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Burden of Pertussis in COPD: A Retrospective Database Study in England

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ABSTRACT

Chronic obstructive pulmonary disease (COPD) may increase the risk and severity of pertussis infection. Health care resource utilization (HCRU) and direct medical costs (DMC) of treating pertussis among patients with COPD are unknown. Reported incidence of pertussis among individuals aged ≥ 50 years with COPD was assessed in Clinical Practice Research Datalink and Hospital Episode Statistics databases during 2009–2018 using a retrospective cohort design. HCRU and DMC from the National Health Service perspective were compared between patients with COPD and pertussis and propensity score-matched patients with COPD without pertussis. Seventy-eight new pertussis events were identified among 387 086 patients with COPD aged ≥ 50 years (incidence rate: 4.73; 95% confidence interval 3.74–5.91 per 100 000 person-years). HCRU and DMC were assessed among 67 patients with COPD and pertussis and 267 matched controls. During the month before the pertussis diagnosis, the rates of general practitioner (GP)/nurse visits (4289 vs. 1774 per 100 patient-years) and accident and emergency visits (182 vs. 18 per 100 patient-years) were higher in the pertussis cohort; GP/nurse visits (2935 vs. 1705 per 100 patient-years) were also higher during the following 2 months (all $p < 0.001$). During the month before the pertussis diagnosis, annualized per-patient total DMC were £2012 higher in the pertussis cohort (£3729 vs. £1717; $p < 0.001$); during the following 2 months, they were £2407 higher (£5498 vs. £3091; $p < 0.001$). In conclusion, a pertussis episode among individuals with COPD resulted in significant increases in HCRU and DMC around the pertussis event.

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KEYWORDS
Chronic obstructive pulmonary disease; direct medical costs; health care resource utilization; incidence; pertussis

Plain language summary

What is the context?

Whooping cough (also known as pertussis) is a highly contagious bacterial respiratory infection. Patients with chronic obstructive pulmonary disease (COPD) are more susceptible to infection with a potential aggravation of the disease. However, the impact of pertussis on patients diagnosed with COPD in England is unknown.

What is new?

In this retrospective study we:

- Determined the rate of people with pertussis among patients with COPD aged ≥ 50 years in England from 2009 to 2018.
- Compared healthcare costs among patients with COPD with and without pertussis.

We found that:

- Among 100,000 patients with COPD, 4.73 of them developed pertussis in a typical year. The rate of new pertussis cases reached its maximum in 2012 and tended to decrease as patients were getting older.
- More general practitioner/nurse visits, prescriptions, hospitalizations, accident and emergency visits occurred one month before the diagnosis in patients with COPD and pertussis.
- During the 2 months after a pertussis diagnosis, general practitioner/nurse visits occurred more often among patients with COPD and pertussis compared to patients without pertussis.
- The infection of patients with COPD and pertussis resulted in significant increase in healthcare costs 1 month before and 2 months after the diagnosis.

What is the impact?

These results quantify the burden and cost linked to pertussis infecting patients diagnosed with COPD. Ultimately, it

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can be used to evaluate if preventive measures such as vaccination among these patients in England have a positive value/cost balance.

Introduction

Pertussis (whooping cough) is a highly contagious bacterial respiratory infection that is most commonly caused by *Bordetella pertussis* [1]. Key clinical features of pertussis are paroxysmal cough, inspiratory whooping, post-tussive vomiting, and absence of fever [2]. However, the clinical presentation of pertussis in adults is often atypical, with less than half of adults demonstrating the inspiratory whoop [3]. In adults, paroxysmal cough and absence of fever have high sensitivity but low specificity for pertussis diagnosis, while inspiratory whooping and post-tussive vomiting have high specificity but low sensitivity [2]. In adults, the cough can last for around 12 weeks [4]. Pertussis can also present with other symptoms (e.g. shortness of breath, post-tussive apnea, disturbed sleep, and sore ribs) [4, 5] and complications (e.g. sinusitis, pneumonia, urinary incontinence, and rib fractures) [4, 6] and can result in hospitalization, particularly among older adults [4, 7–10]. Overall, pertussis can have a detrimental impact on quality of life (20–36 quality adjusted life days lost per laboratory confirmed episode) and result in time off work [5]. The morbidity of pertussis in older adults is also reflected in substantial health care resource utilization (HCRU) and direct medical costs (DMC) [11–13].

Although pertussis is often considered to be a childhood illness, 2707/3681 (73.5%) of laboratory-confirmed pertussis cases in England in 2019 were in people aged ≥ 15 years. The incidence in this age group is around 6 per 100 000, although this varies widely by year, from approximately 0 to 18 per 100 000 during 1998–2019 [14]. Provisional data indicate that approximately 32% of all notified pertussis cases in England in 2019 were in people aged ≥ 45 years [15]. Modeling studies based on seroprevalence data from different European countries indicate that the true incidence of pertussis is hundreds to thousands of times higher than notified cases [16–18], showing that pertussis is severely under-recognized and mis-diagnosed. Of note, the recognition of pertussis in chronic obstructive pulmonary disease (COPD) can be complicated by overlapping symptoms (e.g. cough, shortness of breath).

Globally in 2017, COPD was the most prevalent disease-specific chronic respiratory condition, with an estimated prevalence of 3.9% [19]. The prevalence of COPD in England in 2016 was estimated – using an ontological approach – to be 4.6% among adults aged ≥ 35 years [20]. Based on claims data from the United States (US), individuals with COPD appear to be at increased risk of pertussis infection, as the incidence of pertussis was 1.9–3.6-fold higher among adults with COPD than matched adults without COPD or asthma [21].

A recent seroprevalence study in England showed that 12/87 (13.8%) patients with COPD had evidence of *Bordetella pertussis* exposure, with an estimated 4/87 (4.6%) being exposed in the previous 12 months [22]. Not only are patients with COPD at increased risk of pertussis [21], when they contract the infection, they are more likely to require health care, including pharmaceuticals, outpatient care, and inpatient care than pertussis patients without COPD [21]. Further, among adults hospitalized for pertussis in a study conducted in the US, 18.8% had COPD (26.8% of those aged ≥ 65 years) [23], which is higher than the overall prevalence of COPD in the US (6.1% [11.9% of those aged ≥ 65 years]) [24], suggesting that underlying COPD increases the risk of more severe pertussis clinical expressions [25]. Patients with COPD who suffer pertussis could also experience an exacerbation [26].

No studies have compared the impact of comorbid pertussis – in terms of HCRU and DMC – among patients with COPD. The objectives of the current study were, therefore, to estimate the reported incidence and economic burden of reported pertussis among individuals aged ≥ 50 years with a history of COPD in England between 2009 and 2018; and to compare HCRU and DMC among COPD patients with vs. without pertussis. These results could be used to help evaluate the cost/benefit impact of recommending preventive measures (e.g. pertussis vaccination) among patients with COPD in England.

Materials and methods

Study design

This retrospective, observational study: (1) assessed the reported incidence of pertussis among individuals aged ≥ 50 years with COPD using a retrospective cohort design and (2) evaluated HCRU and DMC among patients with COPD with vs. without pertussis using a propensity score-matched cohort analysis.

