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Immunogenicity and safety of reduced-antigen tetanus, diphtheria and acellular pertussis vaccination in adults treated for obstructive airway diseases

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ABSTRACT

Patients with obstructive airway diseases (OAD), like chronic obstructive pulmonary disease (COPD) and asthma, may be at increased risk of pertussis infection. Pertussis may also trigger COPD and asthma exacerbations. Vaccination against pertussis could help protect OAD patients from the additional burden of pertussis, but there may be hesitancy related to vaccine safety and immunogenicity in such patients. We performed a meta-analysis on 5 clinical trials in adults receiving reduced-antigen tetanus-diphtheria-acellular pertussis vaccine (Tdap, *Boostrix*, GSK), from which we selected participants on active OAD treatment. We compared immunogenicity and reactogenicity outcomes of the meta-analysis with data from the overall populations of Tdap-vaccinated adults from 6 Tdap trials (including the 5 in the meta-analysis). The meta-analysis comprised 222 adults on active standard OAD treatment. One month post-Tdap, 89.0% and 97.2% of these adults, respectively, achieved seroprotective anti-diphtheria and anti-tetanus antibody concentrations; 78.3%–96.1% showed booster responses across the 3 pertussis antigens. These rates were consistent with those in the comparator population. The most frequently reported solicited local and systemic adverse events within 4 days post-Tdap were injection site pain (47.7%) and fatigue (19.3%), with low rates of grade 3 intensity (0.9% and 2.8%). This was consistent with Tdap reactogenicity in the comparator population. Evaluation of unsolicited and serious adverse events within 1 month post-Tdap did not identify safety concerns. In conclusion, Tdap was immunogenic and well tolerated in adults under active standard OAD treatment, with immunogenicity and safety profiles consistent with those in a comparator population representing the general adult population.

PLAIN LANGUAGE SUMMARY

Whooping cough is a very contagious respiratory disease that is most dangerous for young babies but can affect people of all ages. People with chronic lung diseases like asthma or chronic obstructive pulmonary disease (COPD) may be more likely to get ill and suffer from complications from whooping cough. Vaccination against whooping cough is an important way to help protect these people. However, some doctors may hesitate to vaccinate patients because they may worry that vaccination could worsen asthma or COPD symptoms or that drugs taken by these patients could make vaccines work less well. We therefore looked at the immunogenicity and safety of a whooping cough vaccine (*Boostrix*, GSK) in adults treated for chronic lung diseases like asthma or COPD. We analyzed data from 5 previous clinical studies and specifically selected data from patients taking standard medication for chronic lung diseases in these studies. We found that the immune response to whooping cough vaccination in these patients was comparable to that in a comparator group representative of the general adult population receiving *Boostrix*. The vaccine was as well tolerated in patients with chronic lung diseases as in the general adult population. Our results suggest that the whooping cough vaccine *Boostrix* can be safely given to adults taking standard medication for chronic lung diseases to help prevent severe illness and complications from whooping cough.

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Introduction

Pertussis, or whooping cough, is a highly contagious respiratory infection primarily caused by the bacterium *Bordetella pertussis*.[1] Mortality and morbidity of pertussis are highest in young infants, and widespread pediatric vaccination programs have helped reduce the burden of pertussis infection.[1,2] Neither natural *B. pertussis* infection nor vaccination provides lifelong protection, as the immune response induced by infection and vaccination wanes over time.[3–6] Adolescents and adults are thus susceptible to pertussis infection (even if they were vaccinated in childhood) and represent a reservoir for transmission to infants.[1] Adolescent booster vaccination against pertussis is now recommended in many countries worldwide,[7–9] and a growing number of countries, including the United States (US), have recommendations for pertussis booster vaccination in adults.[9–13] However, vaccination coverage in adults remains low.[14]

Pertussis symptoms in adults are usually mild, but individuals with obstructive airway diseases (OAD), such as asthma and chronic obstructive pulmonary disease (COPD), may be at increased risk of pertussis infection and complications.[15–20] Asthma and COPD are the 2 most prevalent chronic

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respiratory diseases[21] and are estimated to each affect between 250 and 400 million people worldwide.[22,23] Exacerbations (episodes of acute worsening of respiratory symptoms, often triggered by viral or bacterial infections) are a major contributor to the burden of both asthma and COPD.[24,25]

A retrospective study in the US showed that the incidence of pertussis was higher among adolescents and adults with preexisting COPD or asthma than among those without and that these patients may experience longer-term negative health consequences from pertussis.[18] Another study of patients hospitalized with pertussis in the US found that 43.5% of patients aged 12–20 years and 26.8% of patients aged ≥65 years had a history of asthma, and 26.8% of patients aged ≥65 years had a history of COPD.[19] Pertussis infection in adults with COPD and asthma may trigger exacerbations of their underlying conditions, which may lead to increased hospitalization rates.[15] Accordingly, retrospective studies have shown that pertussis infection resulted in increased healthcare resource utilization and medical expenses in patients with COPD or asthma.[18,26,27] Furthermore, in a case series in Canada, pertussis was associated with increased use of bronchodilator aerosol in 93% of patients with preexisting pulmonary disease, including COPD and asthma.[28]

Pertussis vaccination could be an important means to better protect adults with OAD from the potential additional burden of pertussis disease and to minimize the occurrence of exacerbations. The US Centers for Disease Control and Prevention (CDC) advise reduced-antigen tetanus, diphtheria and acellular pertussis (Tdap) vaccination for adults with lung diseases, including COPD and asthma.[29] The Global Initiative for Chronic Obstructive Lung Disease guidelines for prevention, diagnosis and management of COPD refer to the CDC position to administer Tdap vaccination in adults with COPD (who were not vaccinated in adolescence) to protect against pertussis.[22]

Nevertheless, healthcare providers and patients may be hesitant about vaccination because of the perception that vaccination may increase the risk of exacerbations in patients with OAD[30–32] or may be less effective due to reduced immunity in these patients or to immunosuppressive effects of some OAD medications.[32,33] Therefore, data are needed to assess the immunogenicity and safety of Tdap vaccination in patients with OAD. As a first attempt to provide such data, we performed a meta-analysis based on data from Tdap-vaccinated adults under active standard OAD treatment collected in clinical trials.

Patients and methods

Selection of studies for the meta-analysis

This study aimed to review available immunogenicity and safety data collected in clinical trials in adults following Tdap or Tdap-inactivated poliovirus (IPV) vaccination (*Boostrix* or *Boostrix-IPV*, GSK). Data were extracted from participants who had agreed to further research on their data in the informed consent forms from the initial studies.

Since COPD predominantly occurs in adults aged 40 years and older,[22] studies were only included in the meta-analysis if a substantial number of the vaccinated participants were over 40 years of age. Studies on pregnant women and follow-up or revaccination studies evaluating the same participants as the primary study were excluded. Studies were also excluded if fewer than 15 adults under OAD treatment were identified. For the safety analysis, studies were excluded if unsolicited adverse events (AEs) were not coded using the Medical Dictionary for Regulatory Activities (MedDRA). Five studies, all evaluating Tdap vaccine, met the inclusion criteria for the meta-analysis: Tdap-002 (NCT01267058),[34] Tdap0.3–007 (NCT00346073),[35] Tdap0.3–008 (NCT00385255),[36,37] Tdap0.3–011 (NCT00835237)[37] and Zoster-042 (NCT02052596)[38] (Table S1). For 1 study (Tdap-002),[34] a waiver of consent for this meta-analysis was obtained from the relevant Independent Ethics Committee. Information on the 5 studies (including relevant eligibility criteria for participants) is shown in Table S2.

