



Respiratory drugs and macrolides prevent asthma exacerbations: A real-world investigation



Andrea Arfè^a, Francesco Blasi^b, Luca Merlino^c, Giovanni Corrao^{a,*}

^a Laboratory of Healthcare Research and Pharmacoepidemiology, Department of Statistics and Quantitative Methods, University of Milano-Bicocca, Milan, Italy

^b Department of Pathophysiology and Transplantation, University of Milano, IRCCS Fondazione Cà Granda Ospedale Maggiore Policlinico, Milan, Italy

^c Operative Unit of Territorial Health Services, Region Lombardia, Milan, Italy

ARTICLE INFO

Article history:

Received 8 November 2015

Received in revised form

26 April 2016

Accepted 3 May 2016

Available online 4 May 2016

Keywords:

Asthma

Beta-agonists

Corticosteroids

Antibiotics

Macrolides

Exacerbations

Effectiveness

Emergency visits

ABSTRACT

Objective: We investigated the real-world effectiveness of several drugs (including short- and long-acting beta-agonists [SABAs and LABAs], inhaled corticosteroids [ICS], and antibiotics) in preventing severe asthma exacerbations by carrying-out a large observational study based on the healthcare utilization databases of the Italian Lombardy Region.

Methods: We identified all patients aged 6–40 years who performed an Emergency Department visit for asthma during 2010–2012 as cases. To address bias due to unmeasured confounders, we implemented a case-crossover (CC) design. Addressing other specific sources of systematic errors (e.g. protopathic bias) was of particular concern in this study.

Results: A total of 7300 cases were included in the study. The CC odds ratios (95% confidence intervals) for current vs. past use were 0.81 (0.71, 0.92) for SABAs, 0.83 (0.72, 0.96) for ICS, 0.78 (0.66, 0.91) for LABA/ICS fixed combinations, 0.79 (0.65, 0.97) for other respiratory drugs, and 0.79 (0.69, 0.92) for macrolides antibiotics. Sensitivity analyses showed that our results were robust with respect to several sources of bias.

Conclusions: Our study provides evidence from the real-world clinical practice on the effectiveness of several respiratory drugs and macrolides in reducing the risk of severe asthma exacerbations.

© 2016 Published by Elsevier Ltd.

1. Introduction

Asthma is a major public health issue worldwide due to its high and increasing prevalence and associated burden [1–4]. Asthma patients are at risk of experiencing exacerbation episodes, i.e. events characterized by a progressive increase in symptoms and decrease in lung functionality that require a change in treatment [1]. Severe exacerbations, which may occur even in patients with mild or well-controlled asthma [5,6], are potentially life-threatening and require emergency medical care [1]. Given their high impact on affected patients, minimizing exacerbations represents one of the main objectives of asthma drug therapy [1].

Several pharmacological agents are commonly used in the

current clinical practice for the care of asthmatic patients. These include, among others, inhaled corticosteroids (ICS) and (possibly improperly) antibiotics [1,7,8]. The use of these drugs to prevent exacerbations is nevertheless supported by varying degrees of evidence. For example, the efficacy of ICS in achieving symptoms control, avoiding exacerbations, and preventing asthma-related hospitalizations has been well established in several randomized clinical trials (RCTs) [6,9,10]. On the other hand, the role of antibiotics in preventing asthma exacerbations is somewhat controversial [11] and limited data is available from clinical trials [8,11]. Therefore, given their widespread use [1,7,12], it is important to assess the effectiveness of all these drugs in reducing the risk of severe exacerbations in the real-world clinical practice.

To address these issues, we conducted a population-based observational study based on the healthcare utilization (HCU) databases of Lombardy, an Italian Region of about 10 million residents. The objective of this study was to assess the association between use of ICS, bronchodilators, or antibiotics and the risk of an Emergency Department (ED) visit for asthma. Addressing specific

* Corresponding author. Unit of Biostatistics, Epidemiology and Public Health, Department of Statistics and Quantitative Methods, University of Milano-Bicocca, Via Bicocca degli Arcimboldi, 8, Edificio U7, 20126 Milano, Italy.

E-mail address: giovanni.corrao@unimib.it (G. Corrao).

sources of systematic errors was of particular concern in this study.

2. Methods

2.1. Data source

Data for this study was extracted from the HCU databases of Lombardy. In Italy, the entire population benefits from healthcare assistance provided by the National Health Service (NHS), which in Lombardy has been associated since 1997 with an automated system of databases. These include: 1) an archive of NHS beneficiaries (practically the whole resident population), reporting demographic and administrative data; 2) an archive of hospital discharges, reporting all diagnoses released from public or private hospitals; 3) an archive of Emergency Department (ED) visits, reporting all diagnoses released from regional hospitals' EDs; 4) an archive of outpatient drug prescriptions, reporting all dispensations of NHS-reimbursable drugs; and 5) an archive of beneficiaries of co-payment exemptions, reporting data on all individuals benefitting of an exemption because they were diagnosed a chronic disease. For each patient, we linked these databases via a single anonymous identification code preserving individuals' privacy [13].

