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SUMMARY

OBJECTIVE Objective of this study is to analyse inter- and intra-country quantitative and qualitative differences in anti-asthmatic prescriptions to children and adolescents.

METHODS A literature search was done in EMBASE and MEDLINE to identify pharmaco-epidemiological studies published from January 1, 2000 to December 31, 2008, in which anti-asthmatic prescription prevalence in out-hospital children was measured. A meta-analytic weighted average and 95% CIs of prescription prevalences were calculated using a random effect model. Comparison of inter- and intra-country quantitative and, where possible, qualitative prescribing patterns was assessed.

RESULTS Twelve studies were found (ten from Europe, one from Canada and one from USA), but epidemiological indicators varied widely and only eight were suitable for meta-analysis. These revealed inter-country quantitative differences in prevalence in the overall population ≤19 years: Italy (19.0%), Canada (18.0%), USA (14.6%), Denmark (13.9%), Norway (9.1%), the Netherlands (6.2%). The overall prevalence was 13.3%. Qualitative inter-country differences: except for Italy, inhalatory short-acting β-agonists (SABA) were the most prescribed, followed by inhalatory corticosteroids (ICS).

CONCLUSIONS This first overall analysis of anti-asthmatic utilization studies in out-of-hospital children indicates a wide variability of anti-asthmatic prescription prevalence. Furthermore, epidemiological evaluations should be improved by using homogeneous indicators and, in order to validate the use of anti-asthmatic prescription as a proxy of disease, the diagnosis of asthma should accompany the data of prescriptions within the same population.

INTRODUCTION

Asthma is the most common chronic childhood illness with a worldwide prevalence ranging between 1.5% and 32.6% in 2002 [1]. According to the global burden of disease from the 2004 WHO Health Report, in the under-14 population asthma accounted for 9.5% (in the US) and 8% (in Europe) of total disability-adjusted life-years (DALY) lost per 1000 [2]. Since asthma is a chronic disease, anti-asthmatic prescriptions should represent a proxy for asthma prevalence and a tool for analyses of therapeutic appropriateness. This, however, is not true as it is for other chronic diseases, because a gap exists between prescription rates and prevalence of disease. The reasons are both over-use and under-use of anti-asthmatics, in particular inhalatory corticosteroids (ICS). International guidelines recommend ICS for long-term control of persistent asthma for all degrees of severity, and inhalatory short-acting β-agonists (SABA), such as salbutamol, as first choice in an acute attack [3-5]. Although adherence to guidelines reduces the number of outpatient and emergency department visits [6], guidelines are far from routinely applied in clinical practice [7-10]. In paediatric practice, the main inadequacy seems to be the use of ICS: over-prescribed in upper respiratory tract infections (URTI) and not prescribed enough for prevention or maintenance therapy between acute attacks in asthmatic children and adults [11,12]. On the other hand, the prescription of SABA for an URTI episode in the youngest patient, which is difficult to diagnose, would differentiate cases in which an asthma attack is triggered by a viral infection from non-asthmatic cases, because only in the first case would therapy be efficacious.

In order to assess the extent of anti-asthmatic prescriptions in children we reviewed drug utilisation studies, evaluating anti-asthmatic drug paediatric consumption data in the community setting from studies published between January 1, 2000 and December 31, 2008 and comparing inter- and intra-country anti-asthmatic prescribing patterns. The quantitative and qualitative

analysis of prescribing patterns and the degree of adherence to guidelines would serve to identify areas in need of educational interventions to improve appropriateness of asthma therapies for children.

METHODS

Search strategy to identify studies

A literature search was done in June 2009 in the MEDLINE and EMBASE databases for all studies with original data concerning the pharmaco-epidemiological evaluation of anti-asthmatic drug prescriptions in outside-hospital communities, published between January 1, 2000 and December 31, 2008 (Figure 1). In order to analyze a comparable observation period, studies collecting data during or before 1998 were excluded.

The MeSH search terms and additional keywords used in the search strategy were: drug utilisation/drug prescriptions/pharmacoepidemiology; child/infant/adolescent; anti-asthmatic agents/asthma. Manual searches for the bibliographies of retrieved articles were used to identify additional pertinent studies. Books and proceedings from meetings and congresses were not considered. The references retrieved were collected using the software program Reference Manager, version 11 (Institute for Scientific Information, Berkeley, California). Only studies evaluating anti-asthmatic drug prescriptions in children in the general population outside the hospital setting were included. Studies focusing on asthmatic child populations only or on one anti-asthmatic class or drug only were excluded. Prevalence (number of children and adolescents who received at least one anti-asthmatic drug prescription per 100 individuals in the population) was used as the indicator. Prevalences were obtained from studies evaluating exclusively anti-asthmatic prescriptions and from studies evaluating all drug classes, including anti-asthmatics.

A qualitative, inter-country prescription analysis was performed by comparing, where it was possible, the percentages of utilization of the main classes of anti-asthmatics, including ICS, SABA, Long-Acting β-Agonist (LABA) and Leukotriene Receptor Antagonist (LTRA).

Anti-asthmatic prescription prevalence and asthma prevalence

Prevalences of antiasthmatic prescriptions obtained from identified studies were compared to asthma prevalences determined worldwide by The International Study of Asthma and Allergy in Childhood (ISAAC) [1]. Since ISAAC data were not available for Denmark, The Netherlands or Norway, a search of studies estimating asthma prevalence in these countries was performed [13-15] using MEDLINE and EMBASE.

Meta-analysis

The meta-analysis took into account only studies comparable for two indicators: source of data and age range. Thus, inclusion criteria for meta-analysis were age range covering both preschoolers and adolescents (from 0 to 14-19); regional, multiregional, national or pharmacy dispensing and insurance plan database as source of prescription data. Exclusion criteria were the smaller age range groups and family paediatrician or general practitioner as source of prescription.

The meta-analytic weighted average and 95% CIs of prescription prevalences were calculated using a random effect model to take into account of the heterogeneity of the various studies [16,17].

RESULTS

A total of 189 articles were retrieved from the literature databases, 86 from EMBASE,83 from Medline, and 20 from both. 176 were excluded mainly because they focused on one class or drug only (30%), evaluated the impact of an educational intervention (30%), or analyzed risk factors for asthma, from socioeconomic indicators to therapy exposure, immunization, etc (30%). Three further studies were excluded because they analysed data collected before 1998 [18-20]. Only ten articles met inclusion criteria (6%). After identification of two additional studies through a manual reference search (they were not retrieved using the database search because not indexed with "anti-asthmatic agents" or "asthma" as a keyword), twelve pharmaco-epidemiological studies [9,10,21-30] met the inclusion criteria (Figure 1). The studies were carried out from 1998 to 2006 in six countries: Italy and The Netherlands (three studies each), Denmark and Norway (two studies each), Canada and US (one each) (Table 1). There were substantial differences between studies with regard to sample size (from a minimum of 6,417 to a maximum of 4,259,103 subjects), source of prescription data, and age classes considered. The data sources were mainly regional/multiregional/national prescription databases taking part in periodical health care monitoring systems (six articles), followed by health insurance databases or pharmacy dispensing databases (two articles each) and family paediatricians or general practitioners (two articles). Regarding age, ten involved both preschool and school-aged children; one 15-year-olds only and one the 6-14 age range group. Seven of the surveys evaluated only anti-asthmatics, and five covered all drug categories. Prescribed anti-asthmatic prevalence ranged from 5 to 26% without any relationship with the observational period or with drug class analyzed. Quantitative differences in anti-asthmatic use emerged among the six countries considered (Table 1). In general, two prescribing patterns could be identified, with some countries having

high anti-asthmatic prescribing levels (Italy,US and Canada) and others low levels (Norway and The Netherlands). Eight out of twelve studies indicated that boys received more anti-asthmatic drug prescriptions than girls and two articles [10,26] reported that, after age 15, an opposite pattern appeared, with girls receiving more prescriptions than boys. The prescription prevalence by age, reported by the majority of the studies, decreased from one-year-old infants to adolescence. One article reported an increase from 0-2 year old to six year old children and then a decrease from six to adolescence [28], and two report the highest prevalence of prescriptions between ages 1 and 4 [21,23].

