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ORIGINAL RESEARCH

Burden of Pertussis in Adults Aged 50 Years and Older: A Retrospective Database Study in England

Lauriane Harrington · Emmanuel Aris · Amit Bhavsar · Nicolas Jamet · Essè Ifèbi Hervé Akpo · Jason C. Simeone · Anna Ramond · Dimitra Lambrelli · John Oppenheimer · Yan Sergerie · Piyali Mukherjee · Kinga Meszaros

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ABSTRACT

Introduction: Pertussis, a highly infectious respiratory disease caused by *Bordetella pertussis*, affects people of all ages. Older adults are particularly susceptible to its severe outcomes and complications.

Methods: In this retrospective cohort study, the incidence rate of pertussis among individuals aged ≥ 50 years was assessed during 2009–2018 using Clinical Practice Research Datalink and Hospital Episode Statistics databases, United Kingdom. Health care resource utilisation (HCRU) and direct medical costs (DMCs) were compared between patients with a pertussis diagnosis and propensity score-matched controls (matched on demographic and clinical variables).

Results: Among 5,222,860 individuals, 1638 had a pertussis diagnosis (incidence rate: 5.8 per 100,000 person-years; 95% confidence interval 5.5–6.0). Baseline (– 18 to – 6 months) HCRU and DMC were similar among 1480 pertussis patients and 1480 matched controls. However, there were increases in HCRU in the pertussis vs. matched cohort around the pertussis diagnosis (from months – 6 to – 1 to 5–11). The most notable increases (pertussis vs. controls) were in the rates of general practitioner (GP)/nurse visits (4.7-fold), clinical assessments (4.1-fold), and accident and emergency visits (3.0-fold) during the month before diagnosis and GP/nurse visits during the 2 months after diagnosis (2.5-fold) (all $p < 0.001$). DMCs were significantly higher in the pertussis cohort ($p < 0.001$). Total excess DMC in the pertussis cohort during months – 1 to + 11 was £318 per patient.

Conclusion: A pertussis diagnosis among adults aged ≥ 50 years resulted in significant increases in HCRU and DMC across several months around diagnosis. These results highlight the need for increased awareness of pertussis infection among adults aged ≥ 50 years and suggest that pertussis booster doses among this population should be considered.

Keywords: Direct medical costs; Health care resource utilisation; Incidence; Pertussis

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40121-023-00774-5.

L. Harrington (✉) · E. Aris · A. Bhavsar · N. Jamet · E. I. H. Akpo · Y. Sergerie · P. Mukherjee · K. Meszaros
GSK, Wavre, Belgium
e-mail: lauriane.x.harrington@gsk.com

J. C. Simeone
Evidera Inc., Waltham, MA, USA

A. Ramond · D. Lambrelli
Evidera Ltd, London, UK

J. Oppenheimer
Rutgers New Jersey Medical School, Newark, NJ, USA

Key Summary Points

Why carry out this study?

Although pertussis (whooping cough) is often perceived to be a childhood disease, hospitalisation rates are second highest in older adults (after infants), highlighting an elevated susceptibility to severe pertussis outcomes.

This study provides data over a recent 10-year span on the incidence rate of pertussis among adults aged ≥ 50 years and their associated health care resource utilisation.

What was learned from the study?

Among adults aged ≥ 50 years, there were approximately six pertussis cases diagnosed per 100,000 people per year in England during 2009–2018.

Patients with pertussis had significantly more general practitioner/nurse, outpatient specialist, and accident and emergency visits, prescriptions, and clinical assessments than matched controls without pertussis around the pertussis diagnosis. The increase in health care utilisation from the month before to 11 months after a pertussis diagnosis resulted in significant increases in direct medical costs, amounting to an average of £318 per patient aged ≥ 50 years.

These results highlight the need for increased awareness of pertussis infection among adults aged ≥ 50 years and suggest that pertussis booster doses among this population should be considered.

DIGITAL FEATURES

This article is published with digital features, including a video abstract to facilitate understanding of the article. To view digital features for this article, go to https://doi.org/10.6084/m9.figshare.22015676.

INTRODUCTION

Pertussis (whooping cough) is a highly infectious respiratory disease caused by *Bordetella pertussis* [1]. Each person with pertussis can infect 12–17 susceptible people [2], making it more contagious than influenza (1–2) [2] or pneumococcus (1–5) [3]. Pertussis is often perceived as a childhood disease [4], and infant vaccination has reduced its burden [5]. However, as immunity wanes over time (4–20 years after infection; 4–12 years after vaccination) [6], adolescents and adults are at risk of pertussis infection [4]. In line with this, increasing proportions of pertussis notifications in England have been reported to be among adults aged ≥ 45 years (3% in 2000, 21% in 2010, and 32% in 2019) [7].

Timely diagnosis and treatment of pertussis are important to mitigate transmission and complications [8]. However, this is challenging because although later symptoms can include the paroxysmal cough, inspiratory whooping, and post-tussive vomiting, early pertussis symptoms are similar to those of a common cold [9]. Cough in adults with pertussis can last around 3 months [10], but symptoms can be atypical [11], which can lead to misdiagnosis and/or delayed diagnosis, potentially resulting in mistreatment, delayed treatment, and increased transmission risk.

In England, vaccination of pregnant women [12], infants [12], and health care workers in regular contact with infants or pregnant women [13] helps to protect infants against pertussis. Children are also recommended to receive pertussis vaccination (at age 3 years) [12], but despite waning immunity [6], adult boosters are not recommended. Infants and older adults are most vulnerable to severe outcomes of pertussis [14], and it can also result in complications in around 28% of infected adults, including pneumonia in 9% of those ≥ 50 years old [10]. Adults with pertussis can also require hospitalisation, with the risk increasing from 2–3% for 45–64-year-olds to 11–14% among ≥ 75-year-

olds [14, 15]. In an Australian study, adulthood pertussis resulted in significant excesses in health care resource utilisation (HCRU), which increased with age [16].

