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ORIGINAL RESEARCH

Epidemiology of Pertussis and Pertussis-Related Complications in Adults: A German Claims Data Analysis

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ABSTRACT

Introduction: Pertussis is a highly contagious respiratory infection. It affects people of all ages, yet evidence of the impact of pertussis in adults with underlying conditions (UCs) is scarce. This study investigated the incidence and complication rate of pertussis in adult patients with and without UC.

Methods: A retrospective analysis was conducted using routinely collected German claims data between 2015 and 2019. Patients with and without different pneumological, cardiovascular, endocrinological, musculoskeletal, and psychological UCs were matched for incidence estimation. Logistic regression models were used to estimate the risk of pertussis depending on the presence of UCs. Negative binomial models were used to assess complication rates in patients with pertussis and with and without UC.

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Results: In total, 4383 patients were diagnosed with pertussis during the study period. Patients with any UC had an increased risk for pertussis compared to matched patients without UC (odds ratio [OR] 1.72; 95% confidence interval [CI]1.60–1.84, $p < 0.0001$). Underlying asthma had the highest risk of pertussis (OR 2.70; 95% CI 2.50–2.91, $p < 0.0001$), followed by chronic obstructive pulmonary disease (OR 2.35; 95% CI 2.10–2.60, $p < 0.0001$) and depression (OR 2.08; 95% CI 1.95–2.22, $p < 0.0001$). Severe complications occurred in 10.8% of the pertussis cohort (13.4% with UC vs. 9.5% without UC). The UC-attributable effect on the risk of severe pertussis-related complications was significantly increased for any UC (incidence rate ratio [IRR] 1.29, 95% CI 1.19–1.39). The severe complication risk was also increased for patients aged 60+ (IRR 1.59, 95% CI 1.46–1.72).

Conclusion: This study shows that adults with certain UCs have an increased risk for pertussis and are more likely to have complications. These results provide further evidence that pertussis is a relevant and impactful infectious disease in adults with and without certain UC, indicating that these patients need to be considered when developing vaccination recommendations to avoid pertussis and its associated complications.

A graphical abstract is available with this article.

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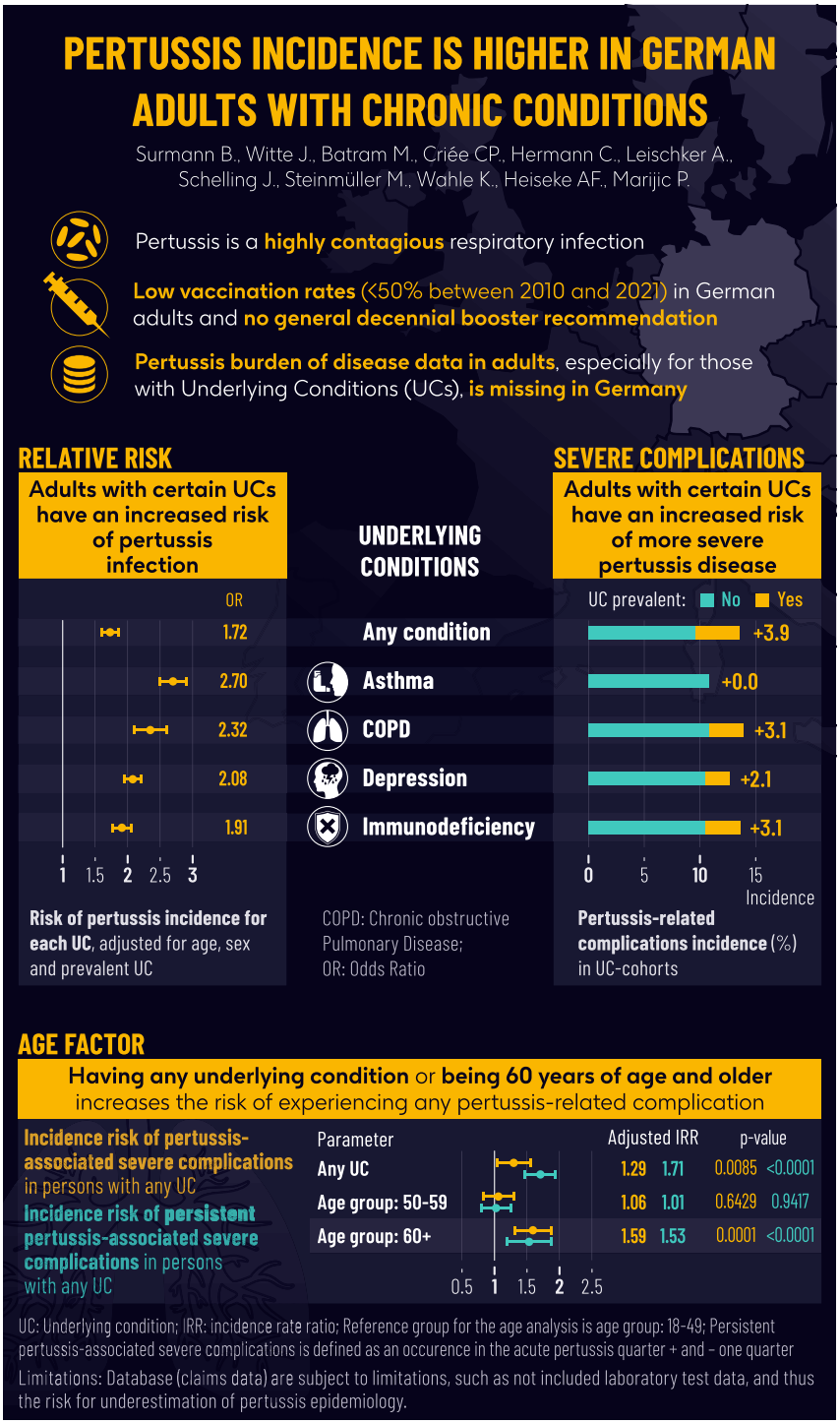
Graphical Abstract:



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PEER-REVIEWED FEATURE

Keywords: Pertussis; Whooping cough; Comorbidity; Risk factor; Real world evidence; Older adults; Incidence

Key Summary Points

Why carry out this study?

