REDS (Respiratory Drugs Survey) Study. Active Surveillance of Respiratory Drugs and in Particular of Inhaled Steroids (IS) in the Paediatric Age

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Abstract: *Background and aims:* Inhaled Steroids (IS) are used inappropriately for children who have been "over prescribed" for conditions such as colds, coughs and sore throats. This practice is not always based on scientific evidence. IS have a modest effectiveness in preventing both recurrent wheezing, viral and bronchiolitis in children.

The aim of the study is to monitor the use of IS with careful analysis of the risk / benefit factor of the treatment, through accuracy of diagnosis, the therapeutic appropriateness and the safe use of these medications.

Methods: In this epidemiological / observational (case-study) and active observational project, the prescribing data for children (0-14 yrs) were collected and processed by Family Pediatricians (FPs). The activities have been divided into four sections**:**

1) Elaboration of the prescriptive data (year 2015-retrospective)

2) Training / information events for FPs and families on the correct use of IS (year 2016)

3) Elaboration of the prescriptive data of the same FPs after the training year (year 2017-prospective)

4) Comparison of the prescriptive data of IS in the age group of 0 - 14 years in the years 2015 and 2017 (before and after the training phase)

Results: After the training phase: the prevalence of use of IS decreased from 20.71% to 15.15% ; the percentage of the appropriate prescriptions increased from 30.65% to 58.02% ; the percentage of the inappropriate prescriptions decreased from 68.67 % to 38.66%; the prevalence of inappropriate prescriptions decreased : a) in the 0-4 yrs from 70.24% to 39.30%; b) in the 5-10 yrs from 66.31% to 35.95%, and c) in the 11-14 yrs from 69.80% to 35.04%; the percentage of inappropriate expenditure decreased from 67.31% to 37.63%; the percentages of inappropriate prescriptions decreased for Beclomethasone from 71.47% to 38.29%, for Budesonide from 69.82% to 43.29%, for Fluticasone from 53.84% to 19.01% and for Flunisolide from 70.45% to 56.93% ; the total number of pieces prescribed decreased from 4.338 to 3.148.

Conclusions: We have highlighted that through training courses for Family Pediatricians and a correct information to families a significant improvement in the use of Inhaled Steroids can be achieved.

Keywords: Children, Adverse drug reactions, Inhaled steroids, Pharmacovigilance, Post-marketing clinical studies.

1. INTRODUCTION

From the Medicines Utilization Monitoring Centre (OsMed) data of pharmaceutical prescription emerges that in children, especially in the age group from 0 to 4 years, there is an increase of the consumption of Inhaled Steroids (Beclomethasone, Budesonide, Flunisolide, Fluticasone, etc) [1].

Despite the growing campaigns undertaken by the AIFA (Italian Medicines Agency), in fact, an high consumption and the unsuitable prescription for certain categories of medications, antibiotics and Inhaled Steroids (IS), is shown in the age group from 0 to 14 years and is also reported an increase in Adverse Reactions related to them [2-3].

For example, OsMed data of 2013 reported that 28% of children aged 0 to 4 years received at least one medication to the respiratory system with the increase in consumption of 1.1% over the previous year, making evident a non-rational use of these medications that are not always prescribed on scientific evidence.

The reference Guidelines (GL) for the treatment of Asthma (GINA- Global Initiative for Asthma) have been well established for years, and, despite the prevalence of this illness, that has settled down to 9.5 and 10.5% in children aged 6 to 11 years, it has been particularly

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noted that asthma medications, such as IS (Beclomethasone, Budesonide, Flunisolide, Fluticasone, etc.), are used inappropriately in children with an "over prescription" for conditions that should not require their use [4-6].

For example, Beclomethasone is one of the most frequently prescribed medication in children. It is estimated that in Italy, it is used by about 2 million children and adolescents every year. Despite being an anti-asthmatic medicine, it is often prescribed for colds, coughs and sore throats, meaning Italian children have a 3 times higher chance of receiving an anti-asthma medication than their peers living in other European countries [7-8]. An independent clinical test has been conducted to evaluate the efficacy of Beclomethasone in the prophylaxis of broncospasm due to viral infections of the airways (viral wheezing) [8].

In the Enbe Study (Effectiveness of Beclomethasone versus placebo in the treatment of preventing viral wheezing in the pre-school age group) Beclomethasone reduced the risk of viral wheezing by 4% (from 11 to 7%) but the difference was not statistically significant [9].

The results of Enbe confirms data already highlighted by other studies: the IS has a modest effectiveness in preventing both recurrent viral wheezing [10] and the wheezing caused by the respiratory syncytial virus (bronchiolitis)[11] in the child. Many times the IS are used improperly in bronchiolitis by pediatricians despite what the Guidelines say (GL NICE 2015- Bronchiolitis in children- Inhaled Steroids should be not used to treat bronchiolitis). In addition, no benefits were noted in reducing symptoms of infection to the respiratory tract [5-10].

Therefore a more rational effort is needed regarding these pharmaceuticals both by pediatricians and above all by parents who frequently administer medicines to children for infections of the respiratory tract, without consulting their pediatrician.

From these considerations, there was a necessity for a Phase IV research project to be conducted by Family Pediatricians (FPs) that can, through training courses for Family Pediatricians and informational talks for families on the correct use of IS, reduce the iatrogenic illness caused by their improper use. Moreover the study may constitute a territorial survey on prescriptive appropriateness and safety of these medications in children aimed at evaluating the risk-benefit balance on usage.

This research wanted to above all, overcome the limitations of the OsMed data in which there is an inability to track diagnosis related to the prescriptions and of a proper assessment of prescriptions of the various pediatric age groups.

Therefore this research will add to current knowledge: a) improvements in the appropriateness of prescriptions; b) the acquisition of epidemiological reference data with the fewest possible error (<5%); c) a reduction in bias enrollment and Protocol drop-outs; d) a reduction in the number of respiratory drug prescriptions compared to historical data (data of prescriptions in previous years); e) a reduction in public spending, through prescriptions and inappropriate hospital admittances; f) a correct valuation, in question, of ADRs related to pharmaceuticals administered and in particular of the effect of IS on growth [14-20]; g) an increase in reports of ADRs after Family Pediatricians training.

All in all ensuring the development of knowledge and facilitating the transfer of the best scientific evidence to the professional practice of the Family Pediatrician. Finally, the study encouraged closer synergy between the Family Pediatrician and families through a better and more accurate information given to families on the use of respiratory pharmaceuticals and in particular of IS [21]. This lead to a reduction of the "do it yourself" and self-prescription used for illnesses that are not reported in GL and certainly a reduction in lost working days for parents and also reducing inappropriate hospital admission.

