La complessità dell'accesso in Italia: applicazioni quantitative sui processi decisionali

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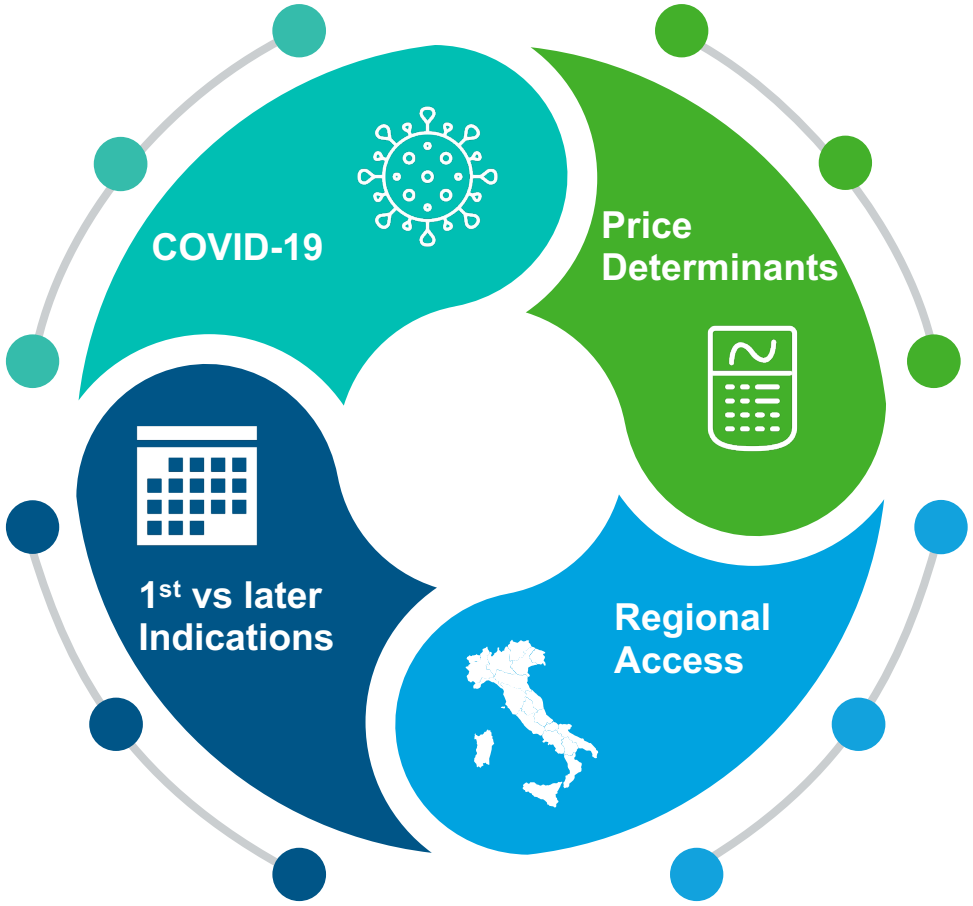
Four analyses on different determinants of negotiation outcomes in the Italian P&R scenario were conducted leveraging IQVIA database

Quantitative assessment of COVID-19 impact on the decision process of the Italian Medicines Agency

BEATRICE CANALI

Impact of negotiating a new therapeutic indication on drug reimbursement conditions and timing

LAURA CANDELORA



Assessment of variables impacting drugs average prices in Italy in the 2016-2021 period

ARIANNA ROVA

Analysis of intra-regional variability of drugs' time to access in Italy

CHIARA FATTORE

To conduct our analyses, data was extracted from an IQVIA proprietary database on negotiation dynamics

A database on **drugs' authorization process in Italy** which can be used to analyze **potential P&R outcomes** by applying advanced statistical methods including Machine Learning

IQVIA Know-how and Proprietary Databases

Leveraging **IQVIA's Know How and more than 5 internal databases** provides the basis for taking decisions on positioning strategies

IQVIA database

Publicly available sources and databases

Publicly available data allow to integrate **information regarding the authorization process and characteristics of drugs**

> 1,400 Observations

Each observation in the database is a unique combination of drug name, indication and package

~ 100 Variables

Collected from several sources and integrating IQVIA's database

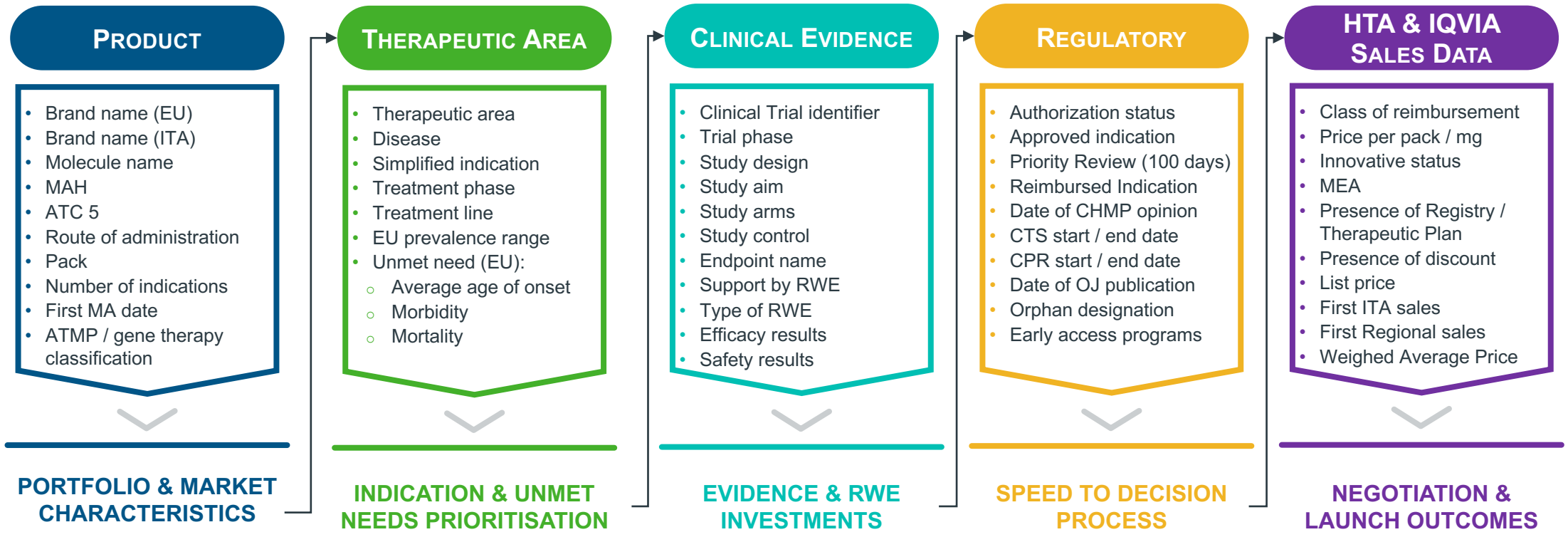
> 10 Sources

EMA Website; CTS and CPR procedures, lists of drugs for compassionate use; Italian Legislation; IQVIA internal databases; etc

Acronyms: P&R = Price and Reimbursement; CTS = Comitato Tecnico-Scientifico *(Technical-Scientifical Committee)*; CPR = Comitato Prezzi e Rimborso *(Price and Reimbursement Committee)*

Each record in the database represents an HTA submission with ~100 features covering product aspects across multiple categories