Evidence on pertussis burden in patients with underlying conditions is scarce but needed for an accurate evaluation of vaccination recommendations and implementation of policy measures in at-risk populations.

This study aims to investigate the incidence and complication rate of pertussis in adults with and without underlying conditions.

What was learned from the study?

The risk of pertussis incidence and pertussis-associated complications is higher in patients with underlying conditions compared to other persons.

Patients with any considered underlying condition, but especially with asthma, chronic obstructive pulmonary disease, and depression, have a significant increased risk of pertussis.

Besides present underlying conditions, age (60+ years) is an additional risk factor for pertussis-related severe complications such as hospitalization.

DIGITAL FEATURES

This article is published with digital features, including a graphical abstract, to facilitate understanding of the article. To view digital features for this article, go to https://doi.org/10.6084/m9.figshare.24877749.

INTRODUCTION

Pertussis (also known as whooping cough) is a highly contagious bacterial disease caused by the bacterium *Bordetella pertussis* that mainly affects the upper respiratory tract [1]. Pertussis is widely considered a childhood disease. In adults, the disease often only manifests itself with atypical non-specific symptoms such as rhinitis, prolonged cough, and sometimes fever, which are usually associated with a common cold. Hence, these symptoms can be misinterpreted as a common cold, though the duration of pertussis is considerably longer and can last up to months [2].

Despite a recommendation of the German Standing Committee on Vaccination (STIKO) to vaccinate adults against pertussis, vaccination rates in adults are relatively low. Based on national vaccination coverage data, more than 50% do not receive a booster in adulthood and the incidence of pertussis remains high in all age groups, with more than 60% of all cases in patients aged 18 years and older, and more than 30% in patients aged 50 years and older [3]. Even fatal pertussis courses have recently been recorded in the 65+ age group [4]. In Germany, pertussis became notifiable in eastern federal states in 2002 and nationwide in March 2013. Yet, underreporting is expected to be around 21–40% [5] indicating that the real burden due to pertussis disease might be higher, given the challenges regarding detecting the disease, especially in adults: pertussis often shows atypical symptoms and, hence, likely underreporting in national surveillance statistics [6, 7].

International evidence suggests that patients 50+ years of age and patients with certain underlying conditions (UCs), i.e., chronic illnesses, are at increased risk of hospitalization and complications of pertussis [4, 8]. However, in most surveillance systems, there is little information about the characteristics of people affected by an infectious disease. For example, in the official national surveillance statistics of the use of German healthcare system [9], no differentiation between at-risk and non-at-risk populations can be made.

This study aims to determine the incidence of pertussis and pertussis-associated severe complications in adults with and without UCs. As evidence on the burden of pertussis in Germany among adults with UCs is lacking, we also aim to determine the disease burden of pertussis in adults with and without UCs.

MATERIAL AND METHODS

Study Design

The study uses a retrospective, matched cohort design, and has been conducted in accordance with applicable subject privacy requirements and the guiding principles of the Declaration of Helsinki of 1964. The analysis was based on secondary claims data and, as such, the consultation of an ethics committee was not required [10].

Database

Analyses were based on anonymized routinely collected claims data from the German Statutory Health Insurance (SHI), covering the period of 2015–2019. The dataset comprises information on up to five million people insured at 19 sickness funds, representing 6.3% of the SHI population in Germany. The data is provided by GWQ ServicePlus AG, a joint venture of medium-sized health insurers in Germany. Overall, 87% of the German population is insured within the SHI system [11]. Based on comparison with official statistics published by the Germany Health Ministry on the German statutory health insurance ("KM6"), the dataset is representative of the German SHI population in terms of age and gender distribution [12]. Diagnostic data include all diagnoses documented during physician outpatient contacts and patient hospital stays. Laboratory or clinical parameters were not included. A general description of the claims database in the German setting can be found in Swart et al. [10].

Study Population

The initial dataset contained all adults aged 18 years and older in the years 2015–2019. Individual information on the year of birth is aggregated to 5-year intervals in the anonymization process. To ensure that all patients are at least 18 years of age, the age was computed as the difference between the year under study and the upper bound of the age interval.

Based on the literature and in consultation with a medical expert panel, the following UCs were defined as potential risks: asthma, chronic obstructive pulmonary disease (COPD), osteoporosis, rheumatoid arthritis, depression, immunodeficiency, heart failure (HF), chronic heart disease (CHD), chronic kidney disease (CKD), diabetes mellitus type 2 (DMT2), and diabetes mellitus type 1 (DMT1). While there may be other UCs with an impact on pertussis, in this manuscript UCs always refer to these risk constellations. For a detailed description of how these diagnoses were validated with the corresponding International Classification of Diseases (ICD), 10th revision, German Modification (ICD-10-GM) diagnosis codes and prescription codes (based on the Anatomical Therapeutic Chemical [ATC] Classification), see Table S1.

