A real-life comparative effectiveness study into the addition of antibiotics to the management of asthma exacerbations in primary care

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Antibiotics are regularly prescribed for asthma exacerbation; however, there is little clinical benefit to the routine addition of antibiotics to usual OCS treatment for managing asthma exacerbations in primary care patients https://bit.ly/2LvYbfT

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Abstract

Background Asthma exacerbations are major contributors to asthma morbidity and mortality. They are usually managed with bronchodilators and oral corticosteroids (OCS), but clinical trial evidence suggests that antibiotics could be beneficial. We aimed to assess whether treatment of asthma exacerbations with antibiotics in addition to OCS improved outcomes in larger, more representative routine-care populations.

Method A retrospective comparative effectiveness study into managing asthma exacerbations with OCS alone *versus* OCS plus antibiotics was conducted using the Optimum Patient Care Research Database. The dataset included 28 637 patients; following propensity score matching 20 024 adults and 4184 children were analysed.

Results Antibiotics in addition to OCS were prescribed for the treatment of asthma exacerbations in 45% of adults and 32% of children. Compared to OCS alone, OCS plus antibiotics was associated with reduced risk of having an asthma/wheeze consultation in the following 2 weeks (children hazard ratio (HR) 0.84 (95% CI 0.73–0.96), p=0.012; adults HR 0.86 (95% CI 0.81–0.91), p<0.001), but an increase in risk of a further OCS prescription for a new/ongoing exacerbation within 6 weeks in adults (HR 1.11 (95% CI 1.01–1.21), p=0.030), but not children. Penicillins, but not macrolides, were associated with a reduction in the odds of a subsequent asthma/wheeze consultation compared to OCS alone, in both adults and children.

Conclusion Antibiotics were frequently prescribed in relation to asthma exacerbations, contrary to guideline recommendations. Overall, the routine addition of antibiotics to OCS in the management of asthma exacerbations appeared to confer little clinical benefit, especially when considering the risks of antibiotic overuse.

Introduction

Asthma exacerbations are the major contributor to morbidity and mortality and a significant burden in terms of healthcare resource utilisation. Therefore, there is a need to optimise management approaches for

asthma exacerbations. Respiratory viruses (especially rhinovirus) are the most common triggers of asthma exacerbations [1, 2] but other factors can increase the risk/severity of exacerbations. Recent evidence suggests atypical bacterial infections may contribute to exacerbation severity [3].

Standard management of asthma exacerbations involves the use of bronchodilators and, in the case of moderate-to-severe exacerbations, systemic steroids [4, 5]. However, there is some evidence to suggest that macrolide antibiotics and the ketolide antibiotic, telithromycin, may have a beneficial effect on asthma exacerbations through their antibacterial and/or anti-inflammatory properties [3]. A double-blind randomised controlled trial (RCT) in adult patients (n=278) with acute asthma exacerbations found a small but significant reduction in asthma symptoms among patients receiving add-on telithromycin compared with placebo [6]. A second open-label randomised study found that in children with acute asthma (n=40) the addition of clarithromycin may offer benefits over standard exacerbation treatment [7]. Current real-world evidence suggests that macrolide use has no significant benefit in acute asthma compared to other common antibiotics such as amoxicillin [8]. A recent Cochrane review found very limited evidence that antibiotics are beneficial to patients having asthma exacerbations; however, their conclusions were limited by a lack of studies [9].

The RCT findings warrant further exploration in a larger more heterogeneous population that is representative of asthma patients who are routinely treated for their exacerbations in primary care. Therefore, we used real-world data to evaluate the comparative effectiveness of managing asthma exacerbations with a single acute course of oral corticosteroids (*i.e.* usual care) *versus* a single course of antibiotics in addition to oral corticosteroids, in adult and paediatric asthma populations.

Methods

Study design

This is an observational primary care database study of the comparative effectiveness of treating patients experiencing an asthma exacerbation with a single course of antibiotics alongside oral corticosteroids (OCS) compared to the usual care of OCS alone.

Data sources and permissions

Historical electronic medical records from the Optimum Patient Care Research Database (OPCRD) were used. At the time of this study, the OPCRD contained anonymised, longitudinal medical records for approximately 6 million UK primary care patients, from more than 525 general practitioner (GP) practices across the UK. The OPCRD is approved by the Trent Multi-Centre Research Ethics Committee for clinical research use. This study was approved by the Anonymised Data Ethics & Protocol Transparency Committee (ADEPT1519) and registered with the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (EUPAS 12 132). We have followed the Strengthening the Reporting of Observational Studies in Epidemiology guidance for reporting observational evidence (strobe-statement.org).

Patient population

Patients were included if they had a prescription for OCS on the same date as a Read code for asthma or wheeze, which was taken to indicate an asthma exacerbation, between January 1, 2004 and December 31, 2014. Index prescription date (IPD) was the first date in this study period when the patient received a prescription for OCS; patients were required to have had no OCS prescriptions (acute or maintenance doses) in the previous 6 months. Patients who received an acute course of OCS were compared to those who received a single acute course of antibiotics in addition to a prescription for OCS at IPD. The first OCS prescription was used so that the IPD represented the start of an exacerbation and not an ongoing exacerbation, and this reduced the chance of previous exacerbation treatment influencing treatment decisions at IPD. Patients were characterised over a 6-month baseline period immediately prior to IPD and outcomes evaluated in the 12 weeks immediately post-IPD (figure 1).

Inclusion criteria were age 2–65 years at IPD; Read codes for asthma (or wheeze if aged ⩽5 years) on three or more occasions ever; at least one Read code for asthma (or wheeze if aged ⩽5 years) during baseline; at least one inhaled corticosteroid or leukotriene receptor antagonists prescription during baseline; and ⩾38 weeks' continuous records (⩾26 weeks prior to IPD and ⩾12 weeks following IPD). Exclusion criteria were having received regular antibiotics (more than five prescriptions during baseline); had an additional chronic respiratory condition; and aged ⩾19 years with a diagnosis of COPD (supplementary figure S1).