2.2. Study design

Since our aim was to study the effects of transient exposures (e.g. availability of certain drugs) as a trigger of acute outcomes (e.g. ED visits), the case-crossover design [14] was implemented in this study. Accordingly, only individuals experiencing the outcome under study (cases) were included. For each case, exposure status during a period prior to the date of outcome onset was compared with exposure status during a more remote period to estimate the exposure-outcome association. Hence, since comparisons are made within each case, potential confounding due to fixed individual characteristics (e.g. gender) is entirely circumvented [14].

In more detail, all individuals aged from 6 to 40 years who were released from an ED visit with a primary diagnosis of asthma between April 1, 2010 until December 31, 2012 were considered as cases. The date of the first identified ED visit was defined the *outcome onset date* (for each patient, ED visits subsequent to the first were not considered). To make the study more relevant to its aim, the following two categories of cases were excluded: 1) cases who did not have at least 2 years of continuous observation prior to the outcome onset date (in order to ensure enough data availability to perform the analyses); 2) cases who experienced a hospitalization for respiratory diseases or cancer in the two years prior to the outcome onset date (in order to exclude cases affected by severe respiratory conditions or neoplasms). All remaining cases were included in the subsequent analyses.

For each included case, all dispensations of drugs used for the management of asthma and antibiotics received during the 2 years prior to the outcome onset date were identified. Drugs used for asthma managements included: inhaled corticosteroids, short-acting beta-agonists, short-acting muscarinic antagonists, long-acting beta-agonists, alone or in fixed combination with ICS, long-acting muscarinic antagonists, or other respiratory drugs (e.g. antileukotrienes).

In the case-crossover analysis, we evaluated whether each case received at least one dispensation of one of the considered drugs during two 90-day periods: one in the 0–90 days (current period) and one in the 180–270 days (referent period) before the outcome onset date. If the frequency of dispensations is stable over time (i.e. if the frequency of drug use in the population that generated the cases is the same in both the referent and current periods), then the odds ratios (ORs) measuring the association between receiving a

dispensation of a specific drug for asthma management in the current period and the risk of an ED visit for asthma, in comparison with receiving no dispensations of the considered drug in the current period, can be estimated by contrasting cases' exposure status in the current vs. referent windows [14]. In practice, ORs and corresponding 95% confidence intervals (CIs) were estimated by means of a conditional logistic regression model [14,15].

In this analysis, we took further steps to address the potential for protopathic bias, a systematic error which occurs when the outcome is associated with an exposure that may result from early signs or symptoms of the outcome under study [16]. In our application, an increased use of drugs for asthma management (exposure) before an ED visit for asthma (outcome) can be expected as a consequence of a worsening of asthma symptoms. Hence, a paradoxical positive exposure-outcome association might be observed. To address this issue, lag-times of 0, 30, 60, ..., 210 days were introduced between the outcome onset date and the start of the current period. For each considered lag-time, the current and referent periods were both moved back in time with respect to the ED visit by an amount of days equal to the lag-time. For each lag-time, we obtained the case-crossover OR measuring the association between use of any drug for chronic respiratory diseases or antibiotics and risk of an ED visit for asthma. In each case, the best lag-time was estimated as the point where a specific regression function for these delayed case-crossover ORs showed a discontinuity [17].

2.3. Additional methodological issues

Two additional analyses were performed to address specific methodological issues. First, we recognized that although case-crossover estimates are not affected by confounding factors that do not change in time, they may be still subjected to bias from population-level temporal trends in exposure (e.g. seasonality in drug prescriptions) [14,18]. Thus, we additionally implemented the case-case-time-control design, an extension of the case-crossover design, to address this possibility [18]. Accordingly, each case in the previous case-crossover analysis (index case) was matched to a control group made up of "future cases". An estimate of the expected temporal trend in exposure was then computed by considering the exposure status of each future case during the current and referent time window of the corresponding index case. This estimate was then used to adjust the case-crossover ORs for the impact of temporal trends in exposure among index cases [18].

In more detail, a random sample of up to 10 future cases was selected for each index case in the case-crossover analysis. Each future case was selected among those who visited the ED after the outcome onset date of the corresponding index case, matching for age (± 1 years) and gender. For each future case, current and referent periods were defined as previously described with respect to the outcome onset date of the corresponding index case. The ORs obtained from a case-crossover analysis carried out among future cases were then used as estimates of the expected temporal trends in exposure. The ratio between the case-crossover ORs for index and future cases then provided estimates of the exposure-outcome ORs adjusted for the impact of time-varying exposure trends. In practice, this analysis was implemented through a conditional logistic regression model [15,18].

Second, as the results of the case-crossover and case-case-time control analyses are dependent on the chosen widths of the current and referent exposure windows, we performed a sensitivity analysis to evaluate the robustness of our results in this respect. Specifically, we varied the width of the exposure windows by plus or minus 30 days, in each case estimating the corresponding ORs for use of any respiratory drug or antibiotics.

The SAS software (v9.3; SAS Institute, Cary, North Carolina, USA) was used for analyses. All tested hypotheses were two-tailed and *p*-values < 0.05 were considered statistically significant. All considered ATC codes (for drug dispensations) and ICD-9 codes (for hospital diagnoses) are reported in the Web-Only [Appendix 1](#).