Ethics and policies

The study protocol received Clinical Practice Research Datalink (CPRD) ethics approval *via* the Independent Scientific Advisory Committee on March 4, 2020 (protocol number 20_043).

Data sources

This study used data from the CPRD GOLD and Aurum datasets, which only include primary care data. For completeness, we also used data from the following linked datasets: Hospital Episode Statistics (HES) Admitted Patient Care, HES Outpatient, HES Accident and Emergency (A&E), and Index of Multiple Deprivation (IMD). Further details on these data sources are provided in Supplementary Text S1.

Study dates

Data were available until November 30, 2018, hence patients were identified during January 1, 2009, to August 31, 2018 to allow for ≥ 3 months of follow-up. For patients with

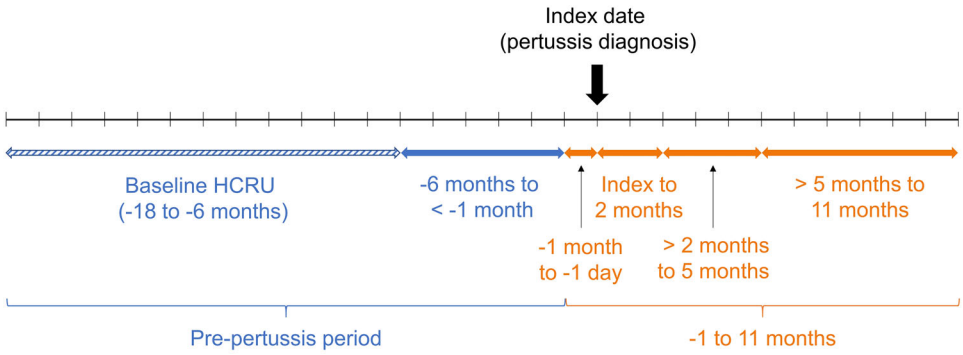

Figure 1. HCRU study periods. HCRU: health care resource utilization.

pertussis, the index date was defined as the date of pertussis diagnosis; for non-pertussis comparators, the index date was defined as the date of pertussis diagnosis of a pertussis case with the same year of birth, sex and general practitioner (GP) practice area.

HCRU & DMC were measured at intervals from −18 months to +11 months from index date (Figure 1). Baseline HCRU and DMC were assessed during −18 to −6 months. A 1-year period was chosen as pertussis and COPD exacerbations vary by season [14, 27]. The 1-year follow-up period started at −1 month to capture HCRU and costs during the time between pertussis symptom onset and diagnosis. The buffer zone during months −6 to −1 was used to ensure that no pertussis-related HCRU was included in the HCRU and DMC baseline period. HCRU was also ascertained on a monthly basis throughout the study. The post-index period was defined as the time from the index date to the earliest of the end of the study period, disenrollment from the database (date of transfer out of the database), or death.

Patients and case definitions

The study population included patients aged ≥ 50 years with COPD (≥ 1 of the specific diagnosis codes detailed in Supplementary Tables S1–S3) who were registered with general practices in the CPRD GOLD and Aurum datasets during the study period. Patients had to have no prior history of pertussis (Supplementary Tables S4 and S5). Incident pertussis was identified using the diagnosis codes shown in Supplementary Tables S6–S8.

For the evaluation of HCRU and DMC, patients were required to have continuous enrollment in CPRD for 18 months prior to the index date, and CPRD GOLD practices were required to have a recorded "up-to-standard" designation prior to 18 months before the index date.

Baseline characteristics

Baseline characteristics after propensity score matching are described: at the index date (age, sex, season, calendar year); or before the index date (smoking status, body mass index [BMI], COPD-specific measures, comorbidities, COPD exacerbations, HCRU, and DMC). COPD-specific measures were: COPD Assessment Test (CAT) scale, modified Medical Research Council (mMRC) dyspnea scale, lung function (forced expiratory volume in the first second [FEV1] % predicted), and number of previous COPD exacerbations during the 18-month baseline period (moderate or severe, as defined by Punekar et al. [28]). These were combined as shown in Supplementary Figure S1 to define COPD severity as significant or non-significant [29, 30].

Propensity score matching

For the HCRU analyses, patients with pertussis were propensity-score matched (1:4) to those without pertussis to minimize between-group differences in baseline characteristics. Variables used to calculate the propensity score were: age, sex, environmental/socioeconomic deprivation (IMD), baseline HCRU cost (−18 to −6 months), composite score for COPD severity categorization (Supplementary Figure S1), number of previous severe and moderate COPD exacerbations during the pre-index period, and presence of asthma. More details on the matching steps and the propensity score matching method can be found in Supplementary Text S2.

Endpoints

Three types of endpoints were determined in this study. Firstly, the incidence of pertussis (first record) among individuals aged ≥ 50 years with COPD was estimated during the whole 10-year study period, for each calendar year, and stratified by age group: 50–54, 55–59, 60–64, 65–69, 70–74, 75–79, 80–84, and ≥ 85 years. For the calculation of pertussis incidence rates, patients contributed to person-time at risk from the latest of: COPD diagnosis date (if that was recorded after the study start date), the study start date, the start date of current registration, the month of their 50th birthday, or the date at which the practice had an "up-to-standard" flag (CPRD GOLD only).

Secondly, HCRU was estimated among patients with COPD aged ≥ 50 years with vs. without pertussis. HCRU included: all-cause GP and nurse consultations (practice visit, home visit, or phone consultation), all-cause GP prescriptions, all-cause outpatient specialist visits, all-cause A&E visits, and all-cause and COPD-related hospitalizations. The latter were defined as hospitalizations with ≥ 1 COPD-related admission (including a primary admission diagnosis

Table 1. Baseline demographic and clinical characteristics for the post-matched cohort.