- The database includes **new medicines approved by EMA** – and related extensions of indications – **from 2015**
- It is updated every six month, with the **last update** being performed in **July 2022**
- Every **observation** in the database is a **unique combination of molecule, indication, pack and negotiation**



Acronyms: HTA = Health Technology Assessment; EMA = European Medicine Agency; ATC = Anatomical Therapeutic Chemical; MAH = Marketing Authorization Holder; CTS = Comitato Tecnico-Scientifico *(Technical-Scientifical Committee)*; CPR = Comitato Prezzi e Rimborso *(Price and Reimbursement Committee)*; OJ = Official Journal; MEA = Managed Entry Agreement

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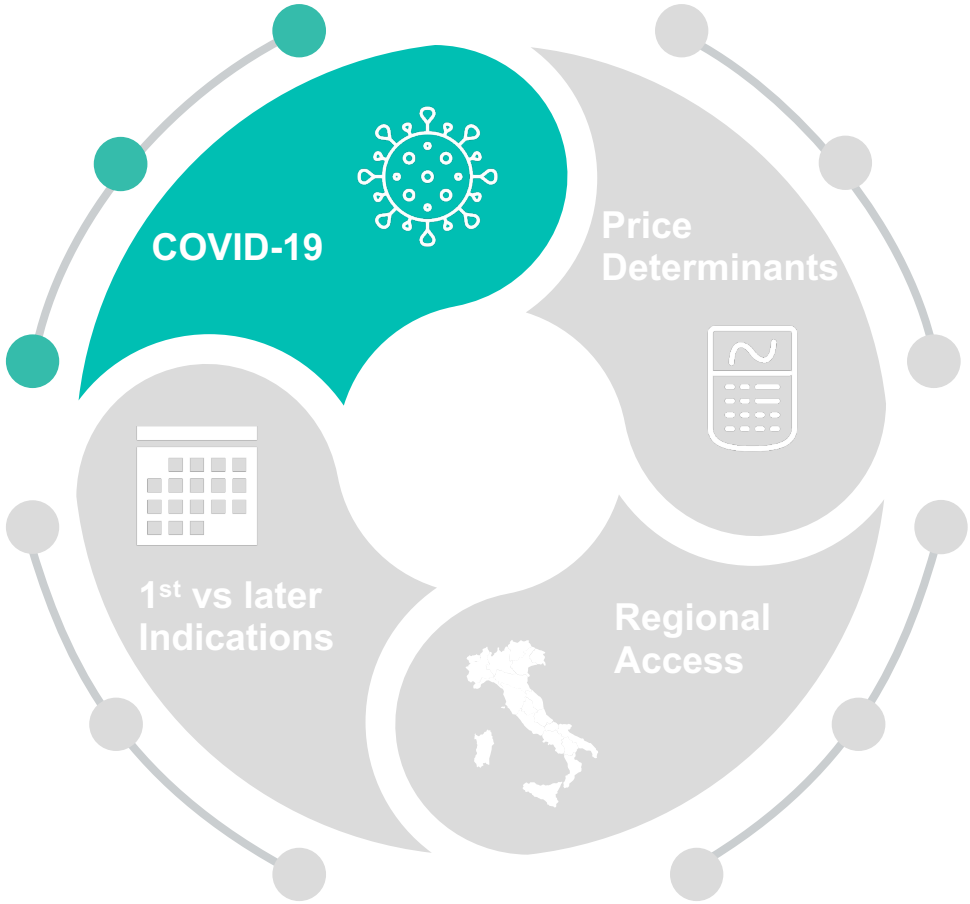

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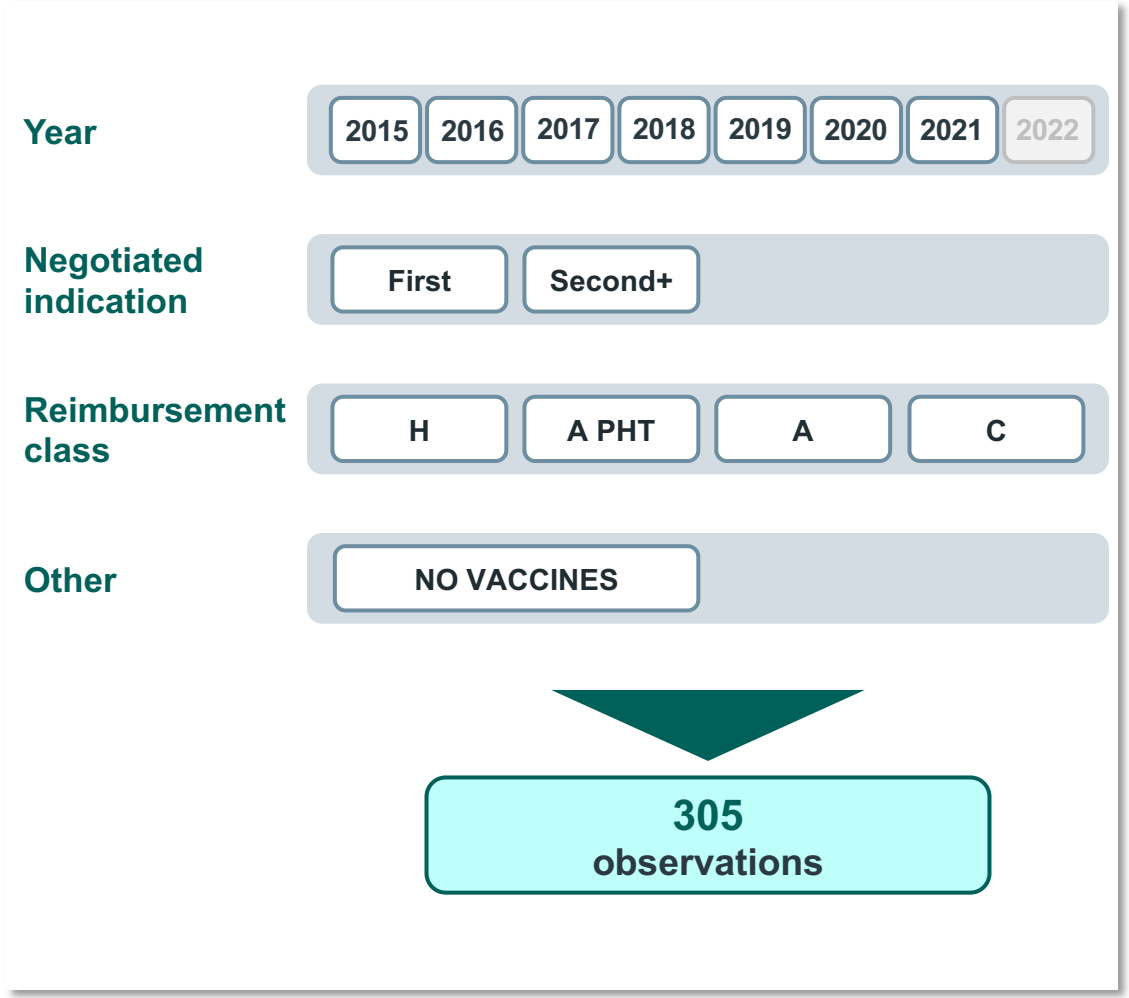
Analysis of intra-regional variability of drugs' time to access in Italy

CHIARA FATTORE

Introduction and Inclusion Criteria

The present analysis aims to **assess the COVID-19 pandemic impact on drugs' time to market (TTM) in Italy**