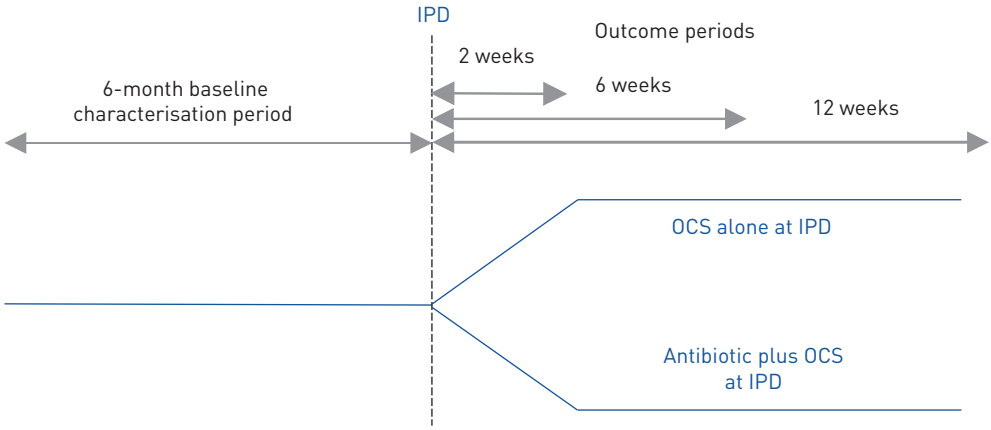

FIGURE 1 Study schematic. IPD: index prescription date; OCS: oral corticosteroid.

Outcomes

The primary study end-point was time to first primary care consultation coded for asthma/wheeze in the 2-week outcome period.

Secondary outcomes were time to first primary care consultation with a Read code for asthma/wheeze resulting in an OCS prescription with or without antibiotics in the 2-, 6- and 12-week periods post IPD and time to first hospitalisation and emergency department attendance for an exacerbation in the 2-, 6- and 12-week periods post-IPD.

Exploratory outcomes included the type of antibiotics prescribed at IPD (macrolides *versus* penicillins), blood eosinophil counts and outcomes in the different paediatric age groups (2–5, 6–12 and 13–18 years).

Statistical analysis

Data were separated into two age groups: paediatric patients (2–18-year-olds) and adults (19–65-year-olds). Demographics and clinical characteristics were compared between those given OCS and those given OCS plus antibiotics at IPD, using Chi-squared tests. Backward stepwise multivariate logistic regression was used to determine the demographic and clinical characteristics that were predictors of a patient receiving OCS plus antibiotics.

To minimise confounding, individuals from the two groups (OCS plus antibiotics and OCS alone) were matched using 1–1 propensity score matching, using the nearest-neighbour method and a caliper width of 0.25. The groups were matched on age, sex, body mass index (BMI) (or BMI z-scores in those aged <18 years as this gives a measure of relative weight adjusted for child age and sex), Global Initiative for Asthma category (based on 2018 guidelines [10]), season of IPD, smoking status, year of IPD and number of consultations for asthma/wheeze in the baseline period. Where matching variables (*i.e.* smoking status or BMI/BMI z-score) were missing, an additional category for missing values was included; 29.1% (1930 out of 6632) of children and 3.7% (818 out of 22 005) of adults had at least one of these two variables missing. The time to primary care consultation for asthma/wheeze and time to primary care consultations for asthma/wheeze resulting in OCS were analysed using Cox proportional hazards regression. The number of patients with at least one primary care consultation and number of those with a respiratory-related emergency department visit or hospitalisation were compared using Chi-squared or Fisher's exact tests as appropriate. All analyses were performed with R software (www.r-project.org/). R packages used were Hmisc 4.2-0, Gmisc 1.8, htmlTable 1.13.1, survival 2.41-3, ggplot2 3.1.0, survminer 0.4.3.999, MatchIt 3.0.2, forcat 0.4.0, MASS v7.3-47 and the World Health Organization macros igrowup_standard.r and who2007.r.

Results

28 637 patients fulfilled the eligibility criteria; 22 005 adults (aged 19–65 years) and 6632 children (aged 2–18 years) (supplementary figure S1). A large proportion of patients received antibiotics in addition to OCS for the treatment of asthma exacerbations at IPD; 10 012 (45%) adults and 2094 (32%) children. There were significant differences in the demographic and clinical characteristics between those who received OCS plus antibiotics compared to those who received OCS alone (supplementary tables S1–S3).

TABLE 1 Predictors of receiving oral corticosteroids plus antibiotics at index prescription date (IPD)

	OR (95% CI)	p-value
Age years		
2–5	0.80 (0.67–0.95)	0.0126
6–12	0.75 (0.66–0.85)	<0.0001
13–18	0.91 (0.80–1.04)	0.1526
19–25	Reference	
26–35	1.07 (0.96–1.20)	0.2305
36–45	1.18 (1.06–1.31)	0.0026
46–55	1.38 (1.24–1.54)	<0.0001
56–65	1.62 (1.45–1.80)	<0.0001
Male	1.10 (1.04–1.15)	<0.0003
Current smoker	1.56 (1.46–1.67)	<0.0001
Ex-smoker	1.09 (1.03–1.17)	0.0051
Obese	1.06 (1.00–1.13)	0.0500
Summer IPD	0.82 (0.76–0.88)	<0.0001
Autumn IPD	1.08 (1.01–1.16)	0.0210
Winter IPD	1.26 (1.18–1.35)	<0.0001
IPD 2004–2007	Reference	
IPD 2007–2009	1.18 (1.11–1.25)	<0.0001
IPD 2010–2012	1.42 (1.33–1.51)	<0.0001
IPD 2013–2014	1.55 (1.43–1.69)	<0.0001
1 SABA consult in baseline	0.95 (0.90–1.00)	0.0373
2 SABA consults in baseline	0.88 (0.81–0.95)	0.0019
Active rhinitis	0.90 (0.84–0.96)	0.0025

SABA: short-acting β-agonist.

The odds of receiving an antibiotic were increased with age, being male, being a smoker or ex-smoker, presenting in winter or in more recent years, while the odds of receiving an antibiotic were decreased in children, those presenting in the summer, those with consultations resulting in a short-acting β-agonist prescription in the previous 6 months or an active rhinitis diagnosis (table 1).

Following matching, 20 024 (10 012 per group) adults and 4184 (2092 per group) children were included in subsequent analyses (tables 2, 3 and supplementary table S4).