Studies used for the comparator population

The results of the meta-analysis were compared with data from the overall populations of Tdap-vaccinated participants from the 5 studies selected for the meta-analysis and from study Tdap-003 (NCT01262924).[39] Study Tdap-003 was excluded from the meta-analysis because it predominantly enrolled adults younger than 40 years. Studies Tdap-002 and −003 are representative studies referred to in the European Union Tdap product label[34,39,40] and Tdap 0.3–007 and −011 in the US product label.[35,37,41] The overall populations of Tdap-vaccinated participants in these 6 studies were considered to represent the general adult population in terms of Tdap vaccination immunogenicity and safety. In total, this comparator population comprised 4171 participants ≥18 years old (total vaccinated cohort, Tdap groups).

Study objectives and endpoints

The primary immunogenicity objective was to evaluate the humoral immune response to Tdap in adults under treatment for OAD in terms of anti-diphtheria (D) and anti-tetanus (T) seroprotection rates and anti-pertussis toxoid (PT), anti-filamentous hemagglutinin (FHA) and anti-pertactin (PRN) booster response rates 1 month after vaccination. The secondary immunogenicity objective was to evaluate the immune response in terms of anti-D, anti-T, anti-PT, anti-FHA and anti-PRN antibody geometric mean concentrations (GMCs) and anti-PT, anti-FHA and anti-PRN seropositivity rates.

The safety objectives were to evaluate the rates of solicited (primary objective) and unsolicited and serious AEs (SAEs) (secondary objective) following Tdap vaccination in OAD-treated adults.

Data extraction

Adults using active standard treatment for OAD were identified based on the coded concomitant medication listings of each study, by using the Anatomical Therapeutic Chemical (ATC) Classification System codes R03 (drugs for OAD) and D07 (corticosteroids, dermatological preparations) and their subclasses. Code D07 was retained because glucocorticoids are often assigned to both the ATC subclasses "glucocorticoids" (R03BA) and "corticosteroids, plain" (D07A). The identified individuals were only retained if the indication for the ATC codes R03 and D07 specified use for asthma, COPD, emphysema or chronic bronchitis, or if the use was very likely to have been for asthma or COPD. This latter assessment was done by a medical doctor with experience in respiratory medicine. Study Tdap-002 used a World Health Organization (WHO) drug coding, in which adults treated for OAD were identified by WHO drug code 28, referring to treatment of asthma. For the data presented here, a post-hoc analysis was therefore performed in which ATC coding was applied retrospectively to study Tdap-002.

Data were extracted from adults in the Tdap groups of the selected studies. For co-administration studies, data were extracted from adults in the sequential administration groups following Tdap administration (Table S1).

Immunogenicity results were extracted pre- and 1 month post-Tdap vaccination. Solicited AEs reported within 4 days post-Tdap vaccination were extracted. Solicited local AEs considered for this study were pain, redness and swelling at the Tdap injection site only. Solicited general AEs were fatigue, fever, headache and gastrointestinal AEs (including nausea, vomiting, diarrhea and/or abdominal pain). Unsolicited AEs and SAEs reported within 31 days post-vaccination were extracted.

Statistical analysis

The meta-analysis was descriptive. Demographic characteristics of the adults included in the meta-analysis were summarized using descriptive statistics. Antibody concentrations had been measured by enzyme-linked immunosorbent assays (ELISAs) as described.[34–38] Two different pertussis ELISAs had been used in the different studies, and a conversion was applied to have comparable data for studies using the assays validated in 1998 or in 2014. The following multiplication factors were applied to the 2014 assay results: 1.783197 for anti-FHA, 1.106106 for anti-PT and 0.995625 for anti-PRN. Seroprotection for anti-D and anti-T was defined as an antibody concentration ≥0.1 international units (IU)/mL. An anti-D and anti-T cutoff of 1.0 IU/mL, indicative of long-term protection,[42] was also evaluated. Seropositivity for pertussis antigens was defined as an antibody concentration ≥5 ELISA units (EU/mL). Booster responses to PT, FHA and PRN were defined as follows: a post-vaccination antibody concentration ≥20 EU/mL for adults with a pre-vaccination concentration <5 EU/mL; a post-vaccination antibody concentration at least 4 times the pre-vaccination concentration for adults with a pre-vaccination concentration between 5 EU/mL and 20 EU/mL; and a post-vaccination antibody concentration at least twice the pre-vaccination concentration for adults with a pre-vaccination concentration ≥20 EU/mL.

The immunogenicity analysis was performed on the according-to-protocol cohort (as defined in each individual study). Anti-D and anti-T seroprotection rates, and pertussis seropositivity and booster response rates were calculated with exact 95% confidence intervals (CIs). GMCs (for all antigens) were calculated with 95% CIs by taking the anti-log of the mean of the $\log_{10}$ concentration transformations. For GMC calculations, antibody concentrations below the assay cutoffs were given an arbitrary value of half the respective cutoffs. No adjustments were done to pre-vaccination levels, and missing or non-evaluable measurements were not replaced.

The safety analysis was performed on the total vaccinated cohort. The percentages of adults reporting each solicited local and general AE were calculated with exact 95% CIs. The same calculations were performed for grade 3 (or other thresholds – see below) and vaccination-related solicited AEs. Solicited local AEs were all considered related to vaccination. Fever was defined as a temperature ≥38.0°C and was also analyzed using a threshold of >40°C. Redness and swelling were analyzed using diameter thresholds of ≥25 mm and ≥50 mm, which were close to the US Food and Drug Administration grading scale.[43] For other solicited AEs, we defined grade 3 as an AE that prevented normal activity. The percentages of adults with unsolicited AEs were tabulated with exact 95% CIs by MedDRA System Organ Class and Preferred Term. The same was done for grade 3 and vaccination-related unsolicited AEs. The percentages of SAEs and SAEs assessed as causally related to vaccination were tabulated. Withdrawals due to AEs and SAEs following Tdap vaccination were also described. For the solicited AE analysis, missing or non-evaluable measurements were not replaced, and only adults with documented safety data were included. For the analysis of unsolicited AEs, including SAEs, all vaccinated adults were considered.

For the comparison with the overall populations of Tdap-vaccinated participants from the 6 selected studies (representing the general adult population), the same definitions as in the meta-analysis were used for the different immunogenicity outcomes. The reactogenicity data (solicited AEs) from the selected representative clinical studies were recalculated post-hoc using the same thresholds for fever, redness and swelling as for the selected studies in the meta-analysis. Study Tdap-003 differed in criteria for evaluation of reactogenicity and was therefore not included in the reactogenicity comparison.

The statistical analyses were performed using SAS software (SAS Institute Inc., Cary, NC, US).

Table 1. Demographics and characteristics of adults under obstructive airway disease treatment (total vaccinated cohort).