- **Time to patient access varies significantly among drugs** and has generally gotten longer in recent years[a]
- The **outbreak of COVID-19 pandemic highlighted the relevance of rapid decision making within the healthcare framework** and placed more attention on the drugs approval process
- In such a situation of emergency and uncertainty, we would expect some **changes** in AIFA's **decision-making process** resulting in an **impact on timing** of the approval pathway of drugs



References: a) EFPIA 2020

Methodology

OUTCOME OF INTEREST

Time to market (TTM)

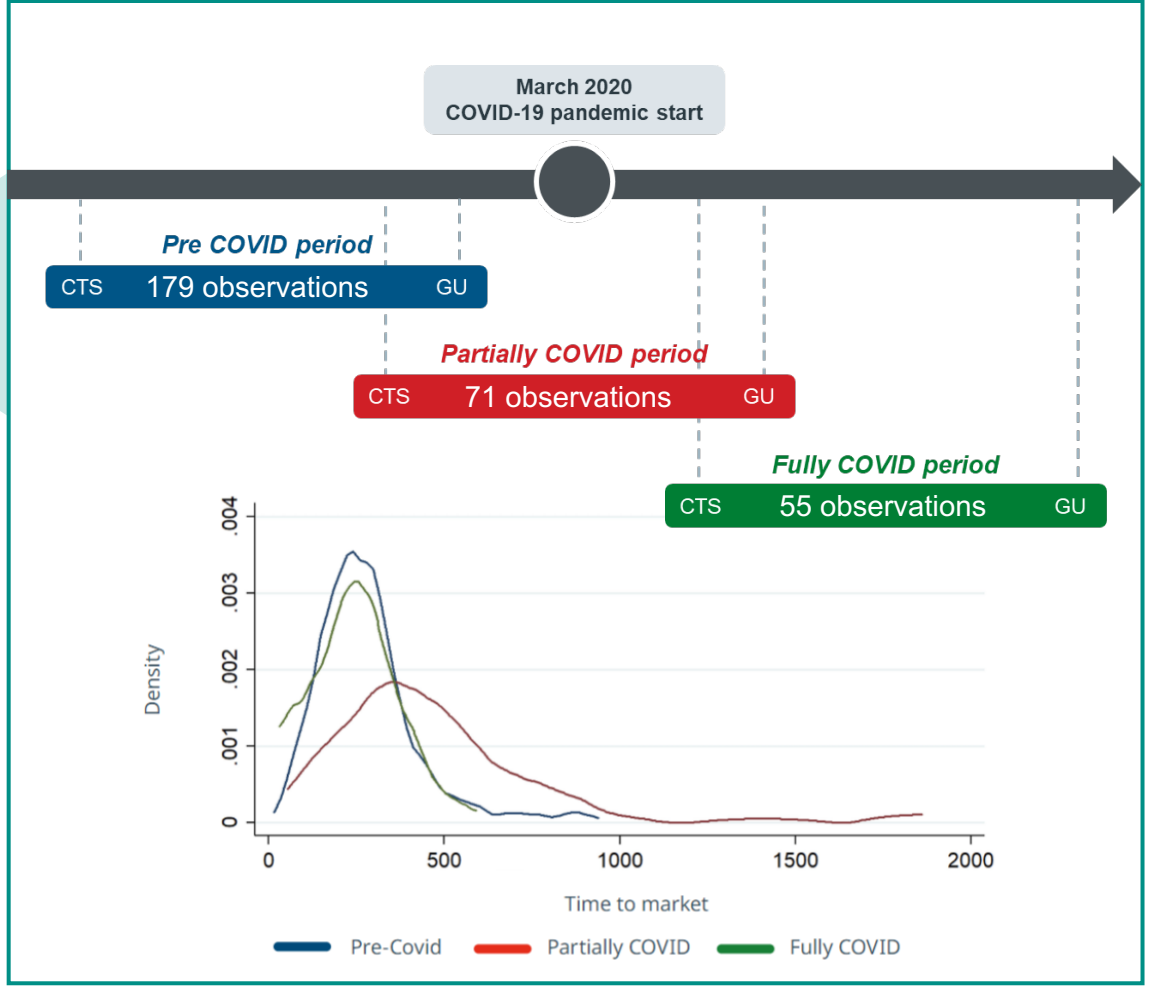
The time from the start of the P&R dossier evaluation by the CTS to the publication of the P&R resolution in the GU

Observations were divided into **three periods** based on the beginning date and end date of their negotiation process

Differences in TTM between periods were **inspected graphically, descriptive statistics** and **two-sample tests** by period were performed to evaluate the potential role of co-variates influencing drugs' TTM

Inferential analysis was performed by implementing a **nearest-neighbor matching estimator** based on the relevant co-variates identified in the previous step

IDENTIFIED PERIODS AND KERNEL DENSITY OF TTM (DAYS) BY PERIOD



Acronyms: TTM = time to market; CTS = Comitato Tecnico-Scientifico *(Technical-Scientifical Committee)*; GU = Gazzetta Ufficiale *(Official Gazzette)*

Results and Discussion

UNIVARIATE ANALYSIS ON COVID PERIODS	Mean time to market		p-value
	NO	YES	
Partially COVID	280.12	474.94	0.01
Fully COVID	280.12	237.45	<0.01

Both variables are tested against the Pre COVID period, represented in the NO column

The two-sample t-test suggested that there are some **differences in time to market** between the three periods (p≤0.01).

Average time to market was:

- **280 days** in the Pre COVID period
- **475 days** in the Partially COVID period
- **237 days** in the Fully COVID period

MATCHING ANALYSIS RESULTS	ATE	SE	p-value
Partially COVID vs Pre COVID	**138.26**	41.15	<0.01
Fully COVID vs Pre COVID	**-42.16**	24.30	0.09

ATE = Average Treatment Effect; SE = Standard Errors

The nearest-neighbor matching analysis included all the significant variables from the two-sample t-test.[1]

COVID-19 had a statistically significant impact on TTM:

- The ATE of the **Partially COVID** period vs the Pre COVID period was estimated to be **138 days** (p<0.01)
- The ATE of the **Fully COVID** period vs the Pre COVID period was estimated to be **-42 days** (p=0.09)

- This study provides original insights on the **impact of the COVID-19 pandemic on the Italian Medicines Agency negotiation outcomes** and in particular on drugs' time to market
- It was discovered that **TTM initially increased with the COVID-19 outbreak and then decreased compared to the Pre COVID period**, indicating that a "new normal" was reached after an adjustment phase

Notes: 1) The included variables were: Exceptional circumstances; Registry; MEA; Negotiation of discount; Therapeutic area
Acronyms: TTM = Time to Market

Four analyses on different determinants of negotiation outcomes in the Italian P&R scenario were conducted leveraging IQVIA database

Quantitative assessment of COVID-19 impact on the decision process of the Italian Medicines Agency