An individual was identified as having a specific UC if either an inpatient or an assured outpatient diagnosis was documented in at least two out of four quarters of two consecutive years. Patients were included in the study population if they were diagnosed with the respective UC in the years from 2016 to 2019. As the year under consideration always had to be validated by the previous year, data from 2015 was used as a wash-in period. A patient may belong to more than one UC group. A matched cohort design was adopted; patients with at least one UC were matched to controls without UC by exact matching. Matching variables also included age in 5-year intervals and sex of the patients. Matched pairs were observed for the same period of time (until one of them died or left the SHI).

Pertussis was broadly defined as having at least one diagnosis of ICD-10-GM A37.0

(Whooping cough due to Bordetella pertussis) or A37.9 (Whooping cough, unspecified). The diagnosis could either be in- or outpatient. As a sensitivity analysis, a narrow definition only considering the diagnosis of ICD-10 A37.0 is reported. Incident pertussis cases were defined as cases without a pertussis diagnosis in the preceding year; hence, information from 2015 was again used as washout period. The index quarter was defined as the quarter when pertussis was first observed.

A pertussis-associated complication was counted if it occurred in the index quarter and was not observed in the four quarters preceding the index quarter and, hence, was incident (except for hospital visits). We distinguished between severe and less severe complications. Severe complications comprised pneumonia, rib fractures, and all-cause hospitalizations but not including the following less severe complications. Otitis media, encephalopathy, abnormalities of breathing, seizures, inguinal and umbilical hernia, intracranial hemorrhage, incontinence, loss of weight, sarcopenia, and gait abnormality were counted as less severe complications (see Table S2 in the supplementary material for used ICD-10-GM codes). Results were also summarized as any complications that occurred. In the sensitivity analyses, the complication could also be diagnosed in the quarter prior to the index quarter and/or in the quarter following the index quarter. In the following, data based on the broad pertussis definition are presented unless described otherwise.

Statistical Analysis

In the analysis of pertussis incidence, rates were calculated for both the narrow and the broad definitions of pertussis and reported separately for patients with any UC, with no UC, and with one of the specific UCs, as well as for age groups (i) 18–49, (ii) 50–59, and (iii) 60 and older.

To analyze the risk of pertussis for each UC, logistic regression models, controlled for age and sex, were fitted to the pooled data of the matched population (cases and controls) from 2016 to 2019. Separate models were fitted for patients with any UC, and for each UC compared to matched persons without UC respectively. In a sensitivity analysis, a model with all UCs as covariates was fitted to check the robustness of the results. As a result of small sample sizes for the narrow case definition, a model with a single coefficient for any UC was fitted, not considering each UC separately. The resulting odds ratios are reported with corresponding 95% confidence intervals (CIs).

In the analysis of pertussis-associated complications, patients with pertussis and UCs were compared to patients with pertussis and no UC. A complication was considered to be pertussis-associated, if it was observed in the same quarter as the pertussis. Complications were counted for all years under study and reported as complication rates in patients with pertussis and with UC and without UC. To estimate the incidence rate of complications, a negative binomial regression model controlled for age, sex, and any UCs was fitted to the number of individual complications in the pertussis cohort. The analyses for complications were rerun in sensitivity analyses, where complications could also be observed in the quarter before or after the pertussis quarter.

To assess whether there is an association between specific age groups and the risk of complications, a negative binomial regression model, including age groups 18–49, 50–59, and 60+ as covariates, was estimated.

All analyses were performed with R (version 4.1.3) using the MatchIt package for matching, the glm function for logistic regression models, and the glm.nb function of the MASS package for negative binomial regression models.

RESULTS

Study Cohort

The size and the characteristics of the study cohorts with and without UC are shown in Table 1. The number of patients with UC ranged from 787,123 in 2016 to 898,479 in 2019, and the number of patients without UC ranged from 2.5 million in 2016 to 2.7 million in 2019. The average age of patients without UC in the years of the study was between 43.1 and 44.6 years

Table 1 Patient characteristics of the study cohorts with and without underlying condition (prior to matching)

	2016		2017		2018		2019	
	UC	No UC	UC	No UC	UC	No UC	UC	No UC
Number of patients	787,123	2,585,614	827,756	2,567,771	870,587	2,743,228	898,479	2,708,832
Age (years)								
Mean (SD)	60.4 (16.7)	44.6 (15.7)	60.6 (16.6)	43.1 (15.6)	60.3 (17.1)	43.7 (16.6)	60.7 (16.9)	43.8 (16.9)
Age groups (%)								
18–49	22.3%	60.7%	23.4%	61.5%	25.4%	65.3%	26.2%	66.1%
50–59	22.1%	21.5%	22.8%	21.3%	23.2%	19.4%	23.8%	19.2%
> 60	55.6%	17.8%	53.8%	17.1%	51.5%	15.2%	50.0%	14.7%
Sex (%)								
Male	46.6%	51.7%	46.8%	41.7%	46.8%	51.7%	46.7%	51.7%
Female	53.4%	48.3%	53.2%	48.3%	53.2%	48.3%	53.3%	48.3%

UC Underlying condition, *SD* standard deviation

and was substantially lower than the age of patients with UC, which was between 60.3 and 60.7 years. The difference between the two study cohorts is also reflected in the proportions of the respective age groups. The percentage of women in the group of patients with UC was always slightly higher than in the group of patients without UC over the years. Table S3 in the supplementary material shows the proportions of patients with specific UCs.