Inter-country differences in anti-asthmatic treatment choices

Data concerning the distribution of prescriptions by anti-asthmatic classes were reported for all countries. In Italy ICS are the most prescribed class and covered 60% of anti-asthmatic prescriptions and 86% of the subjects treated, while SABA were the most prescribed in the other countries, covering from 58% (USA) to 93% (Denmark) of anti-asthmatic users. The percentage of ICS users varied from 25% (USA) to 67% (the Netherlands). Differences were found in the ICS/SABA ratio. These ranged from 0.35 in Denmark [25] to 0.84 in The Netherlands [30]. Three countries reported the most frequently prescribed anti-asthmatic drugs as follows: beclomethasone and salbutamol in Italy [21,22], salbutamol and fluticasone in Canada [26], salbutamol and montelukast in the US [27]. In Italy, beclomethasone and salbutamol are both prescribed mainly as nebulised suspension [21]. Table 2 compares Italy, US and Canada, showing the seven most frequently prescribed anti-asthmatics and showing that montelukast use makes an important inter-country distinction. Four articles compared monotherapy and polytherapy. The proportions of patients receiving more than one class of anti-asthmatic drugs

were 52% for Canada [26], 44% for Italy [20], 39% for The Netherlands [28] and 26% for Denmark [25]. Only two countries reported distribution, analyzing the number of packages of anti-asthmatic drugs prescribed during the period studied: only 29% of Italian [21] and 26% of Dutch [30] subjects received three or more packages. Four articles [21,26,27,30] reported similar percentages for oral steroids, from 4.0% to 4.7%. In only two articles the prevalence of anti-asthmatic prescription was checked against the diagnosis of asthma [28,30], and in both it was double.

Intra-country differences in prescription prevalence

The prevalence of anti-asthmatic prescriptions varies dramatically in Italy, ranging from 12 to 26% [21, 23], and similarly in Denmark, ranging from 7.7 to 13.9% [25,28].

Meta-analysis

The meta-analysis was performed on eight of the twelve articles (Figure 2). Four studies were excluded because age group and source of data were not comparable with the majority of the studies. Basically, the two studies regarding 15-year-olds only and the 6-14 age group [24,28] as well as the two articles whose sources were family paediatricians or general practitioners [22, 30] were excluded from the meta-analysis. The overall prevalence was 13.3% (95% CI 9.4-17.1%), with Italian children the most exposed to anti-asthma therapy (19.0% CI 5.3-32.7%) and Dutch children the least (6.2% CI 3.8-8.5%). However, after adding the four excluded articles the overall prevalence did not change significantly.

Inter-country differences between prescription prevalence and asthma prevalence gap

Comparison of prescription prevalence data with published data on asthma prevalence (Figure 2) indicated that in Denmark, The Netherlands, Norway and Canada asthma prevalence and prescription prevalence are comparable. In the US prescription prevalence appears to be less than asthma prevalence, whereas in Italy prescription prevalence was approximately twice that of asthma prevalence.

DISCUSSION

This is the first analysis specifically comparing published drug utilisation studies on anti-asthmatic prescriptions in the outside-hospital setting in children. A limit, as underlined in a recent review on drug utilization studies [31], is the wide variety of studies, with differences in study type (design and method), populations (in terms of sample size and age groups), and data collected, making comparative evaluation difficult or at best incomplete. Another limit is that data were available for comparison between only six countries, most of which were European. This is very important since countries with the highest asthma prevalence (≥ 10%), as reported by ISAAC [1,32], are theUS, Canada, Australia, New Zealand, South America, England and Scotland, and studies about anti-asthma drug utilization in children from these countries are limited or lacking. However, the main limit is the lack of asthma diagnosis, which would validate the appropriateness of anti-asthmatic utilization. In order to overcome the lack of these data, we attempted to use published asthma prevalence data for comparison with drug prescriptions, but the sources are different (ISAAC reported data from only three out of the six countries analyzed) and this represents another limit.

Inter-country quantitative differences

Large differences in the anti-asthmatic prescription prevalence were found between countries. The highest was in Italy and Canada and the lowest in The Netherlands. If for Canada the high ranking can be justified by a high prevalence of asthma, the same is not true for Italy, where the prescribing pattern for antibiotics shows a similar profile [31,33]. This suggests that the differences in drug prescription rates may be attributable to different prescribing attitudes and national drug regulatory policies more than differences in the prevalence of asthma. Moreover it is likely that anti-asthmatics and antibiotics are both used in URTI, even if this is not the first-line approach suggested by guidelines [3-5].

Inter-country qualitative differences

Together with anti-asthmatic prescription prevalences, some differences also emerged in the quality of the drugs prescribed, though not all studies reported information on anti-asthmatic distribution by class and/or drug. Asthma, by definition, involves acute attacks of wheezing, which guidelines recommend treating with SABA and preventing with ICS, so the percentage of patients receiving only one class of anti-asthma drugs should be minimal. The fact that the prevalence of prescription was validated by a diagnosis of asthma in only two studies was [28,30], and only four studies reported the percentage of children receiving more than one anti-asthma drug class made it difficult to evaluate adherence to guidelines. However, the percentages of patients receiving polytherapy (more than one class of anti-asthmatics) were 52% for Canada [26], 44% for Italy [21], 39% for The Netherlands [28] and 26% for Denmark [25], suggesting either lack of illness or, possibly, underuse of ICS for prevention/maintenance therapy, as underlined in the US study [27]. This is also partly highlighted by the differences in the ICS/SABA ratios, which range from 0.35 in Denmark [25] to 0.84 in The Netherlands [30]. While in the US the low ICS prescription prevalence (low ICS/SABA) might be explained by the

higher rate of montelukast prescription [27], in other countries the low ICS/SABA ratio might suggest that, besides the cases in which SABA are used as therapy in the youngest patients, who are not yet easy to diagnose, the prescribing attitude is not only quantitatively but also qualitatively different.

Only in the US study montelukast was prescribed more than ICS. A detailed comparison of the most prescribed anti-asthma drugs was possible only between the US, Canada and Italy (see Table 2), and even then the observation periods are different. Montelukast entered the market in 1998 and since data collection for the Canadian study was done shortly thereafter, the difference found may not reflect an actual difference, but may be due to the fact that for new drugs prescribing patterns tend to take a year or so to penetrate the market, especially in an area such as asthma where there are many existing, effective agents already approved.

Intra-country differences in prescription prevalence

The prevalence of anti-asthmatic prescriptions varies dramatically in Italy, ranging from 12 to 26% [21, 23] and similarly in Denmark ranging from 7.7 to 13.9% [25,28]. The reason for this diversity in the two Italian articles might be the different geographic setting: a single Local Health Unit versus the multiregional setting. The different prevalences in the two Danish articles might be due to the age group difference: the lower prescription prevalence study regarded 6-14 year olds, an age group in which asthma is theoretically better diagnosed and treated; in the higher prevalence study preschoolers were included, an age in which occasional wheezers are still in high percentage.

Incongruence between prescription prevalence and asthma prevalence

First of all, a precise comparison between prescription prevalence and asthma prevalence is difficult because of the lack of a single source of worldwide asthma prevalence, gathered in a homogenous manner.