Characteristic	OAD-treated adults (meta-analysis) N = 222
Age, years	
Mean ± SD	55.5 ± 17.6
Range	19.0–88.0
Age category, n (%)	
18–39 years	48 (21.6)
40–64 years	83 (37.4)
≥65 years	91 (41.0)
Gender, n (%)	
Female	141 (63.5)
Male	81 (36.5)
Geographical ancestry, n (%)	
White – Caucasian/European Heritage	201 (90.5)
Black or African American	14 (6.3)
Asian – Central/South Asian Heritage	1 (0.5)
Asian – Southeast Asian Heritage	1 (0.5)
Other	5 (2.3)
Country, n (%)	
United States	184 (82.9)
Australia	38 (17.1)
Study, n (%)	
Tdap-002	38 (17.1)
Tdap0.3-007	51 (23.0)
Tdap0.3-008	25 (11.3)
Tdap0.3-011	64 (28.8)
Zoster-042	44 (19.8)
ATC therapeutic class and pharmacological subclass, n (%)	
Drugs for obstructive airway diseases (R03)	222 (100)
Adrenergics, inhalants (R03A)	190 (85.6)
Other drugs for obstructive airway diseases, inhalants (R03B)	80 (36.0)
Adrenergics for systemic use (R03C)	130 (58.6)
Other systemic drugs for obstructive airway diseases (R03D)	22 (9.9)
Corticosteroids, dermatological preparations (D07)	24 (10.8)
Corticosteroids, plain (D07A)	24 (10.8)

OAD, obstructive airway disease; N, number of participants in the total vaccinated cohort; SD, standard deviation; n, number of participants in a given category; ATC, Anatomical Therapeutic Chemical.

Results

Demographics

Across the 5 studies included in the meta-analysis, 222 adults using OAD treatment were identified. In the total vaccinated cohort, the mean age at the time of Tdap vaccination was 55.5 years (standard deviation: 17.6), with 21.6% of adults aged 18–39 years, 37.4% aged 40–64 years and 41.0% aged ≥65 years. Most adults were female (63.5%) and white (90.5%). The percentages of adults identified from each study ranged from 11.3% to 28.8% (Table 1).

Among adults using ATC class R03 OAD drugs, the most commonly used treatments were "selective beta-2-adrenoreceptor agonists" (60.4%), "adrenergics in combination with corticosteroids or other drugs, excluding anticholinergics" (40.1%), "glucocorticoids" (19.4%) and "anticholinergics" (17.1%). Among "other systemic drugs for OAD," the most common was "leukotriene receptor antagonists" (8.6%) (Table S3).

Immunogenicity

One month after Tdap vaccination, 89.0% and 97.2% of adults treated for OAD had seroprotective anti-D and anti-T antibody concentrations (≥0.1 IU/mL); 67.0% and 92.4% had antibody concentrations ≥1.0 IU/mL, respectively (Table 2). GMCs were 1.8 IU/mL (95% CI: 1.4; 2.3) for anti-D and 6.4 IU/mL (5.4; 7.7) for anti-T antibodies. Booster response rates were 78.3% for anti-PT, 96.1% for anti-FHA and 92.2% for anti-PRN (Table 2). Before vaccination, 58.4%, 96.6% and 70.7% of the adults were seropositive for anti-PT, anti-FHA and anti-PRN, respectively (Table 3). One month post-vaccination, seropositivity rates were ≥95.7% across the pertussis antigens. GMCs were 66.9 EU/mL for anti-PT, 796.3 EU/mL for anti-FHA and 307.0 EU/mL for anti-PRN antibodies (Table 3).

The anti-D and anti-T seroprotection rates and pertussis booster response rates in adults under active OAD treatment were consistent with the immune response in the comparator population representing the general adult population. This was the case in cohorts ≥65 years of age from studies Tdap0.3-008 and Tdap 0.3-011 but also in cohorts including younger adults (≥18 years) from studies Tdap-002, Tdap0.3-007, Tdap0.3-008 and Tdap-003 (Table 2).

Safety

Following Tdap vaccination, injection site pain was the most frequently reported solicited local AE (47.7% of adults under

Table 2. Immunogenicity outcomes 1 month post-Tdap vaccination: comparison between adults under active treatment for obstructive airway diseases and the overall study populations of selected studies[a] (according-to-protocol cohort).

	OAD-treated adults	Overall study populations						
Age	Meta-analysis ≥18 years	Tdap-002[b] ≥18 years	Tdap0.3-007 19–64 years	Tdap0.3-008[c] 19–64 years	Tdap0.3-008[d] ≥65 years	Tdap0.3-011 ≥65 years	Zoster-042[b] ≥50 years	Tdap-003[e] ≥18 years
Seroprotection rate, % (95% CI)								
Anti-D	**N = 209**	N = 424	N = 1444	N = 653	N = 98	N = 859	N = 389	N = 95
≥0.1 IU/mL	**89.0 (83.9; 92.9)**	93.6 (90.9; 95.8)	98.2 (97.4; 98.8)	94.0 (91.9; 95.7)	80.6 (71.4; 87.9)	84.9 (82.3; 87.2)	94.3 (91.6; 96.4)	88.4 (80.2; 94.1)
≥1.0 IU/mL	**67.0 (60.2; 73.3)**	64.2 (59.4; 68.7)	87.9 (86.1; 89.5)	80.9 (77.6; 83.8)	50.0 (39.7; 60.3)	52.0 (48.6; 55.4)	75.3 (70.7; 79.5)	70.5 (60.3; 79.4)
Anti-T	**N = 211**	N = 428	N = 1445	N = 654	N = 102	N = 864	N = 394	N = 95
≥0.1 IU/mL	**97.2 (93.9; 98.9)**	99.8 (98.7; 100)	99.6 (99.1; 99.8)	99.8 (99.2; 100)	93.1 (86.4; 97.2)	96.8 (95.4; 97.8)	99.5 (98.2; 99.9)	100 (96.2; 100)
≥1.0 IU/mL	**92.4 (88.0; 95.6)**	96.7 (94.6; 98.2)	98.3 (97.5; 98.9)	95.0 (93.0; 96.5)	82.4 (73.6; 89.2)	88.8 (86.5; 90.8)	95.7 (93.2; 97.5)	100 (96.2; 100)
Booster response rate, % (95% CI)								
Anti-PT	**N = 207**	N = 421	N = 1419	N = 627	N = 97	N = 846	N = 389	N = 95
	78.3 (72.0; 83.7)	88.4 (84.9; 91.3)	77.2 (74.9; 79.3)	84.5 (81.5; 87.3)	70.1 (60.0; 79.0)	69.1 (65.9; 72.2)	71.7 (67.0; 76.1)	93.7 (86.8; 97.6)
Anti-FHA	**N = 204**	N = 415	N = 1433	N = 647	N = 99	N = 821	N = 391	N = 93
	96.1 (92.4; 98.3)	99.8 (98.7; 100)	96.9 (95.8; 97.7)	96.0 (94.2; 97.4)	91.9 (84.7; 96.4)	92.8 (90.8; 94.5)	92.1 (88.9; 94.5)	96.8 (90.9; 99.3)
Anti-PRN	**N = 206**	N = 427	N = 1441	N = 652	N = 100	N = 864	N = 387	N = 95
	92.2 (87.7; 95.5)	94.1 (91.5; 96.2)	93.2 (91.8; 94.4)	90.3 (87.8; 92.5)	77.0 (67.5; 84.8)	73.8 (70.8; 76.7)	83.2 (79.1; 86.8)	97.9 (92.6; 99.7)

Tdap, GSK's reduced-antigen tetanus, diphtheria and acellular pertussis vaccine; OAD, obstructive airway diseases; CI, confidence interval; D, diphtheria toxoid; N, number of adults with available results; IU, international units; T, tetanus toxoid; PT, pertussis toxoid; FHA, filamentous hemagglutinin; PRN, pertactin.

[a]Selected studies for the comparator population were the 5 studies included in the meta-analysis (Table S2) and study Tdap-003. Only the study groups vaccinated with Tdap were considered, and for co-administration studies, only the sequential administration groups following Tdap vaccination were considered.

[b]For studies Tdap-002 and Zoster-042, the immune response to the pertussis antigens was recalculated following the definition used in the meta-analysis.

