Global Variability in Administrative Approval Prescription Criteria for Biologic Therapy in Severe Asthma

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Background and Objectives

Background

- **Five biologics are licensed by the FDA and EMA for severe asthma treatment**
  - Anti-IgE: Omalizumab
  - Anti-IL5/5R: Mepolizumab, benralizumab and reslizumab
  - Anti-IL4Rα: Dupilumab
- Accessibility to biologic therapy is restricted by clinical, administrative and reimbursement criteria that differ across countries
- No previous studies have compared biologic access globally

Objectives

1. Analyze national biologic access criteria in ISAR collaborating countries
2. Study global differences in ease-of-access to biologics
3. Compare national biologic access criteria in ISAR collaborating countries with established regulatory criteria

EMA = European Medicine Agency; FDA = Food and Drug Administration; IgE = Immunoglobulin E; IL4Rα = Interleukin 4 receptor alpha; IL5/5R = Interleukin 5/5 receptor; ISAR = International Severe Asthma Registry

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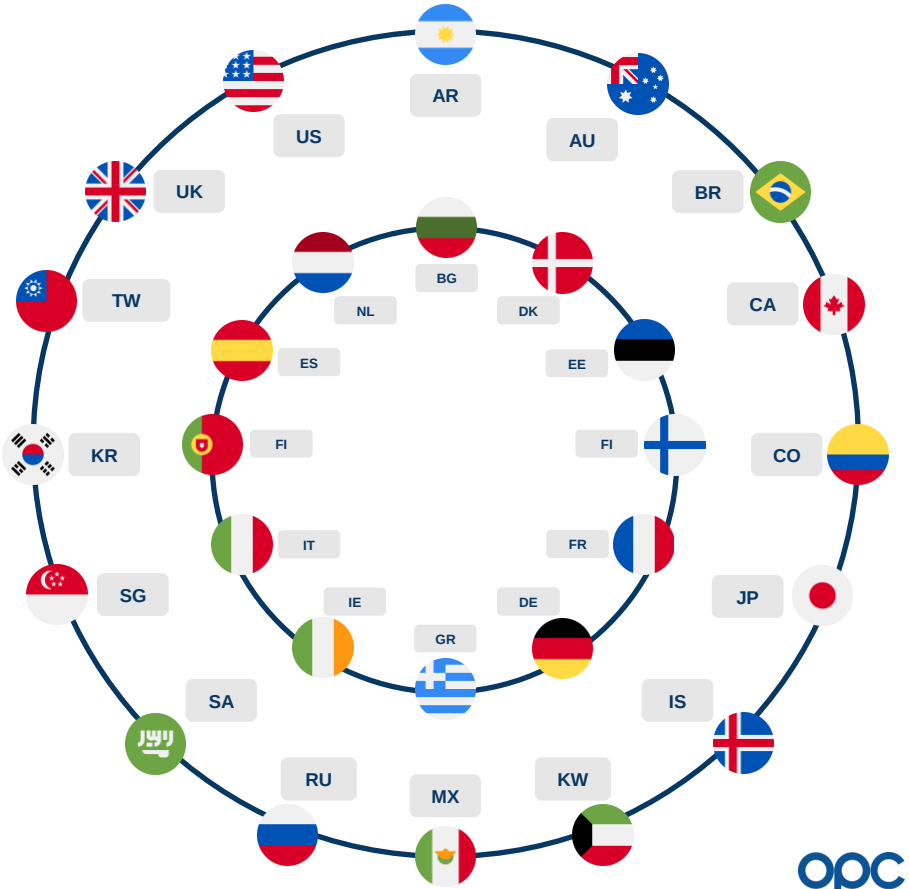
Study design – Data collection

Biologic prescription criteria were obtained from publicly available drug regulation authority websites

A semi-structured survey was sent to severe asthma experts from 29 ISAR countries* to compare official criteria with real-life practice

Tabulated data were re-sent to the ISC members in ISAR countries to check the criteria for all biologics



*Responses were received from all countries except India, which was eventually removed from the data analysis.
ISAR = International Severe Asthma Registry; ISC = ISAR Steering Committee
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Study design – Development of the Biologic ACcessibility Score (BACS)

The composite BACS (ten criteria) compared biologic accessibility across countries. 0 = most difficult access and 10 = easiest access.

