Ranking group	Ranking	2019	2020	2021
Upper	1	Germany	Germany	Germany
	2	Denmark*	Denmark**	Denmark***
Middle	3	The Netherlands*	The Netherlands**	Sweden***
	4	France	Sweden**	The Netherlands***
	5	Italy*	France**	France
	6	Sweden*	Italy**	Italy
Lower	7	England	England	England
	8	Finland	Finland	Finland

* Countries with overlapping confidence intervals in 2019,
** Countries with overlapping confidence intervals in 2020
*** Countries with overlapping confidence intervals in 2021

Asthma is a chronic disease with a high prevalence globally. Many patients suffer substantially from frequent flare ups and rescue medication use. Although there has been significant improvement in asthma treatment over the last 100 years, severe cases of the disease still often receive suboptimal treatment. Several bodies have called for improvements over the last couple of years, addressing the introduction of novel biologic therapies as a potential solution for many patients with a severe asthma onset (9) (47) (48). However, the use of asthma biologics does not seem to be as widespread as desired and long-term use of oral corticosteroids, which present many chronic side effects, still is the main treatment choice. In line with this, this report presents a measure of biologics uptake in various European countries over time, to demonstrate each countries progress and their differences.

1 Introduction

The Voluntary Scheme for branded medicines in pricing and access was established in 2019 by the Department of Health and Social Care, National Health Service (NHS) England, the Association of the British Pharmaceutical Industry (ABPI) and manufacturers or suppliers of branded medicines in England. This scheme, which aims to promote innovation and access to cost effective medicines, includes medicine uptake measurements. In the Voluntary Scheme, NHS England committed itself to be in the upper quartile amongst comparator countries by the middle of the scheme (summer 2021), in terms of innovative medicines uptake (9). Therefore, the collaborating parties commissioned LOGEX to develop a methodology to assess comparative international medicine uptake over time, together with its partner Instituut Verantwoord Medicijngebruik (IVM).

In 2021, LOGEX and IVM developed a standard, repeatable, and scalable methodology to carry out an international comparison of the uptake of five categories of medicines for 2019 and 2020, which were identified by NHS England to deliver High Health Gain (HHG) using open-source data. One of the HHG areas was severe asthma, for which the uptake of biologics treatments was mapped. The 2021 International Comparison in Medicines Uptake (ICMU) report demonstrated that England ranked lower compared to the other included countries in this specific HHG area.

In late 2022 and the first quarter of 2023, LOGEX was asked by AstraZeneca to carry out a follow up measurement focusing exclusively on the severe asthma HHG area. LOGEX commissioned IVM to support in data collection and analysis. The methodology used in the 2021 ICMU report has been largely adopted in this report. Thanks to the opportunity to dedicate all attention to the single topic of severe asthma, it was possible to dive even deeper and improve further the methodology. This report compares ten European countries:

Belgium	Denmark	England	Finland
France	Germany	Italy	The Netherlands
Norway	Sweden		

The analysis is performed for the period 2019-2021, reiterating and completing the ICMU 2019 and 2020 output, and adding the 2021 output.

With this report the understanding of which biologics are being used and in which quantities, across the included countries has improved. The ambition with this report is to encourage countries to consider whether their policy efforts for severe asthma biologics are adequate and to learn from each other where needed. To improve the situation for severe asthma patients across Europe by following the most up to date clinical guidelines.

Reading guide

In repetition of the 2021 ICMU report, this report utilises open-source data where possible. These sources include disease registries, statistical and epidemiological databases, databases on medicine utilisation and reimbursements, medical guidelines, and scientific publications. The uptake is measured by calculating the relation between dispensed medication and population of interest. By using open-source data, a trade-off exists between the availability and precision of the data and consequently the measured uptake. Therefore, the population of interest is determined in a series of metrics, ranging from total population of the countries to severe asthma population in each country. This methodology enables a multi-level metric approach to account for varying data availability, while still providing a robust comparison of medicine uptake. It is comparable to the one used in the 2021 ICMU. However, it was possible to establish more precise eligible populations for the metrics in this waterfall. Specifically, a country-specific prevalence for severe asthma was established, which realises a more accurate output. On the contrary, it was not possible to determine the proportion of used quantities for severe asthma based on open-source data. Dupilumab, mepolizumab and omalizumab can also be prescribed for other indications.

To account for this limitation, the report also includes an additional analysis, largely based on interviews and workshops with asthma market experts from the pharmaceutical industry and from patient groups. Through this approach, further data collection possibilities and insights to reinforce the interpretation of the outcomes based on open-source data have been gathered.

Following this approach, the report is split into two parts. Part A: International Biologics Uptake Comparison includes the international comparison of medicine uptake analysis based on the available open-source data. Part A contains the objective output of the analysis, with as few assumptions as possible and little data interpretation. In Part B: Biologics uptake for severe asthma based on indication-split estimates of the report, the open-source data analysis from Part A is placed in a broader context. The primary analysis is enhanced with interpretation and insights, as well as with further collection of data. Detailed explanation of the methodology will be provided in each section separately. The end of the report contains the Conclusions and Recommendations sections, which unite the outcomes from Part A: International Biologics Uptake Comparison and Part B: Biologics uptake for severe asthma based on indication-split estimates.

About LOGEX

LOGEX is a European healthcare analytics company, headquartered in the Netherlands, which turns data into better healthcare. Besides the Netherlands, LOGEX is active in ten other European countries. LOGEX develops software and data systems to support the digital patient journey, to measure and benchmark treatment insights and outcomes, and to improve financial control in hospitals. A key area of its activities is the monitoring of medicines use and outcomes. LOGEX has expert knowledge and experience with reimbursement systems in the countries it is active in.

About IVM

The Institute for Rational Use of Medicine (IVM) is an independent Dutch research institute, which aims to improve quality, safety, and affordability of medication use. IVM translates policy and science into practical tools for everyday use of medicines.

Role of sponsor

The ICMU Severe Asthma report has been sponsored through funding by AstraZeneca. AstraZeneca had no input or editorial control over the final content of the report. AstraZeneca, along with other industry experts, were approached for medicine indication split estimates for use within LOGEX's calculations in Part B of the report, which was reactively provided with no compulsion to use these data.

2 Disease area

Asthma is a common and chronic respiratory disease with a varying prevalence globally. According to The Global Initiative for Asthma (GINA), the agreed upon definition of asthma is as follows:

"Asthma is a heterogenous disease, usually characterised by chronic airway inflammation. It is defined by the history of respiratory symptoms, such as wheeze, shortness of breath, chest tightness and cough, which vary over time and in intensity, together with variable airflow limitation." (10).

Exacerbations or temporary worsening of asthma symptoms can be triggered by exercise, exposure to allergens or irritants, weather changes, and viral respiratory infections. This often resolves spontaneously or in response to medication. However, some patients experience exacerbations in which asthma symptoms flare up, often resulting in life-threatening conditions. Both asthma and asthma exacerbations heavily impact the quality of life of a person living with asthma. The most recent global burden of disease (GBD) estimates for disability adjusted life years (DALYs) attributed to asthma were around 21.6 million in 2019 (11).

Treatment options

Several types of medicines are used in the treatment of asthma:

- Short-acting beta agonists (SABA)
- Long-acting beta agonists (LABA)
- Long-acting muscarine antagonists (LAMA)
- Inhaled corticosteroids (ICS)
- Leukotriene modifiers (LTRA)
- Azithromycin
- Theophylline
- Oral corticosteroids (OCS)
- Biologics

According to the GINA guidelines 2023, the treatment plan for asthma in adults and adolescents, is split into two tracks. These two tracks of treatment escalation are based upon the likelihood of the patient's adherence to the daily controller.

If patients are deemed to be poorly adherent with a daily controller, then they should follow track 1; using ICS-Formoterol as a reliever as this reduces the risk of exacerbations over SABA relievers. There is a stepwise controller medication escalation plan based on symptoms. Steps one and two using ICS-Formoterol as required, step three utilises the same medication as low dose maintenance therapy whilst step four increases the medication to a medium dose. Step five suggests adding a LAMA, referral for phenotype assessment, consider further increases to

ICS-Formoterol to a high dose and the use of a biologic depending on the phenotype assessment and eligibility criteria.

If patients are expected to be adherent with daily controller therapy, then they should follow track 2; using a SABA as a reliever. Step one would be to use an ICS at the same time as the reliever, step two adds in a low dose ICS as maintenance, step three adds in a LABA as maintenance, whilst step four increases the ICS dose to medium or high. Step five suggests adding a LAMA, referral for phenotype assessment, consider further increases to ICS-LABA inhaler to a high dose and the use of a biologic depending on the phenotype assessment and eligibility criteria.

In either track, additions of LTRA, LAMA, Azithromycin, and a low dose OCS (consider side effects) are suggested as options but are of limited indications and there is less evidence for efficacy or safety when compared to the standard therapies.

The treatment plan for children (6-11 years) with asthma differs slightly. Here, the first step is a low dose ICS whenever relieving therapy is used (SABA as needed). The second step is maintenance therapy with a low dose ICS only. In step three and four, a LABA is added, and the ICS dose is increased. Similar to the adult treatment plan, a biologic is added in the final step.

Several biologics are registered for the treatment of severe asthma. Table 1 provides an overview of the biologics that were approved for use by the European Medicines Agency (EMA) during the assessed period, 2019 to 2021. Tezepelumab, a novel biologic that has been approved for the EU and UK market at the end of 2022, has not been included in this table, as it was not approved at the time and therefore is not covered in the report.

Table 1 Biologics registered for the treatment of severe asthma (in the period 2019-2021). AD= atopic dermatitis, CRSwNP = Chronic rhinosinusitis with nasal polyposis, PN = Prurigo Nodularis, EGPA = Eosinophilic granulomatosis with polyangiitis, HES = Hyper-eosinophilic syndrome.

Drug name	Target	Indication	Other indications	Treatment group
Benralizumab (Fasenra®)	IL-5/Rα	Add-on maintenance in severe eosinophilic asthma after high dose ICS and LABA	No	Adults
Dupilumab (Dupixent®)	IL-4/IL-13	Add-on maintenance in severe asthma with type 2 inflammation	AD, CRSwNP, and PN	Adults, adolescents, and children from 6 years
Mepolizumab (Nucala®)	IL-5	Severe refractory eosinophilic asthma	CRSwNP, EGPA, HES	Adults, adolescents, and children from 6 years
Omalizumab (Xolair®)	IgE	Allergic asthma (IgE mediated asthma)	CRSwNP	Adults, adolescents, and children from 6 years
Reslizumab (Cinqaero®)	IL-5	Add-on maintenance in severe eosinophilic asthma after high dose ICS and LABA	No	Adults

Clinical Asthma severity

The clinical severity of asthma is divided into three categories: mild, moderate, and severe asthma. Assessing asthma severity is done retrospectively by assessing the effectiveness of treatment over a period of several months. Mild asthma is well-controlled with GINA step one and two treatment, moderate asthma is well-controlled with GINA step three and four treatment, and severe asthma remains uncontrolled despite optimised treatment with step three and four medications.

Severe Asthma as a Phenotype

Phenotypes in severe asthma are an evolving topic. The currently established phenotypes are separated based on different elements of assessment. In this context, the asthma phenotype determines which specific treatment options are possible as part of personalised treatments. The first hurdle is to determine if there is inflammation driven by eosinophils or neutrophils, the second hurdle is to review if the patient's disease is driven by an allergy. By combining a clinical assessment in addition to these lab-based tests, a clinician can determine the phenotype of asthma in these patients (12).

3 Part A: International Biologics Uptake

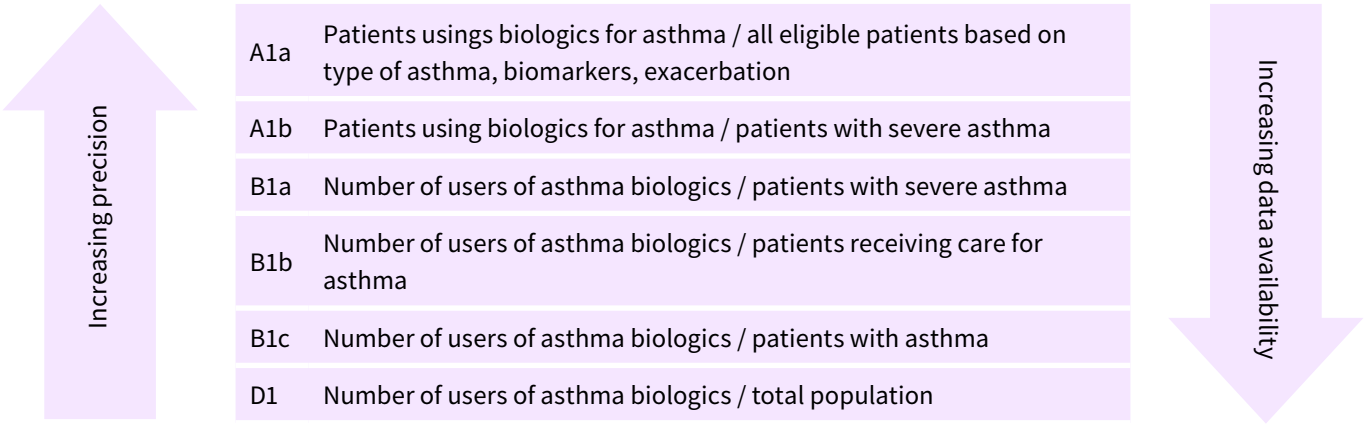
Methodology

The report draws on a general metric model that was developed by LOGEX and IVM for the International Comparison Medicines Uptake 2021 report, as described in appendix I. In the current report, this general model is adapted into a more specific model for severe asthma, depicted in figure 1.