[c]Primary cohort.

[d]Exploratory cohort.

[e]For study Tdap-003, the booster response to PT, FHA and PRN antigens was defined as: post-vaccination antibody concentration ≥5 enzyme-linked immunosorbent assay units (EU)/mL for participants with pre-vaccination antibody concentration <5 EU/mL and post-vaccination antibody concentration ≥2 times the pre-vaccination antibody concentration for participants with pre-vaccination antibody concentration ≥5 EU/mL.

Table 3. Percentage of adults under active treatment for obstructive airway diseases with anti-PT, anti-FHA and anti-PRN antibody concentrations ≥5 EU/mL and antibody GMCs by timepoint (according-to-protocol cohort).

Antibody	Timepoint	N	Seropositivity rate (≥5 EU/mL), % (95% CI)	GMC, EU/mL (95% CI)
Anti-PT	Pre	209	58.4 (51.4; 65.1)	7.4 (6.4; 8.6)
	Post	209	95.7 (92.0; 98.0)	66.9 (56.3; 79.5)
Anti-FHA	Pre	208	96.6 (93.2; 98.6)	44.9 (38.1; 52.9)
	Post	206	100 (98.2; 100)	796.3 (683.3; 927.9)
Anti-PRN	Pre	208	70.7 (64.0; 76.8)	13.1 (10.7; 16.1)
	Post	208	98.1 (95.1: 99.5)	307.0 (241.9; 389.7)

PT, pertussis toxoid; FHA, filamentous hemagglutinin; PRN, pertactin; EU, enzyme-linked immunosorbent assay units; GMC, geometric mean antibody concentration; N, number of adults with available results; CI, confidence interval; pre, pre-vaccination; post, 1 month post-vaccination.

OAD treatment), followed by redness (21.1%) and swelling (13.3%) (Table 4). Grade 3 injection site pain was reported by 0.9% of participants. Injection site redness and swelling with a diameter ≥50 mm were reported by 1.4% and 0.9% of participants, respectively.

Fatigue (19.3%) was the most frequently reported solicited general AE, followed by headache (17.0%) and gastrointestinal symptoms (9.6%). Fever was reported by 0.5% of participants; none had a temperature >40°C (Table 4). Fatigue was the most frequently reported grade 3 solicited general AE (2.8%) followed by gastrointestinal symptoms (1.4%). Fatigue considered related to Tdap vaccination was reported by 12.4% of participants, headache by 10.6% and gastrointestinal symptoms by 6.4% (Table 4). The most frequently reported grade 3 solicited general AEs considered related to Tdap vaccination were fatigue and gastrointestinal symptoms, each reported by 1.4% of participants.

The frequencies of reported solicited AEs in the meta-analysis were within the ranges observed for the comparator population (Table 4).

Within 1 month post-Tdap vaccination, at least 1 unsolicited AE was reported by 30.2% of adults under active OAD treatment. The most frequently reported unsolicited AEs were nasopharyngitis (3.2%), followed by oropharyngeal pain, bronchitis and injection site pruritus (reported each by 1.8% of adults) and sinusitis, upper respiratory tract infection, arthralgia and headache (reported each by 1.4% of participants). Asthma and COPD were also reported, each by 0.9% of adults (Table S4). These results do not suggest an increase in the number of exacerbations after Tdap vaccination. Sixteen adults (7.2%) reported at least 1 unsolicited AE considered causally related to Tdap vaccination, and the most common were injection site pruritus (1.8% of adults) and myalgia (0.9%). Seven adults (3.2%) reported grade 3 unsolicited AEs, and none were considered related to Tdap vaccination.

Within 1 month post-Tdap vaccination, 6 adults (2.7%) under active OAD treatment reported 7 SAEs. One adult reported both diverticulitis and COPD. The other 5 adults reported 1 event each: gastroesophageal reflux disease, enterococcal sepsis, gastroenteritis viral, bronchial carcinoma and cervix carcinoma were reported. There were no fatal SAEs and none of the SAEs or withdrawals due to AEs/SAEs were assessed as related to Tdap vaccination by the investigators.

Discussion

Vaccination against pertussis could benefit adults who may be at risk of pertussis infection, including those suffering from chronic lung diseases. It may avoid the potential additional burden of respiratory disease caused by pertussis illness and may help reduce the occurrence of exacerbations in such patients. This meta-analysis provides further evidence supporting Tdap vaccination in adults with OAD, such as asthma and COPD. We found that adults on active standard treatment for their OAD showed an immune response and a tolerability to Tdap booster vaccination that were consistent with those in the comparator populations representative of the general adult population. We found no evidence for an increase in the number of exacerbations following Tdap vaccination in adults with OAD. Our results suggest that standard OAD treatment does not impact the immunogenicity or safety of adult Tdap vaccination.

Due to gradual weakening of the immune system with age, also called immunosenescence, the response to vaccination in older adults tends to be less robust than in younger adults.[44] In our meta-analysis, the selected clinical trials had to have a substantial number of adults ≥40 years of age to increase the probability of including COPD patients. This resulted in a mean age of 55.5 years and a relatively high proportion of ≥65-years-olds in our study population. Most patients under OAD treatment included in the meta-analysis achieved protective antibody concentrations (≥0.1 IU/mL) for diphtheria and tetanus and showed booster responses to the 3 pertussis antigens. The long-term seroprotection rate for diphtheria (≥1.0 IU/mL) and the anti-PT booster response rate were below 80%. However, these rates were higher than the rates observed in adults ≥65 years old and were comparable to rates obtained in the overall population ≥18 years old from the selected representative clinical studies. The immune response to Tdap vaccination in adults treated for OAD was thus consistent with the immune response in the general adult population, despite the relatively advanced age of the study population in this meta-analysis. Because younger individuals are expected to mount a stronger immune response, the absence of an OAD treatment effect on the immune response to Tdap observed in the current study is likely also valid for younger individuals with COPD or asthma.

Table 4. Reactogenicity outcomes within 4 days post-Tdap vaccination: comparison between adults under active treatment for obstructive airway diseases and the overall study populations of selected studies[a] (total vaccinated cohort).