All of this, together with an information campaign that included, in addition to the Family Pediatrician's direct contact with families through specific informative talks, an implementation of posters, brochures on display at Pediatric's Ambulatories (sent directly to the families) on the proper use of respiratory pharmaceuticals in pediatrics (and in particular ISs).

Therefore it becomes very important to conduct the research in specific environments like that of pediatric ambulatories in which the Family Pediatrician of the area has a more adequate opportunity compared to hospital / university to carry out results of the research especially regarding some illnesses in some categories of medications that do not require hospital admittance. In addition, the large number of case studies, the relationship of close collaboration with the families and the ability to run a proper and careful follow-up, are essential elements for the realization of clinical and scientifically valid studies.

Last but not least emphasizing the uniqueness of this multicenter research in which issues are dealt with regarding prescriptive appropriateness, training for Family Pediatricians, information for families, importance of assessments and reporting of ADRs linked to the medication in question which are the main foundations of a correct formula of active pharmacovigilance in pediatrics.

The REDS Study, conducted by FP-MCRN (Family Pediatricians – Medicines for Children research Network [22-28] was the first multi regional Pharmacovigilance project presented by the Molise Region in the pediatric field (AIFA Pharmacovigilance Call 2010-2011), taking into account that the AIFA places particular relevance to projects focused on special populations such as the pediatric population.

The study, presented at ENCPP, conducted according to ENCEPP Code of Conduct and according to the rules of GVP (Good Pharmacovigilance Practices- GUIDELINES ON GOOD PHARMACOVIGILANCE PRACTICES- MODULE VIII-PASS 8-8-2016. Rev.2), was entered in the EU PAS REGISTER (EUPAS 12410) and obtained the ENCEPP STUDY SEAL on 15 February 2016. The REDS study was also approved by the ASREM Ethics Committee on 22-12-2015.

2. MATERIAL AND METHOD

This multicenter study is composed by an epidemiological / observational (case-control) part and by an active surveillance part (monitoring medications and follow-up).

More in detail this IV phase study was divided in four steps:

a. Elaboration of the prescriptive data of the IS in the age group of 0 - 14 years (year 2015)

b. Training / information meetings for Family Pediatricians and families on the correct use of ISs

c. Elaboration of the prescriptive data of the ISs in the age group of 0 - 14 years (year 2017)

d. Comparison of the prescriptive data of IS in the age group of 0 - 14 years in the years 2015 and 2017 (before and after the training phase)

This research was conducted by Family Pediatricians from two Italian regions: Molise and Umbria.

The enrolled population was represented by children of both sexes, aged between 0 and 14 years who received a prescription of IS for respiratory symptoms.

Each Family Pediatrician, after visiting each child with respiratory symptoms, made a diagnosis based on the International Reference GL (GINA asthma - NICE etc.) also with the help of laboratory tests (ESR, TAS, PCR, Prick tests, rapid tests for GABHS, urine stick and spirometry etc) that can be performed by the Family Pediatrician in his clinic (SELF-HELP). All Family Pediatricians were trained in a specific training course to perform these tests. The pediatrician decided the appropriated treatment and explained to the family when IS was required and also when IS was not indicated.

During the visit each Family Pediatrician filled the medical records in real time, via an electronical database (Infantia, JUNIOR BIT) reporting the clinical evaluation along with body weight.

After the visit each Family Pediatrician monitored the clinical evolution of the patient and reported the occurrence of ADRs related to IS.

The evaluation of growth with careful auxological monitoring was performed in children who received IS, especially when using high doses of IS.

Family Pediatricians, taking care of children from birth to 14 years of age, is a guaranty of the applicability of the database and follow-up without any suspension caused by a failure in the communication with families (few drop-out).

3. RESULTS

a. Elaboration and Processing of Prescription Data of Inhaled Steroids (IS) in the Age Group of 0 - 14 Years (Year 2015)

In the first phase of the project we collected and processed the prescribing data of Inhaled Steroids (IS) used in paediatrics in the age group of 0-14 years for the year 2015 (before 2017, year of the study), in order to have a clear picture of the prescribing activity of Family Paediatricians involved in the project.

We analyzed the IS prescribing data for **13,530 children** aged between 0-14 followed by 17 family paediatricians of whom, 11 of the Molise Region and 6 of the Umbria Region, as shown in Table **1.**

Table 1: Number of FPs and Number of Children (2015)

Region	Family Pediatricians	Children (0-14 yrs)
Molise	11	7.786
Umbria	6	5.744
TOTAL	17	13.530

The data were obtained from the FARMASTAT database and from the Pharmacovigilance Centre of the Umbria Region and were found to be homogeneous and similar to those of the databases (INFANTIA and JUNIOR BIT) of Family Paediatricians.

In particular, we have taken into consideration the following prescription and consumption indicators for the evaluation of outcomes: number of prescriptions, number of pieces, pharmaceutical expenditure and prescriptions of each IS. We also highlighted the number of patients in the individual PdFs in order to be able to calculate prevalence of use of IS in children aged from 0 to 14 as indicators of appropriateness.

In addition, for each paediatrician involved in the study, we analyzed the number of patients aged between 0-14 treated with IS in order to calculate the data of prevalence of use.

As it is well known, the indicators of prescription appropriateness in specialist medicine are expressed in terms of prevalence of use (P = n ° subjects / population * 100). Considering that the number of patients aged between 0-14 for 17 paediatricians for 2015 was **13,530** and that the number of children from 0-14 years who received at least one IS prescription during the year under examination were 2802, it designates that the prevalence of use (P = 13530/2802 * 100) of the ISs prescribed in the age group 0-14 years from the 17 Paediatricians of the family in 2015 was **20.71%** (Figure **1**).

We calculated the prevalence of appropriate prescriptions and the prevalence of inappropriate prescriptions: from the 2802 patients who received at least one IS prescription, we analyzed the number of patients with the prescriptions made according to the Guidelines and the number of patients with inappropriate prescriptions. We obtained the following data (Figure **2**):

1) From the 2802 patients who received at least one prescription, the number of patients with the prescriptions according to the Guidelines were **767** with a prevalence of **5.67%**

2) From the 2082 patients who received at least one prescription, the number of patients with inappropriate prescriptions was found to be 2035 with a prevalence of **15.04%**

Therefore, the prevalence data of the appropriate prescriptions is 5.66%, while that of the inappropriate prescriptions is 15.04%.

We analyzed the percentage of appropriate and inappropriate prescriptions, we found that out of 2802 patients who received at least one prescription, **72.63% (2035**) was the percentage of inappropriate prescriptions while only **27.37% (767**) turned out to be the percentage of appropriate prescriptions (Figure **2**).