The main modifications to the general model are:

- Conversion of all numerators into number of users
- Split in numerator, i.e., patients using biologics for asthma and patients using asthma biologicals for any indication
- Introduction of three new categories of denominator, i.e., A1a, A1b and B1b
- Omission of the metric C1, C2 and E.

Figure 1 General metric model for severe asthma.



In the case of the denominator denoting severe asthma, sufficient data on the prevalence of asthma were available for each country to exclude estimated asthma prevalence metrics based on the use of asthma specific medicines like inhaled corticosteroids (ICS). The number of users of ICS is an overestimation of the number of patients with asthma, since these medicines are also used in COPD and other airway diseases.

This part of the report will focus on the metric D1. Due to the nature of the open-source datasets we cannot differentiate the use of dupilumab, omalizumab, benralizumab, mepolizumab, and reslizumab between different indications. Resultantly in part A we are using all of the drug use including biologic use for other indications in these calculations and do not limit the denominator to (severe) asthma patients. Metrics B1a-c including biologic use for all indications are included in appendix II. In Part B: Biologics uptake for severe asthma based on indication-split estimates, this assumption will be investigated to more accurately compute metrics B1c, B1a, and A1b. Metric A1a cannot be calculated because none of the countries have availability of adequate data on a national level to estimate true eligibility at the biomarker phenotype level.

The numerator

The numerator is composed of the use of the included biologics. Relevant data are either the number of users of asthma biologics or the amount of DDDs measured on a yearly basis. In the main body of this report only data on number of users are included for clarity. Out of the ten countries studied, six countries had available data on the number of users, whilst the remaining four countries had only DDDs available. For these four countries the number of users was estimated based on the average number of DDDs per user per year in countries where both data types were available. The average number was similar in all the countries included for this calculation.

The five included biologics were all EMA approved before 2019. The results for benralizumab, mepolizumab and reslizumab are grouped (hereafter, anti-IL5 agents).

The denominator

The denominator of the uptake metric is the eligible population, i.e., the number of patients that can potentially be treated with a specific medicine, or a reasonable approximation of this eligible population. To determine eligibility, international standards, such as the registered indication of a medicine or international guidelines, are used.

According to 2023 GINA guidelines severe asthma is asthma that is uncontrolled despite adherence with an optimised high dose of ICS-LABA therapy and treatment of contributory factors, or that worsens when high dose treatment is decreased. Approximately three to ten percent of people with asthma have severe asthma (10). Depending on the phenotype and other clinical features, add-on treatments for severe asthma include oral corticosteroids, LABA, LAMA, LTRA, a low dose of azithromycin (in adults), and biological agents. Whereby the specific asthma phenotype will determine which biologic agent can be used.

Data availability
Availability of data for each country focusing on the values in the numerator and the denominator is shown in table 2.

Table 2 Availability of relevant data in each country.

Parameter *Numerator*	**BE**	**DK**	**EN**	**FI**	**FR**	**GE**	**IT**	**NL**	**NO**	**SW**
Users of asthma biologics	√√			√√	√√			√√	√√*	√√
DDD of asthma biologics	√√	√√	√√	√√	√√	√√	√√	√√	√√*	
Prescribing specialities	√√			√√	√					
Denominator										
Total population	√√	√√	√√	√√	√√	√√	√√	√√	√√	√√
Patients with asthma (GBD)	√√	√√	√√	√√	√√	√√	√√	√√	√√	√√
Patients receiving care for asthma	√	√√	√√	√√	√	√	√	√		
Patients with severe asthma		√	√	√	√	√	√	√		√

√√: data from national sources
√: data from literature
*: only for 2019 and 2020

Outcomes

Part A focuses on the outcomes of the metric D1. Metrics B1a-c are included in appendix II.

Table 3 Use of specific model for international severe asthma biologics uptake analysis.

Metric	**Specific metric explanation (per country)**
A1a	Patients using biologics for asthma / All eligible patients based on type of asthma,biomarkers,and/or exacerbations
A1b	Patients using biologics for asthma / Patients with severe asthma
B1a	Total number of users of asthma biologics / Patients with severe asthma
B1b	Total number of users of asthma biologics / Patients receiving care for asthma
B1c	Total number of users of asthma biologics / Patients with asthma
D1	Total number of users of asthma biologics / Total population

Use of asthma biologics in general population

Omission of indication split in Part A
Importantly, the numerator for the metric is calculated by including the total use of the included biologics. No separation of biologics use, based on the indication of the user, has been made for this metric, which is included in Part A of the report.

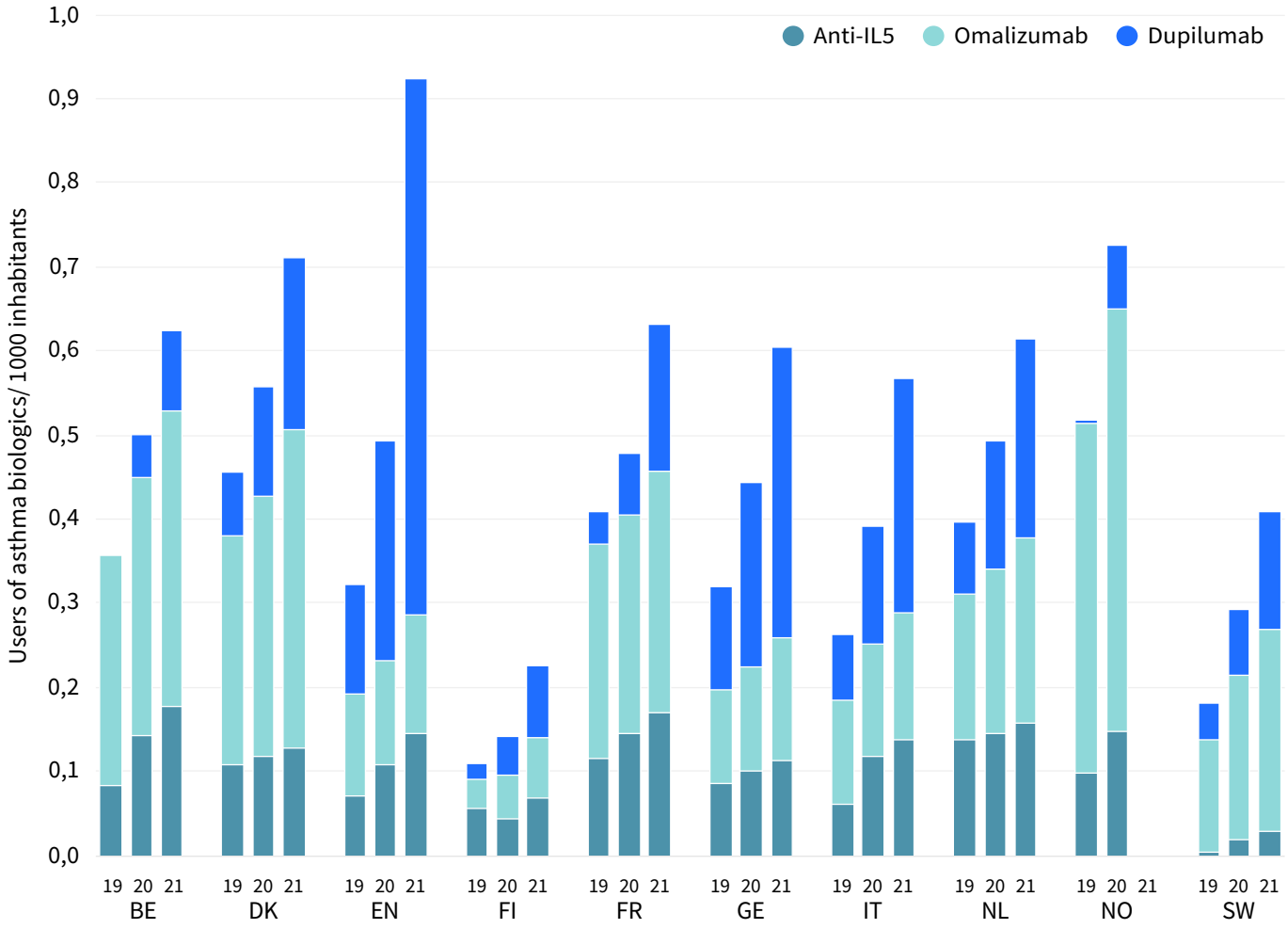
This means that for each country, part of the included uptake is attributable to indications other than (severe) asthma. How large this part is, differs per country. Since little to no open-source data are available on the indication split for biologics, this split has not been included in Part A of the report, which is entirely computed using open-source data. In Part B of the report an inclusion of the indication split, based on both open-source and closed-source data, is demonstrated.

The use of asthma biologics in the general population is calculated as the ratio of the number of biologics users to the total population of each country. The output is shown in figure 2.

The use of the five asthma biologics increased in all countries between 2019 and 2021. In total, omalizumab is the most frequently used biologic, although not in each country. In the total population, the use of omalizumab increased by between four percent (in the Netherlands) and 80 percent (in Sweden). The number of anti-IL5-agent users in the total population increased by between 20 percent (in the Netherlands) and 493 percent (in Sweden). The substantial increase in Sweden is mostly due to the small number of users in 2019. In 2021, the number of users in Sweden was still relatively low when compared to the other countries, despite its relatively large uptake increase. In Belgium, England, and Italy the number of users of anti-IL5-agents in 2021 was more than double compared with 2019. Germany, Denmark, and the Netherlands show smaller increases. Dupilumab, which received EMA approval for severe asthma in 2019, is the biologic with the fastest uptake increase in the studied countries. This increase is presumably (partly) due to its use in other indications. While the graph could appear to suggest that England is leading the way in biologics use in 2021, however in England the NICE Technology appraisal guidance for the use of dupilumab in severe asthma was published on December 8, 2021.

Accordingly, the presence and increase of dupilumab use between 2019 and 2021 in England cannot be considered as use in severe asthma patients but rather its use in other indications.

Figure 2 *Number of users of biologics per 1.000 inhabitants 2019 – 2021. Please note that this also includes users of biologics that have indications other than severe asthma.*



Concentrating specifically on 2021, the overall use of the included medicines was highest in England, Norway (2020) and Denmark and lowest in Finland. The use of **anti-IL5-agents** was highest in Belgium and the France and lowest in Sweden. The use of **omalizumab** was highest in Denmark and Norway (2020) and lowest in Finland. The use of **dupilumab** was highest in England and lowest in Belgium and Finland.

Caveats

The use of the anti-IL5-agent reslizumab is underestimated in Belgium, Finland, and Italy and it might be in France and Sweden as well. Reslizumab is conventionally administered in-hospital, as it is the only asthma biologic which is administered intravenously. Since in-hospital use of medicines is not included in all open-source data, its use is underestimated. An indication of this principle is given by the Belgian Severe Asthma Registry which reported to have 25 users of reslizumab in 2020, out of 305 users of anti-IL5-agents (13). However, the open-source data showed zero users in 2020. Similar findings were obtained for Finland and Italy (14) (15). Literature provides no insights on whether reslizumab was used in France and Sweden. This results in an underestimation of the outcome of all metrics for these countries. Considering the mode of administration and data seen in literature as described above, it is unlikely that this underestimation will significantly impact the results.

Discussion

It is known that for multi-indication drugs, part of the computed uptake should be attributed to other indications than severe asthma. For most countries, the split across the different indications for multi-indication drugs is not attainable through open-source data. Exceptions are Belgium and Finland.

Dupilumab

On the use of dupilumab in severe asthma the following data have been collected:

- In Belgium, up to 2021 dupilumab was not prescribed by pulmonologists (22).
- In Finland, an increasing percentage of users of dupilumab received its prescription from pulmonologists, from 0 percent in 2019 to 18 percent in 2021 (23).
- In the Netherlands, in 2020, seven percent of the participants in the RAPSODI registry were treated with dupilumab (24). These data cannot be extrapolated to the total population with (severe) asthma.
- In Denmark, in 2022, 29 percent of the users of biologics in the Dansk Svær Astma Register used dupilumab. From 2019 onwards, dupilumab has increased its market share amongst patients initiating treatment with biologics. The percentage of patients initiating its biologics treatment with dupilumab increased from four percent in 2019 to 55 percent in 2021 (25).
- In the UK, 0.5 percent of the participants in the UK Severe Asthma Registry were treated with dupilumab between 2014 and 2021 (26). Since the NICE Technology appraisal guidance was only published in December 2021, this percentage is most probably due to use in research settings or in compassionate use programs.

Omalizumab

On the use of omalizumab in severe asthma the following data have been collected:

- In Belgium, the number of DDDs of omalizumab prescribed by pulmonologists was 40 percent in all included years (27).
- In Finland, the percentage of patients that received an omalizumab prescription from pulmonologists has decreased, from 29 percent in 2019 to 25 percent in 2021 (23).
- 15 percent of the current users of biologics in the Dansk Svær Astma Register in 2022 used omalizumab, making it one of the lesser used biologics in Denmark (25).

In part B, we present additional data on the use of dupilumab and omalizumab in severe asthma and other indications, based on sources that are not publicly available.

4 Part B: Biologics uptake for severe asthma based on indication-split estimates

The use of open-source data for the analysis of severe asthma biologics uptake poses various complications, both for the numerator and for the denominator part of each metric. Prevalence data were not always available for each metric. Furthermore, assumptions had to be made about the extent to which biologics uptake can be attributed to severe asthma, resulting in an overestimation of uptake in each country. The most important calculation that has not been performed in Part A is the indication split for dupilumab and omalizumab regarding their use in severe asthma and in other indications.

Industry experts in the field of severe asthma and biologics were consulted to extend and improve the calculations from Part A: International Biologics Uptake Comparison. The general aim was two-fold; to fill any data gaps and to develop an improved understanding of the collected data. The methodology, outcomes, and discussions of these expert sessions will be discussed in the following section.