		OAD-treated adults	Overall study population					
		Meta-analysis	Tdap-002	Tdap0.3-007	Tdap0.3-008[b]	Tdap0.3-008[c]	Tdap0.3-011	Zoster-042
Age		≥18 years	≥18 years	19–64 years	19–64 years	≥65 years	≥65 years	≥50 years
N		218	438	1480	665[d]	104	882	409
Solicited local adverse events, % (95% CI)								
Pain	All	**47.7 (40.9; 54.6)**	71.2 (66.7; 75.4)	60.5 (58.0; 63.0)	48.9 (45.1; 52.8)	28.8 (20.4; 38.6)	21.5 (18.9; 24.4)	37.4 (32.7; 42.3)
	Grade 3	**0.9 (0.1; 3.3)**	0.7 (0.1; 2.0)	1.6 (1.0; 2.3)	1.4 (0.6; 2.6)	1.9 (0.2; 6.8)	0.2 (0.0; 0.8)	0.7 (0.2; 2.1)
Redness	>0 mm	**21.1 (15.9; 27.1)**	31.5 (27.2; 36.1)	21.0 (19.0; 23.2)	18.8 (15.9; 22.0)	14.4 (8.3; 22.7)	10.8 (8.8; 13.0)	15.4 (12.0; 19.3)
	≥25 mm	**3.2 (1.3; 6.5)**	5.3 (3.4; 7.8)	3.8 (2.9; 4.9)	2.3 (1.3; 3.7)	1.9 (0.2; 6.8)	1.4 (0.7; 2.4)	3.4 (1.9; 5.7)
	≥50 mm	**1.4 (0.3; 4.0)**	2.1 (0.9; 3.9)	1.1 (0.7; 1.8)	0.5 (0.1; 1.3)	1.9 (0.2; 6.8)	0.6 (0.2; 1.3)	1.2 (0.4; 2.8)
Swelling	>0 mm	**13.3 (9.1; 18.5)**	19.6 (16.0; 23.7)	17.4 (15.5; 19.4)	15.8 (13.1; 18.8)	7.7 (3.4; 14.6)	7.5 (5.8; 9.4)	13.2 (10.1; 16.9)
	≥25 mm	**3.7 (1.6; 7.1)**	4.6 (2.8; 7.0)	3.5 (2.6; 4.6)	2.4 (1.4; 3.9)	0.0 (0.0; 3.5)	2.2 (1.3; 3.3)	4.2 (2.4; 6.6)
	≥50 mm	**0.9 (0.1; 3.3)**	2.3 (1.1; 4.2)	1.1 (0.6; 1.7)	0.9 (0.3; 2.0)	0.0 (0.0; 3.5)	0.7 (0.3; 1.5)	2.2 (1.0; 4.1)
Solicited general adverse events, % (95% CI)								
Fatigue	All	**19.3 (14.3; 25.1)**	20.3 (16.6; 24.4)	23.0 (20.9; 25.2)	14.3 (11.7; 17.2)	2.9 (0.6; 8.2)	12.5 (10.4; 14.8)	14.7 (11.4; 18.5)
	Grade 3	**2.8 (1.0; 5.9)**	0.7 (0.1; 2.0)	1.5 (0.9; 2.2)	1.8 (0.9; 3.1)	0.0 (0.0; 3.5)	0.7 (0.3; 1.5)	1.5 (0.5; 3.2)
	Related	**12.4 (8.3; 17.5)**	11.6 (8.8; 15.0)	15.7 (13.9; 17.6)	11.4 (9.1; 14.1)	2.9 (0.6; 8.2)	9.4 (7.6; 11.5)	8.8 (6.2; 12.0)
	Grade 3 related	**1.4 (0.3; 4.0)**	0.2 (0.0; 1.3)	0.7 (0.4; 1.3)	1.5 (0.7; 2.7)	0.0 (0.0; 3.5)	0.5 (0.1; 1.2)	0.5 (0.1; 1.8)
Headache	All	**17.0 (12.2; 22.6)**	23.3 (19.4; 27.5)	23.4 (21.2; 25.6)	15.8 (13.1; 18.8)	7.7 (3.4; 14.6)	11.5 (9.4; 13.7)	12.5 (9.4; 16.1)
	Grade 3	**0.5 (0.0; 2.5)**	0.7 (0.1; 2.0)	0.9 (0.5; 1.6)	1.2 (0.5; 2.4)	0.0 (0.0; 3.5)	0.6 (0.2; 1.3)	0.7 (0.2; 2.1)
	Related	**10.6 (6.8; 15.4)**	13.5 (10.4; 17.0)	14.7 (13.0; 16.6)	12.0 (9.7; 14.7)	6.7 (2.7; 13.4)	8.5 (6.7; 10.5)	7.8 (5.4; 10.9)
	Grade 3 related	**0.5 (0.0; 2.5)**	0.0 (0.0; 0.8)	0.6 (0.3; 1.2)	1.2 (0.5; 2.4)	0.0 (0.0; 3.5)	0.5 (0.1; 1.2)	0.0 (0.0; 0.9)
Gastrointestinal symptoms[e]	All	**9.6 (6.1; 14.3)**	1.6 (0.6; 3.3)	12.5 (10.9; 14.3)	5.9 (4.2; 7.9)	0.0 (0.0; 3.5)	7.6 (5.9; 9.5)	7.3 (5.0; 10.3)
	Grade 3	**1.4 (0.3; 4.0)**	0.0 (0.0; 0.8)	0.5 (0.2; 1.0)	0.3 (0.0; 1.1)	0.0 (0.0; 3.5)	0.3 (0.1; 1.0)	0.7 (0.2; 2.1)
	Related	**6.4 (3.6; 10.5)**	0.7 (0.1; 2.0)	7.6 (6.3; 9.0)	3.6 (2.3; 5.3)	0.0 (0.0; 3.5)	5.1 (3.7; 6.8)	3.9 (2.3; 6.3)
	Grade 3 related	**1.4 (0.3; 4.0)**	0.0 (0.0; 0.8)	0.3 (0.1; 0.8)	0.3 (0.0; 1.1)	0.0 (0.0; 3.5)	0.3 (0.1; 1.0)	0.2 (0.0; 1.4)
Fever	≥38.0°C	**0.5 (0.0; 2.5)**	2.3 (1.1; 4.2)	0.9 (0.5; 1.6)	1.5 (0.7; 2.7)	1.9 (0.2; 6.8)	0.2 (0.0; 0.8)	0.5 (0.1; 1.8)
	>40.0°C	**0.0 (0.0; 1.7)**	0.0 (0.0; 0.8)	0.0 (0.0; 0.2)	0.0 (0.0; 0.6)	0.0 (0.0; 3.5)	0.0 (0.0; 0.4)	0.0 (0.0; 0.9)
	Related	**0.0 (0.0; 1.7)**	1.4 (0.5; 3.0)	0.4 (0.1; 0.9)	0.8 (0.2; 1.7)	0.0 (0.0; 3.5)	0.2 (0.0; 0.8)	0.5 (0.1; 1.8)
	>40.0°C related	**0.0 (0.0; 1.7)**	0.0 (0.0; 0.8)	0.0 (0.0; 0.2)	0.0 (0.0; 0.6)	0.0 (0.0; 3.5)	0.0 (0.0; 0.4)	0.0 (0.0; 0.9)
Pain	All	**47.7 (40.9; 54.6)**	71.2 (66.7; 75.4)	60.5 (58.0; 63.0)	48.9 (45.1; 52.8)	28.8 (20.4; 38.6)	21.5 (18.9; 24.4)	37.4 (32.7; 42.3)
	Grade 3	**0.9 (0.1; 3.3)**	0.7 (0.1; 2.0)	1.6 (1.0; 2.3)	1.4 (0.6; 2.6)	1.9 (0.2; 6.8)	0.2 (0.0; 0.8)	0.7 (0.2; 2.1)
Redness	>0 mm	**21.1 (15.9; 27.1)**	31.5 (27.2; 36.1)	21.0 (19.0; 23.2)	18.8 (15.9; 22.0)	14.4 (8.3; 22.7)	10.8 (8.8; 13.0)	15.4 (12.0; 19.3)
	≥25 mm	**3.2 (1.3; 6.5)**	5.3 (3.4; 7.8)	3.8 (2.9; 4.9)	2.3 (1.3; 3.7)	1.9 (0.2; 6.8)	1.4 (0.7; 2.4)	3.4 (1.9; 5.7)
	≥50 mm	**1.4 (0.3; 4.0)**	2.1 (0.9; 3.9)	1.1 (0.7; 1.8)	0.5 (0.1; 1.3)	1.9 (0.2; 6.8)	0.6 (0.2; 1.3)	1.2 (0.4; 2.8)
Swelling	>0 mm	**13.3 (9.1; 18.5)**	19.6 (16.0; 23.7)	17.4 (15.5; 19.4)	15.8 (13.1; 18.8)	7.7 (3.4; 14.6)	7.5 (5.8; 9.4)	13.2 (10.1; 16.9)
	≥25 mm	**3.7 (1.6; 7.1)**	4.6 (2.8; 7.0)	3.5 (2.6; 4.6)	2.4 (1.4; 3.9)	0.0 (0.0; 3.5)	2.2 (1.3; 3.3)	4.2 (2.4; 6.6)
	≥50 mm	**0.9 (0.1; 3.3)**	2.3 (1.1; 4.2)	1.1 (0.6; 1.7)	0.9 (0.3; 2.0)	0.0 (0.0; 3.5)	0.7 (0.3; 1.5)	2.2 (1.0; 4.1)
Solicited general adverse events, % (95% CI)								
Fatigue	All	**19.3 (14.3; 25.1)**	20.3 (16.6; 24.4)	23.0 (20.9; 25.2)	14.3 (11.7; 17.2)	2.9 (0.6; 8.2)	12.5 (10.4; 14.8)	14.7 (11.4; 18.5)
	Grade 3	**2.8 (1.0; 5.9)**	0.7 (0.1; 2.0)	1.5 (0.9; 2.2)	1.8 (0.9; 3.1)	0.0 (0.0; 3.5)	0.7 (0.3; 1.5)	1.5 (0.5; 3.2)
	Related	**12.4 (8.3; 17.5)**	11.6 (8.8; 15.0)	15.7 (13.9; 17.6)	11.4 (9.1; 14.1)	2.9 (0.6; 8.2)	9.4 (7.6; 11.5)	8.8 (6.2; 12.0)
	Grade 3 related	**1.4 (0.3; 4.0)**	0.2 (0.0; 1.3)	0.7 (0.4; 1.3)	1.5 (0.7; 2.7)	0.0 (0.0; 3.5)	0.5 (0.1; 1.2)	0.5 (0.1; 1.8)
Headache	All	**17.0 (12.2; 22.6)**	23.3 (19.4; 27.5)	23.4 (21.2; 25.6)	15.8 (13.1; 18.8)	7.7 (3.4; 14.6)	11.5 (9.4; 13.7)	12.5 (9.4; 16.1)
	Grade 3	**0.5 (0.0; 2.5)**	0.7 (0.1; 2.0)	0.9 (0.5; 1.6)	1.2 (0.5; 2.4)	0.0 (0.0; 3.5)	0.6 (0.2; 1.3)	0.7 (0.2; 2.1)
	Related	**10.6 (6.8; 15.4)**	13.5 (10.4; 17.0)	14.7 (13.0; 16.6)	12.0 (9.7; 14.7)	6.7 (2.7; 13.4)	8.5 (6.7; 10.5)	7.8 (5.4; 10.9)
	Grade 3 related	**0.5 (0.0; 2.5)**	0.0 (0.0; 0.8)	0.6 (0.3; 1.2)	1.2 (0.5; 2.4)	0.0 (0.0; 3.5)	0.5 (0.1; 1.2)	0.0 (0.0; 0.9)
Gastrointestinal symptoms[e]	All	**9.6 (6.1; 14.3)**	1.6 (0.6; 3.3)	12.5 (10.9; 14.3)	5.9 (4.2; 7.9)	0.0 (0.0; 3.5)	7.6 (5.9; 9.5)	7.3 (5.0; 10.3)
	Grade 3	**1.4 (0.3; 4.0)**	0.0 (0.0; 0.8)	0.5 (0.2; 1.0)	0.3 (0.0; 1.1)	0.0 (0.0; 3.5)	0.3 (0.1; 1.0)	0.7 (0.2; 2.1)
	Related	**6.4 (3.6; 10.5)**	0.7 (0.1; 2.0)	7.6 (6.3; 9.0)	3.6 (2.3; 5.3)	0.0 (0.0; 3.5)	5.1 (3.7; 6.8)	3.9 (2.3; 6.3)
	Grade 3 related	**1.4 (0.3; 4.0)**	0.0 (0.0; 0.8)	0.3 (0.1; 0.8)	0.3 (0.0; 1.1)	0.0 (0.0; 3.5)	0.3 (0.1; 1.0)	0.2 (0.0; 1.4)