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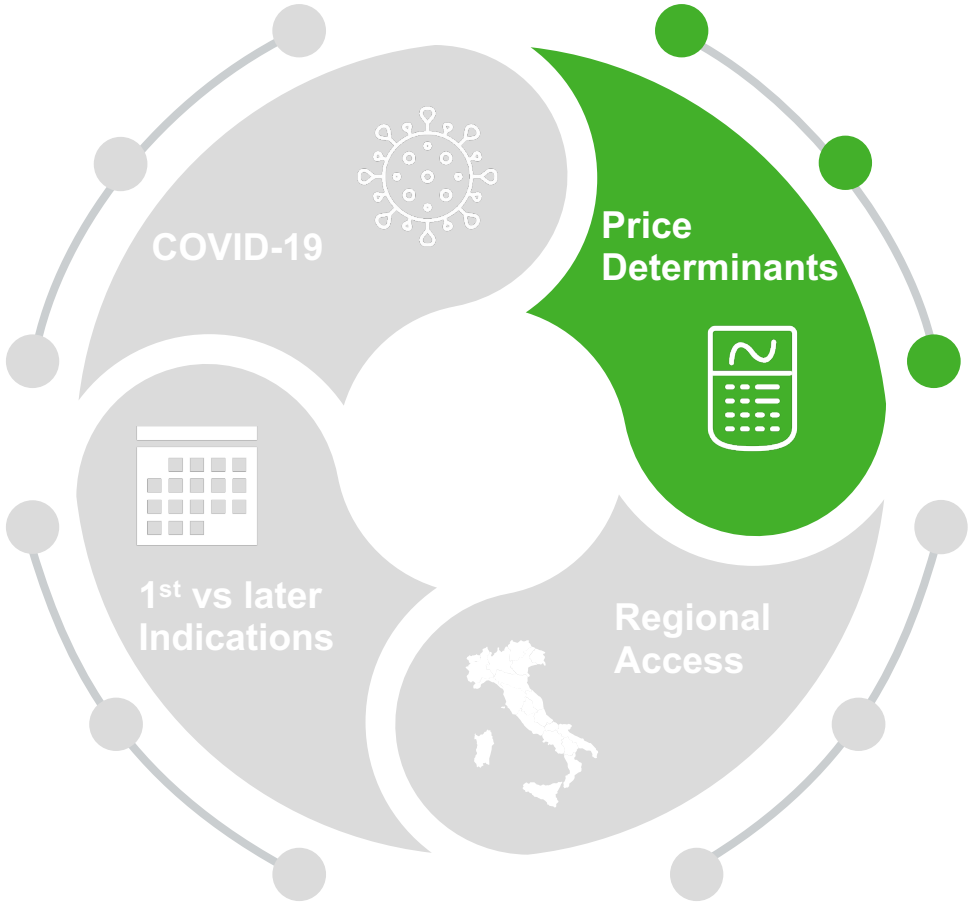

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Analysis of intra-regional variability of drugs' time to access in Italy

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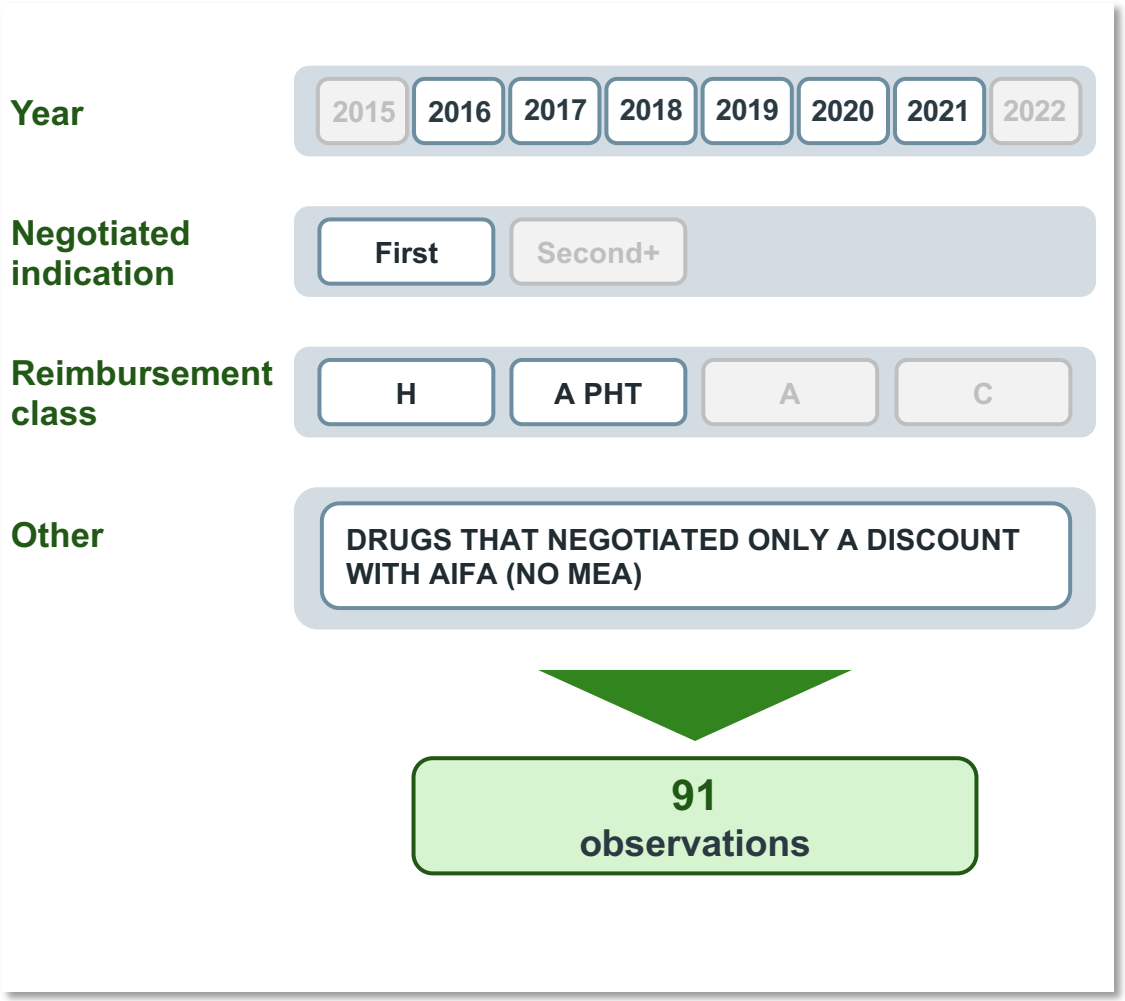
Introduction and Inclusion Criteria

The present analysis aims to **assess the most relevant variables impacting medicines' prices** for their first indication in the period 2016-2021

- During the negotiation process, AIFA considers **several elements related to the product in order to define the final price reimbursed by NHS**, such as the therapeutic unmet need, the place in therapy, and the product's added therapeutic value
- The **final price reimbursed by the NHS for each medicinal product often includes a discount** applied to the ex-factory price, negotiated with AIFA
- IQVIA collects data on consumption and expenditure from a panel of hospital pharmacies across the Italian territory, which allow to estimate **average price** of drugs



Acronyms: NHS = National Healthcare Service; AIFA = Agenzia Italiana del Farmaco *(Italian Medicines Agency)*; P&R = Price and Reimbursement; GU = Gazzetta Ufficiale *(Official Gazzette)*

Methodology

OUTCOME OF INTEREST

Average Discount

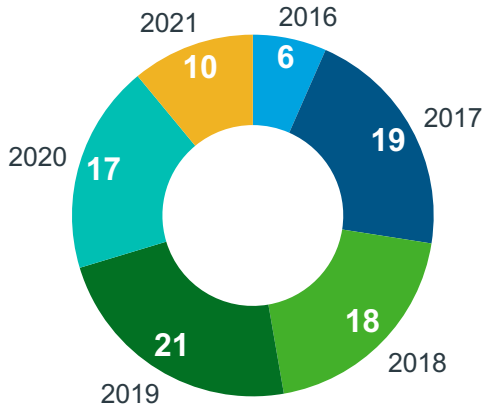
IQVIA statistic elaboration on expenditure data from a hospital panel, which includes discount negotiated with AIFA, tender and commercial discounts