The objectives of the current study were to estimate the incidence rate and clinical and economic burden of reported pertussis among individuals aged ≥ 50 years in England during 2009–2018.

METHODS

Study Design

A retrospective cohort design was used to assess the incidence rate of pertussis among individuals aged ≥ 50 years. A propensity score-matched cohort analysis was used to assess HCRU and direct medical costs (DMCs) among pertussis patients vs. matched controls during various time periods around the index date (date of pertussis diagnosis) as shown in Fig. 1. For the control cohort, the index date was the date of pertussis diagnosis of the matched pertussis patient. The study was conducted similarly to two previous studies among individuals aged ≥ 50 years with diagnoses of chronic obstructive pulmonary disease (COPD) [17] or asthma [18].

Data Sources

This study used data from the primary care Clinical Practice Research Datalink (CPRD) GOLD and Aurum datasets and various linked datasets: Hospital Episode Statistics (HES) Admitted Patient Care, HES Outpatient, HES Accident and Emergency (A&E), and Index of Multiple Deprivation (IMD).

CPRD GOLD covers approximately 8% of the United Kingdom (UK) population, including more than 5 million currently registered and active patients. GOLD Aurum includes more than 10 million patients from clinical practices in England. Further details are in Supplementary Text S1.

Populations

Incidence Rate Population

To estimate pertussis incidence rates, we included individuals aged ≥ 50 years who had a record in the CPRD datasets during January 2009 to November 2018. Individuals with a "history of pertussis" or pertussis diagnosis before study entry were excluded, as were those with an unknown/missing pertussis diagnosis date. Pertussis diagnosis codes are in Supplementary Tables S1–S5.

HCRU and DMC Populations

To evaluate HCRU and DMC, patients aged ≥ 50 years with an incident pertussis diagnosis during January 2009 through August 2018 were propensity score matched (1:1) to controls without a pertussis diagnosis. Further details are in Supplementary Text S2. Patients were followed until the earliest of: the end of

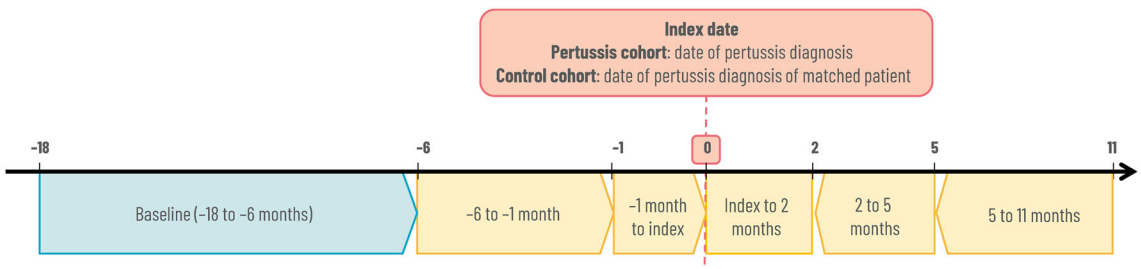


Fig. 1 Baseline (blue) and study periods (yellow). Square arrow ends indicate that the time period starts or ends exactly on the indicated time point; pointed arrow ends indicate that the time period ends the day before (for right-facing arrows) or starts the day after (for left-facing arrows) the indicated time point

the study period, disenrollment from the database, or death.

Endpoints

Incidence Rate Endpoints

Incident pertussis was identified using the diagnosis codes in Supplementary Tables S3–S5. Pertussis incidence rates among individuals aged ≥ 50 years were estimated for the whole 10-year study period (overall and per 5-year age group) and per calendar year.

HCRU Endpoints

All-cause HCRU (general practitioner [GP]/nurse visits, GP prescriptions, clinical assessments, outpatient specialist visits, A&E visits, and hospitalisations) was compared between pertussis and control cohorts. HCRU was measured during various time intervals from 6 months before to 11 months after index (see Fig. 1) and monthly (per 30-day period).

DMC Endpoints

Annualised DMCs (2019 £) from the National Health Service (NHS) perspective were estimated during each of the time intervals shown in Fig. 1 based on the identified HCRU multiplied by the relevant unit costs (as detailed in Supplementary Text S3).

Statistical Analysis

Incidence Rate Statistical Methods

Pertussis incidence rates (overall, by year, and by age group) were estimated by dividing the number of incident pertussis cases by the number of person-years (PY) at risk. Ninety-five percent confidence intervals (CIs) were calculated using the "exact" method by means of the Poisson distribution [19].

HCRU Statistical Methods

Standardised mean differences (SMDs) were used to assess matching in baseline characteristics for continuous and binary variables, with SMDs < 0.20 considered to indicate an absence of imbalance. For multilevel categorical variables where SMD could not be estimated, p values were used. The chi-square test was used for ethnicity, year, season, and smoking status; the Mann-Whitney U test for IMD and number of chronic conditions.

HCRU events were included from index until the earliest of: the end of the study period, disenrollment from the database, or death. All-cause HCRUs are described as rates per 100 PY and number (%) of people with ≥ 1 of each type of HCRU during each study period (see Fig. 1) and per 100 patients in each month from − 18 to + 11. Rates and 95% CIs were estimated by fitting a negative binomial model. As the results showed non-normality, the Wilcoxon rank-sum test was used to compare HCRU between cohorts. To account for multiple testing across time points and endpoints, the threshold for statistical significance was set at $p < 0.001$, approximating a Bonferroni correction of $p < 0.0009$. p values < 0.05 but ≥ 0.001 were considered suggestive of a trend.