In Figure 2 the comparison between prescription prevalence and asthma prevalence indicated that in Denmark, The Netherlands, Norway and in Canada asthma prevalence and prescription prevalence are comparable. In the US, prescription prevalence appears to be less than asthma prevalence and in Italy prescription prevalence is twice the value of asthma prevalence. This comparison is only indicative, because the reported asthma prevalences are measured in >6 year old group of subjects, a time in which the need for asthma medication decreases. Moreover, asthma prevalences were estimated, by ISAAC and the other studies [1, 13-15], by questionnaire and data may overestimate the burden of disease. In the case of US the subjects might be undertreated and in the case of Italy overtreated, as suggested by the authors [23, 27]. However, even in the countries in which asthma and prescription prevalence are similar, the possibility that anti-asthmatics are prescribed for diseases other than asthma as well is still valid because two studies [21,26] found that half the subjects received only one package of anti-asthma drugs per year, suggestive of non-asthmatic illness. Although the two articles reporting diagnosis of asthma [28,30] were from countries (Denmark and The Netherlands) in which the prevalence of asthma is low, the gap between prescription prevalence and burden of disease was large, with a number of treated twice the number of diagnosed cases. Since asthma is more reliably diagnosed in children from the age of six, the discrepancy between prescriptions and actual disease does not necessarily suggest inadequacies in prescription, but points to anti-asthma drug use as therapy in the youngest patients, when asthma is suspected but not diagnosed yet. This was not confirmed by the Dutch report [30] which validated prescription prevalence by asthma diagnosis: in two age

ranges (<6 and ≥6) the gap between asthma prevalence (diagnosed) and prescription prevalence in the youngest did not differ from the older children.

In this analysis two inadequacies in asthma treatment are suggested, the first regarding the sub-optimal prescription of ICS to asthma patients for prevention or maintenance, and the second regarding the prescription of asthma medications to non-asthmatic subjects. For confirmation, the availability of more homogenous studies is needed. Knowledge of the anti-asthmatic prescribing patterns of primary care physicians in the paediatric population is extremely important, since children are a prime target for inadequate prescription. The guidelines alone are not enough to ensure correct use of anti-asthmatics, since physician adherence and compliance to guidelines is not obvious or common. Another widely debated topic related to compliance with asthma treatments is the education of asthmatic children and their carers. A recent meta-analysis [34] of US studies confirms a reduction in hospitalization when children are educated about their disease, including sports practice, under preventive therapy, even if a diagnosis of asthma has been made. In conclusion, this is the first analysis specifically comparing drug utilisation studies on anti-asthmatic prescriptions in children outside the hospital setting. Despite the availability of data on the patterns of medication use in only six countries and the heterogeneity of the included studies, concordance with a divergence from community-based prevalences of asthma and symptoms might indicate different health beliefs among doctors and patients. Multinational collaborative pharmacoepidemiological studies aimed at collecting valid and comparable data are required, especially in those areas indicated by ISAAC as having a very high prevalence of asthma. These studies would be validated by diagnosis and outcome measures (e.g. number of emergency visits to the physician's office or emergency centers, or hospitalizations) and quality of life measures(

e.g. number of exacerbations and days of school missed per year, presence of daily or nightly cough or wheeze, presence of cough or wheeze with exercise).

Competing interests
None declared.

Legends

Figure 1. Flowchart of the bibliographic search

Table 1. Anti-asthmatic prescriptions in children and adolescents (≤ 19 years)

Table 2. The first seven anti-asthmatic drugs prescribed to Italian, American and Canadian children and adolescents (% of treated subjects)

Figure 2. Prevalence (%) of anti-asthmatic prescriptions in children and adolescents

Abbreviations

URTI: Upper respiratory tract infection
ICS: Inhaled corticosteroid
SABA: Short-acting β-agonist
LABA: Long-acting β-agonist
LTRA: Leukotriene receptor antagonist

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Figure 1. Bibliographic search

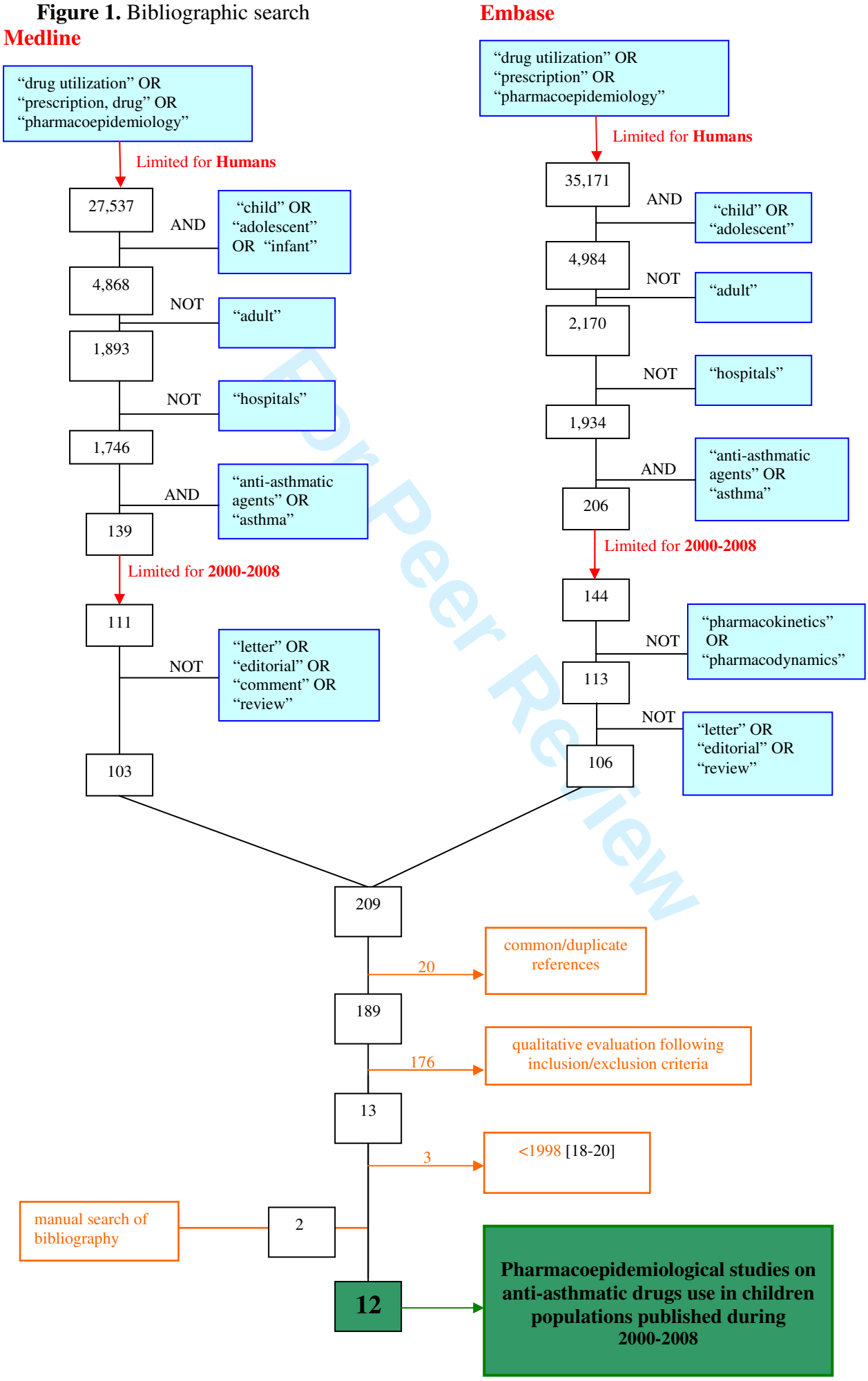

Table 1. Anti-asthmatic prescriptions in children and adolescents (≤ 19 years)