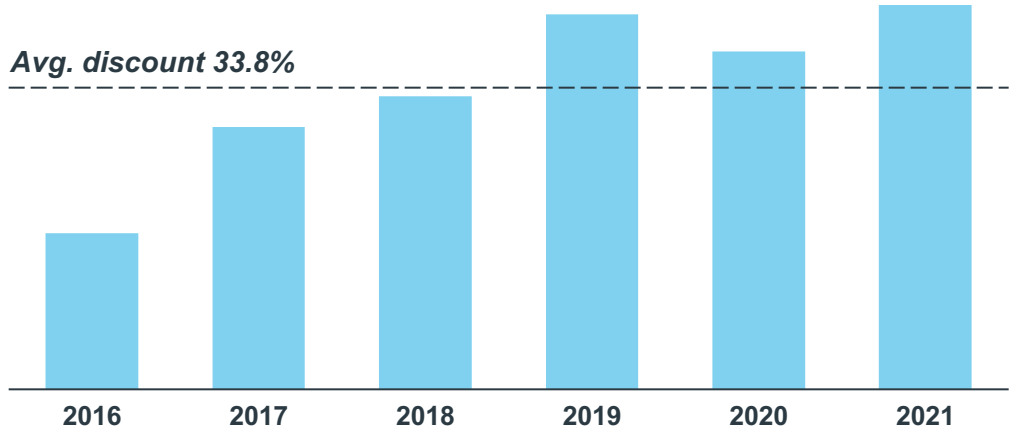
Descriptive statistics by year were analyzed to assess differences and key trends in average discount values over the years of analysis, considering the two different CPR periods (2016-18 vs 2019-21)

Two-sample tests were performed to evaluate the potential role of co-variates influencing drugs' average price

Inferential analysis was performed by implementing an **ordinary least squares multivariate regression** with backward elimination of non-significant cofounders, considering a 10% significance level

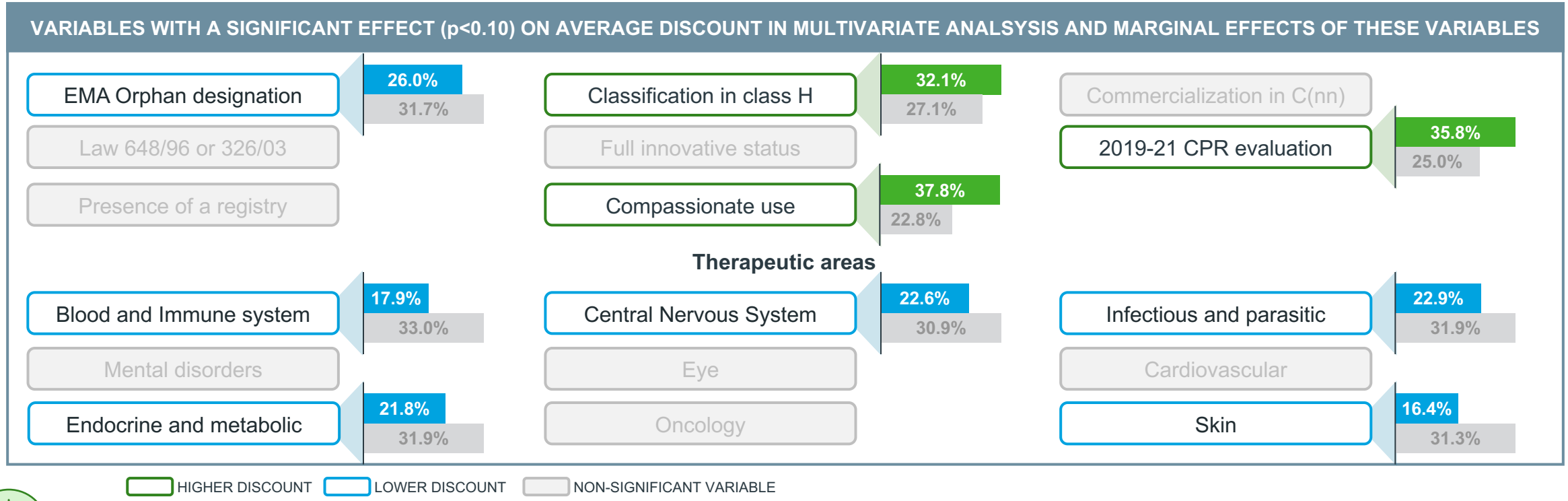
NO. OF DRUGS AND AVERAGE DISCOUNT BY YEAR





Acronyms: CPR = Comitato Prezzi e Rimborso *(Price and Reimbursement Committee)*

Results and Discussion



- The study provides insights on **which features** of new medicines might be **more significant for the definition of drug's final price** reimbursed by NHS
- Continuous monitoring of determinants impacting the Average Price may help to **detect trends in decision making**, especially in areas with high variability

Acronyms: CPR = Comitato Prezzi e Rimborso *(Price and Reimbursement Committee);* NHS = National Healthcare Service

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Analysis of intra-regional variability of drugs' time to access in Italy

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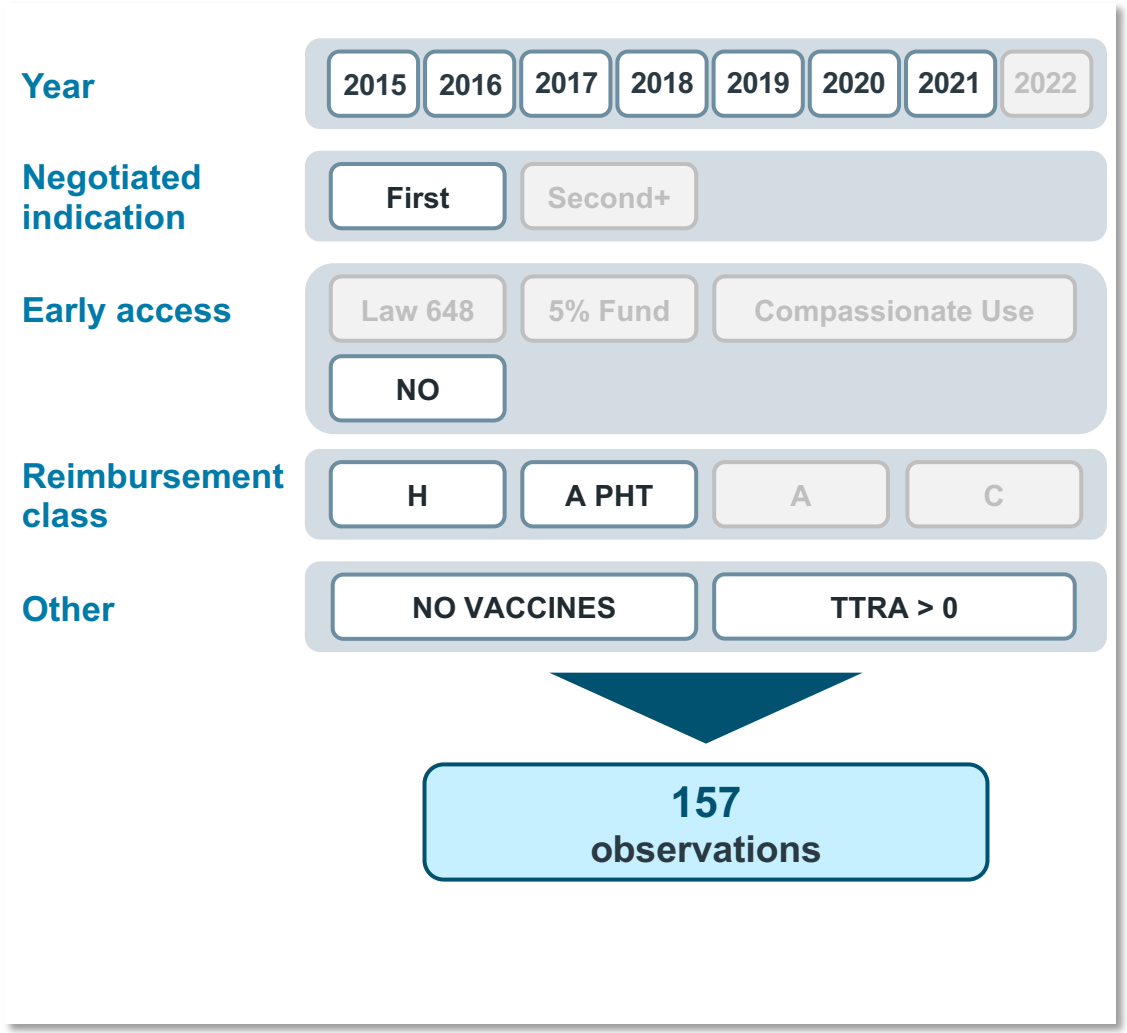
Introduction and Inclusion Criteria