DMC Statistical Methods

DMCs were compared between cohorts at baseline and around the index date using the Wilcoxon rank-sum test, with the same significance thresholds as for HCRU.

Excess DMCs among the pertussis vs. control cohorts during months − 1 to + 11 were estimated using a generalised linear model (GLM) analysis. Details of this analysis can be found in Supplementary Text S4. The threshold for statistical significance was $p < 0.05$.

General Statistical Methods

The numbers of individuals with missing baseline demographics or clinical characteristics are reported, but missing data were not imputed. All statistical programming was performed using SAS software version 9.4.

Compliance with Ethics Guidelines

The study protocol received CPRD approval via the Independent Scientific Advisory Committee on March 4, 2020 (protocol number 20_043). The supply of data through CPRD is governed by regulatory permissions and approvals for the purposes of public health research only. The

study complied with all applicable laws regarding subject privacy.

RESULTS

Reported Incidence Rate

Among 5,222,860 individuals aged ≥ 50 years, there were 28.45 million PY of follow-up (PYFU). Overall, 1638 individuals had a pertussis diagnosis, giving an incidence rate of 5.8 per 100,000 PYFU (95% CI 5.5–6.0) (Fig. 2). The pertussis incidence rate was highest in 2012 (12.4 per 100,000 PYFU; 95% CI 11.1–13.7) and among those aged 50–54 years (8.9 per 100,000 PYFU; 95% CI 8.1–9.7).

HCRU

For the HCRU analysis, 1480 patients with a pertussis diagnosis were propensity score matched with 1480 controls. The baseline characteristics of these cohorts were generally well balanced, but more individuals in the pertussis cohort had chronic/persistent cough (8.9% vs. 2.6%; SMD 0.27) (Table 1).

Rates of GP/nurse visits were significantly higher ($p < 0.001$) in the pertussis vs. control cohort throughout (Fig. 3a). They peaked in the pertussis cohort during the month before index (4.7-fold higher than control; $p < 0.001$). Outpatient specialist visits also peaked in the pertussis cohort during the month before index (1.3-fold higher than control; $p < 0.001$) and remained significantly elevated to months 2 to 5. There were significantly more thoracic medicine, diagnostic imaging, and ear, nose, and throat visits in the pertussis vs. the control cohorts (Supplementary Table S6).

GP prescription and clinical assessment rates were significantly higher ($p < 0.001$) in the pertussis vs. control cohort during months – 6 to – 1, – 1 to index, and index to 2 (Fig. 3b). Both peaked during the month before index, with GP prescriptions 1.5-fold higher in the pertussis vs. control cohort and clinical assessments (mainly blood pressure and blood counts) 4.1-fold higher. There were significantly higher rates of prescriptions for amoxicillin, clarithromycin, omeprazole, salbutamol, and oral prednisolone in the pertussis vs. control cohort (Supplementary Table S7).

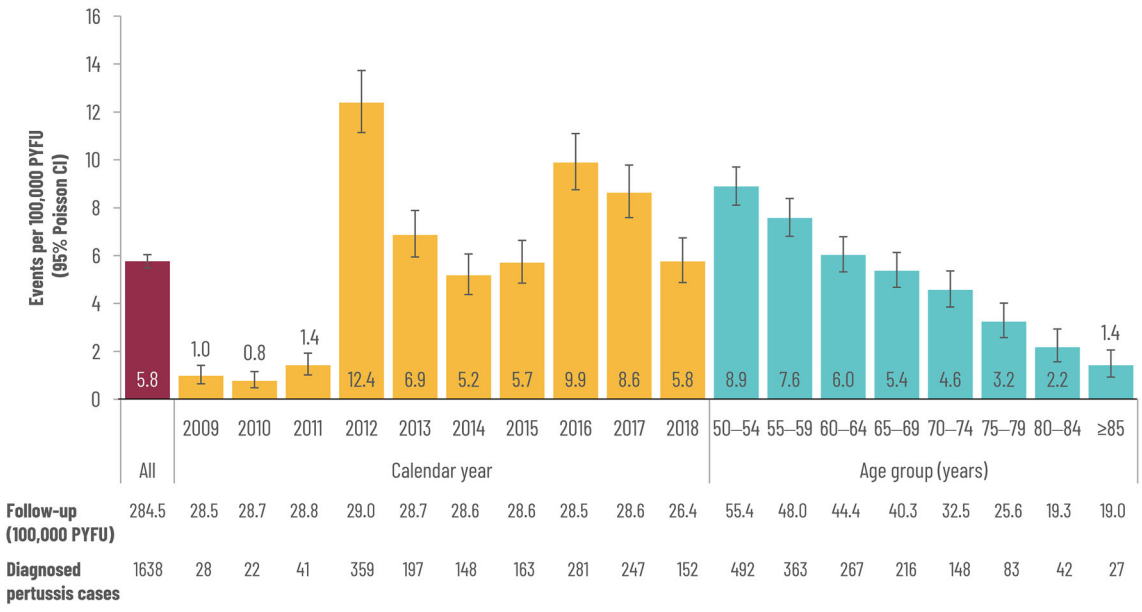


Fig. 2 Incidence rate of reported pertussis among individuals aged ≥ 50 years: overall, by calendar year, and by age group. *CI* confidence interval, *PYFU* person-years of follow-up

Table 1 Baseline demographic and clinical characteristics for the propensity score matched cohorts aged ≥ 50 years