Criterion	Score
Age (years)	
Not required/undecided	10
≥6	8
≥12	4
≥18	0
Severity/Phenotype	
Not required/undecided	10
IgE mediated OR type II driven OR eosinophilic	8
Bronchial asthma refractory OR uncontrolled allergic	6
Moderate to severe (persistent, eosinophilic, OR OCS dependent)	4
Severe (persistent, eosinophilic, with type II inflammation OR allergic)	2
Severe (uncontrolled, uncontrolled + eosinophilic, uncontrolled allergic, refractory, refractory + eosinophilic)	0
Serum IgE (IU/ml)	
Not required/undecided	10
≥30, 35, or elevated	8
≥70, 75 or 76	4
≥150	2
≥400	0
BEC (cells/µL)	
Not required/undecided	10
≥150 or raised	8
≥150 in last 12 months	7
≥150 in last 1 month	6
≥300 or ≥150 on long-term OCS	5
≥300 in last 12 months or historical	4
≥300 x2 in last 12 months	3
≥400 or in last 12 months	2
≥500	0
FeNO (ppb)*	
Not required/undecided	10
≥20 or 25 or raised	5
≥50	0
Allergic Asthma	
Not required/undecided	10
SPT or RAST	5
SPT and RAST	0

Criterion	Score
Background Therapy	
Not required/undecided	10
ICS	8
High dose ICS (+/- LABA or long-term OCS or xanthine or LTRA)	6
Medium dose ICS/LABA (+/- LTRA)	5
High dose ICS/LABA (+/- LAMA or LTRA)	4
High dose ICS/LABA (+/- long-term OCS)	
High dose ICS/LABA + ≥ 1 other controller (not OCS)	2
High dose ICS/LABA + long term OCS	0
OCS†	
Not required/undecided	10
Long term OCS use	0
Exacerbations†	
Not required/undecided	10
≥1	8
≥1 requiring hospital admission, emergency room visit, or rescue OCS	6
≥2	4
≥2 requiring hospital admission, emergency room visit, or rescue OCS	3
≥3	2
≥4	0
Asthma Control	
Not required/undecided	10
Required	0
Lung Function	
Not required/undecided	10
FEV_1 ≤80%	8
≥12% reversibility +/- > 200 ml FEV_1	6
FEV_1 ≤80% & evidence of reversibility	4
FEV_1 ≤80% & 12% reversibility & AHR	2
FEV_1 ≤60%	0
Adherence	
Not required/undecided	10
Required	0

AHR: airway hyperresponsiveness; BACS = Biologic ACessibility Score; BEC: blood eosinophil count; FeNO: fractional exhaled nitric oxide; FEV_1: forced expiratory volume in 1 second; HCP: healthcare professional; ICS: inhaled corticosteroids; IgE: immunoglobulin E; LABA: long-acting beta agonist; LAMA: long-acting muscarinic antagonist; LTRA: leukotriene antagonist; OCS: oral corticosteroids; RAST: radioallergosorbent test; SPT: skin prick test

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Study design – Outcomes

Outcomes

Description of global access to biologics
- World maps were developed to summarize biologic accessibility
- Pearson's correlation testing was used to explore the relationship between BACS and GDP 2019

Individual access criteria
- Per country
- Per biologic

Overall ease-of-access to each biologic
- BACS scores were referenced to EMA regulatory criteria

Availability of the biologics
- Licensing and reimbursement status of omalizumab, mepolizumab, reslizumab, benralizumab and dupilumab

BACS = Biologic ACessibility Score; EMA = European Medicines Agency; GDP = Gross Domestic Product