The present analysis aims to **investigate intra-regional variability** among drugs **in terms of time to regional access (TTRA)**

- After national marketing authorization and definition of conditions of reimbursement by AIFA, **drugs need to undergo further regional and local steps to be acquired by hospitals and/or local health units**
- These steps may differ across regions and drugs' **time to regional access** (TTRA) **is highly variable among different regions** (inter-regional variability)[a-c]
- Inter-regional TTRA has already been evaluated[a-c], but **limited evidence exists on intra-regional variability** and its determinants



References: a) Mantuano et al., 2016; b) Russo et al., 2010; c) Prada et al., 2017
Acronyms: AIFA = Agenzia Italiana del Farmaco *(Italian Medicines Agency);* TTRA = Time to Regional Access

Methodology

OUTCOME OF INTEREST

Time to regional access (TTRA)

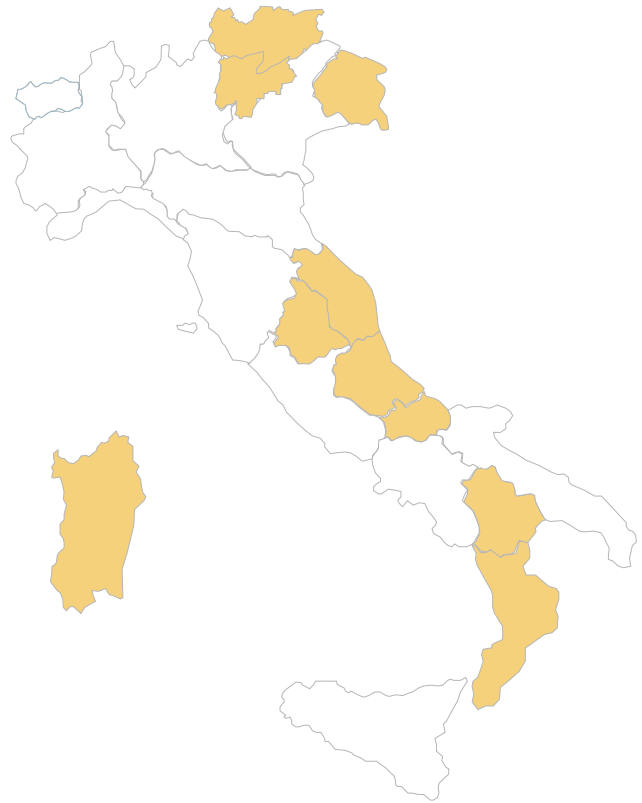
The time from AIFA P&R resolution publication in the Italian GU to first regional sale

Intra-regional variability was assessed by calculating the **Interquartile Range (IQR) for drugs' TTRA** in each region[1] and the top 10 regions by IQR were selected for the analysis

Six **variables** are expected to have an **impact on drugs' TTRA**: innovative status, orphan drug designation, therapeutic area[2], monotherapy use, presence of AIFA monitoring registry, and negotiation of MEAs

Inferential analysis was performed by implementing a **log-link generalized linear model** (GLM) of TTRA on the six identified variables in the 10 selected regions

REGIONS AND COVARIATES SELECTED FOR THE ANALYSIS



ANALYZED REGIONS

Innovative status

Orphan drugs designation

Therapeutic area
Oncology vs non-oncology

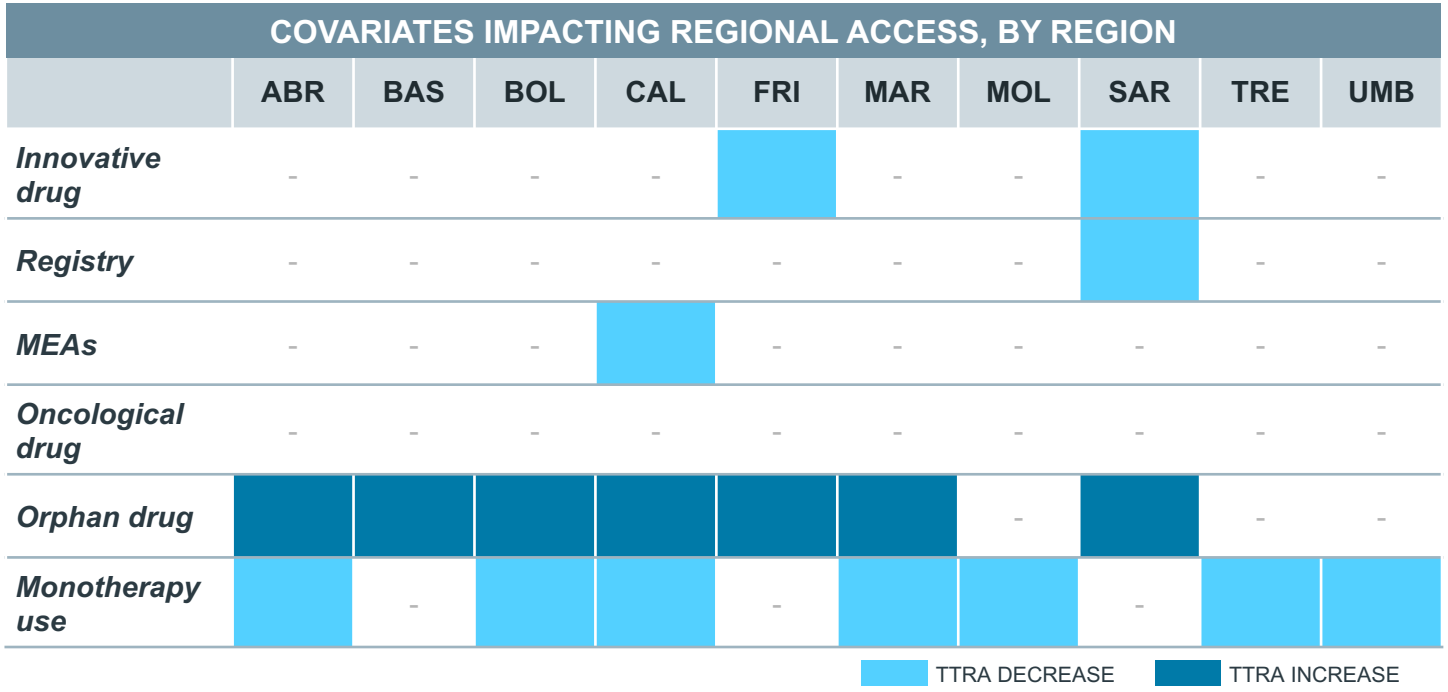
Monotherapy use

Presence of **AIFA's monitoring registry**

Negotiation of **MEAs**

Notes: 1) Regions include 19 regions and the 2 autonomous provinces of Trento and Bolzano; 2) Oncology vs Non-Oncology
Acronyms: AIFA = Agenzia Italiana del Farmaco *(Italian Medicines Agency);* P&R = Price and Reimbursement; GU = Gazzetta Ufficiale *(Official Journal)*; TTRA = Time to Regional Access; MEAs = Managed Entry Agreements