	Pertussis cohort	Control cohort	SMD[a]	*p*-value[b]
Participants, *n* (%)	1480	1480		
Data source, *n* (%)			0.08	–
Aurum	1322 (89.3)	1282 (86.6)		
GOLD	158 (10.7)	198 (13.4)		
Age at index date (years), mean ± SD	61 ± 9	61 ± 9	< 0.01	–
≥ 60 years, *n* (%)	704 (47.6)	725 (49.0)	0.03	–
Female, *n* (%)	815 (55.1)	797 (53.9)	0.02	–
Ethnicity, *n* (%)	(*n* = 1199)	(*n* = 1099)	–	0.156
White	1145 (95.5)	1046 (95.2)		
Asian	23 (1.9)	17 (1.5)		
Black	12 (1.0)	Low[c]		
Mixed	6 (0.5)	Low[c]		
Other	13 (1.1)	21 (1.9)		
Year of index date, *n* (%)			–	0.731
2009	24 (1.6)	16 (1.1)		
2010	20 (1.4)	21 (1.4)		
2011	40 (2.7)	28 (1.9)		
2012	327 (22.1)	318 (21.5)		
2013	188 (12.7)	174 (11.8)		
2014	138 (9.3)	142 (9.6)		
2015	155 (10.5)	169 (11.4)		
2016	257 (17.4)	255 (17.2)		
2017	229 (15.5)	249 (16.8)		
2018	102 (6.9)	108 (7.3)		
Season, *n* (%)			–	0.307
Spring (March–May)	284 (19.2)	261 (17.6)		
Summer (June–August)	400 (27.0)	436 (29.5)		
Autumn (September–November)	473 (32.0)	446 (30.1)		
Winter (December–February)	323 (21.8)	337 (22.8)		
IMD, *n* (%)			–	0.489
Quintile 1	561 (37.9)	585 (39.5)		
Quintile 2	358 (24.2)	355 (24.0)		
Quintile 3	286 (19.3)	251 (17.0)		

Table 1 continued

	Pertussis cohort	Control cohort	SMD[a]	*p*-value[b]
Quintile 4	167 (11.3)	187 (12.6)		
Quintile 5	108 (7.3)	102 (6.9)		
Smoking status,[d] *n* (%)	(*n* = 718)	(*n* = 715)	–	0.801
Current	151 (21.0)	160 (22.4)		
Past	332 (46.2)	329 (46.0)		
Never	235 (32.7)	226 (31.6)		
BMI[e] (kg/m^2), mean ± SD	29 ± 6 (*n* = 768)	29 ± 6 (*n* = 662)	0.03	–
Health conditions (any time before index), *n* (%)				
Hypertension	477 (32.2)	475 (32.1)	< 0.01	–
Asthma	314 (21.2)	318 (21.5)	< 0.01	–
Depression	266 (18.0)	273 (18.4)	0.01	–
Hyperlipidaemia	236 (15.9)	213 (14.4)	0.04	–
Coronary heart disease	206 (13.9)	183 (12.4)	0.05	–
Diabetes mellitus	165 (11.1)	147 (9.9)	0.04	–
Chronic kidney disease	123 (8.3)	110 (7.4)	0.03	–
Anxiety	87 (5.9)	109 (7.4)	0.06	–
Chronic/persistent cough	131 (8.9)	38 (2.6)	0.27	–
COPD	68 (4.6)	67 (4.5)	< 0.01	–
Osteoporosis	58 (3.9)	62 (4.2)	0.01	–
History of stroke	50 (3.4)	45 (3.0)	0.02	–
Heart failure	23 (1.6)	26 (1.8)	0.02	–
Lung cancer	Low[c]	5 (0.3)	0.06	–
HIV positive	Low[c]	Low[c]	0.04	–
Chronic/persistent cough (> 6 months before index), *n* (%)	63 (4.3)	36 (2.4)	0.10	–
Number of chronic conditions,[f] *n* (%)			–	0.686
0	534 (36.1)	557 (37.6)		
1	483 (32.6)	454 (30.7)		
≥ 2	463 (31.3)	469 (31.7)		
Pertussis vaccine in past 10 years, *n* (%)	Low[c]	0 (0.0)	0.05	–

Table 1 continued

	Pertussis cohort	Control cohort	SMD[a]	*p*-value[b]
DMC[g] (£), mean ± SD	1140 ± 2775	1126 ± 3373	< 0.01	–

BMI body mass index, *COPD* chronic obstructive pulmonary disease, *DMC* direct medical costs, *HIV* human immunodeficiency virus, *IMD* Index of Multiple Deprivation, *n (%)* number (percentage) of patients, *SD* standard deviation, *SMD* standardised mean difference

[a]SMD < 0.20 after matching indicates well balanced cohorts

[b]*p*-values were used to assess balance for multilevel categorical variables where the SMD could not be estimated. The chi-square test was used for ethnicity, year, season, and smoking status; the Mann-Whitney U test was used for IMD and number of chronic conditions

[c]"Low" indicates patient counts of 1–4, blinded as per Clinical Practice Research Datalink policy

[d]Most recent record during – 18 to – 6 months

[e]Most recent record during – 18 months to index

[f]Based on hypertension, asthma, depression, coronary heart disease, diabetes mellitus, chronic kidney disease, anxiety, COPD, heart failure at any time before index; chronic/persistent cough any time up to 6 months before index

[g]Baseline DMC included costs for general practitioner/nurse, outpatient specialist, and accident and emergency visits, and inpatient stays from – 18 to – 6 months

A&E visit rates were significantly higher ($p < 0.001$) in the pertussis vs. control cohort during months – 6 to – 1 (1.4-fold) and the month before index (2.9-fold), with trends towards increases in A&E visit and hospitalisation rates during the 2 months after index (Fig. 3c).