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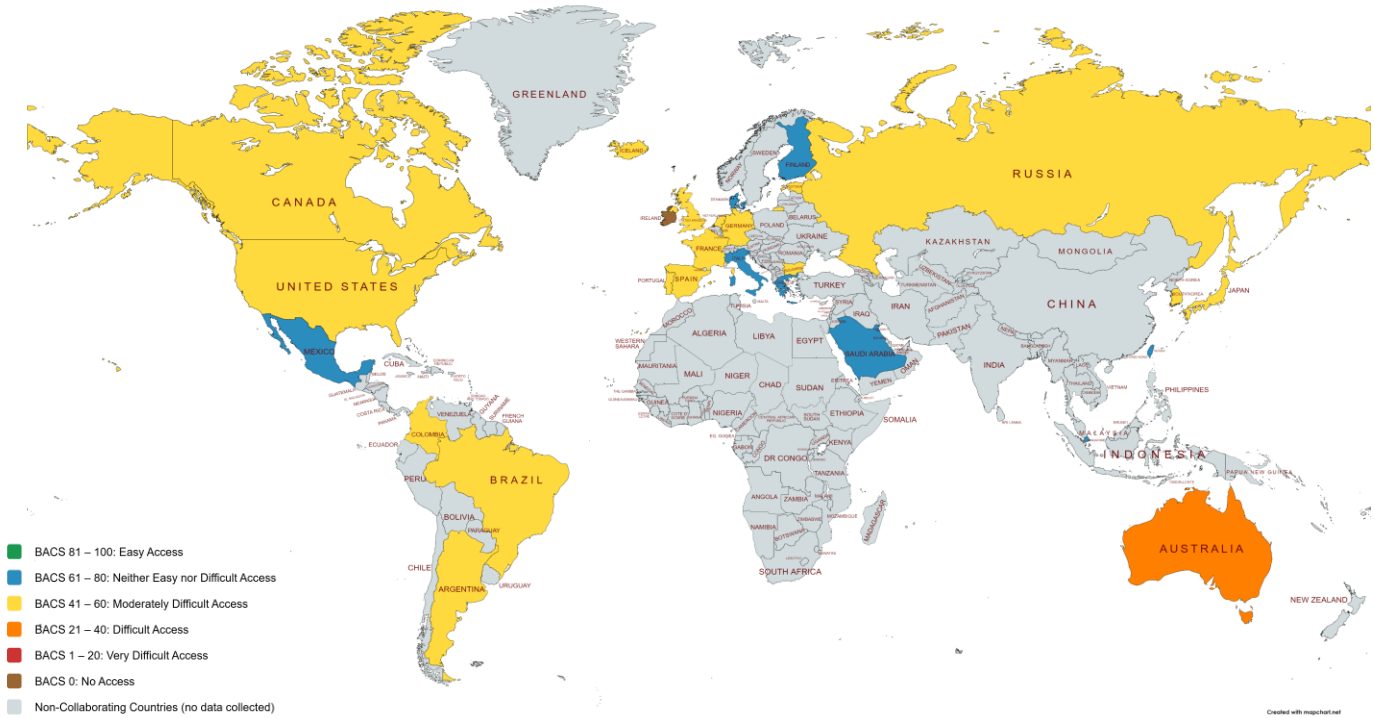
Results – Omalizumab BACS for ISAR countries



- ✓ Licensed in 28 countries
- ✓ **Neither easy nor difficult to access** in 32% of countries
- ✓ **Moderately difficult to access** in 61% of countries
- ✓ **Difficult to access** in Australia
- ✓ **BACS range:** 39 (Australia) to 71 (Denmark)
- ✓ **Mean BACS:** 57, which is lower than EMA BACS of 69
- ✓ All countries (except Denmark and Finland) reported more stringent access to omalizumab than the EMA