(*Continued*)

Table 4. (Continued).

		OAD-treated adults	Overall study population					
		Meta-analysis	Tdap-002	Tdap0.3-007	Tdap0.3-008[b]	Tdap0.3-008[c]	Tdap0.3-011	Zoster-042
Age		≥18 years	≥18 years	19–64 years	19–64 years	≥65 years	≥65 years	≥50 years
N		218	438	1480	665[d]	104	882	409
Fever	≥38.0°C	**0.5 (0.0; 2.5)**	2.3 (1.1; 4.2)	0.9 (0.5; 1.6)	1.5 (0.7; 2.7)	1.9 (0.2; 6.8)	0.2 (0.0; 0.8)	0.5 (0.1; 1.8)
	>40.0°C	**0.0 (0.0; 1.7)**	0.0 (0.0; 0.8)	0.0 (0.0; 0.2)	0.0 (0.0; 0.6)	0.0 (0.0; 3.5)	0.0 (0.0; 0.4)	0.0 (0.0; 0.9)
	Related	**0.0 (0.0; 1.7)**	1.4 (0.5; 3.0)	0.4 (0.1; 0.9)	0.8 (0.2; 1.7)	0.0 (0.0; 3.5)	0.2 (0.0; 0.8)	0.5 (0.1; 1.8)
	>40.0°C related	**0.0 (0.0; 1.7)**	0.0 (0.0; 0.8)	0.0 (0.0; 0.2)	0.0 (0.0; 0.6)	0.0 (0.0; 3.5)	0.0 (0.0; 0.4)	0.0 (0.0; 0.9)

Tdap, GSK's reduced-antigen tetanus, diphtheria and acellular pertussis vaccine; OAD, obstructive airway diseases; N, number of participants with the documented Tdap dose; CI, confidence interval.

[a]Selected studies for the comparator population were the 5 studies included in the meta-analysis (Table S2). Due to the differences in criteria used to evaluate solicited adverse events, study Tdap-003 was not included in the reactogenicity comparison. Only the study groups vaccinated with Tdap were considered, and for co-administration studies, only the sequential administration groups following Tdap were considered.

[b]Primary cohor.

[c]Exploratory cohort.

[d]For study Tdap 0.3-008 in the primary cohort (19–64 years), 1 out of the 665 participants had no data on solicited local adverse events.

[e]Gastrointestinal symptoms included nausea, vomiting, diarrhea and/or abdominal pain. For study Tdap-002, only vomiting was collected.

The safety profile of Tdap in adults under treatment for OAD did not differ from the well-established safety profile in the general adult population.[40,41] Rates of solicited local and general symptoms observed in our meta-analysis were consistent with rates observed in the overall adult population from the selected representative studies used as comparator. The vast majority of reported solicited symptoms did not interfere with everyday activities in OAD-treated adults. Most of the unsolicited AEs occurred at a low frequency and were not considered related to vaccination by the investigator. The most frequent were "infections and infestations," including infections and inflammation of the upper or lower airway, which are often encountered in patients with asthma or COPD.[45,46] In addition, there was no evidence for an increase in the number of exacerbations among adults with OAD based on the observed unsolicited AEs. The frequency of SAEs was low in OAD-treated adults; none of these events were fatal or assessed as causally related to study vaccination by the investigator.