During months – 6 to – 1, more individuals in the pertussis vs. control cohort had ≥ 1 GP/nurse visit (87.0% vs. 72.7%; Supplementary Table S8). In the month before index, more individuals in the pertussis vs. control cohort had ≥ 1 GP/nurse visit (85.8% vs. 34.4%), ≥ 1 GP prescription (78.6% vs. 48.3%), ≥ 1 clinical assessment (63.0% vs. 19.2%), and ≥ 1 outpatient specialist visit (17.0% vs. 11.5%), with 72.2% vs. 15.2% having ≥ 2 GP/nurse visits and 17.5% vs. 1.5% having ≥ 6 GP/nurse visits (Fig. 4).

Descriptive analysis showed that, in the pertussis cohort, GP/nurse visits were elevated from around 4 months before until 3 months after index (Fig. 5a), with GP prescriptions and clinical assessments elevated from around – 3 to + 1 month (Fig. 5b and c). Outpatient specialist visits were slightly higher in the pertussis vs. control cohort from months – 1 to + 10 (Fig. 5d). A&E visits were elevated from around – 5 to + 1 month (Fig. 5e), while hospitalisations peaked in the month from index in the pertussis cohort (Fig. 5f).

DMC

Mean total annualised DMC was significantly higher in the pertussis vs. control cohorts during each time period (Fig. 6; Supplementary Table S9). During the month before and the 2 months from index, mean annualised DMC per patient in the pertussis vs. control cohorts was £2336 vs. £1192 and £1817 vs. £1169, respectively, mainly driven by GP/nurse visits.

For the regression analysis, a GLM model was used with a log-link and a Tweedie distribution. The total estimated DMC increase per patient in the pertussis vs. control cohort during months –1 to + 11 was £318 (95% CI 190–459; 26.7% higher; $p < 0.001$).

DISCUSSION

Using data from CPRD-HES linked databases, the estimated incidence rate of reported pertussis among individuals aged ≥ 50 years was 5.8 events per 100,000 PYFU in England during 2009–2018. During the month before to 11 months after a pertussis diagnosis, the

estimated excess DMC per patient with pertussis was £318.

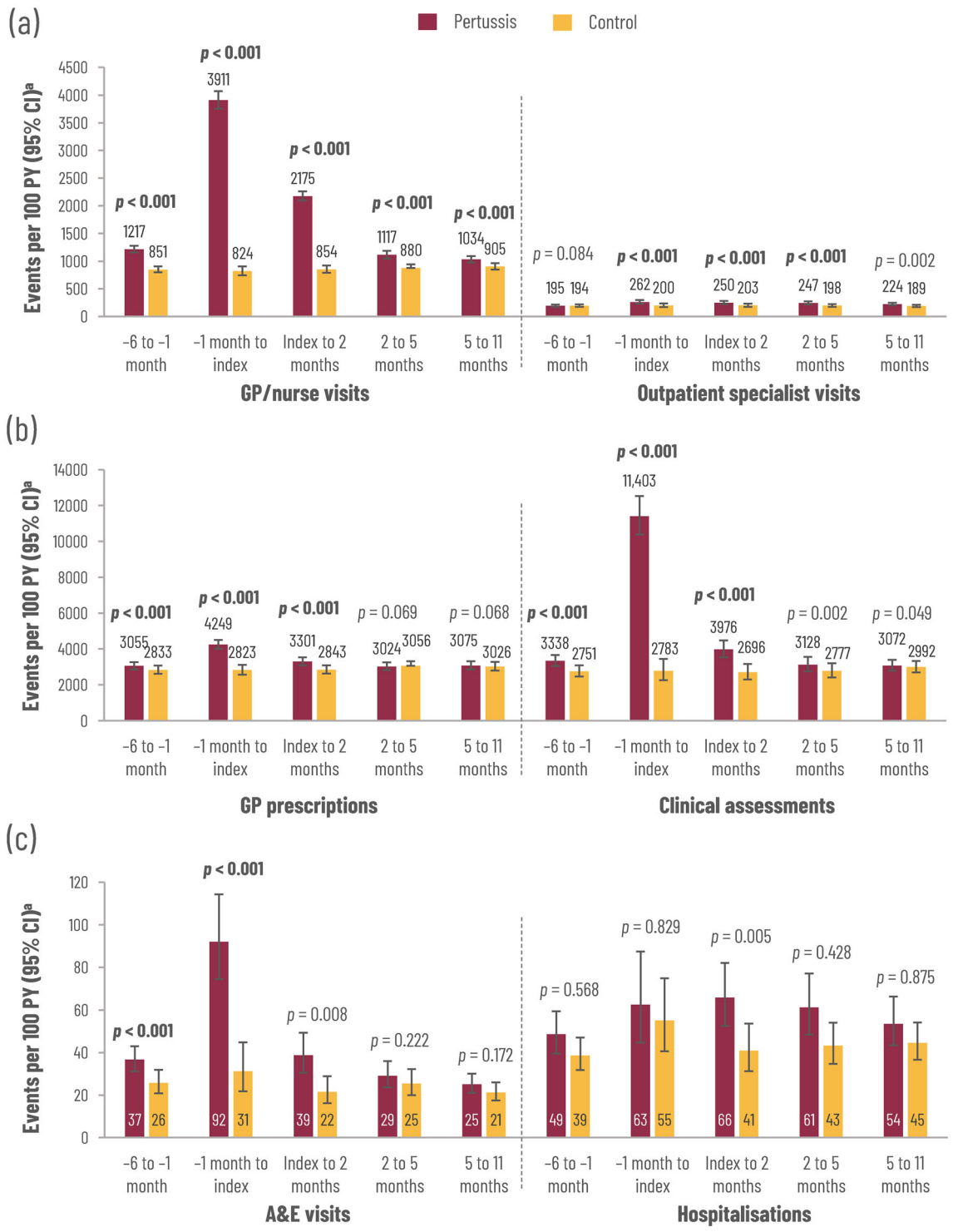
Our overall pertussis incidence rate findings of 5.8 per 100,000 PYFU among individuals aged ≥ 50 years during 2009–2018 is comparable to the incidence rate of 7.6 per 100,000 PY reported in the United States (US) for individuals aged 50–64 years during 2006–2015 [20]. It is lower than among patients aged ≥ 50 years with a diagnosis of asthma (9.6 events per 100,000 PYFU) [18], which aligns with other studies that have reported an increased risk of pertussis among individuals with asthma [15, 21].