BACS data were as of April 2021.
BACS = Biologic ACessibility Score; EMA = European Medicines Agency; ISAR = International Severe Asthma Registry
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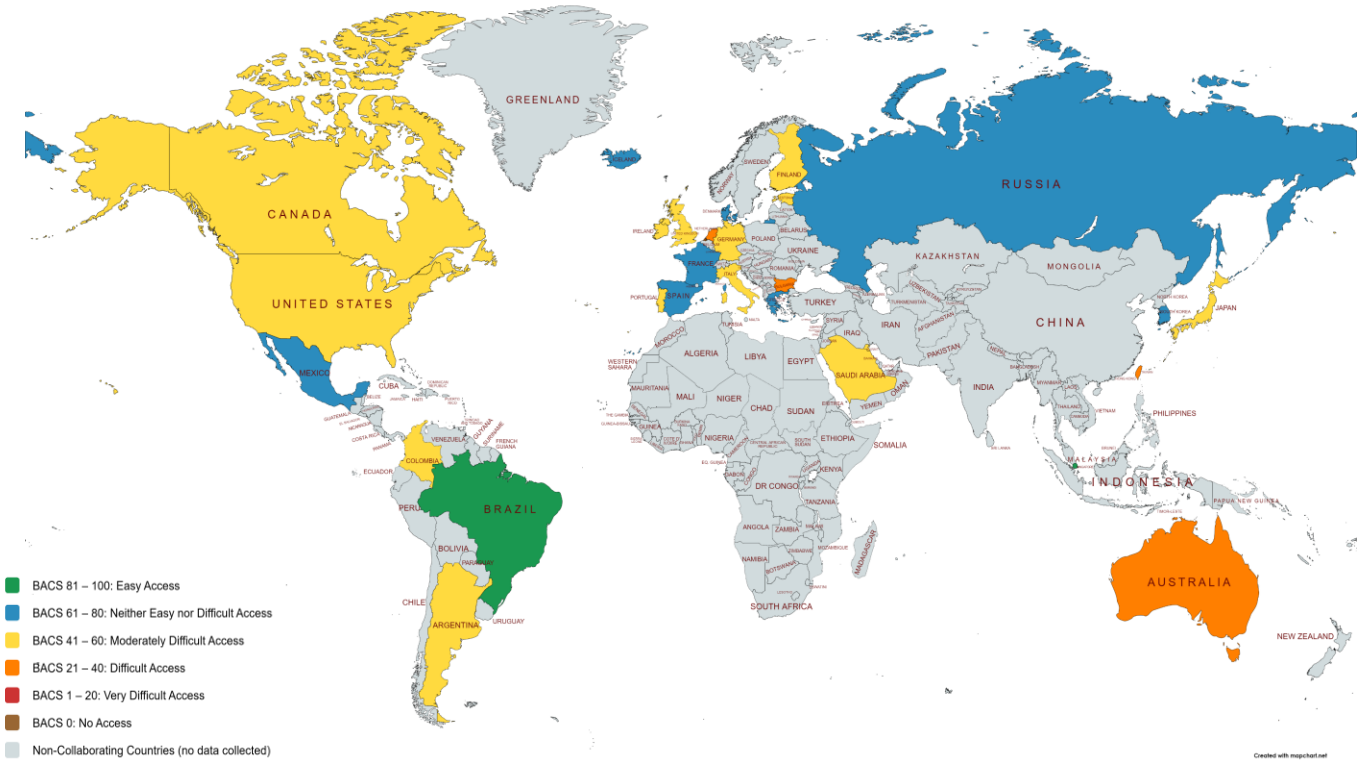
Results – Mepolizumab BACS for ISAR countries



- ✓ Licensed in 28 countries
- ✓ **Neither easy nor difficult to access in** 29% of countries
- ✓ **Moderately difficult to access** in 50% of countries
- ✓ **Difficult to access** in Australia, Bulgaria, the Netherlands and Taiwan
- ✓ **BACS range:** 26 (Bulgaria) to 90 (Brazil)
- ✓ **Mean BACS:** 55, which is lower than EMA BACS of 87
- ✓ All countries (except Brazil and Singapore) reported more stringent access to mepolizumab than the EMA