Pertussis Incidence in Patients With and Without Underlying Condition

The patients' characteristics in the matched population are shown in Table S4, where all patients with UC could be matched. The total number of pertussis cases and the annual incidence of pertussis in patients with and without UCs in the matched cohort are shown in Table 2. In all study years, the incidence of pertussis in persons with any of the UCs was between 28% and 101% higher than in persons with no UCs. The incidence of pertussis was highest among patients with asthma, COPD, rheumatoid arthritis, and depression. Overall, the annual incidence of pertussis showed little variation over the years observed. In addition, there appears to be a decreasing trend in pertussis incidence overall and, apart from depression, COPD, and CHD in pertussis cases in each UC.

In the matched population overall, the incidence of pertussis was highest in patients aged 18–49 years and decreased with increasing age (Table 3). Except for the group of 18–49 years (2016), patients with UC generally had a higher pertussis incidence than patients without UC in all age groups 50+ years. The older the patients, the greater was the difference in pertussis incidence between patients with UC and patients without UC.

The results of the narrow case definition are presented in Tables S5 and S6 in the supplementary material, showing comparable results.

Risk of Pertussis Incidence in Persons with Underlying Condition

Except for heart failure and type 1 diabetes, all considered UCs were associated with a significantly higher risk for pertussis (Fig. 1). With a

Table 2 Total pertussis cases and pertussis incidence (cases per 100,000) in persons with underlying condition per year in the matched cohort

Underlying condition	2016	2017	2018	2019
Total pertussis cases	1136	1274	1055	918
Cases per 100,000				
Total	33.7	37.5	29.3	25.5
No UC	31.6	32.6	24.2	20.4
Any UC	40.4	52.8	45.5	41.1
Asthma	58.0	69.0	64.0	54.6
COPD	51.5	57.8	33.3	48.4
Osteoporosis	30.0	46.8	50.1	44.7
Rheumatoid arthritis	70.9	59.9	65.3	42.5
Depression	47.0	58.7	47.6	57.7
Immunodeficiency	45.9	52.7	49.5	37.5
Heart failure	NA	23.6	41.6	32.5
Chronic heart disease	27.5	33.0	28.2	31.4
Chronic kidney disease	30.8	43.5	34.1	21.3
Type 2 diabetes	28.5	39.6	31.7	21.1
Type 1 diabetes	NA	41.3	NA	NA

NA sample sizes in the database $n < 8$, *COPD* chronic obstructive pulmonary disease, *UC* underlying condition

2.7-fold increase in odds, patients with asthma had the highest risk of incident pertussis diagnosis compared to those without asthma. This is followed by patients with COPD and with depression.

If the narrow case definition was used, the risk of pertussis was also increased with a slightly higher odds ratio (OR 1.89; 95% CI 1.63–2.15, $p < 0.0001$) as compared to the OR for the broad case definition (OR 1.72; 95% CI 1.60–1.84, $p < 0.0001$) for patients with any UC vs. patients without UC.

In the model including all UCs as covariates, the results differ slightly from the main analyses (Fig. S1 in the supplementary material). No significant results were observed for rheumatoid arthritis, heart failure, and chronic kidney disease. All other estimates were significant but had slightly lower ORs compared to the main analysis.

Pertussis-Related Complications

Overall, 10.8% of the pertussis cohort experienced a severe complication, with the rate of complications being higher in patients with any UC compared to those without UC (13.4% vs. 9.5%). Less severe complications occurred also more frequently in patients with any UC (6.4% vs. 5.3%). Regardless of severity, the three most frequently observed pertussis-related complications were hospitalizations (36% of complications), abnormalities of breathing (22%), and pneumonia (21%). The largest differences between patients with and without UC were observed in patients with and without osteoporosis (28.7% vs. 16.2%) and in patients with

Table 3 Pertussis incidence (cases per 100,000) in persons with underlying condition per year and age group

UC	2016			2017			2018			2019		
	18–49	50–59	60+	18–49	50–59	60+	18–49	50–59	60+	18–49	50–59	60+
Total	65.9	26.8	11.1	68.7	32.6	12.4	53.6	21.0	10.6	45.3	19.3	8.5
No UC	69.1	22.0	6.2	68.6	24.7	5.0	51.7	14.0	3.8	42.5	11.0	3.3
Any UC	54.7	43.8	28.5	68.9	58.7	37.0	59.9	45.0	33.8	54.5	46.3	25.5

UC underlying condition

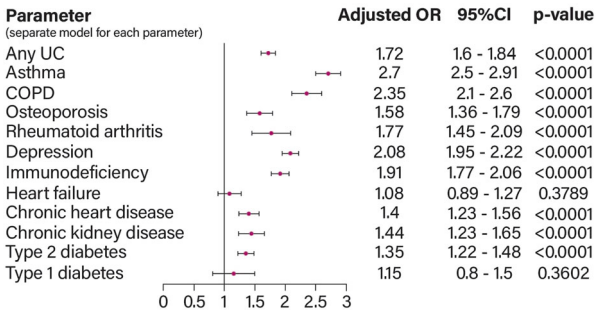

Fig. 1 Risk of pertussis incidence for each underlying condition separately, adjusted for age and sex. Rolling UC prevalence and pertussis incidence cohort, 2016–2019. *CI* confidence interval, *COPD* chronic obstructive pulmonary disease, *OR* odds ratio, *UC* underlying condition. Logistic regression models were used to estimate the risk of pertussis incidence. For each underlying condition and for the "Any UC" group, separate models were estimated. All models controlled for age and sex, but here only adjusted ORs for the UCs are reported

and without heart failure (31.1% vs. 16.3%). Smaller differences were observed for patients with depression, rheumatoid arthritis, and immunodeficiency. The complication rates and the differences in complication rates with and without respective UC are shown in Table 4.