Results and Discussion



- **Orphan designation** is the only variable that consistently **increases TTRA across all regions**, statistically significant in seven
- In **TTRA is always reduced for drugs used in monotherapy**, with statistically significant results in seven regions
- **Innovative** drugs and drugs with **AIFA monitoring registries show shorter TTRA** compared to non-innovative drugs and drugs with no registries in Sardegna ($p<0.05$) and Friuli Venezia Giulia ($p<0.05$), and in Sardegna ($p<0.05$) respectively
- The presence of **MEAs decreases TTRA** ($p<0.05$) in Calabria

- In Italy there is **high intra-regional variability associated with specific drugs' characteristics in some regions**, while still mostly **unexplained in other regions**
- Variability **may be related to distinctive characteristics of the region**[1] or to **companies' regional commercial approach**, which in this analysis is assumed not to differ among therapeutic areas and different types of drugs

Acronyms: AIFA = Agenzia Italiana del Farmaco *(Italian Medicines Agency);* TTRA = time to regional access; MEAs = Managed Entry Agreements
Notes: 1) Such as administrative procedures, different approaches of regional decision makers, and size or presence of healthcare regional debt repayment plans

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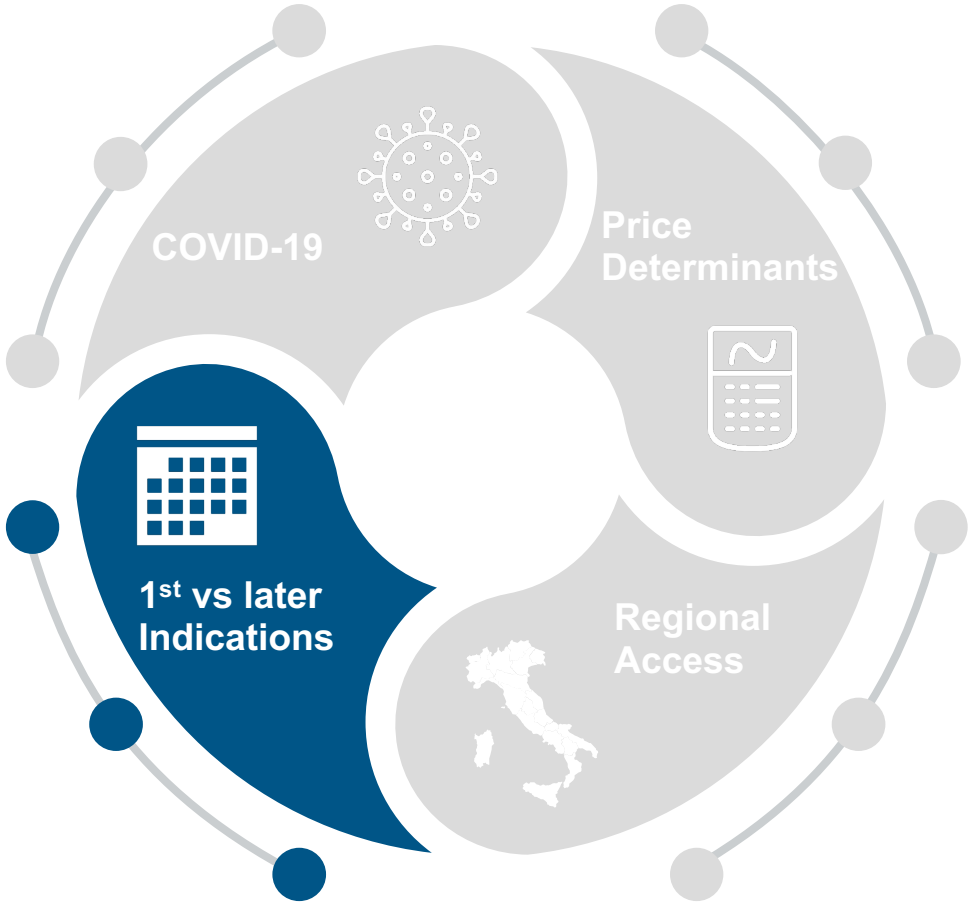

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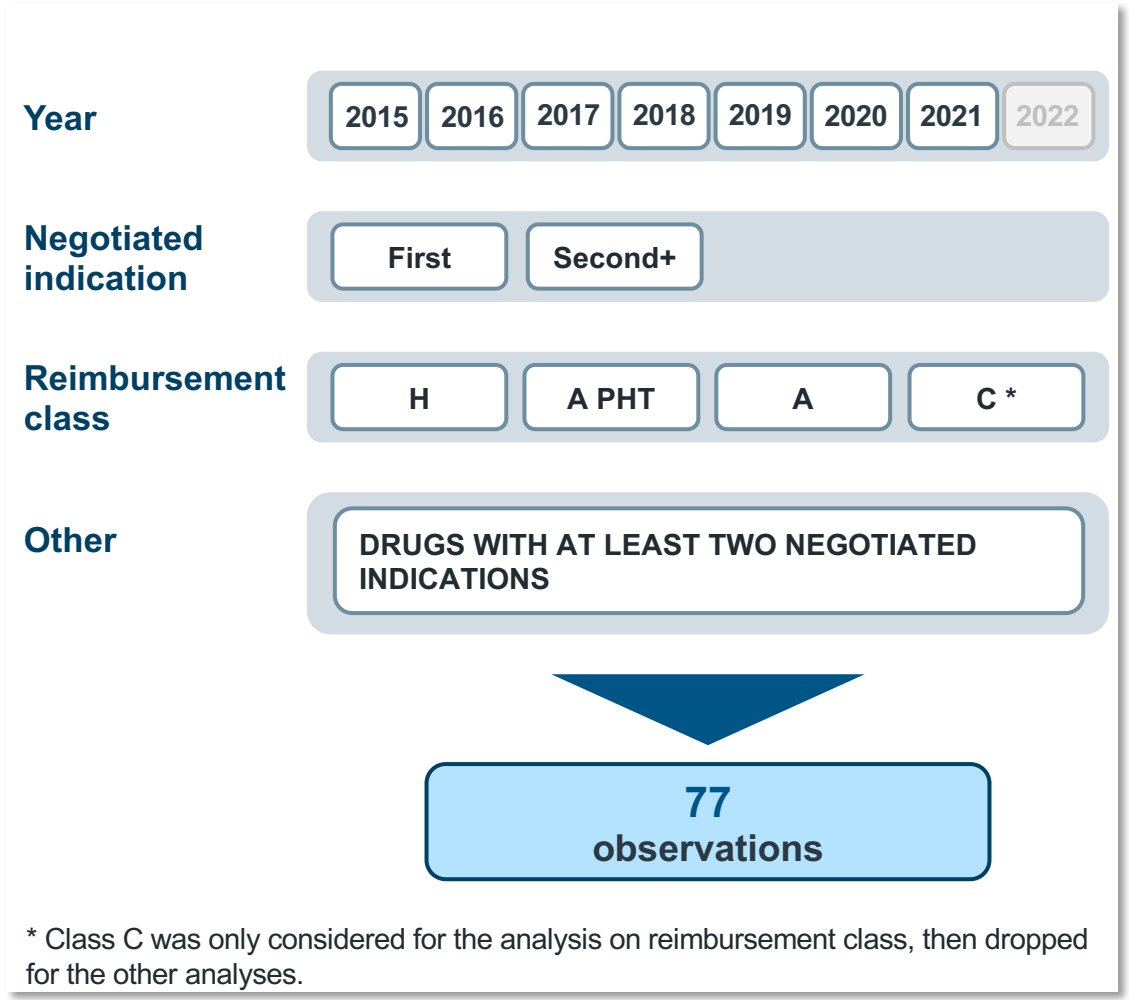
Introduction and Inclusion Criteria