Our study has several limitations. First, the studies included in the meta-analysis enrolled generally healthy adults and excluded those with immunosuppressive conditions or taking immunosuppressants at high doses. Our results may therefore not be generalizable to patients with more severe or unstable OAD. Also, because similar therapeutics are used for both the treatment of asthma and COPD, no distinction could be made between these 2 underlying OAD. No classification of the specific disease stage for asthma or COPD could be performed as there was no information available to do so, nor could the dosage of the drugs administered be considered in the analysis. Moreover, the sample size did not allow for additional sub-analyses within the selected population. Further, the analysis did not include data on concomitant treatment other than treatment for OAD, nor data on comorbidities or medical history. However, comorbidities would have been considered well controlled for individuals to be enrolled in the clinical trials, and, therefore, these comorbidities should not have influenced the current results. The clinical studies included in the meta-analysis only covered study sites in Australia and the US, and results may not be generalizable to different parts of the world. The meta-analysis included more women than men, which might indicate that asthma was more prevalent than COPD in the selected studies. While the COPD prevalence has historically been higher in men than in women, in the last decades, studies from developed countries indicate that the COPD prevalence has become almost equal in both sexes, likely in part related to increased tobacco consumption in women.[47] On the contrary, asthma is less common in adult men than women, with a prevalence of 5.7% and 10.0%, respectively, in the US in 2016–2018.[48] Finally, because the meta-analysis used data extracted from clinical trials on criteria that had not been controlled for, no control group of non-OAD-treated adults from the same trials could be used due to the risk of imbalance in factors such as age and sex. Our data were therefore compared to the total study populations, including OAD-treated adults, of representative clinical studies.

Our study has several strengths. By extracting data previously collected in clinical trials, we could assess Tdap vaccination in patients who were under active OAD treatment. In addition, our meta-analysis applied a consistent approach to evaluate immunogenicity and safety outcomes and allow a valid comparison with data from the overall population considered representative of the general population of Tdap-vaccinated adults. For the immunogenicity assessment, a conversion factor was used to mitigate the effect of assay changes between clinical trials. Moreover, the immune response to the pertussis antigens was calculated using the same definition of booster response in the meta-analysis and in the comparator population. Finally, the safety data related to solicited AEs reported for the comparator population were recalculated post-hoc using the same thresholds for fever, redness and swelling as for the selected adults in the meta-analysis.

In conclusion, the results of our meta-analysis show that the *Boostrix* Tdap vaccine was immunogenic and well tolerated in adults under active OAD treatment, with immunogenicity and safety profiles comparable to those in the overall population representative of the general Tdap-vaccinated adult population. This suggests that standard OAD treatments do not decrease the immune response to Tdap booster vaccination in adults and that Tdap vaccination can be safely performed in patients on active standard therapy for their OAD. Tdap vaccination has the potential to address the unmet medical need for improved prevention of pertussis in adults with chronic lung diseases, who may be at risk of pertussis infection and its complications.

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Authors' contributions

PVdS, BC, QD and LVV were involved in the conception and design of the study. BC was responsible for the statistical analyses. All authors contributed to data interpretation, critically reviewed the article for important intellectual content and approved the final version for submission.

Disclosure statement

PVdS, BC, QD, LVV and DS are GSK employees. PVdS, BC and LVV have restricted shares in GSK. All authors declare financial and non-financial relationships and activities.

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Data availability statement

Study data and documents can be requested for further research from www.clinicalstudydatarequest.com.

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References

1. Nieves DJ, Heininger U. Bordetella pertussis. Microbiol Spectr. 2016;4(3). doi:10.1128/microbiolspec.EI10-0008-2015.
2. World Health Organization. Pertussis vaccines: WHO position paper - September 2015. Wkly Epidemiol Rec. 2015;90 (35):433–58.
3. Klein NP, Bartlett J, Rowhani-Rahbar A, Fireman B, Baxter R. Waning protection after fifth dose of acellular pertussis vaccine in children. N Engl J Med. 2012;367(11):1012–19. doi:10.1056/NEJMoa1200850.
4. Shapiro ED. Acellular vaccines and resurgence of pertussis. JAMA. 2012;308(20):2149–50. doi:10.1001/jama.2012.65031.
5. Tartof SY, Lewis M, Kenyon C, White K, Osborn A, Liko J, Zell E, Martin S, Messonnier NE, Clark TA, et al. Waning immunity to pertussis following 5 doses of DTaP. Pediatrics. 2013;131(4): e1047–1052. doi:10.1542/peds.2012-1928.
6. Wendelboe AM, Van Rie A, Salmaso S, Englund JA. Duration of immunity against pertussis after natural infection or vaccination. Pediatr Infect Dis J. 2005;24(5 Suppl):S58–61. doi:10.1097/01.inf.0000160914.59160.41.
7. Di Mattia G, Nicolai A, Frassanito A, Petrarca L, Nenna R, Midulla F. Pertussis: new preventive strategies for an old disease. Paediatr Respir Rev. 2019;29:68–73. doi:10.1016/j.prrv.2018.03.011.
8. Liang JL, Tiwari T, Moro P, Messonnier NE, Reingold A, Sawyer M, Clark TA. Prevention of pertussis, tetanus, and diphtheria with vaccines in the United States: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep. 2018;67(2):1–44. doi:10.15585/mmwr.rr6702a1.
9. European Centre for Disease Prevention and Control. Vaccine scheduler; [accessed 2022 Jul 11]. https://vaccine-schedule.ecdc.europa.eu/.
10. Australian Government - Department of Health and Aged Care. Australian immunisation handbook - Pertussis (whooping cough); [accessed 2022 Jul 15]. https://immunisationhandbook.health.gov.au/contents/vaccine-preventable-diseases/pertussis-whooping-cough#recommendations.
11. New Zealand Ministry of Health. Immunisation handbook 2020 - 15. Pertussis (whooping cough); [accessed 2022 Jul 15]. https://www.health.govt.nz/our-work/immunisation-handbook-2020/15-pertussis-whooping-cough#14-5.
12. Havers FP, Moro PL, Hunter P, Hariri S, Bernstein H. Use of tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccines: updated recommendations of the advisory committee on immunization practices - United States, 2019. MMWR Morb Mortal Wkly Rep. 2020;69(3):77–83. doi:10.15585/mmwr.mm6903a5.
13. Centers for Disease control and Prevention. Pertussis: summary of vaccine recommendations. For healthcare professionals. Summary of DTaP and Tdap vaccine recommendations across the lifespan; [accessed 2022 Aug 11]. https://www.cdc.gov/vaccines/vpd/pertussis/recs-summary.html .
14. Choi JH, Correia de Sousa J, Fletcher M, Gabutti G, Harrington L, Holden M, Kim H, Michel JP, Mukherjee P, Nolan T, et al. Improving vaccination rates in older adults and at-risk groups: focus on pertussis. Aging Clin Exp Res. 2022;34(1):1–8. doi:10.1007/s40520-021-02018-3.
15. 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. doi:10.1080/21645515.2020.1738168.
16. Capili CR, Hettinger A, Rigelman-Hedberg N, Fink L, Boyce T, Lahr B, Juhn YJ. Increased risk of pertussis in patients with asthma. J Allergy Clin Immunol. 2012;129(4):957–63. doi:10.1016/j.jaci.2011.11.020.
17. 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):1450–56. doi:10.1093/cid/cis627.
18. Buck PO, Meyers JL, Gordon LD, 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. doi:10.1017/s0950268817000887.
19. Mbayei SA, Faulkner A, Miner C, Edge K, Cruz V, Peña SA, Kudish K, Coleman J, Pradhan E, Thomas S, et al. Severe pertussis infections in the United States, 2011–2015. Clin Infect Dis. 2019;69 (2):218–26. doi:10.1093/cid/ciy889.
20. Hoe Nam L, Chiu CH, Heo JY, Ip M, Jung KS, Menzies R, Pearce R, Buchy P, Chen J, Nissen M, et al. The need for pertussis vaccination among older adults and high-risk groups: a perspective from advanced economies of the Asia Pacific region. Expert Rev Vaccines. 2021;20(12):1603–17. doi:10.1080/14760584.2021.1990759.
21. GBD Chronic Respiratory Disease Collaborators. Prevalence and attributable health burden of chronic respiratory diseases, 1990-2017: a systematic analysis for the global burden of disease study 2017. Lancet Respir Med. 2020;8(6):585–96. doi:10.1016/s2213-2600(20)30105-3.
22. Global Initiative for Chronic Obstructive Lung Disease. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. GOLD report 2022; [accessed 2022 Jul 11]. https://goldcopd.org/archived-reports/.
23. Global Asthma Network. The global asthma report 2022. [accessed 2022 Nov 22]. http://globalasthmareport.org/resources/Global_Asthma_Report_2022.pdf.
24. Viniol C, Vogelmeier CF. Exacerbations of COPD. Eur Respir Rev. 2018;27(147):170103. doi:10.1183/16000617.0103-2017.
25. Castillo JR, Peters SP, Busse WW. Asthma exacerbations: pathogenesis, prevention, and treatment. J Allergy Clin Immunol Pract. 2017;5(4):918–27. doi:10.1016/j.jaip.2017.05.001.
26. Aris E, Harrington L, Bhavsar A, Simeone JC, Ramond A, Papi A, Vogelmeier CF, Meszaros K, Lambrelli D, Mukherjee P. Burden of pertussis in COPD: a retrospective database study in England. COPD. 2021;18(2):157–69. doi:10.1080/15412555.2021.1899155.
27. Bhavsar A, Aris E, Harrington L, Simeone JC, Ramond A, Lambrelli D, Papi A, Boulet LP, Meszaros K, Jamet N, 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. doi:10.2147/JAA.S335960.
28. De Serres G, Shadmani R, Duval B, Boulianne N, Déry P, Douville Fradet M, Rochette L, Halperin SA. Morbidity of pertussis in adolescents and adults. J Infect Dis. 2000;182(1):174–79. doi:10.1086/315648.
29. Centers for Disease control and Prevention. Lung disease including asthma and adult vaccination, 2016; [accessed 2022 Jul 11]. https://www.cdc.gov/vaccines/adults/rec-vac/health-conditions/lung-disease.html.
30. Colaneri M, De Filippo M, Licari A, Marseglia A, Maiocchi L, Ricciardi A, Corsico A, Marseglia G, Mondelli MU, Bruno R. COVID vaccination and asthma exacerbation: might there be a link? Int J Infect Dis. 2021;112:243–46. doi:10.1016/j.ijid.2021.09.026.