We considered the total number of prescriptions, the total number of pieces prescribed, the total number of prescriptions according to the Reference Guidelines and the total number of inappropriate prescriptions to calculate the percentages of appropriateness and prescriptive inaccuracy of the ISs in the year 2015 implemented by Family Paediatricians in children aged between 0 to 14.

The results obtained are shown in Table **4** and have shown that the total number of prescriptions of IS carried out by 17 family paediatricians for children aged 0 to 14 years is 4175 corresponding to a number of **4338** quantities prescribed.

Table 4: Prescription Indicators – year 2015

Total prescriptions	4175
Guideline prescriptions	1308
Inappropriate prescriptions	2867
Total pieces	4338
% of prescription inappropriateness	68.67%
% of prescription appropriateness	31.33%

The total number of prescriptions according to the Reference Guidelines is 1308; therefore the number of inappropriate IS prescriptions is 2867 with a percentage of **68.67%.** This data indicates that the total percentage of appropriate prescriptions in children from 0 to 14 years is only 1308 or **31.33%**.

Accomplishing a more detailed analysis of the percentages of appropriateness and inappropriateness of non-prescriptive accuracy of the ISs in the various age groups, it is documented that (Figure **3**):

1) in the age group from **0 to 4 years** there were 2181 total prescriptions with 1532 inappropriate

prescriptions with a percentage of inappropriateness equal to 70.24%;

2) in the **5 to 10 year** age group there were 1600 total prescriptions with 1061 inappropriate prescriptions with a 66.31% percentage of inappropriateness;

3) in the **11-14 age group** there were 394 total prescriptions with 275 inappropriate prescriptions with a 69% percentage rate of inappropriateness;

Subsequently (Figure **4**) we calculated the consumption data, quantifiable in a total of € **57.926,87** for the prescription of IS, in the age group of 0-14 years, during the year 2015 in the two Regions. Valuing the expense for drugs administered inappropriately the indication equal to € 38.992.40, while the expenditure for drugs administered appropriately concluded to be € 18.934,41. Therefore the percentage of inappropriate spending was equal to 67.31%.

Finally, we analyzed the percentages of prescribed inappropriateness of the individual **active principles** of the IS and it was revealed that; (Table **5**):

1) **Beclomethasone Dipropionate** was used in **2429** prescriptions with a percentage of use equal to **58.18%.** The number of inappropriate prescriptions was **1736** with a percentage of inappropriateness equal to **71.47%** (Figure **5**),

2) **Budesonide** was used in **1267** prescriptions with a **30.35%** utilization rate. The number of inappropriate prescriptions was 872 with a 68.82% percentage of inappropriateness, (Figure **6**)

3) **Fluticasone Propionate** was used in **335** prescriptions with a percentage of use equal to **8.02%.** The number of inappropriate prescriptions was 155, with a prescription rate of 53.73% (Figure **7**),

4) **Flunisolide** was used in **132** prescriptions with a percentage of use equal to **3.16%.** The number of inappropriate prescriptions was 93, with a 70.45% percentage of inappropriateness (Figure **8**),

5) **Other active principles** were used in **12** prescriptions with a percentage of use equal to **0.28%.** The number of inappropriate prescriptions was 11 with a 91.67% percentage of inappropriateness.

b. Training / Information Events for Paediatricians and Families on the Correct use of ISs.

The processing of IS prescribing data in the pediatric age, in the age group of 0 - 14 years, indicated a resilient criticality of the prescriptive activity in the Molise and Umbria Regions in the year 2015 examined, with a prevalent use of 20.71% and with a 68.68% inappropriateness rate for this class of drugs.

Therefore, in the light of the above mentioned results, it was regarded necessary to commence an information campaign on the appropriate use of this class of drugs, both through the organization of training / informative events, and through the dissemination of national and international guidelines, on the correct use of IS in therapy.

As acknowledged, in fact, an inappropriate use of IS represents a potential risk not only for individual health, with an increase in the risk of adverse reactions, but also because it conducts to an increase in costs for the National Health Service.

We then proceeded to highlight facts related to the prescriptive inappropriateness by divulging the main aspects of national and international guidelines to family pediatricians through an Investigator's Meeting and more briefing meetings.

It is also emphasized that it has periodically sent communications to Family Pediatricians of the Molise Region and the Umbria Region regarding the project and has intervened in conferences and training events to consider the attention to the purpose of the study

Table 5: Percentage of Prescriptive Inappropriateness of Active Principles - ***year 2015***

Active Principles	Total Prscriptions	Utilization Rate	Inappropriate Prescriptions	% of Inappropriateness
Beclomethasone	2429	58.18%	1736	71.47%
Budesonide	1267	30.35%	872	68.82%
Fluticasone	335	8.02%	155	53.73%
Flunisolide	132	3.17%	93	70.45%
Others	12	0.28%	11	91.67%

with particular reference to the correct use of IS in the age group from 0 to 14 years.

Lastly, the information / training work carried out by Family Paediatricians is eminent in relation to their patients, in order to raise awareness in the correct use of pharmaceuticals in paediatrics especially regarding ISs in the most vulnerable age group, avoiding do-it-yourself and self-prescriptions from the families themselves, that expose children to risks of adverse events. At the end of this current research, other training events are planned for the year 2018.

c. Elaboration and Processing of Prescription data of Inhaled Steroids (IS) in the Age Group of 0 - 14 Years (Year 2017)

In the third phase of the project we collected and processed the prescribing data of Inhaled Steroids (IS) used in paediatrics in the age group of 0-14 years for the year 2017 in order to have a clear picture of the prescribing activity of Family Paediatricians involved in the project after the information/training phase.

We analyzed the IS prescribing data for **13.948** children aged between 0-14 followed by 17 Family Paediatricians of whom, 11 of the Molise Region and 6 of the Umbria Region, as shown in Table **6.**

Table 6: Number of FPs and Number of Children (2017)

Region	Family Pediatricians	Children (0-14 yrs)
Molise	11	8.210
Umbria	6	5.738
TOTAL	17	13.948

Also these data were obtained from the FARMASTAT database and from the Pharmacovigilance Centre of the Umbria Region and were found to be homogeneous and similar to those of the databases (INFANTIA and JUNIOR BIT) of Family Paediatricians.

In particular, as of the year 2015, we have taken into consideration the following prescription and consumption indicators for the evaluation of outcomes: number of prescriptions, number of pieces, pharmaceutical expenditure and prescriptions of each IS. We also highlighted the number of patients in the individual PdFs in order to be able to calculate prevalence of use of IS in children aged from 0 to 14 as indicators of appropriateness.