BACS data were as of April 2021.
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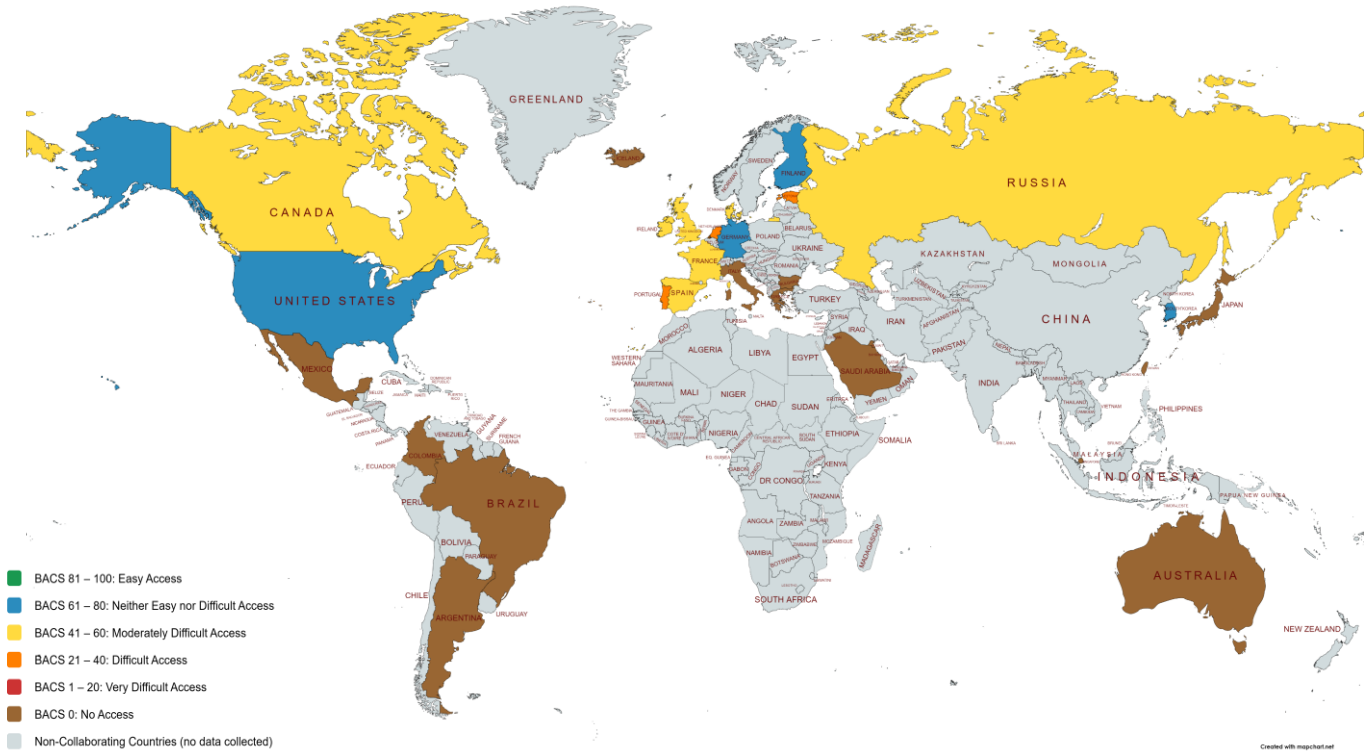
Results – Reslizumab BACS for ISAR countries



- ✓ Licensed in 15 countries
- ✓ **Neither easy nor difficult to access** in Finland, Germany, South Korea and the United States
- ✓ **Difficult or moderately difficult to access** in 67% of countries
- ✓ **BACS range:** 36 (the Netherlands) to 69 (South Korea)
- ✓ **Mean BACS:** 51, which is lower than EMA BACS of 76
- ✓ All countries reported more stringent access to reslizumab than the EMA

BACS data were as of April 2021.
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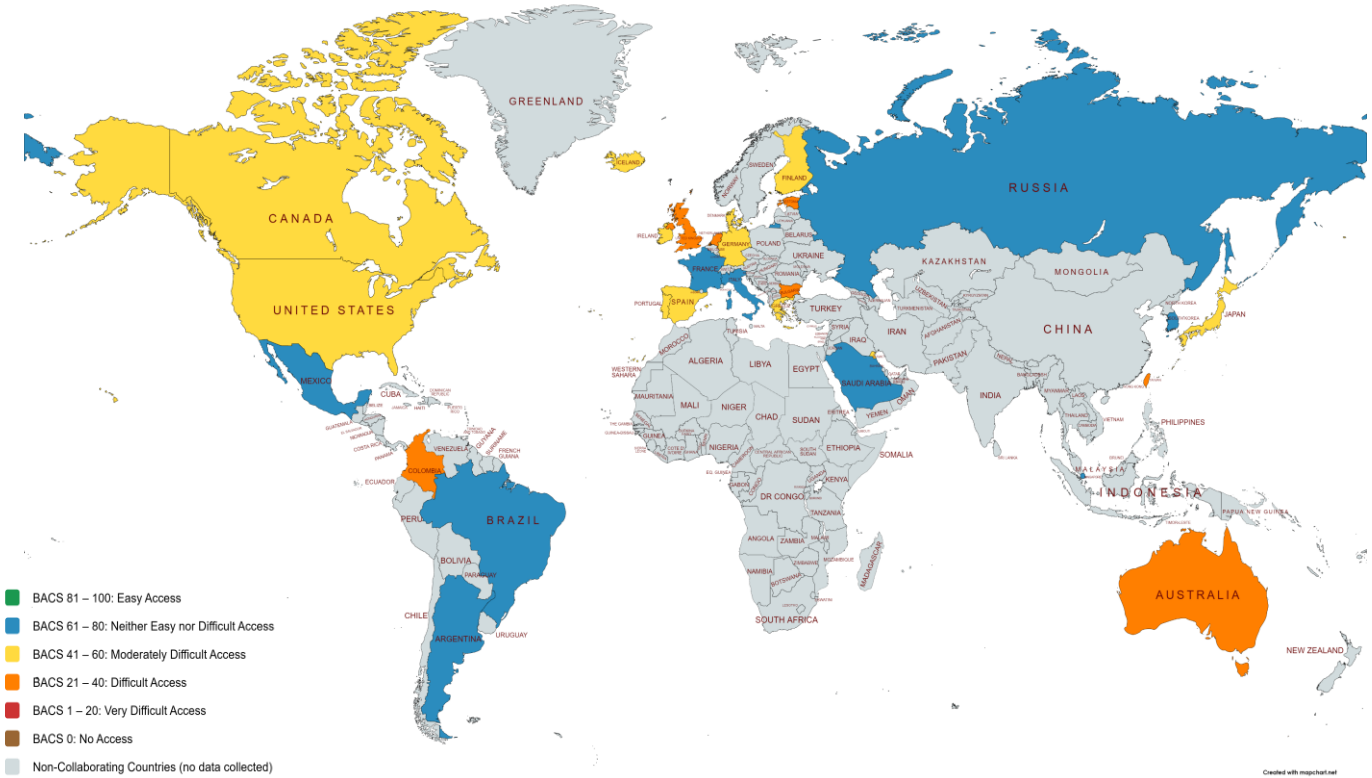
Results – Benralizumab BACS for ISAR countries