Reference	Period	Country	Population (n)	Age (years)	Source of prescription data[a]	Anti-asthmatic Prescription Prevalence (%)
[22][b]	1998	Italy	6,417	≤12	Family paediatricians	20.7
[21]	2003	Italy	55,242	≤17	Regional prescription DB	12.0
[23][b]	2006	Italy	923,353	≤14	Multiregional prescription DB	26.0
[29][b]	1998	The Netherlands	25,020	≤16	Pharmacy dispensing DB	7.4
[30]	2001	The Netherlands	74,580	≤17	General practitioners	7.5
[9]	2002	The Netherlands	72,240	≤14	Pharmacy dispensing DB	5.0
[25]	1998	Denmark	139,727	≤15	National prescription DB	13.9
[28]	2002	Denmark	125,907	6-14	Regional prescription DB	7.7
[24][b]	2000-2002	Norway	11,708	15	National prescription DB	6.5
[10]	2004	Norway	1,192,841	≤19	National prescription DB	9.1
[26][b]	1999	Canada	1,031,731	≤17	Insurance plans DB	18.0
[27]	2004-2005	USA	4,259,103	≤17	Insurance plans DB	14.6

[a] DB database
[b] all drug categories evaluated

Figure 2. Prevalence (%) of anti-asthmatic prescriptions in children and adolescents

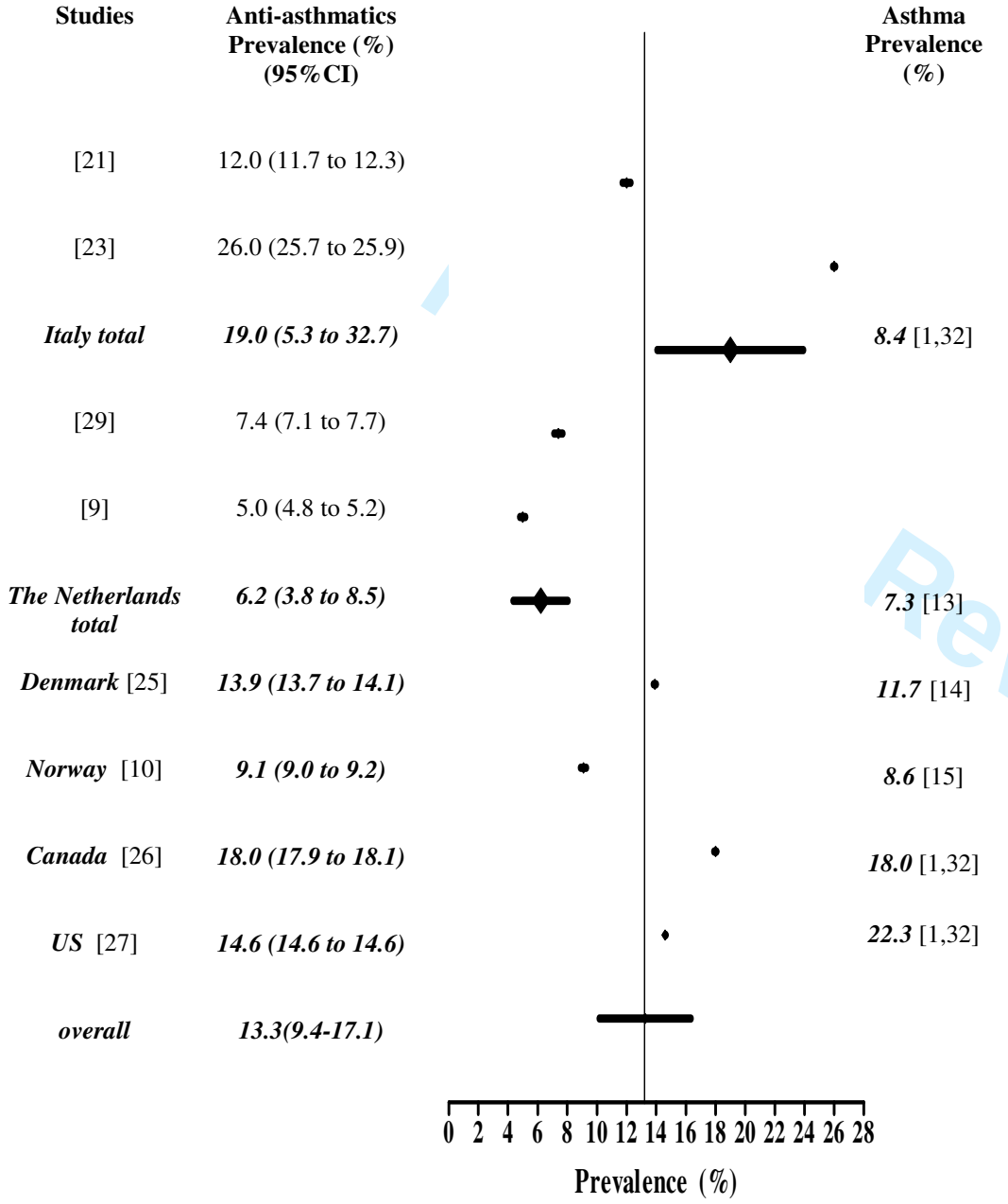

Table 2. The first seven anti-asthmatic drugs prescribed to Italian, American and Canadian children and adolescents (% of treated subjects)

Canada 1999#	Italy 2003#	USA 2005#
Salbutamol (71)	Beclomethasone (57)	Salbutamol (49)
Fluticasone (45)	Salbutamol (33)	Montelukast (22)
Budesonide (14)	Flunisolide (17)	Budesonide (10)
Beclomethasone (14)	Budesonide (15)	Levalbuterol (10)
Terbutaline (8)	Fluticasone (12)	Fluticasone+salmeterol (9)
Montelukast (5)	Salbutamol in combination(5)	Fluticasone (7)
Sodium cromoglycate(2)	Montelukast (3)	Pirbuterol(1)

The sum exceed 100 because some children were prescribed more than one drug.
#observation period

Inter-country variations in anti-asthmatic drug prescriptions for children. Systematic review of studies published during the 2000-2009 period

~~*INTER COUNTRY VARIATIONS IN MEDICATION FOR CHILDHOOD ASTHMA. Analysis of studies published during 2000-2009 period*~~

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SUMMARY

OBJECTIVE Objective of this study is to analyse inter- and intra-country quantitative and qualitative differences in anti-asthmatic prescriptions to children and adolescents.

~~To evaluate inter-country differences in population prevalences of anti-asthmatic prescribing in children and adolescents and to relate these to reported prevalences of asthma and symptoms.~~

METHODS A literature search was done in EMBASE and MEDLINE to identify pharmaco-epidemiological studies published from January 1, 2000 to December 31, 2008~~, 2000 to 2009~~ in which anti-asthmatic prescription prevalence in out-hospital children was measured. A meta-analytic weighted average and 95% CIs of prescription prevalences were calculated using a random effect model. Comparison of inter- and intra-country quantitative and, where possible, qualitative prescribing patterns was assessed.

RESULTS Twelve studies were found (ten from Europe, one from Canada and one from USA), but epidemiological indicators varied widely and only eight were suitable for meta-analysis. These revealed inter-country quantitative differences in prevalence in the overall population ≤19 years: Italy (19.0%), Canada (18.0%), USA (14.6%), Denmark (13.9%), Norway (9.1%), the Netherlands (6.2%). The overall prevalence was 13.3%. Qualitative inter-country differences: except for ~~in~~ Italy, inhalatory short-acting β-agonists (SABA) were the most prescribed, followed by inhalatory corticosteroids (ICS).