3. Results

3.1. Patients

A total of 8391 patients who required ED care for asthma during 2010–2012 were identified. Of these, 523 were excluded because they had less than 2 years of observation before the outcome onset date. An additional 568 were also excluded because they experienced at least one hospitalization for respiratory diseases or cancer in the 2 years preceding the outcome onset date. The remaining 7300 patients were retained as cases. About 22.4% of these individuals were women and their mean (SD) age at outcome onset was 22.4 (11.4).

Table 1 reports the distribution of use of the considered drugs among included cases in three time periods: (a) in the 2 years preceding to the outcome onset date; (b) in the 0–90 days prior to the outcome onset date (current period); (c) in the 180–270 days prior to the outcome onset date (referent period). About 81.6% of cases received at least one dispensation of respiratory drugs or antibiotics in the 2 years preceding the outcome onset date. In this period, the three most used drugs were beta-lactams antibiotics (53.7% of all cases), SABAs (41.1%), and ICS (36.3%). As expected, the frequency of use of the considered drugs was lower than when attention was restricted to the 90-days current and referent periods. The two respiratory drugs most used in the current period were SABAs (17.8%) and ICS (13.0%). Instead, the two antibiotics most used in the current period were beta-lactams (15.8%) and macrolides (10.5%), for a mean course of about 5 days. Paradoxically, use of respiratory drugs and antibiotics was higher in the current period than in the referent period.

3.2. Case-crossover analysis

Fig. 1 shows the trend of in the case-crossover ORs for the effect of receiving any drug for chronic respiratory diseases or antibiotics as a function of different increasing lag-times. In both cases, these trends had a change point at around 120 days, with lag-times of 90

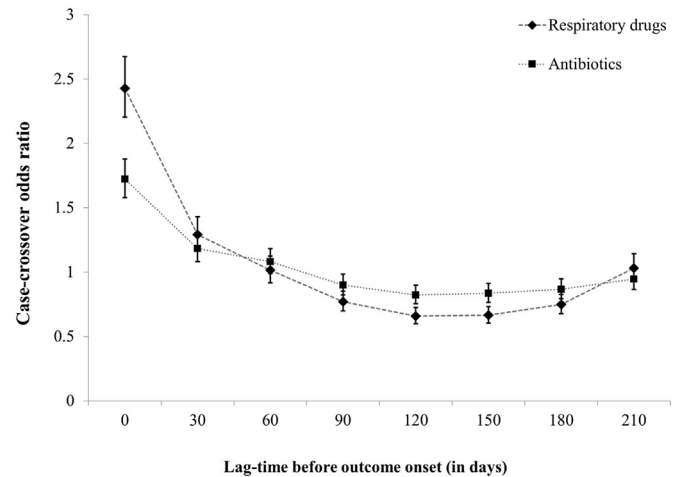


Fig. 1. Trend in case-crossover odds ratio for the association between use of any respiratory drug or antibiotics (exposures) and the risk of ED visits for asthma (outcome) according to increasing lag-time periods before the outcome onset date. **Footnote.** Odds ratios and 95% confidence intervals estimated by conditional logistic regression models contrasting within-case exposure status during current and referent time-windows.

and 150 days providing similar ORs. Hence, a lag-time of 120 days was considered in the subsequent case-crossover analyses.

Fig. 2 instead shows the ORs measuring the association between use of the considered drugs and the outcome obtained in the case-crossover analysis. Most of the considered respiratory drugs were found to be statistically significantly associated with a reduced risk of an ED visit for asthma. Specifically, statistically significant relative reductions in the risk of outcome onset ranging from 17% for ICS to 22% for LABA/ICS and of 21% for macrolides were observed among respiratory drugs and antibiotics, respectively. Additionally, there was some evidence that use of LABAs, LAMAs, beta-lactams, and fluoroquinolones (but not use other antibiotics) also reduced outcome risk, although results were not statistically significant.

3.3. Additional analyses

In addition to the case-crossover results, **Fig. 2** also shows the drug-outcome ORs obtained in the case-case-time-control analysis

Table 1

Distribution of the use of the considered drugs among included cases in three time periods: (a) in the 2 years preceding the outcome onset date (first ED visit for asthma in 2010–2012); (b) in the 0–90 days prior to the outcome onset date (current period); (c) in the 180–270 days prior to the outcome onset date (referent period).