	Pertussis cohort ($n = 67$)	Non-pertussis cohort ($n = 267$)	SMD	p
Data source			0.18	0.149
Aurum	61 (91.0)	255 (95.5)		
Gold	6 (9.0)	12 (4.5)		
Female	37 (55.2)	141 (52.8)	0.05	0.785
Age at index date, years	66 ± 10	66 ± 9	0.02	0.894
≥ 65 years	39 (58.2)	160 (59.9)	0.03	0.889
Year of index date			–	0.500
2009	Low[a]	Low[a]	–	0.473
2010	0	0		
2011	5 (7.5)	16 (6.0)		
2012	18 (26.9)	75 (28.1)		
2013	8 (11.9)	18 (6.7)		
2014	6 (9.0)	21 (7.9)		
2015	Low[a]	Low[a]		
2016	9 (13.4)	41 (15.4)		
2017	10 (14.9)	49 (18.4)		
2018	5 (7.5)	35 (13.1)		
IMD			–	0.939
Quintile 1	13 (19.4)	51 (19.1)		
Quintile 2	16 (23.9)	62 (23.2)		
Quintile 3	14 (20.9)	50 (18.7)		
Quintile 4	12 (17.9)	65 (24.3)		
Quintile 5	12 (17.9)	39 (14.6)		
Smoking status[b]			–	0.024
Current	14/58 (24.1)	104/238 (43.7)		
Past	39/58 (67.2)	118/238 (49.6)		
Never	5/58 (8.6)	16/238 (6.7)		
BMI[b] kg/m^2	30 ± 6 ($n = 52$)	29 ± 6 ($n = 211$)	0.18	0.306
Obesity[c]	22 (32.8)	81 (30.3)	0.05	0.767
Most common comorbidities[d]				
Asthma	37 (55.2)	154 (57.7)	0.05	0.783
Hypertension	34 (50.7)	132 (49.4)	0.03	0.892
Hyperlipidemia	17 (25.4)	77 (28.8)	0.08	0.650
Depression	16 (23.9)	69 (25.8)	0.05	0.875
Diabetes mellitus	14 (20.9)	55 (20.6)	< 0.01	> 0.999
Malignant cancer	10 (14.9)	45 (16.9)	0.05	0.854
COPD exacerbations[e]			–	0.911
No severe, no moderate	25 (37.3)	103 (38.6)		
No severe, ≥ 1 moderate	23 (34.3)	88 (33.0)		
≥ 1 severe	19 (28.4)	76 (28.5)		
Significant COPD[f]	22 (32.8)	83 (31.1)	0.04	0.771
Pertussis vaccine in past ten years	0 (0.0)	0 (0.0)		
HCRU[g] events per 100 patients				
GP/nurse	1660 ± 1443	1699 ± 1357	0.03	0.557
Prescriptions	7800 ± 12 204	7403 ± 8495	0.04	0.414
A&E	48 ± 102	43 ± 81	0.06	0.981
Outpatient	428 ± 674	403 ± 575	0.04	0.833
All-cause hospitalization	58 ± 113	70 ± 147	0.09	0.677
COPD-related hospitalization	19 ± 61	29 ± 67	0.14	0.200
HCRU cost[g] £	1869 ± 2329	2056 ± 2640	0.08	0.750

Data are mean ± SD or n (%).

[a]"Low" indicates cell counts of 1–4, blinded as per CPRD policy. If only one event count in a stratification block was 1–4 and a total was given, the next lowest non-zero event count was marked "low" to prevent identification of any exact cell count of 1–4.

[b]Most recent record during 18 months before the index date.

[c]Most recent BMI ≥ 30 kg/m^2 during 18 months before the index date, or obesity clinical record during 18 months before the index date (and no subsequent BMI < 30 kg/m^2 before the index date).

[d]At any time before the index date.

[e]During 18 months before the index date. Moderate or severe as defined by Punekar et al. [28].

[f]Based on CAT scale, mMRC score, FEV1% predicted score, or COPD exacerbations as per Supplementary Figure S1.

[g]During 18 months to < 6 months before the index date. Baseline HCRU costs (used for matching) only include costs for GP/nurse visits (2019), outpatient visits (2019), A&E visits (2019), and inpatient stays (2018).

A&E: accident and emergency; BMI: body mass index; CAT: chronic obstructive pulmonary disease assessment test; COPD: chronic obstructive pulmonary disease; CPRD: Clinical Practice Research Datalink; FEV1: forced expiratory volume in the first second; GP: general practitioner; HCRU: health care resource utilization; IMD: Index of Multiple Deprivation; mMRC: modified Medical Research Council; SMD: standardized mean difference.

for COPD) with ≥ 1 overnight stay in HES, identified using the HES Admitted Patient Care file.

Thirdly, annualized DMC (calculated in 2019 £ accounting for inflation and variation of the unit costs/pricing over time, from the perspective of the National Health Service [NHS]) of HCRU were estimated from resource use identified in the second endpoint, multiplied by relevant unit costs. Unit costs for GP, nurse, and outpatient specialist visits were derived from the 2019 Unit Costs of Health and Social Care published by the Personal Social Services Research Unit (PSSRU) [31]. Costs of the five most commonly prescribed products and clinical assessments were

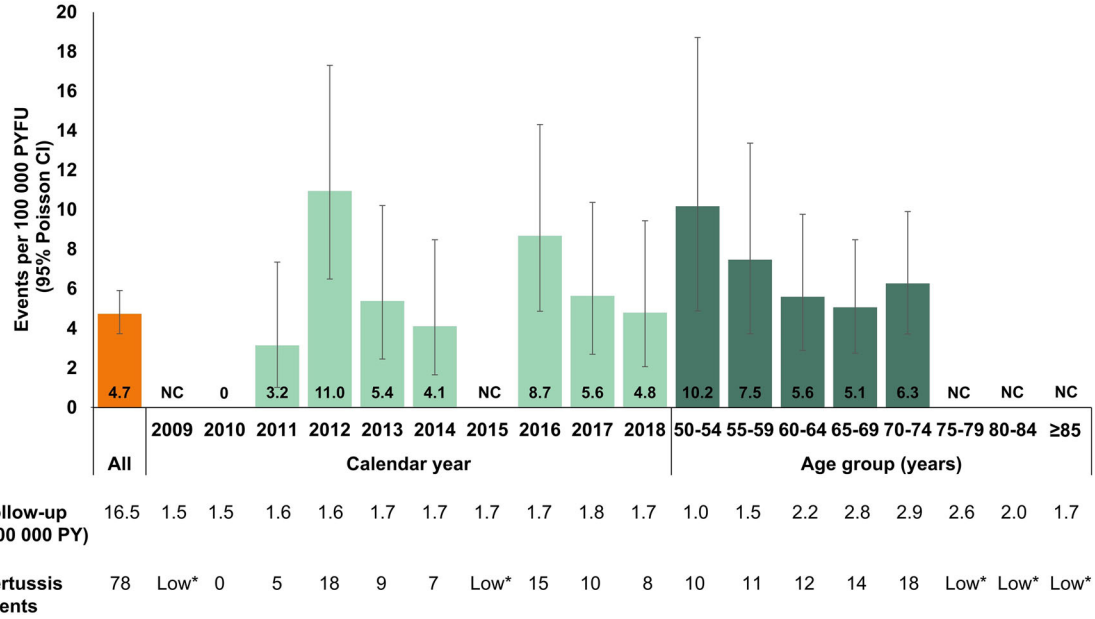

Figure 2. Incidence of pertussis among patients with COPD: overall, by calendar year, and by age group. CI: confidence interval; COPD: chronic obstructive pulmonary disease; CPRD: Clinical Practice Research Datalink; NC: not calculable (*due to low cell counts of 1–4, blinded as per CPRD policy); PYFU: person-years of follow-up.

taken into account. Unit costs for the five most commonly prescribed products were derived from the September 2019 NHS Drug Tariff [32], while those for the five most common clinical assessments were derived from the 2018/2019 National Schedule of NHS Reference Costs [33]. A&E costs were also extracted from the 2018/2019 National Schedule of NHS Reference Costs [33]. As costs for inpatient admissions are financed by Healthcare Resource Group (HRG) groups in the United Kingdom (UK), the 2018/2019 HRG4+ Reference Costs Grouper software [34, 35] was used to assign a HRG code for each inpatient episode of care. Costs were then derived by matching the assigned HRG code and hospitalization type of each inpatient episode with those in the 2018/2019 National Schedule of Reference Costs [36]. Further costing details can be found in Supplementary Text S3.