CONCLUSIONS This first overall analysis of anti-asthmatic utilization studies in out-of-hospital children indicates a wide variability of anti-asthmatic prescription prevalence. Furthermore, epidemiological evaluations should be improved by using homogeneous indicators and, in order to validate the use of anti-asthmatic prescription as a proxy of disease, the diagnosis of asthma should accompany the data of prescriptions within the same population.

~~This first overall analysis of anti-asthmatic utilization studies in out-of-hospital children indicates that epidemiological evaluations should be improved by using homogeneous indicators and possibly with the validation of the disease. The strong data emerged is the need of a multinational collaborative pharmacoepidemiological study aimed at collecting valid and comparable data, specially in those areas indicated by ISAAC as having very high prevalences of asthma.~~

INTRODUCTION

Asthma is the most common chronic childhood illness with a worldwide prevalence ranging between 1.5% and 32.6% in 2002 [1]. According to the global burden of disease from the 2004 WHO Health Report, in the under-14 population asthma accounted for 9.5% (in the US) and 8% (in Europe) of total disability-adjusted life-years (DALY) lost per 1000 [2]. ~~Epidemiological studies suggest that a wide range of pathological conditions are associated with recurrent respiratory airway obstruction and distinguishing them has important implications for management. This group contains different asthma phenotypes the two most common being atopic asthma more common in school age children, and episodic viral wheeze more common in preschool children [3]. Asthma with onset in early adulthood has its origins in early childhood [4].~~ Since asthma is a chronic disease, anti-asthmatic prescriptions should represent a proxy for asthma prevalence and a tool for analyses of therapeutic appropriateness. This, however, is not true as it is for other chronic diseases, because a gap exists between prescription rates and prevalence of disease. The reasons are both over-use and under-use of anti-asthmatics, in particular inhalatory corticosteroids (ICS). International guidelines recommend ICS for long-term control of persistent asthma for all degrees of severity, and inhalatory short-acting β-agonists (SABA), such as salbutamol, as first choice in an acute attack [3-5]. Although adherence to guidelines reduces the number of outpatient and emergency department visits [6],

guidelines are far from routinely applied in clinical practice [7-10]. In paediatric practice, the main inadequacy seems to be the use of ICS: over-prescribed in upper respiratory tract infections (URTI) and not prescribed enough for prevention or maintenance therapy between acute attacks in asthmatic children and adults [11,12]. On the other hand, the prescription of SABA ~~as ex-adjuvantibus therapy during~~ for an URTI episode in the youngest patient, which is difficult to diagnose, would differentiate cases in which an asthma attack is triggered by a viral infection from non-asthmatic cases, because only in the first case would therapy be efficacious.

In order to assess the extent of anti-asthmatic prescriptions in children we reviewed drug utilisation studies, evaluating anti-asthmatic drug paediatric consumption data in the community setting from studies published between January 1, 2000 and December 31, 2008 ~~January 2009~~ and comparing inter- and intra-country anti-asthmatic prescribing patterns. The quantitative and qualitative analysis of prescribing patterns and the degree of adherence to guidelines would serve to identify areas in need of educational interventions to improve appropriateness of asthma therapies for children. ~~Understanding prescribing patterns and the degree of adherence to guidelines would serve as a basis for educational initiatives to improve the appropriateness of prescribing.~~

METHODS

Search strategy to identify studies

A literature search was done in June 2009 in the MEDLINE and EMBASE databases for all studies with original data concerning the pharmaco-epidemiological evaluation of anti-asthmatic drug prescriptions in outside-hospital communities, published between January 1, 2000 and

December 31, 2008 ~~January 2000 and January 2009~~ (Figure 1). In order to analyze a comparable observation period, studies collecting data during or before 1998 were excluded.

The MeSH search terms and additional keywords used in the search strategy were: drug utilisation/drug prescriptions/pharmacoepidemiology; child/infant/adolescent; anti-asthmatic agents/asthma. Manual searches for the bibliographies of retrieved articles were used to identify additional pertinent studies. Books and proceedings from meetings and congresses were not considered. The references retrieved were collected ~~and analysed~~ using the software program Reference Manager, version 11 (Institute for Scientific Information, Berkeley, California). Only studies evaluating anti-asthmatic drug prescriptions in children in the general population outside the hospital setting were included. Studies focusing on asthmatic child populations only or on one anti-asthmatic class or drug only were excluded. Prevalence (number of children and adolescents who received at least one anti-asthmatic drug prescription per 100 individuals in the population) was used as the indicator. Prevalences were obtained from studies evaluating exclusively anti-asthmatic prescriptions and from studies evaluating all drug classes, including anti-asthmatics.

A qualitative, inter-country prescription analysis was performed by comparing, where it was possible, the percentages of utilization of the main classes of anti-asthmatics, including ICS, SABA, Long-Acting β-Agonist (LABA) and Leukotriene Receptor Antagonist (LTRA).

Anti-asthmatic prescription prevalence ~~(PP)~~ and asthma prevalence ~~(AP)~~

Prevalences of antiasthmatic prescriptions obtained from identified studies were compared to asthma prevalences determined worldwide by The International Study of Asthma and Allergy in Childhood (ISAAC) [1]. Since ISAAC data were not available for Denmark, The Netherlands or

Norway, a search of studies estimating asthma prevalence in these countries was performed [13-15] using MEDLINE and EMBASE.

Meta-analysis

The meta-analysis took into account only studies comparable for two indicators: source of data and age range. Thus, inclusion criteria for meta-analysis were age range covering both preschoolers and adolescents (from 0 to 14-19); regional, multiregional, national or pharmacy dispensing and insurance plan database as source of prescription data. Exclusion criteria were the smaller age range groups and family paediatrician or general practitioner as source of prescription. ~~(Figure 1)~~.

The meta-analytic weighted average and 95% CIs of prescription prevalences were calculated using a random effect model to take into account of the heterogeneity of the various studies [16,17].

RESULTS

A total of 189 articles were retrieved from the literature databases, 86 from EMBASE,83 from Medline, and 20 from both. 176 were excluded mainly because they focused on one class or drug only (30%), evaluated the impact of an educational intervention (30%), or analyzed risk factors for asthma, from socioeconomic indicators to therapy exposure, immunization, etc (30%). Three further studies were excluded because they analysed data collected before 1998 [18-20]. Only ten articles met inclusion criteria (6%). ~~179 were excluded because specific to a single anti-asthmatic drug, or a single anti-asthmatic drug subclass, or they only analysed the quality of prescriptions or were done before 1998 and ten articles were suitable for analysis.~~ After

identification of two additional studies through a manual reference search (they were not retrieved using the database search because not indexed with “anti-asthmatic agents” or “asthma” as a keyword), twelve pharmaco-epidemiological studies [9,10,21-30] met the inclusion criteria (Figure 1). ~~(see Table I)~~ The studies were carried out from 1998 to 2006 in six countries: Italy and The Netherlands (three studies each), Denmark and Norway (two studies each), Canada and US (one each) (Table 1). There were substantial differences between studies with regard to sample size (from a minimum of 6,417 to a maximum of 4,259,103 subjects), source of prescription data, and age classes considered. The data sources were mainly regional/multiregional/national prescription databases taking part in periodical health care monitoring systems (six articles), followed by health insurance databases or pharmacy dispensing databases (two articles each) and family paediatricians or general practitioners (two articles). Regarding age, ten involved both preschool and school-aged children; one 15-year-olds only and one the 6-14 age range group. Seven of the surveys evaluated only anti-asthmatics, and five covered all drug categories. Prescribed anti-asthmatic prevalence ranged from 5 to 26% without any relationship with the observational period or with drug class analyzed. ~~Only in the US study was stated the NIH funding.~~**~~Inter-country differences in prescription prevalence~~**