Period	(a) 2 years prior to outcome onset	(b) 0–90 days prior to outcome onset (current period)	(b) 180–270 days prior to outcome onset (referent period)
Variable	N (%)	N (%)	N (%)
Use of drugs for chronic respiratory diseases:			
SABAs	2998 (41.1%)	1302 (17.8%)	693 (9.5%)
SAMAs	127 (1.7%)	43 (0.6%)	26 (0.4%)
LABAs	156 (2.1%)	65 (0.9%)	41 (0.6%)
LABA/ICS	1651 (22.6%)	667 (9.1%)	444 (6.1%)
LAMAs	67 (0.9%)	25 (0.3%)	7 (0.1%)
ICS	2649 (36.3%)	948 (13.0%)	571 (7.8%)
Other respiratory drugs	1133 (15.5%)	416 (5.7%)	317 (4.3%)
Any respiratory drug	4396 (60.2%)	2232 (30.6%)	1405 (19.3%)
Use of antibiotics:			
Beta-lactams	3922 (53.7%)	1151 (15.8%)	849 (11.6%)
Macrolides	2545 (34.9%)	764 (10.5%)	435 (6.0%)
Fluoroquinolones	961 (13.2%)	260 (3.6%)	150 (2.1%)
Other antibiotics	398 (5.5%)	66 (0.9%)	64 (0.9%)
Any antibiotics	5069 (69.4%)	1919 (26.3%)	1323 (18.1%)

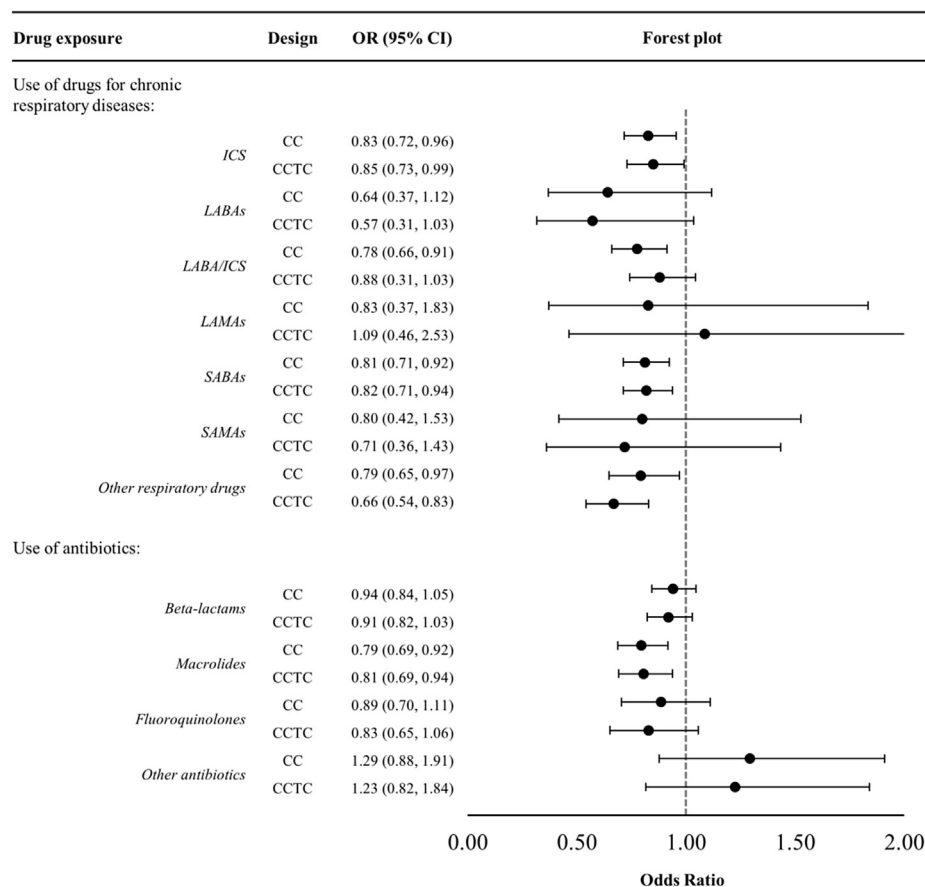


Fig. 2. Forest-plot of the odds ratios for the association between use of individual drugs or antibiotics (exposure) and risk of an ED visit for asthma (outcome) according to the case-crossover and case-case-time-control designs. **Footnote.** Odds ratios and 95% confidence intervals estimated by conditional logistic regression models contrasting within-case exposure status during current and referent time-windows. CC: case-crossover. CCTC: case-case-time-control. CI: confidence interval.

(using the same lag-time as in the case-crossover analysis). The results of this analysis are all compatible with those obtained with the case-crossover design, with a possible exception for LABA/ICS (case-crossover OR, 95% CI: 0.78, 0.66–0.91; case-case-time-

control OR, 95% CI: 0.88, 0.74–1.04).

Table 2 instead reports the ORs for use of respiratory drugs or antibiotics obtained in the case-crossover or case-case-time-control analyses when varying the width or distance of the exposure windows. In all cases, results did not substantially change from those obtained in the main analysis.

Table 2

Odds ratios (ORs) and 95% confidence intervals (CIs) for use of (A) respiratory drugs or (B) antibiotics obtained in the case-crossover (panel 1) or case-case-time-control analyses (panel 2) when the width of the current and referent exposure periods or the distance between the two was set to 60, 90 (main analysis), or 120 days.