Statistical analysis

Descriptive analyses for baseline characteristics of the cohorts were conducted using numbers and proportions for categorical variables and means and standard deviations (SDs) for continuous variables.

The incidence of pertussis among those aged $\geq$ 50 years with COPD was estimated by dividing the number of incident pertussis cases by the number of person-years at risk. Incidence was estimated for the whole 10-year study period (for all patients and by 5-year age group) and per calendar year (for all patients). Ninety-five percent confidence intervals (95% CIs) of the incidence rates were calculated using the "exact" method by means of the Poisson distribution [37].

GP/nurse visits, prescriptions, outpatient appointments, A&E visits, and hospitalizations (all-cause and COPD-related) are described in terms of annualized rates and number (%) of subjects with each HCRU. The rates and 95% CIs of the HCRU events were estimated using a negative binomial model. For A&E visits during month −1 to the day before the index date, a Poisson model was used as the negative binomial model did not converge.

Wilcoxon rank-sum test was used to compare HCRU between cases and controls. In total, 56 tests were performed, given the different HCRU categories and time periods, or pooled time periods. The threshold for statistical significance was set at $p < 0.001$, which roughly corresponds to a Bonferroni correction ($p < 0.0009$), with $p < 0.05$ (but ≥ 0.001) considered suggestive of a trend. HCRU was also measured on a monthly basis throughout the study period, but no statistical analysis was performed for these outcomes.

DMC results were also compared between cohorts using the Wilcoxon rank-sum test, with the same significance thresholds. Excess DMC during the month before to 11 months after the pertussis diagnosis code were estimated using a generalized linear model (GLM). Total DMC (primary and secondary care) was the dependent variable, with log-years as an offset. Smoking status (current/past/never) was used as an explanatory variable. The model used a log link, and three distributions were tested (normal, gamma, and Tweedie) [38]. The threshold for statistical significance for the GLM result was set at $p < 0.05$. All statistical programming was performed using SAS software version 9.4.

Results

Incidence rate

During the whole study period, there were 78 pertussis events among 387 086 patients with COPD aged $\geq$ 50 years (during 1.65 million person-years of follow-up [PYFU]). The incidence rate of pertussis was 4.73 (95% CI 3.74–5.91) per

Table 2. HCRU rates per 100 patient-years during several periods from -6 months to +11 months around the index date.

	−6 to −1 month	−1 month to index	Index to + 2 months	+2 to + 5 months	+5 to + 11 months
GP/nurse					
Pertussis	2124 (1722–2619)	**4289[a] (3503–5250)**	**2935[a] (2412–3572)**	1791 (1395–2299)	1832 (1450–2316)
No pertussis	1835 (1643–2049)	1774 (1520–2071)	1705 (1487–1955)	1865 (1655–2102)	1823 (1635–2033)
Outpatient					
Pertussis	485 (345–681)	436 (268–709)	680[b] (488–947)	441 (300–657)	432 (288–648)
No pertussis	492 (400–605)	433 (337–558)	469 (376–586)	465 (375–575)	475 (381–594)
Prescriptions					
Pertussis	8644 (6836–10 930)	11 376[b] (8991–14 393)	9606 (7270–12 693)	9078 (6993–11 783)	9361 (7023–12 478)
No pertussis	8093 (7167–9140)	7925 (6849–9171)	8205 (7256–9277)	8380 (7433–9447)	8578 (7618–9660)
Clinical assessments					
Pertussis	6645 (4808–9184)	**12 666[a] (8500–18 873)**	6231 (4013–9675)	5670 (3415–9413)	6675 (4617–9650)
No pertussis	5875 (4961–6957)	5773 (4022–8286)	5428 (4187–7037)	6230 (5022–7728)	5751 (4907–6740)
A&E					
Pertussis	82[b] (54–126)	**182[a] (89–372)**	46 (16–138)	39 (16–98)	36 (19–70)
No pertussis	54 (38–76)	18[c] (5–47)	62 (41–95)	59 (38–94)	70 (51–95)
All-cause hospitalization					
Pertussis	103 (61–175)	164 (75–358)	135 (78–232)	71 (37–139)	29[b] (14–64)
No pertussis	81 (62–105)	59 (33–105)	100 (69–145)	84 (58–121)	90 (67–120)
COPD-related hospitalization					
Pertussis	39 (22–71)	73[b] (27–194)	38 (10–143)	19 (6–60)	16 (7–39)
No pertussis	45 (32–63)	14 (4–42)	44 (28–69)	37 (22–64)	46 (33–64)

Data are rates per 100 patient-years (95% CI) estimated using a negative binomial model unless otherwise noted.
[a]**Uncorrected $p < 0.001$ (statistically significant after adjustment for multiplicity).**
[b]Uncorrected $p < 0.05$ (suggestive of a trend).
[c]Estimated by a Poisson model as the negative binomial model did not converge.
A&E: accident and emergency; CI: confidence interval; COPD: chronic obstructive pulmonary disease; GP: general practitioner; HCRU: health care resource utilization.

100 000 PYFU (Figure 2). The pertussis incidence rate, which varied by year, was highest in 2012 (10.95 [95% CI 6.49–17.31] per 100 000 PYFU) and remained higher after 2012 compared to before 2012; and incidence rates tended to decrease with increasing age (Figure 2).

Health care resource utilization (HCRU)

After matching, there were 67 patients with COPD and pertussis and 267 matched non-pertussis controls. These two cohorts were balanced after matching apart from a higher proportion of current smokers in the non-pertussis cohort (Table 1).

During −6 to −1 month, HCRU use per 100 patient-years was similar between cohorts, with a trend for increased number of A&E visits in the pertussis cohort (Table 2). During the month before the index date (i.e. before pertussis diagnosis, but likely after symptom onset), GP/nurse visits (4289 vs. 1774 per 100 patient-years; $p < 0.001$) and A&E visits (182 vs. 18 per 100 patient-years; $p < 0.001$) were significantly higher in the pertussis cohort, with a trend toward an increase in prescriptions and COPD-related inpatient care (Table 2 and Figure 3a). During the 2 months after the index date, GP/nurse visits (2935 vs. 1705 per 100 patient-years; $p < 0.001$) were significantly higher in the pertussis cohort, with a trend toward an increase in outpatient visits (Table 2 and Figure 3b). During 2–5 and 5–11 months after the index date, HCRU was similar in both cohorts, apart from a trend for lower all-cause inpatient stays in the pertussis cohort during Months 5–11.

Considerably more patients in the pertussis vs. non-pertussis cohort had ≥ 1 A&E visit during Months −6 to −1 (28.4% vs. 14.6%); ≥ 1 GP/nurse consultation (86.6% vs. 59.2%), ≥ 1 prescription (95.5% vs. 79.8%), or ≥ 1 A&E visit (11.9% vs. 1.5%) during the month before the index date; and ≥ 1 GP/nurse consultation (95.5% vs. 74.2%) or ≥ 1 outpatient appointment (52.2% vs. 36.7%) during the 2 months after the index date (Table 3).