Quantitative differences in anti-asthmatic use emerged among the six countries considered (Table 1). In general, two prescribing patterns could be identified, with some countries having high anti-asthmatic prescribing levels (Italy,US and Canada) and others low levels (Norway and The Netherlands). Eight out of twelve studies indicated that boys received more anti-asthmatic drug prescriptions than girls and two articles [10,26] reported that, after age 15, an opposite pattern appeared, with girls receiving more prescriptions than boys. The prescription prevalence by age, reported by the majority of the studies, decreased from one-year-old infants to

adolescence. One article reported an increase from 0-2 year old to six year old children and then a decrease from six to adolescence [28], and two report the highest prevalence of prescriptions between ages 1 and 4 [21,23]

~~**Inter-country differences between prescription prevalence (PP) and asthma prevalence (AP) gap**~~

~~Comparison of PP prescription prevalence data with published data on AP asthma prevalence(Table 1)is reported in The comparison indicated that in Denmark, The Netherlands, Norway and in Canada AP asthma prevalence and PP prescription prevalence are comparable. In the US PP prescription prevalence appears to be less than AP asthma prevalence, whereas in Italy PP prescription prevalence was approximately twice that of AP asthma prevalence.~~

Inter-country differences in anti-asthmatic treatment choices

Data concerning the distribution of prescriptions by anti-asthmatic classes were reported for all countries. In Italy ICS are the most prescribed class and covered 60% of anti-asthmatic prescriptions and 86% of the subjects treated, while SABA were the most prescribed in the other countries, covering from 58% (USA) to 93% (Denmark) of anti-asthmatic users. The percentage of ICS users varied from 25% (USA) to 67% (the Netherlands). Differences were found in the ICS/SABA ratio. These ranged from 0.35 in Denmark [25] to 0.84 in The Netherlands [30]. Three countries reported the most frequently prescribed anti-asthmatic drugs as follows: beclomethasone and salbutamol in Italy [21,22], salbutamol and fluticasone in Canada [26], salbutamol and montelukast in the US [27]. In Italy, beclomethasone and salbutamol are both prescribed mainly as nebulised suspension [21]. Table 2 compares Italy, US and Canada,

showing the seven most frequently prescribed anti-asthmatics and showing that montelukast use makes an important inter-country distinction. Four articles compared monotherapy and polytherapy. The proportions of patients receiving more than one class of anti-asthmatic drugs were 52% for Canada [26], 44% for Italy [20], 39% for The Netherlands [28] and 26% for Denmark [25]. Only two countries reported distribution, analyzing the number of packages of anti-asthmatic drugs prescribed during the period studied: only 29% of Italian [21] and 26% of Dutch [30] subjects received three or more packages. Four articles [21,26,27,30] reported ~~close~~ similar percentages for oral steroids, from 4.0% to 4.7%. In only two articles the prevalence of anti-asthmatic prescription was checked against the diagnosis of asthma [28,30], and in both it was double.

Intra-country differences in prescription prevalence

The prevalence of anti-asthmatic prescriptions varies dramatically in Italy, ranging from 12 to 26% ~~between 12 and 26%~~ [21, 23], and similarly in Denmark, ranging from 7.7 to 13.9% ~~between 7.7 and 13.9%~~ [25,28].

Meta-analysis

The meta-analysis was performed on eight of the twelve articles (Figure ~~1~~ 2). Four studies were excluded because age group and source of data were not comparable with the majority of the studies. Basically, the two studies regarding 15-year-olds only and the 6-14 age group [24,28] as well as the two articles whose sources were family paediatricians or general practitioners [22, 30] were excluded from the meta-analysis. The overall prevalence was 13.3% (95% CI 9.4-17.1%), with Italian children the most exposed to anti-asthma therapy (19.0% CI 5.3-32.7%) and Dutch

children the least (6.2% CI 3.8-8.5%). However, after adding the four excluded articles the overall prevalence did not change significantly.

Inter-country differences between prescription prevalence ~~(PP)~~ and asthma prevalence ~~(AP)~~ gap

Comparison of ~~PP~~ prescription prevalence data with published data on ~~AP~~ asthma prevalence (Figure 2)~~is reported in. The comparison~~ indicated that in Denmark, The Netherlands, Norway and Canada ~~AP~~ asthma prevalence and ~~PP~~ prescription prevalence are comparable. In the US ~~PP~~ prescription prevalence appears to be less than ~~AP~~ asthma prevalence, whereas in Italy ~~PP~~ prescription prevalence was approximately twice that of ~~AP~~ asthma prevalence.

DISCUSSION

This is the first analysis specifically comparing published drug utilisation studies on anti-asthmatic prescriptions in the outside-hospital setting in children. A limit, as underlined in a recent review on drug utilization studies [31], is the wide variety of studies, with differences in study type (design and method), populations (in terms of sample size and age groups), and data collected, making comparative evaluation difficult or at best incomplete. Another limit is that data were available for comparison between only six countries, most of which were European. This is very important since countries with the highest asthma prevalence (≥ 10%), as reported by ISAAC [1,32], are theUS, Canada, Australia, New Zealand, South America, England and Scotland, and studies about anti-asthma drug utilization in children from these countries are limited or lacking. However, the main limit is the lack of asthma diagnosis, which would validate the appropriateness of anti-asthmatic utilization. In order to overcome the lack of these

data, we attempted to use published asthma prevalence data for comparison with drug prescriptions, but the sources are different (ISAAC reported data from only three out of the six countries analyzed) and this represents another limit.

Inter-country quantitative differences

Large differences in the anti-asthmatic prescription prevalence were found between countries. The highest was in Italy and Canada and the lowest in The Netherlands. If for Canada the high ranking can be justified by a high prevalence of asthma, the same is not true for Italy, where the prescribing pattern for antibiotics shows a similar profile [31,33]. This suggests that the differences in drug prescription rates may be attributable to different prescribing attitudes and national drug regulatory policies more than differences in the prevalence of asthma. Moreover it is likely that anti-asthmatics and antibiotics are both used in URTI, even if this is not the first-line approach suggested by guidelines [3-5].

~~**Incongruence between** PP prescription prevalence **and** AP asthma prevalence~~

~~First of all, a precise comparison between prescription prevalence and asthma prevalence is difficult because of the lack of a single source of worldwide asthma prevalence, gathered in homogenous manner.~~

~~In Table I Figure 2 the comparison between PP prescription prevalence and AP asthma prevalence indicated that in Denmark, The Netherlands, Norway and in Canada AP asthma prevalence and PP prescription prevalence are comparable. In the US PP prescription prevalence appears to be less than AP asthma prevalence and in Italy PP prescription prevalence is two times the value of AP asthma prevalence. This comparison is only indicative, because the reported AP asthma prevalences are measured in >6 year old group of subjects, time in which asthma medication need decreases. Moreover, AP asthma prevalences were estimated, by ISAAC and the~~

~~other studies [1, 15-17] by questionnaire and data may overestimated the burden of disease. In the case of US the subjects might be undertreated and in the case of Italy overtreated, as suggested by the authors [22, 26]. However, even in the countries where AP asthma prevalence and PP prescription prevalence are similar, the suggestion that anti-asthmatics are prescribed somewhere for diseases other than asthma too is still valid because in two studies [20,25] measured that half the subjects received only one packages of anti-asthma drugs per year, suggestive of non-asthmatic illness. Although there were two articles reporting diagnosis of asthma [27,29] from countries (Denmark and The Netherlands) where the prevalence of asthma is low, the gap between PP prescription prevalence and burden of disease was large, with the number of cases diagnosed only half the number of cases treated. Since asthma is more reliably diagnosed in children from the age of six, the discrepancy between prescriptions and actual disease does not necessarily suggest inadequacies of prescription, but points to anti-asthma drug use as therapy in the youngest patients, when asthma is suspected but not diagnosed yet. This was not confirmed by the Dutch report [29] which validated PP prescription prevalence by asthma diagnosis: in two age ranges (<6 and ≥6) the gap between AP asthma prevalence (diagnosed) and PP prescription prevalence in the youngest did not differ from the older children.~~