Consultations in the 2-, 6- and 12-week outcome period

The addition of antibiotics to OCS is associated with a reduced risk of having an asthma/wheeze consultation in the following 2 weeks (children hazard ratio (HR) 0.84 (95% CI 0.73–0.96), p=0.012; adults HR 0.86 (95% CI 0.81–0.91), p<0.001; figures 2a and b, and 3). In the 2 weeks post-IPD 20.0% (2001 out of 10 012) of adults who received OCS plus antibiotics had a subsequent asthma/wheeze consultation compared to 22.9% (2289 out of 10 012) of those who received OCS alone (p<0.001; supplementary figure S2). Similarly, in children, 19.6% (409 out of 2092) receiving OCS plus antibiotics compared to 22.8% (478 out of 2092) receiving OCS alone had a subsequent consultation within 2 weeks (p=0.010; supplementary figure S2). In the 2 weeks post-IPD there was no difference in the time to first asthma/wheeze consultation resulting in a repeated OCS prescription with or without antibiotics, *i.e.* indicating a new or ongoing exacerbation, for either adults or children (children HR 0.92 (95% CI 0.64–1.33), p=0.650; adults HR 1.10 (95% CI 0.98–1.24), p=0.100). When prescription for OCS and/or antibiotics was used as the outcome at 2 weeks post-IPD, there was no difference between the groups receiving OCS or OCS plus antibiotics prescriptions at IPD in adults, but the risk of a consultation was reduced in children at 2 weeks, but not at 6 or 12 weeks (2 weeks HR 0.69 (95% CI 0.50–0.94), p=0.019; supplementary figure S3).

At 6 weeks, the risk of an asthma/wheeze consultation resulting in a repeat OCS prescription with or without antibiotics was increased in adults who received OCS and antibiotics at IPD compared to OCS alone (HR 1.11 (95% CI 1.01–1.21), p=0.030; figures 2c and 3). Of the adults who received OCS plus antibiotics at IPD, 9.5% (953 out of 10 012) had a subsequent consultation resulting in an OCS prescription with or without antibiotics compared to 8.6% (865 out of 10 012) who received OCS alone at IPD (p=0.032; supplementary figure S2). However, in children at 6 weeks, no significant difference in the risk of an asthma/wheeze consultation resulting in a repeat OCS prescription with or without antibiotics was

TABLE 2 Demographic and clinical characteristics for 2–18-year-olds, following propensity score matching

	Total	Treatment at IPD		
		OCS	OCS+antibiotic	p-value[#]
Patients	4184	2092	2092	
Age years				
2–5	556 (13.3)	271 (13.0)	285 (13.6)	0.280
6–12	2120 (50.7)	1086 (51.9)	1034 (49.4)	
13–18	1508 (36.0)	735 (35.1)	773 (37.0)	
Sex				
Female	1628 (38.9)	816 (39.0)	812 (38.8)	0.92
Male	2556 (61.1)	1276 (61.0)	1280 (61.2)	
BMI z-score				
Underweight	139 (4.2)	64 (3.8)	75 (4.5)	0.860
Normal	1915 (57.8)	966 (58.3)	949 (57.2)	
Overweight	679 (20.5)	333 (20.1)	346 (20.9)	
Obese	582 (17.5)	294 (17.7)	288 (17.4)	
Missing	869 (20.8)	435 (20.8)	434 (20.7)	
Smoking status				
Current smoker	257 (6.8)	124 (6.6)	133 (7.1)	0.79
Ex-smoker	141 (3.7)	75 (4.0)	66 (3.5)	
Nonsmoker	3364 (89.4)	1686 (89.4)	1678 (89.4)	
Missing	422 (10.1)	207 (9.9)	215 (10.3)	
GINA category				
Step 2	1564 (37.4)	764 (36.5)	800 (38.2)	0.23
Step 3	1672 (40.0)	832 (39.8)	840 (40.2)	
Step 4	948 (22.7)	496 (23.7)	452 (21.6)	
Eosinophil count $\times 10^9$ cells $\cdot L^{-1}$				
>0–0.2	141 (27.5)	70 (26.5)	71 (28.6)	0.55
>0.2–0.4	134 (26.2)	70 (26.5)	64 (25.8)	
>0.4–0.6	85 (16.6)	46 (17.4)	39 (15.7)	
>0.6–0.8	62 (12.1)	29 (11.0)	33 (13.3)	
>0.8–1	30 (5.9)	20 (7.8)	10 (4.0)	
>1	60 (11.7)	29 (11.0)	31 (12.5)	
Missing	3672 (87.8)	1828 (87.4)	1844 (88.1)	
Season of index prescription date				
Autumn	1326 (31.7)	667 (31.9)	659 (31.5)	0.99
Winter	1340 (32.0)	666 (31.8)	674 (32.2)	
Spring	838 (20.0)	417 (19.9)	421 (20.1)	
Summer	680 (16.3)	342 (16.4)	338 (16.2)	
Year of index prescription date				
2004–2006	1334 (31.9)	675 (32.3)	659 (31.5)	0.72
2007–2009	1403 (33.5)	711 (34.0)	692 (33.1)	
2010–2012	1080 (25.8)	529 (25.3)	551 (26.3)	
2013–2014	367 (8.8)	177 (8.5)	190 (9.1)	
Asthma/wheeze consults in baseline 6 months				
Total				
0	1544 (36.9)	754 (36.0)	790 (37.8)	0.570
1–5	2567 (61.4)	1301 (62.2)	1266 (60.5)	
6–10	67 (1.6)	33 (1.6)	34 (1.6)	
11–15	6 (0.1)	4 (0.2)	2 (0.1)	
16–20	0 (0.0)	0 (0.0)	0 (0.0)	
With SABA prescription				
0	1544 (36.9)	754 (36.0)	790 (37.8)	0.008
1	2014 (48.1)	989 (47.3)	1025 (49.0)	
2	626 (15.0)	349 (16.7)	277 (13.2)	
With antibiotic prescription				
0	3791 (90.6)	1913 (91.4)	1878 (89.8)	0.084
1	361 (8.6)	167 (8.0)	194 (9.3)	
2	31 (0.7)	11 (0.5)	20 (1.0)	

Continued

TABLE 2 Continued

	Total	Treatment at IPD		
		OCS	OCS+antibiotic	p-value[#]
3	1 (0.0)	1 (0.1)	0 (0.0)	
4	0 (0.0)	0 (0.0)	0 (0.0)	

Data are presented as n or n (%), unless otherwise stated. Percentages are given as non-missing. IPD: index prescription date; OCS: oral corticosteroids; BMI: body mass index; GINA: Global Initiative for Asthma; SABA: short-acting β-agonist. [#]: Chi-squared.

seen between those who received OCS plus antibiotics at IPD compared to OCS alone at IPD (HR 0.93 (95% CI 0.72–1.19), p=0.830; figures 2d and 3). In the 12-week outcome period there was no difference between the OCS plus antibiotics and OCS alone groups in the time to first asthma/wheeze consultation for OCS with or without antibiotics, for either adults (HR 1.07 (95% CI 0.99–1.15), p=0.090) or children (HR 1.07 (95% CI 0.89–1.30), p=0.470). Multivariate Cox proportional hazards regression analysis of the unmatched data produced very similar results for all outcomes.