Based on the negative binomial regression model, the UC-attributable effect on the risk of pertussis-related severe complications for any UC was 1.29 (95% CI 1.19–1.40, $p = 0.0085$). The severe complication risk was also increased for patients aged 60+ (incidence rate ratio [IRR] 1.59, 95% CI 1.46–1.71, $p = 0.0001$, see Fig. S2 in the supplementary material).

In the sensitivity analysis, which also considers complications occurring in the quarter before and after the quarter of pertussis incidence, the complication rate was considerably increased for nearly all UCs. Only the difference in the complication rate for rheumatoid arthritis remained almost the same. The complication rate for patients with COPD was more than three times higher when the quarters before and after pertussis incidence were taken into account. Table S7 shows the complication rates and the difference of complication rate for each UC. In the negative binomial model, a higher risk of severe complications was observed for patients with any UC, when compared to the model in the main analysis (IRR 1.71; 95% CI 1.63–1.79, $p < 0.0001$). When accounting for the quarters before and after pertussis incidence, the risk for those aged 60+ was even higher (IRR 1.53, 95% CI 1.43–1.63, $p < 0.0001$) (see Fig. S3 in the supplementary material).

DISCUSSION

The aim of this study was to determine the incidence of pertussis in patients with and without UCs, and to investigate whether there is an association between UCs in general or certain UCs in particular and the risk of pertussis. Additionally, this study analyzed the occurrence of pertussis-related complications among all patients, as well as patients with and without UCs. To our knowledge, this is the first study to investigate the epidemiology of pertussis in adult patients with various UCs based on a large representative claims dataset in Germany. The results showed an increased risk of incident pertussis diagnoses in patients with UCs in comparison to patients without UC. This

Table 4 Incidence (%) and absolute difference (percentage points) of pertussis-related complications in patients with pertussis and with or without UCs

UC		Severe complications								Less severe complications	
		Overall		Hospitalization		Pneumonia		Rib fractures		Overall	
		%	Δ	%	Δ	%	Δ	%	Δ	%	Δ
Disregarded	–	10.8	–	7.1	–	4.1	–	0.5	-	5.7	–
Any	Yes	13.4	3.9	8.5	2.2	5.5	2.1	0.7	0.3	6.4	1.1
	No	9.5		6.3		3.4		0.4		5.3	
Asthma	Yes	10.8	0.0	7.4	0.3	4.5	0.4	NA	NA	9.8	4.5
	No	10.8		7.1		4.1		NA		5.3	
COPD	Yes	13.8	3.1	9.0	2.0	7.2	3.2	NA	NA	7.2	1.6
	No	10.7		7.0		4.0		NA		5.6	
Osteo	Yes	20.0	9.4	12.2	5.2	7.8	3.8	NA	NA	8.7	3.1
	No	10.6		7.0		4.0		NA		5.6	
RA	Yes	14.3	3.5	NA	NA	NA	NA	NA	NA	5.2	− 0.5
	No	10.8		NA		NA		NA		5.7	
Depr	Yes	12.6	2.1	8.0	1.1	4.6	0.5	NA	NA	6.4	0.8
	No	10.5		6.9		4.1		NA		5.6	
Immun	Yes	13.6	3.1	8.2	1.3	5.6	1.7	NA	NA	5.9	0.2
	No	10.5		7.0		4.0		NA		5.7	
HF	Yes	29.5	19.0	19.7	12.8	14.8	10.8	NA	NA	1.6	− 4.1
	No	10.6		6.9		4.0		NA		5.7	
CHD	Yes	16.6	6.0	10.4	3.5	9.2	5.3	NA	NA	5.5	− 0.2
	No	10.6		7.0		3.9		NA		5.7	
CKD	Yes	16.9	6.2	NA	NA	11.7	7.7	NA	NA	3.9	− 1.8
	No	10.7		NA		4.0		NA		5.7	
DMT2	Yes	17.0	6.6	9.9	3.0	9.1	5.3	NA	NA	5.9	0.3
	No	10.4		6.9		3.8		NA		5.7	
DMT1	Yes	9.1	− 1.7	NA	NA	NA	NA	NA	NA	9.1	3.4
	No	10.8		NA		NA		NA		5.7	

NA sample sizes in the database $n < 8$, *CHD* chronic heart disease, *CKD* chronic kidney disease, *COPD* chronic obstructive pulmonary disease, *Depr* depression, *HF* heart failure, *Immun* immunodeficiency, *Osteo* osteoporosis, *RA* rheumatoid arthritis, *DMT1* type 1 diabetes mellitus, *DMT2* type 2 diabetes mellitus, *UC* underlying condition

concerned almost all investigated UCs, with the greatest risk in patients with asthma, COPD, and depression. Similar to other studies, the risk of being diagnosed with pertussis decreased with age [13, 14]. The general finding of a decreasing pertussis incidence is in line with other recently published results from the UK [13, 14] and with data from German official surveillance statistics [9]. However, the difference between age groups was smaller for patients with UCs than for those without UCs. This study also found an increased risk of pertussis-related complications among patients with UCs, with hospitalizations, breathing abnormalities, and pneumonia being the most common complications.