To keep the open-source analysis as transparent as possible, the input of experts has only been incorporated into Part B of the report.

Methodology

Interviewees

The selected experts are people actively working in the field of respiratory diseases, specifically asthma, biologics, and policies relating to reimbursement in various countries, coming from within the pharmaceutical industry or from patient groups. The experts had either a UK and EU focus or were specialised on a global scale including Asia, Australia, North America, South America, and Europe. Therefore, the included countries could be represented in the discus-

sions. The specific choice of experts has partially been influenced by the data gaps from the open-source analysis, whilst the patient groups were UK focused and were selected based on our prior report and on convenience. The experts could provide insights on these data gaps, judge the policy differences between countries, and could assess the outcomes in a broader light. Therefore, it was significant to gather insights from industry experts and policy professionals.

Furthermore, it is seen as most valuable to include the patient perspective in analyses on medicine uptake. Patient associations can shed a light on biologics use by the user first-hand. Therefore, interviews have also been conducted with patient associations, to widen the perspective on the disease area. The identity and organisations of all interviewees will remain anonymous.

Questions and workshop setup

Main data gaps and questions discussed in expert sessions

1. Asthma prevalence varies significantly amongst different countries. Can you provide an insight or data on prevalence per country to validate our findings?
2. Severe asthma prevalence has large variability amongst countries. Can you provide an insight or data on prevalence per country to validate our findings?
3. Omalizumab, mepolizumab, and dupilumab are multi-indication drugs. Can you provide an insight or prescribing split for severe asthma vs. other indications for each country?
4. In Belgium, France, and Italy data are missing on reslizumab, the only intravenous anti il-5 drug. Could you share any information or data on whether this significantly impacts the overall use of anti-IL-5 drugs?
5. Italy and Belgium both demonstrate a significant uptake increase in 2019 and 2020? Has this been seen and recognised by your experts? Was there any changes to policy at the time to support this rise?
6. There doesn't seem to be one fixed (severe) asthma definition between countries. Why do you think there is variability in the definition of severe asthma between countries?
7. Large differences are visible between countries' biologics uptake. Are there strong political drivers for health improvement in specific countries? How do national guidelines vary in this space? What could be the lessons learnt for those in lower ranking?
8. There seem to be large differences between countries' recorded severe asthma prevalence. Do you have a clear understanding of why severe asthma prevalence and incidence may vary between countries?
9. What is the bottleneck in accessing biologics when you are a severe asthma sufferer? What are the barriers that patients with severe asthma have to access biologics? Can you think of best practices from overseas to resolve these issues?

A total of four online interviews of an hour each were conducted, during which multiple experts were present. A workshop-discussion set up was used for all sessions. Conditional to the focus, expertise, and background of the interviewees, the sessions had slightly different structure and content.

Throughout the interviews, the analysis and output were discussed, concentrating particularly on missing data and assumptions made in the calculation. A predeveloped set of questions were posed during the interviews. These questions aimed to improve the understanding on ambiguous topics, such as the definition of (severe) asthma and potential best practises from different countries.

Response processing
Where concrete data were uncovered, new calculations with these data were made. These new calculations resulted in new graphs, which are presented in the outcomes part of this section. Additional insights that were obtained regarding the analysis outcomes were included in the storyline to increase perspective and place the results in a broader light.

Outcomes

Part A: International biologics uptake comparison was limited to metric D1 comparing the number of users of asthma biologics to the total population. The other metrics mentioned in table 3 of part A are included in appendix II as they are not an accurate representation of the true uptake for the severe asthma cohort. For most countries, the open-source registry data do not include the division between indications. However, the division of prescribing between the various diagnoses should be taken into account to correctly compute the actual uptake for severe asthma patients. Three of the included biologics, namely dupilumab, omalizumab, and mepolizumab, are multi-indication drugs. This means that they are likely to get prescribed to patients suffering from severe asthma, but also to patients with other diagnoses, such as moderate-to-severe eczema.

To achieve a more precise uptake, the calculations of appendix I had to be computed with data obtained during our interview sessions. Through various sessions with industry experts, this indication split was acquired for most countries. Belgium and Finland dupilumab and omalizumab usage data were calculated using the indication split obtained from registry data.

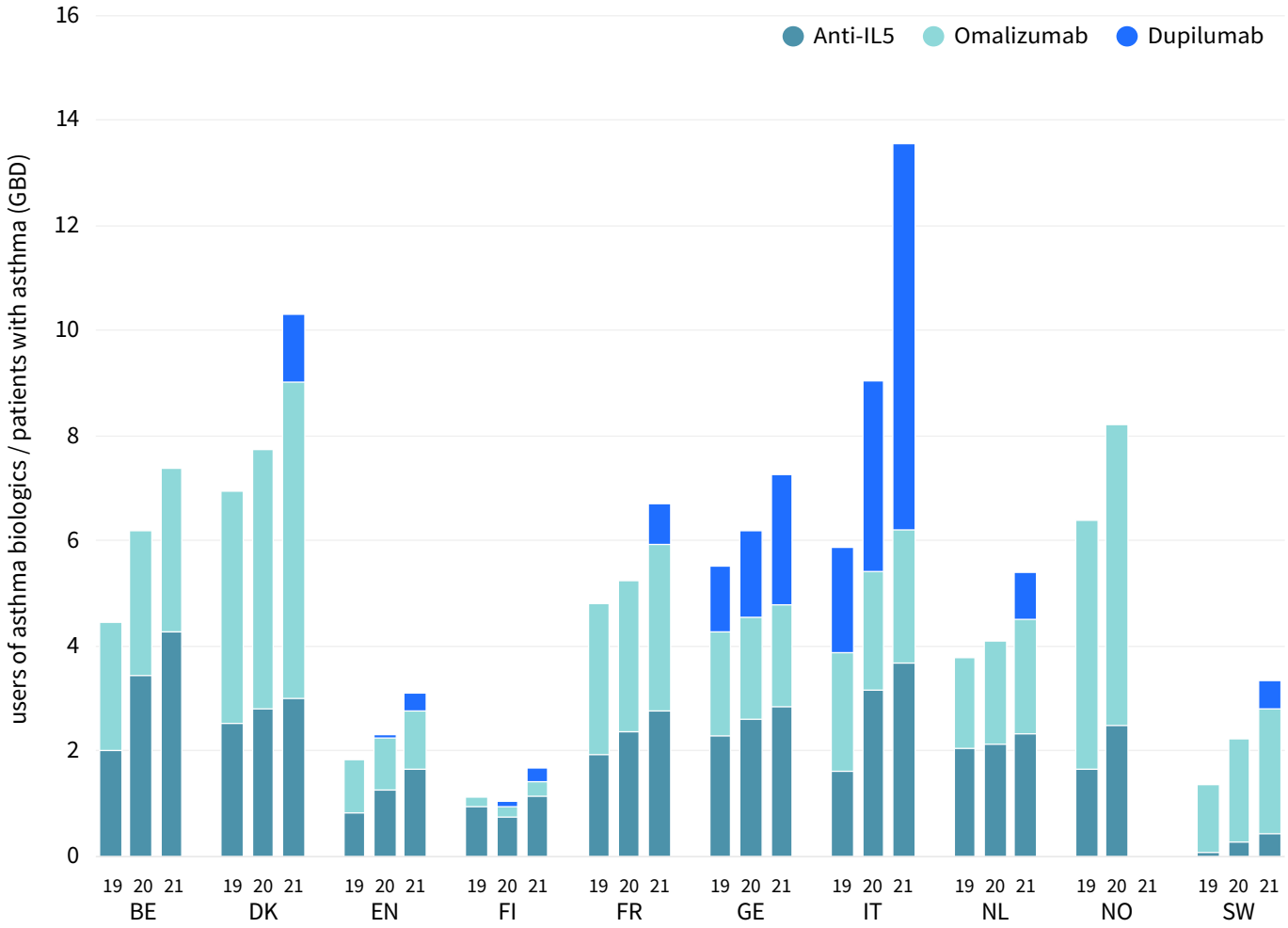
Biologics use in asthma population
The number of asthma patients in a country can be calculated using the prevalence of asthma. Asthma prevalence differs between countries, from 4.4 percent in Italy to 10.6 percent in England (1). As in our 2021 ICMU report, the asthma prevalence from the Global Burden of Disease (GBD) is used (1). The 2019 GBD release provides an estimation of prevalence based on self-reported health status. It offers the convenience of standardised data collection and reporting for all included countries, facilitating international comparison. We took changes in population size into account.

In figure 3 the uptake of biologics in the asthma population is shown for the period 2019 to 2021. Concentrating specifically on 2021, the use of biologics for severe asthma compared to the population with asthma was highest in Italy, and lowest in Finland, England and Sweden.

There is a substantial difference in **dupilumab** uptake for all countries. Dupilumab received approval for severe asthma in 2019 from the EMA and NICE

Technology Appraisal in 2021. It must be remarked that in most EU countries, the dupilumab uptake has mostly set off in 2021, instead of 2019. For England it is to be expected that the uptake is also very low in 2021, as the approval was published in December 2021. The use of **omalizumab** varies strongly between countries. This indication split ranges significantly. In some countries only 25 percent of the uptake is for severe asthma patients, while in other countries that percentage is as high as 70. In the asthma population, the number of users of omalizumab was highest in Denmark and lowest in Finland. Regarding the uptake of **the anti-IL-5 biologics**, almost 100 percent is related to severe asthma patients for most countries. Of the three anti-IL-5 medicines, only mepolizumab is a multi-indication drug. Its primary marketed indication is for patients with a severe asthma diagnosis. The number of users of anti-IL5 agents was highest in Belgium and lowest in Sweden.

Figure 3 *Uptake of biologics in the asthma population (based on GBD data) between 2019 and 2021. For the multi-indication drugs, the part related to severe asthma patients has been computed.*



Biologics use in severe asthma population

Table 4 Use of specific model for international severe asthma biologics uptake analysis.

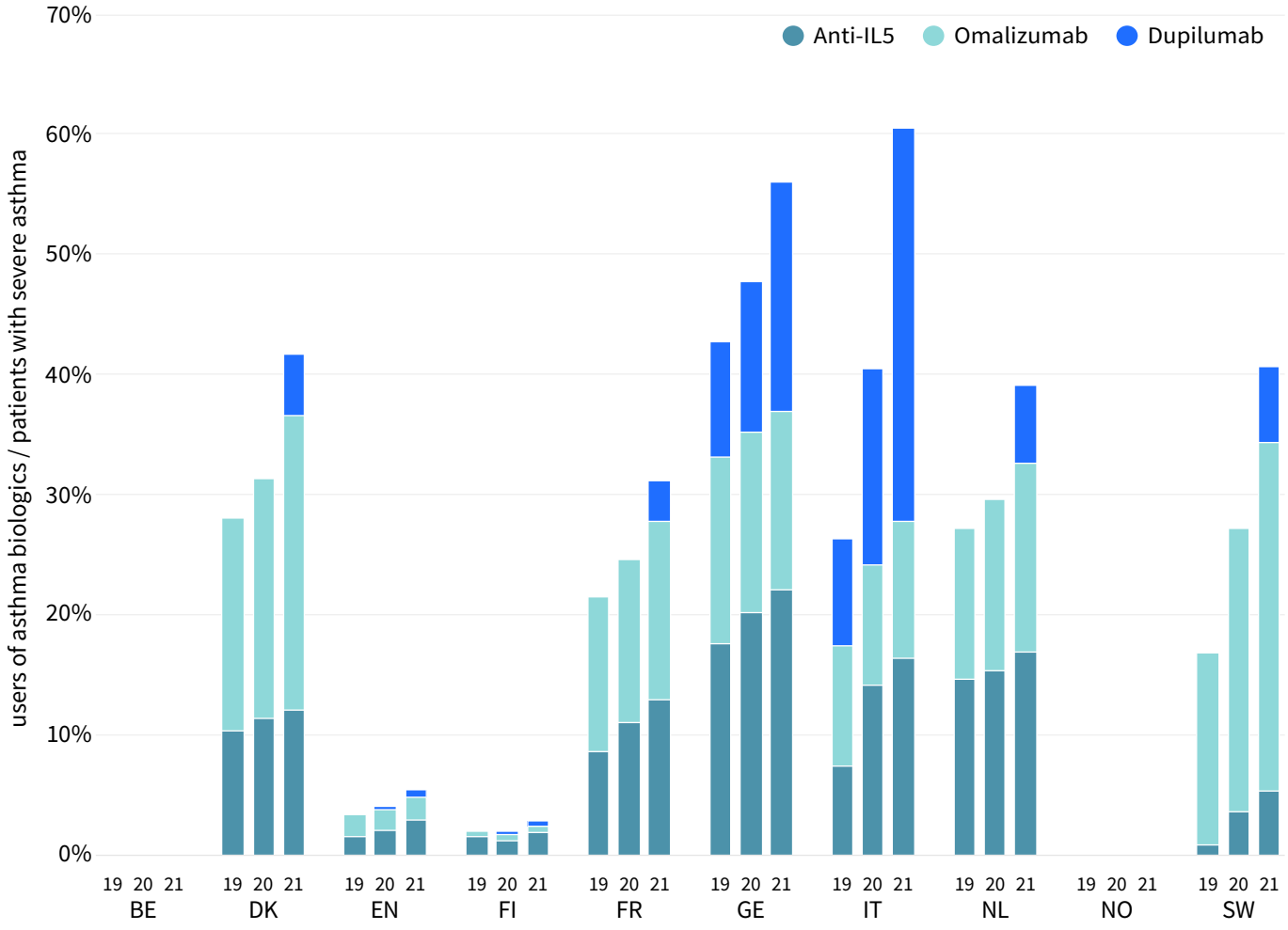
Metric	Specific metric explanation (per country)
A1a	Patients using biologics for asthma / All eligible patients based on type of asthma,biomarkers,and/or exacerbations
A1b	Patients using biologics for asthma / Patients with severe asthma
B1a	Total number of users of asthma biologics / Patients with severe asthma
B1b	Total number of users of asthma biologics / Patients receiving care for asthma
B1c	Total number of users of asthma biologics / Patients with asthma
D1	Total number of users of asthma biologics / Total population

The next metric is computed as the percentage of biologics users in the severe asthma population per country. Again, the indication split for the multi-indication drugs has been taken into account. The results are presented in figure 4, 5 and 6.