The estimated incidence rates of pertussis appeared cyclical in nature and aligned with laboratory-confirmed pertussis cases for individuals aged ≥ 50 years in Europe [7, 22]. Our data well captured the 2012 pertussis outbreak [23] and show that incidence rates since 2012 have not dropped to the low rates seen during 2009–2011. Given the cyclical nature of pertussis, future outbreaks are expected, and these would probably affect older adults as well as younger people. Perhaps surprisingly, the incidence rate of reported pertussis appeared to decrease with increasing age. While this could be due to reduced exposure, it is perhaps more likely due to increased under-diagnosis of pertussis among older adults. In fact, the true incidence of pertussis in older adults is likely several thousand-fold higher than the reported incidence due to gross under-diagnosis [24].

HCRU was similar in the pertussis and control cohorts during baseline, but was higher in the pertussis cohort from months − 6 to − 1 through 5 to 11. There were large peaks in the pertussis cohort during the month before pertussis diagnosis for GP/nurse visits, GP prescriptions, clinical assessments, and A&E visits, the latter highlighting the need for urgent care for some patients. Furthermore, 56.8% of patients in the pertussis cohort had ≥ 3 GP/nurse visits in the month before diagnosis compared to 7.5% in the control group. The increase in outpatient specialist visits was less pronounced, occurred later, and continued for many months, likely indicative of the referral process in England. In an Australian study [16], patients aged ≥ 65 years with pertussis also had peaks in GP visits, prescriptions, and emergency department visits, which occurred in the month after symptoms appeared. This implies that it can take around 2 months for adult pertussis to be diagnosed. However, it could be longer in some patients, as GP/nurse and A&E visits started to increase in our pertussis cohort approximately 4–5 months before pertussis was diagnosed. These results indicate that patients may seek medical care well before receiving a pertussis diagnosis, which is not ideal as pertussis should be treated within 1–2 weeks of cough onset to reduce transmission and aid recovery [8]. The prolonged elevated HCRU use after a pertussis diagnosis indicates possible sequelae.

There were significant early (months − 6 to − 1) excesses in GP prescriptions for amoxicillin and omeprazole in the pertussis cohort, likely indicating misdiagnoses of chest infections and gastroesophageal reflux, respectively. In the month before a pertussis diagnosis, there were also significant excesses in prescriptions for clarithromycin (potentially indicating suspicion of pertussis or misdiagnosis of chest infection), salbutamol (potentially indicating misdiagnoses of asthma or COPD), and prednisolone. Overall, we can hypothesise that patients ultimately diagnosed with pertussis were often prescribed various treatments for cough and only underwent testing for pertussis when their symptoms did not improve. However, this hypothesis would need to be confirmed in future research. These findings are concerning, given (1) the risk of transmission to others before diagnosis/treatment, (2) the potential for adverse effects with systemic corticosteroids [25], and (3) the risk of antibiotic resistance [26] due to the empirical use of amoxicillin, which is not a recommended antibiotic for the treatment of pertussis [8], but was prescribed in over 20% of patients with pertussis in the months leading up to diagnosis in the current study.

In previous studies, we have estimated excess DMC for those with vs. without pertussis during


(a)
Pertussis
Control
Events per 100 PY (95% CI)[a]
p < 0.001
3911
p < 0.001
2175
p < 0.001
1217
851
824
854
p < 0.001
1117
880
p < 0.001
1034
905
p = 0.084
195
194
p < 0.001
262
200
p < 0.001
250
203
p < 0.001
247
198
p = 0.002
224
189
-6 to -1 month
-1 month to index
Index to 2 months
2 to 5 months
5 to 11 months
GP/nurse visits
Outpatient specialist visits
(b)
Events per 100 PY (95% CI)[a]
p < 0.001
3055
2833
p < 0.001
4249
2823
p < 0.001
3301
2843
p = 0.069
3024
3056
p = 0.068
3075
3026
p < 0.001
3338
2751
p < 0.001
11,403
2783
p < 0.001
3976
2696
p = 0.002
3128
2777
p = 0.049
3072
2992
GP prescriptions
Clinical assessments
(c)
Events per 100 PY (95% CI)[a]
p < 0.001
37
26
p < 0.001
92
31
p = 0.008
39
22
p = 0.222
29
25
p = 0.172
25
21
p = 0.568
49
39
p = 0.829
63
55
p = 0.005
66
41
p = 0.428
61
43
p = 0.875
54
45
A&E visits
Hospitalisations

◀**Fig. 3** HCRU per 100 PY in the pertussis and controls cohorts. **a** GP/nurse and outpatient specialist visits; **b** GP prescriptions and clinical assessments; **c** A&E visits and hospitalisations[a]. *A&E* accident and emergency, *CI* confidence interval, *GP* general practitioner, *HCRU* health care resource utilisation, *PY* person-years. [a]Event rates and 95% CIs were estimated by fitting a negative binomial model. Uncorrected $p < 0.001$ (shown in bold) indicates statistically significant after cut-off adjustment for multiplicity. Uncorrected $p < 0.05$ is suggestive of a trend. p values were derived using the Wilcoxon rank-sum test