An exploratory analysis of effect of antibiotics in different paediatric age groups (2–5, 6–12 and 13–18 years) showed similar trends to the group as a whole (data available on request).

An exploratory analysis of adults with low blood eosinophil counts (0–0.2×10^9 cells·L^{-1}) compared to high blood eosinophil counts (>0.2×10^9 cells·L^{-1}) was conducted. The addition of antibiotics at IPD was significantly associated with a reduced risk of an asthma/wheeze consultation in the 2 weeks post-IPD, which was of a similar magnitude in both those with high and low blood eosinophil counts (high eosinophils HR 0.87 (95% CI 0.77–0.98), p=0.018; low eosinophils HR 0.84 (95% CI 0.75–0.94), p=0.003; supplementary figure S4). In both those with a high blood eosinophil count and a low blood eosinophil count there was no difference between the OCS and OCS plus antibiotic groups in the time to first asthma/wheeze consultation for OCS with or without antibiotics in the 2-, 6- and 12-week outcome periods.

Emergency department attendances and hospitalisations

Only a small number of patients experienced a severe exacerbation, defined as requiring an emergency department attendance or hospitalisation (<0.5% of patients had an emergency department attendance or hospitalisation in the 12 weeks post-IPD) so Cox proportional hazards regression was not performed. There were no significant differences between the OCS plus antibiotics and OCS alone groups in the number of patients with an emergency department attendance or hospitalisation (table 4).

Antibiotic type: penicillins versus macrolides

In children given antibiotics at IPD, 86.1% (1802 out of 2092) received penicillins and 10.0% (210 out of 2092) received macrolides. Of those who received OCS plus penicillin, 19.0% had an asthma/wheeze consultation in the 2 weeks post-IPD, which was significantly less than in those who received OCS alone (22.8%, p=0.004). However, in those given macrolides the percentage of children with an asthma/wheeze consultation in the first 2 weeks was not significantly different (23.8%, p=0.82; figure 4a) compared to OCS alone.

In the adults who received antibiotics at IPD, 73.6% (7371 out of 10 012) received penicillins and 17.1% (1708 out of 10 012) received macrolides. Similarly to in children, penicillins, but not macrolides, at IPD were associated with a significant reduction in the number of patients having a subsequent asthma/wheeze consultation in the 2 weeks post-IPD compared to OCS alone (penicillins 19.1% *versus* 22.9% OCS alone, p<0.001; macrolides 21.8% *versus* 22.9% OCS alone, p=0.37; figure 4b).

In both the paediatric and adult groups, neither penicillins nor macrolides were associated with a significant difference in the number of patients having an asthma/wheeze consultation resulting in an OCS prescription with or without an antibiotic, in the 2- or 6-week outcome periods (children 2-week outcome p=0.33, 6-week outcome p=0.68; adults 2-week outcome p=0.29, 6-week outcome p=0.16; figure 4a and b).

Discussion

We have investigated the effectiveness of adding antibiotics alongside OCS for the treatment of asthma exacerbations in a heterogeneous real-life population comprising both adult and paediatric asthma patients.

TABLE 3 Demographic and clinical characteristics for 19–65-year-olds, following propensity score matching

	Total	Treatment at IPD		
		OCS	OCS+antibiotic	p-value[#]
Patients	20024	10012	10012	
Age years				
19–25	1619 (8.1)	839 (8.4)	780 (7.8)	0.003
26–35	3334 (16.7)	1718 (17.2)	1616 (16.1)	
36–45	5099 (25.5)	2600 (26.0)	2499 (25.0)	
46–55	5110 (25.5)	2523 (25.2)	2587 (25.8)	
56–65	4862 (24.3)	2332 (23.3)	2530 (25.3)	
Sex				
Female	12970 (64.8)	6521 (65.1)	6449 (64.4)	0.290
Male	7054 (35.2)	3491 (34.9)	3563 (35.6)	
BMI				
Underweight	330 (1.7)	165 (1.7)	165 (1.7)	0.900
Normal	5114 (26.1)	2578 (26.3)	2536 (25.9)	
Overweight	6327 (32.3)	3174 (32.4)	3153 (32.2)	
Obese	7835 (40.0)	3892 (39.7)	3943 (40.2)	
Missing	418 (2.1)	203 (2.0)	215 (2.1)	
Smoking status				
Current smoker	4738 (24.1)	2219 (22.5)	2519 (25.6)	<0.001
Ex-smoker	5323 (27.0)	2673 (27.2)	2650 (26.9)	
Nonsmoker	9637 (48.9)	4950 (50.3)	4687 (47.6)	
Missing	326 (1.6)	170 (1.7)	156 (1.6)	
GINA category				
Step 2	5903 (29.5)	2949 (29.5)	2954 (29.5)	1.000
Step 3	5552 (27.7)	2777 (27.7)	2775 (27.7)	
Step 4	8569 (42.8)	4286 (42.8)	4283 (42.8)	
Eosinophil count $\times 10^9$ cells·L^{-1}				
>0–0.2	5199 (48.2)	2607 (48.5)	2592 (47.9)	0.26
>0.2–0.4	3645 (33.8)	1804 (33.6)	1841 (34.0)	
>0.4–0.6	1275 (11.8)	610 (11.4)	665 (12.3)	
>0.6–0.8	397 (3.7)	217 (4.0)	180 (3.3)	
>0.8–1	152 (1.4)	79 (1.5)	73 (1.3)	
>1	115 (1.1)	55 (1.0)	60 (1.1)	
Missing	9241 (46.1)	4640 (46.3)	4601 (46.0)	
Season of IPD				
Autumn	5334 (26.6)	2689 (26.9)	2645 (26.4)	0.002
Winter	6772 (33.8)	3265 (32.6)	3507 (35.0)	
Spring	4349 (21.7)	2204 (22.0)	2145 (21.4)	
Summer	3569 (17.8)	1854 (18.5)	1715 (17.1)	
Year of IPD				
2004–2006	5668 (28.3)	2938 (29.3)	2730 (27.3)	<0.001
2007–2009	6524 (32.6)	3325 (33.2)	3199 (32.0)	
2010–2012	5395 (26.9)	2621 (26.2)	2774 (27.7)	
2013–2014	2437 (12.2)	1128 (11.3)	1309 (13.1)	
Asthma/wheeze consults in baseline 6 months				
Total				
0	9537 (47.6)	4716 (47.1)	4821 (48.2)	0.420
1–5	10176 (50.8)	5149 (51.4)	5027 (50.2)	
6–10	272 (1.4)	128 (1.3)	144 (1.4)	
11–15	37 (0.2)	18 (0.2)	19 (0.2)	
16–20	2 (0.0)	1 (0.0)	1 (0.0)	
26–30	0 (0.0)	0 (0.0)	0 (0.0)	
With SABA prescription				
0	9537 (47.6)	4716 (47.1)	4821 (48.2)	0.220
1	8697 (43.4)	4375 (43.7)	4322 (43.2)	
2	1790 (8.9)	921 (9.2)	869 (8.7)	
With antibiotic prescription				
0	18330 (91.5)	9125 (91.1)	9205 (91.9)	0.220
1	1534 (7.7)	804 (8.0)	730 (7.3)	