Varied quantity	(A) Use of respiratory drugs OR (95% CI)	(B) Use of antibiotics OR (95% CI)
1) Case-crossover analysis		
Distance between the exposure periods:		
60	0.77 (0.70, 0.85)	0.91 (0.83, 0.99)
90 (main analysis)	0.66 (0.60, 0.73)	0.82 (0.75, 0.90)
120	0.64 (0.58, 0.70)	0.83 (0.76, 0.91)
Width of the exposure periods:		
60	0.73 (0.66, 0.81)	0.84 (0.76, 0.93)
90 (main analysis)	0.66 (0.60, 0.73)	0.82 (0.75, 0.90)
120	0.64 (0.59, 0.71)	0.85 (0.78, 0.92)
2) Case-case-time-control analysis		
Distance between the exposure periods:		
60	0.74 (0.66, 0.82)	0.85 (0.77, 0.93)
90 (main analysis)	0.68 (0.61, 0.75)	0.81 (0.73, 0.88)
120	0.65 (0.59, 0.72)	0.79 (0.72, 0.87)
Width of the exposure periods:		
60	0.76 (0.68, 0.85)	0.85 (0.77, 0.94)
90 (main analysis)	0.68 (0.61, 0.75)	0.81 (0.73, 0.88)
120	0.66 (0.60, 0.73)	0.82 (0.75, 0.89)

4. Discussion

The results of this retrospective case-only observational study of 7300 patients who required emergency care for asthma provide evidence that several respiratory drugs commonly used for asthma management and specific types of antibiotics reduce the risk of severe exacerbations in the real-world setting. In this study, for instance, ICS reduced the 120-days risk of severe asthma exacerbations by about 17%, SABAs by about 19%, LABA/ICS by about 22%, and macrolides by about 21%.

Current treatment guidelines provide clear recommendations on which drugs should be considered in the therapeutic approach for asthma control, for instance promoting the use of SABAs for quick symptoms relief and ICS (alone or in combination with LABAs) for long-term management [1]. Antibiotics have instead only secondary role, as they are recommended exclusively for patients with clear indications of microbial infections [1]. Such recommendations are based on available evidence from RCTs evaluating the efficacy these drugs in ameliorating asthma's symptoms and outcomes [1]. Nevertheless, evidence supporting the role of antibiotics in asthma is still evolving [11], while

respiratory drugs that demonstrated efficacy in the highly-controlled setting of a RCT may still perform differently in the real-world setting [19]. For this reason, it is important to evaluate the effectiveness of all these frequently-used drugs [1,7,12] in the current clinical practice [20]. Our study constitutes a step forward in this direction.

In particular, consistently with available evidence [1,21], our results highlight how SABAs and ICS are effective in reducing the risk of exacerbations. Our results also provide some evidence that LABA/ICS are effective in reducing the risk of severe asthma exacerbations too, as expected [1,22–24]. These results are comforting, since SABAs, ICS and LABA/ICS were the most frequently used respiratory drugs in our setting. In particular, these results show that guidelines' main recommendations for asthma therapy are well represented in the real-world clinical practice [1], at least in more severe asthma patients.

Interestingly, our results also support the notion that macrolide antibiotics reduce the risk of severe asthma exacerbations. Even though the main indication for antibiotics use was unknown in this study, our findings are compatible with several observational and clinical studies suggesting that macrolides are beneficial in asthma [11,25–29]. For instance, in a meta-analysis of 18 placebo-controlled RCTs which included 1306 asthmatic patients, long-term use of macrolides improved forced expiratory volume in 1 s, forced vital capacity, peak expiratory flow, and airway hyper-responsiveness [25]. Nevertheless, there are still several gaps in the available evidence [1,11,25–27], and in particular it is unclear whether the benefits of macrolides in asthma are due to their anti-inflammatory or anti-microbial effects [11,25,27]. Although this study provides evidence from the real-world clinical practice that macrolides may be beneficial in asthma, it is non-informative with respect to pharmacological mechanisms. More *in-vivo* and *in-vitro* studies are hence needed.

Other results of this study deserve to be mentioned. First, in contrast with other studies [22–24], we found little evidence that LABA/ICS provide a greater protection than ICS alone. The reasons behind this are not entirely clear, but it is possible that more severe patients receiving LABA/ICS (as recommended [1]) may benefit less from combined therapy than less severe patients do from ICS alone. Second, there was no evidence in our study that LAMAs reduce the risk of exacerbations. Although tiotropium, the only currently available LAMA, may be beneficial in asthma [30], too few cases treated with this drug were included in this study to assess its effectiveness with sufficient statistical power. Third, we found some evidence suggesting that fluoroquinolones may reduce the risk of asthma exacerbations. This possibility deserves more future attention, since fluoroquinolones have been shown to have anti-inflammatory effects in several *in vitro* and *in vivo* studies [31,32].

Our study had some limitations. First, since our study lacked randomized treatment assignment, the results may have been affected by uncontrolled fixed or time-varying confounding factors. In our study, for instance, we could not directly control for the specific asthmatic phenotype and severity level, concurrent COPD diagnosis, smoking history, or seasonality effects, which are clearly related to the risk of exacerbations and to drug use [1,33]. The case-crossover and case-case-time-control designs should have helped us in overcoming these issues. Specifically, the case-control design is unaffected by fixed individual-level confounders (e.g. smoking history, asthma phenotype, concurrent COPD) [14]. Instead, the case-case-time-control design adjusts for population level trends in the frequency of use of the considered drugs [18]. Nevertheless, the major limitation of these two designs is that they are both vulnerable to confounding due to within-person factors that may change over time. For instance, one such factor is the belief that a drug is ineffective. If a drug used in the referent period is thought to

have been ineffective, then this may not be used in the current period. As a consequence, because both the case-crossover and case-case-time-control ORs compare the frequency of exposure between the referent and current periods [14,18], the estimated associations may be dragged towards the null value.