Evidence on the risk of pertussis in patients with UCs is scarce. Most previous studies included only small sample sizes, ranging between 33 and 524 pertussis cases in patients with UCs [13, 15–23]. Asthma and COPD are the most common UCs considered in published studies that show some signs of association with the risk of pertussis incidence [4, 8]. For asthma and COPD, the associated adjusted relative risk between the UC and pertussis incidence ranges between 1.64 to 4.06 [15, 17, 20]. Aris et al. and Bhavsar et al. reported incidence rates of pertussis in patients with asthma [16] and COPD [13] based on UK primary care datasets. For COPD, the reported pertussis incidence rate varied by year, with an average incidence rate of 4.73 (95% CI 3.74–5.91) per 100,000 person-years and incidence rates tended to decrease with increasing age [13]. Patients with underlying asthma had a higher incidence rate of 9.6 (95% CI 8.6–10.7) per 100,000 person-years compared to matched controls without asthma. While other studies on the risk of pertussis in patients with asthma relied on patient-reported diagnosis of pertussis, we relied on physicians' diagnoses. Interestingly, the obtained risks were generally consistent with our findings [8]. Other studies examined the association of pertussis incidence and underlying heart disease [15, 19–22], physical disabilities [15, 20], or obesity [15, 20]; two studies evaluated multiple UCs concurrently [21, 24]. These studies cover additional data on the associated risk of underlying gastroesophageal reflux disease, renal disease, autoimmune disease, and hyperlipidemia. Two systematic literature reviews have also already described the association of pertussis and UCs [4, 8]. These systematic reviews show relatively consistent results but also an open need for further research, especially regarding pertussis-associated complications and excess resource use and costs.

While age is not a relevant risk factor for developing pertussis, increasing age plays an important role in the likelihood of experiencing pertussis-related complications. This is in line with the results of several other studies, which have shown that complications occur with greater frequency as age increases [22]. In particular, the pertussis-related rate of hospitalization, the complication most commonly observed in this study, is substantially higher in adults aged 65 and over, and even higher in adults aged 75 and older [20, 25, 26].

The study design and methods face some limitations. First, there is no information on history of pertussis or pertussis vaccination prior to the observational period available to validate an incident study population. As a result of the too small number of cases, we have refrained from differentiating further age groups. However, evidence from the UK suggests that our finding of an absent age-related risk association of pertussis incidence might be biased [13]. In this regard, the effect of UCs and age may be underestimated in our study, as these patients may be more likely to receive vaccination compared to patients without comorbidities and those who are younger and therefore more protected. Second, the underlying data are collected for billing purposes. As no clinical parameters, laboratory test results, or information on health behavior are available in claims data, the analysis of pertussis in patients with UCs is limited by the available data. This relates to the risk of underdiagnosed pertussis cases, especially in persons without UC who may not see a doctor regularly. A comparison of laboratory data, notification data, and claims diagnosis data (only the last of these can be the basis of the present study because of separate data pools) would be a desirable approach to address epidemiological uncertainty [27]. Yet, at least in Germany, these data are stored in

separate data pools which cannot be merged, mostly because of data protection concerns. Additionally, matching was limited to age, sex, and UC. Potentially relevant variables such as the patient's socioeconomic status is not available for analysis because of data protection reasons. Third, the potential for upcoding must be considered for some of the reflected UCs and complications [28]. However, owing to our strict case definition (i.e., the UC had to be present in two consecutive years), this effect should be small. Fourth, self-selection of patients is possible. For example, patients with a severe underlying health condition might be more likely to seek pertussis-associated treatment (and thus be documented in claims data) than patients with fewer health problems. Therefore, the likelihood of being diagnosed with pertussis or being diagnosed with pertussis-related complications might increase with more regular visits to a practitioner, especially in patient with multimorbidity. However, for the complications, this effect might be low, as those are severe and diagnosed by the physician, and therefore less likely to be influenced by self-selection. Fifth, small sample sizes might lead to an underestimation of the UC-attributable effect in patient with heart failure and DMT1 that show no increased risk of pertussis. The strong risk association of underlying depression could in turn be explained by the increased levels of endogenous corticoids. Corticoid levels are continuously elevated in depression causing immunosuppression.

One of the primary strengths of this study is the large dataset, which includes a high number of pertussis cases and cases with UCs, providing a comprehensive database for the risk analyses. Additionally, the long observational period of 5 years allowed a better estimate of the risk association between UCs and pertussis as well as pertussis-associated complications. This study indicates that patients with UCs are vulnerable to pertussis and could require more protection. In addition, age is associated with a higher risk of pertussis-related complications.

CONCLUSIONS

This is the first analysis on the incidence of pertussis for populations with different UCs in the German healthcare setting, based on a representative claims dataset. The results confirm the higher incidence of pertussis diagnoses in German patients with certain UCs, as previously reported in the international context. However, these studies mostly focused on respiratory UCs. The present study confirms the significantly increased risk of incident pertussis diagnoses in persons with COPD and asthma, but also extends the knowledge about other relevant UCs such as osteoporosis, rheumatism, depression, immunodeficiency, chronic kidney disease, and type 2 diabetes. Thus, our findings have potential clinical implications regarding the implementation of vaccination recommendations for at-risk populations, especially in practical care guidelines (disease management program, guidelines).

Considering the consistent, yet still scarce evidence, further research is needed on the observed risk in persons with UCs. Primary data from physician practices and laboratory reference centers represent the best possible additional data source but are not publicly available. For this purpose, data from disease management programs would be useful as clinical and laboratory variables are recorded. Additionally, the pathogenetic mechanisms for the observed risks in depression, which was also associated with an increased risk for herpes zoster [29], need further investigation.