Figure 4 shows a major difference in uptake in England and Finland, when compared to the other countries.

The denominator, the severe asthma population in England and Finland is relatively larger than in other countries. This high severe asthma prevalence is in line with prevalence studies found in literature (28). One might expect a higher biologics uptake in countries with a higher severe asthma population, however this is not found in the open-source data, nor in the data obtained through experts. The numerator, in the use of both **dupilumab** and **anti-IL-5** in Germany is considerably higher than in England and Finland. Likewise in Sweden, a high number of **omalizumab** users is seen when compared to England and Finland, even though the use of anti-IL-5 is comparable between these countries .

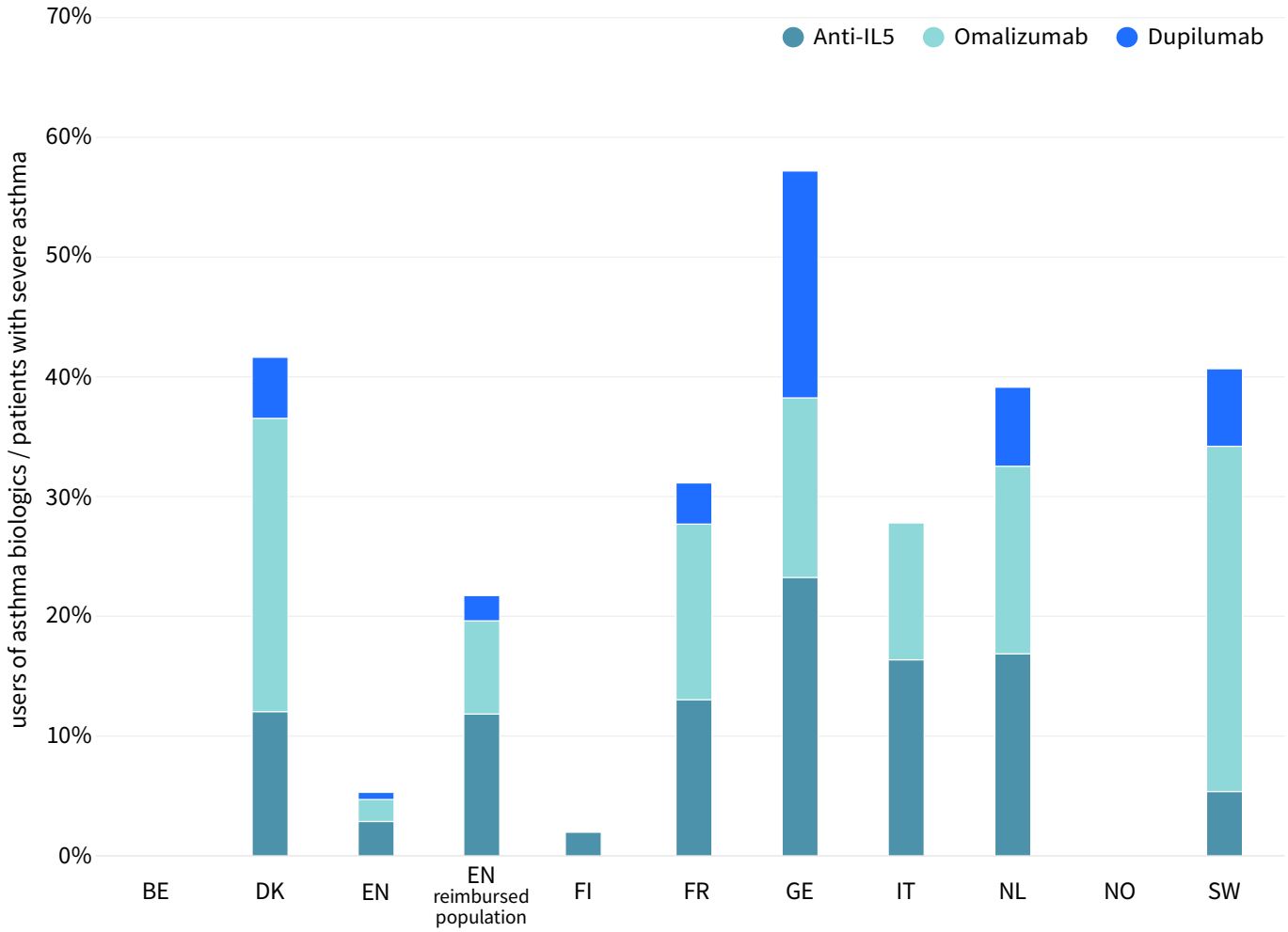
Figure 4 *Uptake of biologics in the severe asthma population between 2019 and 2021. For the multi-indication drugs, the part accounting for severe asthma patients has been computed.*



Focusing on figure 5, in 2021, one can see this differential uptake per medication group per country more clearly. England and Finland lag behind in uptake of all three medication groups.

It should be noted that the countries have a different combination of used specific severe asthma biologics. More patients use **omalizumab** in Sweden and Denmark compared to other countries, while physicians in most countries prescribe little **dupilumab** to their patients with severe asthma, apart from Germany. In the Netherlands and France, of the patients using biologics, nearly half uses **anti-IL-5**, while the other half uses omalizumab. This composition is quite different. A key addition to this bar graph is the inclusion of England's NICE reimbursed population as a separate denominator. This was highlighted in our last report to demonstrate that the ranking did not change for England despite the stricter population size. In this report, the same denominator has been included to highlight that even if we were to use reimbursed population instead of the clinical population for England, the uptake is still in the lowest-ranking group.

Figure 5 *Uptake of biologics in the severe asthma population in 2021. For the multi-indication drugs, the part accounting to severe asthma patients has been computed.*

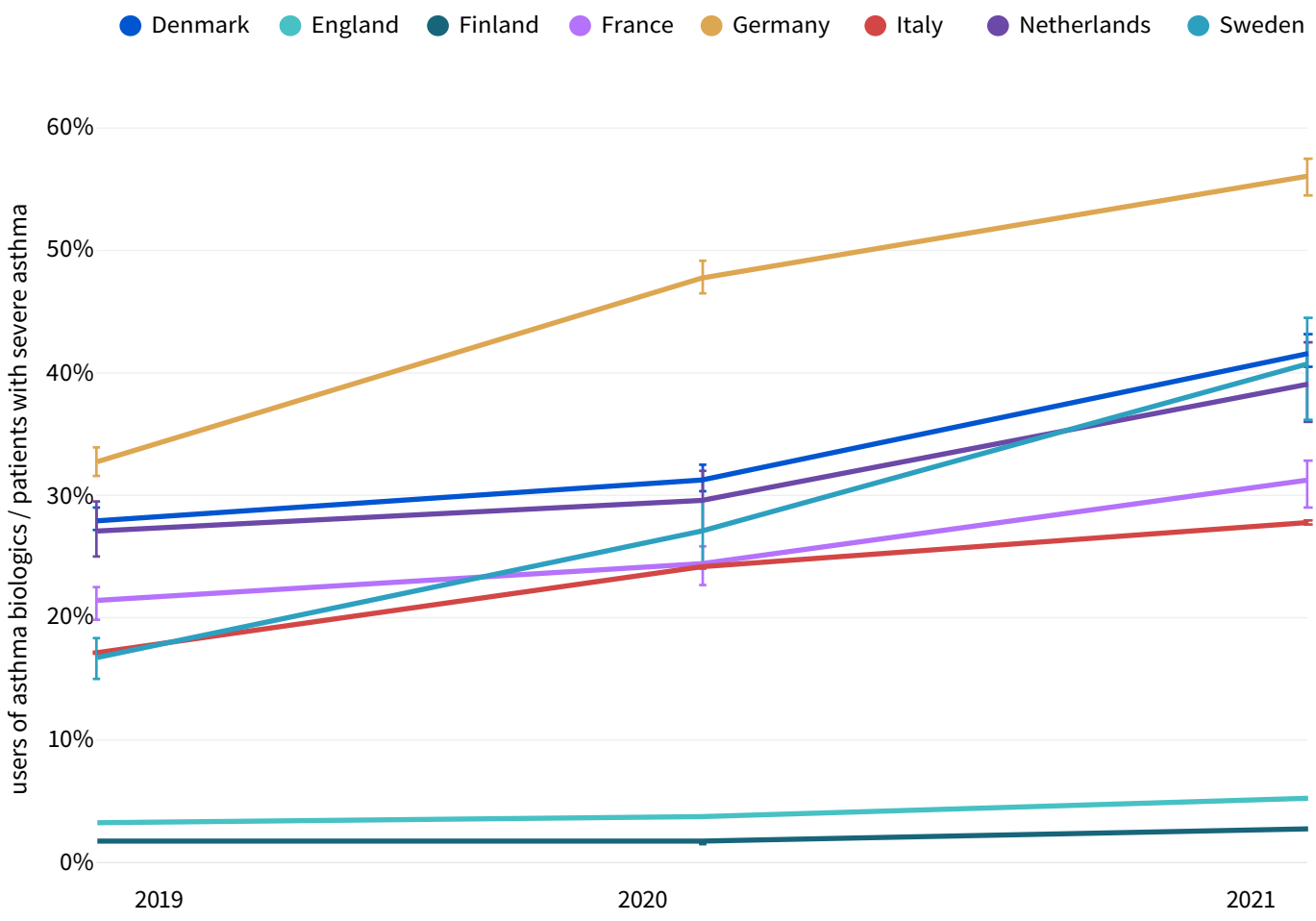


	BE	DK	EN	EN reimbursed population	FI	FR	GE	IT	NL	NO	SW
Dupilumab	0%	5%	1%	2%	0%	3%	19%	0%	6%	0%	6%
Omalizumab	0%	5%	2%	8%	0%	15%	15%	11%	16%	0%	29%
Anti-IL5	0%	12%	3%	12%	2%	13%	23%	16&	17%	0%	5%

Lastly, figure 6 shows the same data as figure 5, but visualised in a line graph where the different biologics are not split. Error bars demonstrate the lower and upper confidence bounds of the numerator value for the severe asthma population. From this graph, it can be established that the trend for overall biologics uptake is increasing over time. Sweden is an example where the biologics uptake increased to almost double in just two years' time. This increase was mostly driven by omalizumab in Sweden.

For most countries, uptake was between 15 percent and 30 percent in 2019 and increased to between 30 percent and 42 percent in 2021. Overall, Germany had a higher uptake than the other studied European countries in 2019, and still had a significantly higher uptake than those countries in 2021. In contrast, Finland and England have a significantly lower uptake during all three included years compared to the other countries. Although all other countries have a steady increase in biologics uptake over time, England and Finland show little increase in uptake.

Figure 6 *Uptake of biologics in the severe asthma population between 2019 and 2021 represented in a line graph. For the multi-indication drugs, the part accounting to severe asthma patients has been computed.*



5 Discussion

In this section, the insights that were obtained in Part A and Part B are put into a broader perspective, based on the interview sessions held with industry experts and patient groups. This facilitates the interpretation of the data in the real world. It should be noted that the content of this section is based on personal and industry perspectives and is not based on objective data collection and analysis.

Distribution of innovative medicines

As described in the previous section of Part B, the uptake of **dupilumab** for the severe asthma indication started several years after the drug was approved by the EMA. This lag in diffusion is recognised by experts in the field and by the patient groups.

Germany has policy efforts in place to speed up the process of innovative medicines diffusing in their healthcare system after approval by the EMA (29) (30) (31). This could explain their relatively fast uptake of dupilumab after EMA approval. It must be noted that some other countries, such as the Netherlands, also have programs for accelerated access in place, though less influence from these programs is seen in the collected data (32). It has also previously been found that physicians in Germany have a particularly high affinity with prescribing innovative medicines. These aspects may possibly have influenced the speed with which dupilumab has diffused in Germany.

Furthermore, the difference in biologics uptake in the severe asthma population between England and Finland, and the other European countries, has been well established in Part B. It has been demonstrated that the increase of uptake over time that was visible in these European countries, did not occur in England and Finland. Over time, this will most likely result in an even more significant difference in uptake between the two country groups.

Questions have been raised by experts on the impact that diffusion lags could have on new innovative medicines reaching the market. In 2022, a new severe asthma biologic, tezepelumab, has obtained market authorisation from the European Commission. In subsequent International Comparison Medicines Uptake reports, tezepelumab will be included in the biologic uptake analysis.

Differences in national healthcare systems

Prescription

Within Europe, across countries differences exist in how healthcare systems and reimbursement of medicines are structured. This naturally influences the way in which medicines are prescribed in each country, subsequently establishing uptake differences. Taking England as an example, biologics cannot be initiated by most healthcare professionals (HCPs). Only HCPs from a specialist asthma clinic are generally allowed to assess and initiate patients for severe asthma biologics use (33). This increases the complexity for a patient to access and attain biologics, even if they are deemed to need it by other physicians. NICE has confirmed that capacity in specialist centres might pose as a barrier to initiate treatment (34).

Furthermore, these specialist centres are not evenly distributed geographically, leading some areas to be under-represented and patients in these areas to have to travel long distances to receive diagnosis and treatment (35). On the contrary and possibly helping to explain the vast divide, German respiratory consultants – outside of consultants within specialist asthma clinics – can initiate a biologic in eligible patients.