Second, the results provided by the case-crossover and case-case-time-control designs depend on the chosen width and distance of the current and reference exposure windows. Nevertheless, in a sensitivity analysis, the findings obtained in the present study using these designs were found to be fairly robust to these choices.

Third, since asthma is a symptomatic disease, our results may have been affected by protopathic bias [16]. To address this issue, we adopted a lag-time before the current and referent exposure periods when assessing the use of the considered drugs [17]. The use of a lag-time, however, has the disadvantage of making the results dependent on its chosen value. Nevertheless, the consistency of the lag-times identified in this study from data on the use of either respiratory drugs or antibiotics lends credence to its chosen value. In addition, different lag-times provided comparable results, which thus should be fairly robust with respect to the chosen lag-time.

Fourth, in absence of a gold standard for case validation, we cannot be certain that only asthma exacerbation cases were included in this study on the basis of ED diagnoses. It is possible, for instance, that wheezing children, patients with an acute infectious bronchitis, patients with panic attacks or vocal cord dysfunction, or patients with COPD or asthma-COPD overlap syndrome may require ED care, where they could be incorrectly classified as asthmatic patients. Nevertheless, results did not change substantially when only cases more likely affected by asthma (i.e. cases who benefitted of co-payment exemptions for asthma) were considered (results shown in Web-Only Appendix 2). In addition, a good agreement was observed between ED and hospital asthma diagnoses (results shown in Web-Only Appendix 2). These findings suggest that potential errors in case ascertainment should have had only a limited impact on our results.

Fifth, no information on the specific asthmatic phenotype (e.g. allergic asthma, bronchial hyper-reactive asthma, etc.) of the included cases was available in this study. More studies are therefore needed to assess the phenotype-specific effectiveness of the considered respiratory drugs antibiotics in reducing the risk of exacerbations.

Sixth and last, because in our study use of specific drugs was assessed from data on drug dispensations, the validity of our findings is based on the assumption that dispensed drugs are actually used by patients. In the real-world, however, some patients may not take the drugs they are dispensed, possibly dragging the estimated associations toward the null [34]. Hence, our results may understate the real effectiveness of the considered drugs.

In conclusion, our results provide evidence from the real-world clinical practice on the effectiveness of different drugs for chronic respiratory diseases and antibiotics in reducing the risk of severe asthma exacerbations among young patients. In particular, our results underscore the importance of SABAs, ICS, and LABA/ICS for asthma control, in agreement with current guidelines recommendations. These are largely based on evidence from RCTs, whose highly-controlled setting may be far from the real-world conditions in which drugs are actually used. Thus, our results from the actual clinical practice provide an important complement to evidence from RCTs. Additionally, our results suggest that macrolides antibiotics may have a role in avoiding asthma exacerbations, although more data on their effectiveness, benefits, and drawbacks are needed.

Conflicts of interest

This work was supported by funding from Novartis. GC collaborated with the advisory boards of Novartis and Roche and participated in projects funded by GSK. FB has received in the last three years speaker or consultant honoraria or research funding from: Almirall, AstraZeneca, Bayer, Boehringer Ingelheim, Chiesi Farmaceutici, GSK, Lab. Guidotti, Malesci, Menarini, Mundifarma, Novartis, Teva, Valeas, Zambon. For all other authors, there have been no involvements that might raise the question of bias in the reported work or in the conclusions, implications, or opinions stated.

Acknowledgments

The authors wish to thank Elena Peruzzi and Laura Rigoni for their support in developing this study.

Appendix A. Supplementary data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.rmed.2016.05.004>.