Descriptive HCRU analysis

Monthly HCRU data are presented in Figure 4. During the 3 months before to 1 month after the index date, pertussis patients averaged 11.2 GP/nurse consultations, compared to 5.8 in the non-pertussis cohort (Figure 4a). Outpatient visits generally ranged from around 30 to 50 per 100 patients per month, but peaked at 54 and 60 per 100 patients during the first and second month after the index date, respectively, in the pertussis cohort (Figure 4b). Patients in the non-pertussis cohort received around 600–700 prescriptions per 100 patients per month, but those in the pertussis cohort received 934 and 840 per 100 patients per month in the months before and after the index date, respectively (Figure 4c). There were about 2–6 A&E visits per 100 patients per month in the non-pertussis cohort, but 15 per 100 patients in the month before the index date in the pertussis cohort (Figure 4d). All-cause hospitalizations ranged from 3 to 11 per 100 patients per month in the non-pertussis cohort but peaked at 18 per 100 patients in Month −3 and remained elevated through to the month after the index date (Figure 4e). COPD-related hospitalizations were slightly higher in the pertussis cohort around the time of the index date (Figure 4f). Additional post-hoc analyses on the discharge diagnosis of the hospitalizations, indicated that during the −1 month and index period, a predominance of diagnosis codes for respiratory conditions was observed in the pertussis cohort whereas these codes were not present in the non-pertussis cohort (Supplementary Tables S9 and S10).

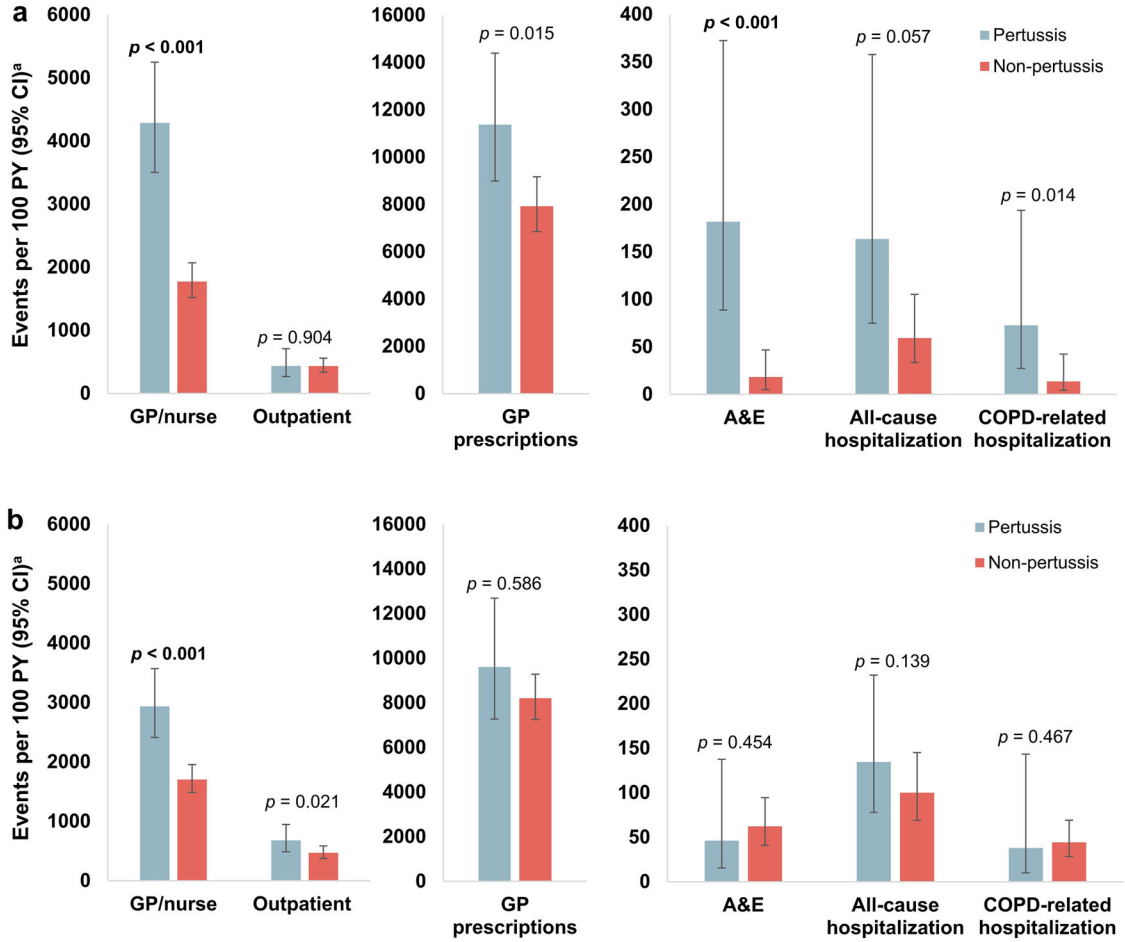

Figure 3. Mean HCRU among patients with COPD from: **a** -1 month to the day before the index date (pertussis diagnosis) and **b** the index date to 2 months.
[a]Rates and 95% CIs were obtained by negative binomial models, except for A&E visits for the non-pertussis cohort between -1 month and -1 day, which were obtained assuming a Poisson distribution as the negative binomial model did not converge. *p* values from unadjusted Wilcoxon rank sum test.
A&E: accident and emergency; CI: confidence interval; COPD: chronic obstructive pulmonary disease; GP: general practitioner; HCRU: health care resource utilization; PY: person years.

Table 3. Number of patients (%) with ≥ 1 of each type of HCRU during several periods from −6 months to +11 months around the index date.

	−18 to −6 months	−6 to −1 month	−1 month to index	Index to 2 months	2–5 months	5–11 months
Time period, months	12	5	1	2	3	6
GP/nurse						
Pertussis	64 (95.5)	62 (92.5)	58 (86.6)	64 (95.5)	53 (82.8)	57 (93.4)
No pertussis	257 (96.3)	250 (93.6)	158 (59.2)	198 (74.2)	225 (84.9)	240 (92.3)
Outpatient						
Pertussis	47 (70.1)	41 (61.2)	17 (25.4)	35 (52.2)	31 (48.4)	36 (59.0)
No pertussis	174 (65.2)	138 (51.7)	66 (24.7)	98 (36.7)	117 (44.2)	132 (50.8)
Prescriptions						
Pertussis	65 (97.0)	67 (100)	64 (95.5)	62 (92.5)	60 (93.8)	58 (95.1)
No pertussis	262 (98.1)	253 (94.8)	213 (79.8)	241 (90.3)	248 (93.6)	248 (95.4)
Clinical assessments						
Pertussis	65 (97.0)	58 (86.6)	47 (70.1)	43 (64.2)	38 (59.4)	50 (82.0)
No pertussis	259 (97.0)	224 (83.9)	91 (34.1)	146 (54.7)	181 (68.3)	220 (84.6)
A&E						
Pertussis	19 (28.4)	19 (28.4)	8 (11.9)	Low[a]	5 (7.8)	9 (14.8)
No pertussis	76 (28.5)	39 (14.6)	Low[a]	24 (9.0)	25 (9.4)	52 (20.0)
All-cause hospitalization						
Pertussis	22 (32.8)	17 (25.4)	7 (10.4)	13 (19.4)	9 (14.1)	7 (11.5)
No pertussis	94 (35.2)	60 (22.5)	12 (4.5)	33 (12.4)	36 (13.6)	62 (23.8)
COPD-related hospitalization						
Pertussis	9 (13.4)	11 (16.4)	Low[a]	Low[a]	Low[a]	5 (8.2)
No pertussis	54 (20.2)	38 (14.2)	Low[a]	19 (7.1)	17 (6.4)	42 (16.2)

[a]"Low" indicates cell counts of 1–4, blinded as per CPRD policy.
A&E: accident and emergency; COPD: chronic obstructive pulmonary disease; GP: general practitioner; HCRU: health care resource utilization.