Diagnosis

As countries adopt different severe asthma definitions, the way in which patients are diagnosed may also differ. In many countries, the extent to which symptoms are uncontrolled while the patient is being treated, is used to assess whether that patient has severe asthma or not. Unfortunately, there is still a limited understanding of severe asthma, and a more refined diagnosis method is not available at this point. This means that a severe asthmatic patient is likely to suffer from several exacerbations before being considered for a diagnosis of severe asthma. Some countries require several exacerbations or long-term oral corticosteroid use before patients will be considered eligible for biologics treatment (36) (37). Overall, the departure point of diagnosis of uncontrolled severe asthma is that it can only be diagnosed after treatment has been proven to be inadequate. Yet, the way in which treatment is deemed inadequate differs between countries, resulting in patients being diagnosed and treated differently across Europe. A definitive method of diagnosing severe asthma patients would be ideal, to both reduce the burden on patients and minimise the overtreatment of patients that do not need them. However, until this happens, having an internationally agreed definition and registry would enable comparisons of similar biologics for similar populations.

Additionally enabling primary care physicians to actively review asthmatic patients who frequently use rescue oral corticosteroids or are frequent hospital attenders, and subsequently refer them for specialist review, could help to identify severe asthmatic patients earlier.

Reimbursed population

As stated, the definition and diagnosis of severe asthma is ambiguous across different countries. This further impacts the demarcation of the country-specific eligible population for severe asthma biologics. In some countries, the reimbursed population for biologics is defined stricter than the clinically eligible population by the national or international regulatory healthcare bodies (37). For example, in England NICE recommendations for registered indications differ from EMA approved indications for all five biologics in terms of eligible population. This leads to fewer eligible patients being able to access the biologics, as they will not be reimbursed. Although it is not known which recommendation, from NICE or EMA, is a more accurate representation of the precise eligible population, it naturally leads to a lower biologic uptake in the severe asthma population in England compared to the other countries. Despite this, as highlighted in figure 5, even if we were to use the reimbursed population (a smaller target population in England) the country still remains in the lowest-ranking group despite the expectations that a more specific population would mean a higher percentage uptake. This implies that uptake in England lags behind other European countries regardless of the population, that we use for severe asthma.

A recent paper by Porsbjerg et al. demonstrated that worldwide access to biologics is affected by strict Health Technology Assessment (HTA) guidelines, regardless of a countries' gross domestic product (GDP). This means that access is affected by more than just by pricing negotiations. The ease of access to biologics in the study refers to the prescription criteria and not to the conditions or barriers to accessing health services. More broadly this paper points to the complexities around prescribing biologics, and presents a potential cause of variations in treatments. (37).

Given the lack of an international registry of severe asthma patients, this report serves as an interim tracker monitoring the uptake of biologics amongst severe asthmatic patients.

Adverse effects of oral corticosteroids

The introduction of biologics into the severe asthma treatment regimen must be evaluated against the currently available treatments. As previously stated, oral corticosteroids (OCS) are frequently used in the severe asthma populations. Long-term use of OCS has many known adverse effects, as stated by scientific research, patient groups, and in GINA guidelines. Adverse effects include increasing numbers of exacerbations and hospital visits, and chronic comorbidities even after stopping OCS treatment (38). The most recent GINA guidelines recommend biologic treatment before OCS treatment in step 5 (10). Lacking access to biologics causes in some of the studied countries biologic-eligible patients to be treated with long-term OCS. Improvement of access to and uptake of biologics for severe asthma patients, could influence the long-term use of OCS for biologic-eligible patients since it would lead to a potential reduction in OCS use. This conceivably will result in a reduction of adverse effects and chronic comorbidities for individual patients, as well as potential reduction in the burdening of hospitals and healthcare systems. Naturally, the adverse effects of biologics and accurate eligible population for biologics need to be considered as well. Not all patients can be considered for biologics, and biologics' post-marketing surveillance and safety data need to be monitored, as their number of years of availability for use are few.

Clinical outcomes for asthmatic patients

This report serves to highlight one aspect of care within the whole pathway for asthmatic patients. Deep diving into the treatment of step 5 of the GINA guidelines, this report does not describe or provide recommendations for the treatment for moderately severe asthmatic patients, or those severe asthmatic patients which are not eligible for biologics. It is key, that although we rank countries based on uptake metrics of biologics, to understand that all countries still have work to improve the care for persons with asthma.

Clinical outcomes in asthmatic patients vary both within a country and internationally. Some examples of outcomes, but not an exhaustive list include; excessive OCS and SABA use, the frequency of asthma attacks and hospitalisations.

A study performed by Tran et al (2020), investigated the overuse of OCS in France, Germany, Italy and the UK looking at datasets between 2011-2018. Overuse was defined as a cumulative dosage ≥450 mg within 90 days, corresponding to an average daily dosage of ≥5 mg. Overuse of OCS is common practise

amongst these countries with the study showing the following percentage of high OCS users as six to nine percent in Germany, seven percent in the UK, nine percent in Italy and nine percent in France. In the severe asthma group (GINA step 4-5) the percentage high OCS users was fifteen percent in Italy, thirteen to fifteen percent in Germany and twelve percent in Italy and France (39). It must be noted that there is no overlap of time with this study and our report, and we cannot draw any correlations between biologics uptake and OCS overuse.

Similarly, Janson et al (2020) described that SABA overuse in all asthma patients in European countries is also common practise. SABA overuse was defined as prescription/dispensing of at least three canisters per year. The countries included in the report were Italy, Germany, Sweden and the UK. The prevalence of overuse was nine percent, 16 percent, 30 percent and 38 percent respectively (40). Interestingly this ranking is similar to the ranking we show in biologics uptake in this report. It must be noted that this paper was looking at data between 2006-2017 which was not in the timeframe of data from this report and there is no overlap with the uptake of biologics. A subsequent report by Di Marco et al (2021), which tried to corroborate the study findings by Janson et al (2020), demonstrated the true value for Italy is likely to be closer to 32 percent. For Germany Worth et al (2020) showed a value closer to 36 percent which highlights the fact that amongst these countries SABA overuse is common practise (41) (42). Correlation between SABA use and biologics uptake has not been investigated and could provide value in future studies.

Looking at hospitalisation rates for asthmatic patients per 100,000 population in 2019, the countries ranked from lowest to highest; Italy (8.9), Sweden (16.4), Norway (21.2), Belgium (27.1), France (29.6 -2015 data), Germany (31.5), the Netherlands (32.6), Finland (42), Denmark (66.5) and the UK/ England (74.5) (43). There is no clear correlation between the use of biologics and hospitalisation rates. Despite the high uptake of biologics in Germany, the hospitalisation rates are shown to be high when compared to the other European countries. In agreement with the low uptake in Finland and England the hospitalisations are as expected.

While biologics uptake amongst eligible patients is important, this is only one element of asthma care, and these studies above demonstrate that even in countries with high uptake of biologics these countries have more to do in terms of optimising their whole asthma care pathway with the aims of reducing frequencies of attacks, reducing hospitalisations and reducing the overuse of both OCS and SABA.

6 Nuances

The interview workshops were organised with the aim to expand and improve our data collection, as well as to provide insights and a broader context to the performed analysis. To interpret the output from the interviews as well as possible, the nuances of the interviews must be mentioned.

Conversations and specifically interviews are vehicles for sharing one's views. Naturally, the interpretations and insights from individual experts in this report likely hold subjectivity. The background, country of residence, and employer might have influenced the experts' viewpoint, either consciously or subconsciously. However, it was necessary for the accuracy of the analysis to get the opinion of experts for a broader context of severe asthma, indications, biologics use, and national or international respiratory policy. It must be noted that due to the limited number of interviews, it was impossible to discuss all conditions that affect biologics uptake due to the limited number of interviews.

Most importantly, it is necessary to acknowledge that there are many different factors that impact the uptake of biologics. Within a country, there are many different aspects which can affect the use of medicines. These can range from concrete aspects, such as availability and reimbursement, to more abstract ones, such as trust in the healthcare providers. Taking all these different conditions into account was not in the scope of this report, although the most impactful ones as seen by experts in the field have been discussed.

7 Conclusions

Drawing on the analysis computed in both Part A: International Biologics Uptake Comparison and Part B: Biologics uptake for severe asthma based on indication-split estimates, this section of the report discusses the conclusions from both main report sections.

The biologics uptake in the severe asthma population, as shown in figure 4, 5 and 6, is used to discuss the final conclusions. For five of the eight included countries, the percentage of the severe asthma population using biologics was between 15 percent and 30 percent in 2019 and increased to between 30 percent and 45 percent in 2021. Germany deviates from the majority of the included countries, with an uptake of 55 percent in 2021. For Sweden, an uptake increase from below 20 percent in 2019 to above 40 percent in 2021 was found. This means that Sweden more than doubled its biologics uptake in the severe asthma population within two years.

England and Finland also have an uptake that deviates from most of the included countries. These two countries have a significantly lower biologics uptake for asthma than most countries, with around five percent and below five percent of the severe asthma population using biologics, respectively. The biologics uptake increased little over the three years included in this report. For England the next few years will be interesting to follow considering national initiatives to improve uptake such as the NHS Accelerated Access Collaborative (AAC) or the VPAS focussing on the five High Health Gain areas. Furthermore, as part of the English government's VPAS commitment in being in the upper quartile amongst comparator countries by summer 2021 for asthma biologics use, in this report it has not been met regardless of which population of severe asthma is used in the calculation.

For each country, the uptake of biologics was split into the three medication groups, namely dupilumab, omalizumab, and anti-IL-5. It was therefore possible to see the relative use of each medication in each country. In Sweden, a relatively high omalizumab use was found. In Germany, a relatively high anti-IL-5 medicines and dupilumab use was found. It should be noted that this does not necessarily mean that the absolute medicine usage was highest in these countries, but that these countries have a relatively high percentage of severe asthma patients using that specific medication.

The relative dupilumab, omalizumab, and anti-IL-5 use in the severe asthma population is lowest in England and Finland. Accordingly, these countries lag behind the bulk of European countries considering the dispensation of all three medication groups for this specific group of patients.

Ranking comparison to ICMU 2021 report

The ranking of the included countries is based on metric A1b as this represents the closest eligible population available in this report and includes the indication split for the multi-indication biologics. Notably both Norway and Belgium are not included in this ranking due to missing data in the severe asthma population.

In the previously report a similar type of ranking was demonstrated. However, this ranking was based on uptake in the asthma population of each country and did not take into account dupilumab or the indication split of multi-indication biologics. Therefore, the ranking presented in table 5 is solely based on the data presented in this report.

Table 5 *Ranking of the included countries based on their asthma biologics uptake in the severe asthma population, including the indication split for omalizumab, dupilumab, and mepolizumab, using the mean uptake. Please note: an accurate ranking for countries with confidence intervals cannot be made and they should be viewed as ranked groups.*

Ranking group	Ranking	2019	2020	2021
Upper	1	Germany	Germany	Germany
	2	Denmark*	Denmark**	Denmark***
Middle	3	The Netherlands*	The Netherlands**	Sweden***
	4	France	Sweden**	The Netherlands***
	5	Italy*	France**	France
	6	Sweden*	Italy**	Italy
Lower	7	England	England	England
	8	Finland	Finland	Finland

* Countries with overlapping confidence intervals in 2019,
** Countries with overlapping confidence intervals in 2020,
*** Countries with overlapping confidence intervals in 2021

Recommendations

Based on the insights gathered in this report, some recommendations can be made.

Recommendations overview

- An internationally agreed definition of severe asthma should be put in place to enable better communication, diagnosis, and treatment for the disease.
- Lower and middle ranked countries should draw lessons from efforts from countries with a higher-ranking and those that were able to increase their uptake significantly; Germany and Sweden.
- Further investigations correlating the uptake metrics in this report with clinical outcomes of severe asthmatic patients will be useful in assessing the impact of biologics on healthcare utilisation.
- Further studies to review the clinical outcomes of biologics amongst the whole asthma population with the aim to reducing the healthcare utilisation of moderately severe asthma patients and those severe asthmatic patients that are not eligible for biologics.

Improving patient access

England and Finland have a substantially lower uptake than the bulk of the included countries in this report. For England this is true regardless of using the clinically eligible or the reimbursed populations for severe asthma.

The NICE adoption team has done a lot of work to identify barriers to adoption and exploring potential solutions, the team has described that both capacity and geographical location of specialist centres are insufficient to enable equity of access (45). A recent study highlighted that the current pathway from referral to a severe asthma centre and biologic initiation is 63.5 weeks. The authors state that this period in related to clinical factors but may also be influenced by availability of multi-disciplinary input (46).

Furthermore, the difference in uptake between England and Finland and the other countries, is only presumed to increase in the following years, drawing on the analysis in this report. The NHS has put policy efforts in place to increase biologics uptake, a crucial step in decreasing the uptake gap with European countries (47). It is currently unknown if, and to which extent, individual Municipalities in Finland have implemented efforts to improve access for their patients.

This report recommends that all countries, and in particular low-ranking group countries should adopt practises to identify severe asthma patient sufferers earlier, this will enable the patients to have optimisation of medications and phenotype analysis. Indirectly this could improve patient access to biologics to prevent a widening of the gap between countries.

Lessons to learn

For all countries, it would be recommended to make inquiries into Sweden's increase in uptake between 2019 and 2021. It is to be expected that policy efforts are behind its success to have well-working biologics to reach more patients. Similarly, in Germany, it is well established that utilising the disease management programme (DMP) for patients with asthma improved the pharmacotherapy and reduced hospitalisation for patients with asthma (48). All countries are encouraged to learn from policy efforts that enable increased uptake of biologics through the latest guidelines, and to apply them to their own situations.