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Author Contributions. All authors designed the study. Bastian Surmann, Manuel Batram and Julian Witte had access to the database and performed the analyses. The statistical methodology was determined after discussion among all researchers. All authors interpreted the results, provided critical feedback, and contributed to the final manuscript.

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Data Availability. Project-specific access to an anonymized, selected study dataset for the analyses was provided by the GWQ ServicePlus AG. The data analyzed in this study are not publicly available due to data protection regulations and national legislation. All data-related processes of Vandage are under the data protection supervision of an external data protection officer.

Declarations

Conflict of Interest. Julian Witte and Manuel Batram own shares of Vandage GmbH. Vandage received funding from GSK to perform the study related to this manuscript. Vandage received payments from GSK, Janssen-Cilag GmbH, Sanofi-Aventis Deutschland GmbH, Viatris, Seqirus GmbH, MSD Sharp & Dohme GmbH and consulting fees and grants from AOK Rheinland/Hamburg, BARMER, DAK-Gesundheit, German G-BA, and Techniker Krankenkasse. Jörg Schelling declares receiving consulting fees and payments or honoraria for lectures, presentations, speakers' bureaus, manuscript writing, or educational events from Sanofi-Pasteur, GSK, MSD, Pfizer, Seqirus, Moderna, Biontech, AstraZeneca, Bavarian Nordic, Takeda and Novavax in the past 36 months. Jörg Schelling also declares participating on advisory boards for the companies listed above. Jörg Schelling has also received support for attending meetings and/or travel from Pfizer. Mirko Steinmüller declares having participated in an advisory board organized by GSK in relation with the current manuscript. Mirko Steinmüller also declares receiving payments or honoraria for lectures, presentations, speakers' bureaus, manuscript writing or educational events and support for attending meetings and/or travel from GSK, Pfizer, MSD and Seqirus. Mirko Steinmüller participated in advisory boards organized by the companies listed above. Andreas Leischker declares receiving honoraria for lectures, presentations, speakers' bureaus, manuscript writing or educational events from Sanofi-Pasteur, GSK, Takeda, Pfizer Vaccines, participating in an advisory board organized by Pfizer Vaccines, Sanofi-Pasteur and GSK and receiving funding from GSK to participate in an expert meeting in Potsdam. Christiane Hermann declares having served on an advisory board organized by GSK and receiving fees for that. Alexander Heiseke and Pavo Marijic are employees of GSK. Alexander Heiseke holds stock options from GSK. Bastian Surmann is an employee of Vandage and participated in advisory boards on behalf of Vandage. Carl Peter Criée and Klaus Wahle declare no financial or non-financial relationships and activities and no conflicts of interest. Bastian Surmann, Julian Witte, Manuel Batram, Christiane Hermann, Andreas Leischker, Jörg Schelling, Mirko Steinmüller, Alexander Heiseke and Pavo Marijic declare no other financial or non-financial relationships and activities and no other conflicts of interest.

Ethical Approval. The analysis was based on secondary claims data and, as such, the consultation of an ethics committee was not required. This study was performed in accordance with the Helsinki Declaration of 1964 and its later amendments.

REFERENCES

1. Mattoo S, Cherry JD. Molecular pathogenesis, epidemiology, and clinical manifestations of respiratory infections due to Bordetella pertussis and other Bordetella subspecies. Clin Microbiol Rev. 2005;18(2):326–82. https://doi.org/10.1128/CMR.18.2.326-382.2005.

2. Senzilet LD, Halperin SA, Spika JS, Alagaratnam M, Morris A, Smith B. Pertussis is a frequent cause of prolonged cough illness in adults and adolescents. Clin Infect Dis. 2001;32(12):1691–7. https://doi.org/10.1086/320754.

3. Robert Koch-Institut. Epidemiologisches Bulletin: Impfquoten bei Erwachsenen in Deutschland; 2022. https://www.rki.de/DE/Content/Infekt/EpidBull/Archiv/2022/Ausgaben/49_22.html. Accessed 6 Mar 2033.

4. Jenkins VA, Savic M, Kandeil W. Pertussis in high-risk groups: an overview of the past quarter-century. Hum Vaccin Immunother. 2020;16(11):2609–17. https://doi.org/10.1080/21645515.2020.1738168.

5. Schielke A, Takla A, von Kries R, Wichmann O, Hellenbrand W. Marked underreporting of pertussis requiring hospitalization in infants as estimated by capture-recapture methodology, Germany, 2013–2015. Pediatr Infect Dis J. 2018;37(2):119–25. https://doi.org/10.1097/INF.0000000000001698.

6. Kandeil W, Atanasov P, Avramioti D, Fu J, Demarteau N, Li X. The burden of pertussis in older adults: what is the role of vaccination? A systematic literature review. Expert Rev Vaccines. 2019;18(5):439–55. https://doi.org/10.1080/14760584.2019.1588727.

7. McGuiness CB, Hill J, Fonseca E, Hess G, Hitchcock W, Krishnarajah G. The disease burden of pertussis in adults 50 years old and older in the United States: a retrospective study. BMC Infect Dis. 2013;13:32. https://doi.org/10.1186/1471-2334-13-32.

8. Macina D, Evans KE. Pertussis in individuals with co-morbidities: a systematic review. Infect Dis Ther. 2021;10(3):1141–70. https://doi.org/10.1007/s40121-021-00465-z.