- ✓ Licensed in 28 countries
- ✓ **Neither easy nor difficult, or moderately difficult to access** in 75% of countries
- ✓ **Difficult to access** in 25% of countries
- ✓ **BACS range:** 30 (Australia) to 80 (Mexico)
- ✓ **Mean BACS:** 54, which is lower than EMA BACS of 76
- ✓ All countries (except Brazil, Mexico, Singapore and South Korea) reported more stringent access to benralizumab than the EMA

BACS data were as of April 2021.
BACS = Biologic ACessibility Score; EMA = European Medicines Agency; ISAR = International Severe Asthma Registry
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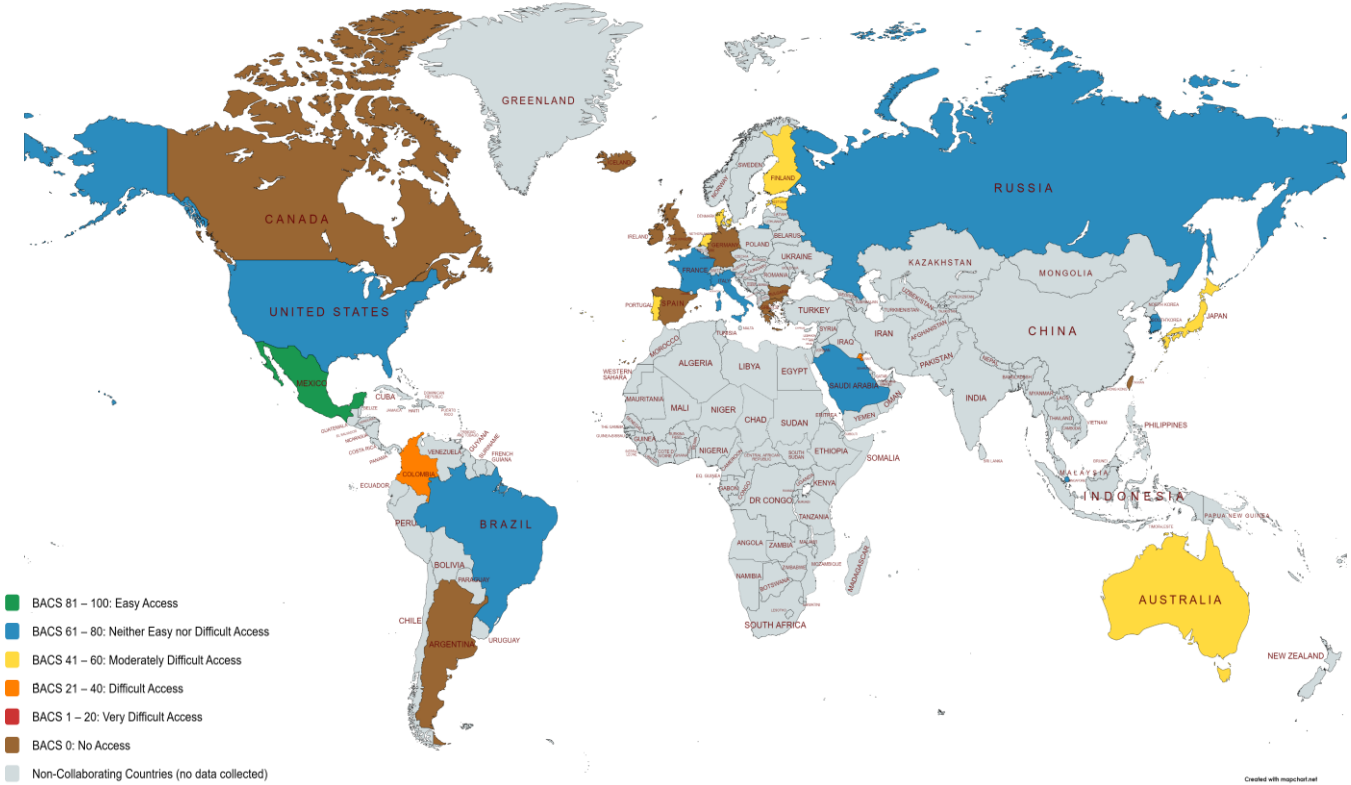
Results – Dupilumab BACS for ISAR countries