Uptake metrics versus clinical outcomes

Both the previous report and this report detail the uptake of biologics amongst European countries. They highlight the differences between countries aiming to describe the compliance to international guidelines. By following guidelines healthcare professionals are able to provide care to their patients using the most up-to-date research. This report however does not correlate to actual clinical outcomes in these countries. This report recommends that further studies are performed to investigate the correlation of the uptake metrics and clinical outcomes for severe asthma patients.

As explained earlier, this report provides insights on the use of biologics in patients with severe asthma. Whilst these patients have a large impact on the healthcare due to frequent exacerbations, hospitalisations and increased use of OCS, we must also consider the moderately severe patients who are not eligible for biologics. Therefore, it is recommended that even in countries where uptake of biologics is high, to review clinical outcome markers amongst the whole asthma population and improve these.

Internationally agreed definitions

Much of this report has been performed using open-source data. It has become clear that for many countries, severe asthma is not well-understood as a disease, as shown by the fact that no one internationally-accepted definition of severe asthma exists. Having an international standard definition of severe asthma would enable patients to be treated better and it would reduce the variety in treatments between countries. Considering specific properties and health structures across countries, having an internationally-agreed definition will not solve all problems. However, it would enable recommendations and care to be more standardised across the countries. Furthermore, data collection on prevalence of severe asthma and use of medicines in severe asthma needs to be improved. Many countries do not have a clear understanding of their severe asthma population, that is the true eligible population for biologics, and of how many and which biologics the patients are receiving.

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9 Appendix I

General metric model

The ideal uptake metric regarding any specific medicine is the ratio of the number of users of this medicine for a specific indication (numerator) to the number of eligible patients (denominator), taking the right dosage of the medicine under consideration. As most open-source data sources do not provide information at this level of detail, the calculation of this metric poses a challenge. To overcome this availability challenge, a combination of precise and less precise metrics are used in this report. Assessed collectively, these metrics contain adequate information for comparing the uptake of asthma biologics.

The report draws on a general metric model that was developed by LOGEX and IVM for the International Comparison Medicines Uptake 2021 report (figure 7). The numerator of each metric represents the use of included medicines, measured in number of users or number of Defined Daily Doses (DDD - defined by the World Health Organisation as assumed average maintenance dose per day for a drug for its main indication in adults). The denominator represents the population that is eligible for the use of the specific medicine. Metrics A1 to B2 are the most precise, as the denominator more accurately resembles the true eligible population for the included medicines. However, open-source data sources on disease prevalence are not always readily available and are less frequently updated than sources on, for example, total population. The alphabetical portion of each metric refers to the different denominators of decreasing precision and the numeric part of the metric refers to the numerator; as either 1; number of users or 2; number of DDD of medicine used.

Figure 7 General metric model developed for the International Comparison Medicines Uptake (ICMU).

Increasing precision, lower level of uncertainty

A1	% patients treated with a specific medicine divided by all eligible patients
A2	Number of DDDs per 1000 eligible patients per day
B1	Number of users of specific medicine per 1000 inhabitants divided by prevalence in a country
B2	Number of DDDs per 1000 inhabitants divided by prevalence in a country
C1	% of users of a specific medicine divided by users of medicine with a similar indication
C2	% of DDDs of a specific medicine divided by DDDs of medicine with a similar indication
D1	Users of a drug in a country divided by all inhabitants of a country, expressed as percentage
D2	Number of DDDs per 1000 inhabitants per day
E	Amount of DDD per user per year

Increasing availability of data for all countries and recent years

10 Appendix II

In this appendix metric B1a-c have been determined using all biologics use including use for other indications as numerator. The denominator focuses on the increasing precision of the eligible population from patients with asthma (B1c) through to the severe asthma population (B1a).

Use of asthma biologics in patients with asthma

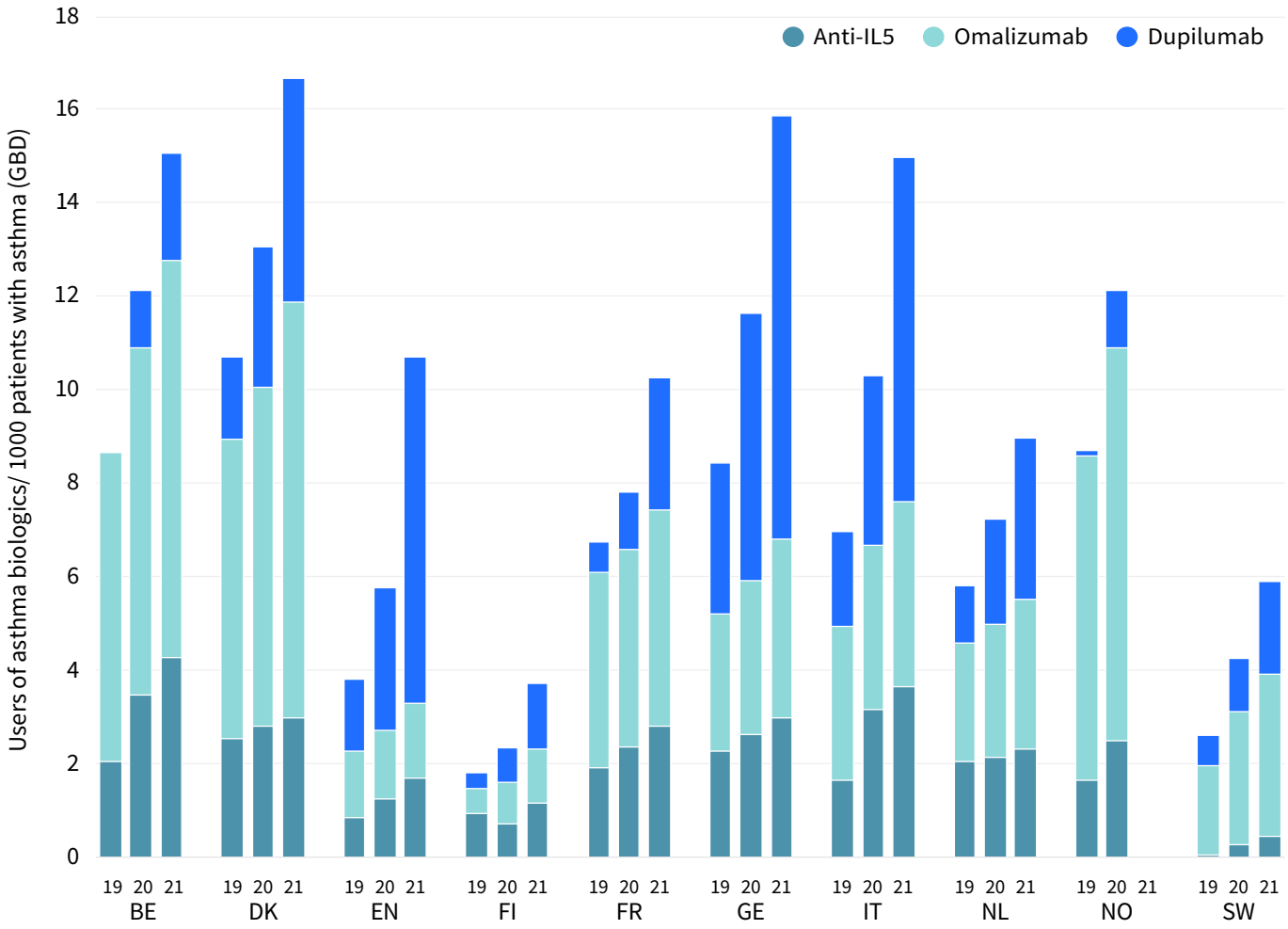
Table 6 Use of specific model for international severe asthma biologics uptake analysis.

Metric	Specific metric explanation (per country)
A1a	Patients using biologics for asthma / All eligible patients based on type of asthma,biomarkers,and/or exacerbations
A1b	Patients using biologics for asthma / Patients with severe asthma
B1a	Total number of users of asthma biologics / Patients with severe asthma
B1b	Total number of users of asthma biologics / Patients receiving care for asthma
B1c	Total number of users of asthma biologics / Patients with asthma
D1	Total number of users of asthma biologics / Total population

The number of asthma patients in a country can be calculated using the prevalence of asthma. Asthma prevalence differs between countries, from 4.4 percent in Italy to 10.6 percent in England (1). As in our 2021 ICMU report, the asthma prevalence from the Global Burden of Disease (GBD) is used (1). The 2019 GBD release provides an estimation of prevalence based on self-reported health status. It offers the convenience of standardised data collection and reporting for all included countries, facilitating international comparison. We took changes in population size into account. As in the previous section, the numerator has been determined using biologics consumption data from national databases.

Concentrating specifically on 2021 in figure 8, the overall use of the included medicines compared to the population with asthma was highest in Denmark, followed closely by Germany. In the asthma population, the number of users of **anti-IL5-agents** was highest in Belgium and lowest in Sweden. The number of users of **omalizumab** was highest in Belgium, Denmark, and lowest in England and Finland. The number of users of **dupilumab** was highest in England and Italy and lowest in Finland.

Figure 8 *Number of users of asthma biologics per 1.000 patients with asthma, based on GBD data, 2019 – 2021. Please note that this also includes users of biologics which have indications other than (severe) asthma.*



Use of asthma biologics in patients receiving care for asthma

Table 7 *Use of specific model for international severe asthma biologics uptake analysis.*

Metric	Specific metric explanation (per country)
A1a	Patients using biologics for asthma / All eligible patients based on type of asthma,biomarkers,and/or exacerbations
A1b	Patients using biologics for asthma / Patients with severe asthma
B1a	Total number of users of asthma biologics / Patients with severe asthma
B1b	Total number of users of asthma biologics / Patients receiving care for asthma
B1c	Total number of users of asthma biologics / Patients with asthma
D1	Total number of users of asthma biologics / Total population

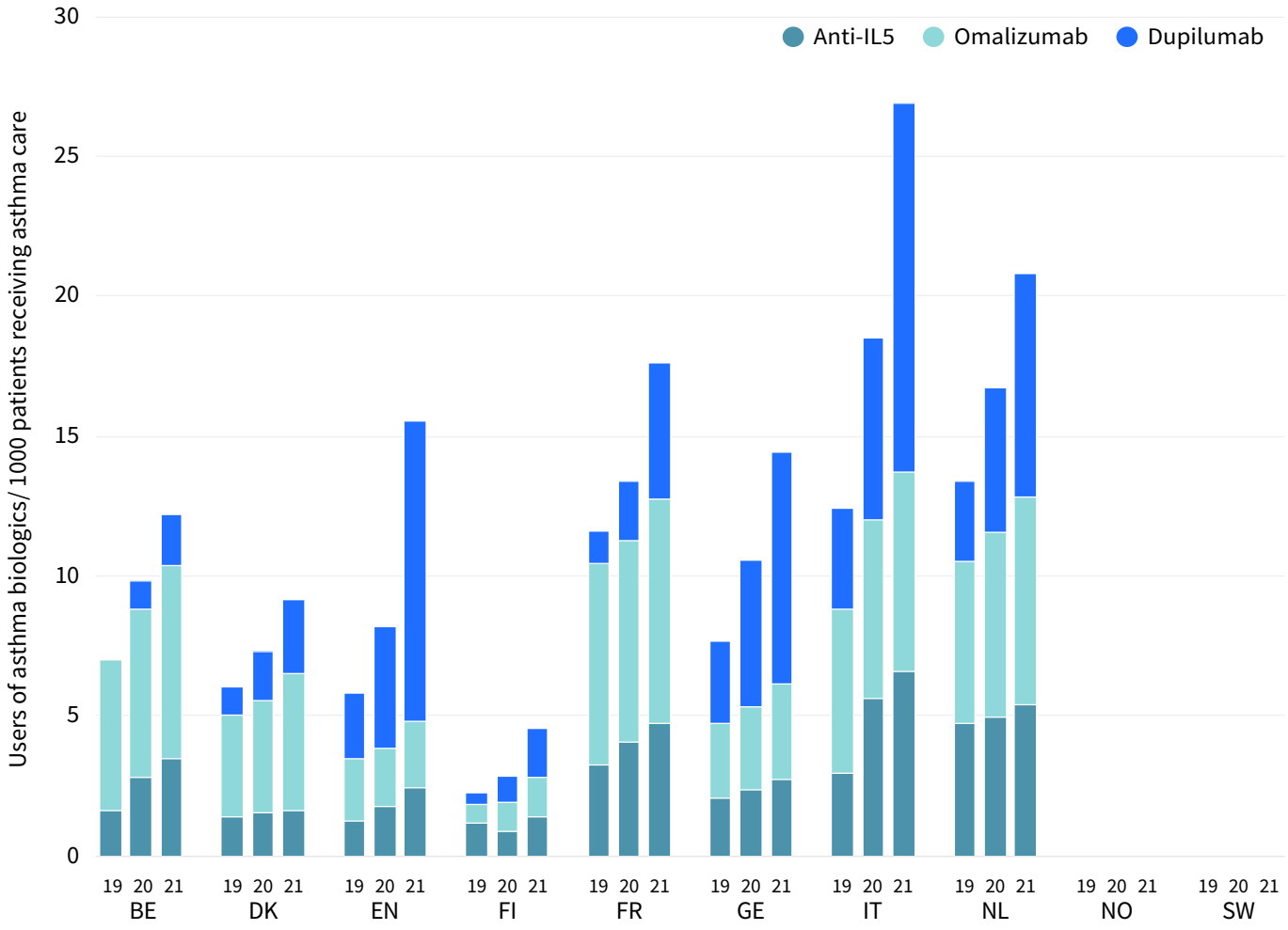
The GBD uses self-reported asthma data as measure for prevalence. Using asthma that is diagnosed by health care professionals means that the asthma indication is validated more accurately. Therefore, a new denominator has been included in this report compared to the 2021 ICMU report, based on the care delivered to asthma patients.