In addition, for each paediatrician involved in the study, we analyzed the number of patients aged between 0-14 treated with IS in order to calculate the data of prevalence of use (P = n ° subjects / population * 100). Considering that the number of patients aged between 0-14 for 17 paediatricians for 2015 was **13.984** and that the number of children from 0-14 years who received at least one IS prescription during the year under examination was **2113,** it designates that the prevalence of use (P = 13984/2113 * 100) of the ISs prescribed in the age group 0-14 years from the 17 Paediatricians of the family in 2017 was **15.15%** (Figure **9**).

We calculated the prevalence of appropriate prescriptions and the prevalence of inappropriate prescriptions: from the 2802 patients who received at least one IS prescription, we analyzed the number of patients with the prescriptions made according to the Guidelines and the number of patients with inappropriate prescriptions. We obtained the following data (Figure **10**):

1) From the **2113** patients who received at least one prescription, the number of patients with the prescriptions according to the Guidelines were **887** with a prevalence of **6.36%;**

2) From the **2113** patients who received at least one prescription, the number of patients with inappropriate prescriptions was found to be **1126** with a prevalence of **8.79%.**

Therefore, the prevalence data of the appropriate prescriptions is **6.36%,** while that of the inappropriate prescriptions is **8.79%.**

We analyzed the percentage of appropriate and inappropriate prescriptions, we found that out of 2802 patients who received at least one prescription, **72.63% (2035**) was the percentage of inappropriate prescriptions while only **27.37% (767**) turned out to be the percentage of appropriate prescriptions (Figure **10**).

Then we analyzed the percentage of appropriate and inappropriate prescriptions. We have shown that out of 2113 patients who had received at least one prescription, 41.98% (887) was the percentage of inappropriate prescriptions, while only 58.02% (1126) was the percent of appropriate prescriptions.

After we considered the total number of prescriptions, the total number of pieces prescribed, the total number of prescriptions according to the

Reference Guidelines and the total number of inappropriate prescriptions to calculate the percentages of appropriateness and prescriptive inaccuracy of the ISs in the year 2017 implemented by Family Paediatricians in children aged between 0 to 14.

The results obtained are shown in Table **9** and have shown that the total number of prescriptions of IS carried out by 17 Family Paediatricians for children aged 0 to 14 years is **3055** corresponding to a number of **3148** quantities prescribed.

Table 9: Prescription Indicators – year 2017

Total prescriptions	3055
Guideline prescriptions	1183
Inappropriate prescriptions	1181
Total pieces	3148
% of prescription inappropriateness	38.66%
% of prescription appropriateness	61.34%

The total number of prescriptions according to the Reference Guidelines was 1873; therefore the number of inappropriate IS prescriptions is 1181 with a percentage of **38.66%.** This data indicates that the total percentage of appropriate prescriptions in children from 0 to 14 years was only 1873 or **61.34%**.

Accomplishing a more detailed analysis of the percentages of appropriateness and inappropriateness of non-prescriptive accuracy of the ISs in the various age groups, it is documented that (Figure **11**):

1) in the age group from **0 to 4 years** there were **2148** total prescriptions with **606** inappropriate prescriptions with a percentage of inappropriateness equal to **39.30 %** ;

2) in the **5 to 10 year** age group there were **1768** total prescriptions with **468** inappropriate prescriptions with a **35.94%** percentage of inappropriateness;

3) in the **11-14 age group** there were 420 total prescriptions with 109 inappropriate prescriptions with a **35.05%** percentage rate of inappropriateness;

Subsequently (Figure **12**) we calculated the consumption data, quantifiable in a total of € **42.281,50** for the prescription of IS, in the age group of 0-14 years, during the year 2017 in the two Regions. Valuing the expense for drugs administered inappropriately the indication equal to € **15.912,47,** while the expenditure for drugs administered appropriately concluded to be **€ 26.369,03**. Therefore the percentage of inappropriate spending was equal to **37.63%**.

Finally, we analyzed the percentages of prescribed inappropriateness of the individual **active principles** of the IS and it was revealed that; (Table **10**):

1) **Beclomethasone Dipropionate** was used in **1925** prescriptions with a percentage of use equal to **63.01%.** The number of inappropriate prescriptions was **737** with a percentage of inappropriateness equal to **38.29%** (Figure **13**),

2**) Budesonide** was used in **730** prescriptions with a **23.90%** utilization rate. The number of inappropriate prescriptions was **316** with a **43.29%** percentage of inappropriateness, (Figure **14**)

3) **Fluticasone Propionate** was used in **263** prescriptions with a percentage of use equal to **8.61%.** The number of inappropriate prescriptions was **50**, with a prescription rate of **19.01%** (Figure **15**),

4) **Flunisolide** was used in **137** prescriptions with a percentage of use equal to **4.48%.** The number of inappropriate prescriptions was **78**, with a **56.93%** percentage of inappropriateness (Figure **16**),

5) No Other active principles have been used.

d. Comparison of the Prescriptive Data of Inhaled Steroids (IS) in the Age Group of 0 - 14 Years, in the Years 2015 and 2017 (after the Training Phase) in the Two Regions

Table 10: Percentage of Prescriptive Inappropriateness of Active Principles – *year 2017*

Active Principle	Total Prescriptions	Utilization Rate	Inappropriate Prescriptions	% of Inappropriateness
Beclomethasone	1925	63.01%	737	38.29%
Budesonide	730	23.90%	316	43.29%
Fluticasone	263	8.61%	50	19.01%
Flunisolide	137	4.48%	78	56.93%
Others	0	0.0%	0	0.0%

In the last phase of the study, we compared prevalence use data, data of prescriptive appropriateness in various age groups, consumption data and data related to the individual IS used, after the training phase carried out both on the Family Pediatricians and on the families themselves.

1) Comparison between the prevalence of use.

2) Comparison between the prevalence of appropriate prescriptions and the prevalence of inappropriate prescriptions.

3) Comparison between the percentage of appropriate and inappropriate prescriptions.

4) Comparison between the percentages of appropriateness and inappropriateness prescription of the ISs in the various age groups.

5) Comparison of consumption data (Pharmaceutical expenditure from appropriate and inappropriate prescriptions).

6) Comparison of the percentages of prescribing inappropriateness of the single active principles of the IS.

We obtained the following results:

1). Comparison of prevalence of use.

As is well known, the value of prescription appropriateness in specialized medicine are expressed in terms of prevalence of use (P = n ° subjects / population * 100). Considering that, in 2015, the number of patients aged between 0-14 for 17 paediatricians were 13,530 and that the number of children from 0-14 years who received at least one IS prescription during that year were 2802, it consequently indicates that the prevalence of use (P = 13530/2802 * 100) of the ISs prescribed in the age group 0-14 years from the 17 Family Pediatricians in 2015 was 20.71%.