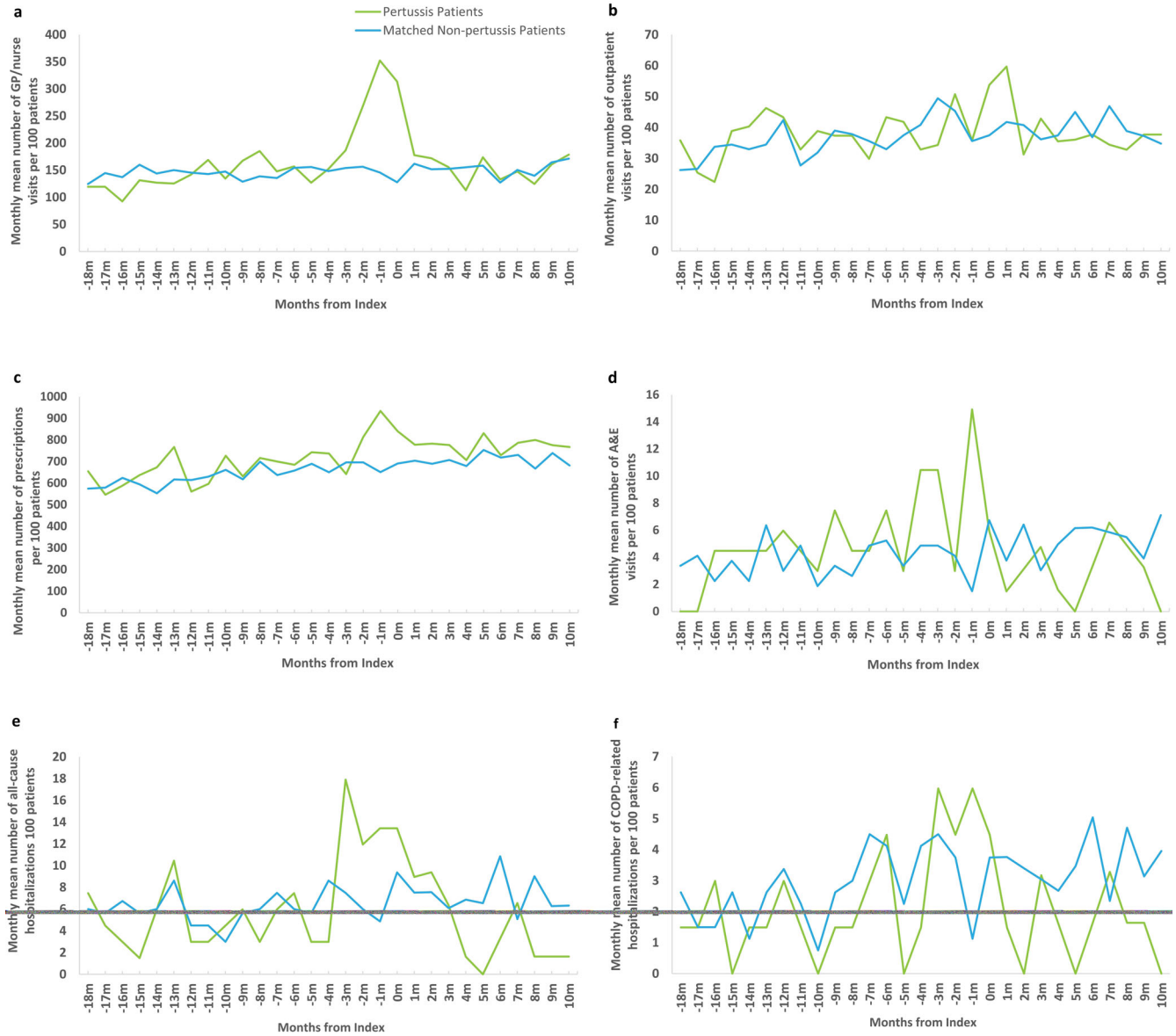

Figure 4. Monthly mean HCRU[a] among patients with COPD and pertussis or COPD alone from 18 months before to 11 months after the index date (pertussis diagnosis) for the following resource utilizations: **a** GP or nurse visits; **b** outpatient visits; **c** GP prescriptions; **d** A&E visits; **e** all-cause hospitalizations; and **f** COPD-related hospitalizations.
[a]Months are labeled according to the start time of each interval, e.g., utilization reported at Month 0 is the average from index day (Day 0) to Day 30.
A&E: accident and emergency; COPD: chronic obstructive pulmonary disease: GP: general practitioner; HCRU: health care resource utilization.

Direct medical costs (DMC)

DMC were comparable in the pertussis and non-pertussis cohorts during Months −6 to −1 (Figure 5 and Supplementary Table S11). During the month before the index date, total annualized per patient DMC were £2012 higher in the pertussis cohort (£3729 vs. £1717; $p < 0.001$), mainly due to a £913 increase in GP/nurse visits (£1491 vs. £578; $p < 0.001$) and an £800 increase in inpatient care (£1204 vs. £404; $p = 0.073$) (Figure 5 and Supplementary Table S11). There was also a significant increase in the annualized per patient costs of A&E visits (£269 vs. £27; $p < 0.001$). During the 2 months after the index date, total annualized per patient DMC were £2407 higher in the pertussis cohort (£5498 vs. £3091; $p < 0.001$), mainly due to a £444 increase in GP/nurse visit costs (£1003 vs. £559; $p < 0.001$) and a £1683 increase in inpatient care (£3454 vs. £1771; $p = 0.105$) (Figure 5 and Supplementary Table S11). Annualized per patient outpatient costs were also increased (£928 vs. £643; $p = 0.021$). Annualized DMC beyond 2 months after the index date were comparable between the two cohorts (Figure 5 and Supplementary Table S11).

Generalized linear model

The Tweedie model was selected among the tested distributions as it was the only model to converge due to the skewness of the data and existence of zero values [38]. The total modeled annualized DMC per patient with vs. without pertussis during the 1 month before to 11 months after pertussis were £3487 vs. £2839 ($p = 0.175$), equating to an adjusted DMC increase of £837 (95% CI −128 to 2187; 32.9% higher; $p = 0.097$) for the pertussis cohort using a GLM.