31. Tata LJ, West J, Harrison T, Farrington P, Smith C, Hubbard R. Does influenza vaccination increase consultations, corticosteroid prescriptions, or exacerbations in subjects with asthma or chronic obstructive pulmonary disease? Thorax. 2003;58(10):835–39. doi:10.1136/thorax.58.10.835.
32. Pesek R, Lockey R. Vaccination of adults with asthma and COPD. Allergy. 2011;66(1):25–31. doi:10.1111/j.1398-9995.2010.02462.x.
33. Vasileiou E, Sheikh A, Butler C, El Ferkh K, von Wissmann B, McMenamin J, Ritchie L, Schwarze J, Papadopoulos NG, Johnston SL, et al. Effectiveness of influenza vaccines in asthma: a systematic review and meta-analysis. Clin Infect Dis. 2017;65 (8):1388–95. doi:10.1093/cid/cix524.
34. Turnbull FM, Heath TC, Jalaludin BB, Burgess MA, Ramalho AC. A randomized trial of two acellular pertussis vaccines (dTpa and pa) and a licensed diphtheria-tetanus vaccine (Td) in adults. Vaccine. 2000;19(6):628–36. doi:10.1016/s0264-410x(00)00252-8.
35. Blatter M, Friedland LR, Weston WM, Li P, Howe B. Immunogenicity and safety of a tetanus toxoid, reduced diphtheria toxoid and three-component acellular pertussis vaccine in adults 19-64 years of age. Vaccine. 2009;27(5):765–72. doi:10.1016/j.vaccine.2008.11.028.
36. Weston WM, Chandrashekar V, Friedland LR, Howe B. Safety and immunogenicity of a tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine when co-administered with influenza vaccine in adults. Hum Vaccin. 2009;5(12):858–66. doi:10.4161/hv.9961.
37. Weston WM, Friedland LR, Wu X, Howe B. Vaccination of adults 65 years of age and older with tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccine (Boostrix(®)): results of two randomized trials. Vaccine. 2012;30(9):1721–28. doi:10.1016/j.vaccine.2011.12.055.
38. Strezova A, Lal H, Enweonye I, Campora L, Beukelaers P, Segall N, Heineman TC, Schuind AE, Oostvogels L. The adjuvanted recombinant zoster vaccine co-administered with a tetanus, diphtheria and pertussis vaccine in adults aged ≥50 years: a randomized trial. Vaccine. 2019;37(39):5877–85. doi:10.1016/j.vaccine.2019.08.001.
39. Van Damme P, Burgess M. Immunogenicity of a combined diphtheria-tetanus-acellular pertussis vaccine in adults. Vaccine. 2004;22(3–4):305–08. doi:10.1016/j.vaccine.2003.08.012.
40. Health Products Regulatory Authority. Boostrix summary of product characteristics; 2022 [accessed 2022 Aug 29]. http://www.hpra.ie/img/uploaded/vaccines/SPC_PA1077020001.pdf.
41. Food and Drug Administration. Package insert - Boostrix. [accessed 2022 Jul 11]. https://www.fda.gov/media/124002/download.
42. Efstratiou A, Maple CPA, World Health Organization. Regional Office for Europe. Laboratory diagnosis of diphtheria. [accessed 2022 Aug 29]. https://apps.who.int/iris/handle/10665/108108.
43. Food and Drug Administration. Guidance document: toxicity grading scale for healthy adult and adolescent volunteers enrolled in preventive vaccine clinical trials. Guidance for industry; 2007 Sep [accessed 2022 Jul 4]. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/toxicity-grading-scale-healthy-adult-and-adolescent-volunteers-enrolled-preventive-vaccine-clinical.
44. Costantini E, D'Angelo C, Reale M. The role of immunosenescence in neurodegenerative diseases. Mediators Inflamm. 2018;2018:6039171. doi:10.1155/2018/6039171.
45. Juhn YJ. Risks for infection in patients with asthma (or other atopic conditions): is asthma more than a chronic airway disease? J Allergy Clin Immunol. 2014;134(2):247–257; quiz 258–259. doi:10.1016/j.jaci.2014.04.024.
46. Lange P. Chronic obstructive pulmonary disease and risk of infection. Pneumonol Alergol Pol. 2009;77(3):284–88. doi:10.5603/ARM.27817.
47. Aryal S, Diaz-Guzman E, Mannino DM. Influence of sex on chronic obstructive pulmonary disease risk and treatment outcomes. Int J Chron Obstruct Pulmon Dis. 2014;9:1145–54. doi:10.2147/COPD.S54476.
48. Pate CA, Zahran HS, Qin X, Johnson C, Hummelman E, Malilay J. Asthma surveillance - United States, 2006-2018. MMWR Surveill Summ. 2021;70(5):1–32. doi:10.15585/mmwr.ss7005a1.