Considering that, in 2017, the number of patients aged 0-14, for 17 pediatricians were 13.948 and that 2113 of these patients were prescribed at least one IS prescription during the year, it implies that the prevalence of use (P = 13530/2802 * 100) of the ISs prescribed for 0-14 years by the 17 family pediatricians in the year 2017 was 15.15%.

In 2015, the prevalence figure for the appropriate prescriptions is 5.47%, while that for inappropriate prescriptions is 15.04%, while in 2017 the prevalence date for the appropriate prescriptions is 6.36%, while that for inappropriate prescriptions is be 8.79% (Figure **1** Figure **9**).

2) Comparison between the Percentage of Appropriate Prescriptions and the Percentage of Inappropriate Prescriptions on the Prevalence of Prescriptions.

In 2015, the percentage of patients with inappropriate prescriptions was 72.63% (2035) while only 27.37% (767) transpired to be the percentage of the patients with appropriate prescription, whereas in 2017 41.98% (887) was the percentage of patients with inappropriate prescriptions, whilst 58.02% (1226) emerged with befitting prescriptions (Figure **2**- Figure **10**).

3) Comparison between the Percentages of Appropriate and Inappropriate Prescriptions on the Total Number of Prescriptions.

In 2015 the total number of prescriptions was 4175 with a number of inappropriate IS prescriptions equal to 2867 (a percentage of 68.67%) while the total

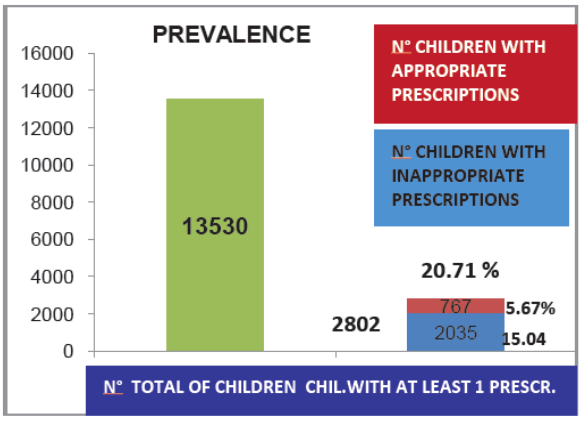

Figure 1: Prevalence 2015.

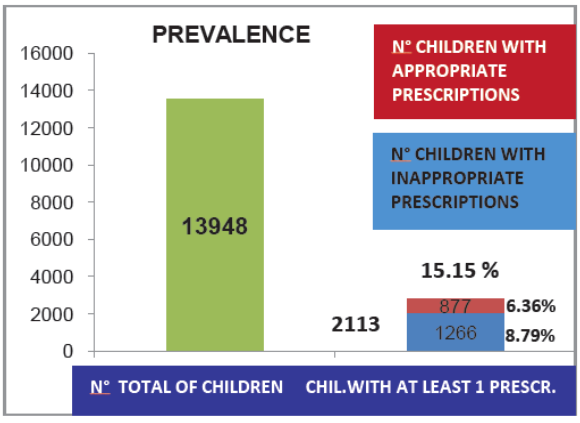

Figure 9: Prevalence 2017.

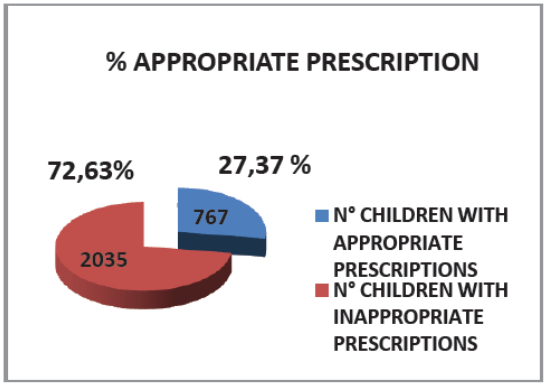

Figure 2: % Appropriate prescriptions 2015.

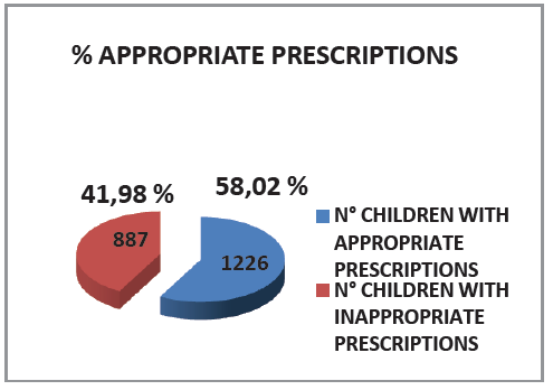

Figure 10: % Appropriate prescriptions 2017.

percentage of appropriate prescriptions for children in the age group of 0 to 14 (according to the Reference Guidelines) resulted in being only 1308 equal to 31.33%.

In 2017 the total number of prescriptions were 3055, improper IS prescriptions were equal to 1181 (a percentage of 38.66%) while the total percentage of appropriate prescriptions in children aged 0 to 14 (according to the Reference Guidelines) was 1874 equal to 61.34%.

4) Comparison between the Percentages of Suitable and Unsuitable Prescribing of ISs in Various Age Groups.

In 2015, in the age group from 0 to 4, there was a percentage of 70.24% of inappropriate prescription; in the age group from 5 to 10 the percentage was equal to 66.31% and in the 11 to 14 age group a percentage of 69.80%.

In 2017, prescriptive inappropriateness, in the age

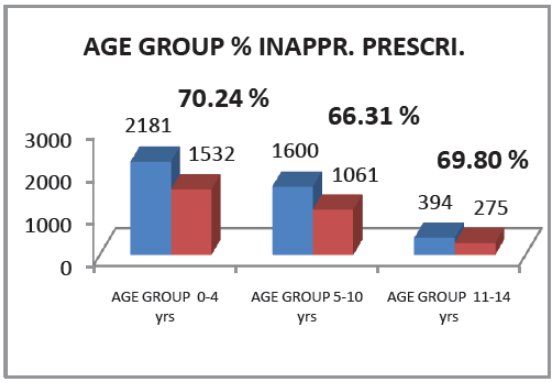

Figure 3: Age group inappropriate prescriptions 2015.

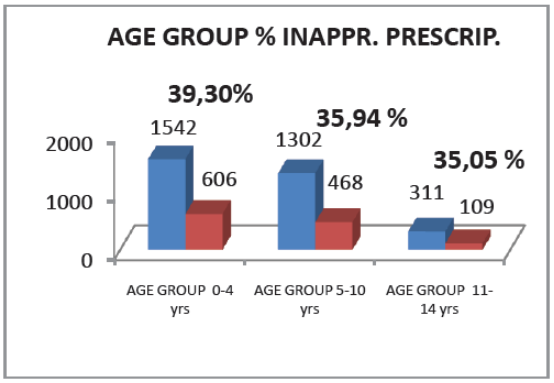

Figure 11: Age group inappropriate prescriptions 2017.