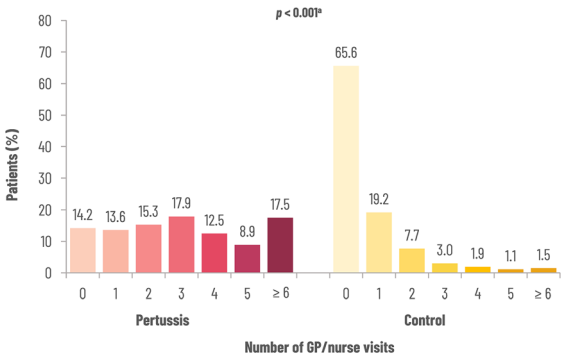


Fig. 4 Distributions of the proportions of patients with each number of GP/nurse visits in the pertussis and control cohorts during the month before index. *GP* general practitioner. [a]Mann-Whitney *U* test for overall comparison between cohorts

months − 1 to + 11 among individuals aged ≥ 50 years with asthma (£370 per patient) [18] and COPD (£837 per patient) [17]. In the current study, the estimated excess cost was £318 per patient, highlighting the cost associated with a pertussis diagnosis even among the general population aged ≥ 50 years. This estimate is considerably higher than the cost of pertussis-related HCRU reported in a 2011–2012 study in England and Wales (£56) [27]. However, the earlier study included younger individuals (≥ 5 years) [27], who may have required less HCRU, and costs were estimated based on patient surveys rather than clinical records. Studies in Spain [28] and the US [20, 29] have also reported considerable costs associated with adult pertussis. The Spanish study reported mean costs of approximately €160 for adults in 2012–2013 [28]. The US studies reported much higher costs: $1835 and $14,428 in outpatient and inpatient settings, respectively, for adults aged ≥ 50 years in 2010 [29], and $2530 and $4849 for adults aged 20–49 and 50–64 years, respectively, in 2015 [20]. These differences are not surprising given the different health care systems in these countries.

Overall, the current data highlight that older adults can contract pertussis infection, which can result in substantial HCRU and DMC. In the current study, < 0.2% of individuals had a record of pertussis vaccination in the previous 10 years, which is in line with the current absence of a recommendation for adult boosters in the UK [12].

Strengths and Limitations

Strengths include the use of a large observational dataset that contains demographic and clinical information in primary and secondary care that is generalisable to adults aged ≥ 50 years in England. One limitation is that we used medical diagnosis codes to define pertussis cases, and laboratory results were not extracted. Although quality control checks were conducted, we could not assess the validity and completeness of individual patient records. Also, deprivation measures were estimated based on residence postcode rather than individual measures. Similarly, the burden of non-diagnosed pertussis cases could not be considered in this study. Further research will be needed to assess whether non-diagnosed pertussis cases bear the same burden as diagnosed ones. The results should also be interpreted while considering potential cofounders that were not accounted for. Indeed, it is possible that some of the excess HCRU in the pertussis cohort was not related to pertussis, although having a matched comparator cohort should have reduced the risk of confounding. However, given that the matching was performed in the − 18 to − 6 months period, if an acute infection had