The aim of this study is to **investigate how drugs' negotiating conditions vary when requesting reimbursement for subsequent indications**, compared to those for the first indication

- In Italy, the Marketing Authorization Holder of a drug reimbursed by the NHS to obtain the **reimbursement for new therapeutic indications**, must initiate a **new P&R procedure** for the new indications being evaluated again by AIFA's CTS and CPR
- Among the negotiating conditions agreed with AIFA, **average discount generally applies to the molecule**
- On the other hand, **Managed Entry Agreements (MEAs) may affect a single therapeutic indication**



* Class C was only considered for the analysis on reimbursement class, then dropped for the other analyses.

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Methodology

OUTCOMES OF INTEREST

Negotiation Conditions

Reimbursement class, negotiation of MEAs, presence of AIFA's monitoring registry, negotiation of discount, average discount (IQVIA statistic elaboration on expenditure data from a hospital panel, which includes discount negotiated with AIFA, tender and commercial discounts)

Time to market (TTM)

The time from the start of the P&R dossier evaluation by the CTS to the publication of the P&R resolution in the GU

Descriptive statistics by indication (first vs subsequent) and **two-sample tests** were performed on the outcomes of interest

Sub-analyses were conducted to assess the differences in the outcomes of interests between first and subsequent indications for drugs with various characteristics

SUB-ANALYSES

T-TEST FOR SUB-SAMPLES

1

Therapeutic area

Oncological vs non-oncological drugs

2

Orphan designation

Orphan vs non-orphan drugs

3

Time period

Drug with first indication negotiated in 2015-17 vs 2018-21 period

4

Innovative status

Full/ potential innovative vs non-innovative first indication

DESCRIPTIVE ANALYSIS

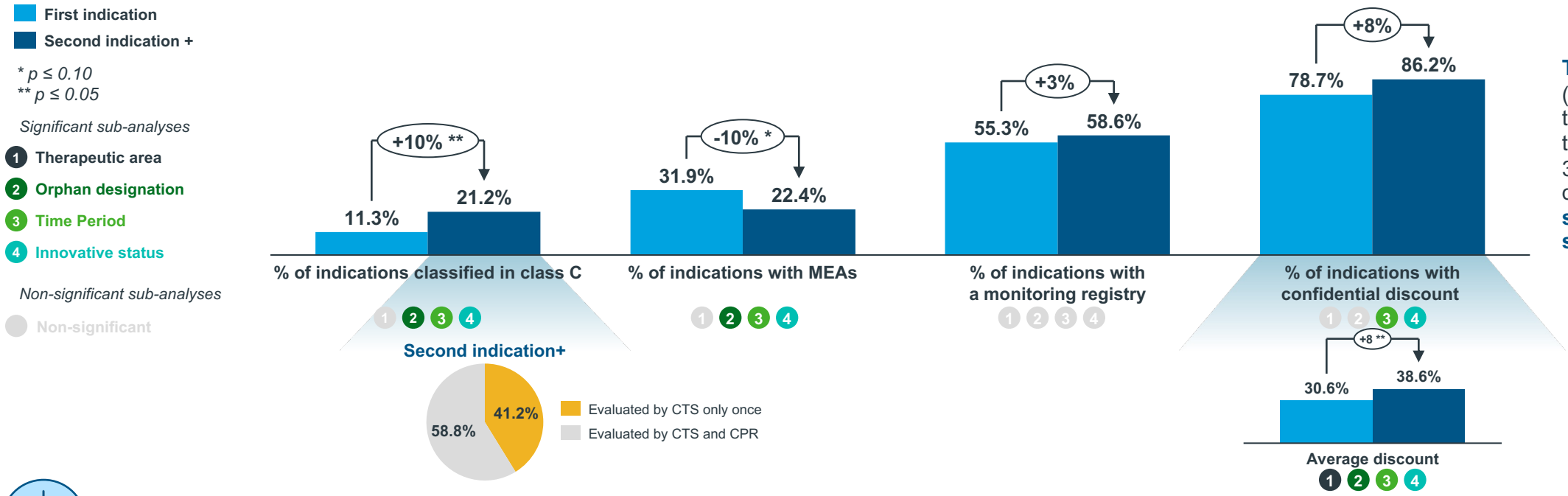
Class C analysis

Assess how many of the drugs classified in class C for their second indication underwent only one CTS evaluation

Acronyms: MEAs = Managed Entry Agreements; AIFA = Agenzia Italiana del Farmaco *(Italian Medicines Agency)*; TTM = Time to Market; P&R = Price and Reimbursement; GU = Gazzetta Ufficiale *(Official Gazzette)*; CTS = Comitato Tecnico-Scientifico *(Technical-Scientifical Committee)*

Results and Discussion

T-TEST ANALYSIS RESULTS (WHOLE SAMPLE AND DETAILS ON SUB-ANALYSES)



The time to market (TTM) **increased** from the first negotiation to the second (295 vs 328 days), but the difference is **not statistically significant**

- **Renegotiating P&R conditions for a new therapeutic indication might have an impact on drug price for all the indications** given that the average discount of the molecule generally increases when subsequent indications are negotiated. On the contrary, the percentage of drugs which negotiated MEAs decreases for subsequent indications
- **The higher rate of non-reimbursed new indications seems, in almost half of cases, to be due to a company decision**

Acronyms: MEA = Managed Entry Agreements; CTS = Comitato Tecnico-Scientifico *(Technical-Scientifical Committee)*; CPR = Comitato Prezzi e Rimborso *(Price and Reimbursement Committee)*; P&R = Price and reimbursement

Conclusion and discussion

Evolution of price & reimbursement process in Italy

- **Drugs' time to market**
- **Time-varying trends** in average price of drugs

Heterogeneity of procedures across multiple dimensions

- **Intra-regional differences** in **time to market** between drugs
- **Negotiation outcome changes** between first and second indication

Analysis of correlation between drugs' characteristics and P&R outcomes

- Insights on which **features of new medicines** might be more **significant for the definition of drug's final price reimbursed**
- **Future analyses** can assess other co-determinants of negotiation outcomes not directly associated with drugs characteristics, such as **disease characteristics**, **institutional frameworks and policies**, and **companies' decision-making strategies**

- How can these evidences stimulate the dialogue between industry and institutional stakeholders?
- How can these evidences enhance transparency in drugs' assessment to promote sustainability of pharmaceutical expenditure?
- What are the drivers of value across stakeholders and what kind of evidence is needed to assess them?
- Which evidence can help understanding the impact of P&R decisions on patient access to drugs?

Thank you!