- ✓ Licensed in 20 countries
- ✓ **Neither easy nor difficult, or moderately difficult to access** in 80% of countries
- ✓ **Difficult to access** in Colombia and Kuwait
- ✓ **BACS range:** 33 (Colombia) to 88 (Mexico)
- ✓ **Mean BACS:** 59, which is lower than EMA BACS of 65
- ✓ 60% of countries reported more stringent access to dupilumab than the EMA

BACS data were as of April 2021.
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Results – Most common biologic prescription criteria globally

Age and phenotype

- **Age**
  - **Omalizumab and mepolizumab:** ≥6 years
  - **Reslizumab, benralizumab and dupilumab:** ≥12 years
- **Phenotype**
  - **Omalizumab:** Severe allergic asthma
  - **Mepolizumab, benralizumab, reslizumab and dupilumab:** Severe persistent or eosinophilic asthma with type 2 inflammation

Biomarkers

- **Serum IgE**
  - **Omalizumab:** ≥30 or ≥35 IU/mL, or elevated
- **Allergic diagnostics**
  - **Omalizumab:** Positive skin prick test or serum-specific IgE
- **Blood eosinophil counts***
  - **Mepolizumab and benralizumab:** ≥300 cells/μL
  - **Reslizumab**: ≥400 cells/μL
  - **Dupilumab**: ≥150 cells/μL
- **FeNO**
  - **Dupilumab:** ≥20 or ≥25 ppb, or raised (50% of countries)

Asthma control

- **Evidence of poor asthma control**
  - **All biologics**
- **Adherence to background therapy**
  - **All biologics except omalizumab**
- **Background therapy**
  - **All biologics:** high-dose ICS/LABA, ± LAMA, LTRA or theophylline
- **Lung function**
  - **Omalizumab:** FEV_1 ≤80% predicted
- **Exacerbations**
  - **All biologics:** ≥2 (range 0 to 4)*

(Up to 21% of countries require LTOCS use)

Biologic prescription criteria varied across the 28 countries

FeNO = Fractional exhaled nitric oxide; FEV_1 = Forced expiratory volume in 1 second; ICS = Inhaled corticosteroids; IgE = Immunoglobulin E; IL4Rα = Interleukin 4 receptor alpha; IL5/5R = Interleukin 5/5 receptor; LABA = Long-acting β-agonists; LAMA = Long-acting muscarinic receptor antagonists; LTOCS = Long-term oral corticosteroids; LTRA = Leukotriene receptor antagonists; ppb = parts per billion