Inter-country qualitative differences

Together with anti-asthmatic prescription prevalences, some differences also emerged in the quality of the drugs prescribed, though not all studies reported information on anti-asthmatic distribution by class and/or drug. Asthma, by definition, involves acute attacks of wheezing, which guidelines recommend treating with SABA and preventing with ICS, so the percentage of patients receiving only one class of anti-asthma drugs should be minimal. The fact that the prevalence of prescription was validated by a diagnosis of asthma in only two studies

was [28,30], and only four studies reported the percentage of children receiving more than one anti-asthma drug class made it difficult to evaluate adherence to guidelines. However, the percentages of patients receiving polytherapy (more than one class of anti-asthmatics) were 52% for Canada [26], 44% for Italy [21], 39% for The Netherlands [28] and 26% for Denmark [25], suggesting either lack of illness or, possibly, underuse of ICS for prevention/maintenance therapy, as underlined in the US study [27]. This is also partly highlighted by the differences in the ICS/SABA ratios, which range from 0.35 in Denmark [25] to 0.84 in The Netherlands [30]. While in the US the low ICS prescription prevalence (low ICS/SABA) might be explained by the higher rate of montelukast prescription [27], in other countries the low ICS/SABA ratio might suggest that, besides the cases in which SABA are used as therapy in the youngest patients, who are not yet easy to diagnose, the prescribing attitude is not only quantitatively but also qualitatively different.

Only in the US study montelukast was prescribed more than ICS. A detailed comparison of the most prescribed anti-asthma drugs was possible only between the US, Canada and Italy (see Table 2), and even then the observation periods are different. Montelukast entered the market in 1998 and since data collection for the Canadian study was done shortly thereafter, the difference found may not reflect an actual difference, but may be due to the fact that for new drugs prescribing patterns tend to take a year or so to penetrate the market, especially in an area such as asthma where there are many existing, effective agents already approved.

Intra-country differences in prescription prevalence

The prevalence of anti-asthmatic prescriptions varies dramatically in Italy, ranging from 12 to 26% [21, 23] and similarly in Denmark ranging from 7.7 to 13.9% [25,28]. The reason for this diversity in the two Italian articles might be the different geographic setting: a single Local

Health Unit versus the multiregional setting. The different prevalences in the two Danish articles might be due to the age group difference: the lower prescription prevalence study regarded 6-14 year olds, an age group in which asthma is theoretically better diagnosed and treated; in the higher prevalence study preschoolers were included, an age in which occasional wheezers are still in high percentage.

Incongruence between ~~PP~~ prescription prevalence and ~~AP~~ asthma prevalence

First of all, a precise comparison between prescription prevalence and asthma prevalence is difficult because of the lack of a single source of worldwide asthma prevalence, gathered in a homogenous manner.

In ~~Table I~~ Figure 2 the comparison between ~~PP~~ prescription prevalence and ~~AP~~ asthma prevalence indicated that in Denmark, The Netherlands, Norway and in Canada asthma prevalence and prescription prevalence are comparable. In the US, ~~PP~~ prescription prevalence appears to be less than ~~AP~~ asthma prevalence and in Italy ~~PP~~ prescription prevalence is twice the value of ~~AP~~ asthma prevalence. This comparison is only indicative, because the reported ~~AP~~ asthma prevalences are measured in >6 year old group of subjects, a time in which the need for asthma medication decreases. Moreover, ~~AP~~ asthma prevalences were estimated, by ISAAC and the other studies [1, 13-15], by questionnaire and data may overestimate the burden of disease. In the case of US the subjects might be undertreated and in the case of Italy overtreated, as suggested by the authors [23, 27]. However, even in the countries in which asthma and prescription prevalence are similar, the possibility that anti-asthmatics are prescribed for diseases other than asthma as well is still valid because two studies [21,26] found that half the subjects received only one package of anti-asthma drugs per year, suggestive of non-asthmatic illness.

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In this analysis two inadequacies in asthma treatment are suggested, the first regarding the sub-optimal prescription of ICS to asthma patients for prevention or maintenance, and the second regarding the prescription of asthma medications to non-asthmatic subjects. For confirmation, the availability of more homogenous studies is needed. Knowledge of the anti-asthmatic prescribing patterns of primary care physicians in the paediatric population is extremely important, since children are a prime target for inadequate prescription. The guidelines alone are not enough to ensure correct use of anti-asthmatics, since physician adherence and compliance to guidelines is not obvious or common. Another widely debated topic related to compliance with asthma treatments is the education of asthmatic children and their carers. A recent meta-analysis [34] of US studies confirms a reduction in hospitalization when children are educated about their disease,

including ~~to practice sport~~ sports practice, under preventive therapy, even if a diagnosis of asthma has been made.

In conclusion, this is the first analysis specifically comparing drug utilisation studies on anti-asthmatic prescriptions in children outside the hospital setting. Despite the availability of data on the patterns of medication use in only six countries and the heterogeneity of the included studies, concordance with a divergence from community-based prevalences of asthma and symptoms might indicate different health beliefs among doctors and patients. Multinational collaborative pharmacoepidemiological studies aimed at collecting valid and comparable data are required, especially in those areas indicated by ISAAC as having a very high prevalence of asthma. These studies would be validated by diagnosis and outcome measures (e.g. number of emergency visits to the physician's office or emergency centers, or hospitalizations) and quality of life measures(e.g. number of exacerbations and days of school missed per year, presence of daily or nightly cough or wheeze, presence of cough or wheeze with exercise).

Competing interests
None declared.

Legends

Figure 1. Flowchart of the bibliographic search

Table 1. Anti-asthmatic prescriptions in children and adolescents (≤ 19 years)

Table 2. The first seven anti-asthmatic drugs prescribed to Italian, American and Canadian children and adolescents ~~(% of all prescribed anti-asthmatic drugs~~) (% of treated subjects)

Figure ~~1.~~ 2. Prevalence (%) of anti-asthmatic prescriptions in children and adolescents

Abbreviations

URTI: Upper respiratory tract infection
ICS: Inhaled corticosteroid
SABA: Short-acting β-agonist
LABA: Long-acting β-agonist
LTRA: Leukotriene receptor antagonist
~~MDI/PDI: Metered-dose inhaler/powder dose inhaler~~
~~PP: Prescription Prevalence~~
~~AP: Asthma Prevalence~~