In this section, the prevalence is based on national databases or large cohort studies. For most countries, data on care consumption linked to diagnosis are available on a national scale or for large cohorts. An example is the number of patients visiting a primary care professional for asthma, which can be extracted from diagnosis codes supplied by the primary care professional. While the exact definition of disease and the way in which care is organised may differ per country, these large databases give an estimation of the number of patients that is being treated for asthma. Consequently, care consumption is a more precise estimation of the eligible population for asthma biologics than can be obtained using GBD.

The percentage of patients receiving care for asthma varies between 2.2 percent (Italy) and 7.8 percent (Denmark). Data on care consumption are not available for Norway and Sweden. Data for Finland may underestimate the total number of patients receiving care, due to the exclusion of mild cases of asthma in the data source. Therefore, if the correct number of patients receiving care would have been used, the uptake metric for Finland in figure 9 would have been lower than its current position due to the inverse relationship of the denominator to the metric.

Concentrating specifically on 2021, the overall use of the included medicines compared to the population with asthma was highest in Italy. In the asthma population receiving care, the use of **anti-IL5-agents** was highest in Italy and lowest in Denmark and Finland. The use of **omalizumab** was highest in France and the Netherlands and lowest in Finland. The use of **dupilumab** was highest in England and Italy and lowest in Finland.

Figure 9 *Number of users of asthma biologics per 1.000 patients receiving care for asthma, 2019 – 2021. Please note that this also includes users of biologics which have indications other than (severe) asthma.*



Use of asthma biologics in patients receiving care for asthma

Table 8 *Use of specific model for international severe asthma biologics uptake analysis.*

Metric	Specific metric explanation (per country)
A1a	Patients using biologics for asthma / All eligible patients based on type of asthma,biomarkers,and/or exacerbations
A1b	Patients using biologics for asthma / Patients with severe asthma
B1a	Total number of users of asthma biologics / Patients with severe asthma
B1b	Total number of users of asthma biologics / Patients receiving care for asthma
B1c	Total number of users of asthma biologics / Patients with asthma
D1	Total number of users of asthma biologics / Total population

A subgroup of asthma patients or of patients who are receiving care for asthma, suffers from severe asthma. No international agreed definition exists for severe asthma and across countries and healthcare organisations different definitions are used. For this report, the severe asthma population was based on reports per country on GINA-step 5 medication and number of exacerbations.

Although there is ambiguity in the definition of severe asthma, the binding factor in various definitions is that the severe asthma population will have had specialist input and optimisation, but despite this, the disease remains uncontrolled without using biologics. By computing the severe asthma population group, an even more precise eligible population for biologics is determined. Since in many countries registry data on severe asthma prevalence are not available, data and estimations from literature sources were combined with previously collected total population and asthma prevalence data. Table 9 shows patients with severe asthma as a percentage of the population with asthma according to GBD data. These data were not available for Belgium and Norway. It is noteworthy that the severe asthma prevalence is especially high in England and Finland.

Ambiguity of severe asthma definition
GINA defines it as patients being uncontrolled on GINA step 4 treatment (ICS with LABA or LAMA) or patients who are receiving treatment step 5¬¬1. The British Thoracic Society guidelines defines it as two asthma attacks a year or persistent symptoms despite SABA use more than twice a week despite specialist level therapy. The International ATS/ERS guidelines by the American Thoracic Society and the European Respiratory Society take a three step approach. Firstly, the diagnosis of asthma must be refractory to specialist treatment, secondly, the patient requires high dose ICS and a controller medicine (LABA/LAMA/LTRA/OCS), thirdly, the asthma symptoms are either uncontrolled despite treatment or become uncontrolled when tapering down OCS treatment. Although these definitions are not starkly different, they would include different patients into the severe asthma population. Each mixes clinical history, clinical outcomes, and therapeutic options together in a different way. Consequently, the group of patients that should be included in the severe asthma population is still being disputed among professionals. This strongly underlines the complexity of defining and subsequently treating severe asthma patients.

Table 9 Percentage of patients with severe asthma compared to all patients with asthma according to GBD in 2021.

	% severe asthma versus asthma according to GBD	Source
Belgium	No data	
Denmark	2,0%	(16)
England	4,7%	(17)
Finland	5,0%	(16)
France	1,8%	(18)
Germany	1,1%	(19)
Italy	1,9%	(20)
The Netherlands	1,2%	(21)
Norway	No data	
Sweden	0,7%	(16)

Concentrating specifically on 2021, as seen in figure 11, the overall use of biologics as a percentage of the population with severe asthma was highest in Germany. In the severe asthma population, the use of **anti-IL5-agents** was highest in Germany and lowest in England and Finland. The use of **omalizumab** was highest in Sweden and Denmark and lowest in England and Finland. The use of **dupilumab** was highest in Germany and lowest in Finland.

Figure 10 *Number of users of asthma biologics as percentage of patients with severe asthma 2019 – 2021. Please note that this also includes users of biologics which have indications other than (severe) asthma, therefore a value of greater than 100 percent is possible.*

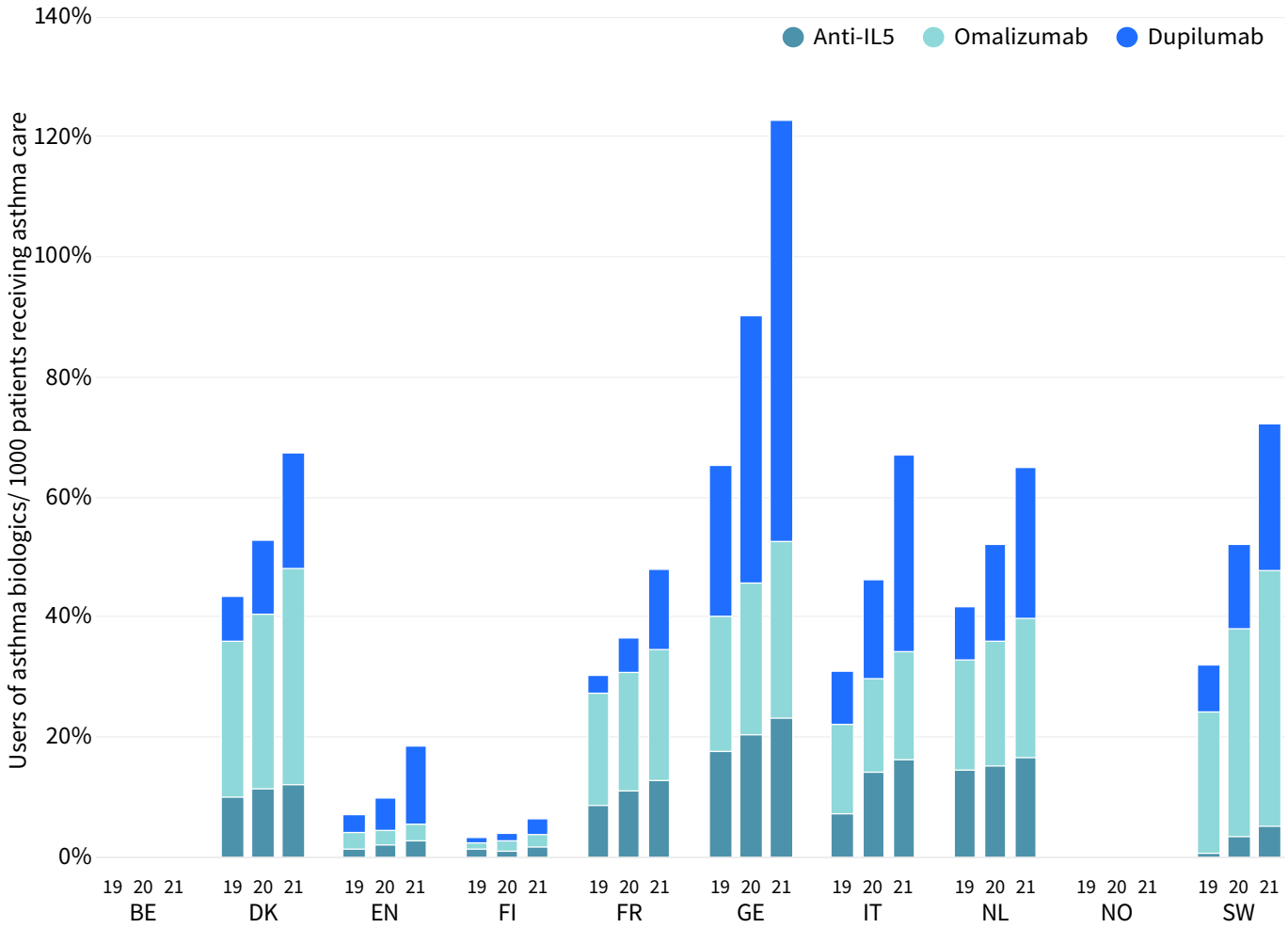
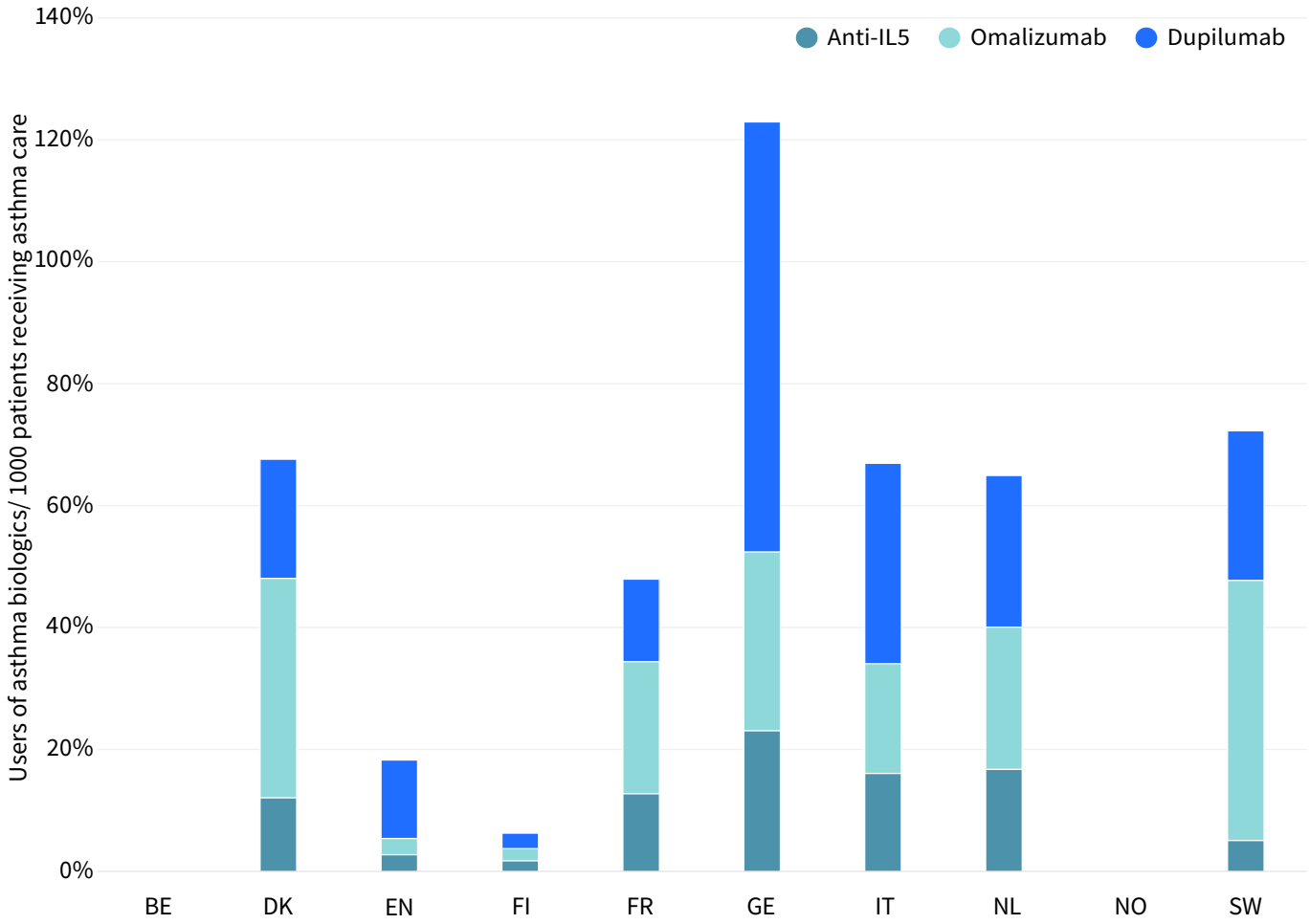


Figure 11 *Number of users of asthma biologics as percentage of patients with severe asthma in 2021. Please note that this also includes users of biologics which have indications other than (severe) asthma, therefore a value of greater than 100 percent is possible.*



Caveats

We established a stepwise improvement of the accuracy of the metric moving from total population to the severe asthmatic population. However, as explained previously in this report, the phenotype of asthma affects which patients are eligible for biologics. Data on the phenotype distribution of asthma and the burden of the disease are not available for most countries, even at the level of literature. This means the eligible population cannot be defined. Although country-specific data are largely lacking, some general data can be found. In one study of patients using medication GINA step 4 or 5 and not currently treated with a biologic treatment, 65-76 percent was not eligible for any biologic (7). On the contrary, another study in severe asthma patients found an eligibility percentage of 62 according to the label criteria of biologics (8).