Continued

TABLE 3 Continued

	Total	Treatment at IPD		
		OCS	OCS+antibiotic	p-value[#]
2	134 (0.7)	68 (0.7)	66 (0.7)	
3	21 (0.1)	11 (0.1)	10 (0.1)	
4	5 (0.0)	4 (0.0)	1 (0.0)	

Data are presented as n or n (%), unless otherwise stated. Percentages are given as non-missing. IPD: index prescription date; OCS: oral corticosteroids; BMI: body mass index; GINA: Global Initiative for Asthma; SABA: short-acting β-agonist. [#]: Chi-squared.

The addition of antibiotics to OCS is associated with a small reduction in the absolute risk of a subsequent asthma/wheeze consultation in the following 2 weeks; ~3% fewer patients having consultations for asthma/wheeze. However, there was no difference in the rates of prescription of OCS and/or antibiotics at 2 weeks. One possible explanation for this is that GPs used a different Read code at follow-up at 2 weeks when further antibiotic treatment was prescribed. In contrast, in adults, but not children, there was a slightly

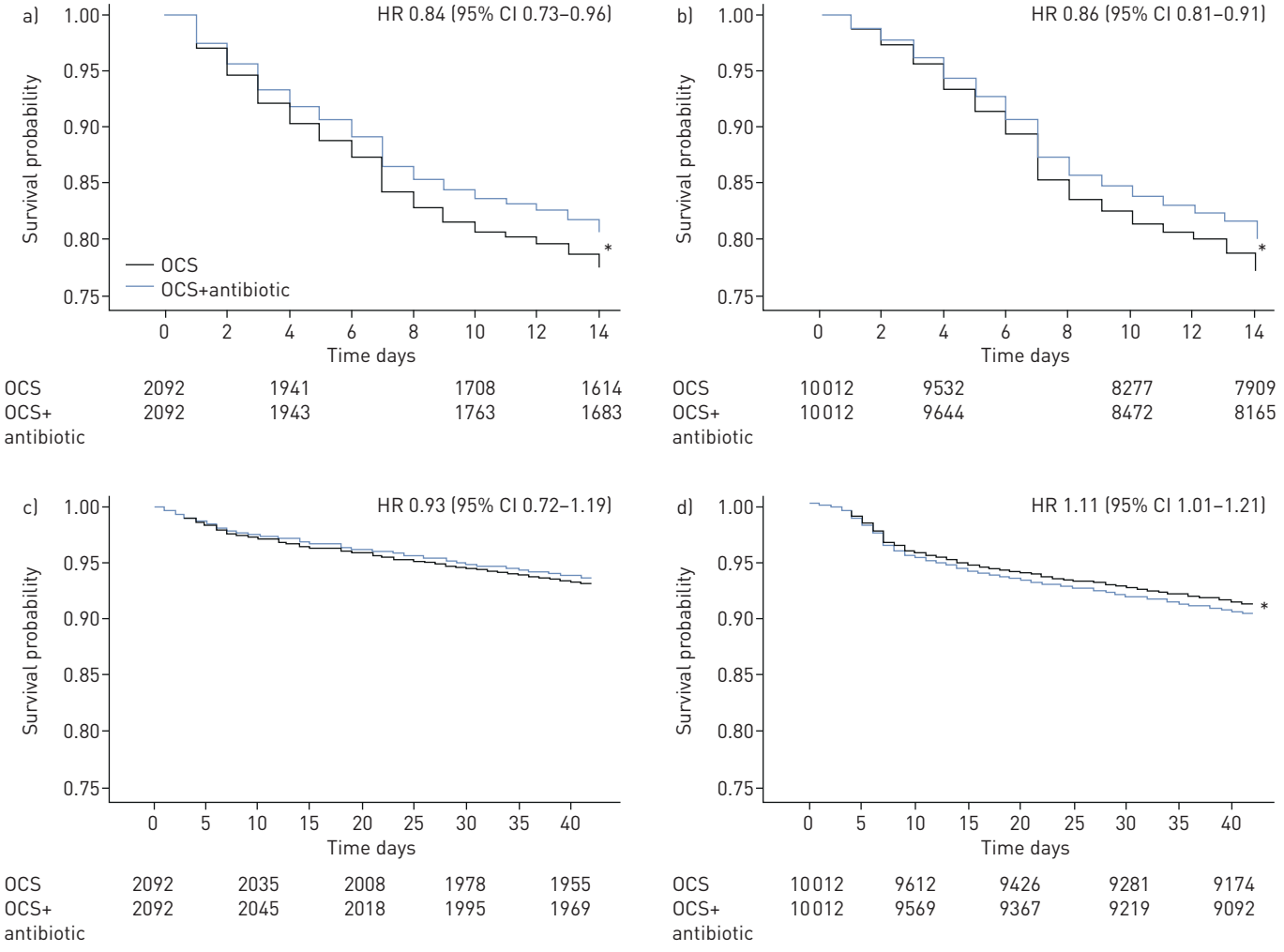

FIGURE 2 Survival analysis of time to first consultation. a) Time to first asthma/wheeze consult in 2-week outcome period for 2–18-year-olds; b) time to first asthma/wheeze consult in 2-week outcome period for 19–65-year-olds; c) time to first asthma/wheeze consult for oral corticosteroids (OCS) with/without antibiotic in 6-week outcome period for 2–18-year-olds; d) time to first asthma/wheeze consult for OCS with/without antibiotics in 6-week outcome period for 19–65-year-olds. *: p<0.05.