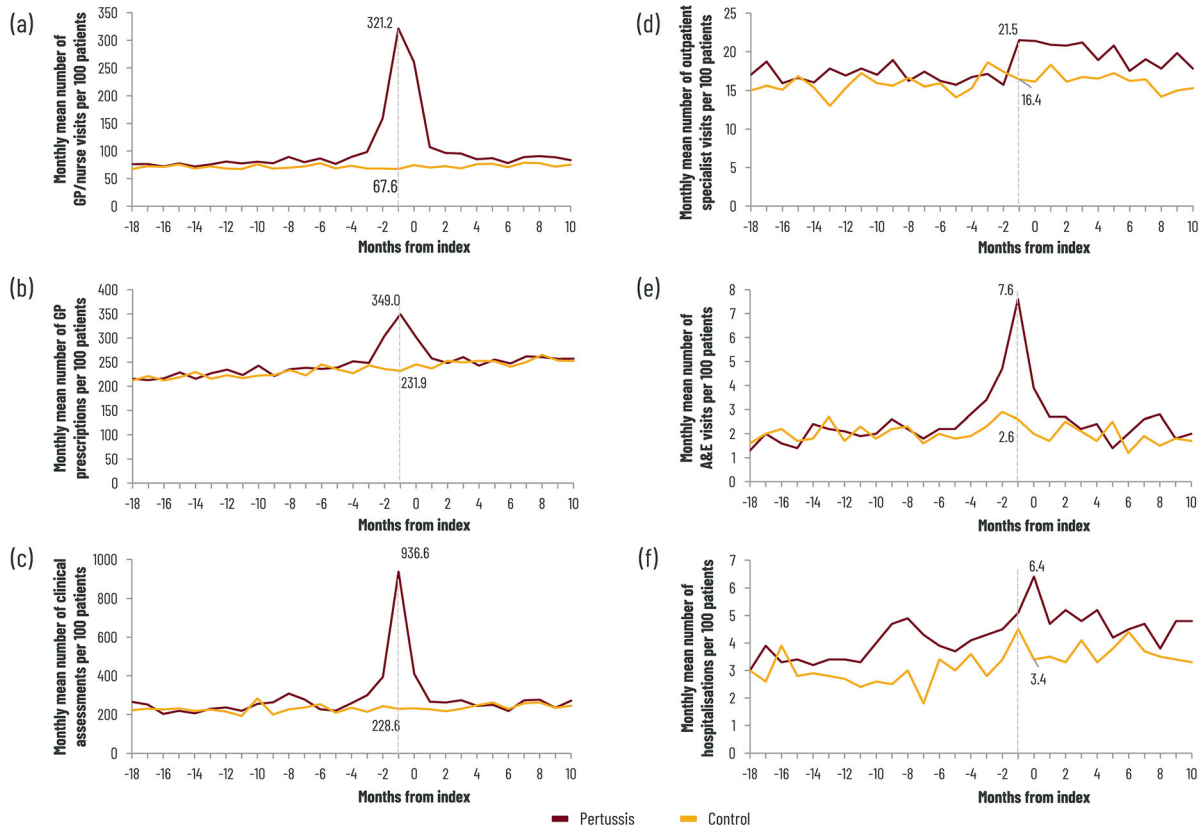


Fig. 5 Monthly[a] mean all-cause HCRU in the pertussis and control cohorts from – 18 months to 11 months around the index date (pertussis diagnosis). **a** GP/nurse visits; **b** GP prescriptions; **c** clinical assessments; **d** outpatient specialist visits; **e** A&E visits; **f** hospitalisations. *A&E* accident and emergency, *GP* general practitioner, *HCRU* health care resource utilisation. [a]Months are labelled according to the start time of each interval, e.g., utilisation reported at 0 m is the average from day 0 to day 30

occurred between – 6 months and the index date in the control group, it would result in an underestimation of the HCRU due to pertussis rather than an overestimation.

The excess cost estimation from the GLM included costs from months – 1 to 11, but some HCRU started to increase as early as 4 months before a pertussis diagnosis, so this cost may also be an underestimation. Only the top five GP prescription medications were included in the DMC estimations; hence, total prescription costs would have been slightly higher. Furthermore, if we had been able to include non-direct costs and quality of life measures, the burden of pertussis would have been higher [11].

Finally, given that sociodemographic characteristics, vaccination schedules, and health care systems vary considerably by country, the results of this study are not expected to be generalisable to other countries.

CONCLUSION

The incidence rate of diagnosed pertussis among adults aged ≥ 50 years in England was 5.8 per 100,000 PYFU. Reported pertussis among these older adults resulted in significantly higher levels of HCRU and DMC. This started several months before diagnosis, suggesting a lengthy time to diagnosis, prescriptions for antibiotics not specific to pertussis, unnecessary corticosteroids, and potentially allowing transmission of this highly infectious

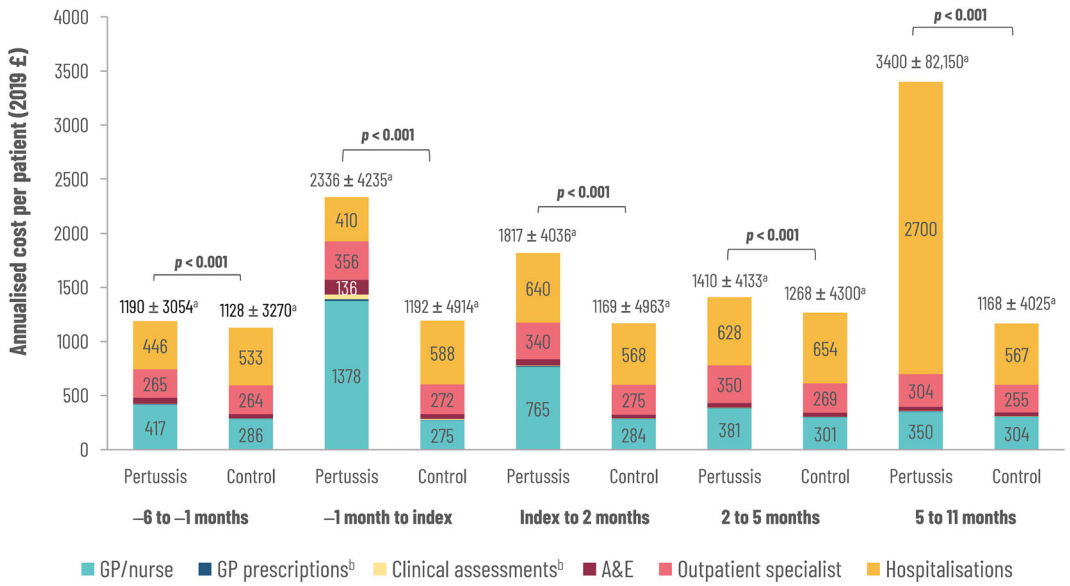


Fig. 6 Annualised DMC[a] per individual in the pertussis and control cohorts during the various time periods of the study. *p*-values were calculated using the Wilcoxon rank-sum test. For details of the unit costs used, please see Supplementary Text S3. *A&E* accident and emergency, *DMC* direct medical costs, *GP* general practitioner, *SD* standard deviation. [a]Values above bars show total mean ± SD annualised DMC per individual. Absolute values can be found in Supplementary Table S9. [b]Top five prescription medications or clinical assessments (in the pertussis cohort; during each time period)

pathogen. Elevated HCRU also persisted for months after a pertussis diagnosis, suggesting a long-term health impact, which deserves further exploration. Overall, these results highlight the need for increased awareness of pertussis infection among adults aged ≥ 50 years and suggest that pertussis booster doses in this population should be considered.

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Ramond, and Dimitra Lambrelli verified the underlying data in the study.

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Compliance with Ethics Guidelines. The study protocol received Clinical Practice Research Datalink (CPRD) approval via the Independent Scientific Advisory Committee on March 4, 2020 (protocol number 20_043). The supply of data through CPRD is governed by regulatory permissions and approvals for the purposes of public health research only. The study complied with all applicable laws regarding subject privacy.

Data Availability. The datasets analysed during the current study are not publicly available as CPRD/HES data are accessed via a license, the terms of which do not allow for the sharing of raw data. The data can be requested via application to the CPRD.

Disclaimer. This study is based in part on data from the CPRD 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.

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