References

- [1] Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention 2015. Available from: www.ginasthma.org.
- [2] K. Bahadori, M.M. Doyle-Waters, C. Marra, L. Lynd, A. Alasaly, J. Swinton, et al., Economic burden of asthma: a systematic review, *BMC Pulm. Med.* 9 (2009) e24.
- [3] R. de Marco, V. Cappa, S. Accordini, M. Rava, L. Antonicalli, O. Bortolami, et al., GEIRD Study Group. Trends in the prevalence of asthma and allergic rhinitis in Italy between 1991 and 2010, *Eur. Respir. J.* 39 (2012) 883–892.
- [4] S. Accordini, A. Corsico, I. Cerveri, D. Gislason, A. Gulsvik, C. Janson, et al., Therapy and health economics working group of the European Community Respiratory Health Survey II. The socio-economic burden of asthma is substantial in Europe, *Allergy* 63 (2008) 116–124.
- [5] H. Reddel, S. Ware, G. Marks, C. Salome, C. Jenkins, A. Woolcock, Differences between asthma exacerbations and poor asthma control [erratum in *Lancet* 1999; 353:758], *Lancet* 353 (1999) 364–369.
- [6] R.A. Pauwels, S. Pedersen, W.W. Busse, W.C. Tan, Y.Z. Chen, S.V. Ohlsson, A. Ullman, C.J. Lamm, P.M. O'Byrne, START Investigators Group. Early intervention with budesonide in mild persistent asthma: a randomised, double-blind trial, *Lancet* 361 (2003) 1071–1076.
- [7] W. Long, L. Li, G. Huang, X. Zhang, Y. Zhang, J. Tang, Y. Zhang, G. Lu, Procalcitonin guidance for reduction of antibiotic use in patients hospitalized with severe acute exacerbations of asthma: a randomized controlled study with 12-month follow-up, *Crit. Care* 18 (2014) 471.
- [8] V. Graham, T.J. Lasserson, B.H. Rowe, Antibiotics for acute asthma, *Cochrane Database Syst. Rev.* (3) (2001). CD002741.
- [9] P.M. O'Byrne, P.J. Barnes, R. Rodriguez-Roisin, E. Runnerstrom, T. Sandstrom, K. Svensson, A. Tattersfield, Low dose inhaled budesonide and formoterol in mild persistent asthma: the OPTIMA randomized trial, *Am. J. Respir. Crit. Care Med.* 164 (2001) 1392–1397.
- [10] N.P. Adams, J.B. Bestall, R. Malouf, T.J. Lasserson, P.W. Jones, Inhaled beclomethasone versus placebo for chronic asthma, *Cochrane Database Syst. Rev.* (1) (2005). CD002738.
- [11] P.N. Black, Antibiotics for the treatment of asthma, *Curr. Opin. Pharmacol.* 7 (2007) 266–271.
- [12] D. Piovani, A. Clavenna, M. Cartabia, M. Bonati, Interregional Italian Drug Utilisation Group. Antibiotic and anti-asthmatic drug prescriptions in Italy: geographic patterns and socio-economic determinants at the district level, *Eur. J. Clin. Pharmacol.* 70 (2014) 331–337.
- [13] G. Corrao, G. Cesana, L. Merlino, Pharmacoepidemiological research and the linking of electronic healthcare databases available in the Italian region of Lombardy, *Biomed. Stat. Clin. Epidemiol.* 2 (2008) 111–125.
- [14] J.A. Delaney, S. Suissa, The case-crossover study design in pharmacoepidemiology, *Stat. Methods Med. Res.* 18 (2009) 53–65.
- [15] D.W. Hosmer, S. Lemeshow, *Applied Logistic Regression*, 3rd ed., John Wiley & Sons, Hoboken, New Jersey, 2013.
- [16] R.I. Horwitz, A.R. Feinstein, The problem of “protopathic bias” in case-control studies, *Am. J. Med.* 68 (1980) 255–258.
- [17] H. Tamim, A.A. Monfared, J. LeLorier, Application of lag-time into exposure definitions to control for protopathic bias, *Pharmacoepidemiol. Drug Saf.* 16 (2007) 250–258.
- [18] S. Wang, C. Linkletter, M. Maclure, D. Dore, V. Mor, S. Buka, et al., Future cases as present controls to adjust for exposure trend bias in case-only studies, *Epidemiology* 22 (2011) 568–574.
- [19] P.M. Rothwell, External validity of randomised controlled trials: “to whom do the results of this trial apply?”, *Lancet* 365 (2005) 82–93.
- [20] B.K. Nallamothu, R.A. Hayward, E.R. Bates, Beyond the randomized clinical trial: the role of effectiveness studies in evaluating cardiovascular therapies, *Circulation* 118 (2008) 1294–1303.
- [21] M.L. Edmonds, S.J. Milan, C.A. Camargo Jr., C.V. Pollack, B.H. Rowe, Early use of inhaled corticosteroids in the emergency department treatment of acute asthma, *Cochrane Database Syst. Rev.* 12 (2012). CD002308.
- [22] C. Marceau, C. Lemière, D. Berbiche, S. Perreault, L. Blais, Persistence, adherence, and effectiveness of combination therapy among adult patients with asthma, *J. Allergy Clin. Immunol.* 118 (2006) 574–581.
- [23] S.J. Edwards, R. von Maltzahn, I.P. Naya, T. Harrison, Budesonide/formoterol for maintenance and reliever therapy of asthma: a meta-analysis of randomised controlled trials, *Int. J. Clin. Pract.* 64 (2010) 619–627.
- [24] K.E. Wells, E.L. Peterson, B.K. Ahmedani, R.K. Severson, J. Gleason-Comstock, L.K. Williams, The relationship between combination inhaled corticosteroid and long-acting β -agonist use and severe asthma exacerbations in a diverse population, *J. Allergy Clin. Immunol.* 129 (2012) 1274–1279.
- [25] X. Tong, T. Guo, S. Liu, S. Peng, Z. Yan, X. Yang, Y. Zhang, H. Fan, Macrolide antibiotics for treatment of asthma in adults: a meta-analysis of 18 randomised controlled clinical studies, *Pulm. Pharmacol. Ther.* 31 (2015) 99–108.
- [26] L. Richeldi, G. Ferrara, L.M. Fabbri, T.J. Lasserson, P.G. Gibson, Macrolides for chronic asthma, *Cochrane Database Syst. Rev.* (4) (2005). CD002997.
- [27] G.G. Brusselle, G. Joos, Is there a role for macrolides in severe asthma? *Curr. Opin. Pulm. Med.* 20 (2014) 95–102.
- [28] R.P. Wenzel, M.T. Wong, Managing antibiotic use – impact of infection control, *Clin. Infect. Dis.* 28 (1999) 1126–1127.
- [29] S.L. Johnston, F. Blasi, P.N. Black, R.J. Martin, D.J. Farrell, R.B. Nieman, TELICAST Investigators. The effect of telithromycin in acute exacerbations of asthma, *N. Engl. J. Med.* 354 (15) (2006 Apr 13) 1589–1600.
- [30] G.J. Rodrigo, J.A. Castro-Rodríguez, What is the role of tiotropium in asthma? A systematic review with meta-analysis, *Chest* 147 (2015) 388–396.
- [31] G.S. Zimmermann, C. Neurohr, H. Villena-Hermoza, R. Hatz, J. Behr, Anti-inflammatory effects of antibacterials on human bronchial epithelial cells, *Respir. Res.* 10 (2009) 89.
- [32] I. Shalit, L. Horev-Azaria, I. Fabian, H. Blau, N. Kariv, I. Shechtman, H. Alterz, Y. Immunomodulatory Kletter, Protective effects of moxifloxacin against *Candida albicans*-induced bronchopneumonia in mice injected with cyclophosphamide, *Antimicrob. Agents Chemother.* 46 (2002) 2442–2449.
- [33] K.B. Van Dole, A.S. Swern, K. Newcomb, L. Nelsen, Seasonal patterns in health care use and pharmaceutical claims for asthma prescriptions for preschool- and school-aged children, *Ann. Allergy Asthma Immunol.* 102 (2009) 198–204.
- [34] G. Corrao, G. Mancia, Generating evidence from computerized healthcare utilization databases, *Hypertension* 65 (2015) 490–498.