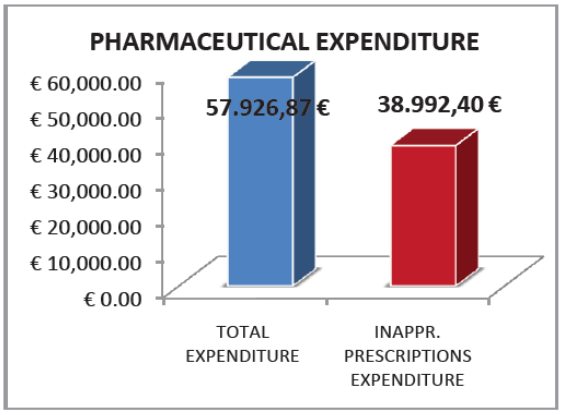

Figure 4: Expenditure 2015.

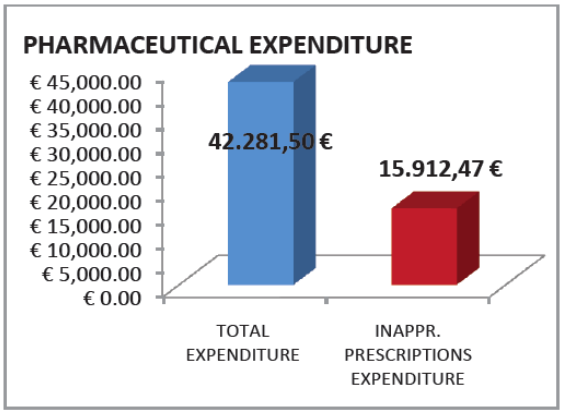

Figure 12: Expenditure 2017.

group from 0 to 4 was 39.30%, in the age group from 5 to 10, 35.94% and from 11 to 14 years the percentage was 35.04% (Figure **3** Figure **11**).

e) Comparability of Consumption Data (Pharmaceutical Expenditure from Appropriate and Inappropriate Prescriptions.)

The total expenditure, for the year 2015, for IS prescriptions was quantifiable to a total of € 57,926.87, in the age group of 0-14 years. Assessing the expenditure for drugs administered inappropriately it was shown that it was equal to € 38.992.40, while the expenditure for drugs administered appropriately emerged as € 18.934,47. Therefore the percentage of inappropriate spending was equal to 67.31%.

In 2017, the total expenditure calculated for IS prescriptions, in the age group of 0-14 had a total of €42,281.50, considering that the expense for drugs administered inappropriately was shown to be equal to € 15.912,47 while the expenditure for drugs administered appropriately was € 26.369,03 Therefore the percentage of inappropriate spending was equal at 37.63% (Figure **4**- Figure **12**).

f) Comparison of the Percentages of Prescribing Inappropriateness of the Single Active Principles of the ISs.

In 2015, it was noted that, for Beclometasone Dipropionate there was a percentage of 71.47% of prescriptive inappropriateness; for Budesonide a percentage of 68.82%; for Fluticasone Propionate a percentage of 53.84%; for Flunisolide a 70.45% percentage of inappropriateness, for other active substances a percentage of inappropriateness equal to 91.67% (Figure **5**-**8** - Figure **13**-**16**).

In 2017, it was recorded that, for Beclometasone Dipropionate there was a percentage of 38.29% of prescriptive inaccuracy; for Budesonide a percentage of 43.29%; for Fluticasone Propionate a percentage of 19.01%; for Flunisolide a percentage of inappropriateness of 56.93%, for other active substances a percentage of inappropriateness of 0% (Figure **2**- Figure **10**).

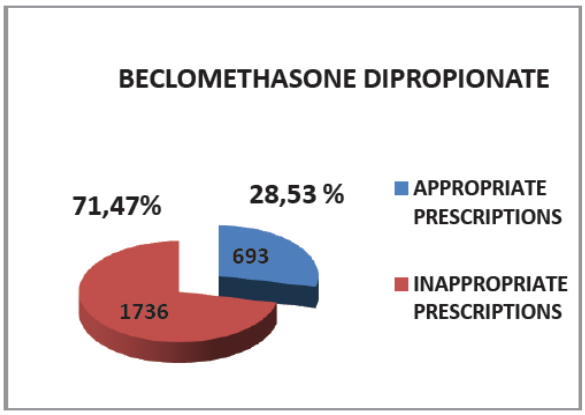

Figure 5: Beclomethasone prescriptions 2015.

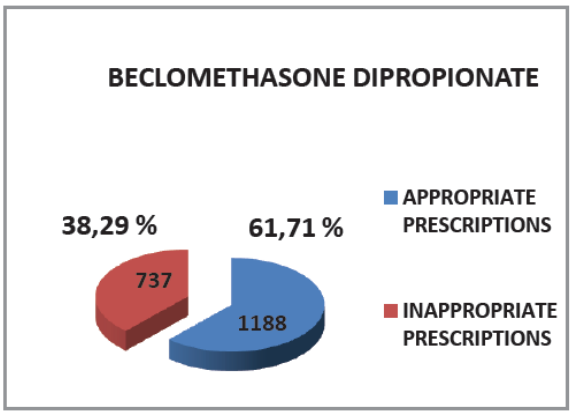

Figure 13: Beclomethasone prescriptions 2017.

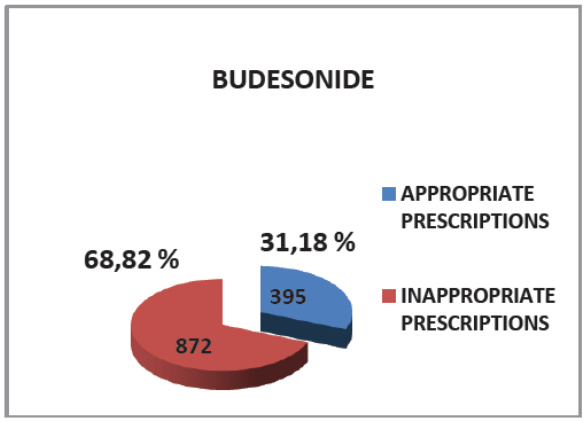

Figure 6: Budesonide prescriptions 2015.