TABLE 4 Number of patients with at least one severe exacerbation

	2–18-year-olds			19–65-year-olds		
	OCS	OCS+antibiotic	p-value[#]	OCS	OCS+antibiotic	p-value[#]
Patients	2092	2092		10012	10012	
2 weeks						
Emergency department visit	4 (0.2)	2 (0.1)	0.69	20 (0.2)	22 (0.2)	0.88
Hospitalisation	3 (0.1)	5 (0.2)	0.73	22 (0.2)	24 (0.2)	0.88
6 weeks						
Emergency department visit	7 (0.3)	5 (0.2)	0.77	33 (0.3)	37 (0.4)	0.72
Hospitalisation	9 (0.4)	6 (0.3)	0.61	35 (0.3)	31 (0.3)	0.71
12 weeks						
Emergency department visit	11 (0.5)	9 (0.4)	0.82	51 (0.5)	54 (0.5)	0.84
Hospitalisation	12 (0.6)	7 (0.3)	0.36	44 (0.4)	48 (0.5)	0.75

Data are presented as n or n (%), unless otherwise stated. OCS: oral corticosteroids. [#]: Chi-squared or Fisher's exact test, as appropriate.

increased risk of a consultation for a new/ongoing exacerbation (defined as a repeated OCS prescription) in the 6 weeks post-IPD in those who received antibiotics alongside OCS at IPD. The very low numbers of emergency department attendances and hospitalisations, which may be due partly to the poor recording of emergency department attendances and hospitalisations in primary-care databases, make it difficult to draw firm conclusions. However, we saw no difference in the numbers of emergency department attendances or hospitalisations associated with the addition of antibiotics. While there were statistically significant differences, the magnitude was relatively small, and needs to be balanced against the adverse effects of antibiotic use, both at individual and at community level. The lack of impact on repeat prescription of OCS and/or antibiotics suggests that addition of antibiotics does not reduce treatment failure and thus healthcare resource utilisation. Our analysis occurred at group aggregated level, hence it is possible that while for most patients the addition of an antibiotic is of no benefit, there may be subgroups who benefit, and this should be a focus of further research. In a *post hoc* analysis looking at blood eosinophil levels we found no significant differences in the any of the outcomes between those with high blood eosinophil levels ($>0.2\times10^9$ cells·L^{-1}) and those with low blood eosinophil counts. In a primary-care population, the routine addition of antibiotics appears to be of minimal, if any, clinical benefit in treating asthma exacerbations, especially when considering the major risk of antibiotic resistance associated with antibiotic overuse [11].

The small increase in time until a subsequent asthma/wheeze consultation in patients prescribed antibiotics may be partly explained by patients receiving antibiotics feeling that their expectations have been met,

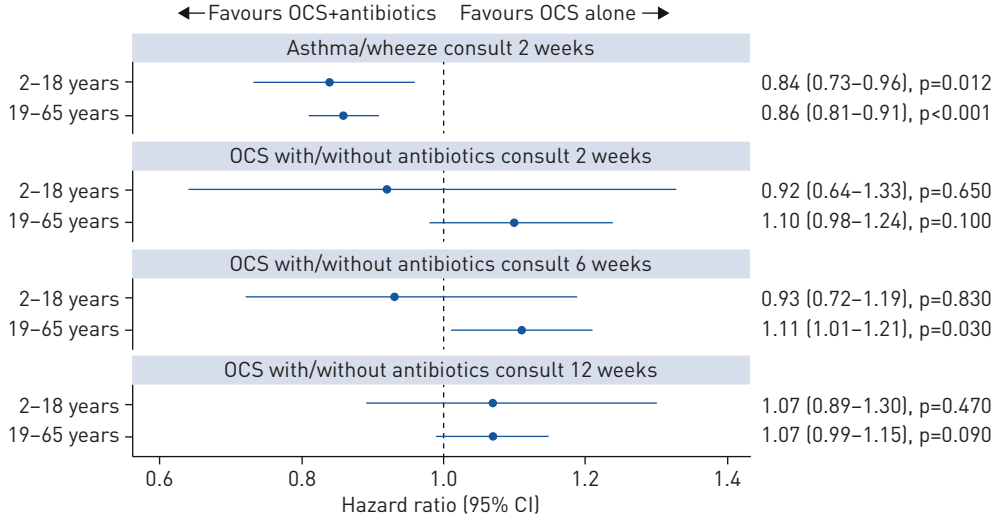

FIGURE 3 Hazard ratios (95% CI) for oral corticosteroids (OCS) plus antibiotics compared to OCS alone.