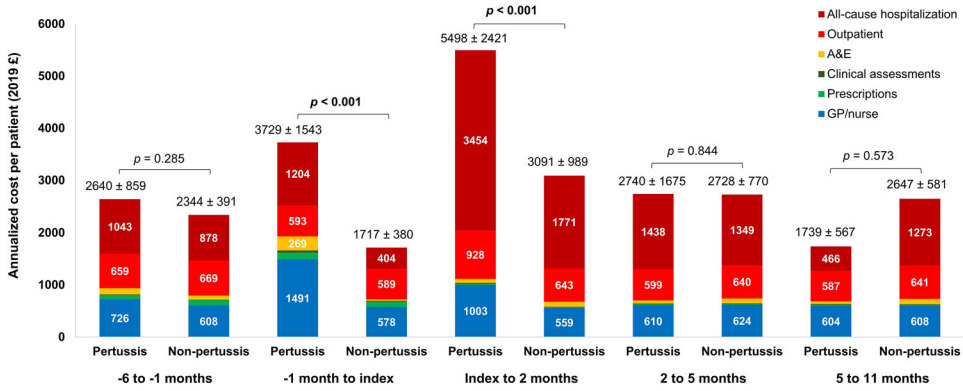

Figure 5. Annualized per-patient DMC[a] during the various time periods of the study.
[a]Values above bars show total mean ± 95% CI annualized DMC per patient including the most common five prescriptions and the most common five clinical assessments (which were added to the cost assessment in order to give a more precise estimate of the total DMC). 95% CI were obtained assuming Student's t distribution for the annualized DMC means. GP, nurse, and outpatient specialist costs were derived from the 2019 Unit Costs of Health and Social Care published by the Personal Social Services Research Unit [31]. Unit costs for the five most commonly prescribed products were derived from the September 2019 NHS Drug Tariff [32]. The unit costs for the five most common clinical assessments and A&E costs were extracted from the 2018/2019 National Schedule of NHS Reference Costs [33]. Inpatient hospitalization costs were derived using reference costs from the 2018/2019 National Schedule of Reference Costs [36].
A&E: accident and emergency; DMC: direct medical costs; CI: confidence interval; GP: general practitioner; NHS: National Health Service.

Discussion

Using merged CPRD Aurum and GOLD data from 2009–2018, we estimated the incidence of reported pertussis among individuals aged ≥ 50 years with COPD to be 4.73 events per 100 000 PYFU. Pertussis incidence varied by year from 0 to 10.95 per 100 000 PYFU, with peaks in 2012 and 2016, which is in line with the numbers of laboratory-confirmed cases from Public Health England [15]. The estimated incidence of pertussis in the current study among people aged ≥ 50 years with COPD was similar to that of a general cohort of people aged ≥ 50 years in the same study period, as reported by Aris et al. (5.76 events per 100 000 PYFU) [39]. Similar results were observed for ≥ 65 years without COPD or asthma cohort in a US claims data study (2006–2014) by Buck et al. [21]. However, in this study, the incidence of pertussis was estimated to be higher among those with COPD than in those without COPD or asthma (age 19–64 years: 20.6 vs. 5.7 per 100 000 person-years; age ≥ 65 years: 11.4 vs. 6.1 per 100 000 person-years).

In 2013, the estimated incidence of diagnosed pertussis among patients with COPD in the current study was 5.38 per 100 000 PYFU. This is much lower than was found in an English seroprevalence study that used sera from people with COPD aged 40–85 years in the same year, in which 4/87 patients (4.6%) showed recent exposure to *Bordetella pertussis* [22]. While comparisons between studies should be undertaken with caution, and only 87 patients were sampled, this implies that the actual incidence rate of pertussis infection could have been several hundred-fold higher than the reported incidence rates estimated in the current study. Similar findings have been reported in various studies, as recently reviewed by Kandeil et al. [40], clearly showing that most pertussis cases among adults (with or without COPD) may be misdiagnosed or not reported.

Patients with pertussis in the current study sought more HCRU in the month before a pertussis diagnosis than matched patients without pertussis. This included more GP/nurse visits (3.5 vs. 1.5 per patient; $p < 0.001$), prescriptions (9.3 vs. 6.5 per patient; $p = 0.015$), A&E visits (14.9 vs. 1.5 per 100 patients; $p < 0.001$), and COPD-related hospitalizations (6.0 vs. 1.1 per 100 patients; $p = 0.014$), the last of which is indicative of a severe exacerbation. During the 2 months after diagnosis, HCRU continued to be elevated, including GP/nurse visits (4.9 vs. 2.9 per patient; $p < 0.001$) and outpatient appointments (1.1 vs. 0.8 per patient; $p = 0.021$), which indicates additional medical follow-up of patients with pertussis.

During the 1 month before to the 5 months after the index date, GP/nurse visits were observed to be 1.5-fold higher (2674 vs. 1803 per 100 patient-years; $p < 0.001$) and A&E visits were 1.3-fold higher, although not significantly (71 vs. 54 per 100 patient-years; $p = 0.409$) in the pertussis vs. matched non-pertussis cohorts (data not shown). In a study by Leong et al. [12] that was conducted in a general population of Australian adults aged ≥ 45 years, GP visits were 1.9-fold higher (1169 vs. 611 events per 100 patient-years) and emergency department visits were 2.2-fold higher (54 vs. 24 events per 100 patient-years) during a similar time interval (30 days before to 120 days after a pertussis diagnosis) among 524 confirmed pertussis cases vs. 524 matched controls without pertussis [12]. Both studies show that diagnosed adult pertussis has an HCRU burden, whether in patients with COPD (current study) or generally in older adults [12].

In the current study, the mean total annual DMC of a patient with COPD without pertussis was £2839. This is similar to the mean annual management cost of treating a patient with COPD in an older UK study after allowing for inflation (£2108 in 2010–2011) [28]. Although the difference was not statistically significant, probably due to the small sample size, patients with COPD and pertussis in the current study had an excess annual DMC of £648 (£837 after GLM adjustment) compared to those with COPD without pertussis. Of note, the cost of treating a case of pertussis infection among patients with COPD was higher than the cost of treating a case of acute respiratory illness during influenza seasons in 2001–2009 in another CPRD study in

the UK (£116 for those aged 50–64 years; £478 for those aged ≥ 65 years) [41].

Patients with COPD are more susceptible to respiratory tract infections [42], and such infections can result in COPD exacerbations and disease progression [43]. In the US, patients with lung diseases (including COPD) are recommended, by the Centers for Disease Control and Prevention (CDC), to receive influenza, pneumococcal, zoster, and tetanus, diphtheria, and acellular pertussis (Tdap) vaccinations [44]. In fact, all adults in the US are recommended to receive a dose of Tdap if they have never received one, plus a tetanus and diphtheria (Td) or Tdap booster every 10 years [45]. Uptake of Td was estimated to be 63.4% in the 10 years up to 2017, but uptake of Tdap was considerably lower, with 31.7% of adults in 2017 having received Tdap in the previous 10 years in the US [46]. Similarly, in a survey of 187 patients with COPD in Belgium, while 64.7% had received influenza vaccination and 40.1%, pneumococcus, only 12.3% had received pertussis vaccination [47].