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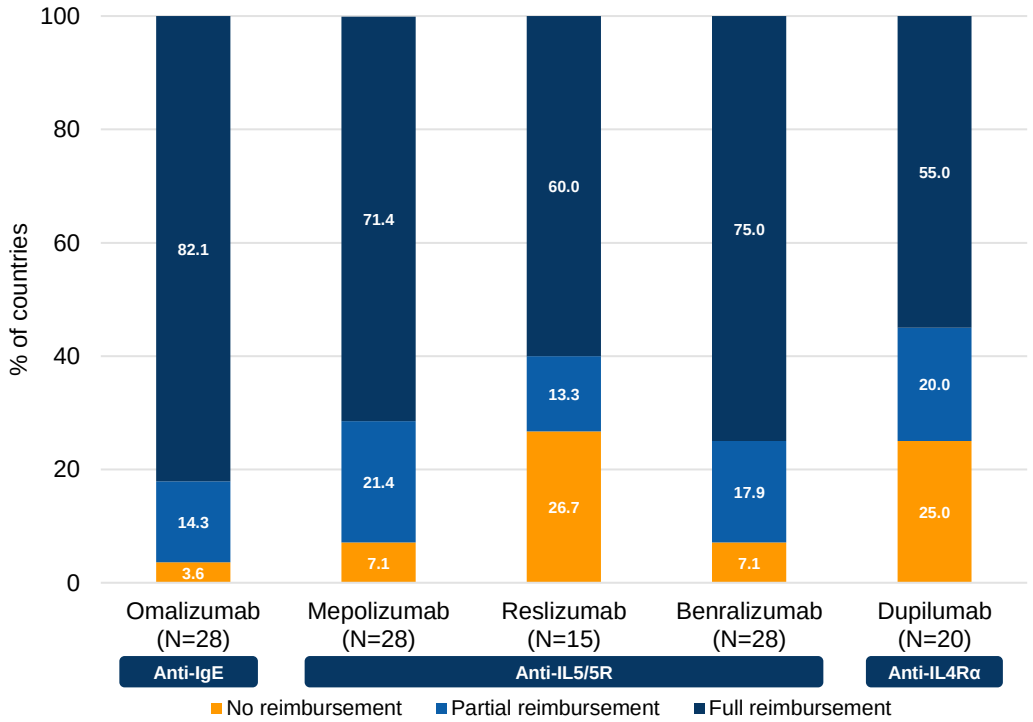
Results – Licensing and reimbursement status of biologics globally

Licensing status

- ✓ **Omalizumab:** 28 countries (100%)
- ✓ **Mepolizumab**: 28 countries (100%)
- ✓ **Benralizumab**: 28 countries (100%)
- ✓ **Reslizumab**: 15 countries (54%)
- ✓ **Dupilumab**: 20 countries (71%)

- Licensing is a central procedure by EMA or FDA, but reimbursement is a national or payer-specific procedure.
- Therefore, patients with similar clinical criteria may have varied access to biologics because of different national or payer reimbursement criteria.

Reimbursement status



Licensing and reimbursement status of the biologics were as of 2021.
EMA = European Medicines Agency; FDA = Food and Drug Administration; IgE = Immunoglobulin E; IL4Rα = Interleukin 4 receptor alpha; IL5/5R = Interleukin 5/5 receptor
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Conclusions

- **There was wide variation in severe asthma biologic accessibility globally**
  - This could be attributed to global differences in clinical prescription criteria, licensing or reimbursement status of biologics
- **We developed BACS to quantify and compare the ease-of-access to biologics in ISAR countries**
  - The BACS highlighted marked between-country differences in accessibility to severe asthma biologics
  - For all biologics, most countries had lower BACS (more stringent access criteria in place) than the EMA
  - There were no significant correlations between BACS and GDP for all biologics, excluding the “overall wealth of a country” as an explanation for BACS variation
- **Biologic prescription criteria differed substantially across countries, though key criteria include:**
  - Blood eosinophil count thresholds (usually ≥300 cells/µL) for anti-IgE and anti-IL5/5R prescription, in ~80% of countries
  - Moderate or severe exacerbation rates of ≥2 (range: 0 to 4) per year for all biologics, in up to 54% of countries
- **The variation in biologic prescription criteria globally may adversely affect personalized medicine**
  - National regulators and payers should focus on minimizing this international variation
  - Standardization of biologic prescription and access criteria is recommended to ensure the availability of personalized treatment options for severe asthma patients globally

BACS = Biologic ACessibility Score; EMA = European Medicines Agency; GDP = Gross Domestic Product; IgE = Immunoglobulin E; IL5/5R = Interleukin 5/5 receptor; ISAR = International Severe Asthma Registry

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ADEPT = Anonymised Data Ethics Protocols and Transparency; ENCePP = European Network of Centres for Pharmacoepidemiology and Pharmacovigilance; ISAR = International Severe Asthma Registry

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