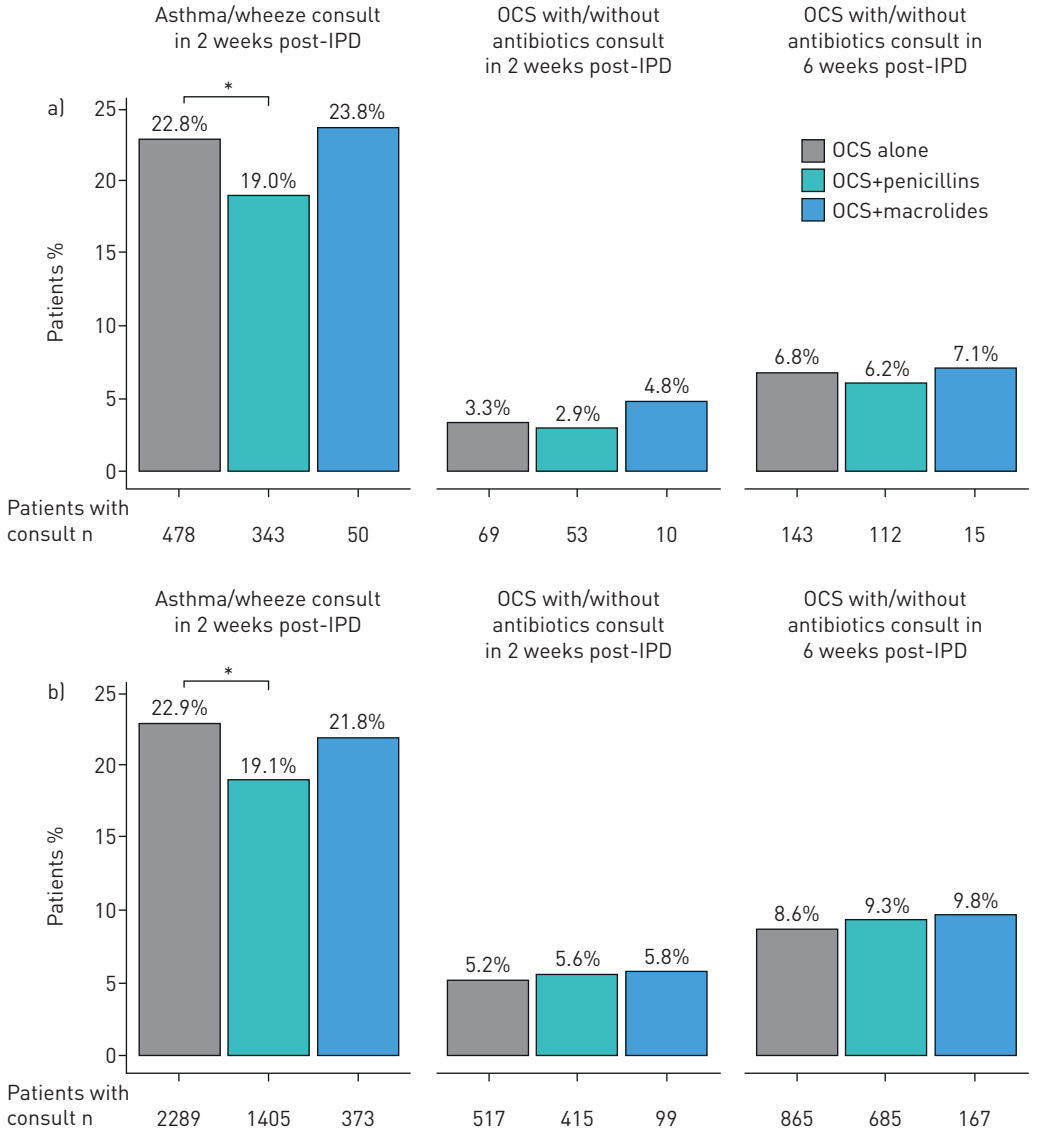

FIGURE 4 Comparison of the effectiveness of penicillins *versus* macrolides. a) Percentage of 2–18-year-olds with at least one primary care consultation by treatment type at index prescription date (IPD) (2092 received oral corticosteroids (OCS) alone, 1802 received OCS+penicillins and 210 received OCS+macrolides); b) percentage of 19–65-year-olds with at least one primary care consultation by treatment type at IPD (10012 received OCS alone, 7371 received OCS+penicillins and 1708 received OCS+macrolides). *: p<0.05.

making them less likely to return for further treatment for ongoing symptoms. A course of antibiotics will probably last for 5–7 days, compared to the usual shorter course of OCS, so it could be expected that patients prescribed antibiotics who have ongoing symptoms are going to finish the longer course of antibiotics, before returning for a subsequent consultation. A limitation of this study is that we do not have information regarding delayed prescribing, as this is not well recorded in primary-care databases. A previous study in UK primary care has suggested that ~18% of antibiotic prescribing for lower respiratory tract infections (LRTI) in adults may be delayed prescribing, where patients are advised to take one treatment first, followed by the second if symptoms are unresolved [12]. Therefore, in patients who received both OCS and antibiotics at IPD the time until those who have ongoing symptoms return for a subsequent consultation could be extended, biasing the primary outcome to favour OCS and antibiotics at IPD. While antibiotics may reduce the chances of patients returning with a LRTI, those with LRTIs are at increased risk of having an exacerbation [13]. This may explain in part why we observed an increased risk of exacerbations at 6 weeks in the antibiotic-treated adult population. Although we matched our patient groups for a number

of variables there is the potential for residual confounding. The higher number of comorbidities in the adult population receiving OCS plus antibiotics may have influenced the prescribing at 2 and 6 weeks if symptoms had not fully resolved. There may have been other factors, such as positive sputum cultures, that guided treatment decisions, which are not well recorded within the database. Time to the first primary-care consultation for asthma/wheeze was only analysed at 2 weeks post-IPD; this outcome included all consultations with an asthma or wheeze Read code. It was felt that patients returning within 2 weeks most probably represent those with ongoing exacerbations rather than routine/follow-up appointments. A further limitation is that we required an asthma/wheeze Read code at follow-up; however, analysis of a very small random subset (0.1% of the sample size) suggests that we have missed ~7.5% of respiratory-related consultations at 2 weeks post-IPD, as other Read codes (*e.g.* for chest infection) were used.

Despite some RCTs suggesting a beneficial effect of macrolide antibiotics in both treating and preventing exacerbations [6, 7, 14], there are a number of studies that have found no benefit in the use of antibiotics in adults receiving hospital treatment for asthma exacerbations. A retrospective cohort study of adult asthmatics hospitalised for asthma exacerbations found an increase in the length of hospital stay in those prescribed antibiotics [15]. A RCT of adult asthmatics hospitalised with asthma exacerbations found amoxicillin compared to placebo had no significant effect on length of hospital stay, symptoms or lung function [16]. Similarly, azithromycin compared to placebo had no significant effect on quality-of-life questionnaire scores, lung function and symptom score in adult asthmatics presenting with asthma exacerbations in secondary care [17].

Our study benefits from a large heterogeneous real-life population that includes both paediatric and adult patients and addresses an important need in assessing antibiotic use in asthma exacerbations, as highlighted by a recent Cochrane review [9]. The mixed population of patients included represent the asthmatic population typically seen in primary care, where most asthma exacerbations are treated, and where it can be difficult to separate what is a noninfective asthma exacerbation and what is a (mostly viral) infection. It can be difficult to distinguish between a noninfective asthma exacerbation and LRTI as the symptoms are often indistinguishable, particularly (but not exclusively), in those with a previous history of asthma [18]. Furthermore, exacerbations and infections are not independent events; respiratory infections are a major trigger of asthma exacerbations [19]. However, viral infections are thought to trigger up to 85% of acute asthma exacerbations in children and ~60% in adults [20]. Bacterial infections are only thought to be responsible for a minority of exacerbations; thus, little or no effect of antibiotics would be expected. It is possible that some of the patients included may have had COPD rather than, or alongside, asthma, particularly in the OCS plus antibiotic group where the number of current smokers is higher. However, in a subanalysis of patients aged <40 years and ⩾40 years, where the risk of COPD is increased, no differences were found between the two groups.