In the UK, patients with COPD are only eligible for free influenza [48] and pneumococcal [49] vaccinations, but not pertussis vaccinations [50]. However, vaccinating adults with COPD against pertussis could help to reduce morbidity and increases in pertussis-related HCRU and DMC, including those related to exacerbations [26, 40]. General vaccination of adults against pertussis can also help to prevent its transmission to susceptible infants before they have received their primary vaccinations [25, 40]. Indeed, the Global Initiative for Chronic Obstructive Lung Disease (GOLD), that previously recommended influenza and pneumococcal vaccines for people with COPD, recently leveraged the CDC recommendation for Tdap vaccination for COPD patients to the 2021 guideline [27]. Although there are no specific studies of Tdap efficacy among patients with COPD, pertussis vaccines have been shown to be immunogenic [51, 52] and effective [53] in older adults.

The results from this study can be used to inform inputs for a cost-effectiveness analysis of Tdap vaccination among patients with COPD in England. Nine previous studies that estimated the cost-effectiveness of Tdap among US healthy adults have recently been reviewed by Leidner et al. [54]. These studies included heterogeneous vaccination strategies and only three of them were specifically assessing the prevention of pertussis infections in the adult population [55–57]. Results showed that the efficiency profile was dependent on the pertussis incidence rate in the population [56, 57]. The only adult Tdap cost-effectiveness study from England examined maternal Tdap vaccination [58]. They concluded that it was effective, but that cost-effectiveness depended on future incidence [58]. Other European studies have concluded that adult Tdap vaccination is cost-effective in Germany [59] and is "likely to be considered as cost-effective" in the Netherlands [60].

Strengths and limitations

This is the first study to estimate the incremental DMC of a reported pertussis case among adults with COPD in England. This incremental approach allowed us to estimate the additional DMC of a pertussis episode among people who already require considerable HCRU. Other strengths of the current study include the use of a large observational dataset that is generalizable to the overall population with COPD of England, with demographic and longitudinal clinical information recorded from both the primary and secondary care settings.

However, individuals who did not obtain health care support for their symptoms or those in the control group with pertussis that was not reported or misdiagnosed, were therefore not assigned as pertussis cases, hence the true pertussis incidence may be considerably higher. On the other hand, pertussis events were derived from medical diagnoses only and no laboratory confirmations were requested because of incomplete recording of such data in the database.

The CPRD consists of information collected for clinical and routine use rather than for research purposes. Although extensive practice-level quality control checks are conducted, the validity and completeness of individual patient records could not be assessed. Inpatient and outpatient care can only be identified using a linkage to the HES database. Also, the CPRD contains data on drug prescriptions, but not use, and, for practical purpose, only the top five prescription medications were included (as unit costs for individual medications need to be identified by generic name, strength and formulation and prescription costs account for only a small percentage of overall DMC). Deprivation measures were included as baseline covariates, but the IMD is estimated based on average material deprivation by residence postcode rather than individual deprivation or socioeconomic status.

This analysis of patients with COPD with and without pertussis was limited in its ability to detect statistically significant differences between cohorts due to the relatively small number of patients identified with COPD and pertussis and the relative rarity of some HCRU endpoints (e.g. inpatient admissions) during time intervals of interest. Further, DMC were estimated based on unit costs, so may not reflect true DMC. We also only assessed DMC, so did not account for other costs, such as productivity losses, caregiver burden, etc.

Despite these limitations, this study provides valuable information on real-world HCRU and DMC of treating patients with COPD and diagnosed pertussis compared to a matched cohort of patients with COPD only.

Conclusions

In this study, the overall incidence rate of reported pertussis among adults with COPD was nearly 5 per 100 000 PYFU, although the true incidence of pertussis infection is likely much higher. Reported pertussis in adults with COPD can result in significant additional health care being sought, and significantly increased DMC, especially around the time of the pertussis diagnosis. Although the greatest DMC increase for patients with COPD and pertussis vs. COPD alone was within the 2 months after a pertussis diagnosis, there was also a significant increase in the month before diagnosis,

likely due to health care related to pertussis symptoms before an actual diagnosis. These results could be used to help evaluate the cost-effectiveness of recommending pertussis vaccination for patients with COPD.

Authorship

All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Author contributions

All authors were involved in the conception and/or design of the study; Emmanuel Aris, Lauriane Harrington, Amit Bhavsar, Jason C. Simeone, Anna Ramond, Kinga Meszaros, Dimitra Lambrelli, and Piyali Mukherjee acquired and analyzed the data; all authors drafted the manuscript and were members of the writing committee.

Prior presentation

1. ERS 2020. Aris E, Akpo EI, Bhavsar A, et al. Burden of pertussis in COPD: a retrospective database study in England [abstract]. Eur Respir J. 2020;56:2468.
2. ERS 2020. Aris E, Akpo EI, Bhavsar A, et al. The burden of pertussis in adults with asthma: a retrospective database study in England [abstract]. Eur Respir J. 2020;56:4926.

Data availability

The datasets generated and/or analyzed during the current study are not publicly available as CPRD data are accessed *via* a license, the terms of which do not allow for the sharing of raw data.

Disclaimer This study is based in part on data from the Clinical Practice Research Datalink obtained under license from the UK Medicines and Healthcare products Regulatory Agency. However, the interpretation and conclusions contained in this report are those of the authors alone.

Declaration of interest

Emmanuel Aris, Lauriane Harrington, Amit Bhavsar, Kinga Meszaros, and Piyali Mukherjee are employed by the GSK group of companies. Emmanuel Aris, Kinga Meszaros, and Piyali Mukherjee hold shares in the GSK group of companies. Jason C. Simeone, Anna Ramond, and Dimitra Lambrelli are employed by Evidera Inc., which received funding from the GSK group of companies to complete the work disclosed in this manuscript. Alberto Papi is a board member of the GSK group of companies, AstraZeneca, Boehringer Ingelheim, Chiesi Farmaceutici, Mundipharma, Novartis, Roche, Sanofi/Regeneron, TEVA and Zambon; he also declares having received consulting and lecturing fees from the GSK group of companies, AstraZeneca, Boehringer Ingelheim, Chiesi Farmaceutici, Mundipharma, Novartis, Sanofi/Regeneron, TEVA and Zambon; and consulting fees from Edmondparma and Roche; and lecturing fees from Menarini; and grant support for vaccine studies from the GSK group of companies, AstraZeneca, Boehringer Ingelheim, Chiesi Farmaceutici, Fondazione Chiesi, Fondazione Maugeri, Menarini and TEVA; and travel expenses reimbursement from the GSK group of companies, AstraZeneca, Boehringer Ingelheim, Chiesi Farmaceutici, Menarini, Mundipharma, Novartis, Roche, Sanofi/Regeneron, TEVA and Zambon. Claus F. Vogelmeier reports grants and personal fees from the GSK group of companies, AstraZeneca, Boehringer Ingelheim, Grifols and Novartis, and personal fees from Chiesi, CSL Behring, MedUpdate, Menarini and Nuvaira.

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