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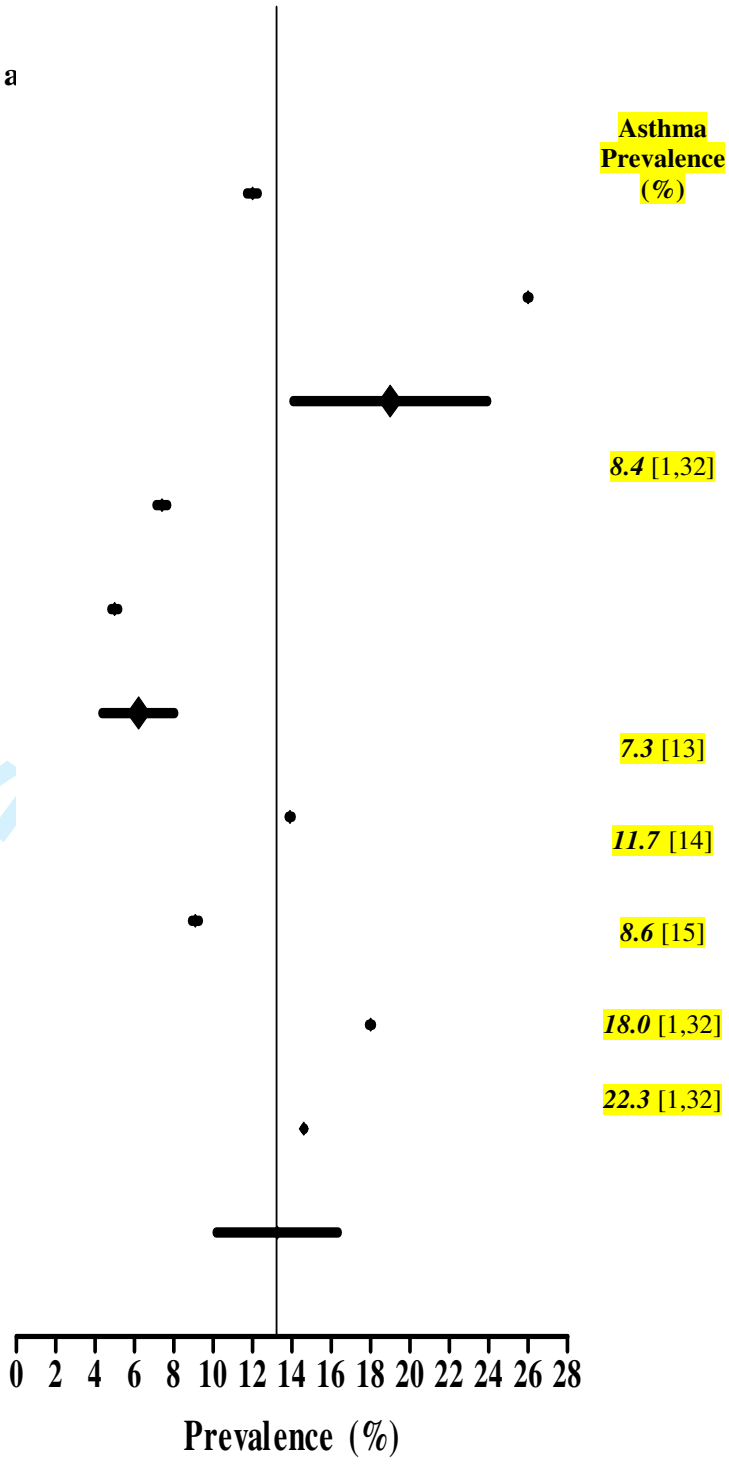
Table 1. Anti-asthmatic prescriptions in children and adolescents (≤ 19 years)

~~Reference~~	Reference	Period analyzed	Country	Population (n)	Age (years)	Source of prescription data[a]	~~Classes of prescription drugs analyzed~~	Anti-asthmatic Prescription Prevalence ~~(PP)~~ (%)	~~Asthma Prevalence (AP) %~~
~~Cazzato (21)~~	[22][b]	1998	Italy	6,417	≤12	Family paediatricians	~~all~~	20.7	
~~Bianchi (20)~~	[21]	2003	Italy	55,242	≤17	Regional prescription DB	~~anti-asthmatic~~	12.0	~~8.4*~~
~~Clavenna (22)~~	[23][b]	2006	Italy	923,353	≤14	Multiregional prescription DB	~~all~~	26.0	
~~Schirm (28)~~	[29][b]	1998	The Netherlands	25,020	≤16	Pharmacy dispensing DB	~~all~~	7.4	
~~Zuidgeest (29)~~	[30]	2001	The Netherlands	74,580	≤17	General practitioners	~~anti-asthmatic~~	7.5	~~7.3 (15)~~
~~De Vries (11)~~	[9]	2002	The Netherlands	72,240	≤14	Pharmacy dispensing DB	~~anti-asthmatic~~	5.0	
~~Ingvardsen (24)~~	[25]	1998	Denmark	139,727	≤15	National prescription DB	~~anti-asthmatic~~	13.9	
~~Moth (27)~~	[28]	2002	Denmark	125,907	6-14	Regional prescription DB	~~anti-asthmatic~~	7.7	~~11.7 (16)~~
~~Furu (23)~~	[24][b]	2000-2002	Norway	11,708	15	National prescription DB	~~all~~	6.5	
~~Furu (12)~~	[10]	2004	Norway	1,192,841	≤19	National prescription DB	~~anti-asthmatic~~	9.1	~~8.6 (17)~~
~~Khaled (25)~~	[26][b]	1999	Canada	1,031,731	≤17	Insurance plans DB	~~all~~	18.0	~~18*~~
~~Korelitz (26)~~	[27]	2004-2005	USA	4,259,103	≤17	Insurance plans DB	~~anti-asthmatic~~	14.6	~~22.3*~~

~~*ISAAC(1,31)~~ [a] DB database [b] all drug categories evaluated

Figure ~~1~~ 2. Prevalence (%) of anti-asthmatic prescriptions in children and a

Studies	Anti-asthmatics Prevalence (%) (95% CI)	~~Period analyzed~~	~~Population (n)~~	~~Anti-asthmatic Prevalence (%)~~	Asthma Prevalence (%)
[21]	12.0 (11.7 to 12.3)	~~2003~~	~~55,242~~	~~12.0~~	
[23]	26.0 (25.7 to 25.9)	~~2006~~	~~923,353~~	~~26.0~~	
Italy total	***19.0 (5.3 to 32.7)***		***~~978,595~~***	***~~19.0~~***	***8.4*** [1,32]
[29]	7.4 (7.1 to 7.7)	~~1998~~	~~25,020~~	~~7.4~~	
[9]	5.0 (4.8 to 5.2)	~~2002~~	~~72,240~~	~~5.0~~	***7.3*** [13]
The Netherlands total	***6.2 (3.8 to 8.5)***		***~~97,260~~***	***~~6.2~~***	***11.7*** [14]
					8.6 [15]
Denmark [25]	***13.9 (13.7 to 14.1)***	~~1998~~	~~139,727~~	~~13.9~~	
					18.0 [1,32]
Norway [10]	***9.1 (9.0 to 9.2)***	~~2004~~	~~1,192,841~~	~~9.1~~	
					22.3 [1,32]
Canada [26]	***18.0 (17.9 to 18.1)***	~~1999~~	~~1,031,731~~	18.0	



US [27]	***14.6 (14.6 to 14.6)***	~~2004-2005~~	~~4,259,103~~	14.6	14.6-14.6
			7,699,257	***13.3***	***9.4-17.1***
overall	***13.3(9.4-17.1)***				

Table II. The first seven anti-asthmatic drugs prescribed to Italian, American and Canadian children and adolescents (% of treated subjects) ~~(% of all prescribed anti-asthmatic drugs)~~

Canada 1999#	Italy 2003#	USA 2005#
Salbutamol (71)	Beclomethasone (57)	Salbutamol (49)
Fluticasone (45)	Salbutamol (33)	Montelukast (22)
Budesonide (14)	Flunisolide (17)	Budesonide (10)
Beclomethasone (14)	Budesonide (15)	Levalbuterol (10)
Terbutaline (8)	Fluticasone (12)	Fluticasone+salmeterol (9)
Montelukast (5)	Salbutamol in combination(5)	Fluticasone (7)
Sodium cromoglycate(2)	Montelukast (3)	Pirbuterol(1)

The sum exceed ~~Total is more than~~ 100 because ~~of polytherapy~~ some children were prescribed more than one drug.
#observation period