Web-Only Appendix 1

International Classification of Diseases (9th revision) codes (ICD-9; <http://www.cdc.gov/nchs/icd/icd9cm.htm>)) used to identify hospital diagnoses:

Asthma: 493.*.

Respiratory diseases: 460.*-519.*.

Cancer: 140.*-239.*.

Anatomic-Therapeutic-Chemical codes (ATC; www.whocc.no) used to identify individual drugs:

Antibiotics: J01*.

Inhaled Corticosteroids (ICS): R03BA01, R03BA02, R03BA03, R03BA05, R03BA08.

Short-Acting Beta-Agonists: R03AB02, R03AB03, R03AC02, R03AC03, R03AC04, R03AC07, R03AC08, R03AC17, R03CB01, R03CB03, R03CB51, R03CB53, R03CC02, R03CC03, R03CC04, R03CC06, R03CC07, R03CC53, R03AK02.

Short-Acting Muscarinic-Antagonists: R03BB01, R03BB02.

Long-Acting Beta-Agonists: R03AC12, R03AC13, R03AC18.

Fixed combination of Long-Acting Beta-Agonists and Inhaled Corticosteroids: R03AK06, R03AK07.

Long-Acting Muscarinic-Antagonists: R03BB04.

Other respiratory drugs: any drug with ATC code R03* not considered above.

Web-Only Appendix 2

Table A1 below reports the ORs for use of respiratory drugs or antibiotics obtained in the case-crossover or case-case-time-control analyses when considering all cases or only cases who benefitted of co-payment exemptions for asthma (1,668 of all included cases). Results did not substantially change between these groups. In addition, 545 cases were hospitalized in the two weeks following the ED visit for asthma. Of these, 405 (73.1%) received a hospital diagnosis of asthma, highlighting a good agreement between ED a hospital asthma diagnoses.

Table A1. Odds ratios (ORs) and 95% confidence intervals (CIs) for use of (A) respiratory drugs or (B) antibiotics obtained in the case-crossover (panel 1) or case-case-time-control analyses (panel 2) when considering either all included cases or only cases who benefitted of co-payment exemptions for asthma.

1) Case-crossover analysis		
Considered cases	(A) Use of respiratory drugs	(B) Use of antibiotics
	OR (95% CI)	OR (95% CI)
<i>All cases (main analysis)</i>	0.66 (0.60, 0.73)	0.82 (0.75, 0.90)
<i>Only cases with asthma exemptions</i>	0.70 (0.60, 0.83)	0.80 (0.67, 0.95)
2) Case-case-time-control analysis		
Considered cases	(A) Use of respiratory drugs	(B) Use of antibiotics
	OR (95% CI)	OR (95% CI)
<i>All cases (main analysis)</i>	0.68 (0.61, 0.75)	0.81 (0.73, 0.88)
<i>Only cases with asthma exemptions</i>	0.69 (0.56, 0.83)	0.72 (0.60, 0.87)