9. Robert Koch-Institut. SurvStat@RKI 2.0. 2023. https://survstat.rki.de/. Accessed 21 Nov 2023.

10. Swart E, Gothe H, Geyer S, et al. Gute Praxis Sekundärdatenanalyse (GPS): leitlinien und empfehlungen. Gesundheitswesen. 2015;77(2):120–6. https://doi.org/10.1055/s-0034-1396815.

11. Busse R, Blümel M, Knieps F, Bärnighausen T. Statutory health insurance in Germany: a health system shaped by 135 years of solidarity, self-governance, and competition. Lancet. 2017;390(10097):882–97. https://doi.org/10.1016/S0140-6736(17)31280-1.

12. Bundesministerium für Gesundheit. Mitglieder und Versicherte der Gesetzlichen Krankenversicherung (GKV): Statistik uber Versicherte, gegliedert nach Status, Alter, Wohnort und Kassenart; 2020. https://www.bundesgesundheitsministerium.de/themen/krankenversicherung/zahlen-und-fakten-zur-krankenversicherung/mitglieder-und-versicherte. Accessed 21 Nov 2023.

13. Aris E, Harrington L, Bhavsar A, et al. Burden of pertussis in COPD: a retrospective database study in England. COPD. 2021;18(2):157–69. https://doi.org/10.1080/15412555.2021.1899155.

14. Harrington L, Aris E, Bhavsar A, et al. Burden of pertussis in adults aged 50 years and older: a retrospective database study in England. Infect Dis Ther. 2023;12(4):1103–18. https://doi.org/10.1007/s40121-023-00774-5.

15. Karki S, McIntyre P, Newall AT, MacIntyre CR, Banks E, Liu B. Risk factors for pertussis hospitalizations in Australians aged 45 years and over: a population based nested case-control study. Vaccine. 2015;33(42):5647–53. https://doi.org/10.1016/j.vaccine.2015.08.068.

16. Bhavsar A, Aris E, Harrington L, et al. Burden of pertussis in individuals with a diagnosis of asthma: a retrospective database study in England. J Asthma Allergy. 2022;15:35–51. https://doi.org/10.2147/JAA.S335960.

17. Buck PO, Meyers JL, Gordon L-D, Parikh R, Kurosky SK, Davis KL. Economic burden of diagnosed pertussis among individuals with asthma or chronic obstructive pulmonary disease in the USA: an analysis of administrative claims. Epidemiol Infect. 2017;145(10):2109–21. https://doi.org/10.1017/S0950268817000887.

18. Capili CR, Hettinger A, Rigelman-Hedberg N, et al. Increased risk of pertussis in patients with asthma. J Allergy Clin Immunol. 2012;129(4):957–63. https://doi.org/10.1016/j.jaci.2011.11.020.

19. Del Cid FJ, Salazar M, Argueta-Sosa EE. Vaccine-preventable disease hospitalized patients with heart failure with reduced ejection fraction. Clin Cardiol. 2022;45(5):474–81. https://doi.org/10.1002/clc.23800.

20. Liu BC, McIntyre P, Kaldor JM, Quinn HE, Ridda I, Banks E. Pertussis in older adults: prospective study of risk factors and morbidity. Clin Infect Dis. 2012;55(11):1450–6. https://doi.org/10.1093/cid/cis627.

21. Wolter N, Cohen C, Tempia S, et al. Epidemiology of pertussis in individuals of all ages hospitalized with respiratory illness in South Africa, January 2013–December 2018. Clin Infect Dis. 2021;73(3):e745–53. https://doi.org/10.1093/cid/ciab089.

22. De Serres G, Shadmani R, Duval B, et al. Morbidity of pertussis in adolescents and adults. J Infect Dis. 2000;182(1):174–9. https://doi.org/10.1086/315648.

23. Leong RNF, Wood JG, Liu B, McIntyre PB, Newall AT. High healthcare resource utilisation due to pertussis in Australian adults aged 65 years and over. Vaccine. 2020;38(19):3553–9. https://doi.org/10.1016/j.vaccine.2020.03.021.

24. Kim H, Shin J-Y, Chen J, et al. Risk factors of pertussis among older adults in South Korea: a nationwide health data-based case-control study. Infect Dis Ther. 2023;12(2):545–61. https://doi.org/10.1007/s40121-022-00747-0.

25. Clarke MF, Rasiah K, Copland J, et al. The pertussis epidemic: informing strategies for prevention of severe disease. Epidemiol Infect. 2013;141(3):463–71. https://doi.org/10.1017/S095026881200091X.

26. Skoff TH, Hadler S, Hariri S. The epidemiology of nationally reported pertussis in the United States, 2000–2016. Clin Infect Dis. 2019;68(10):1634–40. https://doi.org/10.1093/cid/ciy757.

27. Kern DM, Davis J, Williams SA, et al. Validation of an administrative claims-based diagnostic code for pneumonia in a US-based commercially insured COPD population. Int J Chron Obstruct Pulmon Dis. 2015;10:1417–25. https://doi.org/10.2147/COPD.S83135.

28. Kreis K, Neubauer S, Klora M, Lange A, Zeidler J. Status and perspectives of claims data analyses in Germany—a systematic review. Health Policy. 2016;120(2):213–26. https://doi.org/10.1016/j.healthpol.2016.01.007.

29. Batram M, Witte J, Schwarz M, et al. Burden of herpes zoster in adult patients with underlying conditions: analysis of German Claims Data, 2007–2018. Dermatol Ther (Heidelb). 2021;11(3):1009–26. https://doi.org/10.1007/s13555-021-00535-7.

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