11 Appendix III

Belgium

Denominator	2019	2020	2021
Total population	**11,431,406**	**11,492,641**	**11,521,238**
Adult population	**9,126,019**	**9,180,601**	**9,209,116**
Source	1	1	1
Asthma prevalence	**5.04%**	**5.04%**	**5.04%**
Number of patients with asthma	**576,220**	**579,307**	**580,748**
Source		2	2
Prevalence of patients receiving care for asthma in adult population	**6.21%**	**6.21%**	**6.21%**
Number of patients receiving care for asthma	**567,038**	**570,429**	**572,201**
Source	3	3	3
Prevalence of severe asthma	**No data**	**No data**	**No data**
Number of patients with severe asthma	**No data**	**No data**	**No data**
Source			

Numerator	2019	2020	2021
Number of users of dupilumab	**0**	**577**	**1,082**
Number of users of omalizumab	**3,116**	**3,534**	**4,047**
Number of users of benralizumab	**403**	**685**	**917**
Number of users of mepolizumab	**561**	**963**	**1,135**
Number of users of reslizumab	**0**	**0**	**0**
Number of users of anti-IL5-agents	**964**	**1,648**	**2,052**
Source	5	5	5

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Denmark

Denominator	2019	2020	2021
Total population	**5,806,081**	**5,822,768**	**5,840,045**
Population 12 years and over	**4,382,676**	**4,394,714**	**4,410,715**
Source	1	1	1
Asthma prevalence	**5.17%**	**5.17%**	**5.17%**
Number of patients with asthma	**300,398**	**301,206**	**302,156**
Source	2	2	2
Prevalence of patients receiving care for asthma in total population	**7.55%**	**7.67%**	**7.78%**
Number of patients receiving care for asthma	**438.600**	**446.775**	**454.350**
Source	3	3	3
Prevalence of severe asthma in population 12 years and over	**0.14%**	**0.14%**	**0.14%**
Number of patients with severe asthma	**6,129**	**6,146**	**6,169**
Source	4	4	4

Numerator	2019	2020	2021
Number of DDD of dupilumab	**77,000**	**143,000**	**238,000**
Number of DDD of omalizumab	**408,000**	**468,000**	**557,000**
Number of DDD of benralizumab	**34,000**	**47,000**	**55,000**
Number of DDD of mepolizumab	**112,000**	**137,000**	**148,000**
Number of DDD of reslizumab	**14,000**	**1,0000**	**6,000**
Number of users of dupilumab	**430**	**744**	**1,191**
Number of users of omalizumab	**1,589**	**1,800**	**2,213**
Number of users of anti-IL5-agents	**631**	**699**	**752**
Source	5	5	5

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England

Denominator	2019	2020	2021
Total population	**56,286,961**	**56,550,000**	**56,490,053**
Population 6 years and over	**52,296,202**	**52,621,501**	**52,754,406**
Source	1	1	1
Asthma prevalence	**10.61%**	**10.61%**	**10.61%**
Number of patients with asthma	**5,970,006**	**5,997,905**	**5,991,547**
Source	2	2	2
Prevalence of patients receiving primary care for asthma in total population 6 years and over	**5.93%**	**6.48%**	**6.38%**
Number of patients receiving care for asthma	**3,103,054**	**3,411,382**	**3,363,101**
Source	3	3	3
Prevalence of severe asthma in asthma treated in primary care	**7.9%**	**7.9%**	**7.9%**
Number of patients with severe asthma	**263,787**	**289,552**	**284,433**
Source	4	4	4

Numerator	2019	2020	2021
Number of DDD of dupilumab	**1,295,257**	**2,831,785**	**7,188,329**
Number of DDD of omalizumab	**1,746,132**	**1,826,654**	**1,996,322**
Number of DDD of benralizumab	**234,889**	**738,722**	**1,188,389**
Number of DDD of mepolizumab	**757,834**	**937,361**	**1,063,500**
Number of DDD of reslizumab	**39,665**	**34,462**	**42,200**
Number of users of dupilumab	**7,228**	**14,737**	**35,962**
Number of users of omalizumab	**6,802**	**7,026**	**7,932**
Number of users of anti-IL5-agents	**4,072**	**6,164**	**8,252**
Source	5,6	5,6	5,6

Sources

1. Office for National statistics, https://www.ons.gov.uk/
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Finland

Denominator	2019	2020	2021
Total population	**5,517,919**	**5,525,292**	**5,533,793**
Population 12 years and over	**4,817,818**	**4,837,923**	**4,859,082**
Source	1	1	1
Asthma prevalence	**7.30%**	**7.30%**	**7.30%**
Number of patients with asthma	**402,572**	**403,110**	**403,730**
Source	2	2	2
Prevalence of patients receiving care for moderate to severe asthma	**4.90%**	**5.00%**	**5.00%**
Number of patients receiving care for asthma	**270,378**	**276,265**	**276,690**
Source	3	3	3
Prevalence of severe asthma in population 12 years and over	**0.41%**	**0.41%**	**0.41%**
Number of patients with severe asthma	**19,819**	**19,902**	**19,989**
Source	4	4	4

Numerator	2019	2020	2021
Number of users of dupilumab	**104**	**244**	**471**
Number of users of omalizumab	**185**	**291**	**392**
Number of users of benralizumab	**0**	**74**	**119**
Number of users of mepolizumab	**0**	**176**	**269**
Number of users of reslizumab	**0**	**0**	**0**
Number of users of anti-IL5-agents	**318**	**250**	**388**
Source	5	5	5

Sources

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3. Sotkanet.fi, indicator 3207, https://sotkanet.fi/sotkanet/en/index
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France

Denominator	2019	2020	2021
Total population	**64,988,222**	**67,454,122**	**67,626,396**
Adult population	**52,632,223**	**52,909,737**	**53,160,117**
Population 12 years and over	**55,929,995**	**56,210,401**	**56,476,885**
Source	1	1	1
Asthma prevalence	**7.40%**	**7.40%**	**7.40%**
Number of patients with asthma	**4,811,181**	**4,993,735**	**5,006,489**
Source	2	2	2
Prevalence of patients receiving care for asthma in total adult population	**4.31%**	**4.31%**	**4.31%**
Number of patients receiving care for asthma	**2,269,598**	**2,281,565**	**2,292,362**
Source	3	3	3
Prevalence of severe asthma in total population 12 years and over	**0.16%**	**0.16%**	**0.16%**
Number of patients with severe asthma	**88,370**	**88,813**	**89,235**
Source	3	3	3

Numerator	2019	2020	2021
Number of DDD of dupilumab	**452,327**	**1,011,916**	**2,343,542**
Number of DDD of omalizumab	**4,391,489**	**4,754,175**	**5,010,356**
Number of DDD of benralizumab	**625,000**	**1,322,389**	**1,696,667**
Number of DDD of mepolizumab	**1,156,167**	**1,297,389**	**1,449,667**
Number of DDD of reslizumab	**0**	**0**	**0**
Number of users of dupilumab	**2,431**	**4,969**	**11,691**
Number of users of omalizumab	**16,572**	**17,485**	**19,315**
Number of users of anti-IL5-agents	**7,639**	**9,859**	**11,636**
Source	4	4	4

Sources

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2. Global Burden of Disease Collaborative Network. Global Burden of Disease Study 2019 (GBD 2019) Results. Seattle. http://ghdx.healthdata.org/gbd-results-tool.
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Germany

Denominator	2019	2020	2021
Total population	**83,019,213**	**83,166,711**	**83,155,031**
Adult population	**69,421,785**	**69,488,809**	**69,411,087**
Source	1	1	1
Asthma prevalence	**4.46%**	**4.46%**	**4.46%**
Number of patients with asthma	**3,704,255**	**3,710,836**	**3,710,315**
Source	2	2	2
Prevalence of patients receiving care for asthma in total population	**4.20%**	**4.20%**	**4.20%**
Number of patients receiving care for asthma	**3,486,807**	**3,493,002**	**3,492,511**
Source	3	3	3
Prevalence of severe asthma in total adult population	**1.40%**	**1.40%**	**1.40%**
Number of patients with severe asthma	**40,955**	**40,994**	**40,948**
Source	4	4	4

Numerator	2019	2020	2021
Number of DDD of dupilumab	**1,810,900**	**3,491,800**	**5,730,400**
Number of DDD of omalizumab	**2,383,100**	**2,695,300**	**3,027,400**
Number of DDD of benralizumab	**785,200**	**1,093,200**	**1,325,000**
Number of DDD of mepolizumab	**1,011,800**	**1,206,100**	**1,301,900**
Number of DDD of reslizumab	**42,900**	**28,800**	**23,400**
Number of users of dupilumab	**10,105**	**18,172**	**28,668**
Number of users of omalizumab	**9,284**	**10,366**	**12,029**
Number of users of anti-IL5-agents	**7,256**	**8,390**	**9,533**
Source	5	5	5

Sources

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Italy

Denominator	2019	2020	2021
Total population	**59,816,673**	**59,641,488**	**59,236,213**
Population 6 years and over	**56,970,803**	**56,877,806**	**56,526,385**
Source	1	1	1
Asthma prevalence	**4.40%**	**4.40%**	**4.40%**
Number of patients with asthma	**2,632,427**	**2,624,717**	**2,606,882**
Source	2	2	2
Prevalence of patients receiving care for asthma in total population 6 years and over	**2.21%**	**2.21%**	**2.21%**
Number of patients receiving care for asthma	**1,260,930**	**1,258,872**	**1,251,094**
Source	3	3	3
Prevalence of severe asthma in total population 6 years and over	**0.09%**	**0.09%**	**0.09%**
Number of patients with severe asthma	**50,578**	**50,495**	**50,183**
Source	3	3	3

Numerator	2019	2020	2021
Number of DDD of dupilumab per 1000 inhabitants per day	**0.037**	**0.072**	**0.152**
Number of DDD of omalizumab per 1000 inhabitants per day	**0.088**	**0.096**	**0.104**
Number of DDD of benralizumab per 1000 inhabitants per day	**0**	**0.038**	**0.049**
Number of DDD of mepolizumab per 1000 inhabitants per day	**0.043**	**0.053**	**0.057**
Number of DDD of reslizumab per 1000 inhabitants per day	**0**	**0**	**0**
Number of users of dupilumab	**4,522**	**8,147**	**16,424**
Number of users of omalizumab	**7,445**	**7,999**	**8,914**
Number of users of anti-IL5-agents	**3,728**	**7,141**	**8,255**
Source	4	4	4

Sources

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Netherlands

Denominator	2019	2020	2021
Total population	**17,282,163**	**17,407,585**	**17,475,415**
Source	1	1	1
Asthma prevalence	**8.22%**	**8.22%**	**8.22%**
Number of patients with asthma	**1,419,899**	**1,430,204**	**1,435,777**
Source	2	2	2
Prevalence of patients receiving care for asthma	**2.96%**	**2.96%**	**2.96%**
Number of patients receiving care for asthma	**510,762**	**514,469**	**516,473**
Source	3	3	3
Prevalence of severe asthma in population receiving care	**3.21%**	**3.21%**	**3.21%**
Number of patients with severe asthma	**16,397**	**16,516**	**16,580**
Source	4	4	4

Numerator	2019	2020	2021
Number of users of dupilumab	**1,438**	**2,619**	**4,089**
Number of users of omalizumab	**2,979**	**3,408**	**3,844**
Number of users of benralizumab	**704**	**914**	**1,046**
Number of users of mepolizumab	**1,478**	**1,423**	**1,555**
Number of users of reslizumab	**237**	**218**	**199**
Number of users of anti-IL5-agents	**2,419**	**2,555**	**2,800**
Source	5	5	5

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Norway

Denominator	2019	2020	2021
Total population	**5,328,212**	**5,367,580**	**5,391,369**
Source	1	1	1
Asthma prevalence	**7.34%**	**7.34%**	**7.34%**
Number of patients with asthma	**390,864**	**393,751**	**395,497**
Source	2	2	2
Prevalence of patients receiving care for asthma	**No data**	**No data**	**No data**
Number of patients receiving care for asthma	**No data**	**No data**	**No data**
Source			
Prevalence of severe asthma in population	**No data**	**No data**	**No data**
Number of patients with severe asthma	**No data**	**No data**	**No data**
Source			

Numerator	2019	2020	2021
Number of users of dupilumab	**19**	**389**	**No data**
Number of users of omalizumab	**2.208**	**2.700**	**No data**
Number of users of benralizumab	**77**	**89**	**No data**
Number of users of mepolizumab	**442**	**704**	**No data**
Number of users of reslizumab	**12**	**9**	**No data**
Number of users of anti-IL5-agents	**531**	**802**	**No data**
Source	3	3	3

Sources

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Sweden

Denominator	2019	2020	2021
Total population	**10,230,185**	**10,379,295**	**10,452,326**
Population 12 years and over	**8,853,236**	**8,909,887**	**8,986,815**
Source	1	1	1
Asthma prevalence	**8.51%**	**8.51%**	**8.51%**
Number of patients with asthma	**870,804**	**883,497**	**889,713**
Source	2	2	2
Prevalence of patients receiving care for moderate to severe asthma	**No data**	**No data**	**No data**
Number of patients receiving care for asthma	**No data**	**No data**	**No data**
Source			
Prevalence of severe asthma in population 12 years and over	**0.07%**	**0.07%**	**0.07%**
Number of patients with severe asthma	**5,813**	**5,851**	**5,901**
Source	3	3	3

Numerator	2019	2020	2021
Number of users of omalizumab	**1,362**	**2,016**	**2,506**
Number of users of benralizumab	**30**	**77**	**128**
Number of users of mepolizumab	**23**	**138**	**193**
Number of users of reslizumab	**0**	**0**	**0**
Number of users of anti-IL5-agents	**53**	**215**	**321**
Source	**4**	**4**	**4**
Source	3	3	3

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