We found high levels of antibiotic prescribing, which is perhaps surprising given that the addition of antibiotics is currently not recommended within the guidelines for the treatment of asthma exacerbations [4]. Antibiotics may be prescribed due to the uncertainties around the definition and symptoms of asthma exacerbations and there being multiple potential causes of the increased respiratory symptoms, for some of which, antibiotics may be beneficial. It is possible some of the antibiotic prescribing at IPD could be for comorbidities; as this is a real-life population some patients may have presented with other infections, for example otitis media, that prompted the antibiotic prescription, alongside symptoms of an asthma exacerbation. Information on such comorbidities was not collected, but it is likely that many of the other potential diagnoses/infections would be of viral origin. The level of antibiotic prescribing observed here was similar to that reported in previous studies. A 1992/1993 study found that ~40% of asthmatic patients experiencing an exacerbation managed in UK primary care were given antibiotics [21]. In another study, 44.6% of adult asthmatics seeking emergency treatment for an asthma exacerbation had received antibiotics in the previous 4 weeks [17]. Antibiotic prescribing was more common in certain groups: older people, males, smokers or ex-smokers, and was more common in winter, and, interestingly, increased between 2004 and 2014. The increase in antibiotic prescribing could be due to increased time pressures, reduced access to GP appointments over this period, related to increased concern about the consequences of missing something or not meeting increased patient/carer expectations [22–24].

Patients prescribed penicillins alongside OCS had a small reduction in the odds of a subsequent asthma/wheeze consultation compared to OCS alone. This is consistent with a previous study of penicillin use in asthma [8] and studies that have found penicillin treatment for COPD exacerbations, and for LRTIs in patients without respiratory disease, is associated with a lower risk of needing repeat antibiotics [20, 21]. In those prescribed macrolides alongside OCS, the odds of a subsequent asthma/wheeze consultation were not significantly different compared to those receiving OCS alone. Hence the observed statistically

significant benefit was associated with only penicillins, not macrolides. This apparent benefit with penicillins could be an artefact of GPs choosing to prescribe macrolides to those with more severe illness which they may have felt would not be adequately treated with penicillins. This could explain the divergence with previous RCTs that found beneficial effects of macrolides [6, 7], although it should be noted that it is difficult to draw firm conclusions from our study given the number of patients prescribed macrolides is relatively low. The patients in our study and in other studies where the beneficial effect of penicillins have been seen [8, 25, 26] have presented in primary care, whereas the studies showing macrolide benefits have been in patients that have presented in the emergency department [6, 7]. Patients attending the emergency department may have different underlying disease severity or a different microbiome that makes macrolides more effective in that scenario.

In conclusion, we found antibiotic use to be common in asthma exacerbations, but did not find clear evidence of a clinically significant benefit of the addition of antibiotics to usual care.

Conflict of interest: C.S. Murray reports personal fees from AstraZeneca, Thermo Fisher, Boehringer Ingelheim, GSK and Novartis, outside the submitted work. S.J. Lucas has nothing to disclose. J. Blakey reports personal fees and non-financial support from AstraZeneca and Boehringer Ingelheim, personal fees from TEVA, non-financial support from GSK, grants from Novartis, outside the submitted work. A. Kaplan reports personal fees from AstraZeneca, Behring, Boehringer Ingelheim, GSK, Novartis, Reva, Covis, Merck, Trudell, Pfizer, Purdue, NovoNordisk and Griffols, outside the submitted work. A. Papi reports grants, personal fees for advisory board work, lectures and consultancy, and non-financial support (travel expenses reimbursement) from GlaxoSmithKline, AstraZeneca, Boehringer Ingelheim, Chiesi Farmaceutici and TEVA, personal fees for advisory board work, lectures and consultancy, and non-financial support (travel expenses reimbursement) from Mundipharma, Zambon, Novartis and Sanofi/Regeneron, grants, personal fees for lectures and non-financial support (travel expenses reimbursement) from Menarini, personal fees for advisory board work and non-financial support (travel expenses reimbursement) from Roche, grants from Fondazione Maugeri and Chiesi, personal fees for consultancy from Edmondpharma, outside the submitted work. J. Paton has nothing to disclose. W. Phipatanakul reports grants and personal fees for consultancy from Genentech/Novartis and Regeneron/Sanofi, other (reagent support) from Thermo Fisher, other (clinical trial/medication support) from GSK and Kaleo, other (clinical trial support) from Lincoln Diagnostics and Monaghen, during the conduct of the study. D. Price reports grants and personal fees for advisory board work, consultancy and lectures from AstraZeneca, Chiesi, Boehringer Ingelheim, Teva Pharmaceuticals, Novartis, Mylan and Mundipharma, grants and personal fees for advisory board work from Circassia, grants and personal fees for advisory board work and lectures from Regeneron Pharmaceuticals and Sanofi Genzyme, grants and personal fees for consultancy from Pfizer and Theravance, grants from Respiratory Effectiveness Group and UK National Health Service, personal fees for advisory board work and consultancy from Amgen, personal fees for advisory board work, consultancy and lectures from GSK, personal fees for lectures from Cipla and Kyorin, personal fees for advisory board work and travel to meetings from Thermofisher, outside the submitted work; and has stock/stock options from AKL Research and Development Ltd, which produces phytopharmaceuticals; owns 74% of the social enterprise Optimum Patient Care Ltd (Australia and UK) and 74% of Observational and Pragmatic Research Institute Pte Ltd (Singapore); is peer reviewer for grant committees of the Efficacy and Mechanism Evaluation programme, and Health Technology Assessment; and was an expert witness for GlaxoSmithKline. O.H. Teoh has nothing to disclose. M. Thomas reports personal fees from GSK, Novartis and Boehringer Ingelheim, outside the submitted work. S. Turner has nothing to disclose. N.G. Papadopoulos reports personal fees for advisory board work and lectures from Novartis, Nutricia, HAL, Menarini/Faes Farma and Mylan/Meda, personal fees lectures from Sanofi, Biomay, MSD, Asit Biotech and Boehringer Ingelheim, personal fees for advisory board work from AstraZeneca and GSK, grants from Gerolymatos International SA and Capricare, outside the submitted work.

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