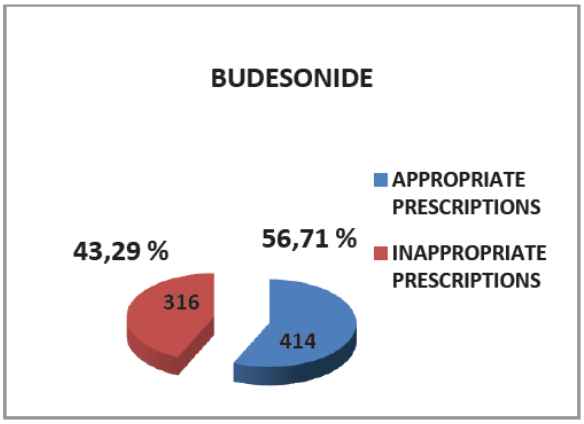

Figure 14: Budesonide prescriptions 2017.

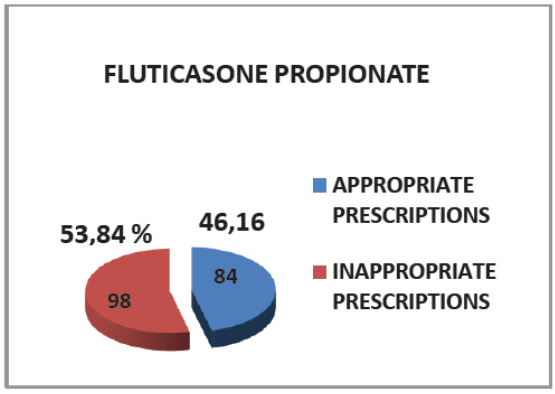

Figure 7: Fluticasone prescriptions 2015.

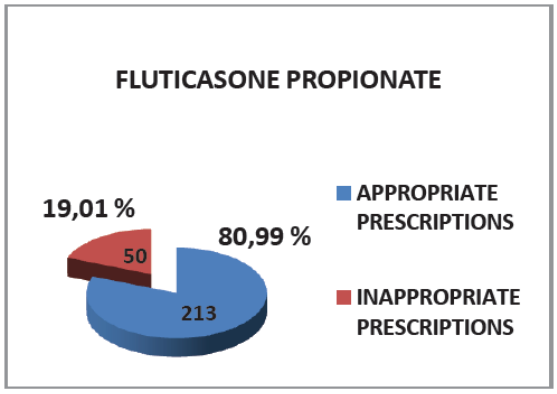

Figure 15: Fluticasone prescriptions 2017.

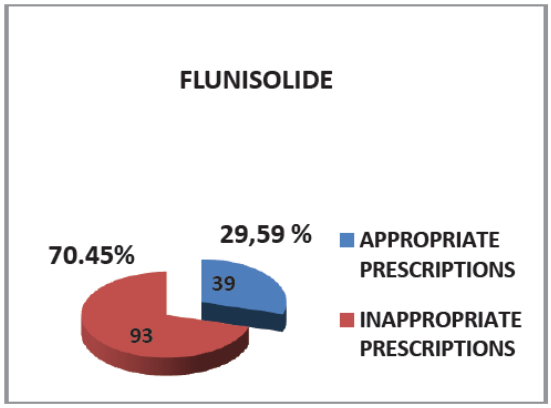

Figure 8: Flunisolide prescriptions 2015.

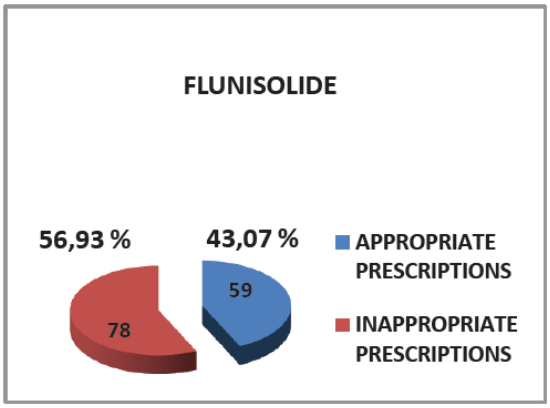

Figure 16: Flunisolide prescriptions 2017.

g) Comparison of the Total Number of Pieces Prescribed.

In 2015 the total number of pieces prescribed was 4328, while in 2017 the total was 3148. There was a reduction in the total number of pieces prescribed (from 4328 to 3148)

From the comparison of the prescription data of 2015 and 2017, after formative training for Family Pediatricians and the correct information given to the family on the rational use of inhaled Corticosteroids, an improvement is highlighted in the followings:

- prevalence of children with at least one prescription by 5.56% (from 20.71% to 15.15%)

- prevalence of children with inappropriate prescriptions by 6.25% (from 15.04% to 8.79%)

- percentage of children (with at least one prescription) with appropriate prescriptions by 30.65% (from 27.37% to 58.02%)

- percentage of children (with at least one prescription) with inappropriate prescriptions by 30.65% (from 72.63% to 41.98%)

- percentage of the appropriate prescriptions by 30.01% (from 31.33% to 61.34%) of the total prescriptions

- percentage of inappropriate prescriptions by 30.01% (from 68.67% to 38.66%) of the total prescriptions

- percentage of inappropriate prescriptions in different age groups:

- in the age group from 0 to 4 years, by 30.94% (from 70.24% to 39.30%);

- in the 5 to 10 year age group, 30.37% (from 66.31% to 35.94%);

- in the 11 to 14 year age group, 34.76% (from 69.80% to 35.04%).

- total expenditure of € 15,645.36 (from € 57.926.87 to € 42.281.50)

- expenditure for improperly administered medicines of € 23.079.93 (from € 38.992.40 to € 15.912.47):

- inappropriate spending 29.68% (from 67.31% to 37.63%).

- percentage of inappropriate prescriptions for single IS:

- for Beclometasone dipropionate, 33.18% (from 71.47% to 38.29%);

- 25.53% for Budesonide (from 69.82% to 43.29%);

- for Fluticasone propionate, 34.83% (from 53.84% to 19.01%).

- for Flunisolide, 13.52% (from 70.45% to 56.93%).

- also the total number of prescribed articles was reduced by 1190 pieces (from 4338 to 3148)

Assessing any adverse events that occurred in the two reference years in children aged 0 to 14 years after medication treatment with CSI, have not revealed any adverse events.

7. DISCUSSION

The REDS Study has been the first multi regional Pharmacovigilance project presented by the Molise Region in the pediatric field (AIFA PV Call -2010-2011) focused on pediatric population.

Specifically the study was a phase IV research project, coordinated by a FP-MCRN (Family Pediatrician-Medicines for Children Research Network), which on the one hand provided training and information regarding the proper use of IS in children and possible iatrogenic diseases caused by their misuse, on the other hand setting up a territorial active survey on prescriptive appropriateness and safety of these medications in children aimed at the risk-benefit balance on usage.

The project's aim is to improve prescriptive awareness, giving an accurate diagnosis and attaining a reduction in pharmaceutical expenditures related to IS use in the population aged 0-14 years.

The study wanted firstly to overcome the limits of OsMed data such as the inability to trace the diagnosis related to the prescription.

Following the National and International Guidelines (GINA, NICE etc.) on the correct use of IS in children, recruiting nearly the 100% of patients, examinating patients in clinics (self-help), reaching collaboration with families and following the protocol, the study conducted by the FP-MCRN has allowed to achieve an overall improvement of prescriptive appropriateness, to have a clear picture of the epidemiological situation, to obtain an effective control of the benefits, a reduction and a proper evaluation of the possible ADRs related to IS.

More specifically, therefore, the project has as objectives the improvement of diagnostic and prescriptive appropriateness, reducing unnecessary hospitalization in pediatrics and achieving reduction in pharmaceutical expenditure relating to the use of IS in the range of ages 0-14 years.

In this epidemiological / observational (case-control) and active surveillance project, the prescribing data for children (0 - 14 years) were collected and processed by Family Pediatricians (FPs). The activities have been divided into four time steps**:** 1) Elaboration of the prescriptive data (year 2015 -retrospective); 2) Training / information events on FPs and families on the correct use of IS (year 2016); 3) Elaboration of the prescriptive data (of the same FPs) (year 2017-prospective) and 4) comparison with those of 2015.

The processing of prescription data of IS in children, particularly in the age group 0-14 years has shown a strong prescriptive critical activity in the two region in the years 2015 and 2017.

Therefore, on the basis of the results mentioned before, there was a clear necessity to undertake an information campaign on the appropriate use of this class of medication, either through the organization of training/information events, and through the dissemination of national and international guidelines on the correct IS use.

As it is known, in fact, an inappropriate use of IS is a potential risk not only for individual health, with an increase in exposure to the risk of adverse reactions, but also for public health and the problem of costs to the National Health Service.

Among the main unjustified use of IS, highlighted is the fact of the high use of this class of medication for the treatment of colds, coughs and sore throats especially in the 0 to 14 years age group, and therefore IS are not effective for treating them.

The high prescription of IS for pediatric respiratory diseases such as strep throat, acute cough, cold and bronchiolitis mainly caused by viruses, is a recognized indicator of inappropriate prescribing. In particular, as shown in the international guidelines (GINA,NICE ,etc),

in the case of a child with a sore throat where there are other signs of concomitant respiratory tract infection (nasal discharge, cough) therapy with IS is not required.

The training events have paid particular attention to the importance of promoting research and pharmacological trial culture, by building an even higher skill aimed especially at protecting the most vulnerable-pediatric population. Moreover attention was paid to the culture of iatrogenic disease for a careful analysis of the risk/benefit ratio of medication used in children. Also pediatrician's colleagues were stimulated to major reporting of adverse reactions in children.

The aims of the project were illustrated and announced, first the data of the pediatric IS prescriptions, promoting awareness on appropriateness of prescription through the communication of the above mentioned national and international guidelines.

Finally it highlights the information/training work done by Family Pediatricians with the families of their patients to stress the concept of the proper use of drugs in children, and in particular of IS in the most vulnerable age group, avoiding the "do it yourself " by families, that expose children to the risk of adverse reactions.

We have tried to reduce the selection bias through the insertion of a homogeneous population of children who needed IS according to the International Guidelines (0- 14 years). Children participating in the research were under the Family Pediatrician's care. In fact, the Italian FP take care of about 900 children from 0 up to 14 years of age. For this reason the case studies are absolutely homogeneous and the risk of drop out is really very low (<5%).

The information biases have been overcome through the collection of data taken directly from the FP database; the databases were always verifiable. This research has been verified by the Steering Committee (SC).

Therefore there was a careful analysis by the SC of the data to be included in the database according to the quality standards and without transcription biases. In addition a further quality control has been guaranteed mainly by a statistically correct interpretation. The confounding factors as age, sex, socio-economic and educational level were not relevant to this epidemiological investigation.

The final phase of the project involved the development and comparison of prescriptive data of IS used in the age group 0-14 years, in the year 2015 and 2017, in order to evaluate a possible improvement in prescribing, following training/information events.

The data were taken from FARMASTAT and pediatric database and in particular data were: the number of prescriptions, number of items and pharmaceutical expenditure. The number of patients assessed was able to calculate the prevalence of use of IS in children 0-14 years as a prescriptive appropriateness indicator.

By comparing prescription data of 2015 and 2017 after the training of Family Pediatricians and the information to families on the proper use of IS and of any adverse events related to their misuse, the data that emerge are: the prevalence of children with at least one prescription decreased from 20.71% to 15.15%; the percentage of the appropriate prescriptions increased from 27.37% to 58.02% ; the percentage of the inappropriate prescriptions decreased from 72.63% to 41.98%; the prevalence of inappropriate prescriptions in the 0-4 yrs decreased from 70.24% to 39.30%; in the 5-10 yrs from 66.31% to 35.94%; and in the 11-14 yrs from 69.80% to 35.04%; the percentage of inappropriate expenditure decreased from 67.31% to 37.63%;. the percentages of inappropriate prescriptions decreased for Beclomethasone from 71.47% to 38.29%; for Budesonide from 69.82% to 43.29%; for Fluticasone from 53.84% to 19.01%; and for Flunisolide from 70.45% to 56.93%.; the total number of pieces prescribed decreased from 4338 to 3148.

Last but not least the uniqueness of this multicenter research should be emphasized in which issues are dealt with regarding prescriptive appropriateness, training for Family Pediatricians, information for families, importance of assessments and reporting of ADRs linked to the medication in question which are the main foundations of a correct formula of active pharmacovigilance in pediatrics.

CONCLUSION

We have highlighted that through training course for pediatricians and correct information to families we can have a significant improvement in the correct use of Inhaled Steroids.

For this reason we need an effort regarding the training on these drugs both by pediatricians and above

all by parents who frequently administer medications to children for infections of the respiratory tract, without consulting their pediatricians.

It is very important to urge pediatricians to pay more attention to the proper use of IS, especially for certain diseases that do not require it, such as a cold, cough, sore throats and bronchiolitis.

ABBREVIATIONS

ADRs – Adverse Drug Reactions

GCP – Good clinical Practice

GVP – Good Pharmacovigilance Practice

IS – Inhaled Steroids

ENCEPP – European Network of Centres Pharmacoepidemiology and Pharmacovigilance

FPs – Family Pediatricians

FP-MCRN – Family Pediatricians - Medicines for Children Research Network

OsMed – Italian Osservatory of Drugs

PASS - Post-Authorization Safety Studies

ACKNOWLEDGEMENTS

The study, conducted according to ENCEPP Code of Conduct and according to the rules of GVP, was entered in the EU PAS REGISTER (EUPAS 12410) and obtained the ENCEPP STUDY SEAL on 15 February 2016.

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